DRIVERS OF INFECTIOUS DISEASE OUTBREAKS: HOW CLIMATE, ENVIRONMENT AND DISEASE CONTROL PROGRAMS INFLUENCE OCCURRENCE OF INFECTIOUS DISEASE OUTBREAKS

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Drivers of Infectious Disease Outbreaks: How Climate, Environment and

Disease Control Programs Influence Occurrence of Infectious Disease Outbreaks

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

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ABSTRACT

This research study described the factors driving infectious disease outbreaks using Foot-and-mouth disease (FMD) in Uganda and Lyme disease in North Dakota (ND), Minnesota (MN) and Wisconsin (WI) as case studies. Retrospective data on FMD vaccines and outbreaks in Uganda (2001 – 2010) and Lyme disease in ND, MN and WI (1990 – 2011) was used. The time (7.5 weeks) taken to respond to FMD outbreaks, limited serotyping/subtyping (9/121) of outbreaks and the low percentage of cattle vaccinated (2.1 – 21.2%) portray ineffective control programs. Similarly, increase in fall temperature ($P = 0.0189$) and annual precipitation ($P = 0.0250$) were associated with increased human Lyme cases. Shrub land coverage and human population also increased in WI, MN and ND while forest coverage increased in ND. These favor tick and deer proliferation leading to increased human exposure to Lyme *Borreliosis*. Therefore ineffective disease control programs, climate and environment factors influence infectious disease occurrence.

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Lastly, I appreciate my siblings Esther and Henry, for their support throughout my stay in Fargo, North Dakota and to the almighty God for his guidance, strength and health throughout my master's degree study period.

DEDICATION

This study is dedicated to my parents Charles Kintu Kaddu and the late Florence Namutebi Kaddu for their selfless sacrifice to give me a descent education; and to my siblings Esther and Henry for their support, inspiration and encouragement.

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LIST OF ABBREVIATIONS

NADDEC…………………….National Animal Disease Diagnostics and Epidemiology Centre, Entebbe, Uganda

MAAIF…………………….Ministry of Agriculture, Animal Industry and Fisheries, Entebbe, Uganda

UBOS………………………Uganda Bureau of Statistics, Entebbe, Uganda

WRL………………………..World Reference laboratory for FMD, Pirbright, Surrey, United Kingdom

FMD………………………..Foot-and-mouth disease

FMDV……………………...Foot-and-mouth disease virus

USAID……………………..United States Agency for International Development

SAT………………………...South African Territories

GIS…………………………Geographic Information System

OIE…………………………World Organization for Animal Health

ND………………………….North Dakota

MN…………………………Minnesota

WI………………………….Wisconsin

+…………………………….Positive

- ....Negative

CHAPTER 1. INTRODUCTION

1.1. Background

Disease outbreaks are defined as the occurrence of cases of disease in excess of what is normally expected in a given population *(74).* The 21st century has been characterized by a worldwide increase in the occurrence of infectious diseases leaving a number of countries with the task of determining which diseases are most likely to establish within their borders *(64).* The most common infectious disease outbreaks are those due to cholera, yellow fever, meningitis, avian influenza and dengue fever *(59).* Annually, the percentages of infectious disease outbreaks attributed to these illnesses are: 29% for cholera, 12% for yellow fever, 9% for meningitis, 9% for avian influenza and 5% for dengue. These infectious disease outbreaks mostly occur in developing countries. Furthermore, 53 per cent of the world's total number of infectious disease outbreaks occurs in Africa *(59).*

Many factors are responsible for the increased occurrence of infectious disease outbreaks, which include inadequate disease control and surveillance strategies, climate change and anthropogenic land use changes *(2*; *59).* In developing countries, failure to implement costly disease control and surveillance strategies may be one of the greatest drivers of disease occurrence. For most countries in Sub-Saharan Africa, improper disease control programs and inadequate institutional capacity to implement effective disease control and prevention strategies overwhelmingly exacerbate the challenge of increased occurrence of infectious disease outbreaks. The widespread limitations in infrastructure and human capacities in developing nations are evidenced by limited laboratory facilities and personnel to diagnose diseases as well as inadequate disease surveillance programs *(13; 61).* Many developing countries have not integrated the one health approach and other control strategies in disease surveillance to facilitate early detection and response to infectious disease threats and to allow effective use of available resources *(13).*

Conversely, climate change drives the occurrence of infectious diseases in both the developed and developing countries *(2)*. The seasonal changes in temperature, precipitation and resource availability are important determinants of host-pathogen interactions. Climate change also influences host behavior, vector-pathogen interaction, host immune protection as well as host and pathogen populations *(2)*. These seasonal variations alter the occurrence of infectious diseases by influencing the spread and persistence of disease pathogens in host populations resulting in annual or multiyear fluctuations in the number of cases of infectious diseases *(2).*

Additionally, land-use changes like agricultural encroachment, deforestation, road construction; wetland demolition and urban modification are primary drivers of a range of infectious diseases outbreaks *(59).* These changes in land use patterns result in destruction of vegetation cover, pollution and human migration exacerbating the emergence of infectious diseases. For instance, forest encroachment for agricultural use as well as increased activity of humans in forested areas promotes interaction between host, vectors and many infectious disease pathogens. These forest habitat human activities have been reported to be highly associated with Lyme disease, Nipah virus, Trypanasomiasis and Yellow fever *(59).* In this paper, the drivers of infectious disease outbreaks are reviewed using foot-and-mouth disease outbreaks and vaccination programs in Uganda as well as Lyme disease occurrence in North Dakota (ND), Minnesota (MN) and Wisconsin (WI) as case studies.

Foot-and-mouth disease (FMD) is a highly contagious viral disease of wild and domestic cloven-hoofed animals *(1)*. The disease in livestock is associated with serious socio-economic consequences due to marked loss in production and/or death of affected animals as well as interference with marketing of livestock products *(4; 60*). The current global burden of FMD is concentrated in Asia, Africa and South America which mirrors low economic development as well as lack of infrastructure and resources to control the disease *(55, 57).* On the same note, seasonal weather changes like droughts influence land use patterns, animal movements, livestock – wildlife interface and herd interactions that are important in the epidemiology of FMD *(20).*

Similarly, Lyme disease is the most commonly reported arthropod-borne illness in the United States, Asia and Europe *(42).* Several studies have linked spring and summer precipitation as well as temperature to the occurrence of Lyme disease *(42).* Additionally, the occurrence of Lyme disease has been associated with changes in land use and environment in many places. For instance, the reversion of farmland in to woodland has been associated with increased population of deer, chipmunks and white-footed mice, the reservoirs of Lyme disease. In a similar way, land cover and soil moisture along river shores has been linked to increased survival of *Ixodes scapularis* ticks that transmit *Borrelia burgdoferi*, the cause of Lyme disease *(66).*

1.2. Problem statement

In Uganda, FMD outbreaks occur every year despite the vigorous vaccination efforts and restriction of animal movements to control the disease. A good example of this situation is the FMD outbreak we encountered in Kumi district during our field visit to eastern Uganda in the summer of 2011.

The 2011 FMD outbreak in Kumi began in three cattle herds that had been vaccinated against the disease three weeks back. No form of control except quarantining animals had been instituted by the third week of the outbreak. The cause could certainly be ascertained but we neither had the resources nor the facilities. From the 2011 FMD outbreak in Kumi, the idea to evaluate the effectiveness of vaccination programs against FMD in Uganda was developed.

The Lyme disease study was developed after a quick review of disease challenges reported by the North Dakota Department of Health (NDDH), where we noticed the increasing number of human Lyme disease cases *(49).* The number of human Lyme disease cases in North Dakota has steadily increased in the last five years from 7 (2006), through 12 (2007), 11(2008), 15 (2009), 33 (2010) to 26 (2011), *(43)*.

Ixodes scapularis have also been discovered in six sub-counties of North Dakota namely Pembina, Eddy, Grand Forks, Rolette, Ramsey and Steel *(51).* This could indicate changing climate conditions and environmental factors resulting in increased survival and extension of *I. scapularis* habitat to North Dakota where these Lyme disease transmitting ticks were never known to occur.

The purpose of this master's paper is to describe the factors driving the occurrence of infectious disease outbreaks using FMD in Uganda (2001 – 2010) and Lyme disease in North Dakota, Minnesota and Wisconsin (1990 – 2011) as case studies.

1.3. Objectives

The specific objectives of the two studies presented in this master's paper were; to describe patterns of FMD outbreak occurrence and vaccine usage in Uganda; to assess the effectiveness of vaccination programs used for the control of FMD as well as other factors influencing occurrence of FMD outbreaks; to describe the occurrence of Lyme disease in ND, MN and WI; as well as analyzing the influence of climate and environmental factors on the occurrence of Lyme disease in North Dakota in comparison to Minnesota and Wisconsin where high number of Lyme disease cases have been reported.

CHAPTER 2. LITERATURE REVIEW

2.1. Epidemiology of Foot-and-mouth disease (FMD) in Uganda

2.1.1. Etiology of FMD

FMD is caused by a virus of the genus *Aphthovirus* and family Picornaviridae *(4).* Seven serotypes of the FMD virus (FMDV) have been identified namely: O, A, C, Asia 1, and South African Territories (SAT) 1, SAT 2 and SAT 3 *(11).*

2.1.2. Hosts and mode of transmission of FMD

The disease is highly contagious and affects wild and domestic cloven-hoofed animals. The domestic animals affected by FMD include cattle, pigs, sheep and goats *(3).* About 70 wildlife species have been reported to be affected by FMD but most of the cases are subclinical or mild *(1).* The African buffalo, bison, kudu, waterbuck, eland, warthog, bush pig among others are some of the wildlife species affected by FMD *(3).*

2.1.3. Clinical signs and economic consequences of FMD

The disease in livestock is associated with serious socio-economic consequences caused by marked loss in production and/or death of affected animals and interference with marketing of livestock and animal products *(4; 60*). FMD in livestock is characterized by formation of vesicles or erosive lesions in the mouth, muzzle, tongue and the hooves, which clinically manifests as lameness and inappetance. The hooves may slough off in pigs and cattle leaving animals with very painful lesions *(3).*

2.1.4. Occurrence of FMD

FMD is endemic in most parts of Africa, Asia and South America *(58)*. The consequences of FMD are more prominent in developing countries, mostly sub-Saharan Africa and disease-free status is an indication of development since most developed countries are disease free *(58).* The first FMD outbreak in Uganda was recorded in 1953 and since then, many outbreaks involving all FMDV serotypes, except for Asia 1, have been reported in the country *(6, 7).* The disease is reported annually in Uganda's 11.4 million cattle with previous studies showing incursions of serotypes O, A, SAT 1 and SAT 2 *(47).*

2.1.5. Prevention and control of FMD

In Uganda, FMD outbreaks are mainly controlled by ring vaccination and quarantine that involves restriction of animal movements from affected districts *(46).* The strategy of ring vaccination involves immunizing animals in areas surrounding a known source of infection *(35).* In a number of countries, but not in Uganda, ring vaccination is usually implemented alongside the slaughter of sick and in-contact animals to prevent spread of the disease *(21; 58).* If used strategically, vaccination can create a barrier between infected and disease free areas provided FMDV vaccine serotypes match with outbreak serotypes and sub-types in a given area *(21).*

2.2. Epidemiology of Lyme disease

2.2.1. Etiology and hosts of Lyme disease

Lyme disease is caused by the spirochete bacteria, *Borrelia spp.* and transmitted by several ticks of the genus *Ixodes (66).* Three species of *Borrelia* are known to cause Lyme disease and they include *B. burgdorferi*, *B. afzelii* and *B. garinii*. Only *B. burgdorferi* has been identified in the U. S. while *B. afzelii* and *B. garinii* are known to cause Lyme disease in Asia.

All the three species of *Borrelia* are occur in Europe where they are reported to cause about 100 – 130 per 100,000 human cases of Lyme disease annually. Similarly, the vectors for Lyme disease are different in the three continents. They include the deer tick (*Ixodes Scapularis* and *Ixodes pacificus*) in the US, the sheep tick (*Ixodes ricinus*) in Europe and the taiga tick (*Ixodes persulcatus*) in Asia *(66).*

2.2.2. Occurrence of Lyme disease

Lyme disease is the most commonly reported arthropod borne illness in the United States (U. S.), Asia and Europe *(64; 66).* The disease occurs in the Northern hemisphere with cases seen in the U. S., Europe and Asia *(66).* The disease derives its name from the town, "Lyme" in Connecticut, U. S., where it was first fully described among children with arthritis symptoms in 1977 *(34).* In the U. S., *B. burgdorferi* causes an estimated 20-100 cases per 100, 000 people *(66).* In 2009, nearly 30,000 cases were confirmed and another 8,500 probable cases were reported to Center for Disease Control and Prevention in the U. S. alone *(45).*

Currently, the disease occurs mainly in the North eastern (Maine to Maryland), North central (Wisconsin and Minnesota) and Western U. S. and is reported to be related to the distribution of the vectors. *Ixodes scapularis* is distributed in the Northeastern and North Central U. S. while *Ixodes pacificus* is found mainly in the western part of the U. S. *(66).*

2.2.3. Pathogenesis of Lyme disease

Borrelia maintains a horizontal cycle of transmission among larval and nymph stages of ticks and certain rodents *(66).* The larval and nymph ticks feed on White-footed mice and chipmunks to maintain this horizontal cycle. Humans and other animals get exposed to these ticks mostly during the late spring and summer when the ticks are active and feed on a number of avian and mammalian hosts. The ticks remain inactive during fall, winter and early spring when the environmental temperatures are low *(66).*

During the dormant stage, the spirochetes express primarily *Osp* (Outer surface protein) *A* for attachment to the mid-gut of the nymph ticks. Soon after the onset of late spring, *Osp A* is down-regulated and *Osp C* is up-regulated. The spirochetes use *Osp C* to bind to plasminogen and its activators in the blood meal taken in by the tick during feeding *(25).* This allows the spirochete to spread within the tick to the salivary gland from where it is deposited by the tick into the hosts' skin *(66).*

Ticks deposit *Borrelia* pathogens in the skin of the human host. This usually results in an erythematous macular painless rash known as erythema migrans which may be followed by flu-like illnesses like fever, malaise and diffuse aches and pain after 3 to 35 days as the bacteria disseminates to other body parts *(66).* Within days to weeks, *Borrelia* migrates to the cerebral spinal fluid, retina, bone, liver, spleen and the brain. Dissemination is by binding to host cells proteins like integrins, proteoglycans and glycoproteins *(66).* Because of the migration of *Borrelia* pathogens in host tissues, 5% of the patients report cardiac conductance abnormalities; mild hepatitis or myositis and 15% of the cases are nervous system problems associated with bilateral facial palsy *(66).*

Persistent infections result in arthritis and approximately 60 per cent of untreated patients experience intermittent joint illness. This has been attributed to neutrophil extravasation into the joints *(63).*

2.2.4. Treatment and diagnosis of Lyme disease

If diagnosed early, Lyme disease cases respond well to short-course doxycycline, ampicillin and other standard antibiotics. Late manifestations rarely respond to antibiotic treatment *(36)*. Lyme disease is mainly diagnosed based on clinical manifestations and history of exposure *(45)*. However confirmatory diagnosis of Lyme disease includes culture as well as the detection of immunoglobulin (Ig) G and IgM serum antibodies against *B. burgdorferi*. Conversely, serology may not differentiate between past and current infections *(65).*

2.2.5. Prevention and control of Lyme disease

Prevention of Lyme disease strategies include protective clothing, use of tick repellants or acaricides, frequent tick checks and landscape modifications to reduce the tick population *(66)*. A vaccine was used in the U. S. from 1994 to 2002 but was withdrawn by the manufacturer due to public reports that the vaccine triggered autoimmune arthritis. Additionally, the low risk of Lyme disease in some parts of the country, the need for annual booster injections and the high cost of the vaccine compared to antibiotics resulted in low sales of the vaccine *(66).*

