GEOGRAPHIC DISTRIBUTION OF MALARIA IN NEPAL

by

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B.S., Delhi University, India, 1998
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AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Geography
College of Arts and Sciences

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Manhattan, Kansas

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Abstract

The malaria burden has decreased in Nepal between 1988 and 2013. However, there are challenges to completely eradicating the disease. Malaria patterns in a few endemic districts have not changed, and higher malaria case rates have been detected within districts which otherwise were categorized as low endemic areas. Underlying biophysical, socioeconomic, and behavioral factors influence malaria transmission and create region-specific patterns. This research employs various concepts, tools, and techniques to understand the geographic distribution of malaria in Nepal. In this research, malaria prevalence patterns were investigated at multiple spatial and temporal scales. The study identifies malaria hot spots, describes their characteristics and examines shifts in malaria hot spots between 1988 and 2013. Within that 26-year time span, 267,121 confirmed malaria cases were recorded. Thirty-nine of 75 districts were identified as malaria hot spots in Nepal. Based on the frequency, persistence and proportion of caseloads each year, the identified hotspots were grouped into five categories; stable, disappearing, emerging, reemerging, and intermittent. The research also investigated the relationship between climatic factors and malaria frequency, and found that temperature and precipitation during the monsoon and non-monsoon seasons played significant roles in determining the absence and presence of malaria and low and high frequency of malaria distribution at the district level. The dissertation also presents the findings of a study that investigated malaria–related knowledge, perceptions and practices among adults in Nepal, specifically knowledge about its signs, symptoms, consequences, and the availability and use of prevention tools. Although a significant portion of respondents had heard of malaria there was wide variation in their knowledge about specific information related to the disease. Locality, age, household size, education, and income were significantly associated with malaria–related knowledge.

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Dedication

This dissertation is dedicated to the people who were with me in every step of this journey: to my parents, Somnath and Jaya Ghimire, who loved me unconditionally, went above and beyond to educate me, kept reminding me to stay true to my dreams and taught me to never give up. My husband, Dr. Neeraj Nepal, has been the biggest supporter, if it was not for his love, patience, positive attitude, confidence in me and most importantly his dedication to science, I would not have been here; and finally this dissertation is dedicated to my daughters, Neeravi and Kaveri, for whom I finished this degree.

Chapter 1 - Introduction

1.1 Background

Malaria is a common vector-borne infectious disease widely distributed in tropical and subtropical regions of the world (Martin and Lafebvre, 1995; WHO, 2013). One of the most ecologically sensitive diseases, malaria is among those undergoing resurgence and redistribution in various parts of the world (Martin and Lafebvre, 1995). It has been reported from the developed countries in North America and Europe to the Amazon Basin in Brazil and within less developed nations in Asia and Africa (Martin and Lafebvre, 1995; Epstein et al., 1998; Packard, 2008; WHO, 2014). According to the World Health Organization (WHO), malaria still occurs in 99 countries (WHO, 2014). In 2013, WHO estimated that there were more than 2.3 billion people at risk of contracting malaria, 200-500 million cases of malaria, and an estimated 584,000 deaths worldwide (WHO, 2014). More than 80% of malaria-related mortality and morbidity occurs in Africa; most of the remaining cases are in Asia, Central and South America, and the Mediterranean Region (Martin and Lefebvre, 1995; WHO, 2014; Gething et al., 2011; Murray et al., 2012). More than 80% of all malaria mortality occurs in children under age 5. Recent findings by Murray et al. (2012) revealed that malaria was the underlying cause of death of 1.24 million individuals in 2010, more than WHO estimated. Their findings also show that global malaria mortality is higher in adult populations than previously estimated.

Nepal is one of the 99 countries identified by WHO where malaria transmission occurs. The first entomological proof of malaria transmission in Nepal was recorded in 1925 (Pradhan et al., 1970; Sakya, 1981; Shrestha et al., 1991). Thereafter, various anti-malarial campaigns and malaria prevention measures started (Pradhan et al., 1970; Sakya, 1981; Jung, 2001; Pant, 2010). Prior to the anti-malarial campaigns, there were about two million cases of malaria annually,

with about 10% of the incidences leading to death (Pradhan et al., 1970; Sakya, 1981; Shrestha et al., 1991; Jung, 2001; Pant, 2010). There has been a considerable decline in malaria cases in the last couple of decades (Sherchand et al., 1996; Jung, 2001; Pant, 2010; Dhimal et al., 2014a). Having said this, malaria is still one of the major public health problems in Nepal. Currently, about 84% of Nepal's populations (23 million people) live in malaria-endemic areas, endemic areas are defined as the regions where the disease is regularly found among particular people (Pant, 2010; WHO, 2013; Dhimal et al., 2014a). The epidemiological, public health and geographic risks associated with malaria are unevenly distributed within the country. Malaria transmission is a perennial and seasonal phenomenon in Nepal. Year to year reporting differs geographically and varies in number of positive cases and intensity of infection (Sherchand et al., 1996; Jung, 2001; Pant, 2010; Dhimal et al., 2014a).

Nepal is one of the eight countries categorized as in the malaria elimination phase by the WHO. WHO has defined malaria elimination as the permanent interruption of vector-borne malaria transmission in a given geographic region (WHO, 2014). WHO's malaria prevention and control program takes place in four distinct phases: control, pre-elimination, elimination, and prevention of reintroduction (WHO, 2014). The government of Nepal is committed to meeting all the criteria of the malaria-elimination phase and is also working to create a malaria-free future by 2026 (Dhimal et al., 2014a).

I have chosen to conduct my research in Nepal (Figure 1.1) because it provides a range of socioeconomic and public-health conditions against the background of biophysical environments suitable for malaria transmission. The socioeconomic status of the population of Nepal ranges from highly affluent to a significant portion of the population living below the poverty line (Shrestha, 2007; CBS, 2012). There are significant geographic differences in availability and

access to health-care facilities because most medical services are concentrated in population centers. Biophysically, the country is divided into three major physiographic regions, based on the altitudinal gradient (Gurung, 2008; CBS, 2012). The combination of various physiographic, climatic, socio-cultural, and economic factors creates a model interactive environment for three major components of malaria: host, parasite, and vector (Jung, 2001; CBS, 2012; DoHS, 2012).

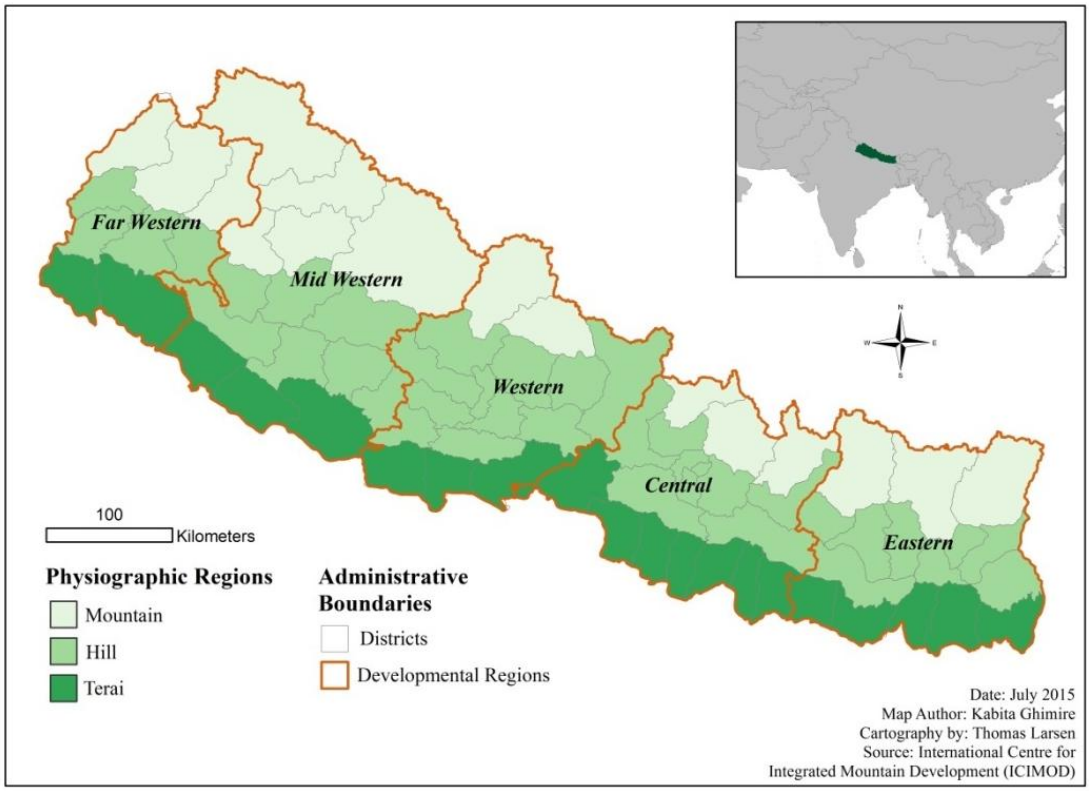

Figure 1.1: Reference map of Nepal showing three physiographic regions, five developmental regions, and 75 districts

1.2 Malaria: Etiology, Ecology and Epidemiology

Malaria is one of the most intensively studied infectious diseases in the world (Hemingway and Bates, 2003; Russells, 2004; Packard, 2008). However, understanding the mechanisms that underlie its emergence and reemergence remains one of the most challenging questions currently under investigation within the field of infectious disease ecology (Wilcox and

Colwell, 2005). Therefore, before starting any research it was very important to understand the fundamental characteristics of malaria, including of the malaria transmission cycle; basic signs, symptoms and consequences of the disease, and factors influencing malaria transmission.

Malaria transmission is possible when three conditions coincide (Figure 1.2). First, the malaria parasite (a protozoan of the genus *Plasmodium*) must be present. The malaria parasite is a single-celled protozoan, which is incapable of surviving outside of its host or vector and has probably existed since about 20,000 BC (Pavlovsky, 1964; Packard, 2008). This parasite requires two hosts to complete its life cycle, the mosquito (the definitive host) and a vertebrate host (the intermediate host); hosts are mostly birds, humans, monkeys, and livestock (Jung, 2001; Packard, 2008; Sadanand, 2010).

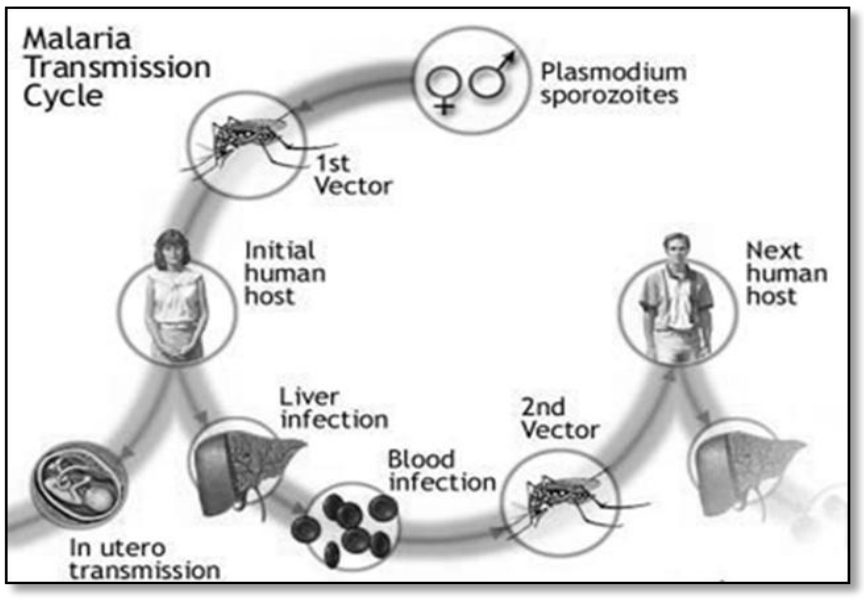

Figure 1.2: Malaria Transmission Cycle (Hale, 2015)

Plasmodium is a protozoan of the kingdom Protista, phylum Apicomplexa, class Aconoidasida, order Haemosporida, and family Plasmodiidae. There are more than 120 *Plasmodium* species, among which four are reported to cause malaria in human beings. These are

Plasmodium falciparum, P. vivax, P. ovale, and *P. malariae* (White 1982; Sah et al., 2002; Packard, 2008; WHO, 2013). These parasites are highly species-specific and there is no known animal reservoir for human malaria parasites (Pavlovsky, 1964; Packard, 2008). The most common among the four are *P. falciparum* and *P. vivax*. The *P. falciparum* parasite causes the most dangerous malaria among the four, with the highest rate of complication and mortality. It is often referred to as "The Killer Parasite" (Dhiman et al., 2010). Malaria caused by *P. falciparum* is usually a medical emergency. Specific characteristics of each species are summarized in Table 1.1 (White 1982; Sah et al., 2002; Packard, 2008; WHO, 2014).

Two species of *Plasmodium, P. falciparum* and *P. vivax,* are endemic to Nepal. Between 80% and 90% of the reported malaria cases in Nepal are due to *P. vivax* (White, 1982; Jung, 2001; Manandhar et al., 2013; Dhimal et al., 2014a). There are fewer deaths from malaria caused *by P. vivax* than those caused by *P. falciparum.* However, all the cases of malaria relapses are associated with *P. vivax* (Manandhar et al., 2013). Due to limited epidemiological knowledge of *P. vivax* in Nepal, malaria elimination has become very complicated, resulting in higher social and economic impacts (Adhikari et al., 2012). There have been reports of *P. malaraie* from a few districts in Southern Nepal (Pradhan et al., 1970; Sherchand et al., 1996; Hada et al., 2011; Manandhar et al., 2013) and a few isolated cases of *P. ovale* among Nepalese soldiers returning from peacekeeping missions in African regions (Sherchand, 2011, personal communication). Creating an epidemiological picture of malaria in Nepal is challenging because the pathogens occur sporadically and their origination is difficult to identify (Sherchand et al., 1996; Adhikari et al., 2012).

Table 1.1: Detailed information of malaria associated with various species of Plasmodium

Basic characteristics	***P. falciparum***	***P. vivax***	***P. malariae***	***P. ovale***
Incubation period (days)	6-25	8-27	16-40	8-27
Severity	Severe, most dangerous of all forms of malaria associated with *Plasmodium species;* normally take 7 to 14 days to show symptoms	Moderate to severe, causes benign types of malaria; seldom fatal; normally take 8 to 14 days to show symptoms	Mild to moderate, less common than the other species; normally takes 7-30 days to show symptoms	Mild; causes more benign types of malaria
Anemia	High	Medium	Medium	Low
Complications	Highest rates of complications and mortality	Weakens immune system	Renal	
Typical symptom duration (untreated)	2-3 weeks	3-8 weeks	3-24 weeks	2.3 weeks
Maximum infection duration (untreated)	6-17 months	5-8 years	20-50 years	12-20 months
Geographic distribution	Worldwide distribution, predominant in Sub-Saharan Africa	Most common in Central America and the Indian Subcontinent	Tropical and subtropical areas of Central and South America, Africa and South East Asia	Primarily in Sub-Saharan Africa, relatively unusual outside of Africa
Endemic to Nepal	Yes	Yes	Rare	No

(Source: Rozendaal, 1997; White, 1982, Sherchand et al., 1996; Sah et al., 2002; WHO, 2014; CDC, 2015)

Mosquitoes serve as the alternate host of malaria, specifically those in the genus *Anopheles,* and hence are the disease vector. The pathogen-carrying capability of *Anopheles* varies with species; some can carry more than one species of the malaria parasite, while others can only transmit one species of the pathogens (Dhiman et al., 2010). The malaria vector can breed in a wide variety of habitats such as forests, build up areas, agricultural fields and others. To complete the life cycle of a malaria vector, availability of water is very important (Rozendaal, 1997; WHO 2014). The larval stage of the vector develops in different kinds of water bodies such as running or stagnant water or fresh or brackish water (Figure 1.3) (Rozendaal, 1997).

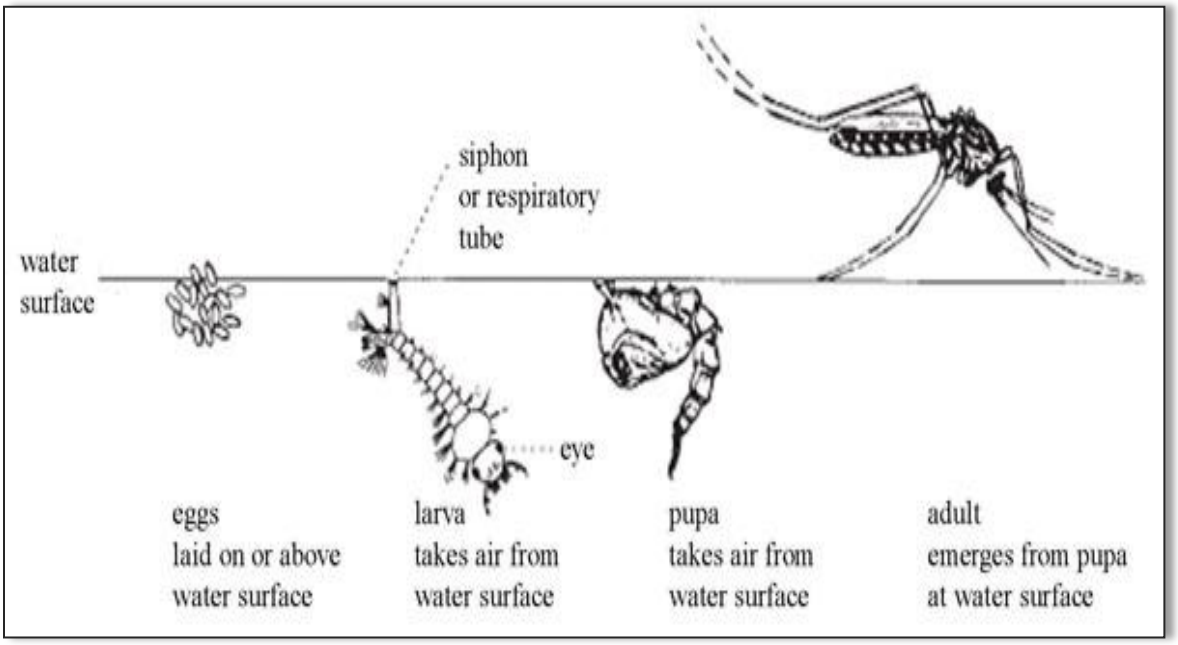

Figure 1.3: Life Cycle of Mosquito (Rozendaal,1997)

There are about 462 *Anopheles* species, of which 70 are capable of transferring the disease (Packard, 2008; Hay et al., 2010). The spatial distribution of the malaria vector is region specific (Sinka et al., 2012). *An. gambiae, An. arabiensis,* and *An. funestus* are dominant vectors in African regions, and *An. darlingi* is a common vector in South America. In the United States,

An. quadrimaculatus and *An. freeborni* are responsible for malaria transmission (Brogdon and McAllister, 1998; Sinka et al., 2012). Vector distribution in the Asia-Pacific region is relatively complex when compared to the other regions due to multi-species coexistence and variability in dominance (Sinka et al., 2012). There are about 40-45 species of *Anopheles* present in Nepal, of which nine have been identified as malaria vectors (Brydon et al., 1961; White, 1982; Kondrashin et al., 1991; Sah et al., 2002; Hay et al., 2010; Dhimal et al., 2014b) (Table 1.2). However, the dominant primary vectors are *An. fluviatilis, An. annularis, An. maculatus* and *An. minimus* (Brydon et al., 1961; White, 1982; Kondrashin et al., 1991; Sah et al., 2002; Hay et al., 2010; Dhimal et al., 2014b).

Finally, there must be a vertebrate host to complete the malaria transmission cycle. Humans are the most common vertebrate host (Pavlovsky, 1964; Packard, 2008), thus humans are both hosts and victims of the disease. The vulnerability of the human host to the disease varies from region to region, depending on the physical environment, overall level of economic development, the availability and accessibility of a medical facility, and the physical environment. Developed countries with better living environments and better access to public health measures have lower chances of infection compared to the populations living in developing countries with less economic development and inadequate public health infrastructure. People living in tropical and subtropical regions are at greater risk of contracting malaria because the biophysical environments there are more favorable for malaria transmission than those at higher latitudes. Malaria can occur year-round in tropical and subtropical area because of these favorable biophysical environments, which further increase the risk.

In Nepal, those living in the highly populated Terai region (Figure 1.1), where the socio-cultural and biophysical environments are more favorable, are at higher risk of malaria

transmission compared to those living at higher altitudes. The favorable socio-cultural and biophysical environments for malaria transmission, such as year round optimal climate, suitable habitat for vectors, a porous border to high endemic regions of India, and a higher prevalence of pathogens, contribute to higher geographic and epidemiological risks to the population living in the region. Lack of high-end medical facilities, poor public health infrastructure, rugged terrain, and general difficulty associated with accessibility to the area pose different kinds of risks for populations from the Hill and the Mountain regions. Certain ethnic groups like the Tharus and Danuwars in Nepal demonstrate a high frequency of the α-thalassemia gene, which provides biological resistance to malaria as compared to the non-Tharu and non -Danuwar communities in the Terai (Terranato et al., 1988; Modiano et al., 1991; Sakai et al., 2000; Suzuki et al., 2007). Therefore, even within a geographic region, susceptibility and vulnerability to malaria varies significantly among different population groups.

Table 1.2: Anopheles species identified as malaria vectors found in Nepal

Vector	Characteristics
An. fluviatilis	A major vector, primary vector; largely responsible for maintenance of intense year round as well as seasonal transmission in lower elevations; found up to about 1300 m above (mean sea level (MSL) in inner as well as forested outer Terai Larvae found in grassy edges of slow moving streams, springs, irrigation channels, sometimes in the edge of swamps and lakes; breeding site in rivers, streams, seepages and slow running water Species are discouraged by human activities such as non-farming practices as the species is known to thrive in water logged rice fields, deforestation leading to rice cultivation promoted the species Resistant to many common insecticides DDT; HCH/Dieldrin Complete susceptibility to an organophosphate (malathion) and a carbamate (bendiocarb)
An. Annularis	One of the predominant vectors in the cultivated outer Terai region Breeds in static water, ponds, paddy fields Resistant to DDT, and HCH/Dieldrin
An. maculatus	Sporadic vector, responsible for high altitude malaria transmission. Has been reported from 2000 m altitude in Nepal Resistant to DDT, and HCH/Dieldrin; susceptible to synthetic pyrethroids
An. minimus	Almost disappeared from Nepal during 1980s, continued disappearance or resurgence unknown, breeds in clean water streams, forests and forest fringes, forest edges, occurs below 671 m above MSL, has shown susceptibility to DDT and other insecticides
An. culicifacies	A non vector species in Nepal but important vector in parts of India and other South Asian regions, resistant to DDT, and HCH/Dieldrin
An. aconitus Donitz	Reported from Nepal, not very common in Nepal but common in Bangladesh, considered secondary or incidental vectors
An. barbirostris, An. sinensis, An. subpictus	Reported from Nepal but not an active malaria vector

Sources: Brydon et al., 1961; White, 1982; Banerjee et al., 1991; Kondrashin et al., 1991; Rana, 2001; Mittal et al., 2004; Wijeyaratne et al., 2004; Kiszewski et al., 2004; Yasuko and Levins 2007; Dhimal et al., 2014b; Dhimal et al., 2014c.

1.2.1 Signs, symptoms and consequences of malaria

Malaria is a febrile (fever-causing) disease. Once the pathogen is transmitted, signs and symptoms start to appear within few days or weeks. The clinical symptoms of malaria include moderate to severe chills, high fever, headache, vomiting, diarrhea, sweating and tiredness (Sadanand, 2010; CDC, 2015). Uncomplicated malaria can be easily treated by local health workers on an outpatient basis. Severe malaria leads to other complications including cerebral coma; anemia; renal failure; spleen rupture; and, in pregnant women, maternal death, stillbirth, and low birth weight in newborns (CDC, 2015). The primary cause of severe malaria is *P. falciparum.* Malaria caused by pathogens other than *P. falciparum* makes patients susceptible to other infectious diseases by weakening their immune systems (Sharma et al., 2010).

1.2.2 Prevention, treatment and control measures related to malaria

Common medications used to treat malaria are chloroquine (CQ), sulphadoxine-pyrimethamine (SP), artemisinin combination therapy (ACT), and quinine (WHO, 2014; CDC, 2015). Doxycycline, chloroquine, primaquine and a few other medications are also used prophylactically (CDC, 2015). In most of the malaria endemic countries, the anti-malarial drugs are available for free at the government health facilities (WHO, 2014). Vector control is another major and conventional malaria prevention and control strategy used worldwide. Common vector control activities include the use of both insecticide treated (ITN) and regular bed nets to prevent mosquito bites, indoor and outdoor insecticide spray, use of repellents, domestic insecticides, and biological control (WHO, 2014). The governments of most of the nations use radio, television, newspapers, and posters to disseminate malaria-related information to the public.

1.2.3 Malaria disease burden

Disease burden is a measure used to assess and compare the impact of diseases on a population (Russells, 2004; WHO, 2014). It quantifies health loss by measuring financial cost, morbidity, mortality, and other health indicators. The disease burden of malaria is very high. Malaria is one of the major causes of morbidity and mortality in many countries (WHO, 2014). Malaria-related illness imposes high and regressive burdens and it is very challenging to quantify the social and economic impacts (Russells, 2004). Quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs) are terms used when quantifying disease burden. DALYs estimate years of life lost due to premature death caused by the disease or healthy life lost due to disability from the disease (Picard and Mills, 1992; Russells, 2004; WHO, 2014). The social impact and economic implications of the disease vary depending on age, sex, and socioeconomic conditions; the severity and duration of the disease among those infected; and the quality and accessibility of public health facilities within a country (Picard and Mills, 1992; WHO, 2014).

1.2.4 Factors influencing malaria transmission

A number of biophysical and socioeconomic factors, public health measures, and human behaviors influence malaria transmission. The occurrence, reoccurrence, and rapid spread of the disease in different regions of the world is associated with specific climatic conditions, landscape features, and the socio-economic conditions of those living in a particular area (Pavlovsky, 1964; Meade et al., 1988)

Climate plays a critical role in regulating mosquito populations (Kiska, 2000; Pascual et al., 2006). Studies have shown that seasonal climatic patterns of rainfall, temperature, and relative humidity strongly influence malaria transmission (Lindsay and Birley, 1996; Epstein, 2000, Kiska, 2000; Pascual et al., 2006). Temperature, rainfall and humidity are the key climate

variables that influence malaria and they cannot be viewed independently. Global warming and sudden increases in temperature not only favor increased geographic spread of malaria vectors but also decrease the lifecycle of the vector, producing greater numbers of individuals within a shorter time span (Kiska, 2000; Pascual et al., 2006). At the same time, higher temperatures also facilitate the reproduction of pathogens within the vector and the rate at which they mature. The immature *Plasmodium falciparum,* takes about 26 days to fully mature at temperatures of 17º - 20º C, but it takes only 13 days to mature at 25º C (Longstreth and Wiseman, 1989; Epstein, 2000). *P. vivax* can complete its life cycle in slightly colder temperature at 15º C (Longstreth, and Wiseman 1989). Rainfall is also an important driver of malaria. Changes in one or any combination of the above-mentioned factors modify the course of the disease process and affect its impact on public health (Pavlovsky, 1964; Meade et al., 1988; Epstein, 2000; Kiska, 2000; Pascual et al., 2006).

The landscape structure and ecological processes of a particular geographical area also strongly influence malaria transmission (Allan et al., 2003; Stefani et al., 2011, 2013). Land Use/Land Cover (LULC) change can either favor or limit transmission of malaria by changing both human behavior and distribution patterns of the vector (Allan et al., 2003; Stefani et al., 2011; 2013; Srivastava et al., 2013). Categorical and/or configurational changes in LULC influence the behavior of both vector and host, and thereby change the epidemiological risk to human populations living in the area (Allan et al., 2003, Brownstein et al., 2005; Stefani et al., 2012). Historic land-cover type and current landscape structures also contribute to disease transmission (Despommier et al., 2006; 2005; Srivastava et al., 2013). Management requiring waterlogged conditions like terrace farming, for example, provide suitable breeding sites for vectors and thus facilitate the transmission of malaria (Yasuko and Levins 2007).

Other important influences on malaria transmission include socioeconomic, cultural and behavioral factors. Changes in demographic parameters such as population density, age-sex ratio, migration status, and the economic, occupational, and educational status of the population also influence malaria transmission by modifying the pattern of disease spread (Banerjee et al., 1991; Bishop and Litch 2000; Graves et al., 2008). In the absence of effective preventive measures, the socio-economic conditions and cultural practices of an affected population may increase or decrease the probability of infection (Sherchand et al., 1996; Budhathoki and B.C 2008; Soleimani-Ahmadi et al., 2014). This is particularly true in developing countries and rural areas, where the medical infrastructure is least developed. Awareness and perceptions of malaria among the population living in any particular region also play important roles in malaria transmission. Knowledge about the biomedical concepts of malaria, the process of transmission and effective preventive measures can result in human behavior changes that contribute to better management of the disease (Budhathoki and BC 2008; Graves et al., 2008; Sharma, 2009).

The various factors that influence malaria do not operate in isolation. The interrelationships among malaria transmission processes, change in human behavior, environmental factors, and socio-economic and cultural influences are complex (Packard, 2008). Both natural and human-induced changes contribute to the complexity of the disease. Interrelationships among biophysical factors, socio-economic variables, and human behaviors create the malaria transmission patterns specific to particular geographic areas (Hay et. al., 2000; Pascual et al., 2006; Kelly-Hope et al., 2011). Identifying these patterns will help in designing and implementing regionally appropriate strategies for malaria control and prevention (Kelly-Hope et al., 2011; Graves et al., 2008). Such knowledge can be used to improve preparedness

for, and response to, malaria epidemics, and can potentially contribute to the eradication of malaria in specific regions of the world.

1.3 Past and current pressing challenges associated with malaria

The global malaria situation has become very difficult to assess (Packard, 2008; WHO, 2014). Medical practitioners and policy makers are still dealing with persistent, decades-long challenges and emerging new problems, which makes tackling the global malaria situation very complicated despite more than 100 years of interventions and research (Hemingway and Bates, 2003). Therefore, it is very important to identify and understand the older problems and current pressing challenges associated with malaria. Some of the decades-long challenges are wide geographic distribution of the disease within suitable geographical, biophysical, and socio-cultural environments; high prevalence and incidence of the disease; under-reporting of the prevalence and incidence of malaria due to lack of a robust malaria information management system in many endemic regions; ineffectiveness of existing prevention, diagnosis, treatment, and control interventions; and weakening and withdrawal of malaria control programs. The newer problems associated with the disease, such as an emerging fifth malaria parasite (*P. knowlesi)* in the East Asian region, emergence and quick spread of drug resistance among new strains of the pathogen, distribution of the disease in wider geographic regions, and the emergence of vectors that are drug-resistant make malaria management even more complicated than it was in the past (Hemingway and Bates 2003; Packard 2008; Cohen et al., 2012; Dhimal et al., 2014a; WHO, 2014). Some of the pressing problems associated with malaria are discussed below in detail.

Non-reporting or under-reporting of malaria is still very common in developing countries due to insufficient health care infrastructure and relatively inefficient health information systems

(Tragard et al., 2010). Therefore, providing reliable estimates of the disease occurrence is still a big challenge. Unreliable estimates of malaria cases directly affect development and implementation of prevention and control measures (Hemingway and Bates, 2003; Dhiman et al., 2010; WHO, 2014). Delayed diagnosis also leads to multiple complications and death of patients (Shah et al., 2002; Sharma et al., 2009).

