ESTIMATING THE BASIC REPRODUCTION NUMBER FOR THE 2015 NYIMBA DISTRICT BUBONIC PLAGUE OUTBREAK

by

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AUTHOR'S DECLARATION

I, **Joseph Sichone,** do hereby solemnly declare that this dissertation represents my own work, except where otherwise acknowledged, and that it has never been previously submitted for a degree at the University of Zambia or any other university.

Signed: _____

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CERTIFICATE OF APPROVAL

This dissertation of **JOSEPH SICHONE** has been approved as fulfilling the partial fulfillment of the requirements for the award of the degree of Masters of Science in One Health Analytical Epidemiology at the University of Zambia.

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ABSTRACT

Plague is a re-emerging flea-borne infectious disease of global importance and in recent years Zambia has periodically experienced increased incidence of bubonic plague outbreaks. However, there are currently no studies in the country that provide a quantitative assessment of the ability of the disease to spread during these outbreaks. This limits our understanding of the epidemiology of the disease especially for planning and implementing quantifiable and cost-effective control measures. To fill this gap, the basic reproduction number, Ro, for bubonic plague was estimated in this study. Ro is the average number of secondary infections arising from a single infectious individual during their infectious period in an entirely susceptible population. It gives a quantitative measure of the transmissibility of an infectious disease in the population and it is used to estimate the expected magnitude and extent of spread for an infectious disease outbreak. More importantly, Ro is used to guide the magnitude of control measures that will be required to control the disease. Secondary epidemic data from the most recent 2015 Nyimba district bubonic plague outbreak in Zambia was analyzed. Ro was estimated as a function of the average epidemic doubling time based on the initial exponential growth rate of the outbreak and the average infectious period for bubonic plague. Ro was estimated to range between 1.5599 [95% CI: 1.382 - 1.7378] and 1.9332 [95% CI: 1.6366 - 2.2297], with average 1.7465 [95% CI: 1.5093 - 1.9838]. Further, an SIR deterministic mathematical model was derived for this infection and this estimated Ro to be about 1.4 to 1.5, which was within the range estimated above considering the 95% confidence interval. This estimated Ro for bubonic plague is an indication that each bubonic plague case can typically give rise to almost two new cases during these outbreaks. This Ro estimate can now be used to quantitatively analyze and develop measurable interventions against future plague outbreaks in Zambia. For example, based on the average Ro estimate in this study, a minimum mass treatment rate of about 43% would be enough to prevent the disease spread in such high risk populations in the country.

DEDICATION

This thesis is dedicated to my loving family.

My Father, Mr. Patson Sichone, a mighty but gentle man. You simply are and will always be my role model in life.

My Mother, Rhoda Nguni, I would not be here or achieve anything if it was not for your unconditional love my entire life.

My siblings, thank you all for the love and support in everything. I love and believe in you all and together we will reach greater heights.

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LIST OF ABBREVIATIONS AND ACRONYMS

ASF : African Swine Fever.

CDC : Centers for Disease Control and Prevention.

CSO : Central Statistics Office.

DFE : Disease free equilibrium point

EEP : Disease endemic equilibrium point.

F1 Antigen : The Fraction 1 capsule-like antigen expressed by the *Yersinia pestis* bacterium.

FMD : Foot and Mouth Disease.

MOH : Ministry of Health of the Republic of Zambia.

PCR : Polymerase chain reaction

R_0 : Basic Reproduction Number or Ratio.

SARS : Sever Acute Respiratory Syndrome.

SIR : Susceptible, Infectious, Removed compartmental mathematical model.

SIR-SI : Susceptible, Infectious, Removed – Susceptible, Infectious compartmental mathematical model.

WHO : World Health Organization.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

In recent years, there has been an increase in the incidence and potential risk of plague outbreaks in Zambia and the global community at large. Plague is an important re-emerging infectious disease caused by the bacterium *Yersinia pestis.* It primarily infects rodents and their fleas but infection can spread to humans and other animals causing outbreaks (Spickler and Steneroden., 2013; WHO 2000; Dennis *et al*., 1999). In Zambia, plague was first recorded in 1917 in Tembwe village of Chama district in the Eastern Province (Nyirenda *et al*., 2016). By 1956, about 247 cases and 205 deaths were recorded from over 13 separate outbreaks in the country (Dennis *et al*., 1999; Nyirenda *et al*, 2016). This was followed by a general period of quiescence with fewer new outbreaks. By the turn of the century however, incidence began to sharply rise again in the country than previously seen. For example, between 1997 and 2007 alone, about 1,447 new cases were recorded from four major outbreaks which is more than five times that recorded from all previous outbreaks in the country put together (Nyirenda *et al*., 2016). As a key step to control this situation, recent studies conducted in Zambia have highlighted important ecological and social cultural factors, and life-style practices that precipitate the occurrence and rapid spread of these plague outbreaks in order to inform public health action (Nyirenda *et al*., 2016; Sinyange *et al*., 2016; Kango *et al.*, 2014; Ngulube *et al.*, 2006). However, the outcome of these studies did not generally include a quantitative assessment of the rapid spread of the infection during these outbreaks in relation to identified factors. This partly limits our understanding of the transmission dynamics of the disease especially for the purpose of developing quantifiable and cost effective control measures. To help fill this gap, the basic reproduction number, R_0, for bubonic plague was estimated in this study based on data from the latest 2015 Nyimba district bubonic plague outbreak in Zambia. R_0 is defined as the average number of secondary infections arising from a single infectious individual during their infectious period in an entirely susceptible population (Driessche and Watmough., 2002; Barongo *et al*., 2015; Dietz, 1993; Heffernan *et al*, 2005). It is the single most important epidemiological parameter that gives a quantitative measure of the

transmissibility of an infectious disease in the population and is used to estimate the expected magnitude and extent of spread for an infectious disease outbreak. More importantly, R_0 is used to guide the magnitude of control measures that will be required to control the disease (Mukandavire *et al*., 2013, 2011; Massin *et al*., 2007; Heffernan *et al*., 2005; Lipsitch *et al*., 2003; Ferguson *et al*., 2001). To estimate R_0, a simplified mathematical approach that estimates R_0 directly from early epidemic incidence data was applied. The result of this study profoundly supplements the existing epidemiological knowledge of bubonic plague infection in the country in order to better understand the epidemiology of the disease as well as meaningfully contribute to its control.

1.2 Problem Statement

Zambia and the global community has faced an increase in the re-emergence of plague outbreaks in recent years. This is despite plague being listed as one of the international notifiable diseases considered to have potential as a weapon for bioterrorism (WHO., 2000; Dennis *et al*., 1999; Henderson., 1999). Additionally, some recent studies suggest that there is possible emergence of drug resistance in some strains of *Yersinia pestis*, the causative agent for plague (Chanteau *et al*., 1998). In Zambia, the incidence of plague has continued to rise in the recent years with the occurrence of some large-scale plague epidemics than ever seen before in the country (Nyirenda *et al.,* 2016). Some examples of disease control responses recently deployed during these outbreaks have included large scale indoor spraying to reduce the flea population as well as mass sensitization campaigns on risk factors for plague (Sinyange *et al*, 2016). The cost effectiveness and the guiding principle on the amounts of such interventions that would be required to effectively control the disease is not clear for Zambia. For a developing and resource strained nation like Zambia, such major public health challenges need to be tackled using the most cost effective, efficient, and sustainable approaches appropriate to the region. This firstly requires developing a sufficient knowledge of the epidemiology of the disease in order to develop optimal disease interventions. Therefore, a comprehensive understanding of the transmission dynamics of these plague epidemics is important for informing future public health action against the disease in Zambia. However, there has been no assessment of the

epidemiological parameters that results in the rapid spread of these plague epidemics in the country. Estimation of the epidemiological parameters such as the basic reproduction number for plague would increase the epidemiological understanding of the disease in the country.

1.3 Study Justification and Significance

The basic reproduction number has been used to analyze the transmission dynamics of various important infectious diseases as well as to assess the effectiveness and magnitude of control measures required to control the disease. Examples include African Swine Fever-ASF (Korennoy *et al.*, 2016; Iglesias *et al*., 2014), cholera (Mukandavire *et al.*, 2013, 2011), Severe Acute Respiratory syndrome-SARS (Lipsitch *et al.*, 2003), Foot and Mouth Disease-FMD (Ferguson *et al.*, 2001) as well as pneumonic and bubonic plague (Dean *et al*., 2017; Massin *et al*., 2007; Gani and Leach., 2004;). Despite the growing threat of plague outbreaks in Zambia, no study has estimated the basic reproduction number for the infection for the local setting in the country. Estimating the basic reproduction number for plague will help improve the epidemiological understanding of the disease as well as in the planning and implementation of disease control measures. The basic reproduction number can therefore be used for the development of quantifiable and cost-effective control measures against the disease as the expected magnitude of the outbreak can be estimated from the onset. This can help the country begin to get a tighter grip in the public health management of the disease.

1.4 Research Question

For the purpose of this study, the following question were answered:

1) What is the basic reproduction number for plague in Nyimba district of Zambia?

1.5 General Objective

The general objective of this study was to estimate the basic reproduction number for bubonic plague in Zambia and briefly characterize its importance for understanding the transmission dynamics and rapid spread of plague outbreaks in the country.

1.6 Specific Objective

1) To estimate the basic reproduction number for the 2015 bubonic plague outbreak which occurred in Nyimba district in Zambia.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Plague Etiology

Plague is a historical and globally important re-emerging zoonotic infectious disease (Neerinckx, *et al.,* 2010, 2008; WHO., 2000; Dennis *et al*., 1999). It is listed among notifiable diseases by the World Health Organization, WHO, due to its high case fatality rate of 50% to 100% if left untreated (Dennis *et al*., 1999). Plague results from infection by a Gram-negative bacillus bacterium called *Yersinia pestis* in the *Enterobacteriaceae* family (Spickler and Steneroden., 2013; Dennis *et al*., 1999). The organism is non-motile and non-spore forming measuring about 1.5 by 0.75 microns and has a characteristic "Bipolar staining" under alkaline stains (Cheesbrough., 2006; Dennis *et al*., 1999). It was discovered by a young French scientist called Alexandre Yersin in 1894 during a plague epidemic in Hong Kong (Butler., 2014).

2.2 Plague Transmission

The most important natural hosts for plague are wild rodents and their fleas. Introduction of infection into human populations and to other susceptible animals occurs after bites from infected wild rodent fleas or by direct contact of skin lesions with infectious materials from these animals or other plague-infected materials (Spickler and Steneroden., 2013; Dennis *et al*., 1999). The most predominant rodent flea vectors for plague transmission are the *Xenopsylla* flea species but many other rodent flea species can carry *Yersinia* (Nyirenda *et al*., 2017; Spickler and Steneroden., 2013; Lorange *et al*., 2005; Dennis *et al*., 1999). Spillover of infection to humans can also occur after wild rodent hosts infect synanthropic rodent species such as the *Rattus* species and their fleas which in turn can infect humans. Likewise, many human plague outbreaks have been immediately preceded by widespread epizootics of plague in rodents living within or near human habitats (Nyirenda *et al*., 2017, 2016; Spickler and Steneroden., 2013; Neerinckx *et al*., 2010; Stenseth *et al*., 2008; McClean., 1995). Human pets such as cats and dogs are also susceptible to plague and can also transfer the infection to humans (Spickler and

Steneroden., 2013). Once an epidemic begins in human populations, human-to-human transmission is then also possible via various transmission routes. These transmission routes may include the transmission through various human ectoparasites, direct close contact during patient care, or airborne infectious droplets as is the case in pneumonic plague (Dean *et al*., 2017; Spickler and Steneroden., 2013; Dennis *et al*., 1999).

2.3 Plague Clinical Signs and Diagnosis

There are basically three clinical forms of plague namely bubonic, septicemic, and pneumonic plague (Spickler and Steneroden., 2013; Dennis *et al*., 1999). Bubonic plague is the most common form and usually results from the inoculation of *Y. pestis* into the skin (Spickler and Steneroden., 2013). It has an incubation period of about 2 to 10 days (Spickler and Steneroden., 2013; Dennis *et al*., 1999). Signs and symptoms usually include sudden high fever, chills, headache, malaise, dizziness, and vomiting (Gonzalez and Miller., 2016; Spickler and Steneroden., 2013; Dennis *et al*., 1999). Bubonic plague is also clinically typified by the presence of painful swollen lymph nodes, called "bubos" (Spickler and Steneroden., 2013; Monecke *et al.*, 2009; Dennis *et al*., 1999). Pneumonic plague occurs after the inhalation of bacteria (primary pneumonic plague) or after blood–borne dissemination to the lungs (secondary pneumonic plague) and it is the most virulent and highly infectious type of all (Pechous *et al.*, 2016; Spickler and Steneroden., 2013; Dennis *et al*., 1999). The incubation period is typically 1 to 3 days (Spickler and Steneroden., 2013). It clinically presents with severe pneumonia, dyspnea, and often hemoptysis in addition to similar symptoms seen in bubonic plague (Spickler and Steneroden., 2013; Kool., 2005; Dennis *et al*., 1999; McClean., 1995). Septicemic plague may occur by direct introduction of *Y. pestis* into the blood stream without involvement of lymph nodes (primary septicemic plague) or as the result of dissemination of the other two forms (Spickler and Steneroden., 2013; Dennis *et al*., 1999). Case fatality rates range from 40% to 66% for bubonic plague but septicemic and pneumonic plague cases are almost always fatal if left untreated (Dean *et al.*, 2017; Spickler and Steneroden., 2013; Dennis *et al*., 1999). Depending on the clinical type, Plague can be diagnosed mainly from bubo aspirates, cerebral spinal fluid, sputum or blood samples through culture or standard

diagnostic staining techniques (WHO, 2010; Cheesbrough., 2006; Dennis *et al*., 1999). Diagnosis can also be done by polymerase chain reaction techniques (PCR) or by detection of antibodies to the capsule-like *Y. pestis* F1 antigen from serum (Sinyange *et al*., 2016; Butler., 2014; WHO, 2010).

2.4 Plague Epidemiology and Distribution; A Global Overview

Plague is an important infectious disease and the world has succumbed to three plague pandemics in recorded human history. The first two pandemics, the 6th century AD Justinian plague and 14th century Black Death plague together caused over 150 million deaths (Spickler and Steneroden., 2013; Dennis *et al*., 1999). The third pandemic, which began in China in the late 1800s and is still ongoing today, has spread the farthest globally forming endemic foci in almost all continents due to increased global movements, transportation and trade. By 1930, this pandemic had caused an estimated 12 million deaths (Spickler and Steneroden., 2013; Dennis *et al*., 1999). However, compared to the first two pandemics, the current third pandemic has been associated with a decline in the total number of deaths caused by the disease especially throughout the second half of the 20th century where only slightly above 6,500 plague deaths were recorded from 38 countries worldwide. This decline in plague fatalities for the third pandemic has been attributed mostly to improvements in standards of living and health services in many parts of the world (WHO., 2000). However, plague still remains a great threat in many countries and since 1980, there has been a steep upward increase in the number of plague cases especially in Africa (Nyirenda *et al*., 2016; Neerinckx *et al*., 2010, 2008; Stenseth *et al*., 2008). For example, between 1980 and 2000, around 80% of plague cases that were reported to the World Health Organization came from Africa (Figure 1) with an average case fatality rate of 9.2% (Neerinckx *et al*., 2010; Stenseth *et al*., 2008; WHO., 2000).

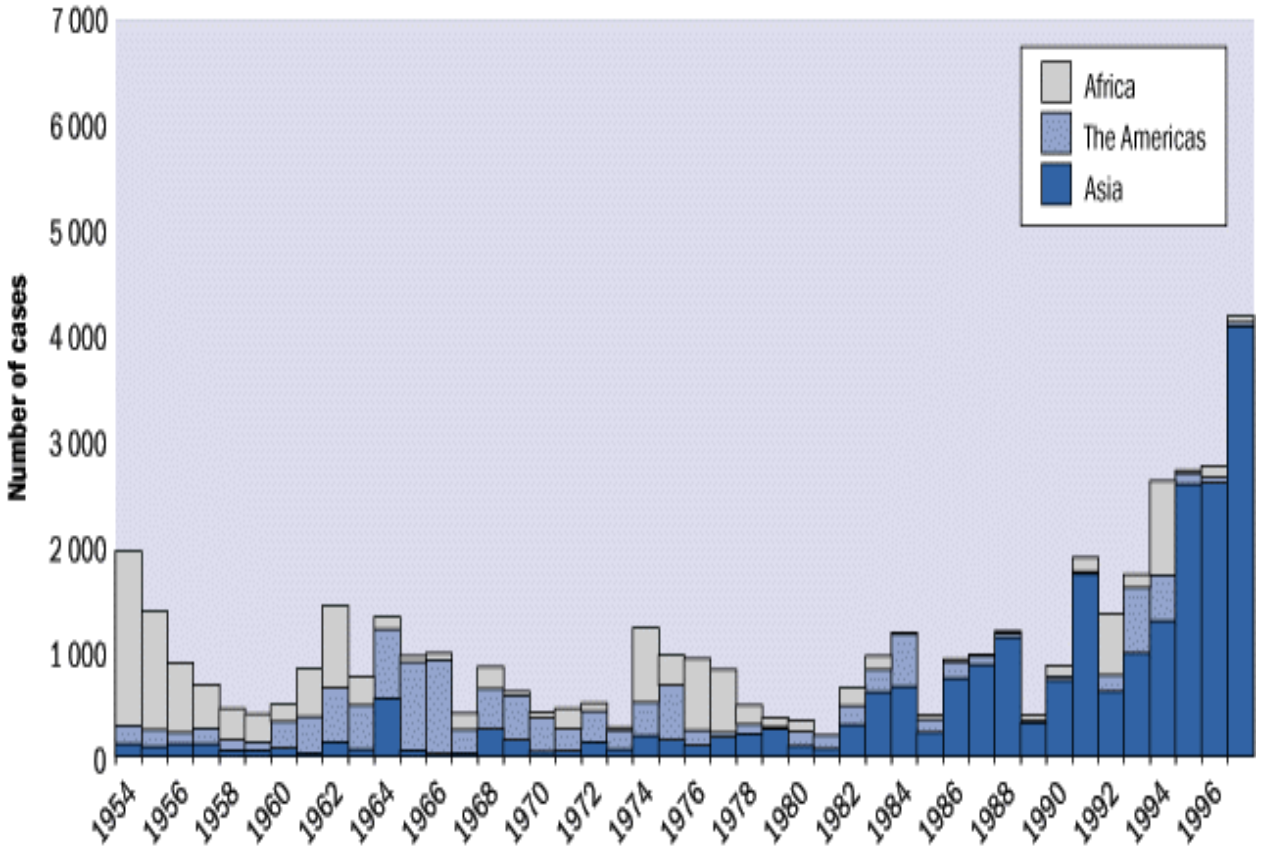

Figure 1. Number of cases of plague reported to WHO 1954-1997-Viet Nam excluded. The steep upward rise in cases can be seen beginning from about 1980 going up especially for Africa and Asia. (WHO 2000).