2.2.6. Lyme disease in animals

Most cases of Lyme disease in dogs manifest with anorexia, dehydration, vomiting, polyuria, polydipsia or lameness during summer and fall months *(41)*. Many of these cases succumb to renal failure within days to weeks. However, most cases occur as co-infections with other diseases that are transmitted by the same vector or other ticks and fleas. The vectors include Anaplasma, Ehrlichia, Babesia and many others *(41)*. Diagnosis is based on evidence of exposure to *B. burgdorferi*, clinical signs, response to treatment and consideration of other differential diagnosis. Tests available to confirm presence of the organism include culture, cytology, polymerase chain reaction and serology. The organism is often found in connective tissue, synovia, skin and fibroblasts and rarely found in blood, urine, joint fluid or cerebral spinal fluid *(41).*

The most common serology tool is the 4Dx snap test that detects antibodies against an immune-dominant surface antigen of *B. burgdoferi* called C6. The concentration of antibodies is reported to be related to presence of viable spirochetes *(22; 62).* Many commercial vaccines are available for immunizing dogs against Lyme disease. These vaccines induce the production of antibodies against OspA *(38).* These antibodies stimulate complement and result in formation of a membrane attack complex that kills *B. burgdorferi* in the midgut of vectors as they take a blood meal from their hosts. The only challenge is that OspA is downregulated as ticks take in a blood meal. Studies have been done to evaluate the possibility of vaccines that induce anti-OspC *(38).*

2.3. Factors influencing the occurrence of Lyme disease

2.3.1. Climate

Many studies have been carried out to study the influence of climate and environment on the occurrence of Lyme disease *(5; 42).* A predictive model developed in 2004 from temperature and precipitation measurements in Northeastern and Midwestern United States showed a high incidence of Lyme cases during the peak summer months when temperatures were between 10.8^{o}C (50^{o}F) and 19.4^{o}c (70^{o}F); and total precipitation between 19.7cm (7.7 inches) and 37.8cm (14.9 inches) *(5).* The ticks are cryptobiotic during fall, winter and early spring and become active in late spring and summer *(73).* Thus majority of the cases are seen during spring and early summer when the nymph ticks feed on human and rodents *(73).*

2.3.2. Land use

Woodland and forests support a large number of vectors and mammalian hosts for *Borrelia burgdorferi* and present one of the risk factors to Lyme disease occurrence *(27).* The high incidence of Lyme disease in forested and shrubby vegetation areas was demonstrated before the Glass et al., 1995 study, that initiated the use of Geographic Information systems in investigation of risk factors to Lyme disease. High Lyme disease incidence is associated with increased residential development in forested areas that in turn increases the number of people exposed to *Ixodes scapularis* ticks *(27).* The presence of human settlements in forested areas (suburban) has in turn resulted in an increase in the deer population. Suburban landscape is characterized by an edge habitat with abundant forage as well as ornamental vegetation that supports white tailed deer. Additionally, there is less hunting pressure and no predators which further fuel the increase in white tailed deer population, the favorable hosts for *Ixodes scapularis (24).*

2.3.3. Presence of suitable reservoir hosts

The presence of suitable reservoir hosts i.e. white tailed deer, white footed rats and chipmunks is important for tick survival and could result in increased Lyme disease cases *(5).* The Midwestern and Northeastern states are have a high deer population as well as a large acreage of both shrub lands and forests which increases survival of both small mammals and the deer *(27).* This could explain the high incidence of the disease in these areas.

CHAPTER 3. METHODOLOGY

3.1. Study areas

3.1.1. Uganda, Africa

Uganda is located on the East African plateau in Sub-Saharan Africa. It is bordered on the east by Kenya, on the north by South Sudan, on the west by the Democratic Republic of the Congo, on the southwest by Rwanda, and on the south by Tanzania. The southern part of the country includes a substantial portion of Lake Victoria, which is also bordered by Kenya and Tanzania.

3.1.2. North Dakota, Minnesota and Wisconsin: North America

North Dakota is the 19^{th} largest state in the U. S. It covers 69,000.80 square miles of land in mid-western United States. It is bordered by Canada in the north, South Dakota in the south, Minnesota in the east and Montana in the west *(70).* North Dakota has three geographic regions that include the Red river valley, composed of fertile farm land in the east; Drift Prairie, an area of hills, valleys and numerous lakes in the west; and the Great Plains east of the Missouri river in the southwest. By 2005, 1.6% of total land in North Dakota; 724,000 acres was covered by forests *(31).*

"Minnesota is the 12th largest state in the U. S. covering an area of 79,626 squares miles of land *(68).* The area is also endowed with stable grasslands and deciduous forests that provide a favorable ecosystem for the deer tick, deer, mouse and chipmunks which are important in the horizontal cycle of Lyme disease (*9; 66).* Minnesota is bordered by Canadian provinces of Ontario and Manitoba in the North, Michigan and Wisconsin in the East, Iowa in the South as well as both South Dakota and North Dakota in the West *(44).*

Wisconsin is the 23rd largest state in the US and covers 54,157.80 sq. miles of land *(69).* It is bordered by Minnesota and Michigan in the north, Illinois in the south, Lake Michigan in the east as well as Minnesota and Iowa in the west. Woodlands in the North-central part of Wisconsin and south of Lake Superior make up about one third of the total area of Wisconsin, which may provide a suitable habitat for reservoirs involved in Lyme epidemiology.

3.2. Data source and type

3.2.1. Data on foot-and-mouth disease

Retrospective data on FMD outbreaks in Ugandan livestock were obtained from the National Animal Disease Diagnostics and Epidemiology Centre (NADDEC), Ministry of Agriculture Animal Industry and Fisheries (MAAIF), Entebbe, Uganda. The data used were for a 10-year period (2001 - 2010) with the expectation that inferences based on these data would provide a snapshot of the current FMD disease situation in the country given that outbreaks occur every year. Also, FMD is a reportable disease in Uganda and as such all outbreaks of the disease must be reported to MAAIF immediately. The information obtained this way therefore reflects the disease situation in the country. The variables of interest included: “time” (year, month and day) and “place” (sub-county, district and region) where the outbreaks occurred; the districts reporting FMD outbreaks; livestock populations (obtained from the 2008 National livestock Census carried out jointly by the Uganda Bureau of Statistics (UBOS) and MAAIF *(72);* vaccine cost; vaccine quantities; vaccine serotypes of imported FMD vaccines; as well as vaccine distribution records.

All vaccines bought and distributed by MAAIF are entered into a stock ledger and these data provided information about FMD vaccine distribution in Uganda. The price list of Kenya Veterinary Vaccines Production Institute (KEVEVAPI) was used to obtain the cost of the imported FMD vaccines. Additionally, data from the serotyping of Ugandan FMD virus field isolates tested at the Pirbright World Reference Laboratory, Surrey, United Kingdom were obtained and compared to serotypes in the vaccines imported. Additional variables created included percentage of cattle vaccinated; time in weeks between outbreaks and vaccination onset (categories 1 = 1 week, 2 = 2 – 4 weeks, 3 = 5-12 weeks and 4 = > 12 weeks) and vaccine type (type 1 = bivalent vaccines, type 2 = trivalent / quadrivalent vaccines). The proportion of livestock vaccinated was calculated by dividing quantity of FMDV doses distributed to districts after reported FMD outbreaks by district livestock populations. Time of onset of vaccination was deduced from the dates when outbreaks were reported to the dates of vaccine distribution.

The response variable was Outbreak sum, which was computed as the number of additional outbreaks observed within each district. For descriptive purposes the study area was divided into 7 regions namely: Northern, Western, Eastern, Central, Southwestern, Northeastern and Northwestern *(8).*

3.2.2. Data on Lyme disease

Data of reported human Lyme disease cases from 1990 – 2011 was obtained from the North Dakota (ND), Minnesota (MN) and Wisconsin (WI) Departments of Health publically available data *(43; 44; 49; 50; 75).* The data from the departments of Health reflects diagnosed cases of human Lyme disease in the state since human Lyme disease is reportable in the U. S. Data of cases of Lyme disease diagnosed in animals from 2000 to 2012 at the North Dakota Veterinary Diagnostic Laboratory (VDL) was also obtained. Lyme disease in animals is not reportable in the United States. However, given the low risk of Lyme disease exposure in North Dakota and the fact that 95% of exposed dogs remain asymptomatic, the cases diagnosed at the VDL could be a representative sample of animal Lyme cases in ND *(15).* The VDL, used the

4DX serology kits that test for antibodies against *B. burgdorferi* throughout the study period. The data were entered in Microsoft excel spreadsheets 2010 to analyze disease trends in animals.

Average monthly temperatures and precipitation data from 1990 to 2011 were obtained from the U. S. department of Commerce, National climate Data Center and the National Oceanic and Atmosphere Administration (NOAA) publically available data *(53).* The data obtained included precipitation and temperature records from four metrological stations (Grand Forks, Williston, Fargo and Bismark) in ND; five metrological stations (Duluth, International falls, Rochester, Minneapolis and St. Cloud) in MN *(53);* and four metrological stations (Milwaukee, Madison, Green bay and La Crosse) in WI. The monthly data of each station were entered in to excel sheets. The average temperatures and precipitation per month per state was obtained by computing the mean of all the average monthly temperatures at each weather station.

The variables of both temperatures and precipitation throughout the year (January to December) were then categorized in seasons. The seasons included summer (June to August), fall (September to November), winter (December to February) and spring (March to May) to obtain seasonal variables. The variables used for data analysis included average spring, summer, fall and winter temperatures; total winter, summer, spring and fall precipitation and annual precipitation per state.

Data on land use in ND, MN and WI was obtained from the National Agricultural Statistics Service (NASS) of the United States department of Agriculture *(48).* This web-based service was created by NASS to monitor change in land use patterns in the U. S. *(12; 30*). The data was categorized and the area covered by each land use category in acres was computed in Microsoft excel and presented as line graphs. Human population data in WI, MN and ND was derived from the U. S. Department of commerce resident population records *(68, 69, 70, 71).*

The incidence of Lyme disease in 1990, 2000 and 2010 was calculated and plotted from the population data and reported human Lyme cases.

3.3. Data analysis

For the FMD case study, the data obtained was entered into Microsoft excel 2010 spread sheet and descriptive statistics generated. Additionally, a Negative Binomial Regression was performed using the GENMOG procedure of SAS using Outbreak sum as the outcome variable with all the other variables (region of occurrence, vaccine type, percentage of cattle vaccinated in outbreak districts and time from onset of outbreaks to response through vaccination) acting as independent variables. All variables were analyzed for their ability to influence occurrence of further FMD outbreaks using 2001 as the reference year.

A statistically significant variable implies that the variable was associated to the occurrence of FMD outbreaks that occurred after 2001, (2002 – 2010). A statistically insignificant variable showed that the variable was not associated to the occurrence of FMD outbreaks after 2001 during the study period. The proportion of cattle vaccinated, time between outbreaks and vaccination onset as well as the cost of FMDV vaccines were used to assess the effectiveness of vaccination programs in Uganda. Vaccine effectiveness was equated to FMD outbreak sum computed as the number of additional outbreaks observed within each district.

Data of Human Lyme cases as well as temperature and precipitation variables were analyzed with the multiple regression (REG procedure of SAS statistical program) to determine temperature and precipitation variables that are associated to the total number of Human Lyme cases per year (dependent variable) with the aim of using significant variables to predict Lyme cases. The temperature and precipitation variables analyzed included; annual precipitation, total winter, summer, fall and spring precipitation as well as spring, fall, winter and summer average temperatures.

3.4. Mapping of drivers of disease outbreaks

Data on FMD outbreak occurrence, FMD vaccine distribution and cattle populations in the various districts of Uganda were imported into Arc-GIS and maps of FMD outbreak occurrence in the country generated. The classes used for mapping the cattle population were in multiples of 50000. The first class (0 – 10000), was determined from the districts with the lowest cattle population, which were all less than 10,000 heads of cattle. The other classes were 10001-50000, 50001 – 150000 and 150001 – 300000, with class ranges of 50000, 100000 and 150000. The last class over 300000 was made to depict Uganda's cattle corridor with the highest number of cattle, mostly above 300000 heads per district.

The class ranges used (1-2, 3-5, 6-9 and 10-14) for mapping FMD outbreaks were in consecutive ranges of 2, 3, 4 and 5 and were based on the highest and lowest number of outbreaks per district with 14 as the maximum. For the FMD vaccine distribution mapping, the districts that received were divided in to 6 groups based on the number of vaccine doses received. The classes used for vaccine mapping were based on these six groups with the class limits based highest and lowest quantity of vaccine doses received by districts in each group. The classes were 1 - 4000, 4001 – 10000, 10001 – 14500, 14501 – 20000, 20001 – 50000 and 50001 – 1465050.

Data of animal Lyme cases was entered in to Arc-GIS to map Lyme cases. Precipitation records in mapping were obtained from the Natural Resources Conservation Service (NRCS), United States Department of Agriculture (USDA) website so as to relate animal Lyme disease occurrence to climate zones based on temperature and precipitation *(54).*

CHAPTER 4. RESULTS

4.1. Patterns of FMD outbreak occurrence and vaccine usage in Uganda (2001 – 2010)

The highest number of FMD outbreaks occurred in the Central region (34 %)) followed by Eastern (19%), Southwestern (17%), Northern (13%), Western (13%), Northeastern (3%) and Northwestern (1%). A total of 121 outbreaks were reported during the study period. The region statistically significantly influenced the occurrence of FMD outbreaks ($P<0.0001$) in the country with the majority of the outbreaks occurring in the central region comprising of Nakasongola / Luwero and Rakai districts (Figure 1).

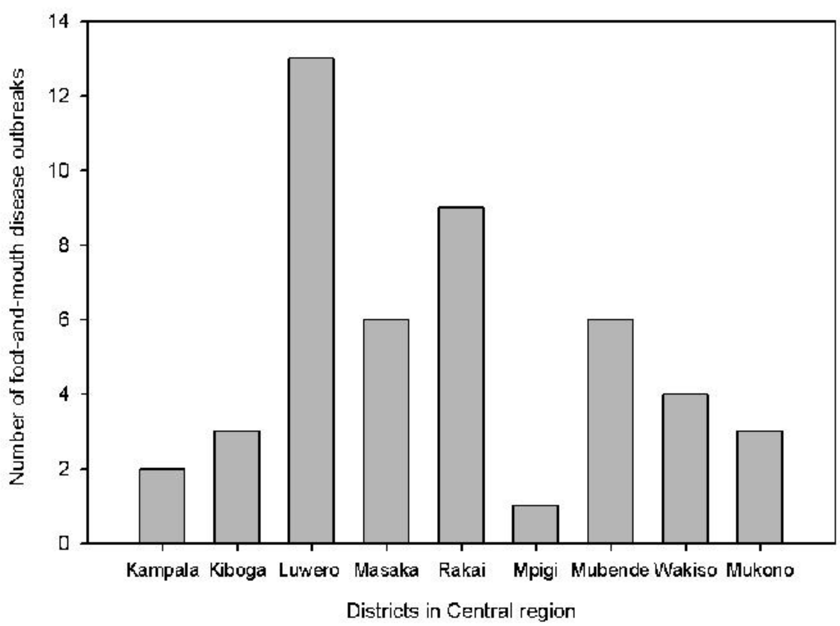


Figure 1: Number of foot-and-mouth disease outbreaks in districts within Uganda's central region from 2001 to 2010. Luwero and Mpigi received the highest (13) and lowest (1) number of FMD outbreaks, respectively, from 2001 – 2010. Data source: National Animal Disease Diagnostics and Epidemiology Center, Entebbe, Uganda.

The Central region received the highest percentage (43%) of FMDV vaccine doses followed by Southwestern (35%), Western (9%), Eastern (7%), Northern (3%), Private farms (2%), Northeastern (1%) and lastly Northwestern (0.3%). A total of 5,690,209 FMD vaccine doses were distributed throughout the study period. Generally, regions where high numbers of outbreaks occurred received the greatest quantities of FMD vaccine; for instance, majority of outbreaks (36%) as well as the greatest percentage of vaccine doses used (43%) occurred in the central region. However, a different trend was observed in the Eastern and Northern regions of Uganda where low percentages of FMD vaccine doses were distributed [7% (Eastern) and 3% (Northern)] despite high percentages of FMD outbreaks [18% (Eastern region) and 13% (Northern)].