There is evidence of regional-scale changes in malaria distribution which suggests the disease is moving to higher elevations in places like Kenya, Uganda, other East African Highlands, and in Asia, including Nepal (Hay et al., 2002; Bishop and Litch 2000; Dhimal et al., 2014b). Although malaria is mostly endemic in tropical and subtropical regions, it is resurging in parts of the world where it was believed to have been eliminated (Kiska, 2000; Patz and Olson, 2006; Cullen and Arguin, 2013). The disease is reemerging in geographic regions like the United States, Canada, and the United Kingdom, where it was believed to have been eradicated (Cullen and Arguin, 2013; PHE, 2013; Beherns et al., 2015; McCarthy et al., 2015). Malaria resurgence is defined as an increasing trend in malaria incidence or prevalence following suppression achieved through implementation of control measures (Cohen et al., 2012). Cohen et al. (2012) identified 75 resurgence events in 61 countries between the 1930s and 2000s. The United States Center for Disease Control and Prevention (CDC) reported a total of 1925 malaria cases in the US in 2011. The majority of the cases, 99%, were classified as imported. The total number of malaria cases reported in 2011 was 14% higher than for the previous year, and it was the largest number of reported cases since 1971 (Cullen and Arguin, 2013). Similarly, the Public Health England (PHE) malaria reference laboratory reported a total of 1378 confirmed malaria cases in the UK in 2012 (50% of those cases were in London). The majorities of the cases in London (82%) were imported cases and originated in Africa (PHE, 2013). Cohen et al. (2012)

provide a systematic review supporting malaria resurgence in different parts of the world, and the causes of the resurgence.

In recent years, the emergence of a fifth human malaria parasite, *Plasmodium knowlesi,* has caught the attention of researchers and the global medical community. There have been reports of hundreds of human cases of *P. Knowlesi,* a species previously thought to cause malaria only in monkeys, in certain forested areas of South-East Asia (Luchavez et al., 2008; Kantele and Jokiranta 2011; WHO 2013). *P. knowlesi* can cause severe malaria with high complication rates, like *P. falciparum* (Sabbatanni et al., 2010; Kantele and Jokiranta 2011).

Many drug-resistant new strains of the pathogens causing malaria have emerged and spread across the world. Cohen et al. (2012) reported that 20% of the events of malaria resurgence in various parts of the world were attributed to drug-resistant pathogen strains. The spread of malaria due to pathogen strains resistant to chloroquine resulted in the loss of millions of lives in the past (Hay et al., 2000; Dhiman et al., 2010; Cohen et al., 2012; WHO, 2014). Similarly, strains resistant to SP, another widely used drug, emerged in South-East Asia and eventually spread to other parts of the world (Mharakurwa et al., 2004; WHO, 2014). The recent discovery of new strains of malaria pathogens resistant to the most effective anti-malarial drug, ACT, again in South-East Asia, has alarmed scientists, policy makers, and health care practitioners. Reports suggest the likelihood of new strains spreading to other parts of the world is very high (Ashley et al., 2014; Mok et al., 2015).

High diversity of mosquito vectors transmitting malaria throughout the world and the capacity of one vector to carry more than one pathogen species also adds substantially to the complexity of malaria dynamics (Brogdon and McAllister, 1998; Packard, 2008; Sinka et al., 2012; Kumar et al., 2014). Vector resistance to insecticides is another significant contemporary

challenge. Vector resistance is considered a major cause in 19% of resurgence events worldwide (Hemingway and Bates, 2003; Cohen et al., 2012). Mosquito resistance to DDT (dichlorodiphenyltrichloroethane) and pyrethroids compound the malaria situation and make it difficult to sustain malaria control almost everywhere in the world (Wilcox and Colwell, 2005; Sabbatanni et al., 2010; Kantele and Jokiranta 2011; Cohen et al., 2012; Dhimal et al., 2014a).

In combination with the problems mentioned above, human-induced global changes like climate change, deforestation, agricultural intensification, and crop modification; construction of infrastructure like roads, railway tracks, dams, and irrigation facilities have contributed to higher rates of malaria in various geographic regions. Other factors that affect malaria transmission are human migration, civil wars, political instability and rising human populations in malaria risk zones (Epstein et al., 1998; Smith et al., 1999; Kiska 2000; Patz and Olson, 2006; Packard, 2008). The effects of all these issues, together with poor living standards, lack of a robust public health infrastructure, poor intervention programs, and a lack of community involvement in prevention and control efforts have made the present situation even more complicated than in the past (Ostfeld et al., 2005; Wilcox and Colwell, 2005; Packard, 2008). Multiple factors, including environmental, social, human behavioral, and public health measures all play vital roles in the spread of malaria. All these factors need to be studied in concert so a comprehensive picture of the interrelationships of factors causing malaria problems can be ascertained and addressed effectively.

1.4 Current research themes on malaria

It has been 113 years since Sir Ronald Ross was awarded the Nobel Prize for his discovery that malaria-causing parasites are found in the gastrointestinal tract of mosquitoes, which ultimately led to the understanding that malaria is transmitted to humans by mosquitoes

(Hemingway and Bates, 2003). More than a century after the discovery the death toll from malaria remains high, and yet there are no licensed vaccines against it (Hemingway and Bates, 2003; Del Prado et al., 2014). Therefore, malaria control remains a complicated challenge.

Having said this, in the past century there have been continuous and significant improvements in understanding malaria from every region of the world. These improvements in understanding have led to reductions in morbidity and mortality related to malaria, enhanced intervention strategies, increased political commitment, and impressive progress in establishing a robust research foundation (WHO, 2014). As a result, malaria research has become broader and deeper, and the number of articles in scientific journals has increased tremendously. Scientists from all over the world, representing multiple disciplines, are conducting research that contributes to the shared goal of ultimately eradicating malaria from the world. The following themes have dominated malaria research in recent times.

Biomedical research is the traditional domain of malaria studies. Scientific communities, working under the broader theme of biomedical research, have devoted their time and expertise to the goal of understanding the fundamental biological and epidemiological aspects of malaria. Specialists in this area focus mainly on examining the biology of parasites, vectors, and the human hosts, and analyzing the role each one plays in the disease process. A few of the many goals of biomedical research include discovering the various species of malaria causing pathogens, finding new strains of these pathogens, learning which strains are resistant to anti-malarial drugs, identifying which vectors carry malaria pathogens, discovering which vectors are resistant to insecticides, and identifying human antigens that suppress malaria (Farooq and Mahajan 2004; Hall and Fauci 2009; Del Prado et al., 2014). Biomedical research includes studying the life cycle of malaria parasites and investigating the complex interactions

among pathogens, mosquito vectors and human hosts (Farooq and Mahajan 2004). Other important biomedical research goals are developing, evaluating, and validating new prevention, control, and treatment tools. These include methods to suppress the malaria gene, anti-malarial drugs, vaccines, insecticides for vector control, insecticide treated nets (ITNs) for mosquito bite prevention, and other research along these lines (Slater, 2009; Hall and Fauci 2009). Biomedical research provides crucial information regarding discoveries and inventions, and has informed us about how far along we have come in terms of malaria control, eradication, and anticipated challenges for the future (Hall and Fauci, 2009).

Social science research, both quantitative and qualitative, adds another perspective to malaria-related studies. Various social science disciplines such as economics, anthropology, sociology, geography and others with their own specialty areas have a lot to offer to malaria-related studies. Social science research includes behavioral studies, economic and policy research, monitoring and evaluation of intervention initiatives, and health system research (Williams et al., 2002; Mwenesi, 2005). Research in the social sciences plays a powerful role in defining, formulating, improving, and implementing malaria-related strategies. Behavioral studies, at both individual and community levels, that investigate individuals' and communities' biomedical knowledge of the disease, their ways of managing the disease, and their treatment-seeking patterns have helped in designing awareness campaigns and other communication efforts to better educate the public (Sherchand et al., 1996; Ahmadi et al., 2014). These efforts have led to better responses during epidemics (Williams et al., 2002). Social science research has contributed tremendously in identifying vulnerable populations and their degree of vulnerability, and it has helped in quantifying the overall disease burden. There is ample evidence to support the usefulness of such research in contributing effective, evidence-based management

interventions in the control and prevention of malaria. Similarly, reviews of social science research related to malaria highlight the important theories, concepts, and tools various disciplines have contributed to the better understanding of malaria (Mwenesi, 2005; Williams et al., 2012).

Applied environmental research is currently a common type of malaria research, second only to biomedical research. This approach involves understanding the environmental aspects related to malaria transmission; the biophysical environment of a region plays an integral role in global and regional malaria transmission (Meade et al., 1988; Ostfeld et al., 2005). The occurrence, resurgence, outbreak, or spread of the disease in different regions of the world is associated with the climatic conditions, landscape features, and their patterns (Lindsay and Birley, 1996; Epstein, 2000; Hay et. al., 2000; Kiska, 2000; Pascual et al., 2006). Studies have shown that seasonal climatic patterns of rainfall, temperature, and relative humidity strongly influence malaria transmission (Lindsay and Birley, 1996; Epstein, 2000, Kiska, 2000; Pascual et al., 2006). The biophysical factors that constrain the disease operate at multiple spatial and temporal scales. Some of these factors favor the disease transmission process, some inhibit it, and others simply do not disturb it but act as a catalyst by maintaining minimum conditions necessary for a disease to circulate in a natural system (Pavlovsky, 1964; Cohen et al., 2010). Identifying the biophysical factors that operate to facilitate or inhibit the disease-transmission process within a geographic region is one of the ways to understand malarial disease dynamics. Significant efforts have been made to identify and understand the environmental factors linked to malaria, such as the climate and ecological conditions of a region. These factors determine the spatial and temporal patterns of the disease, like high and low prevalence, and whether or not the disease is seasonal or year-round (Hay et al., 2000; Ostfeld et al., 2005).

The applied method also works toward creating malaria endemicity maps based on biophysical and social factors, hot spot analysis, identification of social and environmental determinants of malaria transmission, identification of demographic risk factors for specific regions, and investigating malaria and biophysical linkages are a few examples of applied research (Ostfeld et al., 2005; Clennon et al., 2010). Tools and techniques from disciplines such as mathematics, statistics, and geography have been extensively used in malaria-related applied research (Ostfeld et al., 2005; Cohen et al., 2010).

1.5 Theme and direction of my research

My research brings together theoretical, conceptual, and technical aspects of existing research from multiple disciplines. It attempts to realistically create beneficial information that can be used to develop effective intervention programs and exit strategies for the government and the WHO related to malaria in Nepal. The literature suggests that underlying biophysical, socioeconomic, and behavioral factors influence malaria transmission and create region-specific patterns. Each geographic setting is unique; therefore, to generate meaningful outcomes this research employs methods that use various concepts from the disciplines of geography, landscape ecology, climatology, epidemiology, and sociology to understand the geographic distribution of malaria in a specific geographic region, Nepal. Understanding of local epidemiological patterns is important for malaria management. This research uses methods that integrate biophysical, socioeconomic, and public health factors known to influence malaria. The research was conducted at multiple scales, assuming that each of the above-mentioned factors operate at different spatial and temporal scales, and thus that their influences on malaria differ with scale. Geospatial techniques, such as geographic information systems (GIS), remote

sensing, and spatial statistics were used to tie different components of the research together and develop models to identify the geographic pattern of malaria in Nepal.

There has been little malaria research done in Nepal that emphasizes the association of biophysical, socioeconomic, and human behavioral factors within a single research framework. I have chosen to conduct my research in Nepal because it provides a range of socioeconomic and public health conditions against the background of biophysical environments suitable for malaria transmission. The socioeconomic status of the population of Nepal varies widely, with some being highly affluent and many others living below the poverty line. There is a significant difference in availability of and access to health care facilities because most medical services are concentrated in high population centers. Biophysically, the country is divided into three major physiographic regions based on the altitudinal gradient. The combination of various physiographical, climatic, and socio-cultural and economic factors creates a suitable interactive environment for three major components of malaria: host, parasite, and vector.

This research provides valuable, complete and detailed information regarding stable, emerging, disappearing, reemerging, and intermittent malaria hot spots in Nepal, as well as scientific evidence of the geographic extent of malaria and an assessment of biophysical and socio-economic environments of hot spots in relation to malaria transmission. The research also provides assessment of knowledge, perceptions, and practices related to malaria among the populations living in malaria-endemic regions of Nepal, and can be used to inform policy makers about where the nation stands in achieving its goal of malaria elimination by 2026.

1.6 Outline of the dissertation

This dissertation is structured as a series of stand-alone papers which describe the findings of my research. In chapter 2, I provide a review of the malaria research done in Nepal from 1950 through 2015. Chapter 3 contains the results of spatio-temporal and geo-statistical analysis of malaria in Nepal from 1988 to 2013. In this chapter malaria hot spots are identified and various hot spot categories are discussed. In chapter 4, I discuss the association between malaria disease frequency and climatic factors. Chapter 5 includes the results of the cross-sectional study conducted in selected districts to investigate malaria-related knowledge and practices among adults in Nepal. The summary, synthesis, and local, regional, and global implications of this dissertation are discussed in the concluding chapter 6.

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Chapter 2 - A Review of Malaria Research in Nepal: 1950-2015

Abstract

The aim of this paper is to identify and summarize various themes and objectives of journal articles, technical and non-technical reports, book chapters, and documents made available from various sources related to malaria research in Nepal between 1925 and 2015. The studies can broadly be categorized into four major themes: geographic and spatio-temporal studies, social (economic, demographic, behavioral), biomedical, and ecological studies. The geographic studies have tended to focus on investigations of the spatial and temporal distribution of malaria in the country. Social research has focused more on the behavioral aspects of the populations living in the endemic zones. Social-science based studies also measured the cost-effectiveness of malaria control programs, and examined malaria related awareness and treatment seeking patterns among the population living in the endemic zones. Biomedical research has concentrated on understanding the sero-epidemiology of malaria, development and efficacy of diagnostic tests, and the life cycles of pathogens. It has also investigated drug resistance patterns of various pathogen strains and complications associated with malaria infection. Ecological studies have identified vectors and their habitat; stratified the country into various endemic zones based on the biophysical aspects of the country; and assessed the relationships among the spatio-temporal distribution of malaria and environmental factors, such as temperature and precipitation. In this paper each of the themes is discussed in detail.

2.1 Background

This paper is a review of journal articles, technical and non-technical reports, book chapters, and other documents related to malaria research in Nepal between 1950 and 2015.

Systematic malaria research in Nepal began in the 1920s (Brydon et al., 1961, Pradhan et al., 1970; Sakya, 1981). During the early years, most information related to malaria was published in the form of technical and non-technical reports, both by the government of Nepal and other agencies, such as the United States Agency for International Development and the World Health Organization (WHO). For a number of reasons, including lack of systematic documentation protocols within the Nepalese government, reorganization and restructuring of health management agencies within the government, and significant downsizing of malaria-related projects and programs, a majority of older documents are not easily available to the public or the research community. There are also very few published journal articles and scientific papers from the 1920s through the 1970s. Therefore, developing an historic understanding of the malaria situation in Nepal has, by necessity, been based upon the few available information sources, making it a challenging task. Despite this, the available resources have been helpful in providing a good overview of the history of malaria in Nepal.

Nepalese government publications during the 1950s through the early 1990s mainly focused on the spatial and temporal epidemiology of malaria, with particular emphasis on identification of malaria occurrence zones based on the biophysical and demographic characteristics of the regions under consideration. Major efforts were made to identify vector species, describe their habitats, and determine their geographic distributions. Government reports during these four decades also provide a good overview of intervention programs and information relevant to malaria-related health care management institutions. It is interesting to note that the officials and individuals who were directly associated with the malaria control and intervention programs wrote almost all of the published papers, book chapters, and technical reports from the 1950s to the 1980s. There is minimal evidence of independent research being

conducted during this time period.

Independent, non-government sponsored, research on malaria in Nepal started in the late 1980s. The studies conducted during that time focused on quantifying the economic burden of malaria, analyzing the cost-effectiveness of malaria control programs, determining the economic consequences of malaria for households, and assessing the willingness of individuals to travel and pay for malaria treatments at the community level (Mills, 1992, 1993, 1994; Morey et al., 2003). Other independent research, conducted during the 1990s, identified and assessed various malaria diagnostic tools, investigated the sero-epidemiology (identification of antibodies to specific antigens in a population) of malaria in various geographic regions and also examined the knowledge, attitudes, and perceptions of malaria of populations living in malaria endemic regions (Sherchand, 1996; Sherchand et al., 1996; Sherchand and Hommel, 1999; Sherchand, 2002a; Sherchand, 2002b). The depth and the breadth of malaria research in Nepal have increased since the 1990s. Moreover, the studies can be classified into one of four types: spatial or geographic, social (economic, behavioral, demographic), biomedical, and ecological.

In this paper, I will review these four themes of malaria research in Nepal focusing on the literature since 1950 until 2015. The geographic studies have tended to focus on investigations of the spatial and temporal distribution of malaria (Kakchapati and Ardkaew, 2011; Dhimal et al., 2014a). The social research focused more on the behavioral aspects of the populations living in the endemic zones (Sherchand et al., 1996, Sherchand and Hommel, 1999). Social science-based studies also measured the cost-effectiveness of malaria control programs, and examined malaria related awareness and treatment seeking patterns among the population living in the endemic zones (Mills, 1992; 1993, Morey et al. 2003). The biomedical research concentrated on understanding the sero-epidemiology of malaria, development and efficacy of diagnostic tests,

and the life cycles of pathogens (Sherchand, 1996; Sherchand 2002a, 2002b). It also investigated drug resistance patterns of various pathogen strains and complications associated with malaria infection (Chand et al., 2003; Thapa et al., 2007; Sharma et al., 2009). The ecological studies identified vectors and their habitat (Brydon et al., 1960, Pradhan et al., 1970; Shrestha et al., 1991), stratified the country into various endemic zones based on the biophysical aspects of the country (White, 1982), and assessed the relationships among the spatio-temporal distribution of malaria and environmental factors, temperature, and precipitation (Bhandari et al., 2013; Dhimal et al., 2014c).

2.2 Themes and concentration of malaria research in Nepal

2.2.1. Spatio-temporal distribution of malaria

The first proof of entomological malaria transmission in Nepal was recorded in the Chitwan and Makawanpur districts in the Central Terai region as early as 1925, during the epidemiological survey conducted by Major Phillips of the Indian Military Service (Shrestha et al., 1991; Jung, 2001). Despite this early proof of disease presence, considerable time passed before other malaria-related research was conducted. Among the first systematic scientific research projects on malaria in Nepal was a geographic stratification of malaria occurrence zones, done in the 1950s (Jung, 2001; White, 1982). This zoning was done in support of efforts to initiate control intervention, prevention, and eradication of the disease (Jung, 2001; White, 1982). In this stratification, the country was divided into three zones: Eastern, Central, and Western. Due to limited resources, the first phase of intervention was to be carried out only in the Central zone (Figure 2.1). The Central zone was, therefore, further divided into 3 additional sectors: north, middle, and south, which were further subdivided into multiple subsectors. Later, in early 1960s, the intervention campaign was expanded to the Eastern and the Western zones

(Jung, 2001). These zones were also subdivided into multiple subsectors.

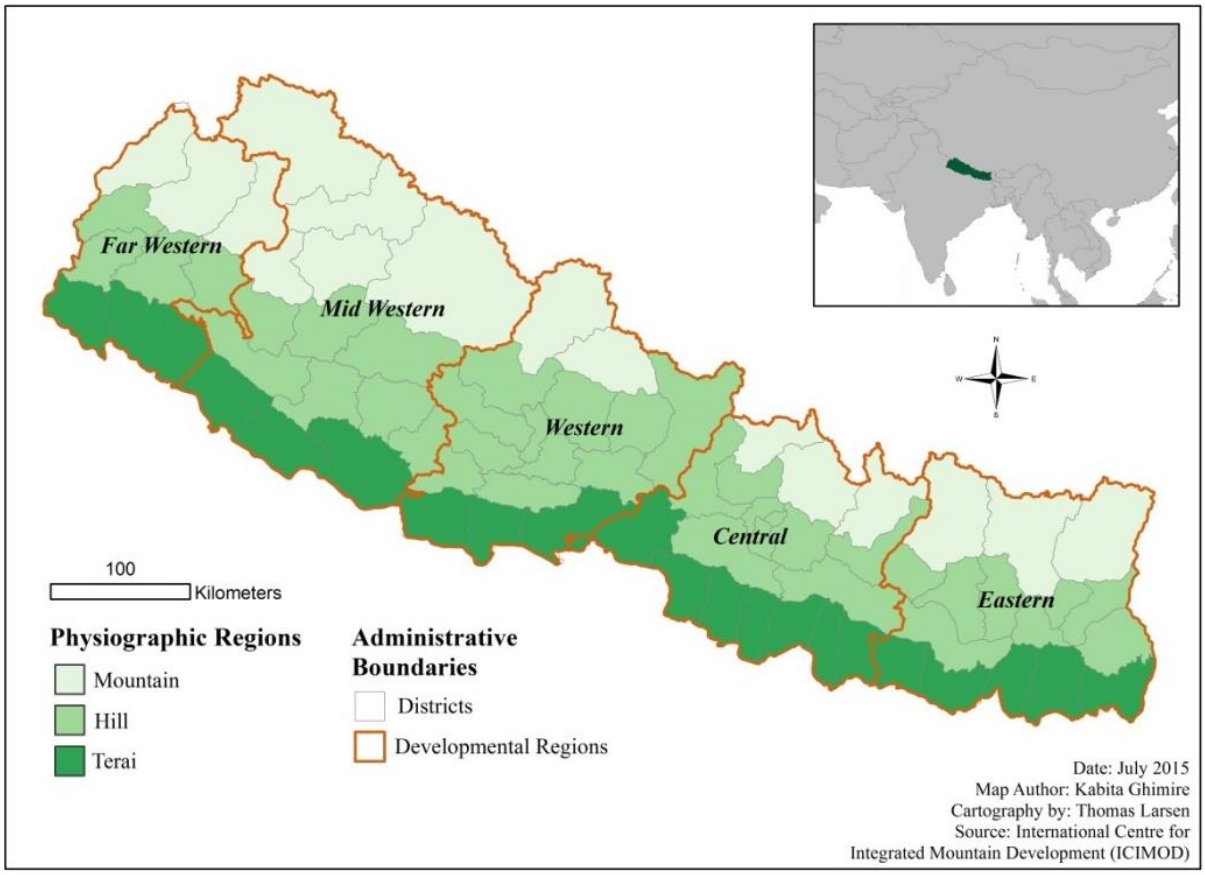

Figure 2.1: Reference map of Nepal showing three physiographic regions, five developmental regions, and 75 districts

Later efforts at creating malaria zones featured stratifications based on physiographical and ecological criteria, rather than simple geographical divisions of the country (White, 1982). During the early 1970s, a regional analysis divided the country into four malariological belts from south to north: 1) cultivated Terai, consisting largely of irrigated paddy fields 2) forested Terai, “Char Kosh Jhadi", heavily forested areas 3) inner Terai, flat elevated valleys upto 800 meters, heavily forested before but largely converted to paddy fields and 4) mountains and upper valleys, 1000 meters or above (White, 1982). In earlier years, between the 1920s and the 1970s, among the four malariological belts, only the forested Terai was hyper-endemic (intense

transmission but periods of no transmission during the dry season) (White, 1982). All other belts were originally meso-endemic (regular seasonal transmission), hypo-endemic (very intermittent transmission), or malaria-free regions (White, 1982; Shrestha et al., 1991; Banerjee et al., 1991; Jung, 2001). The elevations of these belts range from 100 m to 4000 m above sea level. The first two belts together form the outer Terai and are between 75 and 100 m above sea level. The wide range of altitudinal and topographic gradients provides suitable ground for vector breeding and thus facilitate malaria transmission (White, 1982; Banerjee et al., 1991; Jung, 2001).

During the 1980s, the Central region accounted for the highest malaria incidence, 36% of total malaria cases, and 57% of the total *P. falciparum* cases (Banerjee et al., 1991). Three districts, Dhanusha, Mahottari, and Sindhuli were the districts which carried the highest number of caseloads. Within the Central region, forest-related malaria accounted for 50% of malaria cases and 72% of *P. falciparum* during the 1980s (Banerjee et al., 1991; Shrestha et al.1991).

Several studies also established the existence of malaria in high altitude regions of the country (Pradhan, et al., 1970; Bishop and Litch, 2002; Dhimal et al., 2014b). A study conducted in 1969 in the Mugu district in the Mountain region, with the elevations ranging from 1050 m to 3200 m provided information regarding the historic prevalence of malaria in high altitudes. Several indigenous cases (originated in the area) of malaria were recorded, including cases of *P. falciparum, P. vivax, P. malariae* and mixed infections from villages as high as 2000 m (Pradhan et al., 1970). The parasitic rate for these cases was 3-9% (Pradhan et al., 1970). Bishop and Litch (2000) reported a case of malaria caused by *P. vivax* at the very high altitude of 3900 m in the Mount Everest region. Most recent claims of the potential presence of more malaria cases than reported in the high altitude districts were based on a vector survey, which recorded the vectors from as high as 1820 m above MSL (Dhimal et al., 2014b). Several cases of malaria

caused by *P. falciparum* were detected in the Kathmandu valley, which otherwise was categorized as a malaria-free region (Singh et al., 2006). One study provided a summary of distinct regional pattern of malaria epidemiology. The study, conducted during 2007 and 2008 in the Jhapa, Morang, and Dhanusha districts, suggested that malaria in the eastern part of the country is due to imported cases from bordering endemic regions of India whereas the Central region of the country accounts for more indigenous cases (Banjara et al., 2009).

A more recent study showed malaria occurrences in 69 of 75 districts between 1998 and 2009, with districts bordering India having higher incidence rates compared to other districts (Kakchapati and Ardkaew 2011). In 2010, among 75 districts, 65 were categorized as malaria risk districts (Dhimal et al., 2014a). The 65 risk districts were further subdivided into high risk (13), moderate risk (18), and low risk (34). The remaining 10 districts were categorized as no risk districts (Dhimal et al., 2014a).

2.2.2 Vector Identification and distribution

The major themes of malaria publications, mostly during the 1960 through the 1990s, were identification of malaria vectors, understanding their geographic distribution, and analyzing their habitats. The anopheles mosquito is the established vector of malaria (Brydon et al., 1961; Jung, 2001). *Anopheles minimus* was identified as the vector responsible for malaria transmission in the initial cases identified in 1925 (Shrestha et al., 1991). During the 1950s, Brydon et al. (1961) studied the distribution of several *Anopheles* species and their relation to malaria in the central region. They reported collecting 31 different species of *Anopheles*, which were documented and authenticated by WHO. *An. fluviatilis* and *An. minimus* were identified as the main vectors of malaria at that time, with *An. fluviatilis* the primary vector in the Hill region and *An. minimus* dominant in forested and forest fringe areas (Brydon et al., 1961). *An. minimus*

was also reported in open unforested areas in the southern plains. *An. maculatus*, has been detected at high altitude − about 1820 m − in the past, as well as recently (Pradhan et al., 1970; Dhimal et al., 2014b).

Currently, there are about 44 species of *Anopheles* present in Nepal (Dhimal et al., 2014b). However, only seven have been identified as persistent, active vectors across time (Table 2.1). These seven persistent vectors are *An. fluviatilis, An. annularis, An. maculatus, An. minimus, An. dravidicus, An. pseudowillmori*. and *An. willmori* (Brydon, et al,. 1961; Pradhan et al., 1970; White, 1982; Darsie et al, 1991; Banerjee et al., 1991; Shrestha et al., 1991; Kondrashain et al., 1992; Reisen et al., 1993; Dhimal et al., 2014b). Several other *Anopheles* species which have been identified as a malaria vectors in South Asia have also been reported in Nepal (Brydon et al., 1961; Kondrashin, 1992; Hay et al., 2010; Jung, 2001; Darsie et al., 1991; Dhimal et al., 2014b), including *An. sulicifacies, An. aconitus donitz, An. barbirostris, An. sinensis,* and *An. subpictus* (White, 1982; Kondrashain et al., 1991; Banerjee et al., 1991; Shrestha et al., 1991; Mittal et al., 2004; Wijeyaratne et al., 2004). *An. culicifaces,* found abundantly and extensively in the open plain area of the south, was categorized as a suspected vector, as it was active in adjoining India, but not in Nepal (Harrison et al., 1980). Dhimal and Bhushal (2009) mentioned several accounts of mosquitoes in general, and malaria vectors (*An. fluviatilis* and others) specifically, being reported from altitudes as high as 2000 m. These reports were based on the observations of community people and malaria program managers. They also highlighted the lack of scientific literature to back up these reports and emphasized the need for studies verifying these observations. A recent study conducted by the same group of researchers confirmed the northern shift of malaria vectors in Nepal and concluded that climate and other environmental reasons could be the cause of such a shift (Dhimal et al., 2014c). This

entomological survey, done in eastern Nepal during 2011-13, reported about 35% of the total *Anopheles* mosquitoes collected (N=1396) were composed of three species, *An. fluviatilis, An. annularis,* and *An. maculatus,* the current active vectors. The study reported these three malaria vectors at up to 1820 m elevation. The authors also reported larvae of *Anopheles* at 2,310 above MSL; species identification of these larvae is ongoing (Dhimal et al. 2014c).

Table 2.1: Anopheles species identified as malaria vectors found in Nepal

Vector	Characteristics
An. fluviatilis	A primary vector; largely responsible for maintenance of intense year-round and seasonal transmission in lower elevations; found up to about 1300 m above sea level in inner as well as forested outer Terai. Larvae found in grassy edges of slow moving streams, springs, irrigation channels, sometimes at the edge of swamps and lakes; breeding sites in rivers, streams, seepages and slow running water. Species discouraged by human activities such as non-farming practices, as the species is known to thrive in water logged rice fields; deforestation leading to rice cultivation promoted the species. Resistant to many common insecticides, including DDT, and HCH/Dieldrin. Complete susceptibility to an organophosphate (malathion) and a carbamate (bendiocarb).
An. annularis	One of the predominant vectors in the cultivated outer Terai region. Breeds in static water, ponds, paddy fields, resistant to DDT, and HCH/Dieldrin.
An. maculatus	Sporadic vector, responsible for high altitude malaria transmission. Has been reported at an altitude of 2000 meters altitude in Nepal. Resistant to DDT and HCH/Dieldrin; susceptible to synthetic pyrethroids.
An. minimus	Almost disappeared from Nepal during the 1980s, do not know about the continued disappearance or resurgence, seems reoccurred. Breeds in clean water streams, forests and forest fringes, forest edges; occurs below 671 m elevation. Has shown susceptibility to DDT and other insecticides.
An. culicifacies	A non-vector species in Nepal but an important vector in parts of India and other South Asian regions. Resistant to DDT and HCH/Dieldrin.
An. aconitus Donitz	Reported from Nepal, not very common in Nepal but common in Bangladesh, considered secondary or incidental vector in Nepal.
An. barbirostris, *sinensis*, and *subpictus*	Reported in Nepal, but not active malaria vectors.

Sources: Brydon et al., 1961; White, 1982; Kondrashin et al.,1992; Reisen et al., 1993; Mittal et al., 2004; Wijeyaratne et al., 2004; Yasuko and Levins 2007; Dhimal et al., 2014b; Dhimal et al., 2014c.

2.2.3. Biomedical Research

2.2.3.1. Identification of pathogens, their genetic diversity and geographic distribution

Two species of *Plasmodium, P. falciparum* and *P. vivax,* are known to be endemic in Nepal. About 80-90% of the reported malaria cases in Nepal are due to *P. vivax* (White, 1982; EDCD, 2010). There are fewer deaths from malaria caused by *P. vivax* than by *P. falciparum.* However, all the cases of malaria relapses are associated with *P. vivax* (Manandhar et al., 2013). Due to limited epidemiological knowledge of *P. vivax,* malaria elimination is very complicated. (Adhikari et al., 2012). There have been reports of *P. malariae* from a few districts (Pradhan et al,. 1970; Sherchand et al., 1996; Hada et al., 2011), and a few isolated cases of *P. ovale* have been reported among Nepalese soldiers returning from peacekeeping missions in Africa have also been recorded (Sherchand, 2011, personal communication).

Three distinct genotypes of P. vivax have been recorded within the high-endemic Jhapa district (Adhikari et al., 2012). The resulting genetic diversity was high despite the relatively low transmission rate. The diversity was attributed to migration and population movement within the country and between India and Nepal (Adhikari et al., 2012). Identifying genetic diversity of the pathogen is important as different genotypes play different roles in invading and altering host immune mechanisms and helping parasites to survive inside the host. *P. vivax* is the only species responsible for malaria relapse cases in Nepal (Manandhar et al., 2013).