In fact, it has been suggested that these global statistics on plague incidence may even be lower than what is actually prevailing due to under-reporting and poor surveillance systems in some affected regions (Neerinckx *et al*., 2010; WHO., 2000). Nonetheless, this observed increase in cases of plague in Africa may be seen to be caused by poor living conditions, especially in rural Africa (Nyirenda *et al.,* 2016; Banda *et al.,* 2014; Neerinckx *et al*., 2010). Another factor attributed to this rise in plague incidence in Africa could be that plague is associated with long periods of quiescence of up to 30 or 50 years (Nyirenda *et al.*, 2017; Spickler and Steneroden., 2013; McClean., 1995). This causes some resource strained African nations to refocus surveillance health services towards other more eminent diseases such as Tuberculosis and Malaria leaving them vulnerable to plague outbreaks

when they re-emerge (Kango., 2013; Neerinckx *et al*., 2010). In addition, climate changes has been associated with increased re-emergence of plague due to heavy rainfalls, which is one of the risk factors for initiation of many plague epidemics in Africa (Nyirenda *et al.,* 2016; Kango., 2013; Neerinckx *et al.*, 2010; Stenseth *et al.,* 2006). More plague cases are expected in Africa as ecological modeling has also predicted that the geographical distribution and ecological niche for plague in Africa may be wider than previously thought (Neerinckx *et al*., 2008).

2.5 Plague Prevention and Control

In endemic areas, rodent and flea control around human homes, workplaces and recreational areas form an important component of plague control and prevention (Spickler and Steneroden., 2013; Dennis *et al*., 1999). Examples of measures employed are the elimination of sources of food and shelter for rodents near homes, installing physical blockades against rodent access, and regular insecticide treatment for the surroundings and even household pets (Spickler and Steneroden., 2013). Prophylactic treatment with appropriate antibiotics is also available and recommended for exposed people and travelers to high-risk areas (Dennis *et al*., 1999; CDC., 1996). Additionally, maintenance of good self-hygiene practices and use of personal protective equipment when handling patients is recommended. Plague is usually successfully treatable with antibiotic therapy as long as it is commenced early enough especially for the pneumonic form (Dennis *et al*., 1999). Human vaccines may be used in some high-risk areas but they are in limited supply and there are concerns about their safety and efficacy (Pechous *et al.,* 2016; Spickler and Steneroden., 2013; CDC., 1996).

2.6 Plague Occurrence in Zambia

In Zambia, the earliest record of human plague was in 1917 after which over 19 separate outbreaks have been recorded to date (see appendix I for all this data except for the latest outbreak from Nyimba district in 2015). These outbreaks have all occurred in three major plague endemic regions in Zambia: The Southern region, Eastern region, and Northwestern

region (Nyirenda *et al.*, 2016). Bubonic plague has been the most common form seen in these outbreaks but other forms have also been observed including cases with respiratory involvement (McClean., 1995). Case fatalities have varied among these outbreaks with some of the earlier outbreaks having the highest fatality rates of between 97% and 100%. By 1956, a total of about 247 plague cases and 205 deaths across 13 separate outbreaks had been recorded (Nyirenda *et al.*, 2016). This was followed by a general period of quiescence. By the turn of the century however, plague incidence began to sharply rise again in the country than previously seen (see Figure 2). For example, between 1990 and 2007 alone, about 1,452 cases and 43 deaths of plague were recorded from four major outbreaks in the country (Nyirenda *et al.*, 2016).

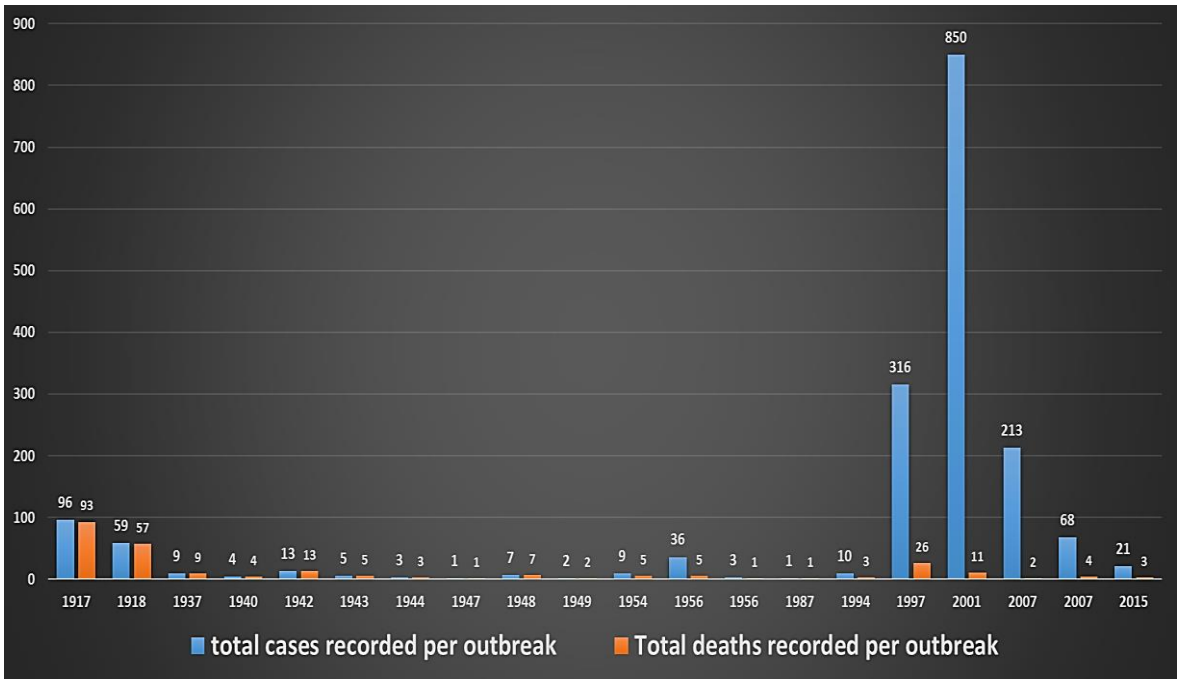

Figure 2. Total recorded cases and deaths per outbreak of plague since 1917 in Zambia. Figure adapted from data in Nyirenda *et al.*, (2016) and Sinyange *et al.*, (2016).

Poor living conditions especially in remote rural areas, poor rodent and flea control, and climate change in the form of heavy rainfalls have been among the major factors associated with increased plague incidence in the country (Banda *et al.*, 2014; Nyirenda *et al.*, 2016). For example, most outbreaks occurred following invasion of human habitats by large

populations of rodents after heavy rainfalls flooded their burrows (Nyirenda *et al.,* 2016; Neerinckx, *et al.,* 2010). Some recent genetic and seroprevalence studies also showed that *Yersinia* still remains in circulation between epidemics in various reservoir hosts in plague endemic regions in the country; maintaining the risk for plague outbreaks whenever conditions become favorable (Nyirenda *et al*., 2017; Hang'ombe, *et al*., 2012). Indeed, the most recent outbreak of bubonic plague in the country occurred in 2015 in Nyimba District of Eastern province which is one of the plague endemic regions in Zambia. 21 cases and three deaths were recorded from the outbreak (Sinyange *et al*., 2016). Another important aspect about the plague outbreaks seen in the country is the significant role various human activities play in the transmission dynamics of the disease during an outbreak. A comprehensive review of Zambian plague data from 1914 to 2014 by Nyirenda *et al.,* (2016) showed that certain socio-cultural human behaviors and life-style practices appeared to have contributed to the occurrence and rapid spread of plague outbreaks in the country. Practices such as wild rodent bush hunting and bush cattle rearing, movements of people from infected to uninfected areas, polygamy with husbands spreading infection between villages, beliefs in witchcraft delaying medical attention, overcrowding and sleeping on floors in poorly maintained households were all among the chief factors identified in this study. Independent reviews of more recent plague outbreaks in the country came to similar conclusions (Sinyange *et al.,* 2016; Kango *et al.,* 2014; Ngulube *et al.,* 2006). Such lessons learned from previous plague outbreaks data provide important insight into the transmission dynamics of the disease in human populations. Therefore, there is a call for further work on plague outbreaks to be done especially including analytical studies to complement or add to such findings in order to help understand and control these outbreaks in future (Nyirenda *et al.,* 2016; Kango *et al.,* 2014; Samia *et al.,* 2011; Neerinckx, *et al*., 2008; Stenseth *et al*., 2008).

2.7 The Basic Reproduction Number (R_0).

The basic reproduction number (R_0) is an important epidemiological parameter that provides important insight into the transmission dynamics of infectious diseases such as plague. R_0 is defined as the average number of secondary infections arising from a single

infectious individual during their infectious period in an entirely susceptible population (Barongo *et al.,* 2015; Heffernan *et al.,* 2005). Practically, R_0 is initially an important threshold parameter indicating if a disease will spread in a population. When R_0 for an infectious disease is greater than one then the disease will spread in the population. On the other hand, if R_0 is below one then the disease will not spread in the population and the infection will eventually die out (Mukandavire *et al.,* 2013, 2011; Heffernan *et al.,* 2005; Driessche and Watmough, 2002). As a corollary, it also follows therefore that the higher above unity the value of R_0 is the more explosive the outbreak will be (Mukandavire *et al.,* 2013, 2011). The second part is that R_0 gives a quantitative measure of the transmissibility of the infectious disease in a defined population. It is therefore used to estimate the magnitude and expected extent of spread for the infection in the population through infectious disease modeling techniques. Most importantly, R_0 is therefore used to assess the efficacy of various control measures on the disease through various disease modeling techniques. The value of R_0 is assessed both before and after a given control measure, or combination of control measures, is applied during the disease modeling process (Mukandavire *et al.,* 2013, 2011; Heffernan *et al.,* 2005; Dietz., 1993). The aim is to determine which control measures and at what magnitudes are able to reduce R_0 to a value less than one (Heffernan *et al.,* 2005; Dietz., 1993). This is important in informing public health action and planning measurable and cost-effective control measures (Mukandavire *et al.,* 2013, 2011; Massin *et al.,* 2007; Heffernan *et al.,* 2005; Lipsitch *et al.,* 2003; Ferguson *et al.,* 2001).

Various factors influence the value of R_0 for a given infectious disease (Driessche., 2017; Heffernan *et al.,* 2005; Dietz., 1993). One such important factor is that the value of R_0 for the infection will depend on the intrinsic biological properties of the pathogen involved in terms of the ease with which that pathogen is transmitted between individuals through its transmission route and its ability to establish an infection (Mukandavire *et al.,* 2013, 2011; Heffernan *et al.,* 2005; Dietz., 1993). Basically, more secondary infections are expected if a highly infectious pathogen is easily transmissible e.g through airborne transmission such as in the case of severe acute respiratory syndrome (SARS) with R_0 ranging from 2.2 to 3.6

(Lipsitch *et al*., 2003), or by "single touch" such as in the case of ebola with R_0 reaching up to 2.2 (Hunt., 2014). Another important factor that influences the value of R_0 is the duration of infectiousness for that disease. For example, the rare occurring airborne transmitted pneumonic plague is documented to be the most infectious, severe, and rapidly fatal form of plague. However, since the cases die rapidly in less than three days (Pechous *et al.*, 2016; Kool., 2005; Dennis *et al*., 1999; McClean., 1995), the infectious period is reduced and therefore it tends to have a lower value of R_0 as compared to the more common bubonic plague (Nishiura *et al.*, 2012; Hinckley *et al*., 2012; Gani and Leach., 2004). Lastly, but not the least, various properties of the affected population itself also play an important role in influencing the value of R_0 for the infectious disease. Two key examples include the level of immunity to the disease in the population (natural or otherwise) and how densely populated that population is (Driessche., 2017; Mukandavire *et al.*, 2013, 2011). Such factors may influence the value of R_0 in that it may be lowered in populations that are more resistant to the infection but it can be higher in densely populated and homogenously mixing populations of susceptible individuals (Mukandavire *et al.*, 2013, 2011; Keeling and Gilligan, 2000). Nevertheless, a typical range of the value of R_0 for a given infectious disease will normally be maintained basically because of the influence of the intrinsic properties of the pathogen involved itself and also because most endemic areas for that given disease tend to have similar population dynamics (Mukandavire *et al.*, 2013, 2011; Heffernan *et al.*, 2005).

On the estimation of the basic reproduction number, there are various methods used for estimating R_0 for an infectious disease. These methods can be grouped into two main categories of approaches. The first approach generally uses simplified mathematical data modeling techniques using simple mathematical formulae to estimate R_0 from various population and epidemiological data, or even epidemic incidence data. This method basically only requires the use of some crude simplified assumptions about the disease process and the underlying population and thus provides for quick and practical ways to estimate R_0 without the use of many parameters (Heffernan *et al.*, 2005; Dietz., 1993). In brief, examples of some methods from this approach include (1) estimating R_0 from the

final fraction of susceptible individuals in the population after an outbreak has run its course. This is estimated using a specified formula called the final size equation (Driessche., 2017; Heffernan *et al*., 2005). (2) Estimating R_0 using the average age at infection. This technique simply uses specified formula L/A where L is the mean lifetime and A is the mean age of acquiring the disease for the affected population (Heffernan *et al*., 2005; Laurenson *et al*. 1998; Mollison., 1995). (3) estimating R_0 from the initial exponential growth rate of the outbreak (Driessche., 2017; Heffernan *et al*., 2005), and (4) estimating R_0 using the survival function which also takes into account the average rate of infection per unit time and the probability of the infectious individual lasting throughout their infectious period (Driessche., 2017; Heffernan *et al*., 2005). One main challenge associated with estimating R_0 using the above mentioned approach is that most of the assumptions made in the methods used are too simplified and may not actually be realized in the practical setting. Another challenge with this approach is that the reliability of the estimate may also depend on the quality of the data used. The second general approach involves estimating R_0 in terms of the parameters of some complete working deterministic mathematical model for the disease. This method is the most widely used for most estimates of the basic reproduction number following the recent advent of the use and application of mathematical modeling as an important tool in the study and management of infectious diseases (Fung., 2014; Heffernan *et al.,* 2005). This means that the basic reproduction number is a key functional component of these deterministic mathematical models and it is collectively represented by various parameters within the model (Fung., 2014; Heffernan *et al.,* 2005). Both these approaches mentioned above have their own strengths and weakness in estimating R_0. The choice of method may depend on availability of data and other objectives of the investigators (Heffernan *et al.,* 2005). However, looking at the relatively increased use of the model method, a brief introduction on mathematical modeling of infectious diseases is given in the following subheading.

2.8 A Brief Introduction on Mathematical Modeling of Infectious Diseases.

The main concerns of public health experts include being able to predict the cause, potential severity and extent of spread of an infectious disease, and the effective measures

required to contain, control, or prevent the infection (Gordis, 2014; Fung., 2014). The relatively "emerging science" of mathematical modeling of infectious diseases ushers in a unique opportunity to provide this information, or most of this information, to experts in a timely, ethical, and efficient manner for public health action (Narjes., 2017; Fung., 2014; Heffernan *et al.,* 2005; Kermack and McKendrick, 1927). Mathematical modeling of infectious diseases is simply the process of describing and representing the real life transmission processes of an infectious disease in form of a conceptual and schematic system. This system is then operationalized using various parameters, mathematical theories and formulae to produce various model outputs that replicate the real life disease process as much as possible so that it can be studied. A key component in developing the model is to come up with assumptions about the disease transmission process in the population using the best available biological information on the disease as well as assumed properties of the population itself. In practice, simplifying such assumptions in a model does produce equally informative and useful models provided the model is properly optimized. More complex models however can still be developed to provide more information about the infection. However, caution should be taken as the construction of more complex models may incorporate the addition of more uncertain parameters and such complex models may also be limited by mathematical theory (Li, 2018. Narjes, 2017; Fung., 2014; Kermack and McKendrick, 1927).

Different types of mathematical models exist but an example of a model type in wide use is the compartmental determinist mathematical model. In this model type, a population is divided into various mutually exclusive compartments of individuals or subjects at different states of the disease condition depending on the assumptions made about the disease process. For example, the simplest model of this type that can be made includes the compartment of individuals that are susceptible (S), another compartment for those individuals that are infectious (I), and another compartment for those individuals that have been removed either by death or recovery (R). This model is therefore denoted as an SIR compartmental mathematical model (Narjes., 2017). The assumption of deterministic models is that the sizes of these compartments of individuals is a continuous function of

time. Therefore, the rate of movement of individuals from one compartment to another during the progression of the epidemic is represented by a series of differential equations and transfer rate constants which operationalize the model (Li, 2018). An SEIR compartmental mathematical model is similar to the SIR model except that this time it also incorporates the compartment of individuals who are exposed to the disease but have not yet become infectious (E). Many more other modifications and compartments of individuals can be added to a model depending on the assumptions and hypotheses used about the disease transmission process (Fung., 2014). Many parameters that determine the rate of movement of individuals into or from a given compartment are estimated from literature. When these estimates are not available from literary sources, some of these parameters are then estimated by the researcher based on biological plausibility and this may add further uncertainty in the results of the model predictions. For example, in an SIR model, some of the parameters that collectively determine the rate at which susceptible individuals become infected includes parameters that describe the rate of contact between infectious individuals and susceptible individuals per unit time, the probability of passing the infection per contact, and the number of infectious individuals available (Fung., 2014; Mukandavire *et al.,* 2013, 2011; Heffernan *et al*., 2005; Dietz., 1993). Note that some of these parameters also determine the value of the basic reproduction number from the model (Driessche., 2017; Mukandavire *et al.,* 2013, 2011; Heffernan *et al*., 2005). In the absence of adequate information, such parameters are difficult to estimate directly and their estimation is based on biological data of the infectious disease and also assumed properties of the population (Narjes., 2017; Fung., 2014; Heffernan *et al.,* 2005; Kermack and McKendrick, 1927). The fact that some parameters are difficult to approximate presents a challenge in developing good and reliable mathematical models. Parameter uncertainties may lead to uncertainties in some model outputs. However, good and highly informative models can still be developed especially after the model has been optimized using epidemic data.