The spatial pattern of FMD vaccine distribution during the study-period (2001-2010) was similar to that of FMD outbreaks and the cattle population in the different regions of Uganda. Additionally, the region was statistically significantly ($P < 0.0001$) related to occurrence of outbreaks as shown in Table 2. This is also shown in Figures 2, 3, and 4, the Southwestern (Mbarara) and Central regions (Nakasongola and Kiboga) which had the highest cattle population also reported the highest number of outbreaks and received the largest quantities of FMD vaccines during the study period. The exceptions were the northeastern region that had high cattle numbers but reported few outbreaks and likewise received low amounts of FMD vaccines, and the northern region which had a low cattle population but reported high numbers of FMD outbreaks and paradoxically received low quantities of FMD vaccine doses.

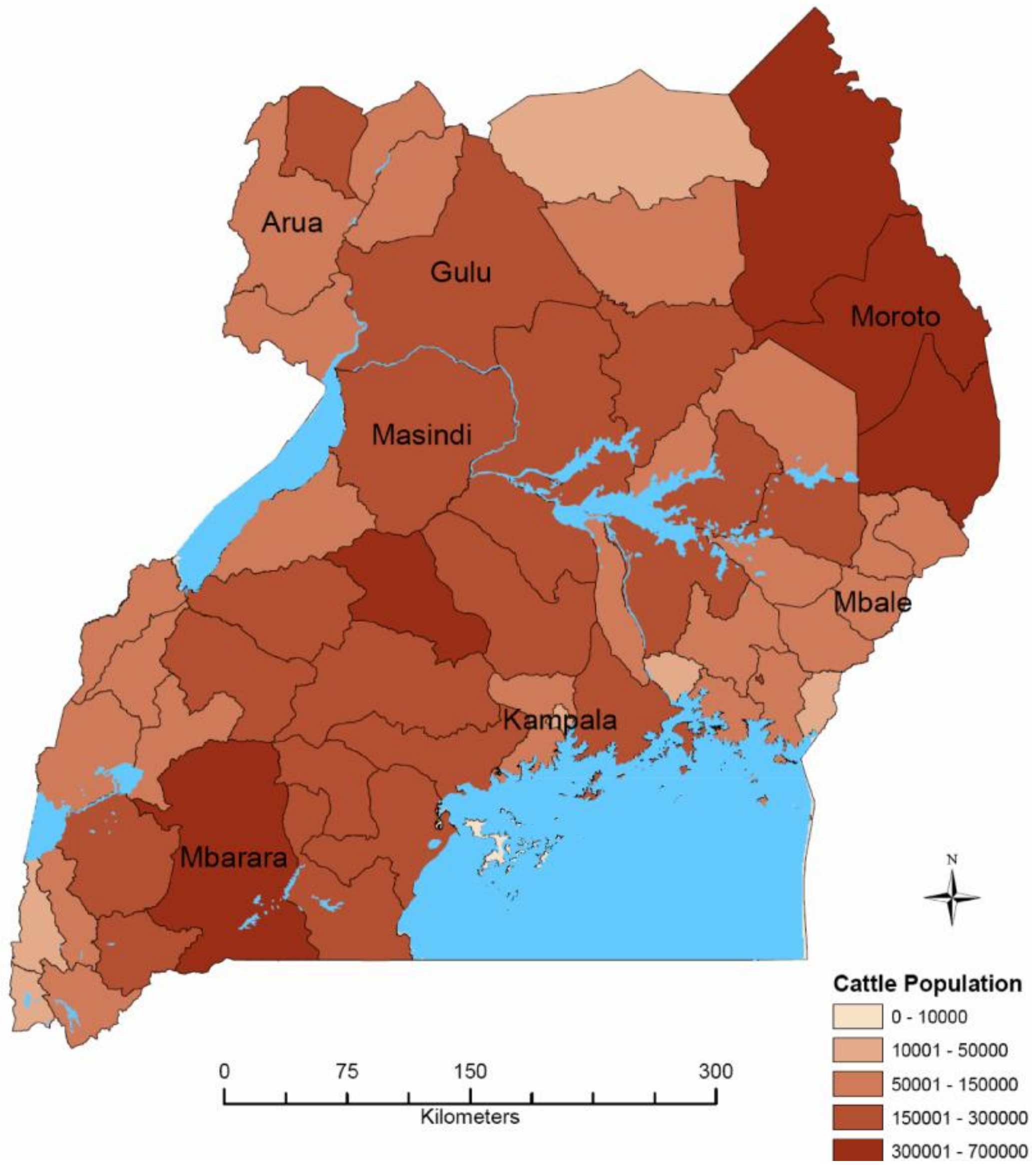


Figure 2: Cattle population in Uganda, 2008. Figure 2 is a map of Uganda showing cattle population in the different regions of Uganda based on the 2008 Uganda National Livestock Census. The increase in intensity of the brown shade corresponds with the cattle population size in districts within the regions. Areas with 0 – 10000 cattle represented with the least intense brown shade; areas with 10001- 50000, 50001 – 150000 and 150001 – 300000 cattle are shown with increasing intensity of brown with increase in cattle population; and areas with over 300,000 cattle shown with a dark brown shade. Data source: National Bureau of Statistics, Kampala, Uganda.

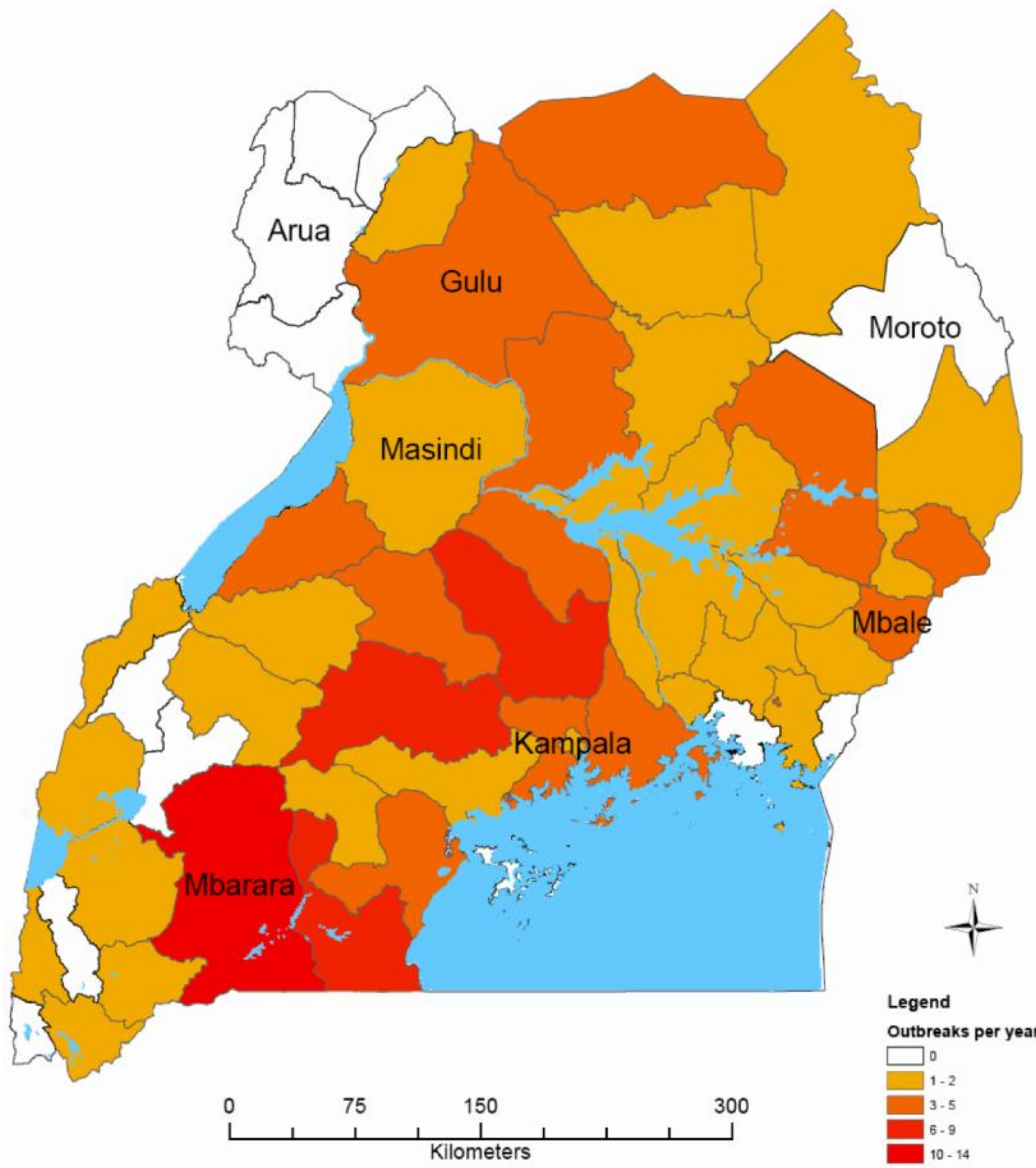


Figure 3: Foot-and-mouth disease outbreaks in Uganda, 2001 to 2010. Figure 3 is a map of Uganda showing the number of foot-and-mouth disease outbreaks that occurred in the different regions of Uganda from 2001 to 2010. Areas that reported no outbreaks are white and those that had outbreaks have red shades. The intensity of the red scale shade increases with number of FMD outbreaks from 1-2, 3-5 and 6-9 to 10-14. Data source: National Animal Disease and Diagnostics Center, Entebbe, Uganda.

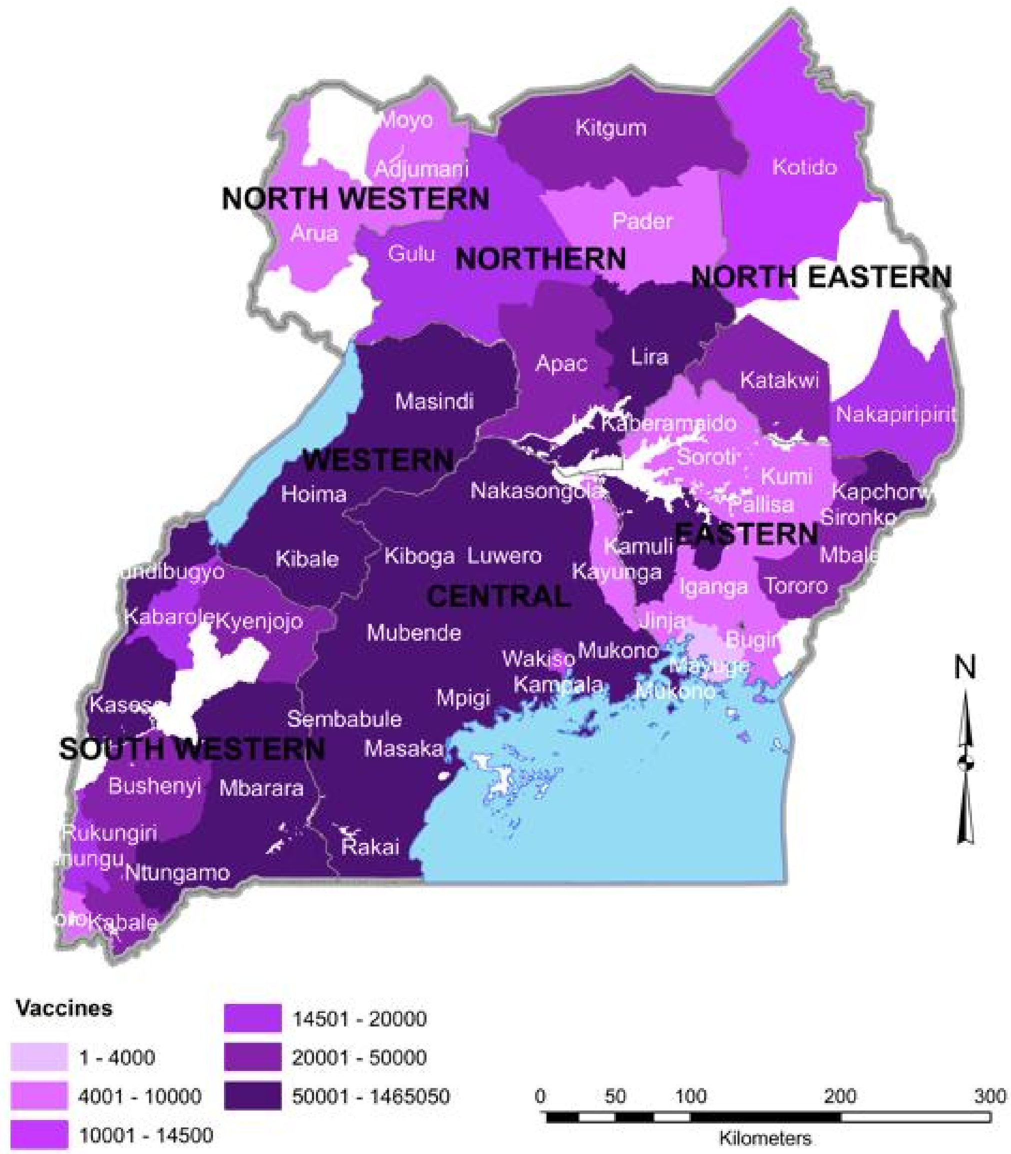


Figure 4: Foot-and-mouth disease virus vaccine distribution in Uganda, 2001 to 2010. Figure 4 is a map of Uganda showing the quantity of foot-and-mouth disease virus vaccines distributed to districts in the different regions of Uganda from 2001 to 2010. The size of the intensity of the color is directly proportional to the quantity of FMDV vaccines distributed and ranges from 1 - 4000, 4001 – 10000, 10001 – 14500, 14501 – 20000, 20001 – 50000, 50001 – 1465050 represented by the highest color intensity. Data source: National Animal Disease Diagnostics and Epidemiology Center, Entebbe, Uganda.

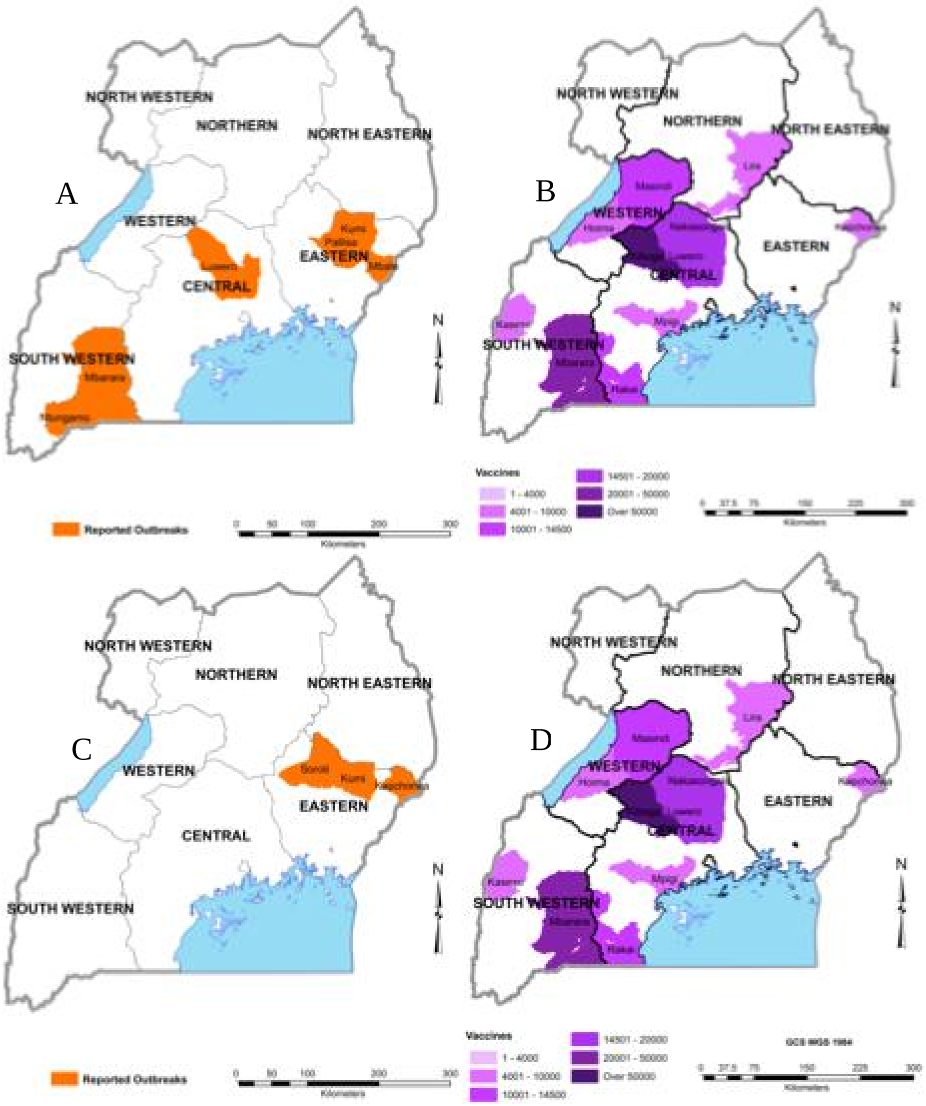


Figure 5: Maps of the spatial distribution of foot-and-mouth outbreaks and vaccine distribution for the years 2001(A & B), 2002 (C & D), 2003 (E & F), 2004 (G & H), 2005 (I & J), 2006 (K & L), 2007 (M & N), 2008 (O & P), 2009 (Q & R) and 2010 (S & T). The spatial distribution of vaccines (purple shade) follows the occurrence of foot-and-mouth disease outbreaks (orange shade), except in 2003 when the outbreaks in Northern and western Uganda were not responded to by vaccination. Data source: National Animal Disease Diagnostics and Epidemiology Center, Entebbe, Uganda.