A retrospective study was conducted in Kailali and Kanchanpur districts from August 2011 to May 2012 to assess the relapse/re-infection of malaria. The prevalence and heterogeneity of the genotypes of the parasite were also identified. The study found that 17% (n=137) of the patients showed evidence of relapse/re-infection during the study period. Two

different genotypes, VK210 and VK247, were detected from the study area. The majority (95%) were of the VK210 genotype. The existence of other genotypes was either isolated or mixed with VK210. A limited number of studies conducted in different geographic regions of Nepal provided evidence of higher genetic diversity of the dominant malaria pathogen, *P. vivax* (Adhikari et al., 2012; Manandhar et al., 2013). Genetic diversity assessment needs to be done nationwide to obtain more complete information on malaria pathogens, their genetic diversity, and geographic distribution.

2.2.3.2. Assessment of diagnostic tools

Sherchand (1996) investigated the efficiency of available malaria diagnostic tools in correctly assessing malaria incidence and prevalence in Nepal as a way of providing feedback for policy makers. His results showed that filter paper strips are more effective blood collection tools than capillary tubes, due to differences in availability and accessibility of electricity and transport. Sherchand's (1996) study was useful in providing information to policy makers to improve the quality of malaria intervention programs and help develop appropriate strategies for malaria control.

Microscopic examination of thick blood film is the standard and traditional method of malaria diagnosis in Nepal. However, newer tools are becoming available. Sherchand and Hommel (1999) tested one of these tools, ParaSight-F, a rapid diagnostic tool, for its sensitivity, specificity, and accuracy in diagnosing *P. falciparum* infection in Nepal. The tool was tested among 377 patients from districts in the Terai region. The overall performance of the ParaSight - F test was encouraging. The authors recommended the method as a complementary, and in some cases replacement, method for microscopic examination of stained blood film. The test in

dipstick format is cost effective, takes only 10 minutes, and is easy for rural health posts and village health workers to administer and interpret the results.

Another new tool, OptiMAL (an immunochromatographic dipstick test), was compared against the standard microscopy tests between August 2000 and October 2001 (Sherchand, 2002). Unlike the ParaSight-F test, the OptiMAL test was designed to detect both *P. falciparum* and *P. vivax*, and to differentiate between them. The test was performed on 180 patients suspected of being infected with malaria. The reported sensitivity and specificity of OptiMAL were 97% and 98%, respectively. Based on these results, Sherchand (2002) recommended it as a useful test for diagnosis. The usefulness of OptiMAL is especially important in Nepal, since microscopic diagnosis is labor-intensive and requires skilled and experienced technicians who still sometime fail to detect lower parasitic density among populations with some level of immunity.

Table 2.2: Detailed information of malaria associated with various species of Plasmodium

Basic characteristics	***P. falciparum***	***P. vivax***	***P. malariae***	***P. ovale***
Incubation period (days)	6-25	8-27	16-40	8-27
Severity	Severe; most dangerous of all forms of malaria associated with *Plasmodium species;* normally takes 7 to 14 days to show symptoms	Moderate to severe, causes benign types of malaria; seldom fatal; normally takes 8 to 14 days to show symptoms	Mild to moderate, less common than the other species; normally takes 7-30 days to show symptoms	mild causes more benign types of malaria
Anemia	High	Medium	Medium	Low
Complications	has the highest rates of complications and mortality; Cerebral	Weakens immune system	Renal	
Typical symptom duration (untreated)	2-3 weeks	3-8 weeks	3-24 weeks	2.3 weeks
Maximum infection duration (untreated)	6-17 months	5-8 years	20-50 years	12-20 months
Geographic distribution	Worldwide distribution, predominant in Sub-Saharan Africa	Most common in Central America and the Indian Subcontinent	Tropical and subtropical areas of Central and South America, Africa and South East Asia	Primarily in Sub-Saharan Africa, relatively unusual outside of Africa
Endemic to Nepal	Yes	Yes	Rare	No

Sources: White, 1982; Rozendaal, 1997; Sherchand et al., 1996; Sah et al., 2002; WHO, 2014; CDC, 2015

Hada et al. (2011) also assessed the diagnostic accuracy of common methods used in malaria diagnosis in Nepal. The methods compared were the conventional microscopy test, a fluorescent microscopy test (QBC), and the OptiMAL test (Sherchand, 2002; Hada et al., 2011). Hada et al. (2011) found that the efficacy of rapid diagnostic tests, such as QBC and OptiMAL, is higher than conventional microscopy. While the QBC is more sensitive, the cost and equipment needed for this method is higher than OptiMAL. Therefore, OptiMAL is likely to play an important role as a malaria diagnostic tool, both for its efficacy and cost effectiveness.

2.2.3.3. Assessment of anti-malaria drugs and drug resistance among pathogens

The efficacy of available malaria drugs and their appropriate use are important factors for prevention and control of malaria. Chand et al. (2003) reported that in Nepal, chloroquine (CQ) was the first-line drug for malaria treatment from the 1950s through 1988. Prior to 1981, CQ resistance was present only in cases imported from India. The government of Nepal modified malaria drug policy in 1988 and sulfadoxine pyrimethamine (SP) was introduced after a higher rate of resistance to CQ was detected for malaria caused by *P. falciparum*. Chand et al. (2003) studied the efficacy of anti-malaria drugs, finding that SP is the most effective first line treatment drug, with the use of quinine as a rescue drug for some malaria patients with co-infections or other complications. The researchers also mentioned the possibility of introducing artesunate (ART) or artemisinin-based combination therapy (ACT) as an alternative treatment for Nepal (Chand et al. 2003).

Pant et al. (2006) assessed the therapeutic efficacy of CQ against *P. vivax* in the Kanchanpur district. They found that using CQ treatment at a dosage of 25mg/kg body weight as a first-line treatment was 100 % effective in 84 of the 92 patients enrolled in 14 a days in vivo tests. In the remaining 8 patients, partial success was recorded. Based on these results, Pant et al.

(2006) recommended continuation of CQ as the first choice of treatment for *P. vivax* malaria. Thapa et al. (2007) compared three anti-malarial drugs, Artemether-Lumefantrine (AL), the first-line ACT, and SP, finding that AL was a more effective drug for uncomplicated *P. falciparum* infection than SP among the 99 adult malaria patients they studied. The paper also confirmed the presence of SP resistance and found that the resistance ranged between 56 and 87%. Ranjitkar et al. (2011) also noted the presence of molecular markers of CQ and SP resistance in *P. falciparum* and *P. vivax*. The study found the presence of CQ and SP resistance-related genes both in *P. falciparum* and *P. vivax*. However, the presence is high in *P. falciparum* and low in *P. vivax*, suggesting CQ can still be administered in *P. vivax* treatment and ACT should be used to treat *P. falciparum.* New lines of treatment, such as artemisinin combination therapy, are replacing SP and CQ for *P. falciparum*, as the parasite has developed resistance to SP and CQ (Ranjitkar et al., 2011).

2.2.3.4 Biological resistance of malaria among certain host population

Innate resistance to malaria has been noted in the Tharu, an ethnic group living in the Terai region (Terrenato et al., 1988). This study concluded that malaria incidence was seven times lower in the Tharu population than in sympatric non-Tharu populations with respect to both *P. falciparum P. vivax* infections. The study suggested the resistance is due to genetic factors yet to be determined and not due to therapeutic measures or socio-cultural habits. These studies were conducted in 10 out of 13 districts where the majority of the Tharu population resides. Follow up research done by the same group also found a higher frequency of the α-thalassemia gene among the Tharus, resulting a 10-fold decrease in malaria related morbidity (Modiano et al., 1991). Another study found that the prevalence of α-thalassemia gene was remarkably high among the Danuwar but relatively low among the Tamang (Sakai et al., 2000).

Caetano et al. (2006) studied the correlation between the distribution of malaria and the presence of protective alleles in the Nepalese population to confirm the genetic basis of resistance to malaria among 18 different ethnic/caste groups. Their study identified the presence of drug resistant alleles and found that the presence of these alleles did not differ significantly between the Hill (susceptible) and the Terai (resistant) population. Caetano et al. (2006) concluded that the presence of such allele and genotype frequencies in the Nepalese population is more due to demographic and other selective factors than to malaria selection pressure acting on these alleles. Individuals from four ethnic groups, the Danuwar, Newar, Parbate, and Tamang, from 30 km east of the Kathmandu valley were tested for the prevalence of hereditary erythrocyte disorders associated with malaria. The prevalence of α-thalassemia as examined in the study is as follows, Danuwar (79%), Newar (20.5%), Parbate (16.5%), and Tamang (8.8%). Since these studies were conducted, the socio-cultural, environmental, and demographic factors have changed. Historically, all these ethnic groups (Danuwar, Tamang, Parbate, and Newar) were each endogamous and inter-ethnic marriage was very unlikely. However, the situation is changing. Therefore, there is a need for follow-up research assessing current malaria resistance among different ethnic groups residing in the region.

2.2.3.5 Malaria and its role in exacerbating other health issues in the population

Malaria is often a complicating factor in mortality due to other causes (Sharma et al., 2009). Delayed diagnosis has been suggested as one of the causes of multiple complications and high mortality. The clinical profiles and biomedical characteristics of 138 adult malaria patients were examined from April 2002 to April 2005 (Sharma et al., 2010). All the patients participating in the study were from the Eastern Region and were admitted to B.P. Koirala Institute of Health Sciences Hospital (Figure 2.1). Hepatic dysfunction, anemia, hypotension,

hypoglycemia, and acute renal failure were the major complications associated with malaria among the patients. Twenty three percent of these patients died from a combination of more than three of the complications mentioned above (Sharma et al., 2010). A few cases of visceral leishmaniasis and malaria co-infection have also been reported from Nepal (Sah et al., 2002). Such concomitant health problems result in delayed diagnosis and require a different line of treatments and potentially lead to increased morbidity and mortality.

Anemia and iron deficiency are common health issues in pregnant women. Dreyfuss et al. (2000) identified malaria as one of the factors contributing to anemia in pregnant women in Nepal. Malarial parasites contribute to anemia by destroying and suppressing red blood cell production. Approximately 20% of pregnant women in the study (n=612) tested positive for *P. vivax*. The study suggested the malaria infection increased the probability of moderate to severe anemia among the pregnant women. This is one of the few community-based studies to identify malaria due *P. vivax* as a contributor to anemia during pregnancy.

2.2.3.6 Disease diffusion, blood donation and malaria.

Despite the ongoing presence of malaria in Nepal, the disease has not substantially affected the nation's blood supply. In 2007, screening for malaria was done on 1200 blood samples collected from the blood donated in the Kathmandu, Banke, and Morang districts. Only 4 samples (<1%) were positive for malarial parasites. All of the malaria-positive samples showed the presence of *P. vivax*. Three samples were from the Banke district (n =300) and 1 sample was from the Morang district (n =300) (Ghimire et al., 2007). No malaria parasites were detected from the blood samples from the Kathmandu district. There are hundreds of blood banks in Nepal and hundreds of blood donation camps are organized through the high endemic regions annually. This study was conducted using blood samples from only three blood banks.

Therefore, to prevent malaria through blood transfusion, screening of malarial parasites in donors from endemic regions was highly recommended.

2.2.4 Social, Economic and Behavioral research

2.2.4.1 Economic evaluation of malaria prevention and control programs

The expenses associated with malaria prevention and control programs in Nepal comprise a sizeable portion of the health sector budget. Therefore, it is very important to study the costs, cost-effectiveness, and consequences of such programs at both government and individual levels (Mills, 1992; 1993; 1994; Picard and Mills, 1992), but there have been few studies related to costs. This is due, in part, to the reluctance of control staff to arrange test studies; lack of technical, financial and human resources; data deficiencies; and difficulty in quantifying all aspects of the disease (Mills, 1993). Mills (1989) conducted a comprehensive study, focusing on the economic aspects of malaria in Nepal. She quantified and evaluated the economic burden of malaria at government and individual levels, assessed the costs, effects, and consequences of the disease at both the household and the individual level in selected districts from the Terai and the Hill regions (Picard and Mills, 1992; Mills, 1992, 1993, 1994). These studies focused both on resource-saving and health consequences of malaria by measuring control costs, cases and deaths prevented, and treatment costs averted (Mills, 1993).

Mills (1992) concluded that major malaria control strategies were focused on vector control (insecticide sprays) and case detection methods. The government control costs were categorized as surveillance costs, spraying costs and total costs by region, district and population percentage of the area (Mills, 1993). The government level costs associated with vector control included spraying of three different insecticides, DDT, Malathion, and Ficam. The cost of vector control was associated with the choice and availability of the insecticides, spraying frequency,

intensity of the disease, and accessibility of the area. Since the vector control activities were solely coordinated and controlled by the government, the individual costs associated with them were minimal. The individuals were required to vacate their houses, remove food and utensils for a few hours, and bear the insecticide smells. These efforts required at the individual level were not identified as activities of major economic importance. Therefore, no attempt was made to assess the cost of insecticide spray at individual level (Mills, 1992).

Mills (1992) also quantified and compared the costs and cost-effectiveness of case detection and treatment strategies. A cost per capita, cost per slide, and cost per case were quantified for major case detection and treatment mechanisms, and compared among the districts studied (Mills, 1992). Active case detection by monthly household visits and blood tests were the most costly per case when compared to passive case detection, detection by volunteers, and detection by malaria clinics. The results were consistent for all the districts (Mills, 1992). Control costs to households were determined by calculating treatment expenditures, loss of work days, and total costs (Mills, 1992, 1993). The study found that individuals spent sizeable amounts of money on private treatment services despite the availability of free malaria detection and treatment at nearby government facilities. The amount of money spent by an individual or a household depended on cash availability and accessibility to treatment facilities (Mills, 1992, 1993). Examples of the itemized costs incurred by an individual are treatment fees, drugs, laboratory expenses, special foods, sacrifices and worship, and travel (Mills, 1992). Mills (1993) found that workers lost 6-14 days of work per household and school-aged children lost 4-14 days of on average each year due to malaria in Nepal. Number of work days and school days lost were dependent upon the age, sex, severity of the disease, and speed of the treatment (Mills, 1993). The number of work days and school days lost varied among the districts (Mills, 1993,

Picard and Mills, 1992).

Researchers have continued to use data collected by Mills during her dissertation research (1984-1985) and have published the results in recent years. Morey et al. (2003) published the findings on willingness to pay and factors influencing the choice of improved malaria treatment. The study concluded that the cost of services was one of the most significant determinants of the choice of treatment. Gender, household size, and income, as well as the severity of malaria, also influenced willingness to pay for treatment and selection of treatments options (Morey et al., 2003). Sharma (2008) assessed treatment-seeking behaviors and analyzed the duration of care-seeking time from the onset of malaria symptoms among 469 malaria patients from the Dhanusha and Nawalparasi districts.

2.2.4.2 Malaria-related information dissemination

A content analysis of primary and secondary school textbooks was done to assess the effectiveness of malaria control programs in South Asian nations, including Nepal (Nonaka et al., 2013). Sixty-nine textbooks were collected from Nepal. All the textbooks evaluated were published by government agencies. Information about malaria first appeared in textbooks used in grade five and higher. The texts contained information related to transmission mode, vector, pathogens, signs, symptoms, and preventive measures. None of the texts provided information related to treatment. The malaria-related information in Nepal was typically found in health and physical education books. The analysis revealed inadequate content related to malaria information (Nonaka et al., 2013).

2.2.4.3 Knowledge, attitudes and perception related to malaria

Sherchand (1996) conducted a questionnaire-based household survey to assess the knowledge, attitudes, and behaviors of populations related to malaria and the role of the National

Malaria Control Program (NMCP) in controlling malaria. The research provided evidence of the presence of both traditional and modern methods and concepts regarding malaria, its treatment, and control (Sherchand, 1996). Presence of self diagnosis and self treatment related to malaria was also documented in the study.

A cross-sectional study was conducted in 2003 in the Kanchanpur district to assess community understanding and practices related to malaria, with comparison between two different ethnic groups, the Tharu and the Pahari (Budathoki and B.C, 2008). This study found that both groups were aware of basic malaria symptoms but did not know much about the severity of the disease in their neighborhoods. In cases of malaria infection, government facilities were used more by the Pahari groups than the Tharus. Both traditional and modern treatment approaches existed in the respondents' households. The Tharus tended to approach the traditional healers before going to the government health facilities because they were unaware that malaria diagnosis and treatment is free at these facilities (Budathoki and B.C, 2008). Joshi and Banjara (2008) conducted a cross sectional study in the Jhapa, Kanchanpur, and Kailali districts during December 2004 to April 2005 to assess malaria-related knowledge, practices and behavior of these Nepalese populations. The study revealed the prevalence of partial knowledge of malaria among the respondents and highlighted the need for malaria-related education to meet desired control goals.

Sharma (2008) assessed treatment-seeking behaviors and analyzed the duration of care-seeking time from the onset of malaria symptoms among 469 malaria patients from the Dhanusha and Nawalparasi districts. The data were collected in 1984 and 1985 (Mills 1994; Morey et al., 2003). The study revealed that care-seeking behavior is low in the first day of infection, then increases sharply within five days of recognizing symptoms before followed by a

gradual decline in treatment-seeking behavior. Since active house-to-house surveillance was going on during the study period, the patients had a tendency to wait for the visit of a malaria surveillance officer before seeking treatment on their own (Mills, 1994; Sharma, 2008). Women tended to wait longer than men, and people within the Dhanusha district had higher rates of wait time than those in the Nawalparasi district. The study also revealed a lack of awareness about malaria in general, its health implications and availability and access to care among the study participants.

Parajuli and Ghimire (2010) conducted a cross-sectional study among the people suspected of having malaria from the two districts, Jhapa and Morang, from the Eastern region. The study evaluated the knowledge, attitudes and practices of the study participants related to prevention and treatment of malaria infection. The study revealed that people in the Jhapa district had a higher rate of malaria infection than those in the Morang district, and that infection was related to recent travel to endemic regions. Knowledge related to malaria and preventive measures was poor in rural villages with inadequate accessibility to healthcare facilities. The study concluded that illiterate members of the population and laborers had higher rates of infection, their knowledge related to bed nets was insufficient, and there was a need for aggressive health education (Parajuli and Ghimire, 2010).

2.2.4.4 Use of chemo-prophylaxis to prevent malaria

Cave et al. (2003) did an assessment of chemoprophylaxis use to prevent malaria in foreigners travelling to Nepal. A cross-sectional questionnaire survey among 1303 respondents, conducted between June 2000 and May 2001, found that only 22% of the respondents were taking chemoprophylaxis specifically for their trip to Nepal. Travelers from the United Kingdom and Denmark took prophylactic medication in higher proportions than those from the United

States and Germany. The study suggested a lack of consensus and varying opinions regarding the necessity for and the actual use of chemoprophylaxis among travelers to Nepal. A need for better information dissemination was identified to protect against the risk of malaria infection and to avoid unnecessary use of the drugs.

2.2.5 Ecological research

A recently published systematic review of literature focused on climate change and the spatiotemporal distribution of vector-borne diseases in Nepal identified 50 papers on malaria out of which eight focused on climate change and spatiotemporal distribution of malaria (Dhimal et al., 2015). Among the eight papers, five were descriptive papers highlighting the fact that malaria transmission is seasonal in Nepal and that the climatic factors, particularly monsoonal precipitation and temperature in the Terai region, are important influences on malaria occurrence (Pradhan et al., 1970; Sakya, 1981; Dahal, 2008). The other three papers assessed the relationship between climatic factors and malaria cases (Bhandari et al., 2013; Dhimal et al., 2014c; Dhimal et al., 2014d). In the Jhapa district (Eastern Terai), Bhandari et al. (2013) did a study that considered the relationship between climatic factors and the incidence of malaria infection between 1987 and 2008. The study revealed a significant relationship between minimum and maximum temperature and rainfall. Dhimal et al. (2014c) investigated the impact of climatic factors along with control intervention in malaria transmission in 31 risk districts from 2004 through 2012. The study suggested that the risk of malaria epidemics in the highlands is likely to increase with increases in temperature.

2.3 Summary

Our current knowledge about malaria in Nepal comes both from government reports and journal articles. The literature suggests that the depth and breadth of malaria research has

increased since the 1990s. However, it has been restricted to selected districts of the Terai region. For example, the Jhapa district in eastern Nepal is one of the districts where most of the research has been conducted (Chand et al., 2003; Thapa, et al., 2007; Joshi and Banjara, 2008; Banjara, et al., 2009; Parajuli and Ghimire 2010; Ranjitkar, et al., 2011; Adhikari, et al., 2012). Other Terai districts which were the study sites for many research projects include Kanchanpur, Kailali, Dhanusha, Nawalparasi, and Morang (Mills, 1992; 1993, Dhimal et al., 2014c). A very limited number of studies have been done in malaria-endemic districts in the Hill and the Mountain regions (Pradhan, et al., 1970; Mills, 1992, 1993a, 1993b; Bishop and Litch, 2002; Singh, et al., 2006; Dhimal, et al., 2014c). Therefore, malaria research needs to be conducted in wider geographic regions. For most of the studies done during the last 10-15 years, sample sizes were small, and the studies were limited to one or two districts from a particular geographic region, with almost no follow-up studies. The topics addressed in these publications are important; follow up studies with larger samples covering wider geographic regions would be very useful.

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Chapter 3 - Space-Time Patterns of Malaria in Nepal: 1988-2013

Abstract

The malaria burden has decreased in Nepal in the last few decades. However, challenges exist in completely eradicating the disease from the country. The malaria patterns in a few high risk districts have not changed, and new patterns have emerged in districts which otherwise are categorized as low risk or no risk districts. This paper identifies malaria hot spots, describes their characteristics, and examines whether there have been shifts in malaria hot spots between 1988 through 2013. In 26 years, a total of 267,121 confirmed malaria cases were recorded. Altogether, 39 out of 75 districts were identified as malaria hot spots in Nepal. The highest average disease frequency (ADF) approximately 1964 was in Kanchanpur in 2003. The lowest ADF about 19 was recorded in Bardia, Surkhet, and Banke during 2013; all three districts are in the Far Western region. The identified hot spots were grouped into five different categories based on the frequency, persistence, and proportion of caseloads each year: stable, emerging, reemerging, intermittent and disappearing. Malaria hot spots were detected in both the Terai and the Hill. The majority of the stable hot spots are located in Far Western Terai, whereas the disappearing hot spots are located in the Central region. The emerging hot spots are located in the eastern parts of the country, whereas the intermittent hot spots are located throughout the country, mostly in the Hill.

3.1. Introduction

It is an established fact that malaria is endemic in Nepal and that the Terai region in the south is a higher risk region compared to the Hill and the Mountain regions (Jung, 2001; Pant et al., 2010; Dhimal et al., 2014b) (Figure 3.1). Malaria distribution in Nepal is geographically heterogeneous. This heterogeneous pattern occurs because malaria transmission is typically a

localized phenomenon. National figures of malaria cases have declined in past decades, however malaria incidence patterns in a few districts have not changed, and increased malaria case rates have been detected from districts which otherwise were categorized as low risk areas (EDCD, 2010; Kakchapati and Ardkaew, 2011; Dhimal et al., 2014b). There are still a few high risk districts, which report malaria incidence many times higher than the national average (DoHS, 2014). Therefore, it is important to analyze malaria prevalence in more detail and at finer spatial scales than it is typically done at the national level. Prevalence patterns need to be explored and investigated at multiple spatial and temporal scales. In order to analyze prevalence patterns at multiple scales, it important to determine if there is any within the country, and if there is, to determine whether the patterns have been transient over the study period, or persistent, or perhaps some combination of both. It is necessary to identify consistent malaria patterns, as well as to determine whether new patterns have emerged. Identification of spatio-temporal clustering and examining the characteristics of these geographic clusters, and determining whether the pattern have changed over time are effective ways to approach this problem. A district or a group of districts representing such geographic clustering pattern is termed as "malaria hot spot" in this paper. A disease hot spot is defined as an area where the concentration of cases or the anticipated numbers of cases are higher than average compared to surrounding areas (Keefe and Sullivan, 2011). Hot spots are detected via the presence of clustering patterns, which are determined by using statistical testing with a reasonable degree of confidence (Kulldorff, 1997; Keefe and Sullivan, 2011).

Annual reports of the Department of Health Services (DoHS), Epidemiology and Disease Control Division of Nepal (EDCD), and units of the Nepalese Ministry of Health have suggested that there has been wide variation in disease location in the country from year to year (EDCD,

2010; DoHS, 2014). According to these reports, malaria has been reported in 65 out of 75 districts, including the high altitude districts, with varying prevalence and intensity (Figure 3.2) (EDCD, 2010; Dhimal et al., 2014a, 2014b; DoHS, 2014). The government has identified 13 districts as high risk, 18 as moderate risk, and 34 as low risk; 10 districts are classified as having no malaria risk (Figure 3.2) (EDCD, 2010; DoHS, 2014; Dhimal et al., 2014b). Although these statistics suggest a heterogeneous distribution of the disease, it is necessary to look deeper into spatiotemporal pattern of malaria prevalence to investigate if there is in fact any spatiotemporal clustering within the country and, if so, where and when those clusters occur.

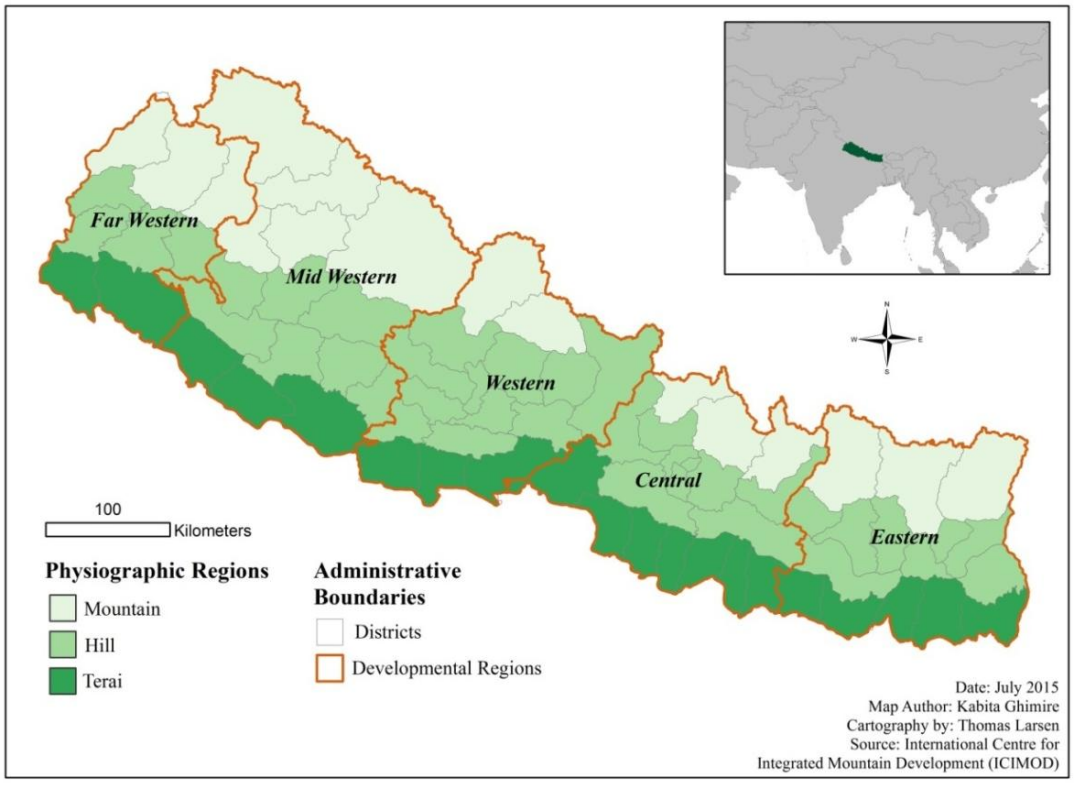


Figure 3.1: Nepal: Three physiographic regions, five developmental regions and 75 districts

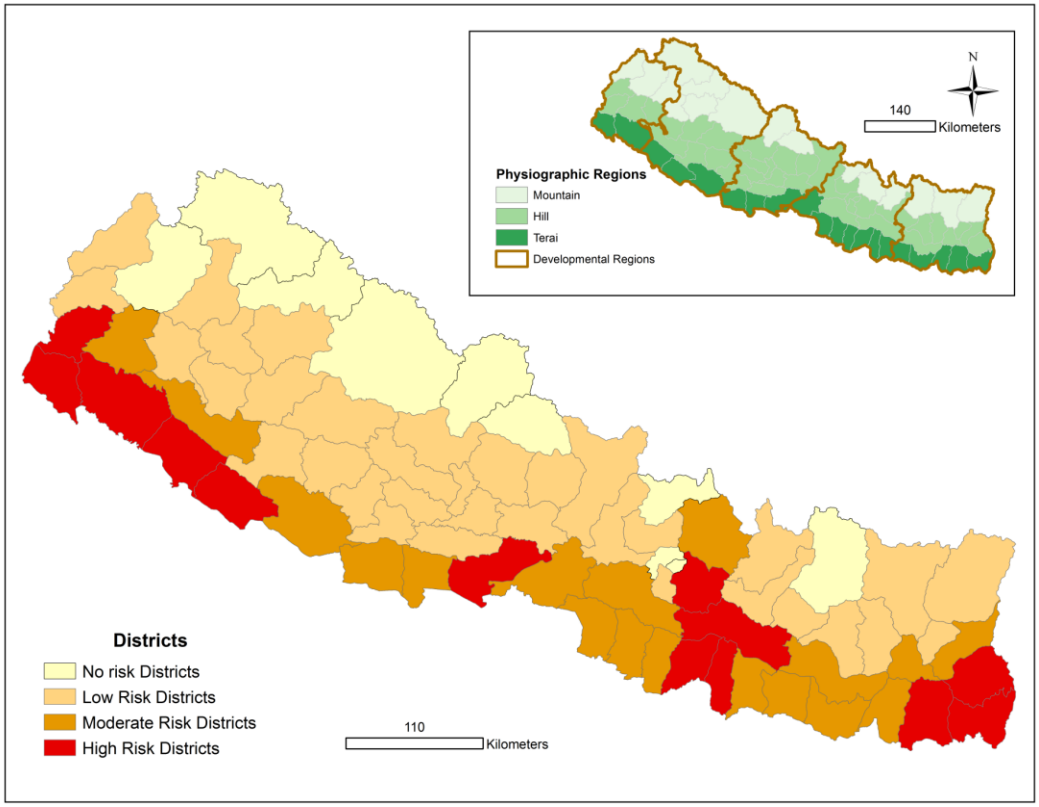


Figure 3.2: Classification of malaria risk by districts in Nepal (EDCD, 2010; Dhimal et al., 2014b; DoHS, 2014)

The objective of this study is to determine whether there is spatial and temporal clustering of malaria cases in Nepal, using districts as the spatial units of analysis between 1988 through 2013. A district or a group of districts representing such geographic clustering pattern is termed as malaria hot spot in this paper. Identified malaria hot spots will be further categorized into five categories, stable, emerging, reemerging, intermittent and disappearing malaria hot spots. Categorizing the malaria hot spots will not only clarify the geographic distribution of the disease, but also facilitate further investigation of its causes.

It is important to know whether there was a shift in malaria hot spots during these 26 years, and if the shift was significant. Identification of such hot spots can in turn shed light on the biophysical and socio-economic factors that influence the malaria transmission process.

Identifying high and low impact areas by detecting disease hot spots, comparing geographic variability of these hot spots, and providing maps of such variability will not only facilitate identification of regionally-specific causation, but also contribute to the formulation of better strategies for managing existing prevention and control programs. Such information will be useful in further investigation of location-specific etiological and non-etiological risk factors.

I will approach this analysis by addressing three general research questions:

1. What were the spatio-temporal patterns of malaria incidence in Nepal between 1988 and 2013?
2. Were there any malaria hot spots in Nepal between1988 and 2013?
3. Did the geographic patterns of malaria change between 1988 and 2013? Was there a shift in malaria hot spots between 1988 and 2013?