2.9 The Basic Reproduction Number for Human Plague.

Estimates of the basic reproduction number for plague have previously been made and these have mostly come from mathematical models developed for the disease (Dean *et al.,* 2017; Hinckley *et al.,* 2012; Nishiura *et al.,* 2012, 2006; Gani and Leach., 2004). However, in human populations, the transmission dynamics of plague are complex due to involvement of various transmission routes for the infection (Spickler and Steneroden., 2013). This makes mathematical modeling of plague and estimation of R_0 challenging. In spite of this, three main transmission routes are thought to be important depending on the type of plague epidemic. The first transmission route involve the wild rodent flea vector-to-human transmission in bubonic plague (Spickler and Steneroden., 2013), the second route include the possible direct human-to-human transmission in bubonic plague through human ectoparasites e.g. human fleas, *P. irritans,* or human body lice, *P.humanus humanus,* (Dean *et al*., 2017; Hufthammer and Walloe., 2013; Spickler and Steneroden., 2013; Drancourt *et al.,* 2006; Houhamdi *et al.,* 2006; Dennis *et al*., 1999), while the third route is the direct human-to-human transmission through aerosolized infectious droplets in pneumonic plague (Spickler and Steneroden., 2013; Kool., 2005). Despite bubonic plague being the most common form of plague, there have been more studies that have estimated the basic reproduction number for known pneumonic plague outbreaks instead. For example, Gani and Leach (2004) modeled the transmission of primary pneumonic plague based on data from eight pneumonic plague outbreaks that occurred worldwide between 1907 and 1997. The basic reproduction number for primary pneumonic plague in this study was estimated to be about 1.3. Similar estimates of R_0 for pneumonic plague were obtained in studies by Nishiura *et al.,* (2012) (R_0 = 1.13 based on 19 outbreaks worldwide between 1906 and 2006) and Hinckley *et al*., (2012) (R_0 = 1.18 based on pneumonic plague data in the USA between 1900 and 2009). Nishiura *et al.,* (2006) obtained slightly higher estimates of R_0 for primary pneumonic plague ranging from 2.8 to 3.5. This study was based on primary pneumonic plague data from outbreaks in Mukden, China (1946 outbreak) and Madagascar (1950 outbreak). The reason for this slight difference is not clear but may be attributed to differences in location and modeling approaches used (Heffernan *et al*., 2005).

On the other hand, to the best of the researcher's knowledge only one study by Dean *et al.,* (2017) was found to have estimated the basic reproduction number for bubonic plague outbreaks. To explain the rapid spread nature of the mediaeval black death bubonic plague epidemics, Dean and colleagues hypothesized that direct human-to-human transmission of bubonic plague through human ectoparasites played a central role in describing the fast spread of infection in these epidemics. In their study, they developed a compartmental mathematical model for bubonic plague described by the direct human-to-human transmission route through human ectoparasites such as human fleas and body lice. Their model had better fit to mortality data from nine different plague epidemics that occurred across Europe during the second pandemic black death plague as compared to alternative models described by other modes of transmission. Through their model, they estimated the basic reproduction number for bubonic plague to range between 1.5 and 1.9. The success of this model in explaining historic second pandemic bubonic plague epidemics data gave support to other proponents of this direct human-to-human transmission route through human ectoparasites as being the important transmission route for some rapid spreading bubonic plague infections (Hufthammer and Walloe., 2013; Piarroux *et al*., 2013; Ayyadurai *et al*., 2010; Drancourt *et al.,* 2006; Houhamdi *et al.,* 2006;). Except for the study by Nishiura *et al.,* (2006), R_0 estimates for primary pneumonic plague outbreaks are slightly lower than the estimates obtained for bubonic plague in the model by Dean *et al.,* (2017) discussed above. This has been partly attributed to the fact that primary pneumonic plague outbreaks are usually fast limiting since cases die rapidly and hence tend to have a shorter infectious period in that manner (Pechous *et al.,* 2016; Kool 2005; Gani and Leach., 2004). It is worth noting that in their study, Dean *et al.,* (2017) showed that a bubonic plague model described by the wild rodent flea vector-to-human transmission route alone predicted much slower growth of the outbreak than was actually seen in the rapid spreading medieval bubonic plague epidemics. This result partly showed that rise of cases as a result of direct contact with infected rodents and their fleas alone is not sufficient to drive or explain rapidly spreading bubonic plague epidemics in human populations. This brings attention to the importance to carry out further assessments of the human to human transmission of bubonic plague infection during these outbreaks even for modern

epidemics especially since we are seeing a rise in plague incidence (Stenseth *et al*., 2008; WHO., 2000)

The estimates of the basic reproduction number in the reviewed studies above were valuable for understanding and explaining the transmission dynamics of plague. These R_0 estimates were also used to evaluate possible future plague outbreaks. For example, based on their estimated R_0 for pneumonic plague, Gani and Leach (2004) used separate model simulations to explore the potential extent of a pneumonic plague outbreak in case of delayed implementation of control interventions. The pneumonic plague R_0 estimate from this study was then later used in a similar approach by Massin *et al.,* (2007) to simulate the spread of an epidemic of pneumonic plague in case of a plague bioterrorism attack on modern day France and the impact of various control measures on such an epidemic. Zambia has seen an increased incidence of some rapidly spreading plague outbreaks in recent years (Nyirenda *et al*., 2016). Estimating the basic reproduction number for bubonic plague in the local Zambian setting would similarly help increase the epidemiologic understanding of these outbreaks and for planning appropriate control measures.

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Study Area

This study was based on the most recent outbreak of bubonic plague in Zambia which occurred in Nyimba district of Eastern Province between March 26th and May 5th, 2015 (Sinyange *et al*., 2016). This outbreak was selected as it had the most complete epidemic data available for reliable analysis at the time of the study. Nyimba district is located in the Eastern plague endemic region of Zambia and this was the first outbreak of bubonic plague experienced in the district (Nyirenda *et al*., 2016). The outbreak occurred in a small village but the village characteristics information was generally limited (Sinyange *et al*., 2016). However, Similar to other districts in the Eastern province; Agriculture, hunting, and forestry comprise some of the main economic activities practiced in the rural areas of Nyimba district (CSO., 2014). Such activities increase interactions between the humans and wildlife which can increase chances of spread of zoonotic infections to humans (Keeling and Gilligan, 2000). Additionally, by 2010 Nyimba reached a population size of slightly over 85, 000 people giving about a 1.9 percent annual population growth rate from its population of about 70,425 people in the year 2000 (CSO., 2014). The population density stood at about 8.1 persons per square kilometer with more than 80% of its population living in rural settings. The average household size in the rural areas was about 5.3 members making it the second highest for the province (CSO., 2014). This increase in the population size over the years and the consequent higher population densities in such plague endemic areas poses a threat for rapid spread of plague outbreaks due to overcrowding and increased human contact (Nyirenda *et al*., 2016; Kango *et al*., 2014; Ngulube *et al*, 2006). All these factors may have played a role in causing and propagating the bubonic plague outbreak in Nyimba analyzed in this study.

3.2 Study Design

Complete online secondary epidemic incidence data for the 2015 Nyimba district bubonic plague outbreak, made publicly available in 2016 (Sinyange *et al*., 2016), was electronically retrieved and analyzed.

3.3 Case Definition and Outbreak Data

As detailed in the data source in Sinyange *et al*., (2016), The Nyimba bubonic plague outbreak occurred between March 26–May 5, 2015. During the outbreak, the Nyimba District Medical Office urgently initiated active case finding in the affected health center catchment areas after the initial report of possible plague cases. A total of 111 patients with fever or recent history of fever, and swollen lymph nodes were therefore identified and evaluated for possible plague during the entire outbreak. 82 (75%) of these patients were admitted, treated with intravenous gentamycin and benzyl penicillin, and observed for at least one night (Sinyange *et al*., 2016). The remaining 29 patients received oral doxycycline and cotrimoxazole as outpatients (Sinyange *et al*., 2016). Out of this total 111 suspected patients, 21 actual cases of plague were identified using case definition based on evidence of clinical illness compatible with bubonic plague and these were used for the analysis in this study (Sinyange *et al*., 2016). Clinical illness compatible with bubonic plague for this outbreak was defined as temperature ≥38°C or history of recent fever, and at least one of the following signs or symptoms: 1) painful, visibly enlarged cervical, axillary, or inguinal lymph nodes; 2) evidence of sepsis (prostration, reduced responsiveness, or hypotension); or 3) severe pneumonia (cough with respiratory distress or hemoptysis). The median age for these identified cases was 8 years (range = 3–18 years) and all came from the same village. 95% were aged below 15 years old and Eleven (52%) were male (Sinyange *et al*., 2016). *Yersinia pestis* was detected in six (29%) of the cases through polymerase chain reaction (PCR). It was reported however that 12 of these cases actually tested positive for malaria during initial evaluation and this includes all six who tested PCR-positive for plague. In fact, all of the first four cases (based on date of symptom onset) tested positive for malaria and were hence initially only treated with anti-malarial drugs on their first visit to the health center (Sinyange *et al*., 2016). Three of these first four patients had antibiotics added to their treatment regimen only on their second visits to the clinic. Two of the three patients who experienced this delayed initiation of antibiotic therapy died (Sinyange *et al*., 2016). Apart from the antibiotic treatment of patients during the outbreak, indoor spraying of about 1,303 (96%) households in the affected catchment areas was conducted aimed at reducing the flea population, and recommendations were made to local leaders regarding risks for plague transmission

(Sinyange *et al*., 2016). Figure 3 below shows the epidemic curve for the cases as was officially published in the data source in Sinyange *et al.*, (2016) while Figure 4 shows this epidemic curve reproduced in this study for further analysis. Note that the epidemic curve is plotted based on date of onset of symptoms for all the 21 cases. As seen in these graphs, the earliest onset of symptoms among the cases was on the 26th of March 2015 and cases peaked by 6th - 7th April 2015. After this period, the incidence seemed to suddenly drop and generally leveled out and the outbreak finally died out with the last case being recorded on 1st May 2015.

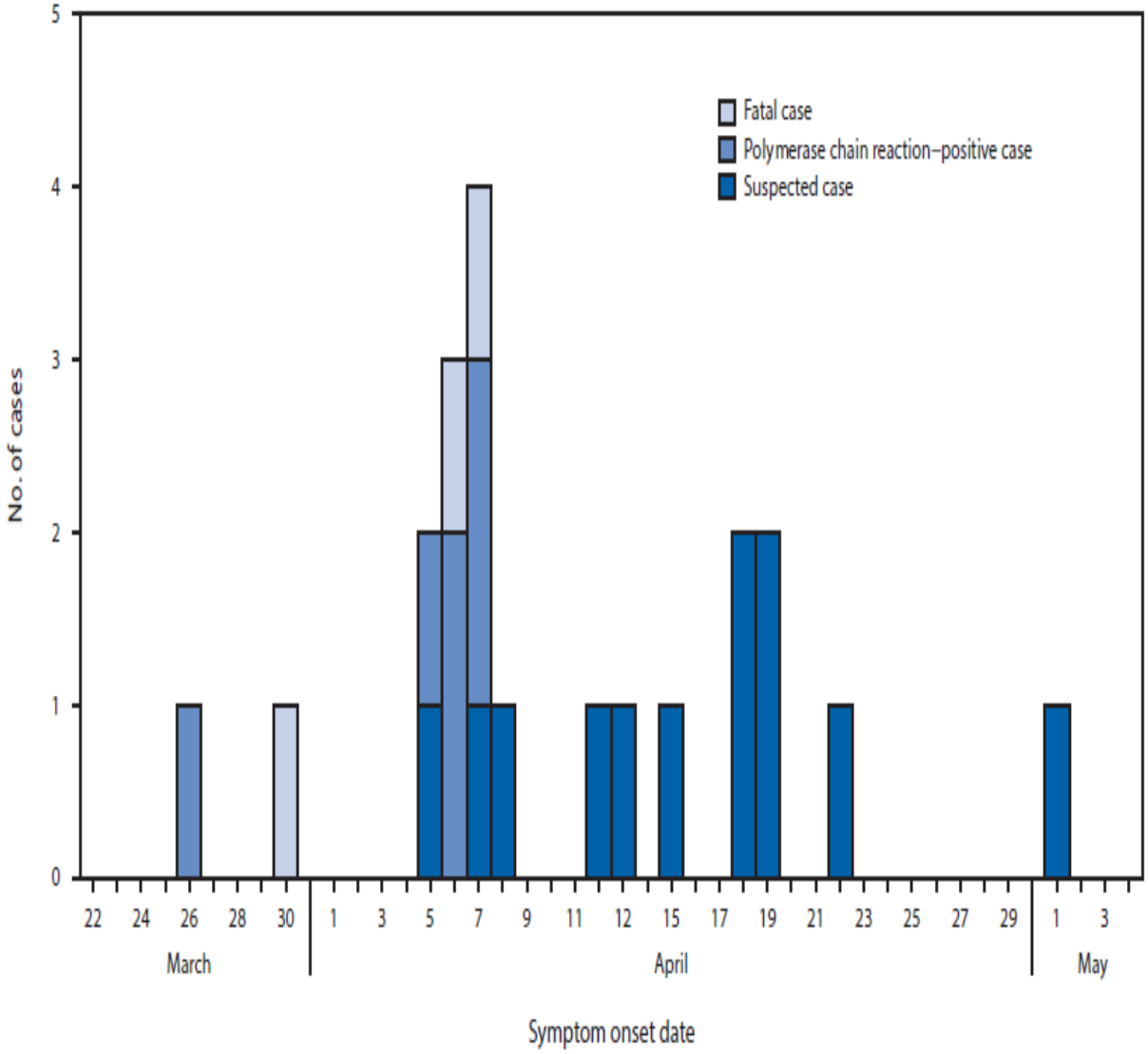

Figure 3. Epidemic curve for the bubonic plague outbreak in Nyimba district (26th March to 5th May 2015). Adapted as published by Sinyange *et al.*, (2016).

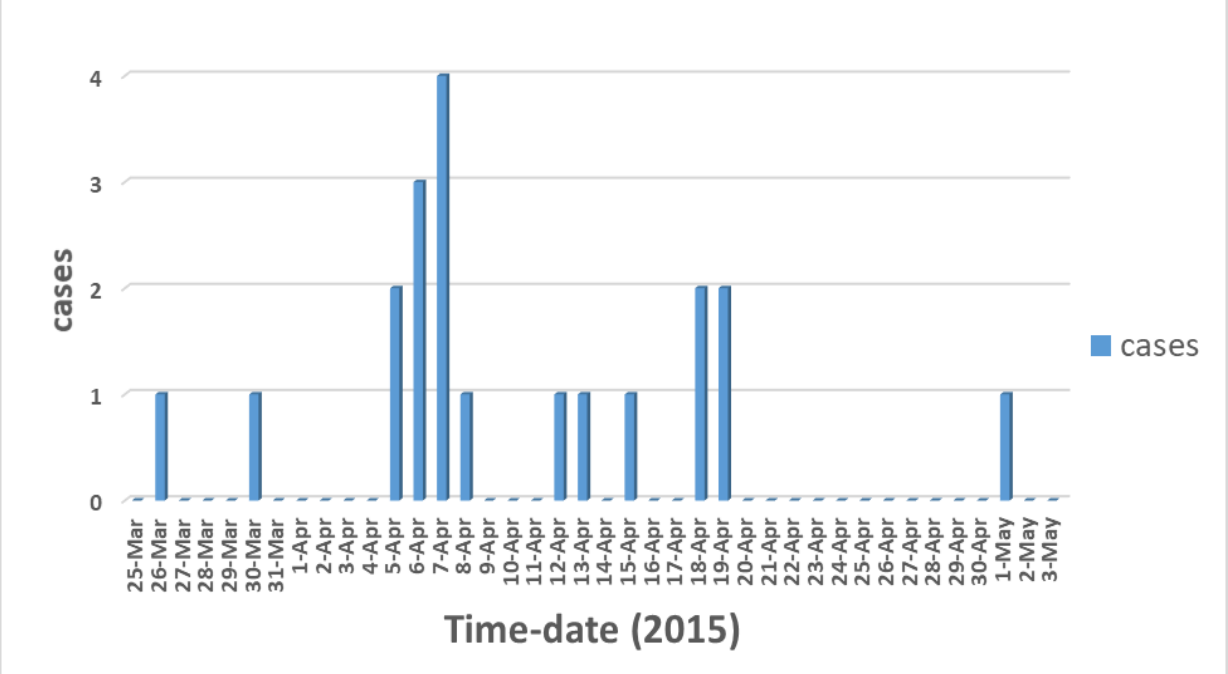

Figure 4. Epidemic curve for the bubonic plague outbreak in Nyimba district (26th March to 5th May 2015). Adapted and reproduced as published by Sinyange *et al.*, (2016).

3.4 Analytical Approach to the Estimation of the Basic Reproduction Number

Two general analytical techniques were used to estimate the basic reproduction number (R0) for bubonic plague and both methods relied on the following two underlying assumptions made about the Nyimba bubonic plague outbreak. For the first assumption, it was assumed that the disease interventions applied during the course of this outbreak (i.e antibiotic treatment of patients, indoor spraying, and sensitization) must have effectively influenced the outcome of the outbreak through curtailing further spread of the infection which saw the outbreak being brought under control just after its peak around the 7th of April 2015 (Figure 3) (Onyejekwe, *et al*., 2019; Gervas *et al*., 2018; Mojeeb and Yang., 2017; Zamir *et al*., 2016; Spickler and Steneroden., 2013; Neilan *et al*., 2010; Dennis *et al*., 1999). Therefore, it was assumed in this study that the disease transmission dynamics for plague infection must have occurred naturally in the community only during the early stages of the Nyimba outbreak which caused this initial peak in cases. This assumption can be further supported by the reported delay in diagnosis and appropriate treatment of the infection in the first few cases during the outbreak as earlier mentioned (Sinyange *et al.*,

2016). As these cases were sent back home, their plague infection must have continued to develop and spread naturally in the community due to the delayed diagnosis. In fact, all of the three cases who died during the entire outbreak were among the cases captured in this period of initial growth of the outbreak which suggests that the infection was allowed to develop fully in this period. For this reason, both methods of R_0 estimation used in this study relied only on analysis of the data from the initial growth phase of the Nyimba bubonic plague outbreak leading up to its peak; i.e before the provided interventions took full effect (Massad *et al*., 2010). For the second assumption, it was further assumed in this study that during the outbreak, bubonic plague infection was transmitted from human to human through various human ectoparasites vectors (such as body lice and human fleas) which are capable of transmitting plague (Dean *et al*., 2017; Zhao *et al*., 2016; Hufthammer and Walloe., 2013; Piarroux *et al*., 2013: Spickler and Steneroden., 2013; Ayyadurai *et al*., 2010; Drancourt *et al.,* 2006; Houhamdi *et al.,* 2006). As described in section 2.9, this mode of transmission of the infection has been recognised to be prominent especially for rapid spreading bubonic plague outbreaks and this could be the case for the recent bubonic plague outbreaks seen in Zambia with higher case incidence (Dean *et al*., 2017; Nyirenda *et al*., 2016; Keeling and Gilligan, 2000). Note that current epidemiological knowledge indicates that modern bubonic plague outbreaks generally follow epizootics of rats and only later include ectoparasites [Dean *et al*., 2017]. However, as report of an overt rat epizootic was generally not available for the study outbreak in Nyimba [Sinyange *et al.,* 2016], it was assumed in this study that the outbreak data used therefore was based on propagated human to human transmission of the infection through human ectoparasites after the infection had already spilled over into the human population.