Figure 5: (Continued)

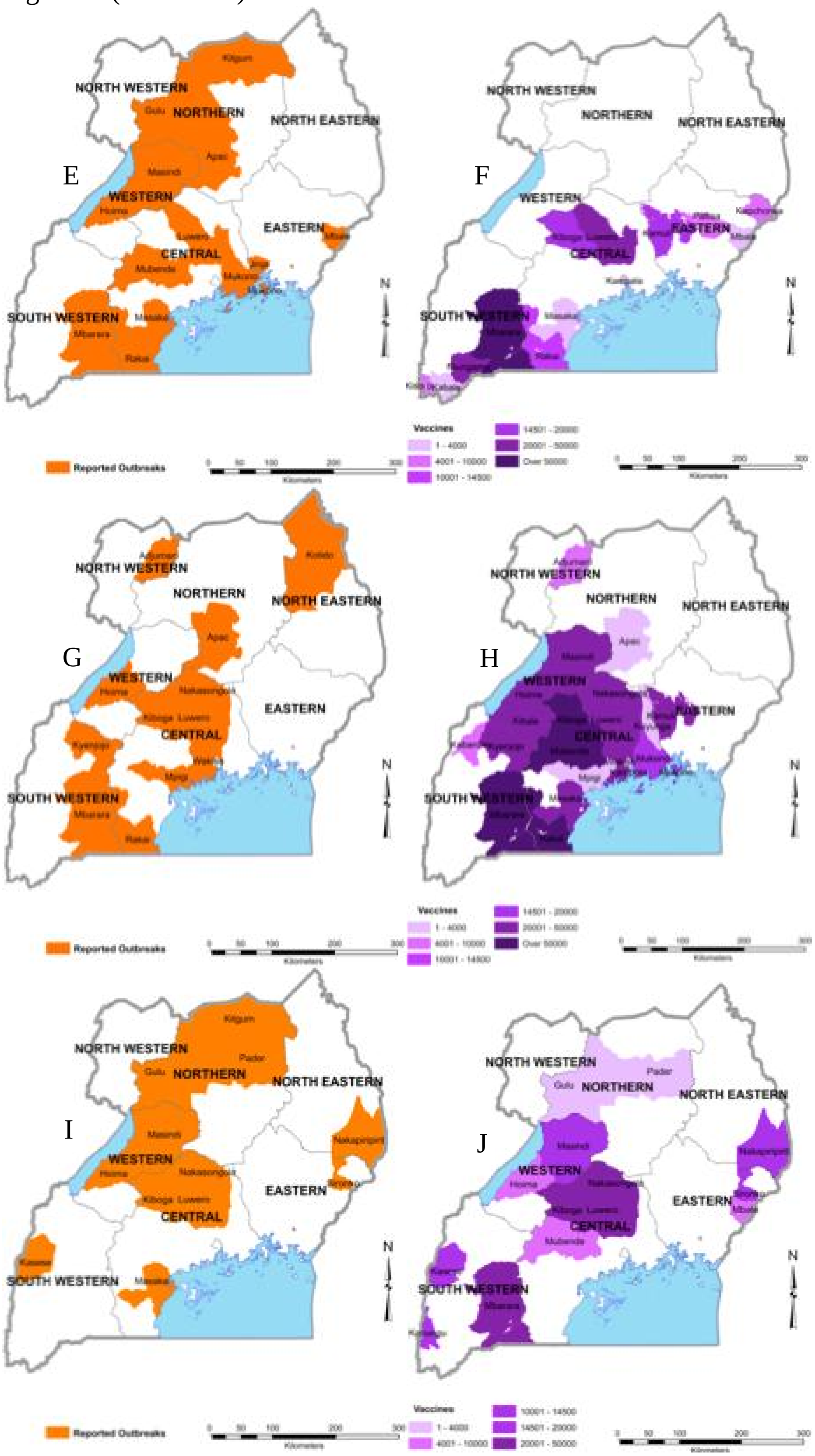


Figure 5: (Continued)

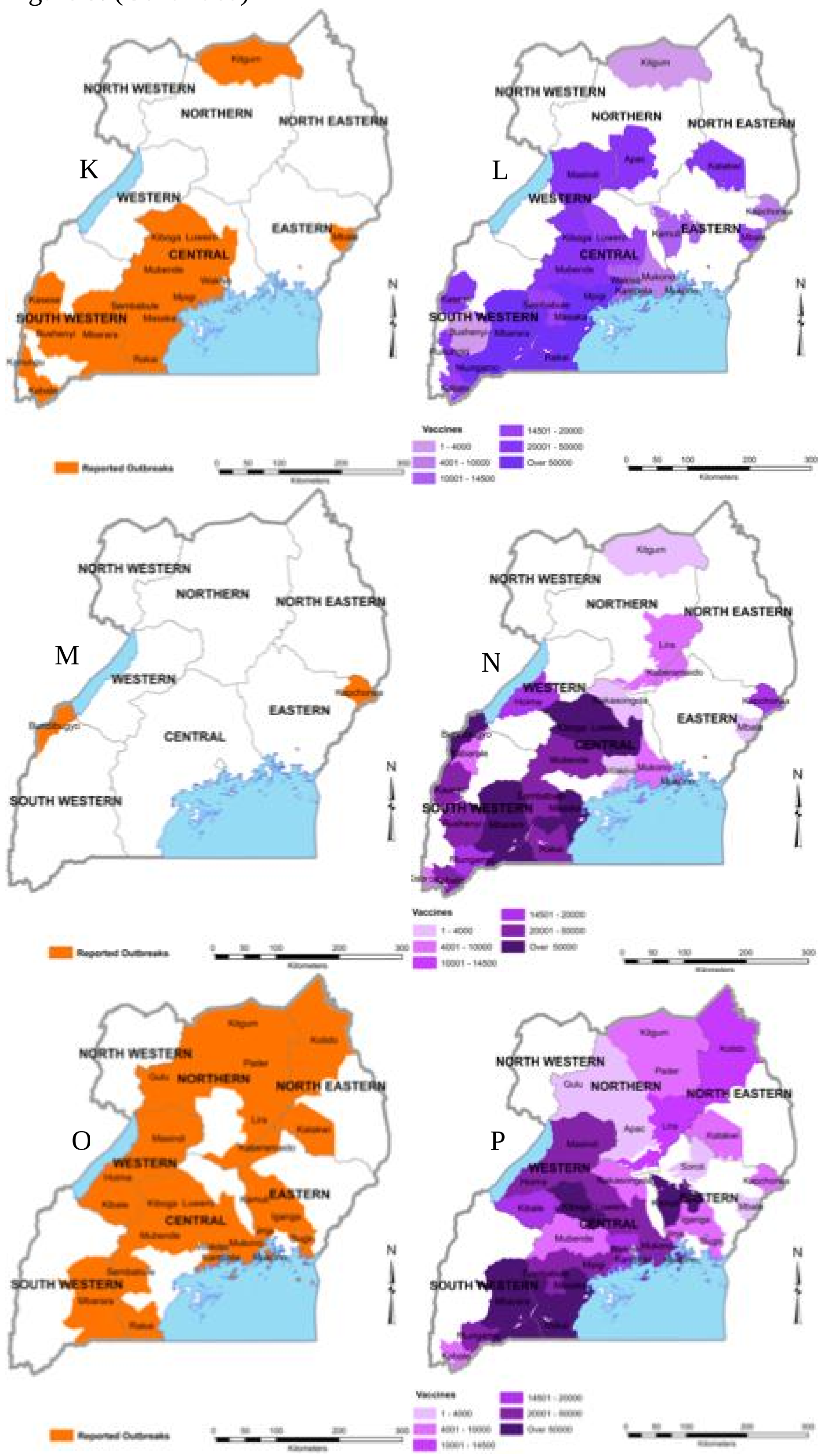
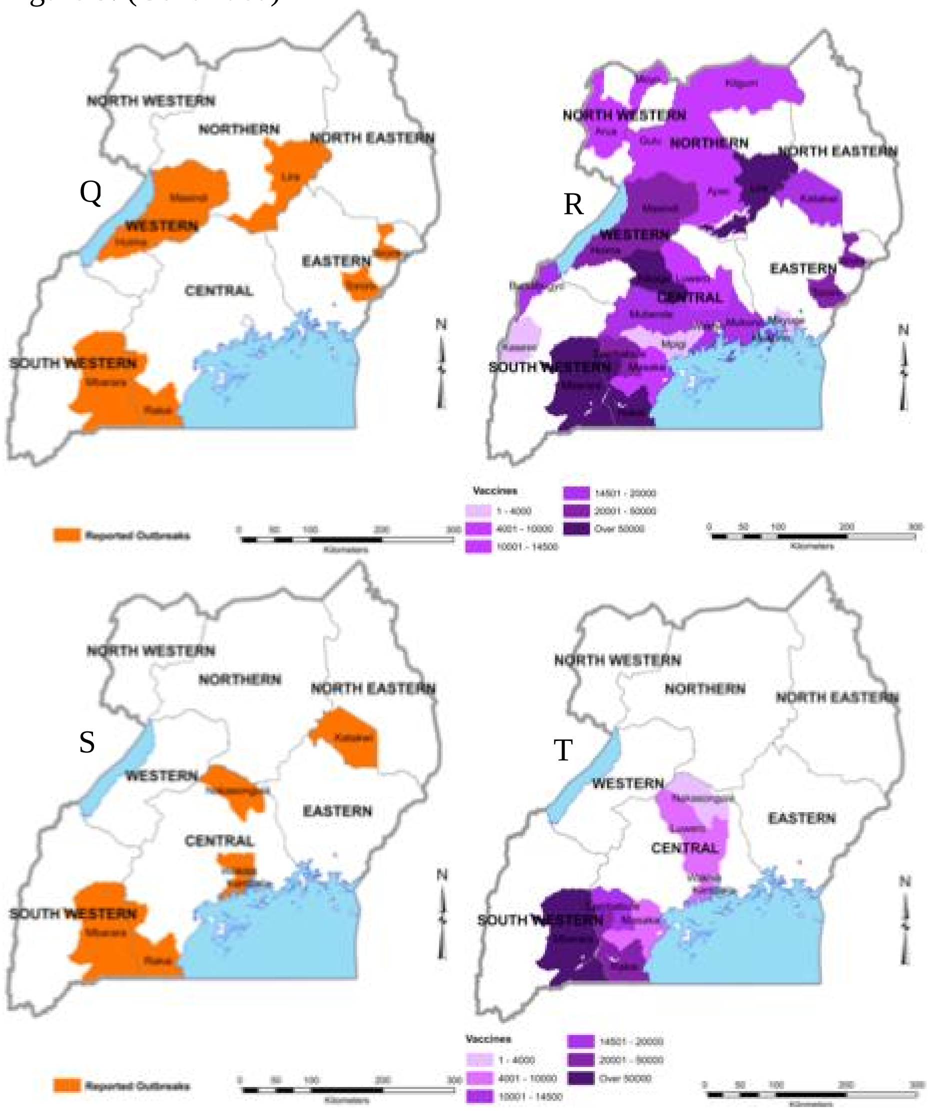


Figure 5: (Continued)



4.2. FMD control strategies and other factors driving the occurrence of FMD in Uganda

4.2.1. Proportion of cattle vaccinated during FMD outbreaks

All FMD vaccines distributed during the 10-year-study period were used for vaccinating cattle and there were no records of vaccine usage in other animals like sheep, goats and pigs. The proportion of cattle vaccinated per year in districts that reported outbreaks are shown in Figure 6, and ranged from 2.1% to 21.2%. These proportions of cattle vaccinated per district did not result in statistically significantly results when analyzed (P = 0.869).

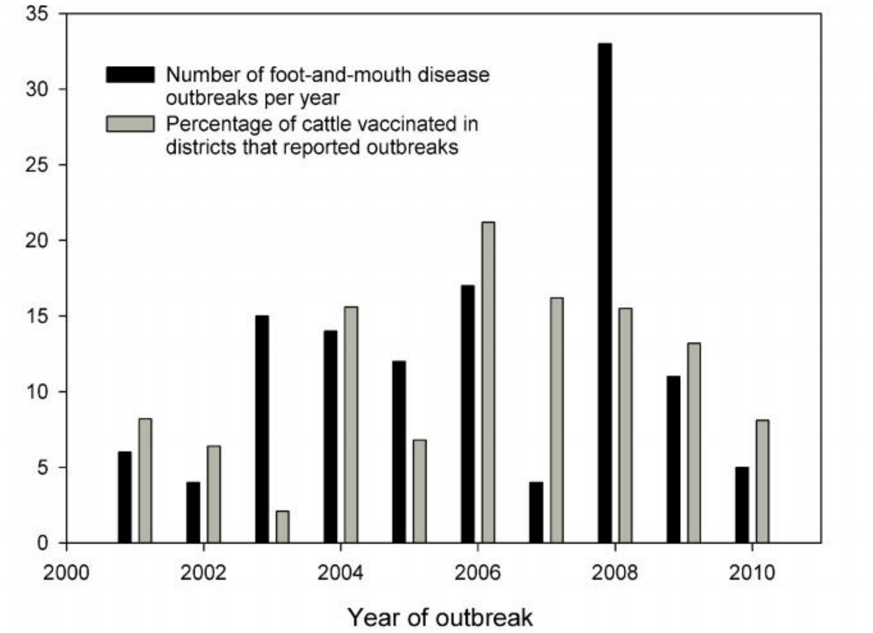


Figure 6: Number of foot-and-mouth disease outbreaks that occurred per year from 2001-2010 (represented by black bars) and the percentage of cattle vaccinated in districts that reported outbreaks (represented by grey bars). Data source: National Bureau of Statics, Kampala, Uganda and National Animal Disease Diagnostics and Epidemiology Center, Entebbe, Uganda.