3.2. Study area

Nepal is a landlocked country, situated in South Asia between India and China, covering approximately 147, 181 square kilometers (Figure 3.1). The shape of the country is elongated, with approximate east–west length of close to 885 km and average north-south width of about 196 km, with a maximum of 241 km and a minimum of 145 km (Jung, 2001). The country is divided into three physiographic regions (Figure 3.1). To the south lie the humid plains, commonly referred as Terai, comprising 23% of the land area. Further north is the Hill region, encompassing 42% of the land area. The Mountain region, covering 35% of the land area, lies still further north, and is a region with increasing altitude.

Among the three physiographic regions, the Terai is the most densely populated, with about 50% of the country's population residing in the region; within the Terai, the eastern districts are more populated than the western districts. About 43% of the population lives in the

Hill region and 7% live in the Mountain region (Jung, 2001; CBS, 2012; Kakchapati and Ardkaew, 2011). For administrative purposes, the country is divided into 5 developmental regions, 14 zones, and 75 districts (Figure 3.1). The districts are further divided into 59 municipalities and more than 3000 Village Development Committees (VDCs). The VDCs are further divided into wards, which are the smallest administrative units in the country. Most Nepalese people (80%) live in rural areas. Agriculture and subsistence farming are the main economic activities, and provide livelihoods for more than 70% of the population.

3.3 Data and Methods

3.3.1. Data

3.3.1.1 Malariometric data

The research in this paper is based on secondary data obtained from the government of Nepal and World Health Organization (WHO) publications. Three major data sources are used to create a district-wise malariometric database for a 26-year study period (1988-2013). The primary sources of data are the Nepal Epidemiology and Disease Control Division (EDCD), Nepal Office of Health Management Information System (HMIS), Nepal Department of Health Services (DoSH), Government of Nepal, and WHO publications. Information for the study period 1988-1996 was transcribed from a WHO publication (Jung, 2001). Epidemiological information from 1997-2013 were transcribed from DoHS annual reports (DoHS, 1997-2014). The data were transcribed electronically using an Optical Character Recognition (OCR) technique (ASI, 2015). The data were crosschecked with both electronic and hard copies of DoHS annual reports and WHO publications to maintain the quality and consistency of the information during the transcription process.

Currently the government of Nepal relies on the passive surveillance, regular reporting of disease by local staff, of malaria indicators at different administrative levels of public health facilities in each district. As a routine monitoring program, the government collects malariometric indicators at health care facilities throughout Nepal. The national center at EDCD in Kathmandu maintains the aggregated database for each district, collected primarily at the community level, Sub-Health Post, and Health Post of the districts. At the end of the fiscal year, national and district-level malaria information is released in an annual report, along with other health-related information. The data acquisition process, analysis methods, and dissemination details are described in HMIS annual reports (DoHS, 1997-2014)

Common malariometric indicators used to measure and record malaria incidence and prevalence in the country include:

1. Malaria cases: A person becomes a malaria case when he or she is infected with a malaria parasite as evidenced by microscopic examination of their blood, regardless of the presence or absence of clinical symptoms (Jung, 2001; DoHS, 2013).
2. Clinical malaria: A passive way of malaria surveillance in high endemic countries where the resources are limited. A case is detected based on the clinical manifestation such as fever, chills, and shivering. This method does not detect individuals who may carry parasites without symptoms; over-diagnosis can also happen when episodes of fever are not malaria (Jung, 2001; Olotu et al., 2011).
3. Population at risk: the number of individuals living in malaria risk regions (Jung, 2001; Kulldorff, 1999).

4. Annual Parasitic Incidence (API): (Confirmed cases during a year)/ (population under surveillance) x 1000. This index is calculated based on blood slide examination. The number of blood slides examined and the slide positivity rate influence the value of API (Jung, 2001; EDCD, 2010).
5. Average Disease Frequency (ADF): Average disease frequency is the ratio of the total case count over the total population at risk for the particular year, reported as the number of positive cases per 100,000 population (Kulldorff, 1999).

Yearly ADFs for each of the 75 districts between 1988 and 2013 were used in the analysis. ADF was used because it considers the total population of the district and accounts for differences in population across time and space (Kulldorff, 1999). The years 1988-2013 are considered because of the availability of the data. The district-wise malaria cases (spatial unit used for data analysis in this paper), are available only from 1988. The time frame also provides a good overview of malaria in the past and at the current time.

3.3.1.2. Spatial data

Spatial data for this study were obtained from the International Center for Integrated Mountain Development (ICIMOD) (geoportal.icimod.org/downloads). The data include national, regional, and district-level vector layers (shape files of administrative and physiographic boundaries). The vector layers were later edited to create a geo-database of malariometric indicators for each of 75 districts for 26 years, 1988-2013 using *ArcGIS* 10.2 (Appendix-A) (ESRI, Redlands, CA).

3.3.1.3. Census data

Population data were obtained from the Census Bureau of Statistics (CBS) for the census years 1981, 1991, 2001, and 2011, and statistical yearbooks of Nepal published by the CBS, National Planning Commission Secretariat (NPCS), and Government of Nepal (CBS, 1992; CBS, 2002; CBS, 2012). Linear interpolation based on the population at the census times preceding and following was used to calculate the population for the non-census years. Like malariometric data, the census data were also transcribed electronically using an Optical Character Recognition (OCR) technique at Kansas State University. Scanned data were cross-checked with both electronic and hard copies of the census reports and statistical yearbooks to maintain quality and consistency.

3.3.2. Spatial analysis methods

Spatial autocorrelation measures the degree of similarity between space and phenomenon under study, malaria case distribution in this case. Such measurement is done by detecting clusters, identifying contagious area of higher or lower occurrence, which are not likely to appear by chance (Jacquez et al., 2002). Two techniques are used commonly in detecting such similarity. The first of these measures, global spatial autocorrelation, detects global clustering effects, overall pattern and trend of the data (Goodchild, 1986; Griffith, 1987; Andy, 2005). Global methods determine the second order clustering effects and only detects the presence or absence of spatial patterns within an entire study area; they do not provide specific details such as location, size, and characteristics of the clusters (Goodchild, 1986; Griffith, 1987; Ord and Getis 2001; Andy, 2005; Wen et al., 2015). Geary's C and Moran’s I are the two most widely used statistical techniques for detecting global spatial patterns. Of the two, Moran’s I is , more commonly used, a weighted correlation coefficient used to detect departures from spatial

randomness (Moran, 1950; Ord and Getis, 2001;Andy, 2005). The Moran's I statistics for spatial autocorrelation is given as (Moran, 1950; Griffith, 1987; Andy, 2005):

$$I = \frac{n}{S_0} \frac{\sum_{i=1}^{n} \sum_{j=1}^{n} w_{i,j} \ Z_i Z_j}{\sum_{i=1}^{n} z_i^2} \qquad (3.1)$$

where z_i is the derivative of an attribute for feature *i* from its mean $(x_i\text{-}X)$, $w_{i,j}$ is the spatial weight matrix between spatial unit *i* and *j*, *n* is equal to the total number of spatial units, and S_o is the aggregate of all the spatial weights.

$$S_0 = \sum_{i=1}^{n} \sum_{j=1}^{n} w_{i,j} \qquad (3.2)$$

The Z_I-score for the statistic is computed as:

$$z_I = \frac{I - E[I]}{\sqrt{V[I]}} \qquad (3.2)$$

where

$$E[I] = -1/(n-1) \qquad (3.4)$$

$$V[I^2] = E[I]^2 \qquad (3.5)$$

The second is a localized spatial autocorrelation technique which measures the first order spatial clustering effects (Anselin, 1995; Ord and Getis, 2001; Wen et al., 2015). It evaluates the spatial arrangement of features for each of an areal subunits and identifies an existence of clusters within a study area (Wen et al., 2015; Jacquez et al., 2002; Kulldorff, 1997). Localized clusters account for the difference in pattern in different parts of the study area. This approach provides specific and detailed information about clusters, such as location, size and magnitude of the phenomenon being analyzed − in this case malaria incidence (Jacquez et al., 2002; Kulldorff,

1997; Keefe and Sullivan, 2011). LISA (Local Indicator of Spatial Association) (Anselin,1995), Getis-Ord G (Ord and Getis, 2001), Kulldorff's scan (Kulldorff, 1997) are few statistical techniques commonly used to measure local spatial autocorrelation. The commonly used local Moran's I statistics for spatial autocorrelation is given as (Anselin, 1995):

$$I_i = \frac{\sum_{i=1}^{n}\sum_{j=1}^{n} w_{i,j}(z_i - \overline{z})(z_j - \overline{z})}{S_z^2 \sum_{i=0}^{n} w_{ij}} \tag{3.6}$$

where i and j represents various spatial units, z_i and z_j is the residuals of location i and j respectively, $\overline{z}$ is the mean of the residual and w_{ij} is the spatial weight matrix for measuring proximity between i and j locations.

Both global and local spatial autocorrelation detection techniques were used to determine the space-time pattern of malaria in Nepal (Appendix-B, C). Oden's I_{pop} technique, a population-adjusted form of the global Moran's I, was used to detect the global spatial pattern (Moran, 1950; Oden, 1995; Jacquez et al., 2002; Fosgate et al., 2002; Jackson et al., 2010). The Oden's I_{pop} was developed as an alternative for data with varying population size. This techniques is used to test for global spatial autocorrelation adjusting for heterogeneous population among the spatial units. The Oden's I_{pop} statistic is two-sided and calculates a standard normal z score. Positive values of I_{pop} indicate that connected areas are similar and show a tendency toward a clustered pattern, whereas negative values indicate that the distribution in connected areas is uniform. I_{pop} is large when there is clustering within or among spatial units. The Oden's I_{pop} is defined as (Oden, 1995):

$$I\,pop = \left[n^2 \sum_i \sum_j w_{ij}^* \,(e_i - v_i)(\,(e_j - v_j) \right.$$

$$- \; n\,(1 - 2\bar{b}) \sum_i w_{ii}^* \, e_i$$

$$\left. - \bar{b} \sum_i w_{ii}^* \, v_i \right] x \frac{1}{\bar{b}(1-\bar{b})(n^2 + \sum_i \sum_j v_i v_j w_{ij}^* - x \sum_i v_i \, w_{ii}^*)}$$

(3.7)

where $\bar{b} = y + \frac{1}{n+} =$, $v_i = n_i/n_+$, $v_j = n_j/n_+$, $e_i = y_i/y_+$, $e_j = y_j/y_+$, and $w_{ij}^* = w_{ij}/\sqrt{v_i v_j}$. Oden noted that symmetry is not required for I^*_{pop} and $w_{ii} \neq 0$ (but can be fixed at any specified value). Global clustering was evaluated on a year-by year basis for the entire 26 years of the study period using Cluster Seer 2.9 (Biomedware, 2015; Jacquez et al., 2002).

Kulldorff's scan technique was used to investigate local clustering patterns. The Kulldorff's technique detects local clusters by analyzing the aggregated count of disease for given geographic regions, taking population into consideration. The technique works on the assumption that the number of cases in each area is Poisson distributed proportionally to its population (Kulldorff, 1997; Boscoe et al., 2003). This method identifies the clusters by searching over a given set of spatial regions, which maximizes a likelihood ratio statistics. The goal of this statistics is to find areas where the disease rate is higher inside the area than the outside. The Kulldorff's Likelihood ratio (LLR) for given zone z, may be given by (Kuldorff, 1997):

$$LLR = \frac{P(Data|H_1(s))}{P(Data|H_0)} \quad (3.8)$$

where the null hypothesis H_0 assumes a uniform disease rate $q=q_{all}$. Under $H_1(S)$, here the assumption is that $q=q_{in}$ for all $s_i \in S$ and $q=q_{out}$ for all$s_i \in G - S$, for some constant $q_{in}>q_{out}$. Using maximum likelihood estimate of q_{in}, q_{out}, and q_{all}:

$$LLR = \left(\frac{C_{in}}{Pop_{in}}\right)^{C_{in}} \left(\frac{C_{out}}{Pop_{out}}\right)^{C_{out}} \left(\frac{C_{all}}{Pop_{all}}\right)^{-C_{all}} \quad , \quad \text{if } \left(\frac{C_{in}}{Pop_{in}}\right)^{C_{in}} > \left(\frac{C_{out}}{Pop_{out}}\right)^{C_{out}},$$

LLR =1 otherwise.

In the expression $C_{in} = \sum_S C_i$, $C_{out} = \sum_{G-S} C_i$, $C_{all} = \sum_G C_i$, and similarly, $Pop_{in} = \sum_S Pop_i$, $Pop_{out} = \sum_{G-S} Pop_i$, $Pop_{all} = \sum_G Pop_i$.

where q = disease rate probability ; q_{out} = probability of disease rate outside the spatial unit S_i; q_{in} = probability of disease rate inside the spatial unit S_i; G= total spatial units; C_{in} =disease cluster inside the current location; C_{out} = disease rate outside current location; Pop_{in} = Population inside the current location; Pop_{out} = population outside the current location; Pop_{all} = Total population of the study area.

Kulldorff's scan is gaining popularity as a tool for identifying disease clusters and unusual disease patterns because it is conceptually straight-forward and is capable of identifying clusters of any size, located anywhere within a study area (Kulldorff 1997, Boscoe et al., 2003; Kulldorff, 2014). The Kulldorff technique can use purely spatial, purely temporal, and/or spatio-temporal approaches to identify and evaluate clusters. The biggest advantage of this method is, the uneven geographic density of a background population is adjusted in scan statistics for all discrete probability models. For this application, the analysis focused on the total number of observed cases (Kulldorff, 2014). In this paper, the purely spatial technique is used (Appendix-C).

3.4. Results

3.4.1. Spatio-temporal distribution of malaria by physiographic regions

Altogether, 267,121 confirmed malaria cases were recorded from 1988 through 2013. The number of cases decreased markedly during the study period: the highest ADF of approximately 157 (29,019 cases) was recorded in 1991 and the lowest ADF of about eight (2167 cases) was recorded in 2013 (Table 3.1). The higher numbers of cases in 1991 were likely due to a resurgence of outbreaks during that year. After the onset of outbreaks, there was an increase in intervention efforts, which led to a sharp decline in cases during 1992-94. This brief resurgence, followed by an effective intervention campaign, resulted in a new trend in malaria incidence in Nepal. Since then, the annual ADF has stayed under 55. After 1996, when the ADF was close to 43, slight increases in case numbers were noticed only in 2002 (ADF 44) and 2003 (ADF 51). The ADF has remained near 20 since 2008 (Table 3.1; Figure 3.3).

Out of 75 districts in Nepal, only five remained malaria-free throughout the 26-year study period. Among the 70 districts where cases were reported, the Terai region had the highest percentage of total malaria reports at 67%, 29% of the malaria cases were reported from the Hill region, and the Mountain region contributed 4% of total malaria cases (Figure 3.4). Humla, Manang, and Solukhumbu were the three malaria-free districts from the Mountain region. The other two malaria-free districts, Kathmandu and Bhaktapur, were located in the Hill region. Fourteen districts, mostly from the Mountain and the Hill regions had less than 100 cases of malaria during the study period. Seven districts from the Terai and the Hill accounted for more than 10,000 cases each in the last 26 years. Kanchanpur district, in the Far Western Terai (total cases, 33,489) and Kavre district from the Central Hill (total cases 25,880) accounted for the highest number of cases during the study period.

Since 1988 a total of 9836 malaria cases were reported from 13 out of 16 mountain districts. Humla, Manang, and Solukhumbu are the only three districts from the Mountain region which remained malaria-free throughout the study period. The districts of Mustang and Dolpa each recorded one case in 1998 and two cases in 2003. Sindhupalchowk (5316), Darchula (1792), Sankhuwasabha (1212), Taplejung (727), and Rasuwa (532) are four of the 16 mountain districts which recorded the highest caseloads. Reports from the Mountain region show decreasing trends in malaria cases. The majority of cases from these districts were recorded during the earlier phase of the study period, mostly before 2001. Sindhupalchowk district saw a sharp decline in malaria cases after 2000. There was no record of malaria in the district after 2007, except for one case in 2011. Malaria case distribution averages for the research period are shown in Figure 3.4.

Table 3.1: Malaria cases in Nepal, 1988-2013.

Year	Risk population (millions)	Total cases	ADF (cases per 100,000 population)	No of Districts with cases higher than ADF	No of Districts with no malaria cases
1988	17.45	24548	141	19	26
1989	17.79	22133	124	21	26
1990	18.14	20414	112	19	25
1991	18.49	29019	157	17	25
1992	18.95	23046	122	22	25
1993	19.42	16386	84	24	25
1994	19.88	9942	50	24	28
1995	20.35	9530	47	21	29
1996	20.82	8978	43	15	24
1997	21.28	8165	38	17	20
1998	21.75	8513	39	20	20
1999	22.21	7328	33	13	15
2000	22.68	9313	41	13	20
2001	23.15	6188	27	13	23
2002	23.48	10446	44	9	21
2003	23.82	12086	51	7	21
2004	24.15	6365	26	9	24
2005	24.48	4563	18	11	16
2006	24.82	5691	23	9	16
2007	25.15	5293	21	12	21
2008	25.49	4574	18	15	25
2009	25.82	3589	14	19	25
2010	26.16	3051	12	17	22
2011	26.49	2991	11	13	27
2012	26.45	2802	11	15	28
2013	26.78	2167	8	18	26

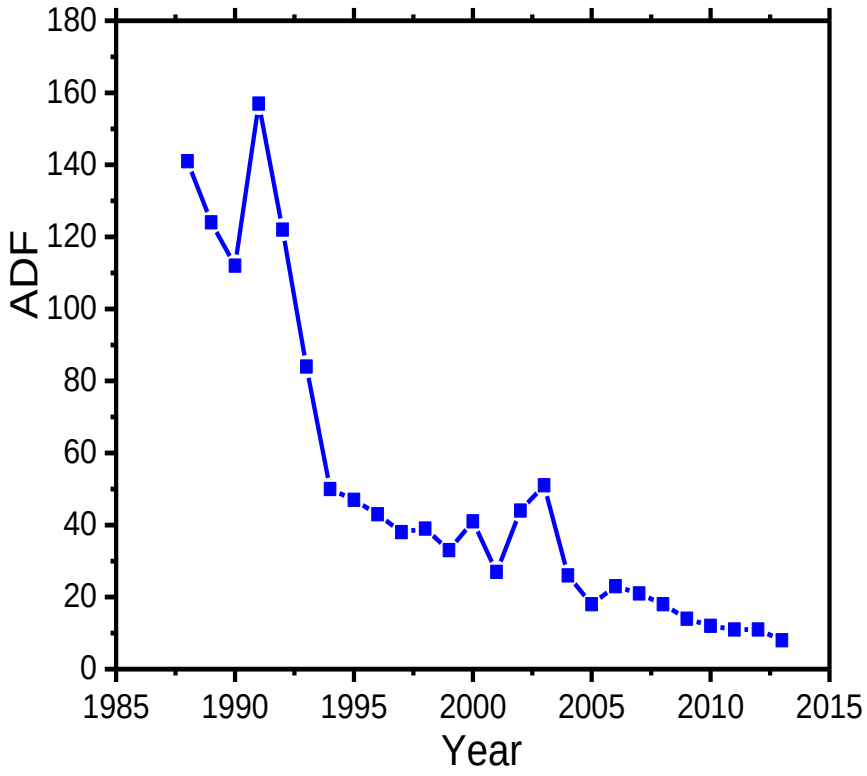
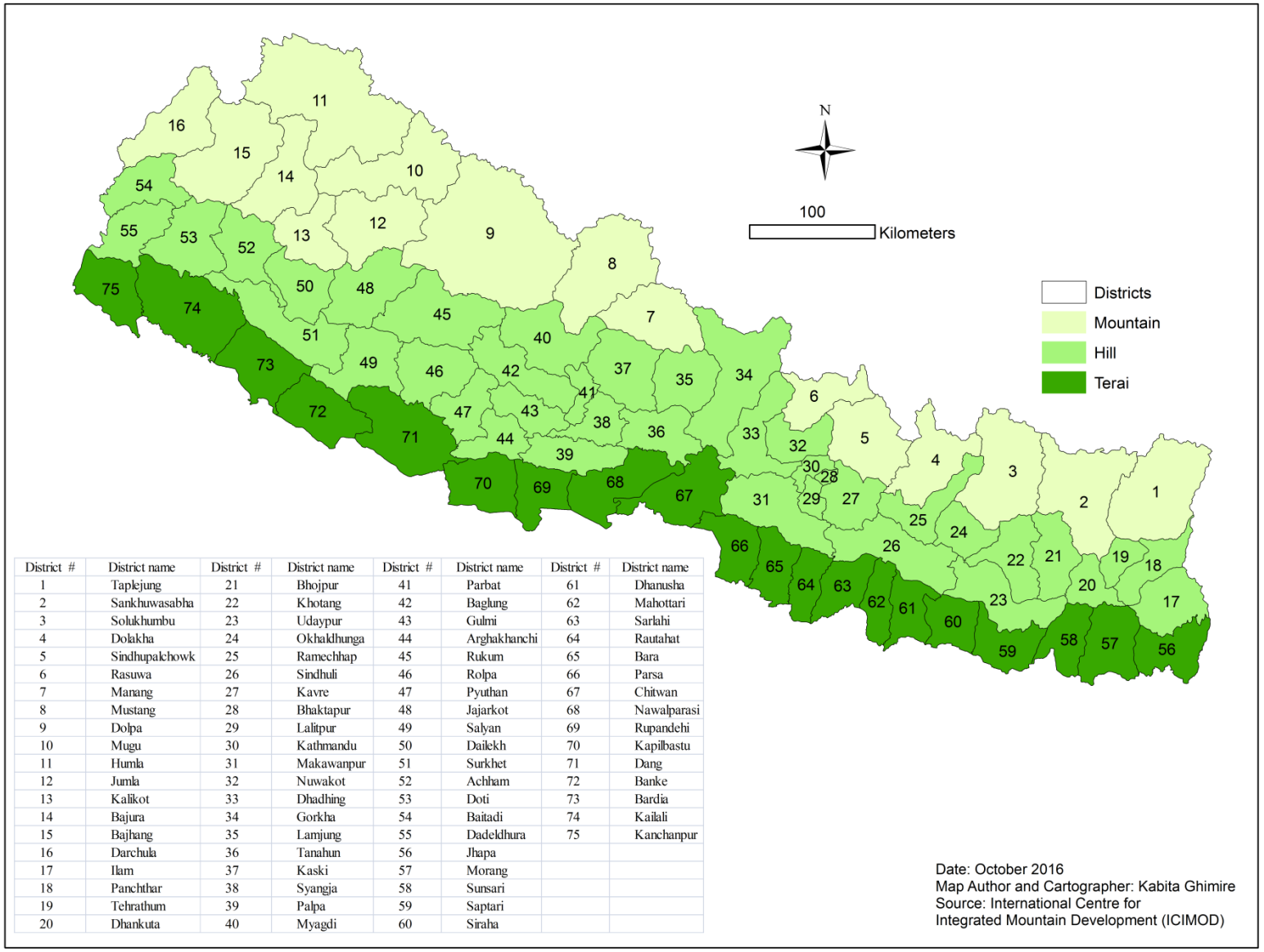


Figure 3.3: Annual Average Disease Frequency (ADF) (malaria frequency per 100, 000 populations), 1988-2013. (Data Sources: Jung, 2001; EDCD, 2010; DoHS, 1997-2014)



District #	District name	District #	District name	District #	District name	District #	District name
1	Taplejung	21	Bhojpur	41	Parbat	61	Dhanusha
2	Sankhuwasabha	22	Khotang	42	Baglung	62	Mahottari
3	Solukhumbu	23	Udaypur	43	Gulmi	63	Sarlahi
4	Dolakha	24	Okhaldhunga	44	Arghakhanchi	64	Rautahat
5	Sindhupalchowk	25	Ramechhap	45	Rukum	65	Bara
6	Rasuwa	26	Sindhuli	46	Rolpa	66	Parsa
7	Manang	27	Kavre	47	Pyuthan	67	Chitwan
8	Mustang	28	Bhaktapur	48	Jajarkot	68	Nawalparasi
9	Dolpa	29	Lalitpur	49	Salyan	69	Rupandehi
10	Mugu	30	Kathmandu	50	Dailekh	70	Kapilbastu
11	Humla	31	Makawanpur	51	Surkhet	71	Dang
12	Jumla	32	Nuwakot	52	Achham	72	Banke
13	Kalikot	33	Dhadhing	53	Doti	73	Bardia
14	Bajura	34	Gorkha	54	Baitadi	74	Kailali
15	Bajhang	35	Lamjung	55	Dadeldhura	75	Kanchanpur
16	Darchula	36	Tanahun	56	Jhapa		
17	Ilam	37	Kaski	57	Morang		
18	Panchthar	38	Syangja	58	Sunsari		
19	Tehrathum	39	Palpa	59	Saptari		
20	Dhankuta	40	Myagdi	60	Siraha		

Figure 3.4: Nepal Districts

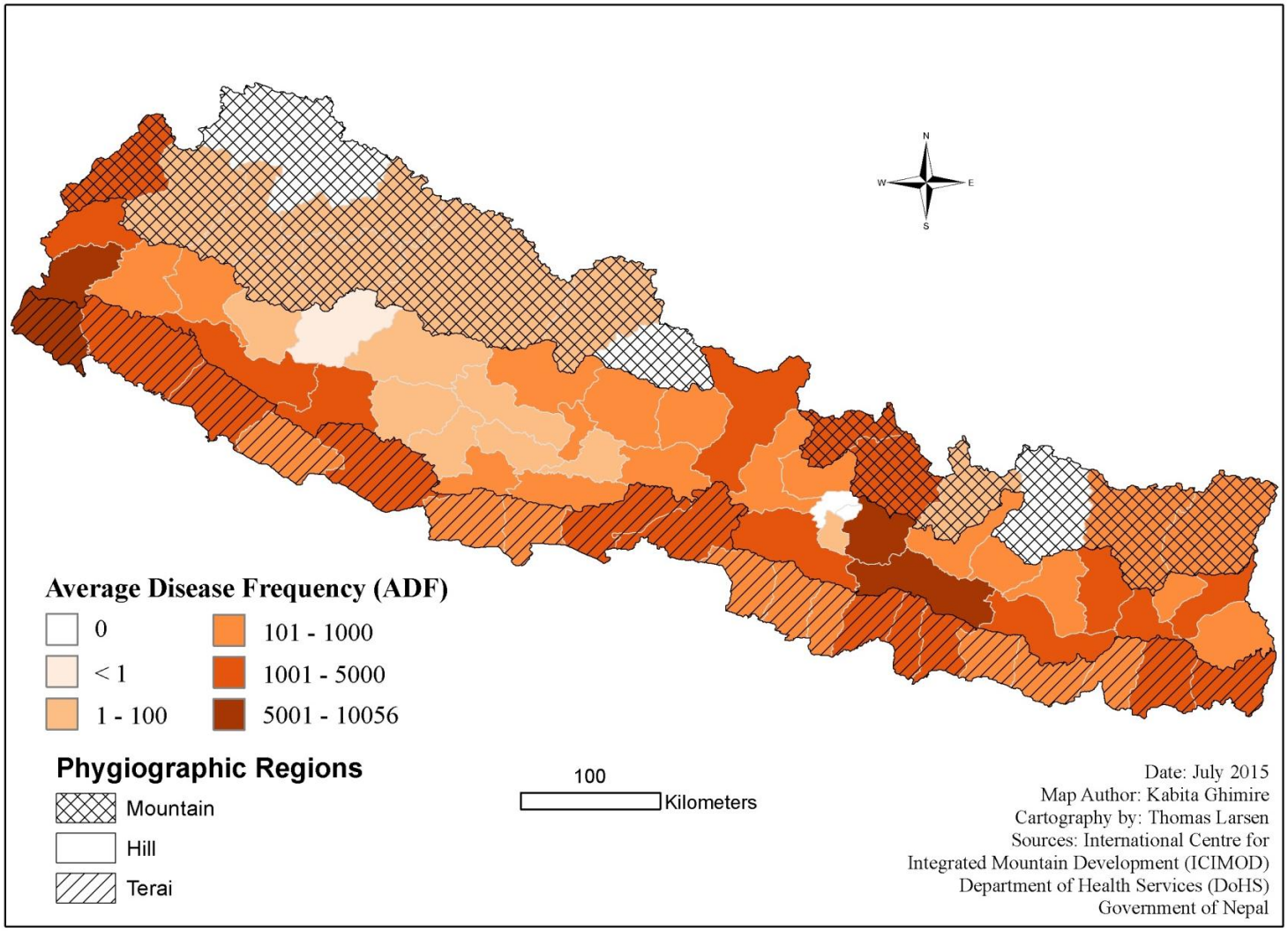


Figure 3.5: Annual Average Disease Frequency (ADF) (malaria frequency per 100, 000 population), 1988-2013 (Data Sources: Jung, 2001; DoHS, 1997-2013)

Malaria cases were reported in 36 of 38 districts from the Hill region. Kathmandu and Bhaktapur districts from the Kathmandu valley were the two districts which did not have any record of malaria cases. Jajarkot, from the Western Hill region, reported only one case during the 26-year study period. In aggregate, Kavre, Dadeldhura, Surkhet, Bhojpur, and Makawanpur districts had high numbers of cases during the study period. At the end of the study period, in 2013, Dadeldhura, Baitadi, Surkhet, and Palpa had the highest caseloads from the Hill region. Within the Terai, six districts − Kanchanpur, Dhanusha, Jhapa, Sindhuli, Kailali and Bardiya, from highest to lowest − had the largest numbers of caseloads. These observations suggest that there is a distinct pattern in geographic distribution of malaria in Nepal.

3.4.2 Spatiotemporal distribution of malaria hot spots

Analysis of Oden's I_{pop} suggests that significant spatial clustering occurred throughout the study period, and confirms the presence of malaria hot spots (Table 3.2). The $I_{pop'}$ was positive for all 26 years, suggesting the presence of spatial autocorrelation in each year. The highest $I_{pop'}$ was observed in years 2002 (6.622) and 2003 (8.24). The lowest $I_{pop'}$ was observed in 1994 (0.68) and 1995 (0.88). Analysis of Oden's I_{pop} also suggests a clustering pattern within and among districts (Figure 3.5). The clustering effect in all years resulted more from the number of cases within districts than from cases in adjacent districts, except for the most recent two years. For the years 2012 and 2013, the clustering effects of adjoining districts were more than the clustering effects within the districts. The contribution of adjacent districts to the clustering effect started decreasing in 1994, but then started increasing again in 2002, reaching approximately 41% in 2011. With the declining number of cases in higher incidence districts, the effect of lower incidence districts becomes more apparent.

Table 3.2: Population-adjusted Moran's I (Oden I_{pop}) for spatial clustering of reported malaria cases in Nepal, 1988-2013.