3.4.1 Method 1 (Primary Method): Estimation of the Basic Reproduction Number for Bubonic Plague using the Epidemic Doubling Time.

The first method used to estimate the basic reproduction number (R_0) for bubonic plague was chosen as the main or primary method of estimation for the study because it is quick, robust, and suited for estimating R_0 when there is limited epidemiological data; as was the case for the study outbreak in Nyimba. For this method, a simplified mathematical

modeling technique of epidemic incidence data as described in detail elsewhere was applied (Korennoy *et al.*, 2016; Barongo *et al.*, 2015; Iglesias *et al.*, 2014, 2011). In brief, this method assumes that in a homogeneously mixing population of susceptible subjects, the number of new cases increases exponentially during the initial stages of the epidemic. The basic reproduction number is then estimated from the initial exponential growth rate of the epidemic based on the analysis of the initial segment of the epidemic curve. According to Iglesias *et al.*, (2011), R_0 in this natural system can be estimated using Equation 1 below: which was therefore used to estimate R_0 in this current study.

Equation. 1. $$Ro = 1 + \left(\frac{D}{Td}\right) ln2$$

Where Td is the epidemic doubling-time (the time it takes for the number of cases to double), D is the average infectious period for bubonic plague, and $ln2$ is simply the natural log of 2. The epidemic doubling time (Td) was estimated using the exponential epidemic growth rate of the initial growth segment of the epidemic curve as summarized in the following steps.

(a) Estimating the epidemic doubling time (Td) using initial exponential epidemic growth rate.

Step 1.

Firstly, a plot of the cumulative number of cases plotted against time for the period of initial rise of cases (initial growth segment) for the Nyimba bubonic plague outbreak up to its peak was generated. An initial 17-day time period from the 23rd of March, 2015 to the 8th of April, 2015 was taken to approximately represent this period.

Step 2:

To assess the assumption of initial exponential growth of the outbreak, an exponential curve was fitted to the plot generated in step one. The R-squared (coefficient of determination) value was used to assess how well the exponential model fit this observed

data (Korennoy *et al.*, 2016). The fitted exponential model described the initial exponential growth rate of the epidemic through the following general expression for the exponential function:

$$C(t) \approx C(0)e^{\alpha(t)}$$

Where $C(t)$ is the total number of cases at a given time (t), $C(0)$ is the initial number of cases at the start time, e is the mathematical constant and α is the epidemic growth rate (Hunt., 2014). To obtain the 95% confidence interval for this estimated epidemic growth rate (α), a log transformation of the plotted epidemic curve in step one was made by simply plotting the natural log of the cumulative number of cases against time. This produced a linear relation between the log cumulative number of cases and time. This linear relation was arithmetically derived by simply taking the natural log of both sides of the general expression for the exponential function given above to produce the following linear expression:

$$ln\big(C(t)\big) = ln\big(C(0)\big) + \alpha(t)$$

Therefore, a linear regression was run for this plot and the 95% confidence interval for the already estimated epidemic growth rate α (gradient) was obtained from the linear regression output. Here the R-squared value was equally used to assess how well the linear regression model fit the observed data (Korennoy *et al.*, 2016).

Step 3:

Using the epidemic growth rate and its 95% confidence interval estimated in step two above, the average epidemic doubling time was estimated using the relation between the epidemic doubling time and the epidemic growth rate given by the expression below:

$$Td = \frac{ln2}{\alpha}$$

where Td is the epidemic doubling time and α is the epidemic growth rate obtained in the preceding steps (Wallinga and Lipsitch., 2007). The 95% confidence interval lower and

upper limits for the epidemic doubling time (Td) were therefore determined by the interval for the estimated epidemic growth rate (α).

(b) Estimating the average duration of infectiousness (*D*) for bubonic plague in human populations.

In the primary method, the duration of infectiousness for bubonic plague infection was the only parameter that was estimated from literature. Despite estimations greatly varying in literature, this parameter was simply estimated to range from three to five days. This simply represents the most central estimate of the average period that the infectious individual may pass the infection to susceptible human ectoparasites vectors which transmit the infection to other susceptible individuals before these vectors die from the infection themselves; assuming an early phase transmission cycle in the vectors (Dean *et al*., 2017; Gonzalez and Miller., 2016; Zhao *et al*., 2016; Spickler and Steneroden, 2013; Ayyadurai *et al*., 2010; Houhamdi *et al*., 2006; Eisen *et al*., 2006; Dennis *et al*., 1999).

The estimated value of the epidemic doubling time and the approximate duration of infectiousness for bubonic plague given above were then used in Equation 1 to estimate R_0 for bubonic plague. The 95% confidence interval lower and upper limits for R_0 were therefore equally delimitated by the interval for the epidemic doubling time. All calculations were done in Microsoft Excel Software.

3.4.2 Method 2 (Secondary Method): Estimation of the Basic Reproduction Number for Bubonic Plague using the derived SIR Deterministic Compartmental Mathematical Model for Bubonic Plague.

For the second method, a deterministic compartmental mathematical model was created for the Nyimba bubonic plague outbreak and this model was used to estimate the basic reproduction number for bubonic plague. This approach was used as an alternative method of estimating R_0 for the same bubonic plague outbreak in Nyimba in order to provide credence to the results of the method explained earlier. Since bubonic plague is a vector borne infection, the Ross Macdonald type of model was initially created as a first step in the modelling process (Macdonald., 1957). This model type, originally developed for

malaria, is a standard mathematical model for vector-borne pathogens that tracks the infections in both the human and the vector populations (Pandey *et al*., 2013; Macdonald., 1957). The model is generally denoted as SIR-SI model and it has been used extensively in various forms in the modeling of vector-borne infectious diseases (Gervas *et al*., 2018; Koutou *et al*.,2018; Mubayi *et al*., 2018; Boret *et al*., 2017; Dean *et al*., 2017; Mojeeb and Yang., 2017; Brauer *et al*., 2016; Driessche., 2017; Zamir *et al*., 2016; Pandey *et al*., 2013). The parameter values used for creating the model in this study were obtained using various information on bubonic plague transmission from literature and where such information could not be readily found the parameter values were estimated based on reasonable assumption and biological plausibility. Furthermore, for accurate estimation of R_0 from the model, the model in this study was developed without the inclusion of disease interventions. This means that this model was designed to simulate the transmission dynamics of bubonic plague infection as it occurred naturally in the community assuming no interventions such as treatment of the infected individuals or flea control were initiated. As this was assumed to be the case for the period of initial growth of the Nyimba bubonic plague outbreak up to its peak, data from this period of the outbreak was therefore used to calibrate and validate the model. For the purpose of this model, the following main assumptions were made about the disease transmission dynamics for bubonic plague for the study outbreak:

1) The human population was initially completely susceptible to the infection.
2) Individuals in the population were considered to be homogenously mixing.
3) It was assumed that during the outbreak the infection was transmitted from human to human through various human ectoparasites as previously described (Hufthammer and Walloe., 2013; Piarroux *et al*., 2013; Ayyadurai *et al*., 2010; Drancourt *et al.*, 2006; Houhamdi *et al*., 2006). A similar assumption was used in a recent study that created a similar model for bubonic plague infection. (Dean *et al*., 2017).
4) The human population was constant. The effects of natural birth and natural death rates or immigration and emigration of people in the population were considered to be negligible owing to the short duration of the Nyimba bubonic plague outbreak.
5) The infection is immunizing (Dean *et al*., 2017; Keeling and Gilligan, 2000).

6) The human flea vectors (human ectoparasites) do not recover from the infection.

Table 1 shows the parameters and variables used for the SIR-SI model and a schematic representation of this disease model system is shown in Figure 5.

Table 1: Parameters and variables used for the SIR-SI deterministic compartmental mathematical model system for bubonic plague disease outbreak.

Parameters and variables	**Description**	**Value**
β_f	Transmission rate of bubonic plague from infectious human ectoparasites to humans per unit time. (Dean *et al.*, 2017)	Range (0.05 – 0.123) was considered
β_h	Transmission rate of bubonic plague from infectious humans to human ectoparasites per unit time. (Dean *et al*., 2017)	0.5
α^{-1}	Duration for which infectious humans transmit the infection to susceptible human ectoparasites (days). (Dean *et al*., 2017; Gonzalez and Miller., 2016; Spickler and Steneroden, 2013; Dennis *et al*., 1999)	4.5
μ^{-1}	Duration for which infectious human ectoparasites transmit the infection to susceptible humans (days). (Dean *et al*., 2017; Zhao *et al*., 2016; Ayyadurai *et al*., 2010; Houhamdi *et al*., 2006)	5.5
$S_h(t)$	Total susceptible humans at a given time (t)	Is a function of time
$I_h(t)$	Total infectious humans at a given time (t).	Is a function of time
R_h	Total number of removed humans at a given time (t) (this includes both those that die from the infection as well as those that recover)	Is a function of time
N_h	The total human population (approximated for the village of the outbreak by local health experts in Nyimba District)	350
$S_f(t)$	Total number of susceptible human ectoparasites at a given time (t)	Is a function of time
$I_f(t)$	Total number of infectious human ectoparasites at a given time (t)	Is a function of time
N_f	The total human ectoparasites population (dean *et al*., 2017)	Range ($10.5 * N_h$) to ($67.7 * N_h$)

Note: * means multiplication.

All single values given as approximate point estimates for the deterministic model.

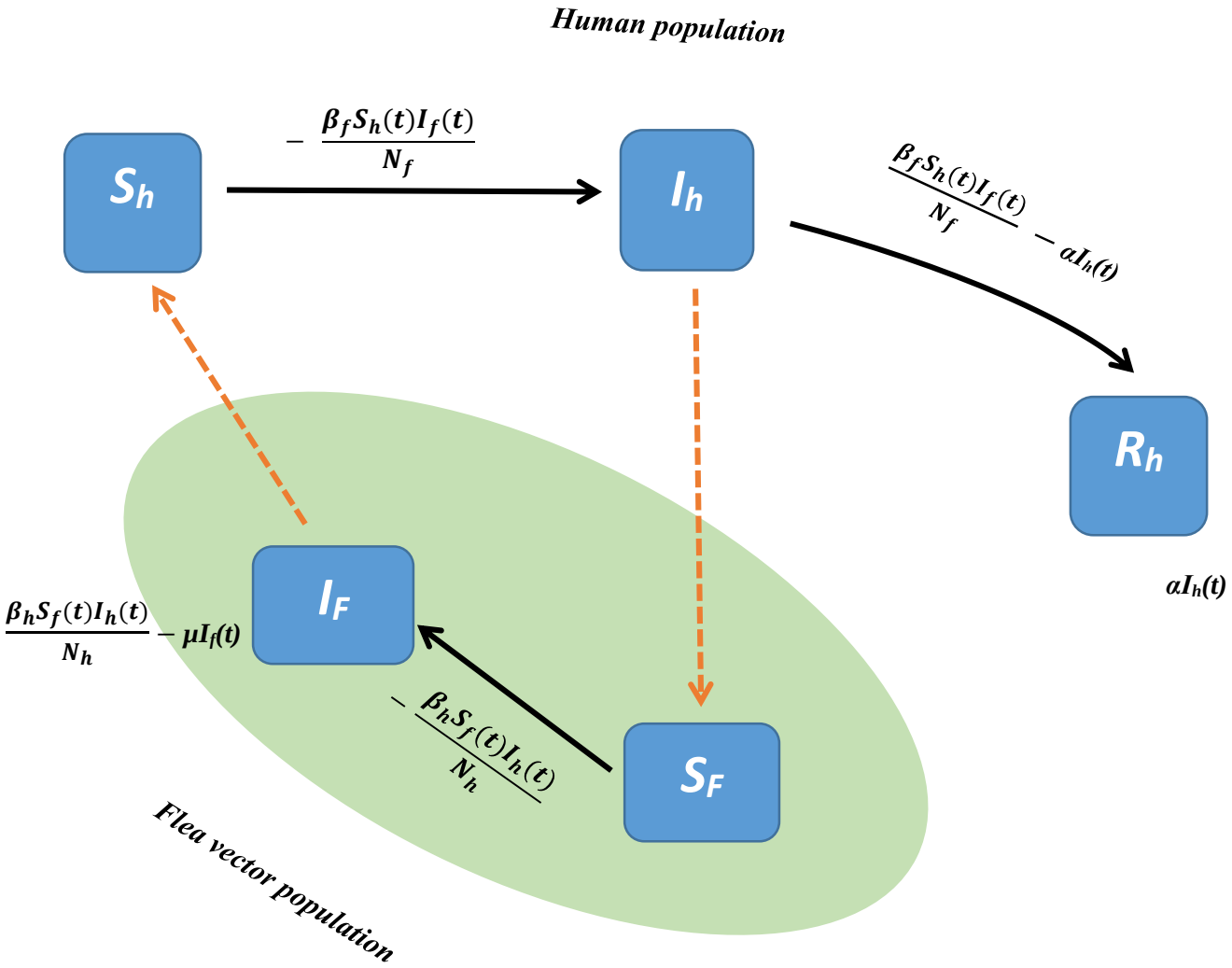

Figure 5. Schematic diagram for the SIR-SI deterministic compartmental mathematical model system for bubonic plague disease. The dotted arrows indicate the direction of the infection and the solid arrows represent the transition from one compartment to another.

The series of deferential equations developed for the SIR-SI model system were therefore described as follows:

Equation 2 (for the SIR-SI model for bubonic plague infection)

(a) $\frac{dS_h(t)}{dt} = -\frac{\beta_f S_h(t) I_f(t)}{N_f}$

(b) $\frac{dI_h(t)}{dt} = \frac{\beta_f S_h(t) I_f(t)}{N_f} - \alpha I_h(t)$

(c) $\frac{dR_h(t)}{dt} = \alpha I_h(t)$

(d) $\frac{dS_f(t)}{dt} = -\frac{\beta_h S_f(t) I_h(t)}{N_h}$

(e) $\frac{dI_f(t)}{dt} = \frac{\beta_h S_f(t) I_h(t)}{N_h} - \mu I_f(t)$

A similar model system to equation 2 was developed in other studies to model outbreaks of dengue hemorrhagic fever (Pandey *et al*., 2013), chikungunya fever (Brauer *et al*., 2016), Zika virus infections (Brauer *et al*., 2016; Driessche., 2017), and Human African Trypanosomiasis infections (Gervas *et al*., 2018).

SIR-SI model explained.

In this model, the transmission of bubonic plague by the infectious humans through various human ectoparasites is modeled by five equations as given in equation 2. The model tracks the infection in the human population through three compartments that are a function of time: susceptible (S_h), infectious (I_h), and removed (R_h) humans. The total human population N_h is given as $N_h = (S_h) + (I_h) + (R_h)$ and it is assumed to be constant. For the model, N_h represented the total population size for the village of the outbreak in Nyimba and this was estimated to be about 350 people based on estimates by local health experts in Nyimba District. The human ectoparasites vector population is modeled in two compartments: susceptible ectoparasites (S_f) and infectious ectoparasites (I_f) with the total ectoparasites population given as N_f. The total value of N_f in the population was assumed to

depend on the total human population size N_h. This is because some recent studies estimated the amount of human ectoparasites infestation and abundance (such as the body louse) in affected human populations ranges from 10.5 to 67.7 lice on average per person (Piarroux *et al*., 2013; Foucault *et al*., 2006). Therefore, the total value of N_f in the entire population in the affected village was assumed to range from 10.5 multiplied by N_h to about 67.7 multiplied by N_h. Picking it up from the human ectoparasites vector population, susceptible human ectoparasites acquire bubonic plague infection from infectious humans at the rate β_h for a period α^{-1}. This period α^{-1} is considered to be the duration of time for which the infectious humans are infectious to the susceptible ectoparasites (assuming no treatment or other intervention is given to the infectious humans) and it comprises of both the pre-clinical stage and a symptomatic clinical stage of the infectious individual. In this model, this period all together is considered to last about 4.5 days on average taking from the wide and varied ranges estimated for this parameter in literature (Dean *et al*., 2017; Gonzalez and Miller., 2016; Spickler and Steneroden, 2013; Dennis *et al*., 1999). In the entire infectious period α^{-1}, the susceptible ectoparasites vectors expectedly acquire the infection from the infectious human firstly at a slightly lower rate during the preclinical stage and at a much higher rate during the symptomatic clinical stage of the infectious individual (Dean *et al*., 2017). However, for simplification of the model a constant transmission rate of 0.5 was used for this transmission rate, β_h, for the entire period α^{-1} as this is approximately a midway average estimate of the transmission rate for both the pre-clinical and the clinical stages combined as estimated in literature (Dean *et al*., 2017). After acquiring the infection, the infected human ectoparasites are considered to be infectious in that they are able to transmit the infection to susceptible humans by way of an early phase transmission that does not require a long extrinsic incubation period; an alternative to blocked transmission observed in rat fleas such as *Xenopsylla species* (Dean *et al*., 2017; Eisen *et al*., 2006). It was assumed in the model that the infectious human ectoparasites do not recover from the infection (Dean *et al*., 2017). These infectious human ectoparasites transmit the infection to susceptible humans at a rate β_f for a period μ^{-1} where μ is the rate at which the infectious fleas are dying. The period μ^{-1} was approximated to be about 5.5 days based on similar values estimated in literature (Dean *et al*., 2017; Zhao *et al*., 2016; Houhamdi *et al*., 2006) while for β_f a narrow range of about

0.05 – 0.123 was considered as compared to the fixed estimate of 0.05 used for this parameter in a similar model created for bubonic plague infection by Dean *et al*., (2017). The reason for accommodating this short range for the value of β_f is because currently there are limited studies that have investigated the potency of these human ectoparasites (such as the human fleas and body lice) as vectors for bubonic plague infection (Dean *et al*., 2017; Piarroux *et al*., 2013; Spickler and Steneroden, 2013). In fact, as was clarified in their work, the value of 0.05 used for this transmission rate in the model by Dean *et al*., (2017) was specific for body lice only but it was taken to represent on average the rate at which all the human ectoparasites (both human fleas and body lice) transmit the infection to susceptible humans. Therefore, since this combined average transmission rate of infection from the infectious human fleas and body lice to susceptible humans may not be precisely known, the range given above was used for β_f in this study. Once the susceptible individual gets successfully infected by the infectious human ectoparasites vectors, they move to the infectious compartment where they transmit the infection to the susceptible fleas for the period α^{-1} as given earlier. It is assumed that all infectious individuals eventually either die from the infection at the end of this period α^{-1} and become removed from the infectious compartment or they may naturally recover from the infection (Dean *et al*.,2017; Gonzalez and Miller., 2016). Here it is assumed that recovering from the infection at the end of the period α^{-1} means that the infectious individual's natural body defense systems eventually overcome the infection such that they are no longer able to transmit it to the susceptible ectoparasites. At this point therefore, both the dead people and those that recover from the infection exit the infectious compartment and enter the removed compartment. The exact proportions of those that die from the infection and those that survive it in the removed compartment therefore is not described in the model but may depend on the typical case fatality rates for bubonic plague infection (Spickler and Steneroden., 2013; Dennis *et al*., 1999).