4.2.2. Time taken to respond to FMD outbreaks through vaccination

The time from onset of FMD outbreaks to intervention or response through vaccination ranged from 1 to 40 weeks with an average of 7.5 weeks (Table 1). The time taken to respond to outbreaks through vaccination statistically significantly influenced occurrence of FMD outbreaks ($P<0.0001$) (Table 2)

Table 1**:** Districts that reported foot-and-mouth disease (FMD) outbreaks 2001- 2010

Year	**Districts where Foot-and-Mouth Disease outbreaks occurred**	**Serotype identified**	**Serotype of vaccine used**	**Time between outbreak and vaccination (weeks)**
2001	Mbarara, Ntungamo	_	O/SAT 1/SAT 2	**10**
	Luweero	_	O/SAT 1/SAT 2	**4**
	Pallisa, Mbale	_	O/SAT 1/SAT 2	**2**
	Kumi	_	No record	_
2002	**Soroti**	***A***	O/A/SAT 2	**40**
	Kapchora, Kumi	***SAT 2***	O/ SAT 1/SAT 2, O/A/SAT 2	**4**
2003	Hoima, Jinja, Mbale, Masaka, Rakai	***O***	O/ SAT 1/SAT 2	**18**
	Masindi, Kayunga, Mbarara, Apac	_	O/ SAT 1/SAT 2	**30**
	Kitgum, Gulu, Kibaale, Nakasongola, Luwero, Mubende	_	O/ SAT 1/ SAT 2	**9**
2004	Luwero, Rakai, Apac, Wakiso,	***O, SAT 2***	O/ SAT 1/ SAT 2	**1**
	Hoima, Kotido, Kiboga, Adjumani, Kyenjojo	_	O/ SAT 1/ SAT 2	**4**
	Rakai, Luwero, Nakasongola, Mubende, Mbarara	_	O/ SAT 1/ SAT 2	**8**
2005	Nakapiripit, Hoima, Masindi, Sironko	_	O/ SAT 1/ SAT 2	**20**
	Kitgum, Kasese, Gulu, Luwero	_	O/ SAT 1/ SAT 2	**4**
	Luwero, Pader, Nakasongola, Kiboga	_	O/ SAT 1/ SAT 2	**1**
2006	Manafa, Amuria, Kitgum, Isingiro, Masaka, Rakai, Mpigi	***O***	O/ SAT 1/ SAT 2	**1**
	Kasese, Mubende, Nakaseke, Bushenyi, Luwero, Kabale, Mityana, Wakiso	_	O/ SAT 1/ SAT 2	**2**
	Kanungu, Mityana, Sembabule	_	O/ SAT 1/ SAT 2	**1**

The table contains districts that reported outbreaks (column 2), the serotypes identified (column 3), the serotypes contained in the vaccines used (column 4) and the time taken to respond to outbreaks through vaccination (column 5). Serotyping done in 9/121 outbreaks, average time between outbreaks and onset of vaccination is 7.5weeks and ranged from 1 - 40 weeks.
Data source: National Animal Disease Diagnostics and Epidemiology Center, Entebbe, Uganda.

Table 1: (Continued)

Year	**Districts where Foot-and-Mouth Disease outbreaks occurred**	***Serotype identified***	Serotype of vaccine used	**Time between outbreak and vaccination (weeks)**
2007	**Bundibugyo**, **Sembabule**, **Bukwa**	***O, SAT 1, SAT 2***	O/ SAT 1/ SAT 2	**1**
2008	Isingiro, Masaka, Rakai, Kibaale, Bullisa	**_**	O/ SAT 1/ SAT 2	**1**
	Kiboga, Mityana, Sembabule, Jinja, Hoima	**_**	O/ SAT 1/ SAT 2	**1**
	Wakiso, Bugiri, Mbarara, Mukono, Kiruhura	**_**	O/ SAT 1/ SAT 2	**1**
	Kamuli, Luwero, Wakiso, Kaberamaido	**_**	O/ SAT 1/ SAT 2	**1**
	Amuria, Katakwi, Iganga, Lira, Amolatar	**_**	O/ SAT 1/ SAT 2	**1**
	Kitgum, Pader, Kayunga, Kampala	**_**	O/ SAT 1/ SAT 2	**1**
	Kotido, Oyam, Gulu	**_**	No record	**_**
2009	Apac, lira, Masindi, Tororo, Rakai, Dokolo,	**_**	O/ SAT 1/ SAT 2	**20**
	Isingiro, Buliisa, Sironko, Kiruhura, Hoima	**_**	O/ SAT 1/ SAT 2	**12**
2010	Isingiro, Katakwi, Nakasongola, Rakai	**_**	O/ SAT 1/ SAT 2	**4**

Table 2: Results of the negative binomial regression analysis of foot-and-mouth disease (FMD) vaccine and outbreak variables

Variables	**DF**	**F value**	**P-value**
Region	5	6.16	<0.0001
Time between outbreaks and vaccination onset	3	7.51	<0.0001
Vaccine type	1	0.01	0.9155
Percentage of cattle vaccinated	1	0	0.9885

The region where the FMD outbreaks occurred as well as the time taken to respond to outbreaks by vaccination was highly significant for the occurrence of additional outbreaks.

4.2.3. Cost of vaccines used per year (2001 – 2010)

The Cost of FMD vaccines imported during the study period ranged from $58,000 in 2003 to $1,088,820 in 2009 (Table 3). Generally the quantities of FMD vaccines imported increased with the increase in the number of FMD outbreaks except for the years 2003, 2005, 2007 and 2009.

Table 3: The quantity and cost of foot-and-mouth disease virus imported to control outbreaks, 2001 – 2010

Year	Vaccine doses distributed per year	Cost per dose of vaccines in United states dollars	Cost of vaccines in United states dollars	Total Cost of vaccines in United states dollars
2001	249500	1	249500	**249500**
2002	35500	1.2	42600	**210700**
	168100	1	168100	
2003	58000	1	58000	**58000**
2004	736300	1	736300	**736300**
2005	240100	1	240100	**240100**
2006	818400	1	818400	**1062400**
	305000	0.8	244000	
2007	920150	1	920150	**920150**
2008	655400	1	485250	**833170**
	434900	0.8	347920	
2009	7400	0.8	5920	**1088820**
	715577	1	1082900	
2010	183700	1	183700	**183700**

Data source: Kenya Veterinary Vaccine Production Institute, Kenya and National Animal Disease Diagnostics and Epidemiology Center, Entebbe, Uganda.

4.2.4. Comparison between field and vaccine FMD virus serotypes (2000 – 2010)

Serotyping was done for only nine out of the 121 (7.4%) FMD outbreaks serotypes which occurred in Uganda during the study period. Serotypes of FMD virus identified during the study period are shown in Table 1. From 2001 to 2010, 93% of the vaccines doses were of trivalent composition and included serotypes O/SAT1/SAT2; 0.5% contained serotypes A/O/SAT2, 0.7% was quadrivalent (O/A/SAT1/SAT2), and 5.7%were bivalent (O/SAT1). There was no statistical difference between the vaccine types used (P=0.8659) in regard to preventing FMD outbreaks.

4.2.5. Results of the negative binomial regression analysis of FMD outbreaks and vaccination variables

Results using the GENMOD procedure showed that the region and the time between occurrence of outbreaks and vaccination onset were highly significant for the occurrence of additional FMD outbreaks as shown in Table 2. The vaccine type and the percentage of cattle vaccinated were not significantly associated with occurrence of additional FMD outbreaks.

4.3. Distribution of human and animal Lyme disease cases in North Dakota, Minnesota and Wisconsin

4.3.1. Number of Human Lyme cases in North Dakota, Minnesota and Wisconsin

There has been a general increase in the number of human Lyme cases in all the three states: North Dakota (ND), Minnesota (MN) and Wisconsin (WI) from 1990 – 2010 as shown in figures 7, 8 and 9. In ND, the cases increased to above 5 in 2006 to reach a maximum of 33 cases in 2010; in MN, the cases increased to above 400 in 2000 to reach a maximum of 1293 cases in 2010; while in WI, the cases increased to above 1000 in 2002 to reach a maximum of 3508 cases in 2010.

The numbers of human Lyme cases in North Dakota ranged from 0 to 33 with a general increase in the number of cases from 7 in 2006 to 12 in 2007, 11 in 2008, 15 in 2009 and 33 in 2010 as shown in figure 7. The number of cases in Minnesota and Wisconsin ranged from 67 to 1293 and 329 to 3508, respectively, as shown in figure 8 and 9.

4.3.2. Distribution of Lyme cases diagnosed at the Veterinary Diagnostic Laboratory

Cases of animal Lyme disease diagnosed at the ND Veterinary Diagnostic Laboratory were from North Dakota, Minnesota and Wisconsin. A majority of the animals (69/78) that tested positive were dogs. The rest (9) were horses. Three horses tested positive of Lyme disease in 2000, 2 in 2001, 1 in 2002, 2 in 2003 and 1 in 2008. The cases came from Stusman, Cass and Ward counties as shown in Table 4. The number of positive Lyme cases per year ranged from 1 (2000, 2007) to 11 in (2008); see Table 5 for details. The spatial distribution of Lyme cases reported at the Veterinary Diagnostic Laboratory is shown in Figure 10 with the majority of cases occurring in dogs within Cass County.

Table 4: Positive cases of Lyme disease in horses diagnosed at the North Dakota Veterinary Diagnostic Laboratory, 2000 - 2012

Date	**State**	**County**	**Diagnostic Test used**
02/23/2000	ND	Stutsman	4DX
02/23/2000	ND	Stutsman	4DX
05/03/2000	ND	Cass	4DX
07/26/2001	ND	Cass	4DX
11/21/2001	ND	Cass	4DX
05/08/2002	ND	Cass	4DX
07/02/2003	ND	Ward	4DX
09/03/2003	ND	Ward	4DX
03/03/2008	ND	Cass	4DX

Data source: Veterinary Diagnostic Laboratory, North Dakota.

Table 5: Spatial distribution of dog and horse cases of Lyme disease reported at the Veterinary Diagnostic Laboratory.

State	**Counties**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**+**	**-**	***Total***
ND	Adams	_	_	_	_	_	_	_	_	_	_	_	_	_	**0**	2	*2*
ND	Barnes	2	1	_	_	1	_	_	_	_	_	_	_	1	**5**	12	*17*
ND	Bottineau	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	4	*4*
ND	Burke	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	1	*1*
ND	Burleigh	_	_	_	_	_	_	1	_	1	2	_	_	_	**4**	7	*11*
ND	Cass	2	3	1	_	_	_	_	_	3	2	4	2	2	**19**	74	*93*
ND	Cavalier	_	_	_	_	_	_	_	_	_	_	1	1	_	**3**	6	*9*
ND	Dickey	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	1	*1*
ND	Eddy	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	1	*1*
ND	Emmons	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	5	*5*
ND	Golden Valley	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	1	*1*
ND	Grand Folks	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	5	*5*
ND	Griggs	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	2	*2*
ND	Hettinger	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	1	*1*
ND	La Moure	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	6	*6*
ND	Morton	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	5	*5*
ND	Foster	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	2	*2*
ND	McIntosh	_	_	_	_	_	_	_	_	_	_	_	1		**1**	_	*1*
ND	McLean	_	_	_	_	_	_	_	1	_	_	_	_	_	**1**	2	*3*
ND	Mountrail	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	1	*1*
ND	Nelson	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	5	*5*
ND	Pembina	_	_	_	_	_	_	_	_	_	1	_	_	_	**1**	14	*15*
ND	Polk	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	2	*2*
ND	Ramsey	_	_	_	1	_	1	_	_	1	_	_	_	_	**3**	17	*20*
ND	Ransom	_	_	_	_	_	_	_	_	_	_	_	1	_	**1**	_	*1*
ND	Logan	_	_	_	_	_	_	_	_	_	_	_	_	_		1	*1*
ND	Richland	_	1	_	_	_	_	_	_	2			_	_	**3**	3	*6*
ND	Rolette	_	_	_	_	_	_	_	_	1		1	_	_	**2**	_	*2*
ND	Sargent	_	_	_	_	_	_	_	_	_	_	1	2	_	**3**	2	*5*
ND	Stark	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	2	*2*
ND	Steel	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	1	*1*
ND	Stutsman	2	_	_	_	_	_	_	_	_	_	_	_	_	**2**	9	*11*
ND	Towner	_	_	_	_	_	_	_	_	_	_	1	_		**1**	7	*8*
ND	Traill	_	_	_	_	_	_	_	_	_	_	1	_	_	**1**	3	*4*
ND	Unknown	_	_	_	_	_	_	_	_	_	_	2	_	_	**2**	_	*2*
ND	Walsh	_	_	_	_	_	_	_	_	_	2	_	1	_	**3**	12	*15*
ND	Ward	_	_	_	2	_	_	_	_	_	_	_	_	_	**2**	_	*2*
ND	Wells	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	1	*1*

ND- North Dakota, MN- Minnesota, WI- Wisconsin, (+) Positive cases, (-) Negative cases

Figure 5: (Continued)

State	**Counties**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**+**	**-**	**Total**
ND	Williams	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	1	*1*
	Subtotal	6	5	1	3	1	1	1	1	8	7	11	8	3	**57**	238	*295*
MN	Aitkin	_	_	_	_	_	1	_	_	_	_	_	_	_	**1**	_	*1*
MN	Becker	_	_	_	_	_	_	_	_	_	_	1	_	_	**2**	4	*6*
MN	Clay	_	1	1	_	_	_	_	_	3	1	1	_	_	**7**	14	*21*
MN	Crow Wing	_	_	_	_	_	_	_	_	_	_	_	_	_	**1**	_	*1*
MN	Habbard	_	_	_	_	_	_	_	_	_			_	_	**_**	1	*1*
MN	Kittson	_	_	_	_	_	_	_	_	_	1		_	_	**1**	4	*5*
MN	Lake Of The Woods	1	_	_	_	1	_	_	_	_	_	_	_	_	**2**	_	*2*
MN	Marshal	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	3	*3*
MN	Norman	_	_	_	_	_	_	_	_	_	_	_	_	_	**1**	4	*5*
MN	Otter Tail	2	_	_	_	_	_	_	_	_	_	_	_	_	**_**	7	*7*
MN	Pennington	_	_	_	_	_	_	_	_	_	1	_	_	_	**1**	6	*7*
MN	Roseau	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	14	*14*
MN	Nobles	_	_	_	_	_	_	_	_	_		_	_	_	**_**	10	*10*
MN	Wadena	2	_	_	_	_	_	_	_	_	_	_	_	_	**3**	2	*5*
MN	Wellkin	_	_	_	_	_	_	_	_	_	_	_	_	_	**_**	2	*2*
	Subtotal	5	1	1		1	1	_	_	3	3	2	_	_	**19**	56	*75*
WI	Unknown		_	_	_	_	_	1	_	_	_	1	_	_	**2**	2	*4*
Total no. of cases per year		11	6	2	3	2	2	2	1	11	10	14	8	3	**78**	296	*374*

4.4. Assessment of the influence of climate and environmental factors on the occurrence of Lyme disease in North Dakota, Minnesota and Wisconsin

4.4.1. Precipitation and human Lyme disease cases

During the study period (1990 – 2010), the total annual precipitation ranged from 13.72 – 25.44 inches in ND, 22.56 – 35.79 inches in MN and 26.81 – 39.60 inches in WI. Increase in total annual precipitation (P = 0.0250) was associated with increased numbers of Lyme disease cases with WI which had the highest total annual precipitation range reporting the highest number of cases of Lyme disease (329 to 3508) as shown in figures 7, 8 and 9.

Generally, the total summer, fall, winter and spring precipitation were higher in WI, followed by MN and lowest in ND. The total precipitation ranged from 4.31 – 16.01in (ND), 8.85 – 16.38 (MN) and 7.53 – 20.31in (WI) in summer; 1.72 – 8.29in (ND), 4.65 - 11.41in (MN), 4.53 – 12.14in (WI) in fall; 1.02 – 3.03in (ND), 1.25 – 3.93in (MN), 2.52 – 8.15in (WI) in winter; and 3.1- 7.54in (ND), 4.48 – 12.46in (MN), 5.91 – 14.58in (WI) in spring.