Year	I_{pop}	I_{pop}' (Test (statistics)	E[I]	Alpha level	% within[a]	% among[b]	p-value
1988	0.00168961	1.2011	-5.73E-08	0.05	66.613889	33.386111	0.002
1989	0.00163025	1.3109	-5.62E-08	0.05	67.224394	32.775606	0.002
1990	0.00123484	1.09755	-5.51E-08	0.05	67.557205	32.442795	0.002
1991	0.00273116	1.74031	-5.41E-08	0.05	62.099586	37.900414	0.002
1992	0.00141609	1.16485	-5.28E-08	0.05	68.505967	31.494033	0.002
1993	0.00078392	0.92922	-5.15E-08	0.05	77.548929	22.451071	0.002
1994	0.000344859	0.689898	-5.03E-08	0.05	104.302932	-4.302932[b]	0.002
1995	0.00041513	0.886681	-4.91E-08	0.05	108.928484	-8.928484 [b]	0.002
1996	0.000671754	1.5579	-4.80E-08	0.05	94.22626	5.77374	0.002
1997	0.000337036	0.878701	-4.70E-08	0.05	84.911026	15.088974	0.002
1998	0.000311594	0.796217	-4.60E-08	0.05	95.425018	4.574982	0.002
1999	0.000444838	1.3488	-4.50E-08	0.05	88.480024	11.519976	0.002
2000	0.000718128	1.74928	-4.41E-08	0.05	111.445449	-11.445449 [b]	0.002
2001	0.000469785	1.75763	-4.32E-08	0.05	104.104698	-4.104698 [b]	0.002
2002	0.00294537	6.62208	-4.26E-08	0.05	92.346867	7.653133	0.002
2003	0.00418488	8.24789	-4.20E-08	0.05	91.123403	8.876597	0.002
2004	0.000939824	3.56651	-4.14E-08	0.05	82.753244	17.246756	0.002
2005	0.000394146	2.1153	-4.08E-08	0.05	85.458984	14.541016	0.002
2006	0.000565387	2.4661	-4.03E-08	0.05	91.683681	8.316319	0.002
2007	0.000353533	1.68032	-3.97E-08	0.05	79.041979	20.958021	0.002
2008	0.000214783	1.19702	-3.92E-08	0.05	78.498115	21.501885	0.002
2009	0.000110919	0.798155	-3.87E-08	0.05	61.042731	38.957269	0.002
2010	0.000138719	1.18941	-3.82E-08	0.05	63.797234	36.202766	0.002
2011	0.000239076	2.11775	-3.77E-08	0.05	58.044426	41.955574	0.002
2012	0.00012388	1.18615	-3.73E-08	0.05	37.37873	62.62127	0.002
2013	0.00012254	1.53607	-3.68E-08	0.05	47.843653	52.156347	0.002

Percentage of estimated spatial clustering attributed to cases in the same districts and in adjacent districts. [b]All identified clustering attributed to cases in the same district. [b] Identified clustering attributed to cases among the districts. Negative value in % demonstrates dispersion of cases in adjacent districts. The Monte Carlo simulation method is used because the data may not be normally distributed.

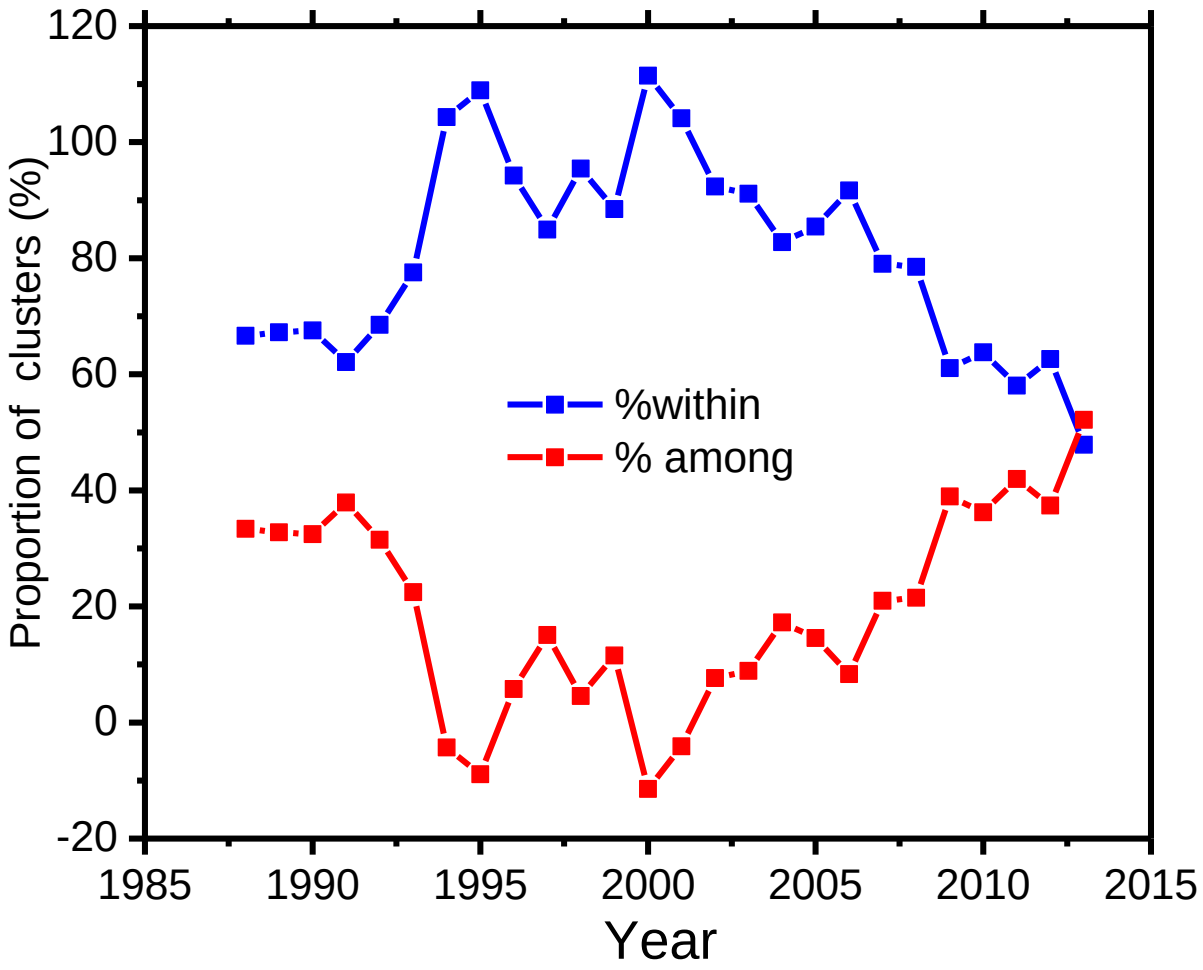


Figure 3.6: Population-adjusted Moran's I (I_{pop}) analysis for spatial clustering of reported malaria in Nepal, 1988-2013. Percentage of estimated spatial clustering attributed to cases in same districts and in adjacent districts. Negative values for among district percentages in years 1994, 1995, 2000, 2001 demonstrate dispersion (no cluster) of cases in adjacent districts.

Analysis of Oden's I_{pop} also suggests a clustering pattern within and among districts (Figure 3.6). Kulldorff's spatial scan analysis was therefore used to identify the locations and durations of these hot spots within the country. The Kulldorff's scan identifies three distinct clusters: the first likely cluster, the second likely cluster, and the third likely cluster. The technique also provides an Overall Average Disease Frequency (OADF) for the study period and

an ADF for each cluster. The location, size, and magnitude of malaria incidence in these hot spots varied with time. In some years, hot spots were comprised of single district clusters; in other years multiple districts constituted a single hot spot.

Since malaria incidences declined significantly in the country over 26 years studied, it is important to evaluate the clustering patterns at multiple time scales to see if there were shifts in the location of hot spots. When data aggregation is done for longer time periods, a few high incidence years and districts with higher caseloads tend to dominate the formation of clusters. At the coarsest time scale, relatively low intensity areas do not contribute to the formation of clusters. Therefore, while studying and investigating a disease pattern in space, analysis should be done at multiple time scales to get a better understanding of patterns.

To better understand these space-time patterns, the entire study period was subdivided into four different time intervals. The first analysis was done for all 26 years of aggregated data and revealed clustering at the coarsest temporal scale (Figure 3.6). Subsequent analyses were done at progressively finer time scales, dividing the 26 years into 13-year, 5-year, and 1-year intervals. The one-year interval is the finest time scale of the study. Using this approach hot spots were identified in both in the Terai and in the Hill regions of the country. At the coarser scale (scale of analysis 26 years; 1 interval), nine districts were identified in three clusters. The second time interval (13 years; two periods) identified 13 districts in three clusters. The third analysis, at a 5 year time interval, identified 15 districts in three clusters. The final analysis, at the finest temporal scale with a 1-year time interval (26 intervals), identified 39 districts in four clusters.

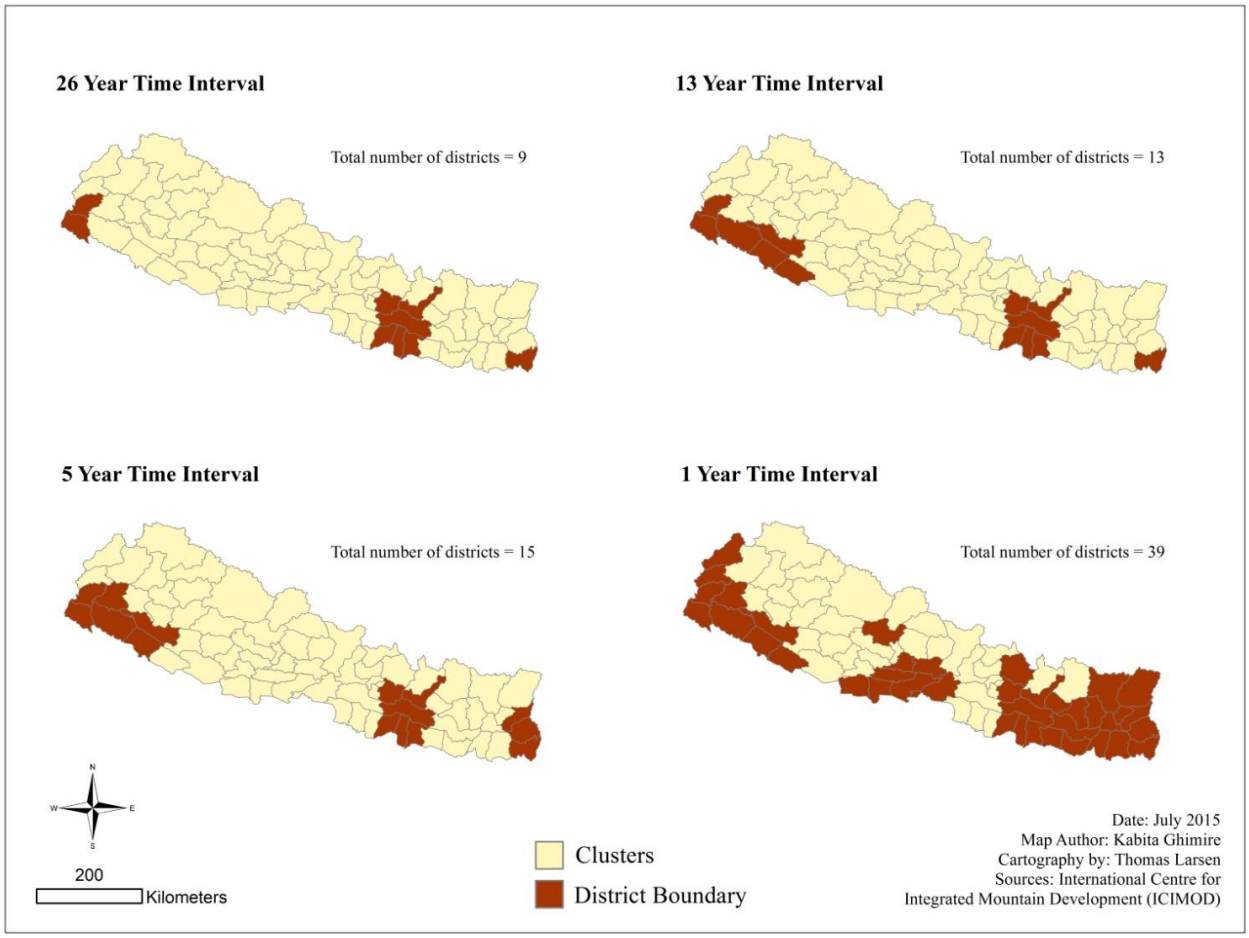


Figure 3.7: Summary of the district-based distribution of clusters at four different time intervals.

3.4.2.1. Malaria hot spot at the 26-year time scale

Among the three clusters identified for the entire 26-year study period (Table 3.3, Figure 3.7), the most likely cluster included Kanchanpur and Dadeldhura districts from the Far Western region. The second cluster included six districts and was detected in the Central region. The districts are Sindhuli, Mahottari, Ramechhap, Dhanusha, Sarlahi, and Kavre. Among these 6 districts, Dhanusha, Mahottari and Sarlahi are from the Terai region, whereas Kavre, Ramechhap, and Sindhuli are from the Hill region. The ADF for the first likely cluster was

approximately 319, almost 7 times higher than the OADF (46) for the 26-year time interval. The ADF of the second likely cluster was close to 122, approximately 3 times more than the OADF, and the third likely cluster includes an isolated cluster within a single district, Jhapa, from the Eastern Terai of Nepal. The ADF of this cluster was about 100, more than 2 times higher than the OADF.

Table 3.3: Kulldorff's Spatial Scan at the 26-year time scale and 13-year time scale

Year/Cluster	Districts	ADF	LLR	P-value
26 years(1988-2013)		**45.55***		
First likely cluster	Kanchanpur, Dadeldhura	318.792	45844.00	0.001
Second likely cluster	Sindhuli, Mahottari, Ramechhap, Dhanusha, Sarlahi, Kavre	121.54	36060.1	0.001
Third likely cluster	Jhapa	99.9906	4535.8	0.001
13 years (1988-2000)		**76***		
First likely cluster	Sindhuli, Mahottari, Ramechhap, Dhanusha, Sarlahi, Kavre	236.899	41350.1	0.001
Second likely cluster	Kanchanpur, Dadeldhura	253.82	14633.2	0.001
Third likely cluster	Bardiya, Surkhet	168.92	3185.09	0.001
13 years (2001-2013)		**21.34***		
First likely cluster	Kanchanpur	372.155	42098	0.001
Second likely cluster	Jhapa	100	8035.35	0.001
Third likely cluster	Bardiya, Surkhet, Banke, Kailali	49.69	3756.17	0.001

*Overall Average Disease Frequency (OADF) for that study period; ADF = Average Disease Frequency ; LLR = Log Likelihood Ratio (compares the goodness of fit of two models, null model and the alternative model)

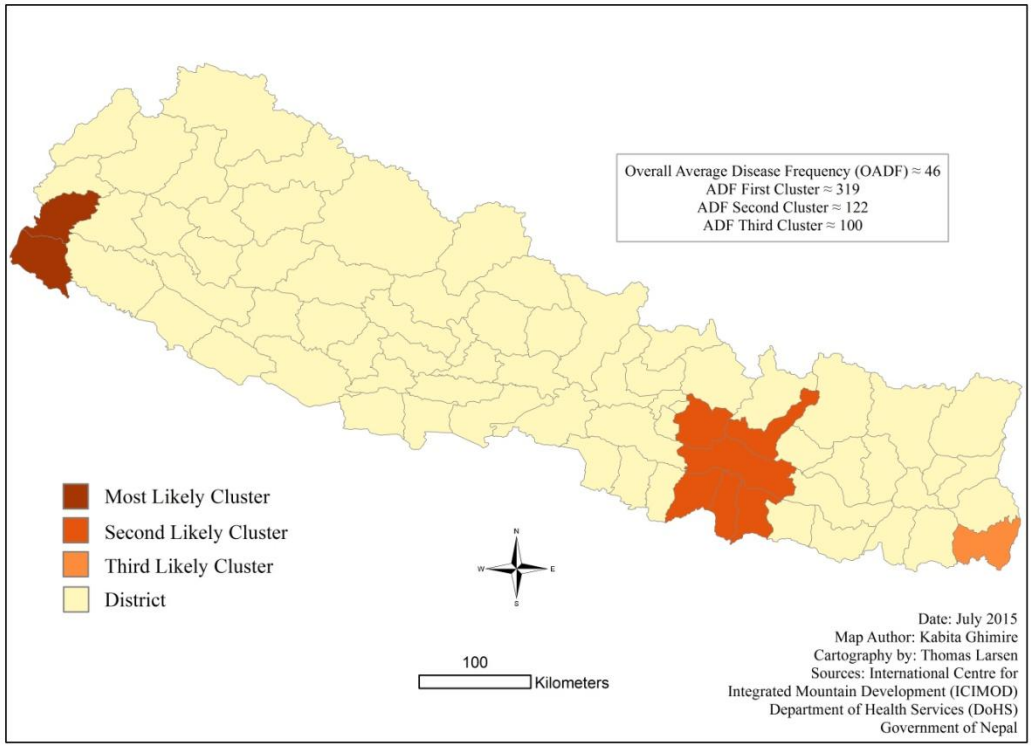


Figure 3.8: Malaria hot spots detected at the coarsest temporal scale, 26-year time interval.

3.4.2.2. Malaria hot spot at the 13 year time scale

Dividing the study period into two time intervals of 13 years, the Kulldorff's scan technique identified clusters comprised of 13 districts, an increase of four districts as compared to the overall 26-year time frame. The analysis revealed that the OADF during the first 13- year interval (OADF ≈ 76) was more than three times higher than that the of the second 13-year interval period (OADF ≈ 21) (Figure 3.8). The first and second likely clusters were located in the Far Western part of the country; the third likely cluster was located in the Central part of Nepal during the first 13- year interval. In the second 13 years, the Central region cluster identified earlier disappeared. A new cluster in the Eastern part of the country, the Jhapa district, emerged and the cluster from the Far Western region remained with changed size.

During the first 13-year time interval, six districts from the Central region, Sindhuli, Mahottari, Ramechhap, Dhanusha, Sarlahi, and Kavre, were identified in the first likely cluster. The second cluster included two districts from the Western region, Kanchanpur and Dadeldhura. Finally, the third cluster consisted of Bardiya and Surkhet districts from the Western region. The ADF of the first, second, and third likely clusters were approximately 273, 254, and 169, respectively. A total of six districts were identified during the second 13-year time interval. The first and second likely clusters included one district each, Kanchanpur from the Far Western region and Jhapa from the Eastern region. The third cluster included four districts, Kailali, Bardiya, Banke, and Surkhet from the Far Western and Western regions. The first likely cluster had an ADF of ≈372, which was 18 times higher than the OADF of ≈21 for that time interval. The second and third likely clusters had ADFs of approximately 100 and 50, respectively.

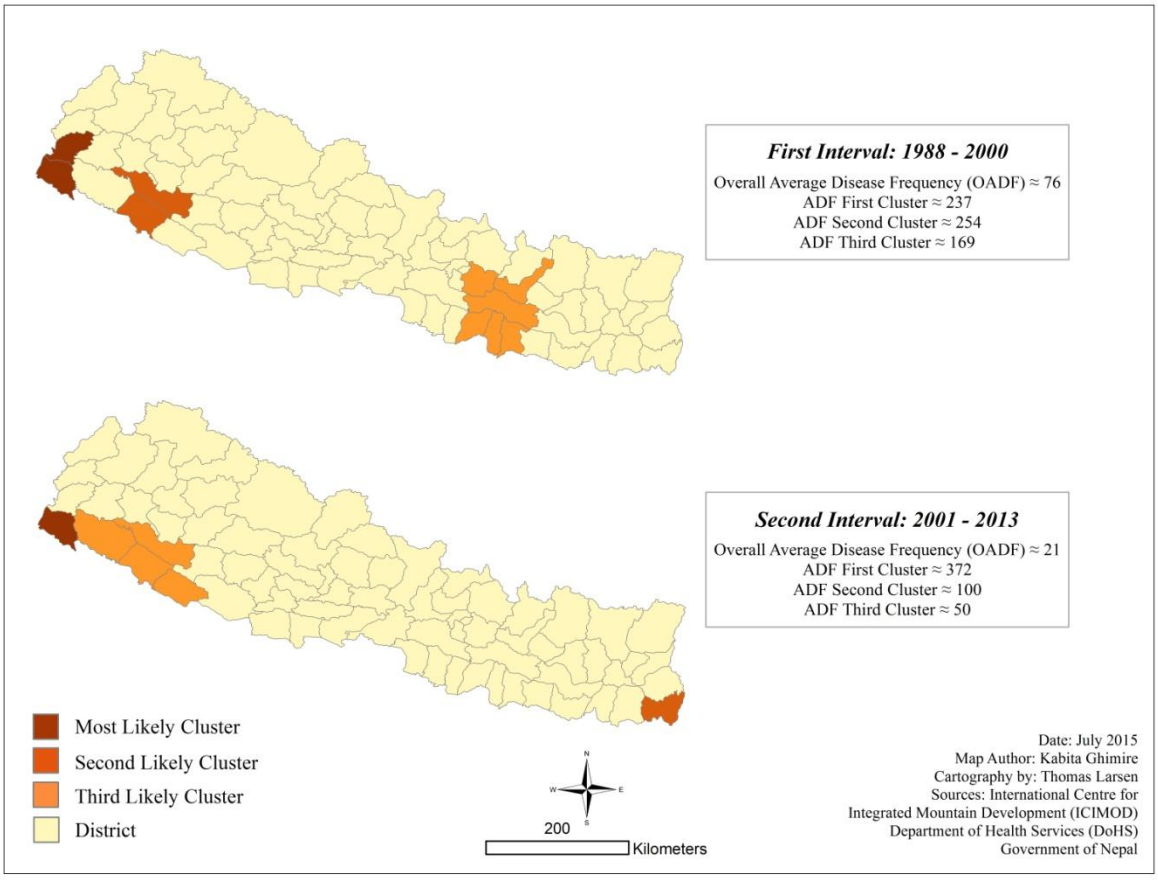


Figure 3.9: Details of malaria hot spots at the 13-year time interval, a total of 13 districts were identified as hot spots.

3.4.2.3. Malaria hot spots at the 5-year time scale

For the 5-year time scale, the study period was subdivided into 5 intervals; interval 1 (1988-1992), interval 2 (1993-1997), interval 3 (1998-2002), interval 4 (2003-2007), and interval 5 (2008-2013). Since the entire study period was 26 years the 5th interval consists of six years instead of five. The analysis shows a gradual decrease in ADF in consecutive time intervals. The average disease frequency for the first, second, third, fourth and fifth time intervals was close to 131, 52, 36, 28 and 12, respectively. The first interval had an OADF higher than that for the 26-year time interval and for the first interval of the 13-year time scale. The remaining four

5-year time intervals had OADF values less than the previous 26-year and 13-year periods (Tables 3.3-3.4). The analyses at this time scale identified 15 districts in clusters (Figure 3.8). The 12 districts identified at the 13-year time interval were part of these 15 districts. The three new districts were Ilam and Panchthar from the Eastern part of the country and Doti from the Western part of the country, all from the Hill region. The Doti district emerged as a hot spot during the third time interval (1998-2002). Panchthar and Ilam emerged during the fourth time interval (2008-2013).

3.4.2.4. Malaria hot spots at annual time scale (or 1 year time scale)

At the finest temporal scale, the analysis was run for individual years. A total of 39 districts were clustered to identify disease hot spots throughout the study period. The numbers of districts identified were more than 4 times higher than for the 26-year time scale, three times higher than for the 13-year time scale, and more than double that of the five-year time scale. Analysis of 2009, with an OADF of ≈14, yielded the highest number of districts (23). There were 19 districts with an ADF ≈25 in the first likely clusters, 3 districts with an ADF ≈47, and 1 district with an ADF ≈32 (Table 3.6). The OADF for the year at the beginning of the study period, 1988, was 141, the ADF for first likely, second likely, and the third likely clusters were ≈1225, ≈392, and ≈904, respectively. Years 1991 and 2002, the peak years, had OADF values of ≈157 and ≈45. Similarly, the OADF, for the year at the end of the study, 2013 was ≈8. In 2013, the first likely, second likely, and the third likely clusters had ADF values of ≈45, ≈22, and ≈19, respectively.

Table 3.4: Kulldorff's Spatial Scan results, with first, second, and third cluster details at 5-year time intervals.

Year	District	ADF	LLR	p-value
Interval 1 (1988-1992)		**131***		
First likely cluster	Sindhuli, Mahottari, Ramechhap, Dhanusha, Sarlahi, Kavre	422.9	27549.6	0.001
Second likely cluster	Kanchanpur, Dadeldhura	690.46	10784.2	0.001
Third likely cluster	Bardiya, Surkhet	298.27	2028.96	0.001
Interval 2 (1993-1997)		**52***		
First likely cluster	Kavre	557.00	15008.5	0.001
Second likely cluster	Kanchanpur, Dadeldhura	211.56	2983.17	0.001
Third likely cluster	Mahottari, Dhanusha, Sarlahi, Sindhuli	97.26	1654.14	0.001
Interval 3 (1998-2002)		**36***		
First likely cluster	Kailali, Doti, Kanchanpur, Dadeldhura, Bardiya	179.61	13781.2	0.001
Second likely cluster	Kavre	339.89	8964.74	0.001
Third likely cluster	Dhanusha	120.81	2049.85	0.001
Interval 4 (2003-2007)		**28***		
First likely cluster	Kanchanpur	623.95	29934.8	0.001
Second likely cluster	Jhapa	184.51	7650.05	0.001
Third likely cluster	Kailali	72.64	885.764	0.001
Interval 5 (2008-2013)		**12***		
First likely cluster	Kanchanpur, Dadeldhura, Kailali	60.70	4464.80.09	0.001
Second likely cluster	Ilam, Panchthar, Jhapa	38.167	1483.6	0.001
Third likely cluster	Dhanusha, Mahottari	27.90	662.849	0.001

***Overall Average Disease Frequency (OADF) for that study period ; ADF = Average Disease Frequency; LLR = Log Likelihood Ratio**

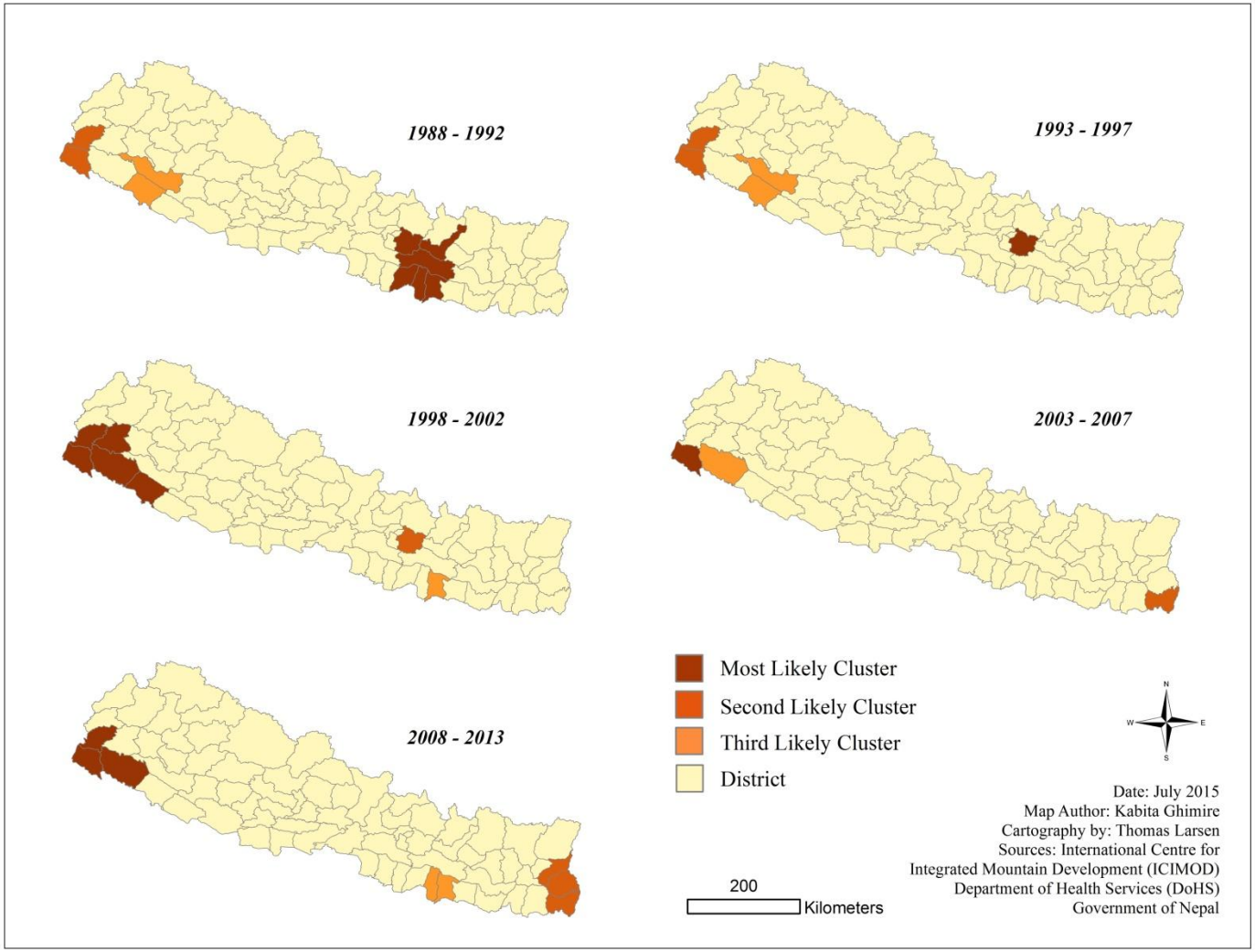


Figure 3.10: Malaria hot spots at 5-year time intervals

Table 3.5: Kulldorff's Spatial Scan with first, second, and third cluster details, 1 year time scale

Year/cluster	Districts	ADF	LLR	p-value
1988		**141***		
First	Kanchanpur, Dadeldhura	1224.98	5460.04	0.001
Second	Sindhuli, Mahottari, Ramechhap, Dhanusha	391.75	2234.31	0.001
Third	Surkhet	903.817	1961.83	0.001
1989		**124***		
First	Dadeldhura, Baitadi, Kanchanpur	999.42	7050.86	0.001
Second	Sindhuli, Mahottari, Ramechhap, Dhanusha, Sarlahi, Kavre	303.706	2372.11	0.001
Third	Darchula	539	377.838	0.001
1990		**112***		
First	Mahottari, Dhanusha, Sarlahi, Sindhuli	402.74	4421.67	0.001
Second	Bardiya	1009.65	3872.43	0.001
Third	Kanchanpur	569.85	1196	0.001
1991		**157***		
First	Sindhuli, Mahottari, Ramechhap, Dhanusha, Sarlahi, Kavre	704.4	14772.9	0.001
Second	Dadeldhura	431.928	171.285	0.001
Third	Jhapa	209.184	48.427	0.001
1992		**121***		
First	Sindhuli, Mahottari, Ramechhap, Dhanusha, Sarlahi, Kavre	451.387	7527.76	0.001
Second	Dadeldhura	497.196	350.281	0.001
Third	Sindhupalchowk	312.985	283.356	0.001
1993		**84***		
First	Ramechhap, Sindhuli, Kavre, Sindhupalchowk, Dhanusha,	306.4	4279.66	0.001
Second	Kanchanpur, Dadeldhura, Kailali	157.9	228.558	0.001
Third	Jhapa, Morang, Ilam	127.927	166.939	0.001
1994		**50***		
First	Kavre	510.6	2623.05	0.001
Second	Mahottari, Dhanusha, Sarlahi, Sindhuli	103.03	447.837	0.001
Third	Dadeldhura, Baitadi, Kanchanpur	212.9743	283.657	0.001
1995		**47***		
First	Kavre	580.1	3432.24	0.001
Second	Kanchanpur, Dadeldhura, Kailali	136.269	552.59	0.001
Third	Bhojpur	171.091	198.679	0.001
1996		**43***		
First	Sindhupalchowk, Kavre	438.724	4380.55	0.001
Second	Kanchanpur, Dadeldhura	322.173	1685.61	0.001

Third	Chitwan, Tanahu, Nawalparasi	73.5595	114.665	0.001
Year/ Cluster	**Districts**	**ADF**	**LLR**	**p-value**
1997		**38***		
First	Sindhupalchowk, Kavre	228.947	1519.93	0.001
Second	Kanchanpur, Dadeldhura	236	1085.12	0.001
Third	Chitwan, Tanahu, Nawalparasi	120.703	761.425	0.001
1998		**39***		
First	Nawalparasi	272.827	1649.49	0.001
Second	Kavre	245.869	935.794	0.001
Third	Kailali, Doti, Kanchanpur, Dadeldhura, Bardiya	107.158	701.749	0.001
1999		**33***		
First	Bardiya, Surkhet	281.337	2463.35	0.001
Second	Bhojpur	314.089	885.664	0.001
Third	Sindhupalchowk, Kavre	151.575	800.856	0.001
2000		**41***		
First	Kavre	720.6	5660	0.001
Second	Dhanusha	211.815	1237.39	0.001
Third	Kailali, Doti, Kanchanpur, Dadeldhura, Bardiya, Surkhet	110.4	888.843	0.001
2001		**27***		
First	Kavre	431.45	3287.32	0.001
Second	Kailali, Doti, Kanchanpur, Dadeldhura, Bardiya	107.923	1371.45	0.001
Third	Dhanusha	83.859	272.69	0.001
2002		**44***		
First	Kanchanpur	1546	17417	0.001
Second	Bardiya	227.82	756.297	0.001
Third	Dhanusha	96.9538	163.184	0.001
2003		**51***		
First	Kanchanpur	1964.5	23829	0.001
Second	Kailali	126.13	266.29	0.001
Third	Kavre	127.038	158.765	0.001
2004		**26***		
First	Kanchanpur	598.8	5673.18	0.001
Second	Jhapa	157.829	1173.51	0.001
Third	Bardiya, Surkhet, Banke, Kailali	63.86	379.163	0.001
2005		**19***		
First	Kanchanpur	301.052	2422.94	0.001
Second	Jhapa	131.043	1139.83	0.001
Third	Taplejung, Panchthar	77.3283	173.563	0.001

Year/ Cluster	Districts	ADF	LLR	p-value
2006		**23***		
First	Jhapa	305.045	4278.35	0.001
Second	Kanchanpur	268.71	1821.96	0.001
Third	Panchthar	96.9853	131.525	0.001
2007		**21***		
First	Illam, Panchthar, Jhapa	168.296	2910.34	0.001
Second	Banke	93.5156	311.427	0.001
Thrd	Dhanusha, Mahottari	56.0881	285.173	0.001
2008		**18***		
First	Illam, Panchthar, Jhapa	97.67	1201.11	0.001
Second	Dhanusha	89.6194	560.883	0.001
Third	Kanchanpur, Dadeldhura, Kailali	55.54	354.04	0.001
2009		**14***		
First	Saptari, Udaypur, Siraha, Sunsari, Khotang, Bhojpur, Dhankuta, Dhanusha, Morang, Okhaldhunga, Mahottari, Sindhuli, Tehrathum, Ramechhap, Sankhuwasabha, Panchthar, Jhapa, Illam, Sarlahi	24.5461	448.405	0.001
Second	Kanchanpur, Dadeldhura, Kailali	46.4608	338.529	0.001
Third	Kapilbastu	32.8553	53.1685	0.001
2010		**12***		
First	Kailali, Doti, Kanchanpur, Dadeldhura, Bardiya, Surkhet	463.342	808.988	0.001
Second	Jhapa	61.85	452.819	0.001
Third	Bhojpur	48.7765	61.0758	0.001
2011		**11***		
First	Kanchanpur, Dadeldhura, Kailali	90.5006	1734.9	0.001
Second	Jhapa	37.5315	223.837	0.001
Third	Bardiya, Surkhet	32.0307	102.993	0.001
2012		**11***		
First	Dadeldhura, Baitadi, Kanchanpur, Doti, Kailali	52.2425	915.612	0.001
Second	Dhanusha, Mahottari	25.24	112.91	0.001
Third	Myagdi	70.4473	85.4071	0.001
2013		**8***		
First	Dadeldhura, Baitadi, Kanchanpur, Doti, Kailali	45.4501	926.069	0.001
Second	Rupandehi, Palpa	22.312	108.168	0.001
Third	Bardiya, Surkhet, Banke	18.6113	72.1125	0.001

***Overall Average Disease Frequency (OADF) for that study period ; ADF = Average Disease Frequency; LLR = Log Likelihood Ratio**

3.4.2.5. Categories and characteristics of malaria hot spots

Malaria cases in Nepal have been geographically clustered. In 26 years, 39 districts contributed to the formation of hot spots whose location, size, and magnitude varied over time (Tables 3.3-3.5; Figures 3.4- 3.7). Based on this space-time pattern, the identified malaria hot spots are grouped into five different categories: 1) stable, 2) disappearing, 3) reemerging, 4) emerging, and 5) intermittent hot spots (Figure 3.11). The stable hot spots are those areas where malaria incidences were persistently and proportionately higher throughout the study period. Disappearing hot spots are the areas where malaria incidences were higher during the beginning of the study period and where the clustering effect diminished in subsequent years and finally disappeared toward the end. The reemerging hot spots are those areas where the clustering effect was present at the beginning of the study period, disappeared in the middle years, and reemerged in later years. Emerging hot spots are areas where the clusters begin to appear in the later years. Intermittent hot spots are in the districts that were identified only once or twice during the study time. Based on the ADF of the cluster, the number of times a district appeared to form the hot spots, and the time period they appeared as a hot spot, 24 districts were placed into one of the first four hot spot categories. The remaining 15 districts that appeared as hot spots only once or twice are included in the intermittent hot spot category (Figure 3.11).