Estimating the basic reproduction number for the SIR-SI model.

The following notation was used for the initial conditions for the SIR-SI model:

Initial number of Susceptible humans $S_h(t) = S_h(0)$,

Initial number of infectious people $I_h(t) = I_h(0)$,

Initial number of Removed people $R_h(t) = R_h(0)$

Initial number of Susceptible human ectoparasites vectors $S_f(t) = S_f(0)$

Initial number of infectious human ectoparasites vectors $I_f(t) = I_f(0)$,

Where $S_h(0)$, $I_h(0)$, $S_f(0)$, $I_f(0) > 0$ are initial number of Susceptible people, Infectious people, susceptible human ectoparasites vectors and infectious human ectoparasites vectors respectively and $R_h(0) = 0$ are initial number of removed people. In each of the parts of equations 2 above the term on the left denotes the rate of change of the respective variables (compartments) at any given time *(t).* The term on the right hand side gives this rate of change. The basic reproduction number (R_0) can be estimated directly from the SIR-SI model system in equation 2 above as $R_0 = \frac{\beta_f \beta_h}{\alpha \mu}$ (Boret *et al*., 2017; Brauer *et al*., 2016; Driessche., 2017; Pandey *et al*., 2013). This solution for R_0 from the model system was derived as follows:

If the infection is spreading in the population such as during an outbreak, then we expect the number of new human infections to be increasing in the population. This means that:

$$\frac{dI_h(t)}{dt} > 0$$

If we remove the *(t)* notation for convenience, this statement means that from equation 2 (b) above we have:

$\frac{\beta_f S_h I_f}{N_f} - \alpha I_h > 0$ which can be re-written as

$\frac{\beta_f S_h I_f}{N_f} > \alpha I_h$ which yields

Inequality 1 $\dfrac{\frac{1}{N_f}\beta_f S_h I_f}{\alpha} > I_h$

Similarly, if the number of new infections is increasing in the human population such as during an outbreak then we expect the number of infections in the human ectoparasites vector population to be equally increasing along. This means that:

$\dfrac{dI_f(t)}{dt} > 0$

Equally removing the *(t)* notation for convenience, this statement means that from equation 2 (e) above we have:

$\frac{\beta_h S_f I_h}{N_h} - \mu I_f > 0$ which can be re-written as

$\frac{1}{N_h}\beta_h S_f I_h > \mu I_f$ which yields

Inequality 2 $I_h > \dfrac{\mu I_f}{\frac{1}{N_h}\beta_h S_f}$

Considering inequality 1 and 2, we have:

$\dfrac{\frac{1}{N_f}\beta_f S_h I_f}{\alpha} > I_h$ and $I_h > \dfrac{\mu I_f}{\frac{1}{N_h}\beta_h S_f}$

Which means that:

$\dfrac{\frac{1}{N_f}\beta_f S_h I_f}{\alpha} > \dfrac{\mu I_f}{\frac{1}{N_h}\beta_h S_f}$ which can be simplified as

$\frac{1}{N_f}\beta_f S_h \frac{1}{N_h}\beta_h S_f > \alpha\mu$ which yields

Inequality 3 $\dfrac{\frac{1}{N_f}\beta_f S_h \frac{1}{N_h}\beta_h S_f}{\alpha\mu} > 1$

Now based on the definition of R_0, inequality 3 will be analyzed at the starting point of the outbreak where the entire population can still be considered to be completely susceptible

except for the one infectious individual at $I_h(0)$ introduced in the population which is the index case. This means that at this point $N_h \approx S_h(0)$. The same applies to the human ectoparasites vector population in that at the starting point of the outbreak almost all the ectoparasites vectors in the population are considered to be susceptible and free of the infection except for the first few ectoparasites that acquire the infection from the index case (i.e which are on the body of the index case). This means that at this point $N_f \approx S_f(0)$. The appropriate notation for inequality 3 at this point can therefore be given as:

Inequality 3 $$\frac{\frac{1}{N_f}\beta_f S_h(0)\frac{1}{N_h}\beta_h S_f(0)}{\alpha\mu} > 1$$

Now with the conditions given at this point that $N_h \approx S_h(0)$ and $N_f \approx S_f(0)$ when the index case is introduced in the population, it means that the entire inequality 3 simplifies as:

$$\frac{\frac{1}{N_f}\beta_f S_h(0)\frac{1}{N_h}\beta_h S_f(0)}{\alpha\mu} > 1 \Rightarrow \frac{\beta_f\beta_h}{\alpha\mu} > 1$$

From this we have that $R_0 = \frac{\beta_f\beta_h}{\alpha\mu}$ and it is expected to be greater than one for the infection to spread in the population – at the disease endemic equilibrium point, EEP, (Heffernan *et al*., 2005).

This solution for R_0 can also be obtained using the next generation method as follows:

From the right-sides of the equations for the infected states (I_h and I_f) of equation 2, we decide which terms represent new infections, $\boldsymbol{f}$. The remainder is $-\boldsymbol{v}$ as shown below:

$$\boldsymbol{f} = \begin{pmatrix} \frac{\beta_f S_h I_f}{N_f} \\ 0 \end{pmatrix}, \quad \boldsymbol{v} = \begin{pmatrix} \alpha I_h \\ \frac{-\beta_h S_f}{N_h} I_h + \mu I_f \end{pmatrix}$$

let $f_1 = \beta_f S_h I_f$, $f_2 = 0$, $v_1 = \alpha I_h$, and $v_2 = \frac{-\beta_h S_f I_h}{N_h} + \mu I_f$

The respective Jacobian matrices are given below:

$$\mathbf{F} = \begin{pmatrix} \frac{\partial f_1}{\partial I_h} & \frac{\partial f_1}{\partial I_f} \\ \frac{\partial f_2}{\partial I_h} & \frac{\partial f_2}{\partial I_f} \end{pmatrix} = \begin{pmatrix} 0 & \frac{\beta_f S_h}{N_f} \\ 0 & 0 \end{pmatrix} \qquad \mathbf{V} = \begin{pmatrix} \frac{\partial v_1}{\partial I_h} & \frac{\partial v_1}{\partial I_f} \\ \frac{\partial v_2}{\partial I_h} & \frac{\partial v_2}{\partial I_f} \end{pmatrix} = \begin{pmatrix} \alpha & 0 \\ \frac{-\beta_h S_f}{N_h} & \mu \end{pmatrix}$$

$$\mathbf{V^{-1}} = \frac{1}{\alpha\mu} \begin{pmatrix} \mu & 0 \\ \frac{\beta_h S_f}{N_h} & \alpha \end{pmatrix} = \begin{pmatrix} \frac{1}{\alpha} & 0 \\ \frac{\beta_h S_f}{\alpha\mu N_h} & \frac{1}{\mu} \end{pmatrix}$$

$$\mathbf{FV^{-1}} = \begin{pmatrix} 0 & \frac{\beta_f S_h}{N_f} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{\alpha} & 0 \\ \frac{\beta_h S_f}{\alpha\mu N_h} & \frac{1}{\mu} \end{pmatrix} = \begin{pmatrix} \frac{\beta_f S_h \beta_h S_f}{\alpha\mu N_f N_h} & \frac{\beta_f S_h}{\mu N_f} \\ 0 & 0 \end{pmatrix}$$

Eigenvalues of $\mathbf{F\,V^{-1}}$ satisfy

$\det [\, \lambda I - FV^{-1}] = 0$ where $\lambda I = \begin{pmatrix} \lambda & 0 \\ 0 & \lambda \end{pmatrix}$

$$\lambda I - FV^{-1} = \begin{pmatrix} \lambda - \frac{\beta_f S_h \beta_h S_f}{\alpha\mu N_f N_h} & \frac{-\beta_f S_h}{\mu N_f} \\ 0 & \lambda \end{pmatrix}$$

$$\det [\, \lambda I - FV^{-1}] = \lambda \left(\lambda - \frac{\beta_f S_h \beta_h S_f}{\alpha\mu N_f N_h}\right) = 0$$

which means

$$\lambda = 0, \text{ or } \lambda - \frac{\beta_f S_h \beta_h S_f}{\alpha\mu N_f N_h} = 0$$

which is the same as,

$$\lambda = 0, \text{ or } \lambda = \frac{\beta_f S_h \beta_h S_f}{\alpha\mu N_f N_h}$$

and $\rho(\mathbf{FV^{-1}}) = \frac{\beta_f S_h \beta_h S_f}{\alpha\mu N_f N_h}$ is the largest eigenvalue of $\mathbf{FV^{-1}}$.

Evaluating at the disease free equilibrium point, DFE point P (S_h=N_h, S_f=N_f, I_h=0, I_f=0, R_h=0), we have:

$$\rho(\mathbf{FV^{-1}}) = \frac{\beta_f \beta_h}{\alpha\mu}.$$

By the next generation method

$R_0 = \rho(\mathbf{FV^{-1}}) = \frac{\beta_f \beta_h}{\alpha \mu}$.

Deriving the SIR model from the SIR-SI model system for bubonic plague infection.

An amalgamated SIR model can be derived directly from an SIR-SI model such as the one created for bubonic plague infection in this study (Pandey *et al*., 2013). The derived SIR model can be used to track the growth of the infection in the human population alone with the concomitant spread of the infection in the human ectoparasites vector population already accounted for in the model; assuming that infection dynamics in the vector population are fast compared to those of the human population (Pandey *et al*., 2013). This derived SIR model is preferred when the main population of interest is the human population (as was the case for this study) and also because SIR models are simpler than SIR-SI models which makes analysis and parameter estimation easier (Pandey *et al*., 2013). Additionally, it may not always be necessary to explicitly incorporate the vector population when modeling the transmission of some vector borne diseases in some populations (Pandey *et al*., 2013). For example, in the study done by Pandey *et al*., (2013), a derived SIR model was substantially better than the SIR-SI version of the model in explaining dengue Hemorrhagic fever data from Thailand between January 1984 to March 1985. In this study therefore, an SIR deterministic compartmental mathematical model was similarly derived from the inceptive SIR-SI model created for bubonic plague infection for the study and this derived SIR model was used for the actual model simulation, data analysis, and estimation of the basic reproduction number for bubonic plague. Figure 6 below therefore shows a schematic representation of the derived SIR model system for the bubonic plague infection (based on the foundation of the initial SIR-SI version of the model) while equation 3 shows the series of deferential equations developed for this derived SIR model.

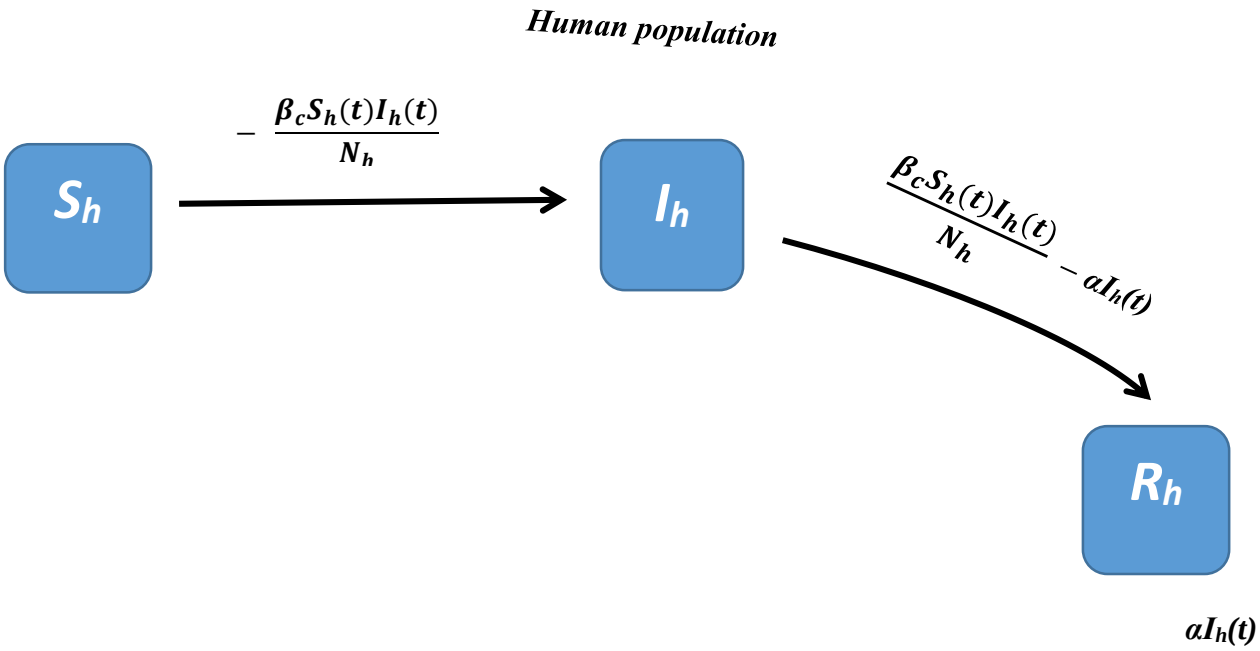

Figure 6. Schematic diagram for the derived SIR deterministic compartmental mathematical model system for bubonic plague disease.

Equation 3 (for the derived SIR model for bubonic plague infection tracking the infection in the human population)

(a) $\frac{dS_h(t)}{dt} = -\frac{\beta_c S_h(t) I_h(t)}{N_h}$

(b) $\frac{dI_h(t)}{dt} = \frac{\beta_c S_h(t) I_h(t)}{N_h} - \alpha I_h(t)$

(c) $\frac{dR_h(t)}{dt} = \alpha I_h(t)$

Derived SIR model explained.

In the derived SIR model, the transmission of bubonic plague by the infectious humans through various human ectoparasites is modeled by three equations as given in equation 3.

This model tracks the infection in the human population through the three compartments that are a function of time: susceptible (S_h), infectious (I_h), and removed (R_h) humans. The constant total human population N_h is given as N_h = (S_h) + (I_h) + (R_h) and this was estimated to be about 350 people in this study as initially given. For this model, susceptible people in the population (S_h) acquire the infection from the infectious people in the population (I_h) at the rate β_c for a period α^{-1}. This transmission rate β_c is called the composite human to human transmission rate of the infection and from the foundation of the initial SIR-SI version of the model it is given as $\beta_c = \frac{\beta_f \beta_h}{\mu}$ (Pandey *et al*., 2013). This composite transmission rate is therefore the rate at which infectious humans transmit the infection to susceptible humans through the intermediate human ectoparasites vectors and it already accounts for the dynamics of the transmission of the infection from these infected human ectoparasites vectors to susceptible humans. The infectious humans leave the infectious compartment at the rate α as initially given to enter the removed compartment. Similarly, the removed compartment is therefore comprised of both the recovered individuals and those that die from the infection.

SIR model simulation.

The ability of the derived SIR model to reproduce the general disease incidence pattern of the Nyimba bubonic plague outbreak for the period of initial growth of the outbreak up to its peak was assessed. This was done to optimize and validate the model through model simulation against the actual outbreak data. The model simulation was done using the systems dynamics modeling software Vensim - personal learning edition (https://vensim.com/vensim-personal-learning-edition/; Hosseinabad and Moraga., 2017; Vafa-Arani *et al*., 2014; Shahgholian and Hajihosseini., 2010). Figure 7 below shows the flow diagram of the human population system for the derived SIR model for bubonic plague infection as was generated in Vensim software for the model simulation.