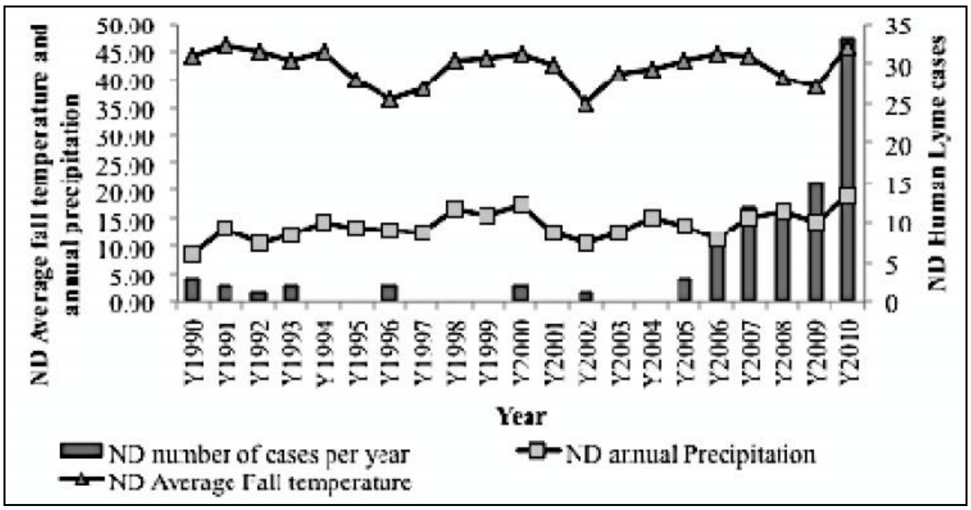


Figure 7: The variation in average fall temperatures and total annual precipitation with number of Human Lyme disease cases in North Dakota 2000 – 2010.

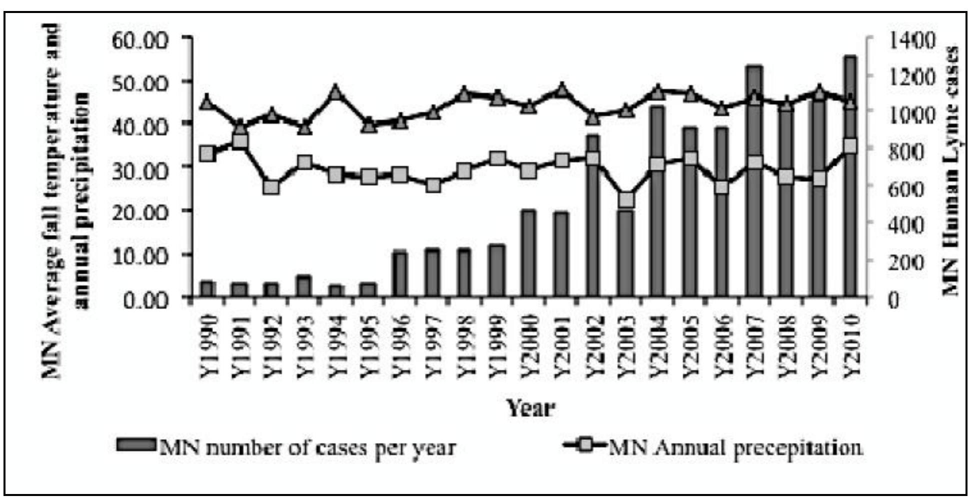


Figure 8: The variation in average fall temperatures and total annual precipitation with number of Human Lyme disease cases in Minnesota, 2000 – 2010

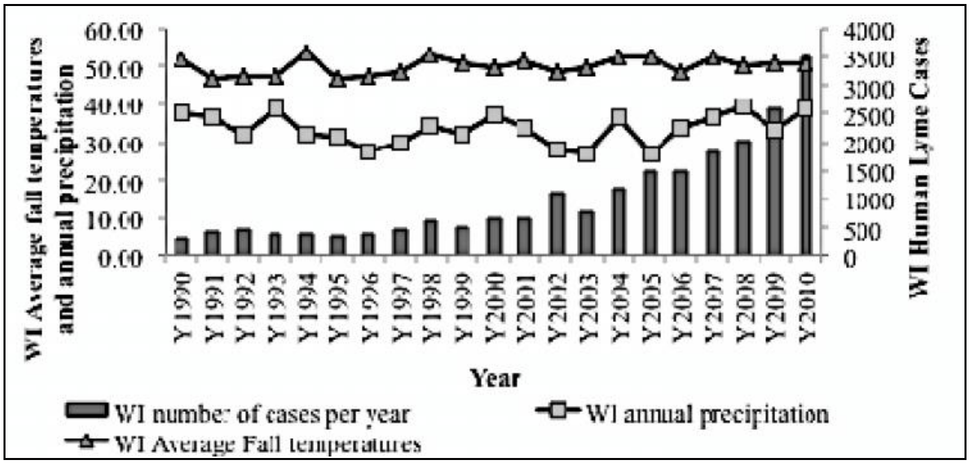


Figure 9: The variation in average fall temperatures and total annual precipitation with number of Human Lyme disease cases in Wisconsin, 2000 – 2010.

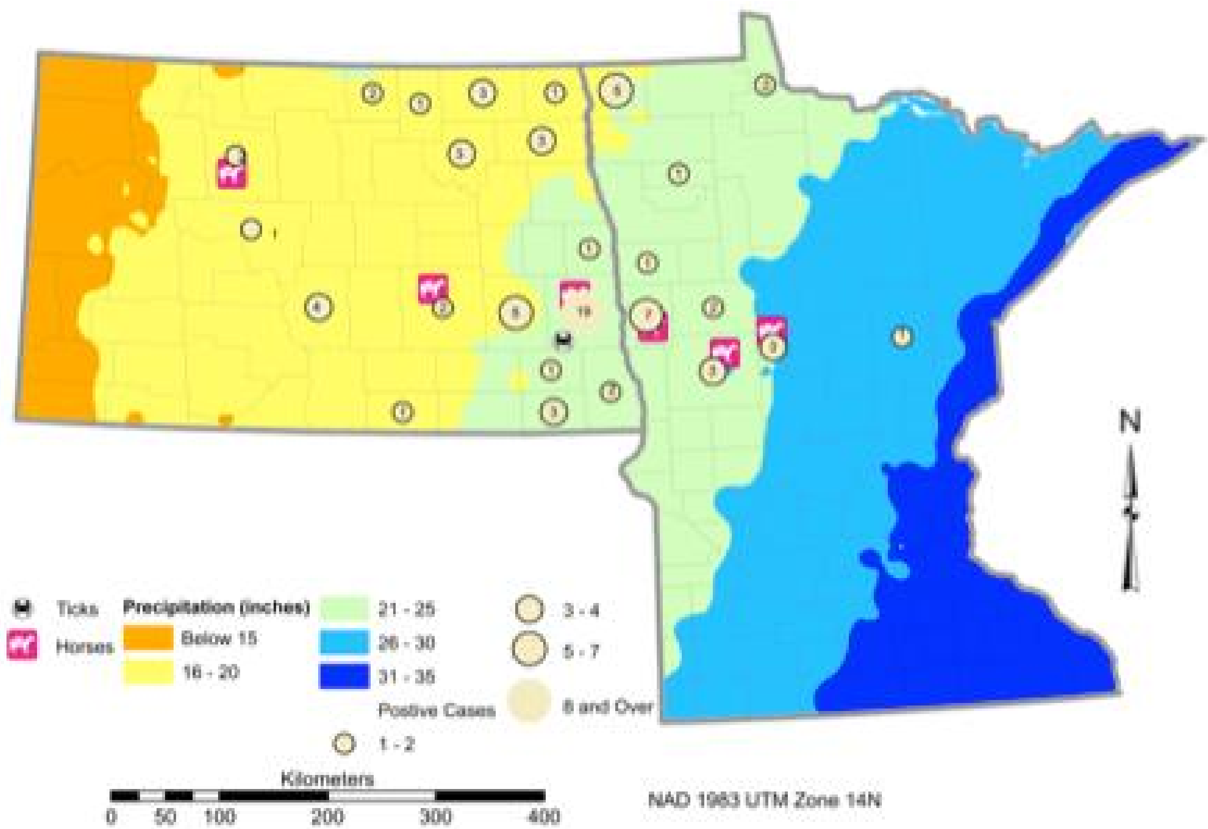


Figure 10: Spatial distribution of animal Lyme disease cases and diagnosed at the North Dakota Veterinary Diagnostic Laboratory from 2001 – 2012**.** Data source: Veterinary Diagnostic Laboratory, Fargo, North Dakota and Natural Resources Conservation Service, United States Department of Agriculture.

4.4.2. Seasonal temperatures and human Lyme disease cases

Generally, the mean monthly temperatures in summer, fall, winter and spring precipitation were highest in WI, followed by MN and lowest in ND. The mean temperatures ranged from 63.65 – 72.70 (ND), 63.15 – 72.70 (MN) and 65.71 – 74.19 (WI) in summer; 7.31 – 20.32 (ND), 9.36 – 22.06 (MN), 17.47 – 29.18 (WI) in winter; 39.15 – 47.04 (ND), 39.15 – 47.83 (MN), 2.52 – 8.15 (WI) in winter; and 35.48 – 45.93 (ND), 36.85 – 48.22 (MN), 41.50 – 50.34 (WI) in spring.   The average fall temperatures were significantly associated ($p = 0.0189$) with Lyme disease cases with a one degree rise in average fall temperatures resulting in a 62 rise in number of Lyme disease cases as shown in Table 7.

4.4.3. Land use in North Dakota, Minnesota and Wisconsin

The total land under forests has generally slightly increased in ND and decreased in MN and WI as shown in Figures 11, 12 and 13. There was a general increase in land covered by woody wetland in all the three states from 2007 – 2011 (Figures 11, 12 and 13).

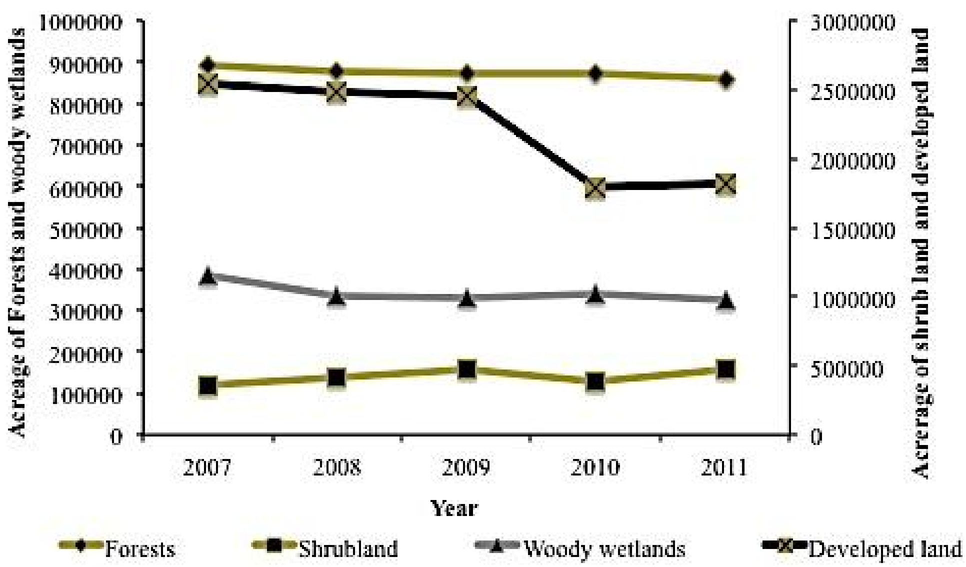


Figure 11: Land use pattern in North Dakota from 2006 – 2011. Shrubs and forest land use coverage has increased slightly while woody wetlands and developed land have decreased slightly.

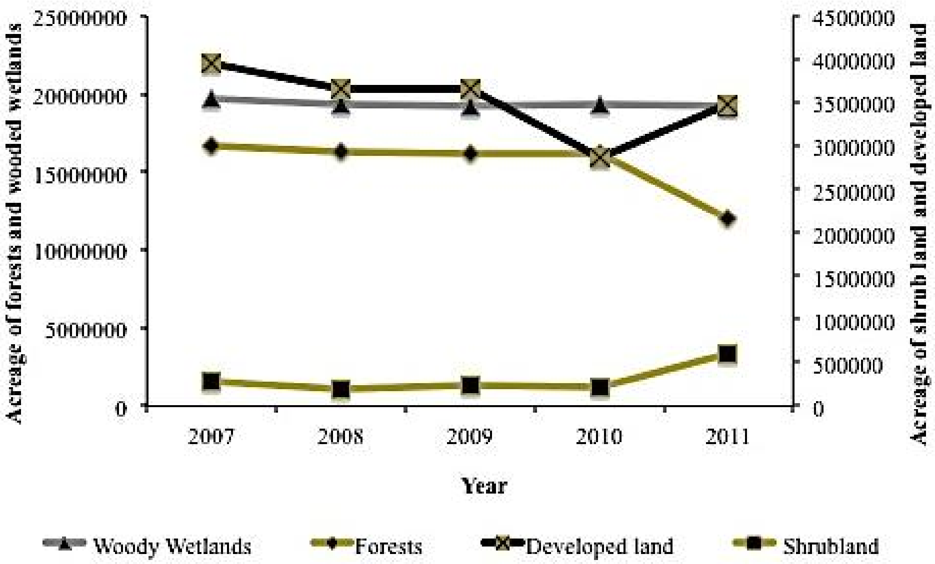


Figure 12: Land use patterns in Minnesota from 2006 - 2011. There is a general in both shrub land and woody wetlands from 2010 to 2011 and a decrease in forest and developed land from 2010 to 2011 and 2009 to 2010 and 2011 respectively as shown in the figure above.

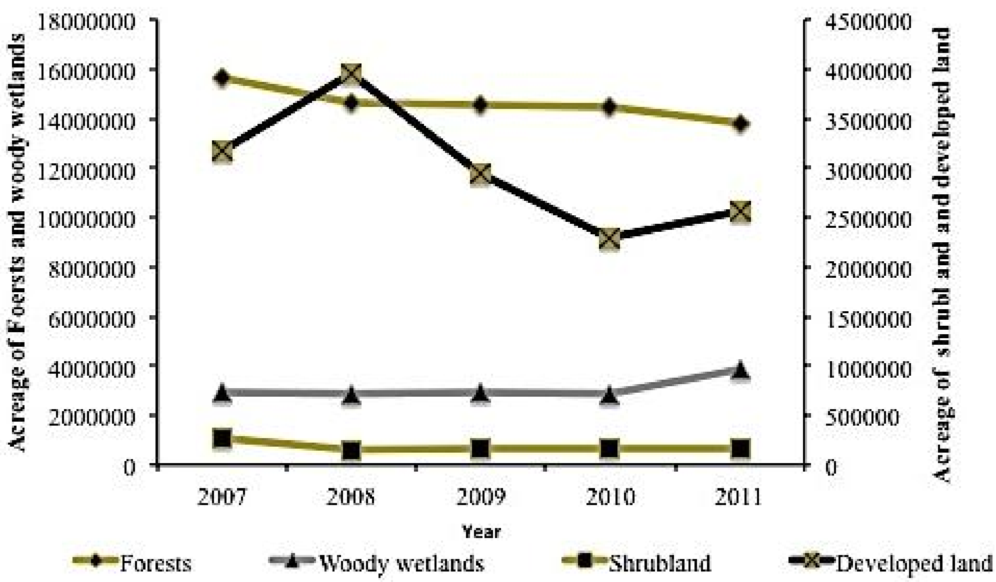


Figure 13: Land use patterns in Wisconsin from 2006 – 2011. Forestland coverage decreased from 2007 to 2011 while coverage decreased from 2008 to 2011. The area covered by shrub land generally remained constant from 2006 – 2011and woody wetland area increased slightly from 2006 to 2010 with a steep rise from 2010 to 2011.

The area covered by shrub land increased in ND to above 1000,000 acres while that in WI and MN fluctuated below 1000,000 acres. Forest land coverage ranged 500,000 – 1000,000 acres in ND, 12,000,000 – 16,000,000 acres in MN and from 13,500,000 – 16,000,000 acres in WI.