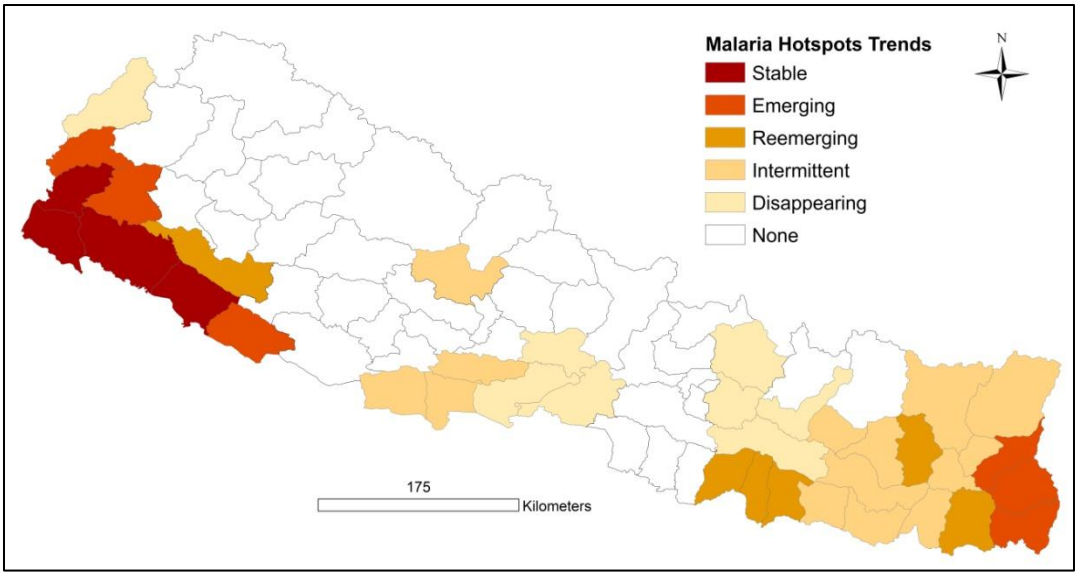


Figure 3.11: Stable, emerging, reemerging, intermittent, and disappearing malaria hot spots in Nepal, 1988-2013.

5. Discussion and Conclusion

The epidemiology of malaria infection has changed in Nepal, with the number of reported cases declining significantly. Various malaria prevention and control campaigns contributed significantly in reducing the malaria burden in the country. Major successful control activities identified include vector control through insecticide sprays, distribution and use of both insecticide treated and regular bed nets, and introduction of artemisinin-based combination therapy (ACT) as an alternative treatment for *P. falciparum* cases (Dhimal et al., 2014b).

The government of Nepal has categorized its 75 districts into 4 malaria risk zones: high, moderate, low, and no risk zones, based on the annual parasite incidence (API) in the districts. API is calculated based on the number of blood slides examined and does not account for the differences in population size. Among the 75 districts, 13 were categorized as a high-risk, 18 as moderate risk, 34 as low risk, and 10 as no risk districts (Figure 3.2) (ECDC, 2010; Dhimal et al.,

2014b). The details of malaria distribution within risk zones have not been provided and the disease distributions among the districts within the risk zones are assumed to be uniform. Nepal is preparing to eradicate malaria by 2026; therefore it is very important to identify the characteristics of the risk zones in more detail. This research investigated and provides space-time patterns of disease distribution by district, considering the population and annual reported malaria cases for each district. The results of this study suggest that there was a distinct space-time pattern of malaria distribution in Nepal between 1988 and 2013. The distribution pattern of disease within the risk zones also varies significantly.

Multiple disease hot spots have identified in this research. The study also revealed that malaria hot spots shifted from the Central region to the Eastern region, while the stable hot spots include four districts, Kanchanpur, Kailali, Dadeldhura, and Bardiya within the Far Western region. The location of the sporadic or intermittent hot spots varied year to year. Intermittent hotspots are located in the Far Western, Western, Central, and Eastern administrative regions, the majority are in the Hill physiographic region.. Almost all of the stable, emerging, and reemerging hotspots are in the districts bordering the endemic malaria areas in India, similar to the findings of Kakchapati and Ardkaew (2011).

Identification of the disease clusters, or hot spots, is an approach to identifying geographic variation. It does not identify the causation of such patterns. If one is to identify the causes of the geographic patterns of the disease, identifying the hotspots is a necessary preliminary step. If we are to understand the spatial pattern of the disease in the country, it is important to identify and examine the contributing factors, both biophysical and socioeconomic, which play important roles in creating such patterns. In general, the Far Western region, home to the stable malaria hot spots, is relatively inaccessible and underdeveloped as compared to the

other regions of the country. Every year during the monsoon season the region faces several flooding events which lead to conditions that favor mosquito breeding; the population living below the poverty line is higher and the availability and accessibility of medical infrastructure is limited in the region. Especially in the Terai, the region has a suitable climate for malaria occurrence and transmission year round.

The diminishing pattern observed within the Central region is a result of multiple malaria control and prevention efforts in the area: the malaria control program in Nepal was initiated in the Central region Jung, 2001; Dhimal et al., 2014b). Significant efforts to control, eliminate and eradicate malaria from the region have been made since the 1950s and continue to the present time. The emerging and reemerging hotspots became apparent once the disease started declining and the annual ADF started decreasing significantly. Most of the time, the emerging and reemerging hotspots, such as Jhapa, Bhojpur, Dhanusha, and Mahottari districts, accounted for average or above average disease frequency each year. However, due to the presence of other dominant malaria hot spots, the pattern became less visible and started becoming more apparent in subsequent years as the case rate in the other districts started declining. Identifying the contributing factors behind the intermittent malaria hot spots is a challenge because the hot spots are distributed throughout the country and each year they are somewhat different. The presence of intermittent malaria hot spots suggests the contribution of local scale phenomena, such as microclimate, land use/land cover changes at a finer scale, local socio-cultural practices, or demographic and economic conditions in creating patterns which differ year-to-year.

The cases reported from the Mountain region were based on passive surveillance, a common practice where healthcare providers report the disease on a case by case basis, suggesting incomplete and inadequate reporting from the area access to health care is highly

limited in the region. There is a need for independent studies focusing on the Mountain region with the aims of understanding the occurrence and distribution patterns specific to the region and investigating the reasons behind the occurrence of malaria. Five of the 75 districts, three from the Mountain region and two from Kathmandu Valley in the Hill region, did not record any malaria cases throughout the study period. Kakchapati and Ardkaew (2011) reported six districts without malaria between 1998 and 2009. In the last few decades, there has been significant population growth in the two districts from the Kathmandu Valley, Kathmandu and Bhaktapur; these have been identified as 'no malaria risk' districts. The demographic change within the valley, with the majority of migrating populations coming from high endemic regions and a noticeable increase of mosquitoes in the area, suggest the potential existence of malaria transmission in the valley ((CBS, 1992, 2002, 2012; DoHS 2014; Dhimal et al., 2014a). A recent independent study also suggests the presence of malaria in the Kathmandu Valley (Singh et al., 2006). Therefore, independent studies need to be conducted in the valley to identify the current malaria situation as the environmental and socioeconomic conditions are increasingly favorable for malaria occurrence and transmission. The population of the districts has increased more than 60% in the last decade, and the influx of travelers to the valley from within and outside the country is very high. The country's only international airport is located in the valley and is the only entry and exit point for all visitors traveling by air.

This research has identified the geographic distribution of malaria hot spots at the district level in Nepal, complementing existing knowledge and providing a more detailed picture of malaria distribution within the country. Identification of malaria hot spots at a finer scale, both spatial (Village Development Committee or municipality level) and temporal (monthly, weekly), needs to be conducted to further understand the patterns within the five identified malaria hot

spot categories. The microclimate, land use practices, medical infrastructure, and population distribution vary significantly within the district-level hot spots. Identifying the hot spots at finer scales will help identify areas for priority attention and prime time of malaria occurrence, and will facilitate the efficient allocation of limited malaria control and prevention resources within districts. This will also help identify the areas of frequent epidemics, which were not visible at the scale of the analysis done here. Separating cases by (pathogen-specific) infection types and differentiating indigenous cases versus imported cases while identifying local scale hot spots will also help provide specific details of disease incidence, ultimately contributing to the overall goal of malaria eradication.

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Chapter 4 - Detecting Relationships between Climatic Factors and Malaria Distribution in Nepal using Panel Data Models, 1988-2013

Abstract

The aim of this paper is to investigate the relationship between the climate variables, during the monsoon and non-monsoon seasons, and malaria disease frequency in Nepal at the district level during 1988 through 2013 using panel data models based regression analysis. The first panel analysis tested if the presence and absence of malaria is related to climatic factors. The results of the first analysis revealed that the likelihood ratio chi square ($LR\chi^2$) is 97.57 with a p-value <0.00, indicating that the relationship is highly significant. The monsoon maximum temperature, monsoon minimum temperature, non-monsoon minimum temperature, and monsoon precipitation showed significance in the model with $p < 0.05$. The odds ratio (OR) is greater than 1 for two out of six predictors; monsoon minimum temperature (OR=1.27) and non-monsoon minimum temperature (OR=1.84) suggesting that the monsoon and non-monsoon minimum temperatures are the best predictors of the absence and presence of malaria at the district level. The second analysis tested the relationship between the climatic factors and the low and high frequency of malaria. The $LR\chi^2$ for the second analysis is 37.43 with a p-value <0.00, suggesting the significance of the model. Out of six predictors only three variables, monsoon maximum temperature, monsoon precipitation, and non-monsoon precipitation have shown significance in the model with p-value <0.05. The OR is >1 for monsoon maximum temperature and almost 1 for precipitation variables. The second analysis identified maximum temperature during monsoon season is the likely predictor of high and low frequency of malaria along with both monsoon and non-monsoon precipitation. The third and final analysis investigated the relationship between the climatic factors and malaria hotspots and non-hotspots. The LR χ^2 is

4.34 with p-value of < 0.63, suggesting that the model is not significant. The results of the panel data analysis suggest that between 1988 and 2013, climatic factors did play a significant role in the distribution of malaria in Nepal. The most influential climatic factors in determining the presence and absence of malaria in a district were minimum temperatures of both monsoon and non-monsoon seasons.

4. 1 Introduction

Malaria is a febrile disease, characterized by moderate to severe chills, high fever, headache, vomiting, diarrhea, sweating and tiredness (Sadanand, 2012; CDC, 2015). Especially severe strains of malaria may cause death, especially in older, younger, or health-compromised individuals. Malaria is caused by the parasites of the genus *Plasmodium,* and is transmitted to human through the bites of infected female *Anopheles* mosquitoes (WHO, 2014). Among the four major malaria causing parasites, *Plasmodium vivax,* contributes to approximately 80% of cases in Nepal (Pant, 2010; Jung, 2001, Dhimal et al., 2014a). *Plasmodium falciparum,* though less in proportion, causes a particularly severe form of malaria and is responsible more for malaria related deaths in the country (Jung, 2001, DoHS, 2014). The second condition required for malaria transmission is the presence of a vector, which transfers the parasite to a new host. The *Plasmodium* is transferred to human beings during blood feeding by an infected female A*nopheles* mosquito (Jung, 2001). The dominant primary vectors in Nepal are *An. fluviatilis, An. annularis, An. Maculatus,* and *An. minimus* (Brydon et al., 1961; White, 1982; Kondrashin, 1992; Sah et al., 2002; Hay et al., 2010; Dhimal et al., 2014b). Finally, there must be a vertebrate host to complete the malaria transmission cycle. Humans are the most common vertebrate host (Pavlovsky, 1964; Packard, 2008), thus humans are both hosts and victims of the disease.

In Nepal, 84 percent of the population (26 million) lives in areas with some degree of malaria risk (Dhimal et al., 2014a). Malaria transmission is both a perennial and seasonal phenomena in Nepal (Jung, 2001). Year to year reporting, varies geographically, especially in number of positive cases and in the intensity of infection (Sherchand et al., 1996; Jung, 2001; Pant, 2010; Dhimal et al., 2014a; Ghimire et al., 2016). The combination of various physiographical, climatic, socio-cultural, and economic factors creates a complex interactive environment for the three major components of the malaria disease system; which are host, parasite and vector (Jung, 2001; CBS, 2012; DoHS, 2012; Dhimal et al., 2015a). From 1988 through 2013, a total of 267,121 confirmed malaria cases were recorded in Nepal (Table 4.1). The distribution of these cases varies greatly in both time and space (Ghimire et al., 2016). The highest average disease frequency (ADF) of 157 cases per 100 000 population, was recorded in 1991 and the lowest ADF of 8 was recorded in 2013. The ADF has remained near 20 since 2008. Only five of 75 districts of Nepal remained malaria-free between 1988 through 2013 (Ghimire et al., 2016). The distribution of malaria cases in the remaining 70 districts varied both among the districts and between years. The highest caseloads (that is the largest number of reported cases) were found in the warmer, wetter low altitude areas, fewer cases occurred in the higher altitude foothills areas, and the small number of cases occurred in higher altitude areas (DoHS, 2014; Dhimal et al., 2014a, Ghimire et al., 2016). The Kathmandu and Bhaktapur districts, from the Hill region (Figure 4.1), were among the five districts that did not have any official record of malaria cases. However, the demographic change within these districts, with the majority of migrating populations coming from high risk regions and a noticeable increase of mosquitoes in the area suggest the potential existence of malaria transmission in Kathmandu. A recent study also suggests the presence of malaria in the Kathmandu valley (Singh et al., 2006).

Table 4.1: Summary of malaria cases in Nepal, 1988-2013.

Year	Risk population in millions	Total cases	ADF *	ADF of primary hot spot
1988	17.45	24548	141	1224
1989	17.79	22133	124	999
1990	18.14	20414	112	1009
1991	18.49	29019	157	704
1992	18.95	23046	122	497
1993	19.42	16386	84	306
1994	19.88	9942	50	510
1995	20.35	9530	47	580
1996	20.82	8978	43	438
1997	21.28	8165	38	236
1998	21.75	8513	39	273
1999	22.21	7328	33	314
2000	22.68	9313	41	720
2001	23.15	6188	27	431
2002	23.48	10446	44	1546
2003	23.82	12086	51	1964
2004	24.15	6365	26	599
2005	24.48	4563	18	301
2006	24.82	5691	23	305
2007	25.15	5293	21	169
2008	25.49	4574	18	98
2009	25.82	3589	14	46
2010	26.16	3051	12	463
2011	26.49	2991	11	90
2012	26.45	2802	11	70
2013	26.78	2167	8	45

* ADF = Average disease frequency (malaria cases per 100, 000 populations); Hot spot, areas where the concentration of the cases is higher than average compared to the surrounding areas (Keefe and Sullivan, 2011)

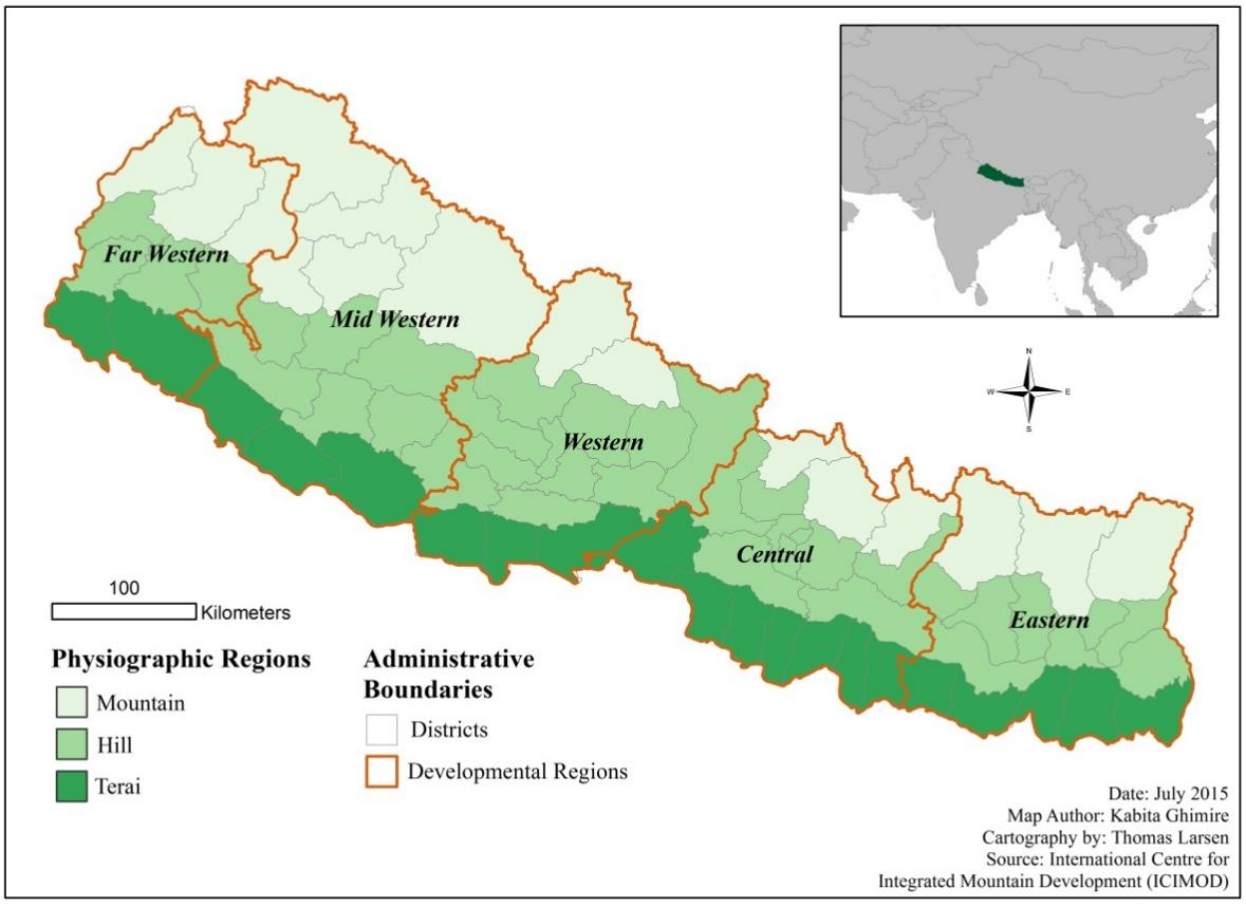

Figure 4.1: Nepal's three physiographic regions, five development regions, and 75 districts.

It is clear from the above discussion that the epidemiological, geographic and public health risks associated with malaria are unevenly distributed within the country. In certain districts the case loads are 5 or 10 times higher than the national annual average (Ghimire et al., 2016). These hot spots, areas where the concentration of cases is higher than average compared to the surrounding areas (Keefe and Sullivan, 2011), have been identified (Ghimire et al., 2016) (Figure 4.2). Identification of these disease hot spots provides important evidence about the presence and extent of geographic variation of malaria distribution in the country. However, hot spot analysis does not provide the causal reasons behind the presence of such patterns. Each of

the hot spots identified from various regions of Nepal likely has its own biophysical characteristics, which may result in a unique environment for malaria occurrence and transmission. Therefore, if we are to understand the disease pattern further, it is important to identify and investigate the association between biophysical characteristics and malaria disease frequency at the same temporal and spatial scale at which the hot spots have been identified.

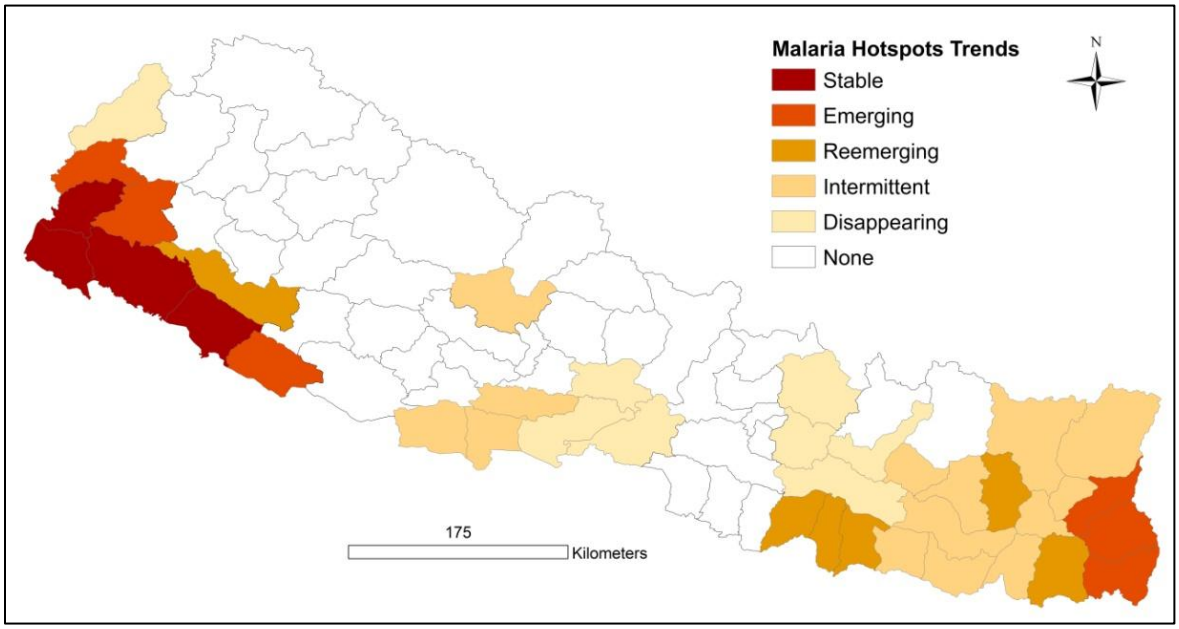

Figure 4.2: Malaria hot spots in Nepal, 1988-2013 (Ghimire et al., 2016)

4.2. Malaria-climate association

Malaria is one of the most ecologically sensitive diseases (Githeko et al., 2000). Like many infectious diseases, the transmission dynamics of malaria are controlled at least in part by the ecological context in which this transmission occurs (Githeko et al., 2000; Kiska, 2000; Pascual et al., 2006). Various biophysical factors, such as climate and landscape structure are known to influence malaria transmission (Pavlovsky, 1964; Kiska, 2000; Epstein, 2000). In

particular, there is ample evidence of an association between climate and malaria transmission at various spatial and temporal scales. In particular, climate plays a critical role in regulating the populations of mosquitoes, the vector of malaria (Githeko et al., 2000; Kiska, 2000; Pascual et al., 2006). Studies have shown that seasonal patterns of rainfall, temperature and relative humidity strongly influence malaria transmission (Lindsay and Birley, 1996; Epstein, 2000, Kiska, 2000; Pascual et al., 2006). While temperature, rainfall and humidity are the key climate variables that influence malaria, they cannot be viewed independently. The mosquito, a vector of many diseases including malaria, cannot survive winter minimum temperatures less than 14°C – 16°C (Lindsay and Birley, 1996; Epstein, 2000). Sudden increases in temperature not only favor increased geographic spread of mosquitoes but also decrease the time of their reproductive cycle, producing greater numbers of individuals within a shorter time span (Kiska, 2000; Pascual et al. 2006). At the same time, higher temperatures also facilitate the reproduction of pathogens within the vector, as well as the rate at which the pathogens mature. The immature *Plasmodium falciparum*, a parasite that causes malaria, takes about 26 days to fully mature at temperature of 17°- 20°C but it takes only 13 days to mature at 25°C (Longstreth and Wiseman, 1989; Epstein, 2000). *Plasmodium vivax*, another species of malaria causing parasite, can complete its life cycle in slightly colder temperature at 15°C (Longstreth and Wiseman, 1989). Rainfall is also an important driver of malaria. Optimal precipitation help create a suitable environment for vector by creating a ample breeding habitats. Increased precipitation lead to malaria outbreaks in some regions of Africa (Githeko et al., 2000). Positive relationships between precipitation and malaria incidence were observed in areas with few wetlands and negative relationships between precipitation and malaria incidence in areas with extensive wetlands was observed in the Amazon Basin (Olson et al., 2009). Modification in one or any combination of the above-

mentioned factors changes the course of the disease process and affects its impact on public health. Rainfall seasonality was significant in explaining malaria seasonality in Sri Lanka in areas of low transmission (Briet et al., 2008).

Malaria epidemics in the recent past have been associated with the El Niño phase of the Southern Oscillation (ENSO) (Hay et al., 2000; Githeko et al., 2000). The Southern Oscillation is a periodic inter annual biphasic variation in sea-level pressure across the Pacific Ocean (Hay et al., 2000; Githeko et al., 2000). Increased precipitation and temperature due to global scale El Niño events of 1996-97, have led to malaria outbreaks in some regions of Kenya, but also to reduced malaria transmission in Tanzania (Githeko et al., 2000). This suggests that the same climatic events can influence disease transmission differently in different regions. It is therefore very important to conduct the regional analysis of climate -malaria association.

4.2.1 Malaria - climate association in Nepal

In Nepal, people living in the highly populated Terai region are at higher risk for malaria transmission than those living at higher altitudes (Dhimal et al., 2014a). This increased risk is due to a number of biophysical and socio-cultural factors, including but not limited to a year-round favorable climate for transmission between vector and host; presence of suitable vector habitats, and common practices such as sleeping outside at night (Shrestha et al., 1991; Banerjee et al., 1991; Sherchand et al., 1996; Bhandari et al., 2013). The elevation of the region ranged between 70 meters to 1000 meters, with average elevation of 450 meters (Gurung, 2008). The region receives mean annual precipitation of approximately 1600 mm. The average summer temperature is between 27°C to 32°C (Gurung, 2008). These biophysical environments create a suitable environment for malaria transmission in Nepal.

All malaria-related epidemiological survey, intervention, and control programs in Nepal are planned and implemented on district-wise basis. However, district-wise stratification of biophysical parameters associated with malaria has not been done. A goal of this paper is, therefore, to assess the relationship between the climatic variables (maximum and minimum temperature, and precipitation) and malaria disease frequency at the district level. While the relationships between climate and malaria has been investigated in a number of other places, including Africa and South Asia, comparable studies in Nepal are limited in scope and number (Bhandari et al., 2013; Dhimal et al., 2014a). A recently published systematic synthesis of literature focused on climate change and spatiotemporal distribution of vector borne diseases in Nepal identified 8 papers focused on malaria (Dhimal et al., 2015). Five out of eight papers were descriptive, noting that malaria transmission is seasonal and that the monsoon precipitation and temperature in the Terai region are the principal climatic factors that influence malaria occurrence (Pradhan et al., 1970; Sakya, 1981; Dahal, 2008). The other three papers used climate data and malaria case data, and quantitatively assess the relationships between the malaria cases and temperature, precipitation and relative humidity (Bhandari et al., 2013; Dhimal et al., 2014c; Dhimal et al., 2014d). Bhandari et al., (2013) conducted a study in one district, Jhapa from the Eastern Terai, considering the climatic factors and malaria cases between 1987 to 2008. Their study revealed a significant positive relationship between the climatic factors, minimum and maximum temperature and rainfall of the district and monthly malaria cases. Dhimal et al., (2014c) investigated impact of climatic factors along with control intervention in malaria transmission in 31 risk districts from 2004 through 2012. This study showed that the risk of malaria epidemics in highlands increased due to climate change, increase in temperature and

decrease in precipitation. In this context, any contribution in malaria-climate based research based in Nepal holds a high significance.