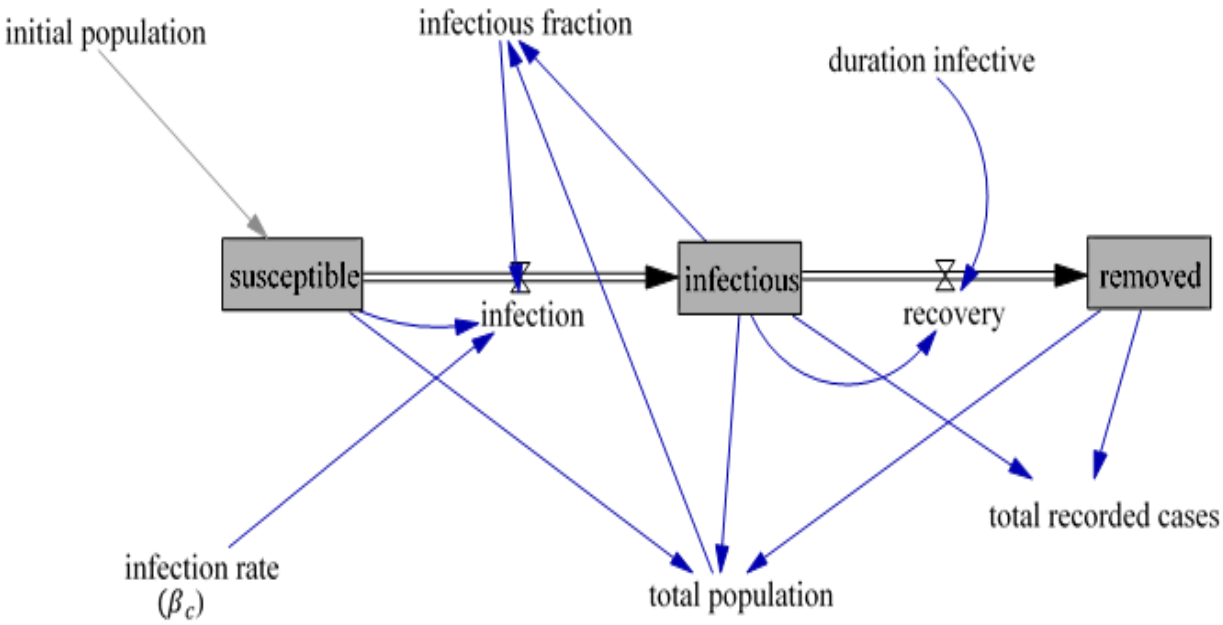

Figure 7. Flow diagram of the human population system for the derived SIR deterministic compartmental mathematical model for bubonic plague infection in Vensim systems dynamics modeling software.

In the diagram (Figure 7), the initial population is the total initial number of the humans in the population (N_h) and at the start the number of susceptible people in the population is given as initial population minus one. This is based on the assumption that at the beginning of the outbreak the entire population was susceptible to the infection except for the one infectious individual which is the index case. This initial population is equal to the total population for the model system (total number of individuals in the compartments) at any given time (t) during the outbreak: Initial population = total population = susceptible + infectious + removed. The infection term in the diagram describes the flow of individuals from the susceptible compartment to the infectious compartment. It is the product of the number of susceptible individuals, the infectious fraction (infectious/total population), and the infection rate (composite human to human transmission rate) and it is given as the quantity $\frac{\beta_c S_h(t) I_h(t)}{N_h}$ in equation 3. On the other hand, the recovery term in the diagram

describes the flow of individuals from the infectious compartment to the removed compartment. It is given by the total infectious individuals/infectious period (α^{-1}). This is therefore given as $\alpha I_h(t)$ in equation 3. For the model simulation, the general initial conditions $N_h = 350$, $S_h(0) = N_h - 1$, $I_h(0) = 1$, $R_h(0) = 0$ were used. Fixed parameter values used for the model were as given in Table 1. However, initial random parameter sensitivity analysis for the model showed that the model output was more sensitive to changes in the value of the composite human to human transmission rate β_c (infection rate in Figure 7). Note that this composite parameter β_c is comprised of the parameters β_f, β_h and μ of which β_f was the more uncertain parameter value. Therefore, for the model simulation the fixed values for the other parameters β_h and μ were maintained as given in Table 1 while different values for β_f were used from the possible range of values given for this parameter. 16 model simulations were consequently run by appropriately altering the value of β_f which gave different values of β_c per run until a value of β_c that produced the best model fit to the targeted Nyimba bubonic plague epidemic data was found. This was statistically confirmed using the chi-square goodness of fit test at a significance level of 0.05. The value of β_c which produced better model fit to the outbreak data was therefore used in the estimation of the basic reproduction number (R_0) for bubonic plague

The model was simulated over a 45-day time period which was approximately the duration of the Nyimba bubonic plague outbreak (Sinyange *et al.*, 2016). In the model, the first day for the simulation was set as the 23rd of March 2015 even though the date of onset of symptoms for the first recorded case during the actual outbreak was the 26th of March 2015. This was done so as to accommodate the brief preclinical stage of the infection which is considered in the model for the first case before this patient became symptomatic and recorded on the 26th of March 2016. The model validation was done based on data from the first 17-days' time period of the outbreak which approximately corresponds to the period of initial growth of the outbreak up to its peak as seen in Figure 3 and Figure 4.

Estimating the basic reproduction number for bubonic plague for the derived SIR model.

Similar to the initial SIR-SI version of the model, the basic reproduction number for bubonic plague can be estimated directly from the derived SIR model. The following notation were used for the initial conditions for the SIR model:

Initial number of Susceptible people $S_h(t) = S_h(0)$,

Initial number of infectious people $I_h(t) = I_h(0)$,

Initial number of Removed people $R_h(t) = R_h(0)$

Where $S_h(0)$, $I_h(0)$, > 0 are initial number of Susceptible people and Infectious people respectively, and $R_h(0) = 0$, are initial number of removed people. The basic reproduction number (R_0) for bubonic plague was estimated directly from the derived SIR model system of Equation 3 as $R_0 = \frac{\beta_c}{\alpha}$ (Narjes., 2017; Boret *et al*., 2017; Driessche., 2017; Pandey *et al*., 2013). This solution for R_0 was derived as follows:

If the infection is spreading in the population such as during an outbreak, then we expect the number of new human infections to be increasing in the population. This means that:

$$\frac{dI_h(t)}{dt} > 0$$

Removing the *(t)* notation for convenience, this statement means that from equation 3 (b) above we have:

$\frac{\beta_c S_h I_h}{N_h} - \alpha I_h > 0$ which can be re-written as

$\frac{\beta_c S_h I_h}{N_h} > \alpha I_h$ which yields

Inequality 4 $\qquad \frac{\frac{1}{N_h}\beta_c S_h}{\alpha} > 1$

As per definition of R_0, inequality 4 is equally analyzed at the starting point of the outbreak where the entire population can still be considered to be completely susceptible except for

the one infectious individual at $I_h(0)$ introduced in the population which is the index case. At this point, $N_h \approx S_h(0)$. The appropriate notation for inequality 4 at this point can therefore be given as:

Inequality 4 $\frac{\frac{1}{N_h}\beta_c S_h(0)}{\alpha} > 1$

With the conditions given at this point as $N_h \approx S_h(0)$ when the index case is introduced in the population, it means that the entire inequality 4 simplifies as:

$$\frac{\frac{1}{N_h}\beta_c S_h(0)}{\alpha} > 1 \Rightarrow \frac{\beta_c}{\alpha} > 1$$

From this we have that $R_0 = \frac{\beta_c}{\alpha}$ and it is expected to be greater than one for the infection to spread in the population – at the disease endemic equilibrium point, EEP, (Heffernan *et al*., 2005). This was used to estimate R_0 for bubonic plague in this study. Note that this solution for R_0 for the SIR model ($\frac{\beta_c}{\alpha}$) is equally just a direct simplification of the solution for R_0 given for the SIR-SI version of the model ($\frac{\beta_f \beta_h}{\alpha\mu}$) since $\beta_c = \frac{\beta_f \beta_h}{\mu}$.

3.5 Ethical Consideration

No ethical issues were encountered as no human or animal subjects were used in this study and cases were anonymous.

CHAPTER FOUR

4.0 RESULTS

4.1 The Estimated Value of the Basic Reproduction Number (R_0) for Bubonic Plague using the Epidemic Doubling Time (Primary method results).

In the first method, R_0 for bubonic plague was estimated using the epidemic doubling time for the Nyimba bubonic plague outbreak determined by the epidemic growth rate assuming an initial exponential growth of the outbreak. Figure 8 shows the plot of the cumulative number of cases plotted against time for the period of initial rise of cases for the Nyimba bubonic outbreak up to its peak. During the outbreak, the first case was recorded on the 26th of March, 2015 which corresponds to day four in the graph in Figure 8 while the 8th of April, when the outbreak was at its peak, corresponds to day 17.

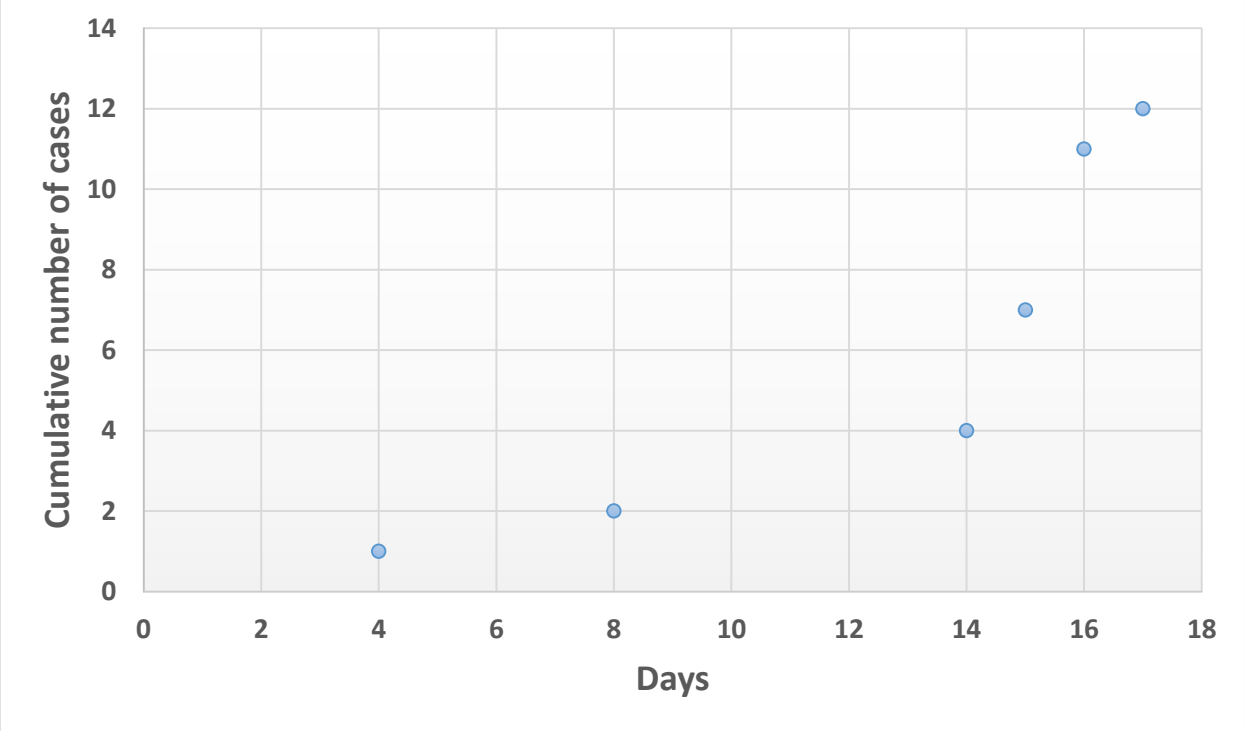

Figure 8. Cumulative number of cases plotted against time for segment of initial rise of cases during the 2015 Nyimba district bubonic plague outbreak.

Figure 9 shows the results for the fitted exponential curve to the plot in Figure 8. An R^2 (coefficient of determination) value of 0.9502 was accepted as significant for the fitted exponential curve to this observed data set (Korennoy *et al.*, 2016).

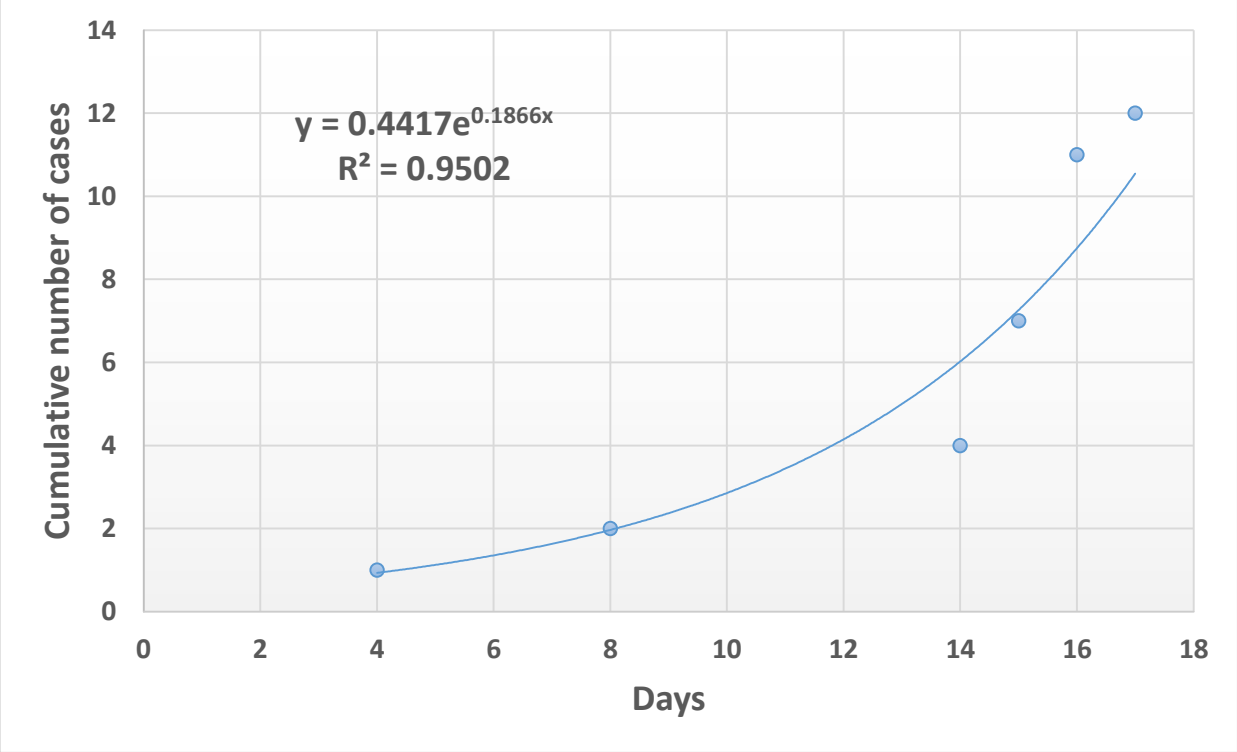

Figure 9. Cumulative number of cases plotted against time with fitted exponential curve for segment of initial rise of cases during the 2015 Nyimba district bubonic plague outbreak.

The equation for the fitted exponential curve was given as $Y = 0.4417e^{0.1866x}$ as seen in Figure 9. Therefore, the fitted exponential model predicted an average initial epidemic growth rate of about 0.1866 cases/day (Hunt., 2014). Figure 10 shows the plot of the log cumulative number of cases plotted against time for the same period and the fitted linear regression model to the data set. The R^2 value of 0.9502 for the fitted linear model was equally accepted as significant for this data set as shown in the figure (Korennoy *et al.*, 2016).

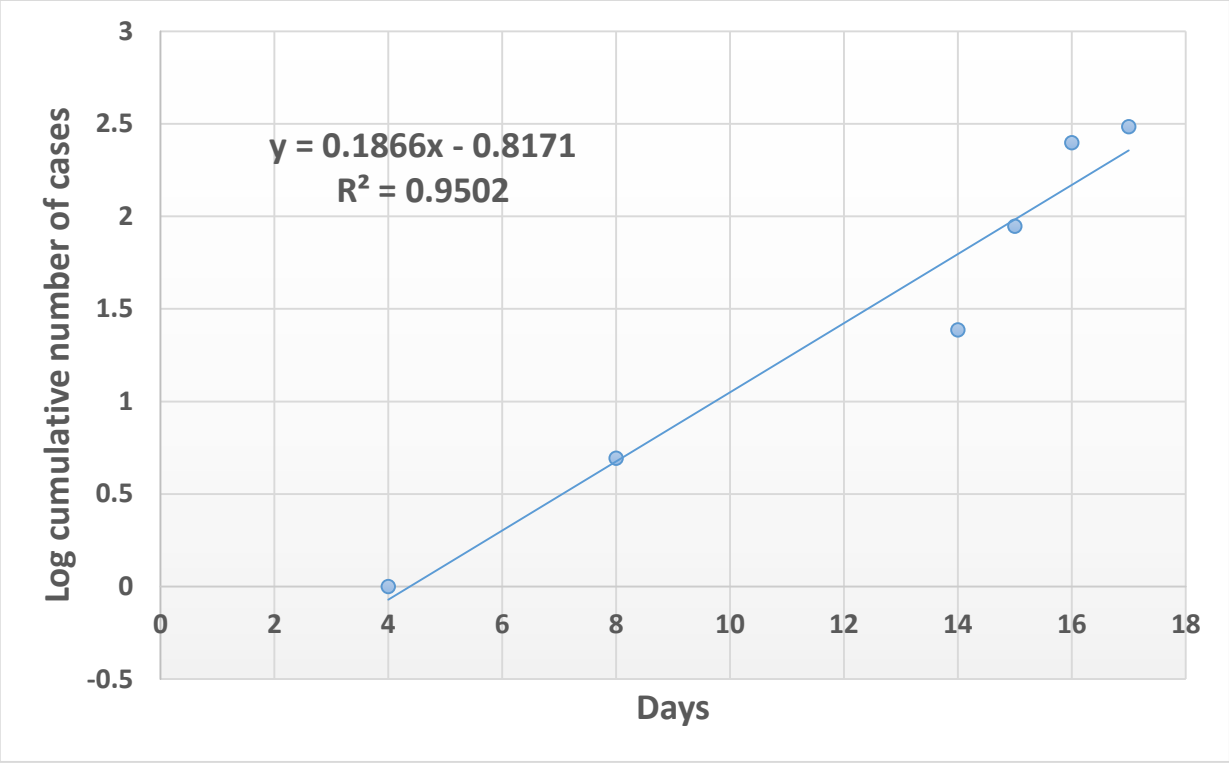

Figure 10. Log cumulative number of cases against time for segment of initial rise of cases during the 2015 Nyimba district bubonic plague outbreak and the fitted linear regression model.

The equation for the fitted linear regression model was given as $Y = 0.1866x - 0.8171$. The 95% confidence interval for the epidemic growth rate (gradient of the slope) was estimated to be between 0.1273 cases/day to 0.2459 cases/day as given in Table 2 which shows the linear regression output for the fitted linear regression model (given as 95% confidence interval for the coefficient of the X variable). Consequently, the epidemic doubling time for the outbreak was estimated to be between 2.8183 days and 5.4439 days with an average of 3.7139 days.

Table 2. The linear regression output for the fitted linear regression model to the Log cumulative number of cases plotted against time for segment of initial rise of cases during the 2015 Nyimba district bubonic plague outbreak.