4.4.4. Variation of human population and number of human Lyme disease cases

There is a general increase in human population size as well as an increase in reported Lyme Borreliosis from 1990 to 2010 as shown in table 7. The incidence of Lyme disease in 1990, 2000 and 2010 was highest in Wisconsin and lowest in North Dakota as shown in Figure 13. There was a general increase in the incidence of Lyme disease in ND, MN and WI. However, there was a decrease in the incidence of Lyme disease in ND from 1990 to 2000 as shown in Figure 10.

Table 6: Human population and number of Lyme cases in North Dakota, Minnesota and Wisconsin in 1990, 2000, 2010

Year	North Dakota		Minnesota		Wisconsin	
	Human Population	Number of Lyme cases	Human population	Number of Lyme cases	Human population	Number of Lyme cases
1990	638200	3	4375099	94	4891769	329
2000	642200	2	4919479	465	5363675	658
2010	672591	33	5303925	1293	5686986	3508

Data sources: United States Census, 2010 and State Departments of Health of North Dakota, Minnesota and Wisconsin.

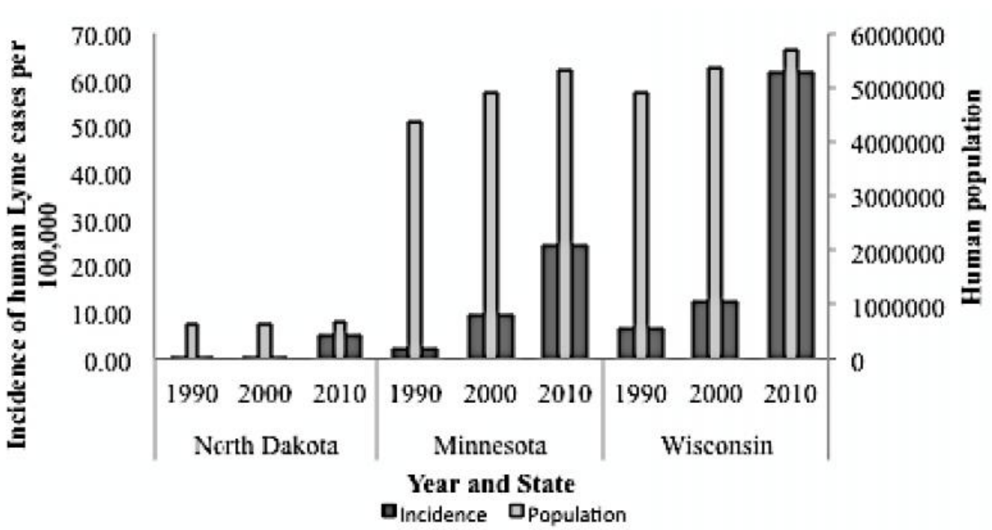


Figure 14: The incidence of Lyme disease and population size in North Dakota, Minnesota and Wisconsin in 1990, 2000 as well as 2010. Data sources: United States Census, 2010 and State Departments of Health of North Dakota, Minnesota and Wisconsin.

4.4.5. Results of the REG procedure statistical analysis of climate variable and number of human Lyme cases

Using 64 observations of average temperatures in winter, Spring, Fall and Summer; annual precipitation; as well as winter, summer, spring and fall total precipitation; a predictive model was generated using the REG procedure of SAS program. Analysis of variance showed that the model was highly significant for prediction of Lyme cases (P <0.0001, F value = 7.59 and DF = 10). Average fall temperatures (P = 0.0189, CI = 95%) and annual precipitation (P = 0.0250) were highly associated to the variation in the total Lyme cases reported per year as shown in Table 7. The model can be used to predict human Lyme disease in North Dakota, Minnesota and Wisconsin.

Table 7: Results of the REG procedure model for predicting Lyme cases

Variable	**DF**	**Estimate**	**Standard Error**	**t Value**	**Pr > |t|**
Average summer temperature	1	53.577	36.23	1.48	0.1451
Total summer precipitation	1	-33.501	42.77	-0.78	0.4370
Duration of Summer temperatures	1	30.642	93.84	0.33	0.7453
Annual precipitation	1	82.742	35.87	2.31	0.0250
Total Winter precipitation	1	-41.481	35.74	-1.16	0.2510
Average winter temperature	1	-11.258	14.38	-0.78	0.4371
Total spring precipitation	1	-104.04	64.73	-1.61	0.1139
Average spring temperature	1	-9.972	9.89	-1.01	0.3178
Total fall precipitation	1	-95.66	57.44	-1.67	0.1018
Average fall temperature	1	61.06	25.21	2.42	0.0189

Variation in annual precipitation and average fall temperatures (with grey shade) were associated with changes in the number of human Lyme disease cases per year 1990 – 2010 and may be used in prediction of Lyme disease occurrence.

CHAPTER 5. DISCUSSION

5.1. Factors driving the unsuccessful Foot-and-mouth disease control program in Uganda and associated outbreaks of the disease

The highest number of FMD outbreaks occurred in the Central region, followed by the Eastern and Southwestern regions. This concurs with Ayebazibwe et al. (2010a) who reported that the central, eastern and western regions had the highest number of FMD outbreaks. Additionally, the highest quantity of FMDV vaccine doses was distributed to the central region. Within the central region, many of the outbreaks occurred in Rakai, Luwero / Nakasongola and Mubende (Figure 1). This is because Rakai is located along the Uganda – Tanzania boarder where there is frequent and uncontrolled movement of cattle along the border, which predisposes cattle to diseases including FMD *(8)*.

The livestock disease control strategies in Tanzania are not as stringent as compared to Kenya and Rwanda, where border movement of livestock is strictly controlled *(8).* Thus livestock that cross the Tanzania border stand greater risk of contracting contagious livestock diseases compared to those at the Kenya and Rwanda border. However, uncontrolled movement of cattle across all Ugandan borders pose a risk to the control of livestock diseases especially FMD. It is therefore crucial that regional livestock disease control standards are set and followed by all countries in the East African region including Southern Sudan and the Democratic Republic of Congo.

Similarly, the eastern region has a communal grazing system coupled to its proximity to the Kenyan boarder where animal movements across the border are rampant *(8).* It is likely that introduction of animals with FMD may be responsible for the high number of FMD outbreaks

(19 %) *(8).* Thus communal grazing and movement of cattle across the Kenyan border, which involve interaction of cattle herds from different locations, increase the risk of disease spread.

Additionally, several sub-counties of Luwero, Nakagongola and Mubende suffer long periods of drought that are usually accompanied with animal movements and loss of condition that predisposes animals to FMD *(8).* Furthermore, Mubende, Luwero and Nakasongola are popular for livestock trade especially towards the dry season when farmers anticipate cattle losses due to scarcity of pastures and water. Livestock from different sub-counties and neighboring districts are brought to a market place which increases the risk of disease spread may possibly be an additional explanation to the high number of FMD outbreaks in the districts. All the above show how seasonal variation in the availability of pastures and water and uncontrolled cattle movements influence the occurrence of FMD.

However, Eastern region received less FMDV vaccine doses (7%) than other regions where fewer outbreaks occurred. For example, Southwestern region received 35 per cent of the vaccine doses distributed although it reported fewer outbreaks (17%). This is because the communal grazing in the Eastern region may have frustrated government control strategies *(67).* In communal grazing, cattle are moved to a grazing land that has pastures throughout the year especially during the dry season. This practice may hinder disease control efforts like vaccination because it makes it hard to trace animal owners who most of the times leave the animals to herdsmen. Vaccination of livestock requires the owner’s consent and since most FMD outbreaks occur in the dry season when communal grazing is practiced, fewer animals were vaccinated.

Additionally, herd sizes are larger in the Western region than in the Eastern region. In the Western region the cattle herd size owned per farmer is large while those in Eastern region the herds are smaller possibly due to seasonal scarcity of water and pastures. Thus the farmer perceived risk is bigger in Western than Eastern region. This could probably result in a higher farmer participation in livestock disease control programs like FMD vaccination in the Western rather than the Eastern region.

The Southwestern region had lower numbers of FMD outbreaks than the Eastern and Central regions possibly due to the paddock grazing system practiced by the majority of farmers. The high quantities of FMDV vaccines (35%) distributed to the Southwestern region may indicate pre-outbreak FMD vaccination probably done when outbreaks had been reported in other regions. The Northwestern region had the lowest number of FMD outbreaks possibly due to the low cattle population and the natural barrier provided by the River Nile, which limits cattle movement in to the region thus reducing chances of FMD transmission.

The spatial pattern of FMDV vaccine distribution during the study period was similar to that of outbreaks and cattle population (Figures 2 -5) probably due to the governments “fire brigade” response of vaccinating cattle against FMD after outbreaks are reported. The trend was different in the northern and northeastern regions. The high number of FMD outbreaks with limited vaccination in the northern region may have been due to the Lord’s resistance army rebellion that caused insecurity *(67)* in the area thus hindering vaccination exercises.

The few outbreaks reported in Northeastern Uganda despite its high cattle population may possibly be due to under-reporting of FMD outbreaks. The Northeastern region, also known as Karamoja region, has inadequate veterinary services. The transhumance way of life of the Karamojong has contributed to their reliance on traditional ethno-veterinary knowledge to treat and prevent livestock diseases *(28).* Thus it is likely that most outbreaks were not reported to the veterinarian at the districts as most pastoralists may have resorted to their local ethno-veterinary knowledge to treat symptoms of FMD. All the above explain how regional differences in livestock production systems, some of which are climate driven, significantly influenced the occurrence of additional FMD outbreaks within the study period.

The proportions of cattle vaccinated (2.1% to 21.2%) after outbreaks were not statistically significant for the occurrence of subsequent FMD outbreaks. Vaccination programs are effective when a large proportion of the population is protected: usually at least 72% of the susceptible cattle need to be vaccinated *(35).* Therefore vaccination of cattle below the recommended levels (2.1% – 21.2%) may not have any impact on the occurrence of the disease since no herd immunity is developed. This explains why the percentage of cattle vaccinated was not statistically significant (P = 0.9885). Limited ring vaccination could also be responsible for outbreaks occurring within three months after previous outbreak because unvaccinated animals may be sources of subsequent infections *(35).* Herd immunity results when protective antibody levels have developed in 80-85% of the susceptible animals *(7)*. The low proportion of cattle vaccinated after FMD outbreaks thus reduces the effectiveness of post-outbreak FMD vaccination.

No records were available about FMDV vaccine distributed for pigs and small ruminants. This agrees with Balinda et al., (2009) who noticed that control of foot-and-mouth disease involves vaccination of cattle in affected area leaving out small ruminants and pigs. Small ruminants and may be responsible for the maintenance of FMDV on farms since cattle, sheep and pigs are most of the times reared together *(40).* This may play a major role in the epidemiology of foot-and-mouth disease. FMD vaccination programs should therefore include pigs and small ruminants.

The time between FMD outbreaks and onset of vaccination ranged from 1week to 40 weeks. The average time for onset of vaccination after reported FMD outbreaks was 7.5 weeks which, according to Chowell et al. (2005) is too high for effective post-outbreak vaccination. Chowell et al. (2005) noticed that the time required for effective post-outbreak vaccination is brief starting at day five for high potency vaccines and day twelve for regular vaccines. He further reported that only marginal reductions in FMD cases could be achieved if vaccination is done after the fifteenth day in to the outbreak *(18)*. Thus time taken to respond to outbreaks through vaccination is highly significant for the effectiveness of FMD control. Most animals should therefore be vaccinated before the fifteenth day of the outbreak.

The cost of FMDV vaccines used ($58,000 - $1,088,820) is high. This may hinder FMD control efforts given the small sized budgets that Uganda and other developing countries operate with. The expenditure of $58,000 per year on FMD alone could result in limited control for other diseases and may eventually hinder animal disease control programs, which require higher budgets that Uganda and other developing countries may not afford.

Importation of FMDV vaccines delays the onset of vaccination activities. This is evidenced by the general delay in onset of vaccination in districts that reported outbreaks from 2001 – 2010 as shown in table 1 since vaccines used to control FMD in Uganda are imported from Kenya. This delays control efforts since these vaccines take at least a week to be transported to Uganda. This limited time does not allow any serotyping to be done and may probably result in the importation of serotypes/subtypes that are different from those causing outbreaks. Additionally, because of the occurrence of multiple outbreaks every year as described in table 1, it is possible that FMDV vaccines run out of stock and must be ordered from other countries resulting in delayed response as well as FMD spread to unprotected herds. Outbreaks should therefore be responded to in the shortest time possible to reduce the risk of spread of FMD *(76).*

Furthermore, the possibility of inadequate temperature conditions during delivery, storage and transportation of vaccines to the field cannot be ruled out. The above possible irregularities underscore the importance of local FMDV vaccine development and manufacture particularly with the recent increase in the number of public-private partnerships and inter-governmental organizations investing in biotechnology especially animal disease diagnostics and vaccine production *(23)*. A good example is the newly established Uganda Industrial Research Institute (UIRI), a public-private partnership making Newcastle vaccines *(66).*

Serotyping was done for only 9 of the 121 outbreaks that occurred during the study period. This was possibly due to lack of infrastructure and personnel to identify the serotype of FMDV in samples *(11).* Because Uganda lacks such infrastructure, the samples were transported to reference laboratories i.e. the World Reference Laboratory, Pirbright, United Kingdom *(11).* This involves significant costs of transportation and the samples have to be collected and stored under appropriate conditions until they are submitted to the reference laboratories *(11).* This is difficult due to the high ambient temperatures and the distances from the points of collection to the national laboratory *(11).* It is therefore crucial that laboratory facilities and personnel be established to carry out regular serotyping of FMDV causing outbreaks *(34).*

Multivalent FMDV vaccines were used to control outbreaks during the study period with 93% of which contained O/SAT1/SAT2. This was done to cover all the possible serotypes that are likely to occur in field situations given the limitations of FMDV serotyping in Uganda. Since all vaccines were multivalent the type of vaccine used had no statistically significant ($P = 0.9155$) influence on occurrence of FMD outbreaks of additional outbreaks. However, outbreaks occurred annually despite the rigorous vaccination efforts. This may be due to a mismatch in field and vaccine sub-serotypes and variants given the wide genetic variation of the virus *(40).* This wide genetic heterogeneity presents the greatest obstacle to control efforts by vaccination *(40).*

Additionally, vaccine potency tests should be done to determine the effectiveness of vaccines used. Uganda's endemic status of FMD affects its gross domestic product and leads to loss of revenue from the sale of animals and animal products to FMD free countries *(60).* It is therefore important that regular virus typing, vaccine matching and monitoring of antibodies in vaccinated populations be undertaken for creation of FMD-free zones as well as a basis for vaccine manufacture *(50).*

The long time for onset of vaccination after FMD outbreaks (7.5 weeks), the low proportion vaccinated cattle (10%) in affected districts and unsettled grazing systems may contribute to the endemicity of FMD in Uganda. Although multivalent FMD vaccines were used, the vaccine and field virus subtypes and variants may not be homologous underscoring the need for regular virus typing, vaccine matching and monitoring of antibody production in vaccinated cattle as a basis for creation of disease free zones as well as vaccine manufacture.

5.2. Distribution of Lyme disease cases and influence of climate and environmental factors on the occurrence of the disease in North Dakota, Minnesota and Wisconsin

The low number of Lyme cases reported before 2006, 2000 and 2002 in ND, MN and WI respectively could have been due to fewer diagnostic methods and limited knowledge about the disease among the public and health workers. The Center for Disease Control and Prevention (CDC) recommended the two-way test endorsed at the second national conference on the diagnosis of Lyme disease in 1995. The two way test involves an enzyme immunoassay or indirect immunofluorescence assay as the first step followed by an immune-blot assay, the commonest being the western blot assay. The second step cannot be used if the first assay is negative *(14; 16; 17)*. This recommendation by CDC could have led to an increase in the diagnosis of Lyme disease.