While the research reviewed above showed some relationship between climate and malaria case frequency, none of the studies provided a comprehensive analysis of such relationships over the entire extent of Nepal. Our goal in this paper is to provide such an assessment. Our analysis is the first of its kind done in malaria research in Nepal, both in terms of spatio-temporal coverage and statistical methods used in the research. We will investigate the relationships between the climatic variables and malaria disease frequency at the district level in Nepal during 1988-2013.

4. 3 Materials and Methods

4.3.1 Study site

Nepal is a landlocked country, situated in South Asia between India and China, covering approximately 147,181 km². The shape of the country is elongated, with an approximate east–west length of 885 kms and an average north- south width of about 196 kms (Jung, 2001; Shrestha, 2007; Gurung, 2008). For administrative purposes, the country is divided into 5 developmental regions, 14 zones, 75 districts (Figure 4.1), 59 municipalities, and more than 3000 Village Development Committees (VDCs). The VDCs are further divided into wards, which are the smallest administrative units in the country (Jung, 2001; Shrestha, 2009; Gurung, 2008). Forest and agriculture cover about 39.1% and 29.83%, of the total land area of the country, respectively (Uddin, et al., 2015). Most Nepalese people (80%) live in rural areas. Agriculture and subsistence farming are the main economic activities, and provide livelihoods for more than 70% of the population (Shrestha, 2007; Gurung, 2008).

Nepal is divided into five climatic zones based on the altitudinal and latitudinal gradients. These are; 1) the tropical and sub-tropical zone below 1,200 meters in altitude; 2) the cool temperate zone at 1200 to 2400 meters in altitude; 3) the cold zone at 2,400 to 3,600 meters in altitude; 4) the Alpine zone or subarctic zone at 3,600 to 4,400 meters in altitude; and 5) the Tundra or arctic zone above 4,400 meters in altitude (Shrestha, 2007; Gurung, 2008). All the climatic zones have distinct ecological belts running from the east to west occasionally intersected by the river systems (Jung, 2001; Gurung 2008). There are three distinct seasons in Nepal; summer (March-June), rainy season (July –October), and winter (November –February) (Jung, 2001). The seasons are also divided into monsoon and non-monsoon seasons. In this paper, two seasons: monsoon (May-September) and non-monsoon (October –April) are used.

The country is also divided into three physiographic regions. To the south, lie the humid plains, commonly referred as the Terai, comprising 23% of the total land area of the country (Shrestha 2007; Gurung, 2008). There are 20 districts in the Terai region. The elevation of the region ranged between 70 meters to 1000 meters, with average elevation of 450 meters (Gurung, 2008). The region receives mean annual precipitation of approximately 1600 mm (Gurung, 2008). The average summer temperature is between 27°C to 32°C (Gurung, 2008). The land use types of the region mostly consist of cultivated land, forests, swamps and urban areas. The Terai is the most densely populated, with about 50% of the country's population residing in the region (CBS, 2012). Within the Terai, the eastern districts are more populated than the western districts.

Further north is the Hill region, encompassing 42% of the land area. There are 39 districts in the Hill region, including the Kathmandu valley, home to the Nation's capital. The elevation ranges between 500 meters to 3000 meters (Gurung, 2008). The region receives mean annual precipitation of approximately 1800 mm (Gurung, 2008). The average summer temperature is

between 15°C to 27°C (Gurung, 2008). The major land use types of the region are forest, cultivated area, shrub lands, slides and slips and urban areas About 43% of the population lives in the Hill region (Jung, 2001; Gurung, 2008; CBS, 2012).

The Mountain region, covering the remaining 35% of the land area, lies still further, and is a region of increasing altitude (Shrestha, 2007; Gurung, 2008). There are 16 districts in the Mountain region. The elevation ranges between 3000 meters to 8848 meters. The Mountain region of Nepal is home to eight of the highest peaks of the world including Mount Everest highest point in the Earth (Gurung, 2008). The region receives mean annual precipitation of approximately 600 mm. The average summer temperature is below 0°C to 10°C (Gurung, 2008). The land cover types of the area are grazing lands, rocks, rocky outcrop, forest and permanent snow and ice. About 7% of the country's population lives in the Mountain region (CBS, 2012).

4.3.2 Data

4.3.2.1 Malariometric data

The research in this paper is based on secondary data obtained from the government of Nepal and the World Health Organization (WHO) publications. Three major data sources were used to create a district-wise malariometric geo-database for a 26-year study period (1988-2013). The data used for this research came from reports published by the Epidemiology and Disease Control Division (EDCD) and Office of Health Management Information System (HMIS), Department of Health Services (DoSH), Government of Nepal and the WHO. Information for the study period 1988 -1996 was transcribed from a WHO publication (Jung, 2001). Malariometric information from 1997-2013 was transcribed from the DoHS annual reports (DoHS, 1997-2013). The data were transcribed electronically using the Optical Character Recognition (OCR) technique at Kansas State University ASI, 2015). The transcribed data were crosschecked with

both electronic and hard copies of the DoHS annual reports and WHO publications to assure the quality and consistency of the information during the transcription process.

Various malariometric indicators were used to measure and record malaria incidence and prevalence in the country. A few of the common indicators used were malaria cases, clinical malaria, population at risk, Annual Parasitic Incidence (API), and Average Disease Frequency (ADF). API is calculated as the ratio of confirmed cases during a year) per population under surveillance. This index is calculated based on blood slide examination. The number of blood slides examined and the slide positivity rate influence the value of API (Jung, 2001; EDCD, 2010). ADF is the ratio of the total case count per total population at risk for the particular year, (Kulldorff, 1999). Among the various malariometric indices, yearly ADFs for each of the 75 districts between 1988 and 2013 were used in the analysis. ADF is used because it considers the total population of the district and accounts for district-wise differences in population across time and space. The years 1988-2013 are considered because of the availability of the data. The district-wise malaria cases (spatial unit used for data analysis in this paper), are available only from 1988. The time-frame also provides a good overview of malaria in the past and current time.

4.3.2.2 Census data

Population data were obtained for the census years 1981, 1991, 2001, and 2011 from the statistical yearbooks of Nepal published by the Central Bureau of Statistics (CBS), the National Planning Commission Secretariat (NPCS), and the Government of Nepal (CBS, 1982; CBS, 1992; CBS, 2002; CBS, 2012). Linear interpolation based on the population at the census times preceding and following was used to calculate the population for the non-census years. The census data were transcribed electronically using the Optical Character Recognition (OCR)

technique at Kansas State University (ASI, 2015). Scanned data were cross- checked with both electronic and hard copies of the census reports and statistical yearbooks to assure quality and consistency.

4.3.2.3 Climate data

The climate data were obtained from the Climate Research Unit (CRU), University of East Anglia, Norwich, UK (http://www.cru.uea.ac.uk/data) (Harris et al. 2014). Gridded time series raster data at 0.25° resolution for three climate variables; monthly average daily maximum temperature (T_{max}), monthly average daily minimum temperature (T_{min}), and monthly average daily precipitation (Ppt) were obtained from the CRU. CRUTS V.3.2, the most recent version, was released on July 2014 and covers the time period from 1901 through 2013 (Harris et al. 2014). Each variable in the data set was organized as a multiband (120 bands) raster data set for 10 years, with each month saved as 1 single band for all land area of the world except for Antarctica (Harris et al. 2014). The pre-processing of the data set, converting single raster file consisting of multiple bands into multiple raster files consisting of a single band, extracting variables for each of the areal units (district of Nepal) for the study period 1988-2013, was done using the Orfeo toolbox (Inglada and Christophe 2009) and Zonal Statistics functions using QGIS Desktop 2.4.0 (QGIS, 2014). The mean monthly data for all three variables, maximum temperature (T_{max}), minimum temperature (T_{min}), and precipitation (Ppt) were aggregated into two seasons, the monsoon (May -September) and non-monsoon (October-April) and seasonal means were calculated for each variable. We choose two seasons to account for variation in annual climate pattern. The aggregation was also done to account for the malaria cases data, which were aggregated at the annual scale.

4.3.3 Statistical Analysis

4.3.3.1 Logistic regression using panel data models

Logistic regression using panel data models was used to identify the association between the malaria disease frequency and the climatic variables. In the logistic regression, also known as the logit model, the dependent or the response variable is categorical and can be binomial, ordinal or multinomial (StataCorp, 2015). Binary or binomial logistic regression is the case where the dependent variable is dichotomous, and can have only two possible types (e.g. presence/absence, win/loss). The log odds of the response variable is modeled as linear combination of the predictor variables and the odds of an event that occur with probability P is defined as, odds = P (1-P) (Hosmer, 2013; StataCorp, 2015). The generalized linear model (GLM) is the foundation of the logistic panel model estimation. However, the model of logistic regression is based on different assumptions than that of linear regression (Hosmer, 2013). Because the response variable is categorical, the first assumption of the logit model is that the distribution is Bernoulli distribution and not Gaussian distribution and the second is, the logistic regression predicts the probability of the outcomes, which is restricted to the logistic function, where the output always takes values between zero and one and therefore, is interpreted as a probability (Hosmer 2013; StataCorp, 2015).

A simple linear model with a dependent variable Y and the independent variable X can be written as:

$$Y_{it} = \beta X_{it} + \varepsilon_{it} \quad (4.2.3.1)$$

Where i represents the cross section dimension and t represents the time dimension, Y_{it} is the dependent variable in i space at t time and X is the predictor variable with an error term ε (StataCorps, 2015)

We choose panel data analysis for this research because it allows for conducting regression analysis with both a spatial and a temporal dimension in a single analysis. Panel data model based regression analysis is an advanced form of cross-sectional and time-series analysis, as the data model considers both the time and space components together (Wooldridge, 2002; Elhorst, 2003). The error term also has two dimensions, help partition error between time and space. There are two types of data sets used in panel data analysis, commonly referred to as balanced and unbalanced panels. In the balanced panel data observations are present for all spatial and temporal units with no missing values, whereas in the unbalanced panel data there are spatial and temporal units with no observations. For example, if any analysis if all the spatial units have data for all the years considered the panel is called strongly balanced panel and if one or more spatial units do not have data for one year then the data is referred as unbalanced panel.

Panel analysis considers both spatial and temporal heterogeneity and addresses of the spatial dependence in the data, which is not addressed by traditional linear uni- or multivariate regression models. Panel analysis is therefore a robust method that provides less collinearity among the variables, greater availability of degrees of freedom, and increases the estimation efficiency (Elhorst, 2003).

There are multiple panel analytical models, fixed effects models, random effect models, and constant coefficients models. In this paper fixed effects logistic regression analysis is done to assess the relationship between the dependent and predictor variables. The fixed effects models explores the relationship between the dependent and independent variables within an entity (e.g districts), and refer to an independent effect for each entity that is possibly correlated with the regressors. It accounts for spatial and temporal heterogeneity (StataCorp, 2015). Another important assumption of the fixed effects model is that those time-invariant characteristics are

unique to the individual unit and should not be correlated with other unit's characteristics (Williams, 2015).

The regression panel data model with spatial and temporal heterogeneity dependence with 2 explanatory variables can be written as,

$$Y_{it}=\alpha_0+\beta_1 X_{1it}+\beta_2 X_{2it}+\varepsilon_{it} \quad (4.2.3.2)$$

Where i is the index for cross-section dimension (spatial units, i=1…..N), t is the index for time dimension (time period, t= 1…..T), Y_{it} is an observation to the dependent variable, X_i denotes a spatial effect, X_t represents temporal effect, X_{it} is the observation on the independent variable (1-by-K row vector), α is the unknown parameter (a matching K-by-1 fixed vector) and ε_{it} is the independently and identically distributed error term for i and t with zero mean and variance (Wooldridge, 2002; Elhorst 2003, Wang et al., 2015).

4.4. Results

4.4.1 Spatio-temporal distribution of climatic factors

4.4.1.1 Precipitation trends and patterns

In Nepal, more than 85% of precipitation occurs during the monsoon season. The highest and the lowest precipitation trends during both the monsoon and non-monsoon seasons are plotted in Figure 4.3. The annual average monsoon precipitation ranges between ≈ 63 cm to ≈ 500cm (Figure 4.3a). The annual average non-monsoon precipitation ranged between ≈ 6.5 cm to ≈102 cm (Figure 4.3b). Overall the precipitation has decreased over time, which can be seen clearly in the monsoon season precipitation trend.

Figure 4.4 shows district-wise distribution of precipitation during the monsoon and non-monsoon seasons from 1988 to 2013. The districts in the figure are custom numbered based on physiographic division from the East to the West. For example the North -Eastern most district, in the Mountain region, is numbered 1 and the South -Western most district, in the Terai, is numbered 75. District-wise variation in inter-annual precipitation is greatest in the monsoon season compared to non-monsoon season (Figure 4.4). In general, the Eastern districts receive higher rainfall compared to the Western districts of Nepal during the monsoon season. The highest annual precipitation amounts of approximately 550cm and 570 cm were recorded in the year 2011 from Jhapa district (56) in the Eastern Terai and Nawalparasi (68) in the Western Terai, respectively (Figure 4.4). Similarly, lowest rainfall (≈ 63cm) was recorded in Darchula district (16) from the Far Western Mountain region, in the year 2004. During the study period, Jhapa (56) and Nawalparasi (68) from the Terai are the highest precipitation districts whereas Mugu (10), Humla (11) and Darchula (16) districts from the Mountain region received the lowest rainfall (Figure 4.4). Annual non-monsoon precipitation was highest in the Jhapa (56), Parbat

(41), and Dadeldhura(55) districts. Dhanusha(61), Mahottari(62) and Kanchanpur(75) received the least rainfall during the season (Figure 4.4).

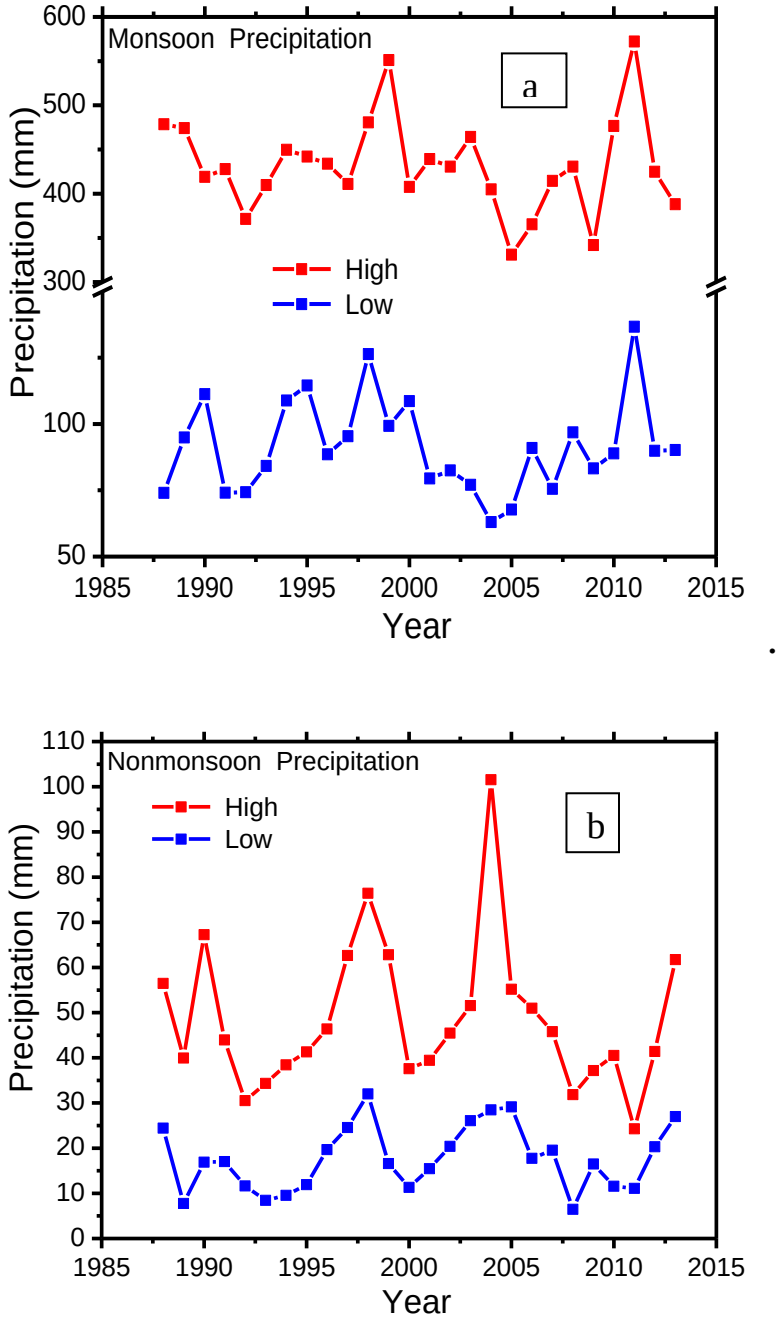

Figure 4.3: Highest and lowest precipitation, 1988-2013, during monsoon season and non-monsoon season.

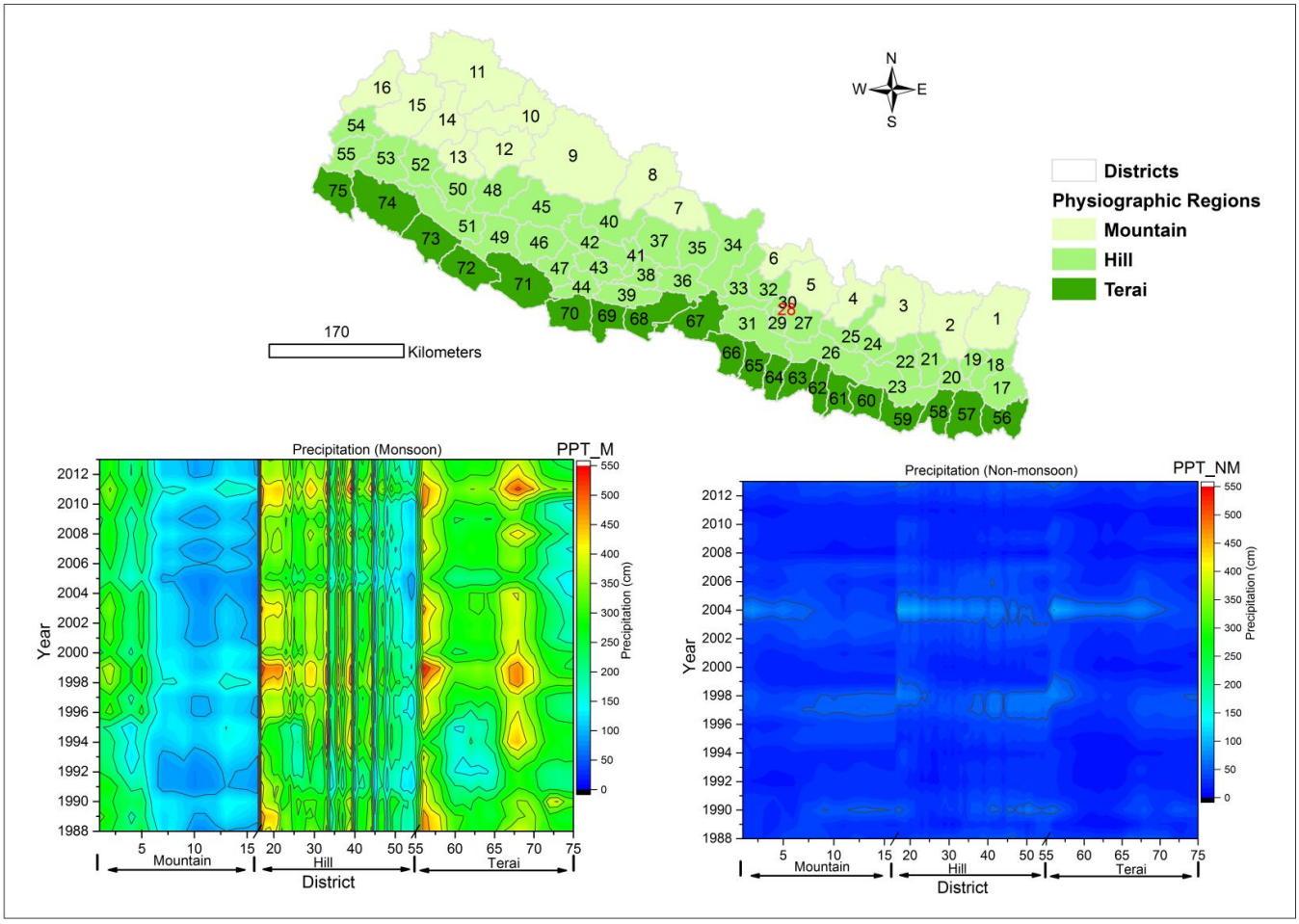

Figure 4.4: District-wise distribution of precipitation during the monsoon and non-monsoon seasons between 1988 and 2013. The district are custom numbered based on physiographic division and from the East to the West. e.g the North -Eastern most district, in the Mountain region, is numbered 1 and the South -Western most district, in the Terai, is numbered 75.

4.4.1.2 Maximum temperature trends and patterns

To study T_{max} trend during the study period, the highest and the lowest T_{max} during two seasons were plotted in Fig 4.5 (a) and (b), respectively. During the monsoon season the T_{max} ranges between ≈ 7°C to 34.2°C, with highest values (> 30°C) in the Terai region and

lowest values (< 10°C) in the Mountain region. The average non-monsoon T_{max} ranges from -2.7°C to 29°C. Both in the monsoon and non-monsoon seasons, the plots show the increasing trend for the maximum temperature. Figure 4.6 shows a district-wise distribution of maximum temperature (T_{max}) for the two seasons. During the monsoon season, the highest temperatures were recorded from Mahottari district (62) from the Central Terai region, with an average temperature of 32.5°C (Figure 4.6). The district recorded the highest temperature of 34.2°C in 2009. Manang (7), district from the Western Mountain region is the coldest district with average monsoon T_{max} of ≈ 7°C. The highest temperature recorded during the monsoon from the district was 8.4°C in 2009. The highest non-monsoon T_{max} was observed from the Mahottari (62) district and the lowest T_{max} of -2.7°C was recorded from Manang (7) in the year of 1989.

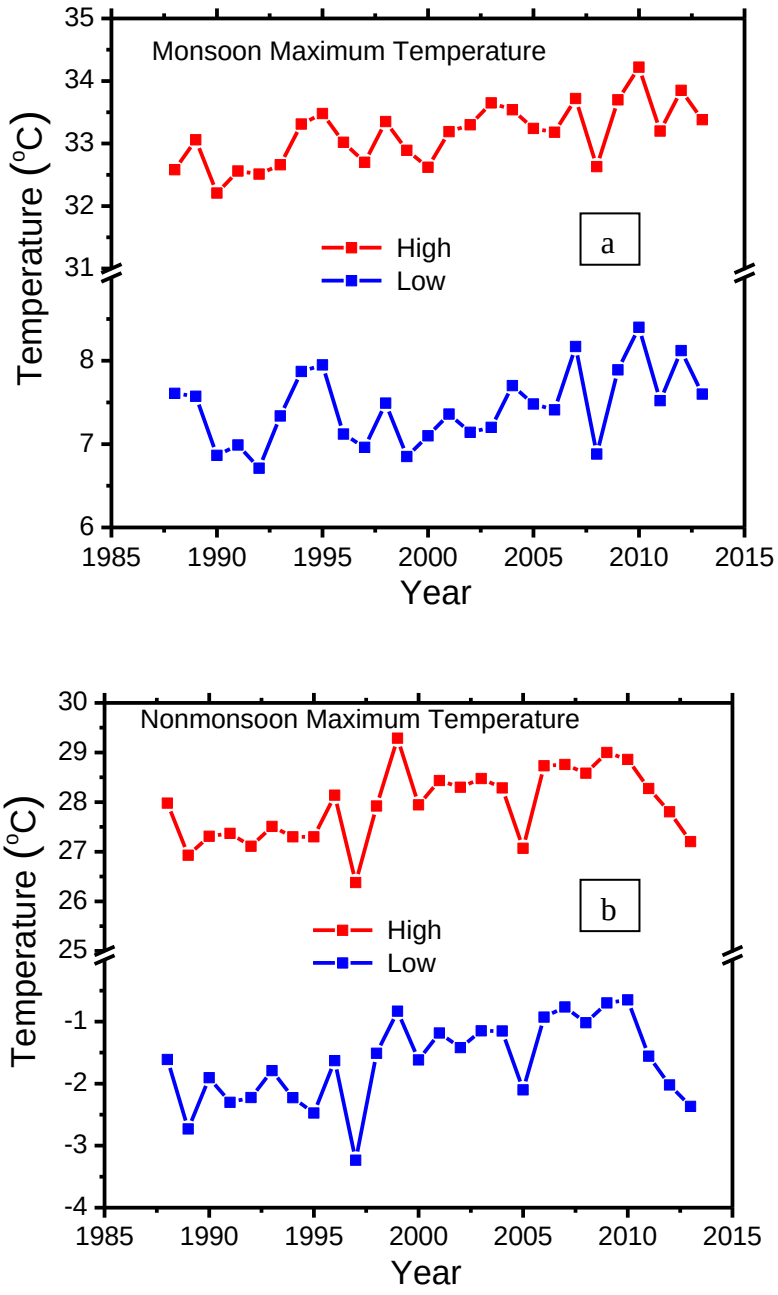

Figure 4.5: Highest and lowest T_{max} during monsoon season and non-monsoon seasons, 1988 to 2013.

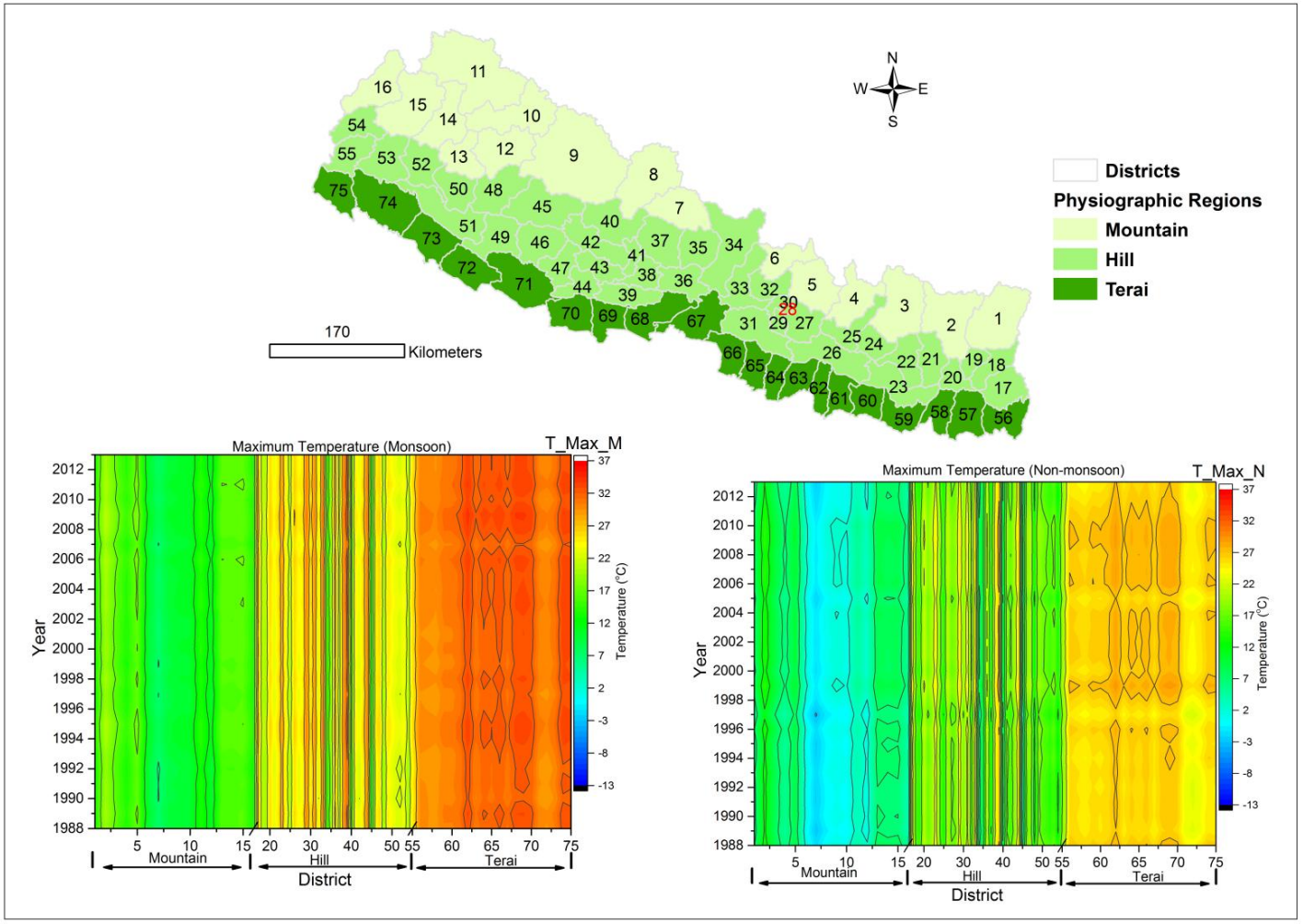

Figure 4.6: District-wise distribution of maximum temperature (T_{max}) in the monsoon season between 1988 to 2013. The district are custom numbered based on physiographic division and from the East to the West. e.g the North -Eastern most district, in the Mountain region, is numbered 1 and the South -Western most district, in the Terai, is numbered 75.

4.4.1.3 Minimum temperature trends and patterns

District-wise variations of minimum temperature (T_{min}) during monsoon and non-monsoon season from 1988 through 2013 are shown in contour plots (a) and (b), respectively in Figure 4. 7. The monsoon T_{min} ranges between -3°C to ≈ 25°C. In the non-monsoon season, T_{min} ranges between ≈ -19°C to ≈ 15.5°C. Similar to that of the T_{max}, the T_{min} is the highest (> 20°C) in the Terai district and the lowest (< -3°C) in the Mountain region. During both monsoon and non monsoon seasons, Mahottari (62) district from the Central Terai recorded the highest T_{min} of ≈ 25°C and ≈ 15.5°C, respectively, in the year 2009 (Figure 4.8). Manang (7) from the Mountain region recorded the lowest T_{min} of -5.9°C in the monsoon season in 1992 and T_{min} of ≈ -19°C in the non-monsoon season in 1995. (Figure 4.8). The T_{min} shows increasing trend during the study period 1998-2013..