	Coefficients	***Standard Error***	***t-Statistic***	***P-value***	***95% Confidence interval***	
					Lower (95%)	***Upper (95%)***
Intercept	-0.81712030	0.28203999	-2.89717890	0.04424295	-1.6001888	-0.0340518
***X* Variable**	0.18663345	0.02136095	8.73713443	0.00094552	0.12732596	0.24594094

Table 3 therefore shows the list of parameter estimates used to calculate R_0 using Equation 1 and Table 4 shows the estimated value of R_0. The 95% confidence interval limits for R_0 in Table 4 corresponds to the upper and lower bounds of the interval for the average epidemic doubling time. The range in the possible values of R_0 is due to the estimated duration of infectiousness for bubonic plague which was used.

Table 3: Final list of parameters used to estimate the basic reproduction number for bubonic plague using equation 1 in materials and methods.

Parameter	**Symbol**	**Value**	**95% Confidence interval**		**Unit**
			Lower limit	**Upper limit**	
$ln\,2$	$ln\,2$	0.693147181	N/A	N/A	N/A
Average epidemic growth rate	α	0.186633452	0.127325959	0.245940944	cases/day
Corresponding average epidemic doubling time	Td	3.713949314	2.81834805	5.443879499	days
Infectious period (lower limit)	D	3 (Dean *et al*,2017)	N/A	N/A	days
Average infectious period	D	4 (Dean *et al*,2017)	N/A	N/A	days
Infectious period (upper limit)	D	5 (Dean *et al*,2017)	N/A	N/A	days

Table 4: The estimated range of the basic reproduction number for plague for the 2015 Nyimba bubonic plague outbreak.

Infectious period	The basic reproduction number (R_0)	95% Confidence interval	
		Lower limit	Upper limit
Infectious period = 3 days	1.5599	1.382	1.7378
Infectious period = 4 days	1.7465	1.5093	1.9838
Infectious period = 5 days	1.9332	1.6366	2.2297

The basic reproduction number for bubonic plague in this study was therefore estimated to range between 1.5599 – 1.9332 with an average estimate of 1.7465 as seen in Table 4 above.

4.2 The Estimated Value of the Basic Reproduction Number (R_0) for Bubonic Plague from the Derived SIR Deterministic Compartmental Mathematical Model (Secondary method results).).

A simple SIR deterministic compartmental mathematical model for bubonic plague infection was developed and this was used as an alternative method for estimating the basic reproduction number (R_0). From this approach, R_0 for bubonic plague was estimated to range between 1.4 to 1.5 which is comparable to that estimated using the other epidemic doubling time method because it falls within its 95% confidence interval. Figure 11 shows the model predicted total (cummulative) number of cases over time for the Nyimba bubonic plague outbreak for the different runs (simulations) of the model assuming no intervention. Each separate line (simulation) in the graph represents the model output for each corresponding value of β_c used per simulation after altering the values of β_f. The shaded area represents the period of initial rise of cases (initial growth segment) for the outbreak up to its peak while the un-shaded area shows the model predicted growth of the outbreak without interventions for the Nyimba outbreak over a 45-day period.

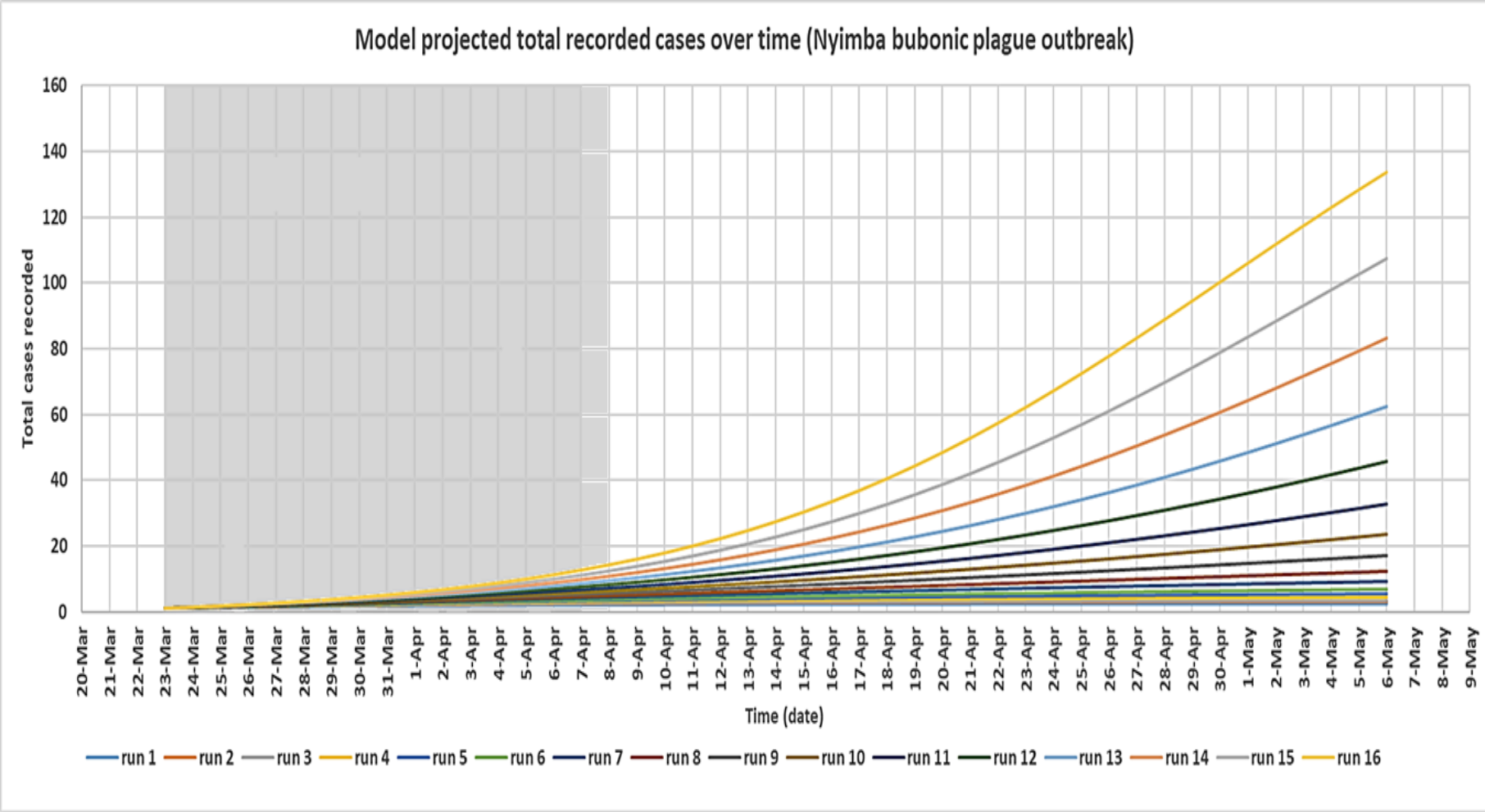

Figure 11. Derived SIR model simulations showing the model predicted total (cumulative) cases recorded over time for the Nyimba bubonic plague outbreak assuming no intervention was provided (model simulation over a 45-day period).

The optimal configuration of the model was determined by analysing the outbreak data for the period of initial growth of the outbreak up to its peak (shaded area). This is because it was expected in this study that the disease transmission dynamics occurred naturally during this period of the outbreak; an assumption implicit in the model design. Therefore, the model predicted total (cummulative) over time for each simulation for this period was compared to the actual cummulative cases recorded during the Nyimba outbreak for the same period. During the Nyimba outbreak, new plague cases for this period were recorded on the 26th of March, 30th March, 5th April, 6th April, 7th April, and 8th April 2015 (see Figures 3 and 4). These dates correspond to day 4, day 8, day 14, day 15, 16, and day 17 respectively of the model simulation. As seen in Table 5, the corresponding actual number of cummulative cases that were recorded during the Nyimba outbreak on these days were: day 4 = 1, day 8 = 2, day 14 = 4, day 15 = 7, day 16 = 11 and day 17 = 12 (red colour). In the same Table, the model predicted cummulative number of cases for each of these days is also given for each different run of the model simulation. Considering the whole number values of the model predicted cummulative number of cases, it was found that run 14 and run 15 of the model simulation (Heighted in Table 5) together had the best fit to the outbreak data for the selected dates; P-value 0.202 and 0.064 respectively (see Fig 12). Therefore, the values of β_f on these runs of the model were taken to be the most optimal estimates for this parameter based on the available outbreak data for the Nyimba bubonic plague outbreak. The values determined for this parameter were therefore given as β_f= 0.113 for run 14 and β_f= 0.118 for run 15 (see Table 5). The corresponding values of β_c for these estimated values of β_f therefore gave the estimates of R_0 for bubonic plague as R_0 = 1.4 for run 14 and R_0 = 1.5 for run 15 based on the formula $R_0 = \frac{\beta_c}{\alpha}$. Figures 13 and 14 give the most likely progression of the Nyimba outbreak without intervention for the diferent infection states of individuals for the entire projected 45 day period for runs 14 and 15 of the model simulation respectively. It can be noted from this graph that according to the model predictions, the infections in the human population during the Nyimba outbreak could have continued to rise and peak with more than 80 total recorded cases about 45 days later had it not been for the prompt action and interventions initiated by the

Nyimba district health team, Zambia Ministry of Health, and other stakeholders that took action (Sinyange *et al*.,2016).

Table 5: The model predicted cumulative cases on day 4, 8, 14, 15, 16, and 17 for the 2015 Nyimba bubonic plague outbreak based on the different values of β_f and β_c and the corresponding estimates of R_0 (Data generated in Vensim systems dynamics modeling software - personal learning edition. R_0 values calculated in Excel).

			Day 4	Day 8	Day 14	Day 15	Day 16	Day 17	
β_f	β_c	Outbreak total cases / Model total cases	1	2	4	7	11	12	R_0
0.050	0.138	Model predicted case incidence for Run 1	1.3772	1.7458	2.1016	2.1445	2.1837	2.2195	0.6188
0.055	0.151	Model predicted case incidence for Run 2	1.4195	1.8505	2.2965	2.3532	2.4058	2.4545	0.6789
0.060	0.164	Model predicted case incidence for Run 3	1.4630	1.9624	2.5164	2.5906	2.6603	2.7259	0.7391
0.065	0.178	Model predicted case incidence for Run 4	1.5075	2.0822	2.7646	2.8607	2.9524	3.0398	0.7993
0.069	0.191	Model predicted case incidence for Run 5	1.5531	2.2101	3.0450	3.1685	3.2879	3.4033	0.8594
0.074	0.204	Model predicted case incidence for Run 6	1.5998	2.3469	3.3618	3.5193	3.6736	3.8247	0.9196
0.079	0.218	Model predicted case incidence for Run 7	1.6476	2.4929	3.7197	3.9192	4.1172	4.3137	0.9798
0.084	0.231	Model predicted case incidence for Run 8	1.6965	2.6488	4.1242	4.3751	4.6275	4.8811	1.0400
0.089	0.244	Model predicted case incidence for Run 9	1.7466	2.8152	4.5811	4.8950	5.2147	5.5400	1.1001
0.094	0.258	Model predicted case incidence for Run 10	1.7979	2.9926	5.0973	5.4877	5.8901	6.3048	1.1603
0.099	0.271	Model predicted case incidence for Run 11	1.8503	3.1817	5.6800	6.1631	6.6670	7.1924	1.2205
0.103	0.285	Model predicted case incidence for Run 12	1.9040	3.3832	6.3376	6.9322	7.5599	8.2219	1.2807
0.108	0.298	Model predicted case incidence for Run 13	1.9588	3.5978	7.0791	7.8077	8.5854	9.4149	1.3408
0.113	0.311	Model predicted case incidence for Run 14	2.0148	3.8263	7.9148	8.8032	9.7620	10.7959	1.4010
0.118	0.325	Model predicted case incidence for Run 15	2.0721	4.0693	8.8556	9.9341	11.1106	12.3923	1.4612
0.123	0.338	Model predicted case incidence for Run 16	2.1306	4.3278	9.9137	11.2174	12.6540	14.2348	1.5214

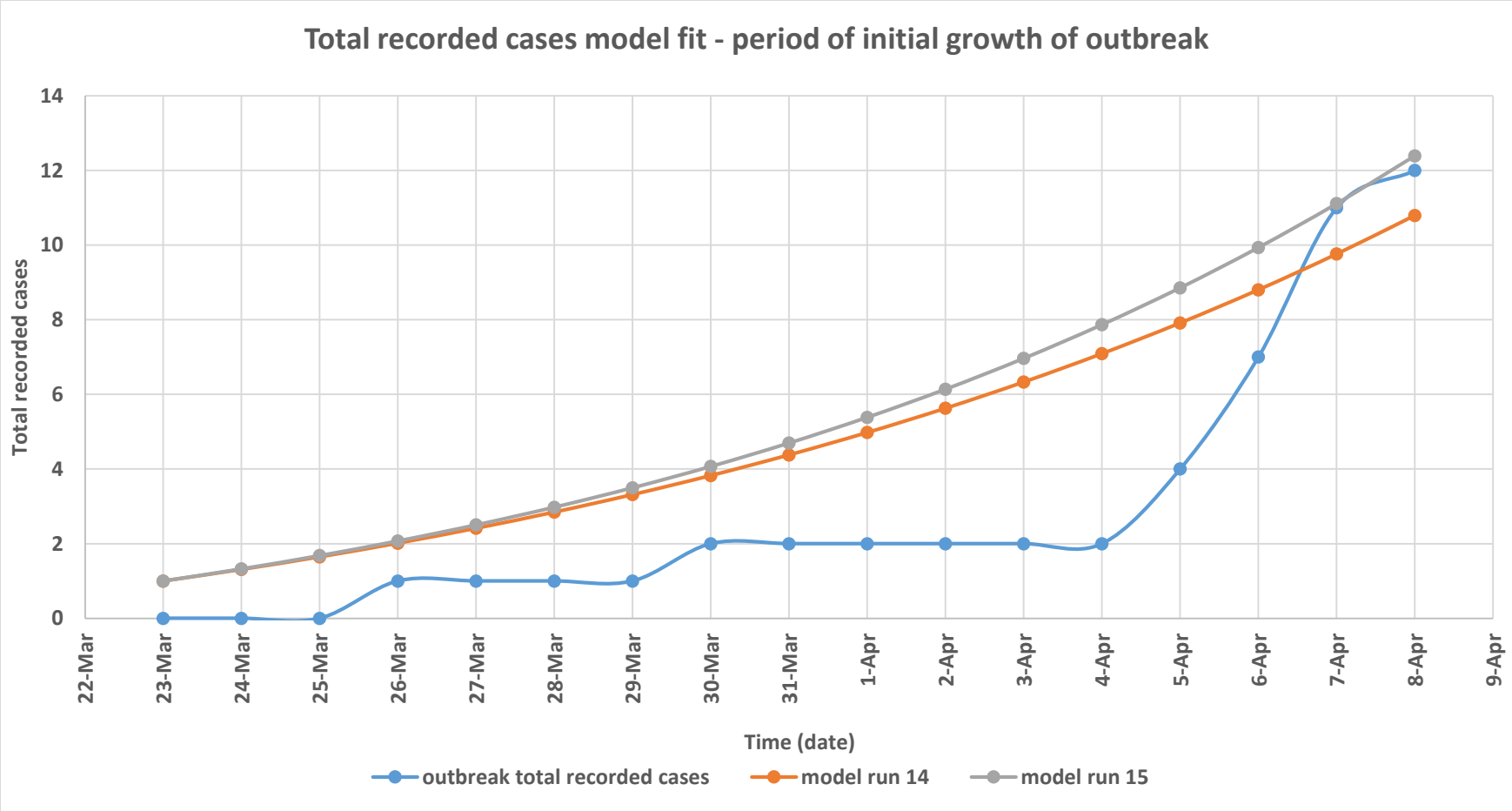

Figure 12. Derived SIR model simulation showing the model fit time for runs 14 and 15 to the total (cumulative) number of recorded cases over time during the period of initial rise of cases for Nyimba bubonic plague outbreak. Goodness of fit: run 14 (P-value 0.202), run 15 (P-value 0.064)

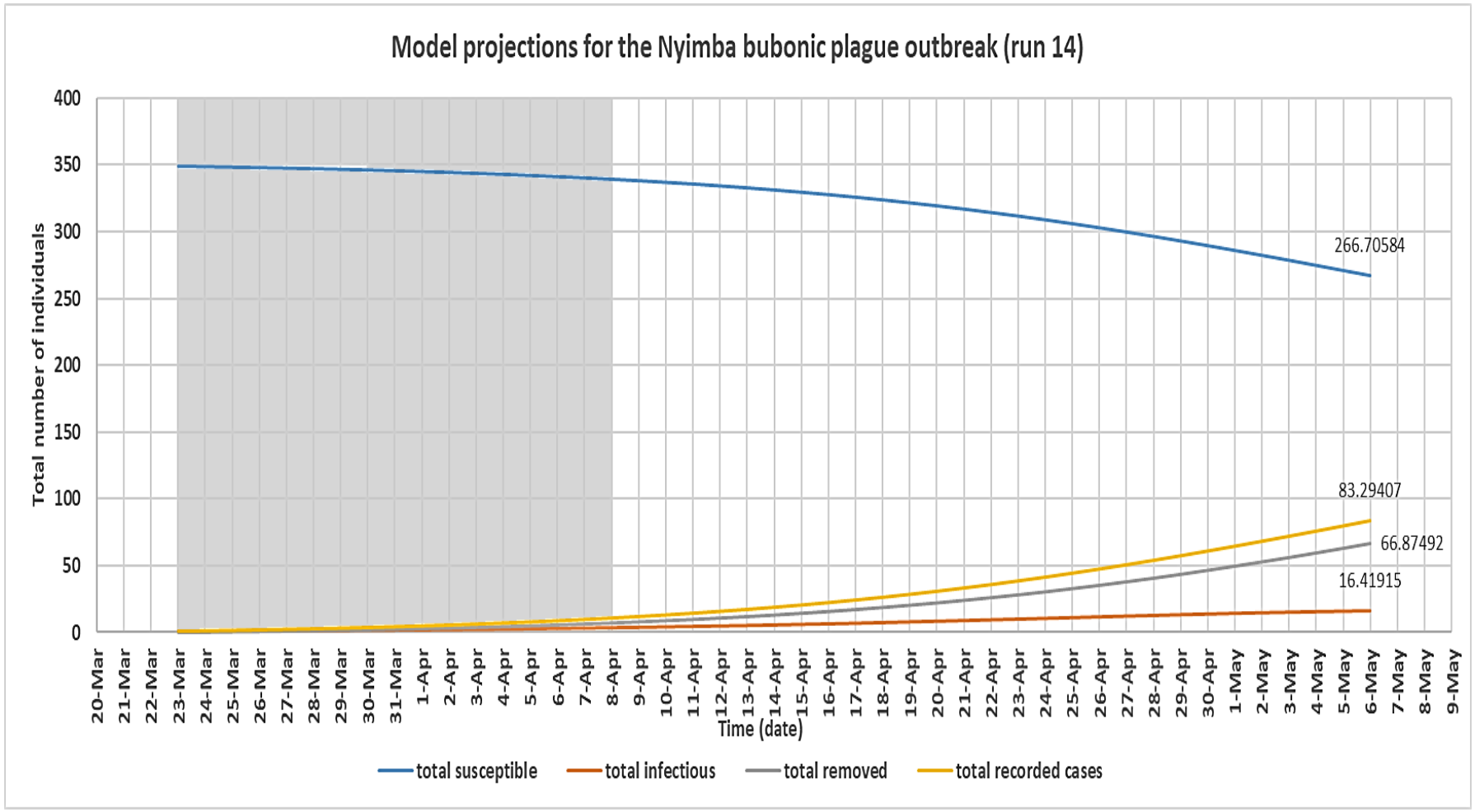

Figure 13. Derived SIR model simulation showing the model predicted most likely progression of the Nyimba bubonic plague outbreak for the diferent infection states of individuals for run 14 of the model simulation assuming no intervention was provided (model simulation over a 45-day period).