Additionally, the low number of Lyme cases before the year 2000, could also have resulted from increased immunity of the population due to vaccination. A Lyme disease vaccine is reported to have been used between 1994 and 2002 *(66).* Another human Lyme disease vaccine was licensed by the Food and Drug Administration (FDA) on 21st December 1998 and may have helped in the reduction of the number of Lyme cases *(52).*

Vaccination was found to be the only strategy that can empirically prevent Lyme disease *(32).* Many of the other prevention strategies which include: sensitization of the public on how Lyme is transmitted, use of repellants, dressing in protective clothes as well as checking themselves for ticks, have not been demonstrated to be conclusively effective in prevention of Lyme disease even though they are inexpensive and unlikely to cause any harm when used *(32).* Additionally, although Lyme disease is said to be rarely fatal, it has been reported that 10–20 per cent of exposed individuals who show no erythema migrans and ignore the disease and seek no treatment, end up with neurologic signs or joint arthritis *(32).*

The vaccine was too expensive in the public's perception and the requirement to repeat immunization every year coupled to the effectiveness of antibiotics in the treatment of Lyme disease further dampened vaccination as a prevention strategy *(32).* Individuals treated early with antibiotics like Amoxycillin and doxycycline have an excellent response and recovery *(32).* Thus many individuals resorted to antibiotic therapy instead of vaccination.

The higher number of cases in WI (329 – 3508) and MN (67 – 1293) compared to ND due to the woodland ecosystem and high deer population that favor survival of ticks (*I. scapularis*) that transmits Lyme disease *(39).* The Mid-Western States (Wisconsin, Minnesota and Michigan are known to report the second highest bulk of human Lyme cases in the U.S. after the North Eastern States of Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New Yolk, Pennsylvania, Rhode Island and Vermont *(33).*

On the other hand, *I. scapularis* ticks were for a long known not to exist in ND. Many of the cases that occurred were thought to be resulting from out-of-state exposure since Lyme disease cases are reported basing on place of residence rather than the areas in which individuals get exposed *(33).* Thus, the low numbers of Lyme cases (less than 5 per year) from 1990 to 2005 are probably a result of out-of-state exposure to *I. scapularis* or other ticks that transmit Lyme disease.

Surprisingly, the number of cases of Lyme Borreliosis in ND increased drastically from 7 cases in from 2006 to 33 in 2010 as shown in Figure 6. This is most likely due to invasion of parts of ND by *Ixodes scapularis* ticks. A statewide survey done by the University of North Dakota and The ND department of health in 2010 discovered ticks in 6 counties of Pembina, Ramsey, Steele, Grand Forks, Eddy and Rolette *(51).* Additionally, many reports showed an increase in woodland habitat coverage within ND by 2008 *(29).* This woodland habitat and the wild rodents it shelters as well as the wet soil moisture along the Red River and Missouri River could have favored the colonization of some areas of ND by *I. scapularis* ticks. Because of the drastic increase in the number of cases after 2006, It is very likely that these ticks could have colonized counties near the Minnesota boarder much earlier than 2010 when the statewide tick survey was carried out.

The ND Veterinary Diagnostic Laboratory receives cases from ND, MN and WI, and given the low incidence of cases Lyme disease in ND as well as the short lifetime of the diagnostic kits (1 year). It is most likely that most clinicians will prefer to use either clinical signs / history of exposure or refer the cases to the diagnostic laboratories thus making Lyme disease surveillance in places of low case burden like ND challenging.

Although, it is impractical to make inferences about Lyme disease incidence rates in animals from the cases reported at the VDL because the disease is not a reportable disease, the distribution of clinical cases along the ND state border towards Minnesota cannot be overlooked. This distribution of cases reported to the VDL in counties along the ND - MN boarder as shown in figure 10 could be due to frequent movement of pets to areas of high risk of exposure to Lyme disease in the neighboring Minnesota. Alternatively, this could be a result of invasion of these boarder counties by Lyme transmitting *I. scapularis* implying an extension of the ecological habitat of these ticks.

Additionally, the presence of horses positive of Lyme disease as early as 2000 (see table 4) in ND suggests a much earlier presence of Lyme transmitting ticks given short distance horses move compared to dogs. Horses are usually used for recreation and do not move for long distances to places away from the owner's county of residency. Thus, the cases could either have been exposed within ND or were shipped from areas with a high Lyme disease burden.

More information regarding the animal travel history to places outside ND could give a clue on the exposure status of these horse cases. However, this information was not available because data of cases reported to the VDL is kept for only 7 years. Nonetheless, horses can make good indicators of Lyme disease risk since they are not as mobile as pets in the United States. Gall and Pfister, 2010 reported that the risk of exhibiting clinical signs in infected horses is fairly high unlike in dogs, where most exposed dogs (95 per cent) are asymptomatic *(26).* This further makes horses more suitable as indicator species for the occurrence of Lyme disease and can be incorporated in to early warning systems of managing diseases in populations.

Increase in annual precipitation was directly associated to higher number of Lyme disease cases and was highly significant ($P = 0.0250$) for the prediction of Lyme disease cases in ND, WI and MN. This observation was similar to what was reported by McCabe and Bunnell, 2004; these authors reported that increased number of Lyme cases during high precipitation was possibly due to increased activity and survival of the ticks in wet environmental conditions *(42).* Ticks are active during summer and high precipitation may result in less desiccation leading to increased survival of ticks and subsequent multiplication of tick numbers that transmit *Borrelia* to humans or dogs *(42).* This explains why WI, which had the highest annual precipitation, reported the highest number of Lyme cases and ND, which received the lowest precipitation, reported the lowest number of Lyme disease cases.

Additionally, higher average fall temperatures were associated with increased number of Lyme disease cases and were significant ($P = 0.0189$) for prediction of future Lyme cases. High fall temperatures imply an extended period of warm summer weather resulting in prolonged tick activity as well as human exposure due to outdoor activities. In places where high fall (August to September) temperatures occur, there is increased exposure of individuals to *Ixodes scapularis* nymphs as a result of outdoor activities like camping, sport hunting and nature walks that are mostly done in warm weather.

Although, the area covered by forests decreased in MN and WI, the ND forest slightly increased as shown in figure 10, 11 and 12. There was also a slight increase in the area covered by shrubs in ND, MN and WI. ND had the largest area covered by shrub land of all the three states. Shrubs provide suitable food to white tailed deer and an increase in the area shrub land cover may lead to an increase in deer, the favorable reservoir host of *Ixodes scapularis* and Lyme disease. Additionally, there was an increase in human population as shown in figure 6 and figure 14 as well as an increase in incidence of Lyme disease in all the three states. The only exception was ND from 1990 to 2000 where both the human population and Lyme disease incidence reduced. This increase in population and incidence of Lyme disease could signify increased number of people exposed to the disease as a result of activities in Lyme-risk ecosystems like forests.

The increased Lyme disease burden in ND, MN and WI from 1990 – 2011 is associated to increase in total annual precipitation and average fall temperature which have been reported to favor tick survival and human exposure. These could be important variables for the prediction of Lyme disease cases in ND, MN and WI. Additionally, the increased shrub land, woody wetland and forest coverage in ND which favor the proliferation of tick, deer and small mammal populations could be contributing factors to the increased incidence of Lyme disease.

5.3. Drivers of Infectious disease outbreaks

There are several factors driving the increased occurrence of infectious diseases in the world. Some of which can be inferred from the above two case studies of FMD in Uganda and Lyme disease in ND, MN and WI. The major drivers of infectious disease outbreaks include; climate change, change in land-use patterns, political instability, increased population growth, national economic constraints and diminished food production.

5.3.1. Climate as a driver of infectious disease outbreaks

Climate change has substantial influence on the burden of vector-borne and water-borne diseases as well as infections whose spread is affected by rainfall and temperature patterns

(Shuman, 2010). Global atmospheric temperatures have been proved to have increased and are anticipated to increase further by about 1.8 – 5.8^{o}C (Shuman, 2010).

Arthropod vectors are more active in warmer climate and the current global warming has resulted in increased occurrence of vector-borne diseases like Rift Valley fever, Trypanasomiasis, Lyme disease, Rocky Mountain spotted fever, among others. For instance, the Lyme transmitting nymphs do not survive very cold winters and the incidence of Lyme disease is known to be low in areas with prolonged cold weather *(2).* On the other hand, higher summer and fall temperatures increase the activity of these Lyme transmitting nymphs and places with such climate have a high incidence of Lyme disease *(2).* The case study on Lyme disease discussed in this Master's paper reveals a significant association between high fall temperatures ($p = 0.0189$) and annual precipitation $P = 0.025$) with a rise in number of Lyme disease cases in MN, WI and ND.

Similarly, in many developing countries seasonal extreme weather conditions accelerate the spread of infectious diseases. Livestock production systems like nomadism and communal grazing which are driven by extreme weather conditions often result in interaction between herds. This interaction between different herds is key to transmission of contagious diseases like FMD and contagious bovine pleuro-pneumonia. A study done by Ayebazibwe et al. 2010a reported that the number of FMD outbreaks in Uganda were higher when rainfall received was below average. Ayebazibwe et al., 2010a also noted that FMD outbreaks were reported in June and July, which are dry months. Movement of cattle characterizes the dry season in some regions of Uganda over long distances to the communal grazing and watering areas. Additionally, the pastures and water are inadequate resulting in loss of weight and increased animal susceptibility to diseases.

5.3.2. Change in land use patterns

Changes in land use patterns result in cross species interaction as well as extension of the geographical range of pathogens, vectors and hosts. Major land use changes associated with infectious disease outbreaks include deforestation, agricultural encroachment, dam building and road construction. These activities result in habitat destruction and change in favorable hosts' equilibrium for pathogens *(56).* For instance, research shows that forest fragmentation as a result of urban sprawl has led to decrease in host diversity of small mammals in forest habitats in North Eastern United States. This is decrease in small mammal host diversity is reported to have increased the susceptibility of white-footed mouse to *Ixodes scapularis* ticks. White - footed mice are effective in the transmission of Lyme disease, which in turn resulted in increased incidence of the disease *(56).*

Similarly, agricultural encroachment and other human activities in wildlife ecosystems have resulted in increased transmission of infectious diseases between wildlife, livestock and humans. Over 75 per cent of human diseases are zoonotic and have been associated with increased human, wildlife and livestock interface. Present examples of diseases spread through the human-livestock-wildlife interaction include Nipah virus, Ebola virus and Hantavirus syndrome. These diseases have a high incidence rate and have no reliable therapies or vaccines *(59).*

Additionally, the high number of FMD and CBPP outbreaks in sub-Saharan Africa are related to the interaction of wildlife and livestock. A study done by Ayebazibwe et al. 2010a reported that the interaction of livestock with buffalos, impalas, wild kobs and other wild ungulates contributes to the maintenance of FMD in Uganda. In Uganda, livestock and wildlife interact freely and share the same watering and grazing space due to the lack of physical barriers around the national parks, which presents a big challenge to disease control efforts *(8)*

5.3.3. Political instability

Conflicts exacerbate negative effects of disasters. These negative effects include disease epidemics, drought and prevention of the implementation of disease control programs. Most of the war-torn areas remain reservoirs of major diseases. For example, the horn of Africa is a known reservoir of FMD, CBPP and Rift valley fever because the long-term conflicts in the region have precluded disease control efforts including vaccination *(37).* The study on FMD vaccination in Uganda described in this paper, reports high numbers of FMD outbreaks (Figures 2, 3, 4 and Figure 5, map of 2003) in the northern region followed by no/low quantities of vaccine distribution due to political instabilities that were present in the region during the study period.

5.3.4. Socio-economic drivers of infectious disease outbreaks

The most effective strategy of controlling infectious diseases is through sensitive disease control and surveillance programs. Effective surveillance allows early detection of infectious disease threats and provides data for designing efficient disease control programs. Such surveillance programs are well established in many developed nations. Unfortunately, most developing countries lack laboratory and epidemiological capacity to detect, contain and prevent the spread of infectious diseases in human and livestock populations *(33).* The public health infrastructures in these countries are weak making all surveillance and control efforts difficult to implement *(59).* This is evident by the global distribution of infectious diseases where 53 per cent of which occur in sub-Saharan Africa, 11% in Eastern Mediterranean, 11% in Western

Pacific, 10% in Amprias and 7% in South East Asia *(59).* Therefore poverty and economic instability still remains a global driver of infectious disease occurrence.

Additionally, the FMD outbreaks in Uganda could be driven by economic instability like in many other developing nations. The absence of laboratory infrastructure to identify virus serotypes causing FMD outbreaks and the inability to carryout vaccine matching seem to be a hindering factor to effective control of the disease. This scenario seems to be similar to many other disease control programs in developing nations. Diseases like Ebola and Marburg often take months to be identified because they require isolation in biosafety level 4 facilities that are absent in developing countries where the outbreaks occur *(33).*

Other factors contributing to the global surge in infectious disease outbreaks include urbanization as well as international trade and travel. The world's population was reported to have nearly doubled by the second half of the 20th century *(33).* Similarly, the percentage of the world's population leaving in urban areas has continually increased and is projected to reach 65% by 2030 *(59).*

The increase in air travel and trade in food has also facilitated global movement of infectious disease pathogens in to new environments *(59).* For example, the high incidence of SARS in was linked to international travelers *(59).* International travel is also linked to increased pet movement, which has been associated with the spread of infectious diseases. The increased occurrence of monkey pox, for example, is linked to movement of *Procolobus badius* monkeys *(59).*

On the other hand, pathogens adapt to hosts, environments and develop resistance mechanisms to many therapies that have been developed *(33).* Organisms avoid recognition by host immune systems through the use of hyper variable surface molecules that allow them multiply without being eliminated by the host defenses *(19).* This mechanism of using hyper variable surface molecules to evade host immune defenses is known as antigenic variation. Different organisms use different mechanisms of antigenic variation. Human Immune Virus - 1 (HIV-1), the cause of AIDS disease, uses spontaneous mutation; while *Treponema pallidum*, the cause of syphilis, uses transcriptional regulation to produce different surface molecules at various phases of the pathogens multiplication *(19).*

Other pathogenic organisms like *Borrelia spp., Anaplasma marginale* and *Babesia spp.* use gene conversions to evade their host immunity resulting in antigenic variation. These pathogens move or transfer entire genes or portions of genes within their genome to prevent attack or elimination by their hosts *(19)*. Infectious organisms like *Mycoplasma, Salmonella* and *Plasmodium* poses drug resistant genes that pose a great challenge to treatment of these diseases. All these antigenic variation and drug resistant characteristics of pathogenic organisms are a contributing factor to the increased occurrence of infectious disease outbreaks.

With all the above factors posing an increased challenge to infectious disease control, a model needs to be designed that uses the different factors to predict both temporal and spatial risk of disease. One example of such a model is the structural equation modeling. However preliminary studies need to be done to ascertain the contribution of the different factors to disease causation. Similarly, there is need for formalization of international collaborations and regulations on matters of health. These international collaborations should involve inter-governmental agencies, regional and national governments as well as non-governmental organizations as a way of providing joint technical advice on disease surveillance, detection and reporting.

CHAPTER 6. CONCLUSSIONS AND RECOMMENDATIONS

Ineffective disease control programs revealed by the limited serotyping of FMD outbreaks (9/121), the prolonged response to disease outbreaks (mean = 7.5 weeks) and the low proportions of vaccinated animals (2.1 – 21.2) as described in the case study on FMD in Uganda; influence the occurrence of infectious disease outbreaks.

Similarly, the significant association of increased total annual precipitation ($P = 0.025$) and average fall temperature ($P = 0.0189$) with the rising number of Lyme disease cases as well as the occurrence of FMD outbreaks due to unsettled grazing systems during extreme weather conditions, portray climate as a driver of infectious disease occurrence.

Lastly, the increase in shrub land, forest and woody wetland coverage in ND, which are reported to favor proliferation of ticks, deer and small mammals, could be contributing factors to the increased occurrence of Lyme disease. Thus climate, environment and disease control programs are important drivers of infectious disease outbreaks.

It is therefore crucial that disease control strategies must take care of the various factors driving disease occurrence. There is need to understand the contributions of the different factors to the epidemiology of infectious diseases. One tool that could be adopted and designed to be used in both disease control and surveillance programs is the structural equation modeling technique. However, this requires systematic infectious disease studies to ascertain and quantify the contributions of the different factors influencing infectious disease occurrence.

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