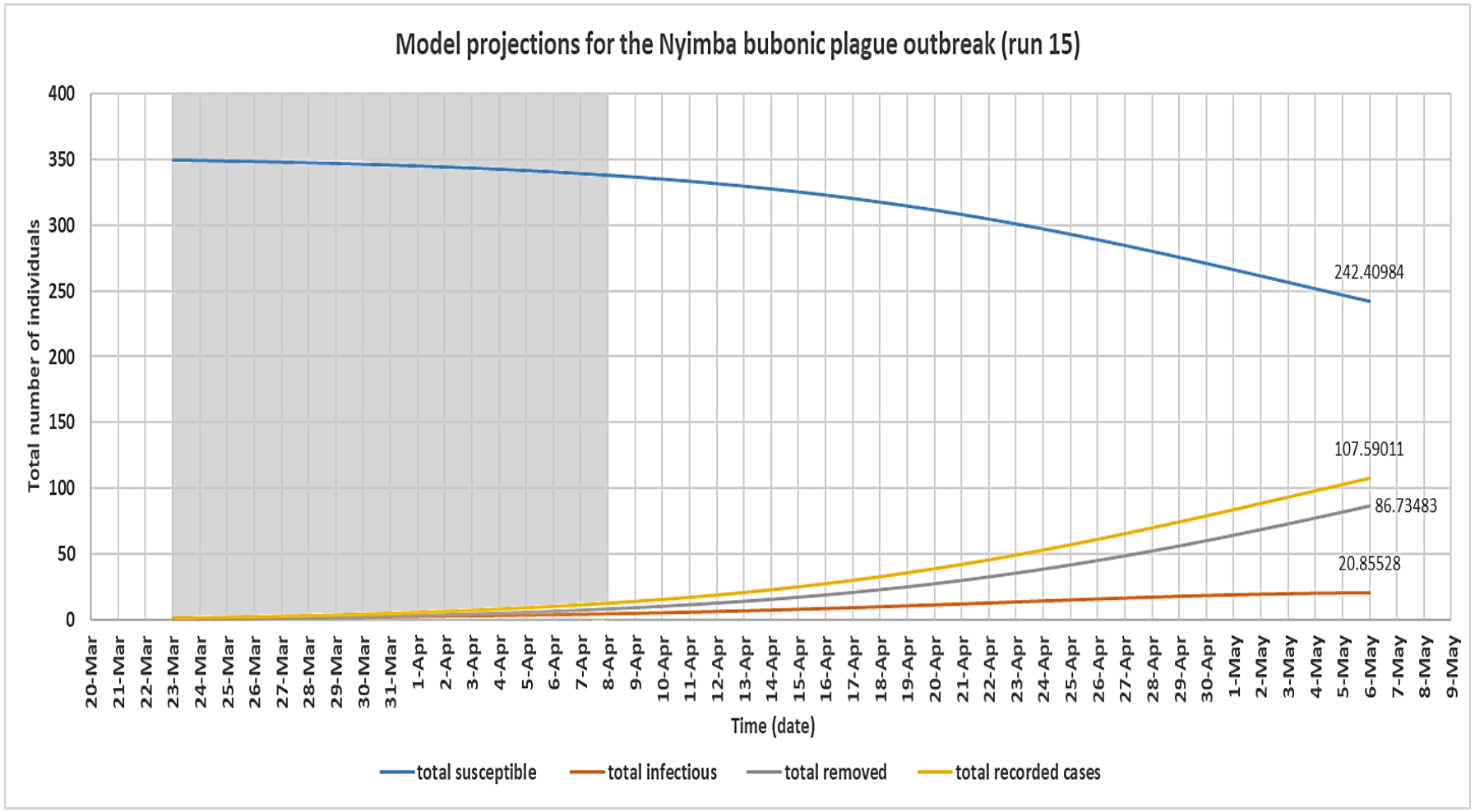

Figure 14. Derived SIR model simulation showing the model predicted most likely progression of the Nyimba bubonic plague outbreak for the diferent infection states of individuals for run 15 of the model simulation assuming no intervention was provided (model simulation over a 45-day period)

CHAPTER FIVE

5.0 DISCUSSION

In this study, the basic reproduction number (R_0) for the most recent outbreak of bubonic plague which occurred in Nyimba district of Eastern province in Zambia in 2015 was estimated. R_0 for bubonic plague was estimated to be effectively above unity ranging from 1.5599 – 1.9332 with an average of 1.7465. To estimate this R_0, a simplified mathematical method that estimates R_0 directly from epidemic incidence data as described by others was utilized (Korennoy *et al.*, 2016; Barongo *et al*., 2015; Iglesias *et al*., 2014, 2011; Heffernan *et al*., 2005; Dietz., 1993). This method was chosen as it is quick and robust even in the absence of abundant epidemiological data. The Nyimba outbreak reached its peak as early as the 7th of April 2015 after which it was generally brought under control with the last case recorded on the 1st of May 2015 (Sinyange *et al.*, 2016). However, it is the data from the initial exponential growth phase of the epidemic that the basic reproduction number was estimated i.e. when the population was still considered to be completely susceptible.

In the first instance, the R^2 value of 0.9502 for the fitted exponential curve to the observed early epidemic incidence data in the study was taken to validate the assumption of initial exponential growth of the outbreak. This assumption is further upheld by the estimated value of R_0 that is entirely above unity as has been previously reported in other studies that an exponential epidemic curve will normally form during an outbreak if $R_0 > 1$ for the infectious disease (Massad *et al.*, 2010). Further, regarding the assumption of homogenous mixing of individuals in the population, it was noted in this outbreak that all the identified cases came from the same village and their median age was eight years (range of 3 to 18 years old) with about 95% of them below the age of 15 years old (Sinyange *et al.*, 2016). This means that the main victims of the outbreak were children. Children of this age, especially in remote villages, usually come together to play through various activities allowing for frequent random contact and homogenous mixing amongst themselves. Therefore, after introduction of the infection into the population, it is highly possible that it

was during such events of interaction that some infected children may have spread the infection to other susceptible children. Additionally, it is suspected that the ordinary human ectoparasites (such as human fleas and body lice) may have played a major role as vectors in the transmission of the infection. This is because human ectoparasites are believed to be capable of transmitting plague (Dean *et al*., 2017; Hufthammer and Walloe., 2013; Spickler and Steneroden., 2013; Drancourt *et al*., 2006; Houhamdi *et al*., 2006; Dennis *et al*., 1999). A recent study by Banda *et al.*, (2014) in Zambia reported that plague occurs more frequently in poorly maintained households with dirty surroundings. There is therefore a possibility that the victims in this study may have also lived in such dwellings of lowered hygiene standards, since the outbreak occurred in a village setting, and therefore these victims could have harbored human ectoparasites. In fact, it is usually expected that hygiene standards are lower in children and young adolescents as compared to adults and therefore these children could have indeed carried various human ectoparasites that could spread the infection. It should also be noted that in this village the children were reported to have slept together on the floor while adults slept on beds elevated off the floor (Sinyange *et al*., 2016). This could have lead the children to always be in contact with various human ectoparasites. The close contact during sleep on these floors may have also been another way through which children spread the infection to each other.

The estimated value of R_0 for bubonic plague in this study shows that the disease is capable of epidemic spread if it occurs in susceptible populations in the country (Mukandavire *et al.*, 2013, 2011; Heffernan *et al*., 2005; Dietz., 1993). This is because the value of R_0 estimated here shows that each infectious individual with bubonic plague may infect at least one other susceptible individual or up to two other susceptible individuals in a worst case scenario (depending on the infectious period and other population parameters). As seen in the epidemic curve for the Nyimba bubonic plague outbreak in Figure 4, the first two cases appeared on the 26th and the 30th of March 2015. After this, a period of a five to nine days passed before a large cluster of cases suddenly appeared again around the 5^{th} – 7^{th} of April 2015. It is therefore possible that those initial captured cases,

and possibly other uncaptured cases, may have given rise to some of those new cases after the gap period if one considers the assumed infectious period for bubonic plague, a possible brief pre-clinical stage, and the estimated R_0 for the infection in this study (Spickler and Steneroden., 2013; Monecke *et al.*, 2009; Dennis *et al.*, 1999). This may not be the exact evolution of the events during the Nyimba outbreak but it is very plausible based on the estimations from this study. It is therefore possible that the value of R_0 estimated in this study could indeed be the most likely quantitative representation of the transmissibility of bubonic plague infections during such outbreaks in Zambia.

A simple SIR deterministic compartmental mathematical model for bubonic plague infection was also developed in this study. As seen in Table 5 (runs 14 and 15), the model was generally able to predict similar epidemc spread paterns as those seen during the Nyimba outbreak in terms of the cummulative number of cases recorded over time for the period of initial growth of the outbreak. The success of this model, despite its possible theoretical limitations, in reproducing the general spread pattern for the Nyimba outbreak provided the opportunity to use it as a secondary approach for estimating the basic reproduction number for plague in order to give credence to the results of the first and main method for this study. The basic reproduction number for bubonic plague was therefore estimated from the model to be about 1.4 to 1.5. This value of R_0 was slightly lower but still fell well within the 95% confidence interval of the estimated range for R_0 using the first method. This outcome was taken to validate the results of this study to some extent since there was a general consistency in the estimates of R_0 for the same bubonic plague outbreak despite using two very different methods of estimation. This observed "agreement" in the two results (although not a perfect agreement) is despite the uncertainties associated with estimating R_0 using various parameters of a compartmental model. For example, in this model used, all the parameters (β_c and α) on which R_0 depends generally had to be estimated from literature which can introduce unavoidable uncertainty in the R_0 estimate because these parameter values also greatly vary in literature. For this study, this was of great significance because changes in the composite parameter β_c (which comprised of various parameters estimated from literature) had the greatest effect on

changes in both the model predicted number of cases and the estimated value of R_0 for bubonic plague. Other parameter values were kept constant for simplification of the model.

The estimated value of R_0 for bubonic plague in this study was also found to be essentially within the same range as that estimated for previous rapid spreading bubonic plague outbreaks of the 14th century Black Death plague in Europe for which R_0 was estimated to range between 1.5 and 1.9 (Dean *et al*., 2017). As is generally known, medieval bubonic plague outbreaks (14th to 18th century), among which is the well-known Black Death plague, were popularly documented to have been more devastating with higher attack rates than modern day third pandemic outbreaks (Dean *et al*., 2017; Hufthammer and Walloe., 2013; Monecke *et al.*, 2009). A viable explanation, at least in part, for this similar R_0 between our modern day third pandemic bubonic plague outbreak and the black death plague is that in old days, outbreaks used to last long possibly due to poor knowledge and management of the disease, while in present time, antibiotics and other remedial measures are given immediately the disease is diagnosed as prophylactic treatment, thus reducing the susceptible population (Dean *et al.*, 2017; Nyirenda *et al.*, 2016; Hufthammer and Walloe., 2013; Stenseth *et al.*, 2008). This could be the reason for the observed difference in the magnitude of outbreaks seen between these pandemics despite having a similar estimated R_0 for the infection. However, both methods used to estimate the basic reproduction number in this study were able to "capture" this typical value of R_0 for bubonic plague infection due to the analysis of the early epidemic incidence data for the current outbreak possibly before the impact of applied interventions could take full effect. The result of this study therefore puts forward some scientific evidence that bubonic plague outbreaks today are still inherently capable of widespread transmission with devastating effects if left unchecked. In the case of Zambia, this raises a particular concern after closely examining Figure 2 which shows that starting from about 1997 there has been a sudden occurrence of large plague epidemics than ever recorded before in the country. The reason for these seemingly "more intense" plague outbreaks is not well known but may point to delayed intervention. Additionally, recent studies in Zambia reported that some social-cultural factors including certain lifestyle practices as described in section 2.6 may have also

played a major role in providing favorable conditions for sustaining and further propagation of the infection between humans (Nyirenda *et al*., 2016; Sinyange *et al*., 2016; Kango *et al.,* 2014; Ngulube *et al*, 2006). By estimating R_0, this current study was able to attach a quantitative aspect to describing and understanding the transmission dynamics of bubonic plague infection during these outbreaks. With this new added knowledge of R_0, we can now use this estimate to predict the size and progression of future outbreaks of bubonic plague and quantitatively asses the effects of various control measures required to prevent the spread of infection through further mathematical modelling techniques (Onyejekwe, *et al*., 2019; Gervas *et al*., 2018; Mojeeb and Yang., 2017; Driessche., 2017; Zamir *et al*., 2016; Neilan *et al*., 2010; Heffernan *et al*., 2005; Gani and Leach 2004; Dietz., 1993). For example, one simple and classical demonstration of the invaluable use of R_0 is that it is used to determine the minimum mass treatment or vaccination coverage rate required to prevent spread of the infectious disease in a population (Driessche., 2017; Dietz., 1993). Therefore, based on the average value of R_0 estimated in this study, a minimum vaccination (or prophylactic treatment) coverage rate of about 43% would be required to prevent the spread of bubonic plague infection in an identified risk population: using formula, coverage = $1 - 1/R_0$, assuming vaccination provides full protection (Driessche., 2017; Mukandavire *et al*., 2013, 2011; Dietz., 1993).

It is noted however that the result of this study may not be readily representative for all recent bubonic plague outbreaks seen in the country since the value of R_0 may vary from one area to another depending on population dynamics and other factors. Additionally, it is also acknowledged that the methods used here for estimating R_0 are still subject to certain weaknesses most important of which is the completeness and quality of the reported epidemic incidence data used for the analysis. For example, 29 out of all the 111 patients suspected to have bubonic plague during the Nyimba outbreak were not available for physical examination (Sinyange *et al*., 2016). This could have caused the value of R_0 to be underestimated in this study as it is generally possible that some cases during the outbreak may have been misdiagnosed, never reported, or even died before they went to the hospital. This could have particularly affected the result from the model as it is possible

that the model used in this study may have been fit to data that was incomplete. Another limitation of the study is the small sample size available for the analysis despite use of a robust method of estimating R_0 as well as the limited background data about the affected population. More similar studies with larger sample sizes will need to be conducted. In spite of this, it is the researcher's recommendation that the estimate of R_0 for bubonic plague obtained in this study can still be used as a primary reference value in the analysis of future outbreaks of the disease in similar populations in the country especially in emergency situations. Alternatively, this study has demonstrated the practical use of a quick and robust method for estimating R_0 directly from outbreak incidence data for an infectious disease such as bubonic plague. Therefore, this method can still be employed in future to obtain an updated estimate of R_0 during the early stages of an outbreak of bubonic plague or other infectious disease using the outbreaks incidence data.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

The basic reproduction number (R_0) for the 2015 Nyimba district bubonic plague outbreak was estimated to range between 1.5599 and 1.9332 with an average of 1.7465. This was comparable to the estimate obtained using an SIR model for the outbreak which estimated R_0 to be between 1.4 to 1.5. This value of R_0 which is above unity is a quantitative indicator that indeed bubonic plague is capable of epidemic spread in Zambia as was seen in Nyimba. The value of R_0 estimated here also suggests that there is a present potential threat of the occurrence of large bubonic plague outbreaks in Zambia if conditions become favorable. R_0 estimated here can now be used in the planning and development of various quantifiable, efficient, and cost-effective control measures against future outbreaks of bubonic plague in the country through infectious disease modeling techniques.

6.2 Recommendations

1. Surveillance services for bubonic plague should be increased in the country as this is an important infectious disease.
2. Further complex mathematical modeling studies of the infection should be done to better control the disease in Zambia.
3. Health policy makers can consider exploring the option of at least 43% preventive mass treatment coverage to prevent the spread of the disease in a high risk endemic area.

7.0 APPENDICES

Appendix I.

Summary of Plague Epidemics in Zambia, 1914 To 2014. Source: Nyirenda *et al.*, (2016).

Serial number	year	district	location	No. of recorded cases	No. of recorded deaths
1	• 1917 • 1918	Chama	Tembwe	• 96	• 93
2	• 1937 • 1940 • 1942 • 1943 • 1944 • 1947 • 1948 • 1949 • 1954	Zambezi plain (Balovale)	Barotseland Barotseland Barotseland Barotseland Barotseland Barotseland Barotseland Barotseland Chitikoloki (CMML Mission)	• 9 • 4 • 13 • 5 • 3 • 1 • 7 • 2 • 9	• 9 • 4 • 13 • 5 • 3 • 1 • 7 • 2 • 5
3	• 1956	Chama	Tembwe	• 36	• 5
4	• 1956	Lundazi	Mukomba	• 3	• 1
5	• 1987	*	Zambia	• 1	• 1
6	• 1994	Zambezi plain	Chitokoloki	• 10	• 3
7	• 1997	Namwala	Namwala district	• 316	• 26
8	• 2001	Sinda	Nyanje	• 850	• 11
9	• 2007	Sinda	Nyanje	• 213	• 2
10	• 2007	Namwala	Namwala	• 68	• 4

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