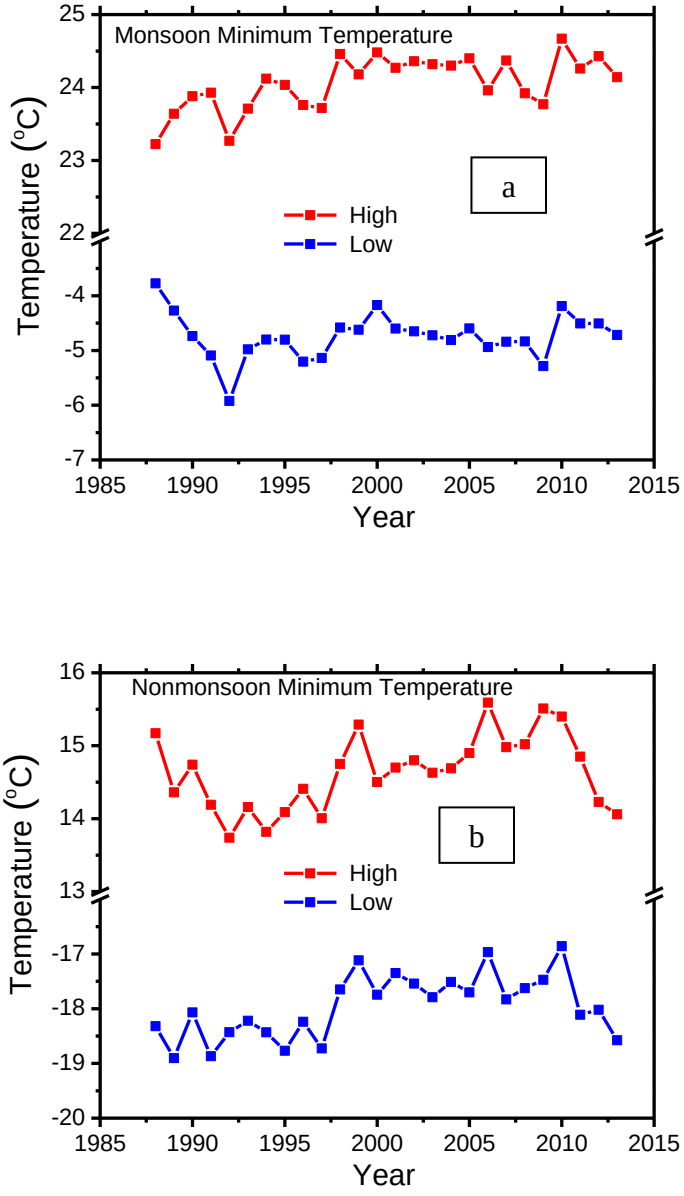

Figure 4.7 Highest and lowest minimum temperature during each year of monsoon and non-monsoon season

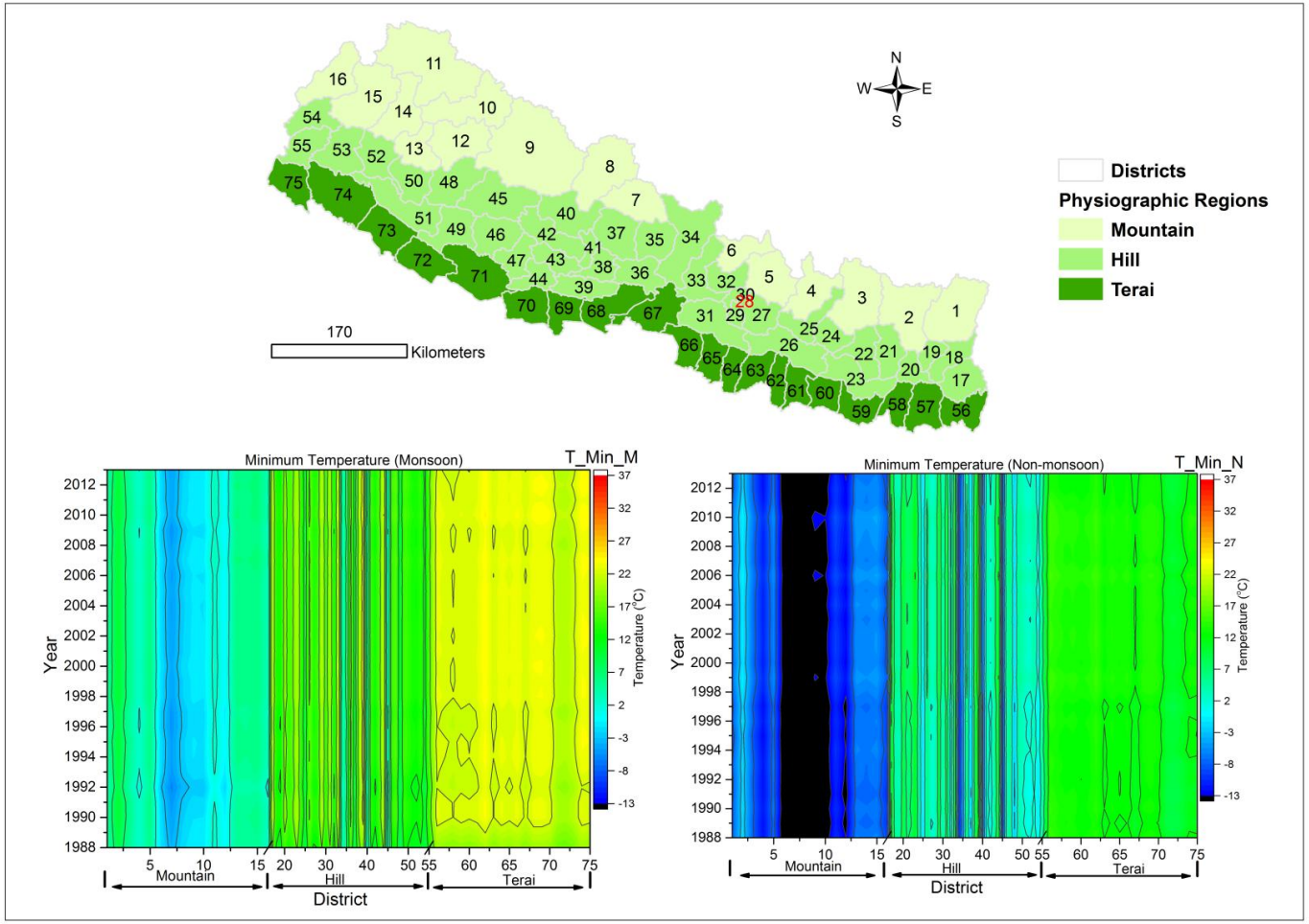

Figure 4.8 District-wise variation in minimum temperature in the monsoon season during 1988 to 2013. The district are custom numbered based on physiographic division and from the East to the West. e.g the North -Eastern most district, in the Mountain region, is numbered 1 and the South -Western most district, in the Terai, is numbered 75.

4.4.2 Association between climatic variables and malaria disease frequency

Three separate logistic regression using panel data models were run, using average malaria disease frequency as the dependent variable and the six climatic variables described in section 4.2.2.3 as the independent variables. In all models, the spatial unit of analysis is a district and the temporal unit of analysis is a year. The first panel analysis tested if the presence and absence of malaria is related to climatic factors. In this analysis, all 75 districts were considered for 26 years study period (1988-2013). The data set for this analysis is a strongly balance panel , where there is an observation for all the districts for all the years and there are altogether 1950 observations. The second model examined if there is any relationship between climatic factors and low and high presence of malaria. The data are unbalanced in the second model, as all the districts do not have observation for all the years. This unbalanced panel model has 1327 observations from 65 districts. The third and the last model looked into the relationship between the climatic variables and malaria hot spots and non-hotspots. Non- hotspots districts are those in which, ADF is more than the average for the year but not categorized as the malaria hotspot. There are 49 districts in this model with total 396 observations. Like second model, the third one is also a model with unbalance data.

For the first model, the iteration log is six, meaning the model converged within six iterations. The likelihood ratio chi square (LR χ^2) is 97.57 with p-value of < 0.00, indicating that the relationship is highly significant. Table 4.2 shows the coefficients, odd ratio, z-score, p-value and 95% confidence interval (CI) of the coefficients for absence and presence of malaria. Out of six predictors, four variables; monsoon maximum temperature, monsoon minimum temperature, non-monsoon minimum temperature, and monsoon precipitation showed significance in the model with p <0.052 (Table 4.1). The odd ratio (OR), the probability of

absence and presence ($ADF_{absence}/ADF_{presence}$), is greater than 1 for two out of six predictors; monsoon minimum temperature (OR= 1.27) and non-monsoon minimum temperature (OR=1.84). Therefore, the model suggests that the monsoon and non-monsoon minimum temperatures are the best predictors of the absence and presence of malaria at the district level. Increase in monsoon and non-monsoon minimum temperatures increases the odds of presence of malaria.

The second model tested the relationship between the climatic factors and the low and high frequency of malaria. For the second model the iteration log is 5, meaning the model converged within five iterations. The likelihood ratio chi square (LR χ^2) is 37.43 with p-value of < 0.00, suggesting the significance of the model. Table 4.3 shows the coefficients, odd ratio, z-score, p-value and 95% CI of the coefficients for low and high frequency of malaria. Out of six predictors only three variables, monsoon T_{max}, monsoon and non-monsoon precipitation have shown significance in the model with p-value < 0.05 (Table 4.2). The OR is >1 for Monsoon T_{max} and almost 1 for precipitation variables. The model identified monsoon T_{max} is the likely predictor of high and low frequency of malaria along with both monsoon and non-monsoon precipitation.

Table 4.2: Results of the logistic regression using panel data model; Model 1 with dependent variable, absence (0) and presence (1) of malaria

Variables	coefficient	Odd ratio	z - score	p-value	95% CI
T_{max} (Monsoon)	**-0.319**	**0.726**	**-2.35**	**0.019**	-0.584 to -0.053
T_{max} (Non-monsoon)	-0.262	0.768	-1.51	0.132	-0.604 to 0.079
T_{min} (Monsoon)	**0.242**	**1.273**	**1.94**	**0.052**	-0.002 to 0.486
T_{min} (Non-monsoon)	**0.612**	**1.845**	**3.08**	**0.002**	0.222 to 1.0034
Ppt (Monsoon)	-0.009	0.990	-5.26	0	-0.013 to -0.006
Ppt (Non-monsoon)	0.001	1.001	0.33	0.743	-0.009 to 0.013
Log likelihood ratio	-674.917				
LR χ2	97.57(p <0.000)				

Table 4.3: Results of the logistic regression using panel data model; Model 2 with dependent variable, low (0) and high (1) frequency of malaria

Variables	coefficient	Odd ratio	z -score	p-value	95% CI
T_{max} (Monsoon)	0.355	1.426	2.48	**0.013**	0.074 to 0.636
T_{max} (Non-monsoon)	-0.240	0.786	-1.39	0.165	-0.580 to 0.099
T_{min} (Monsoon)	-0.015	0.984	-0.12	0.902	-0.258 to -0.354
T_{min} (Non-monsoon)	0.0154	1.015	0.08	0.935	-0.006 to -0.034
Ppt (Monsoon)	-0.003	0.996	-1.9	**0.057**	0.227 to 0.385
Ppt (Non-monsoon)	-0.021	0.978	-3.25	**0.001**	8.83E-05 to -0.0084
Log likelihood ratio	-580.619				
LRχ *2*	37.43 (p< 0.000)				

Table 4.4: Results of the logistic regression using panel data model; Model 3 with dependent variable, malaria non-hotspots (0) and hotspots (1)

Variables	coefficient	Odd ratio	z -score	p-value	95% CI
T_{max} (Monsoon)	-0.122	0.884	-0.64	0.521	-0.495 to 0.251
T_{max} (Non-monsoon)	0.060	1.065	0.26	0.794	-0.394 to 0.553
T_{min} (Monsoon)	0.137	1.147	0.81	0.416	0.193 to 0.468
T_{min} (Non-monsoon)	-0.073	0.929	-0.34	0.731	-0.491 to 0.344
Ppt (Monsoon)	-0.000	0.999	-0.13	0.896	-0.004 to 0.003
Ppt (Non-monsoon)	0.0194	1.019	1.77	0.077	-0.002 to 0.0409
Log likelihood	-234.9124				
LR χ*2*	4.34 (p=0.630)				

The third and final model investigated the relationship between the climatic factors and malaria hotspots and non-hotspots. The iteration log for this model is 4, meaning the model converged within four iterations. The likelihood ratio chi square (LR χ^2) is 4.34 with p-value of < 0.630, indicating the model is not significant. Table 4.3 shows the coefficients, odd ratio, z-score, p-value and 95% CI of the coefficients for malaria hotspots and non-hotspots. Out of six predictors only one variable, non-monsoon precipitation has shown slight significance in the model with p-value < 0.07 (Table 4.4). The OR is >1 for non-monsoon $T_{max,}$ monsoon T_{min} and non-monsoon precipitation. Though the model is not significant, non-monsoon precipitation could be the likely predictor of malaria hotspots and non-hotspots. Further analysis examining the relationship between non-monsoon precipitation and presence and absence of hot-spots is needed.

4.5 Discussion and Conclusion

The paper presents the trends and patterns of the three climatic variables, known to be associated with malaria prevalence, minimum temperature, maximum temperature, and precipitation, during the monsoon and non-monsoon seasons. The annual average precipitation in the monsoon season ranged between 63 cm to 500 cm. The annual non-monsoon precipitation ranged between 6.5 cm to 102 cm. District-wise variations in inter-annual precipitation is the greatest in the monsoon season. Similarly, the maximum temperature ranged between 7°C to 34.2°C and -2.7°C to 29°C during the monsoon and the non-monsoon seasons, respectively. Both the monsoon and the non-monsoon maximum temperatures showed the increasing trends. Likewise, the minimum temperature also showed the increasing trends in both the monsoon and non-monsoon season with higher variation among the district in the monsoon season compare to the non-monsoon season. The minimum temperature required for the pathogen development

ranges between 14° to 19°C and for the vector is between 8° to 10°C and both the vector and pathogens development occurs comfortable up to the maximum temperature of 40°C (Martens et al., 1995; Mcmichael et al., 1998; Niringiye and Douglason 2010). The trends and patterns of the climatic variables in Nepal suggest favorable year round climatic conditions for malaria transmission in most of the districts from the Hill and the Terai regions. The climatic conditions are also favorable in few of the districts from the Mountain region during the certain months of the year.

An additional contribution of our study is the adaptation of an analysis technique that, up to now, had not been used for analyzing environment-disease interaction. This paper has, for the first time, adopted panel data models to explore the relationship between the climate variables and malaria disease frequency at the 26-year time span including all the 75 districts in Nepal. The method was appropriate for the analysis because the longitudinal data were available for multiple spatial units and the spatial autocorrelation existed. Panel data analysis considers both spatial and temporal heterogeneity and address the issue of spatial dependence in the data, which is not addressed by the traditional linear model. The most influential climatic factors in determining the presence and absence of malaria in a district were minimum temperatures of both monsoon and non-monsoon seasons. The analysis showed the positive relationship between absence and presence of malaria and the monsoon and non-monsoon minimum temperatures. The study found that precipitation was negatively associated with the occurrence of malaria among the districts during the study period. The study also revealed that maximum temperature during the monsoon season determined the high and low presence of malaria. The relationship between the maximum temperature and the presence of malaria is positive. Higher the maximum temperature in the monsoon season the presence of malaria in a district was found to be higher.

The results suggest that with increasing temperature trends the likelihood of disease spreading to a newer area is high. The results of the panel data analysis suggest that between 1988 and 2013, climatic factors did play a significant role in the distribution of malaria in Nepal.

The results of the study are consistent with the climate-malaria study done in the Kenyan highlands and the one in Nepal (Githeko and Ndegwa, 2001; Bhandari et al 2013). The increasing trend in maximum temperatures and an association of malaria cases and high maximum temperatures was found in the Kenyan highlands (Githeko and Ndegwa, 2001). Change in precipitation pattern also resulted in increased malaria epidemics. Other study has shown an association between increased malaria cases with reduced rainfall combined with increased temperature (Lindsay and Birley, 1996). Bhandari et al (2013) also found a correlation between malaria occurrence and climate variables, temperature and rainfall in the study conducted in one of the high risk district, Jhapa from the Eastern Nepal.

Understanding the factors that are associated with the distribution of malaria is crucial for decision making and designing a policy to control and eventually eradicate malaria. Keeping the complexity of malaria-climate relationship in mind, it would be beneficial to investigate the relationship further using disaggregated data at the finer scale. The finer scale study would be looking into the relationship at the VDC/municipality level, lowest administrative unit, with monthly and weekly climate variables considering the monthly and weekly malaria frequency. The effect of climate covariates on malaria distribution was assumed to be uniform for all the districts in this paper. Malaria distribution may not always be and only be a function of climatic factors. Many other confounding factors contribute in malaria distribution dynamics. The paper did not consider other underlying biophysical, socio-economic and public health factors. The factors such as deforestation, drug resistance among pathogen and vectors, population growth,

limited access to the healthcare facilities and failure of the malaria control programs, are known to influence malaria transmission. Therefore, there is a need for further study considering multiple factors that are associated with malaria prevalence in Nepal.

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Chapter 5 - Malaria-Related Knowledge among Adults in Nepal

Abstract

Investigating and understanding Nepalese citizens' knowledge and beliefs about malaria, its transmission, signs and symptoms, consequences, available treatments, and current preventive strategies are important if malaria is to be eradicated in Nepal. A cross-sectional study was conducted between August 2012 and December 2013. A close-ended questionnaire survey was developed and administered to one adult in each of 826 households via personal interview. The majority of participants (81%) had heard of malaria. More than half (69%) correctly associated mosquito bites as a cause of malaria and 71% knew that everyone is susceptible to malaria infection regardless of gender or age. Sixty-five percent of participants could name more than one symptom of malaria. The most recognized malaria symptoms were headache and fever (78%), followed by chills (56%), and stomach pain and vomiting (3%). Some participants recognized physical weakness (37%), anemia (16%), and death (25%) as major consequences of malaria infection. Radio and television were the most prevalent sources of malaria information (41%), followed by health care providers (14%), school teachers (11%) and posters (9%).

5.1. Introduction

Malaria is a common vector-borne infectious disease widely distributed in tropical and subtropical regions of the world (Martin and Lafebvre, 1995; WHO, 2014). According to the World Health Organization (WHO), malaria transmission still occurs in 99 countries and territories. The organization estimated that there were about 3.2 billion people at risk of malaria in 2013 (WHO, 2014). Every year, more than 1000 cases per 1000 population occur in high risk areas, and in 2013 approximately 198 million cases and 584,000 deaths were estimated

worldwide (WHO, 2014). More than 75% of malaria-related mortality and morbidity occurs in Africa; most of the remaining cases are in Asia and Central and South America (Martin and Lefebvre, 1995; WHO, 2013; Murray et al., 2012; WHO, 2014).

Malaria is a febrile (fever-causing) disease caused by parasitic protozoa of the genus *Plasmodium*, transmitted to humans by female *Anopheles* mosquitoes. Once the infected mosquito bites, malaria symptoms start showing up in few days to weeks. There are four common species of *Plasmodium* which are known to cause malaria in humans. They are *P. falciparum, P. vivax, P. ovale,* and *P. malariae* (White, 1982; Sah et al., 2002; Packard, 2008; WHO, 2013). The most common among the four are *P. falciparum* and *P. vivax*. *Plasmodium falciparum* is the most dangerous among the four, with the highest rate of complications and mortality. The basic clinical symptoms of malaria include moderate to severe chills, high fever, headache, vomiting, diarrhea, sweating, and fatigue (CDC, 2015). Malarial parasites can live in the human body in a dormant stage for days, weeks, or even years (CDC, 2015). Malaria relapses can occur after months or years, when the parasites reactivate.

Timely detected malaria can easily be treated by local health workers and on an outpatient-basis. The common medications used to treat malaria are artemisinin combination therapy, sulphadoxine-pyrimethamine, chloroquine, and quinine (White, 1996; WHO, 2014; CDC, 2015). Doxycycline, chloroquine, primaquine, and a few other medications are used as prophylaxes to prevent the contraction of malaria (CDC, 2015). The other major and common malaria prevention and control strategies worldwide focus on vector (mosquito) control. Common control activities include mosquito netting to prevent bites, indoor and outdoor insecticide spray, use of repellents and domestic insecticides, larvicides, and biological control

(Rozendaal, 1997; WHO, 2014). National governments use mass media − radio, television, newspaper, and posters − to disseminate malaria-related information to the public.

Malaria is a major public health problem in Nepal. Approximately 84% of Nepal's 26 million people live in malaria-risk areas (Dhimal et al., 2014a). Malaria transmission is year-round in Nepal, but more prominent between March and November. Transmission reaches its peak during June, July, and August (EDCD, 2010; Ranjitkar et al., 2011). Usually malaria transmission is a very localized phenomenon in Nepal. Year to year reporting varies geographically in number of positive cases and intensity of infection (Sherchand et al., 1996; Jung, 2001; Pant, 2010; Dhimal et al., 2014a). Nepal has received financial support to fight malaria from multiple international agencies, including the United States Agency for International Development, Global Fund, and Roll Back Malaria initiatives. The political commitment within Nepal has successfully reduced the malaria disease burden, and the country is moving toward a malaria-free future. Nepal is marked for malaria elimination by WHO, and the nation is working to create a malaria-free future by 2026 (Dhimal et al., 2014a). However, malaria management remains a significant challenge for medical practitioners and program implementers.

Different traditional concepts and practices are used to characterize and categorize malaria in various regions of the world. In Nepal, various local terms have been used to identify or describe the disease. Malaria is commonly known as "judi tap" (hot chills), "judi-bukhar" (chills and fever), aulo (fever of swampy area), or "kaam jworo" (shivering fever) (Sherchand et al., 1996; Jung, 2001). The disease is associated with mosquitoes, humid climate, and the dense forest belt running east to west in southern Nepal (Sherchand et al., 1996; Jung, 2001, Budathoki and BC, 2008). It is frequently perceived as a rural disease that rarely occurs in urban areas

(Sherchand et al., 1996; Jung, 2001). Studies have shown that such misconceptions can adversely affect implementation of malaria prevention and control programs (Rodriguez et al., 2003; Erhun, 2005). Additionally, self-diagnosis and self-treatment is common among people with high fever in Nepal (Sherchand et al., 1996), with use of traditional medicines. However, the effectiveness of these treatments is not well documented (Sherchand et al., 1996). Assessing knowledge of the disease, which would affect prevention and treatment responses, is needed to improve effectiveness of malaria programs.

Nepal has to tackle several challenges before achieving the goal of being malaria-free. Political instability, discontinuity and disruption of preventive programs, a porous border with high malaria risk regions of India, reporting of malaria vectors in higher altitudes (perhaps due to climate change), and ineffectiveness of malaria prevention and control interventions in parts of the country are among the challenges the nation has to contend with if malaria is to be eliminated (Tragard and Shrestha, 2010; Dhimal et al., 2014a). The involvement of civil society is very important if a malaria-free future is to be realized in Nepal. Reports and studies have shown successful results in disease management where civil society is more aware and involved in interventions (Tragard and Shrestha, 2010).

One of the ways to help overcome the challenges, to increase civil society's involvement in malaria prevention, and to facilitate malaria elimination is to determine the level of knowledge residents of Nepal hold regarding the biomedical concept of malaria, including how it is transmitted and how to prevent and treat the disease. Understanding the level of knowledge is critical to prevent infection and the spread of malaria. By investigating malaria knowledge and related practices of residents, the results of the study may be used to develop awareness campaigns in specific geographic regions and to enhance malaria-related education strategies.

The intent of a knowledge and practices study is to reveal what a community knows about a particular phenomenon, and how community members behave to avoid it or respond to it when it occurs (Ul Haq et al., 2012). The knowledge of disease is an individual's way of defining and characterizing disease based on their personal views and beliefs sometime rooted in tradition, and day-to-day practices (Ahorlu, et al., 1997). Therefore, the knowledge is both subjective and specific. How an individual understands an illness − characterizes its signs, symptoms, causes, and consequences − depends on locality, traditional beliefs, and demographic, socio-cultural, and geographic characteristics of the area (Sherchand et. al., 1996: Ahorlu et al., 1997; Mwenesi, 2005; Das et al., 2013), as well as modern knowledge. There are very few household level baseline surveys to assess malaria-related knowledge and practices in Nepal (Sherchand et al., 1996; Joshi and Banjara, 2008; Dhimal et al., 2014b). Those that have been done have focused on one or two high risk districts from the Terai region. This paper focuses on six districts from the Terai and Hill regions, representing high, medium, and low risk areas.

5.2 Study Purpose and Research Questions

The purpose of this study was to gather information about public awareness of malaria symptoms, mosquito ecology, preventive measures, and cure availability for the six selected districts of Nepal. This study examines knowledge related to malaria among adults in Nepal, specifically, its signs, symptoms, consequences, and availability and use of prevention tools. I will address two research questions:

1. Do residents of Nepal have adequate knowledge related to malaria?
2. Is there a relationship between malaria-related knowledge and demographic, socioeconomic, and geographic characteristics of the residents?

5.3 Study area

Nepal is a landlocked country, situated in South Asia between India and China, covering approximately 147,181 square kms (Figure 5.1). The country is elongated, with approximate east-west length of close to 885 km and the average north-south width about 196 km (maximum of 241 km and minimum of 145 km) (Jung, 2001). Nepal is divided into three physiographic regions. To the south lie the humid plains, commonly referred to as the Terai, comprising 23% of the land area; further north is the Hill region, encompassing 42% of the country. The Mountain region, covering 35% of the land area, lies still further north. Among the three physiographic regions, the Terai is the most densely populated, with about 50% of the country's population; the eastern districts are more populated than the western districts. About 43% of the population lives in the Hill region and 7% live in the Mountain region (Jung, 2001; CBS, 2011; Kakchapati and Ardkaew, 2011).

For administrative purposes, the country is divided into 5 developmental regions, 14 zones, and 75 districts. The districts are further divided into 59 municipalities and more than 3000 Village Development Committees (VDCs). The VDCs are further divided into wards, which are the smallest administrative units in the country. Most Nepalese people (80%) live in rural areas (CBS, 2011). Agriculture and subsistence farming are the main economic activities, and provide livelihoods for more than 70% of the population (CBS, 2011). Nepal is ethnically and culturally very diverse. Nepali is the national language, spoken by about 48% of the population. There are 92 other languages and dialects spoken in the country. The predominant religion is Hindu (80%) and the country has more than 100 ethnic groups (CBS, 2011).

The government of Nepal categorized 75 districts into four malaria risk zones: high, moderate, low, and no risk zones. Among the 75 districts, 13 are categorized as high-risk

districts, 18 as a moderate risk districts, 34 as a low risk districts, and 10 as a no risk districts (ECDC, 2010; Dhimal et al., 2014a).

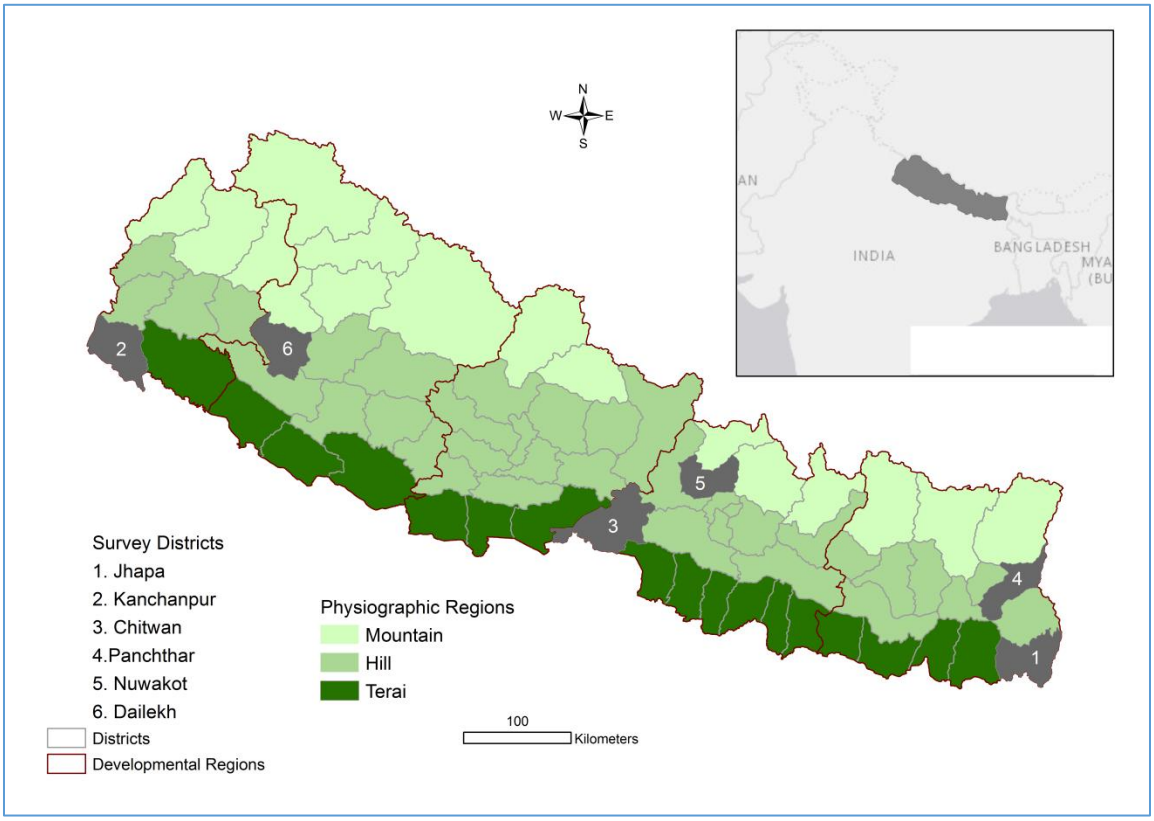

Figure 5.1: Study districts along with Nepal's three physiographic regions, five developmental regions, and 75 districts.

The six study districts (Table 5.1) were purposely selected to capture geographic and physiographic variations, differences in malaria risk, demographic distribution, and access to healthcare facilities. Healthcare providers, policy makers, and experts working to prevent and treat malaria in Nepal were also consulted during the district selection process. The six selected districts capture various malarial situations in Nepal. Two districts are considered high risk—

Jhapa in the Eastern Terai, and Kanchanpur in the Far Western Terai (Figure 5.1). Chitwan, in the Central Terai, and Panchthar, in the Eastern Hill region, represent medium risk districts. Nuwakot, in the Central Hills, and Dailekh, in the Mid Western Hill region, represent low malaria risk regions.

Table 5.1: Profile of study districts. (Sources: Shrestha, 2007; Gurung 2008; CBS, 2011)

	Jhapa	Kanchanpur	Chitwan	Panchthar	Nuwakot	Dailekh
Malaria risk	High	High	Medium	Medium	Low	Low
Region	Eastern Terai	Western Terai	Central Terai	Eastern Hills	Central Hills	Western Hills
Area (sq. km)	1606	1610	2218	1241	1121	1505
Population density (km^{-2})	506	280	261	155	248	174

5.4 Methods

5.4.1 Sampling technique

The sample size for the study was derived using a probability-proportionate-to-size method, the method which considers varying size of clusters within the population when selecting the sample (Chromy, 2008). The sampling is based on the total number of households from all the 65 malaria risk districts in Nepal (5,479,841) and from the six studied districts (544,879) (CBS, 2012). The sample size of 826 households, based on the number of households of 65 malaria risk districts, with 3.41% margin of error, were calculated using a sample size calculator (Raosoft, 2004). The sample size n and margin of error E are given by:

$$x=Z(^{c}/100)^{2}r\ (100-r) \quad \text{.... (1)}$$

$$n= {}^{Nx}/((N-1)E^{2}+X \quad \text{.... (2)}$$

$$E=sqrt[{}^{N-n)x}/n(N-1)] \quad \text{....(3)}$$

where N is the population size, r=fraction of responses, Z(c/100) is the critical value for the confidence level c (Roasoft, 2004).

One of the advantage of considering household instead of population of districts as sampling unit is to provide bigger sample size. The recommended sample size was proportionately divided within the six study districts based on the number of households in each district. The number of VDCs (rural areas) or municipalities (urban areas) within a district and the number of households within a VDC or municipality were also selected using the probability proportionate to size method (Roasoft, 2004). Individual VDCs and municipalities were selected using a cluster sampling and multistage sampling procedure once the proportion was determined. Within the VDC and municipality, households were selected in consultation with local leaders, based on the availability and willingness of the household members to participate.

The study was conducted between December 2011 and December 2013 in 36 VDCs and 8 municipalities of the six chosen districts. High, medium, low-risk regions were represented among study participants (50%, 26%, and 24%, respectively). The study was conducted at the household level to obtain information at a finer spatial scale, but it should be recognized that households include space occupied by both nuclear and extended family members.

5.4.2 Questionnaire design and administration

The closed questionnaire, with multiple answers where respondent had options to choose from, (see Appendix) was designed based on malaria-related literature from different regions of the world such as Nepal, India, Bangladesh, and Nigeria, including the malaria indicatory survey designed by *Roll Back Malaria Monitoring and Evaluation Reference Group* (Sherchand et al., 1996; Ahmed et al., 2008; Enato et al., 2007; Yadav et al., 2005; Joshi and Banjara, 2008). The questionnaire included demographic, geographic, and socio-economic characteristics of the

respondents and their migration patterns. The other part of the questionnaire included questions and statements about malaria and its transmission, signs and symptoms, causes, perception of consequences, disease vector, vector habitat, prevention, and treatment strategies. Respondents have options to choose from multiple answers for each question/statement. The questionnaire was developed in English and translated to Nepali before administration. Altogether, 52 variables were collected including demographic profile, migration information, physical characteristics of the house, community and household illness profile, and information related to malaria.

The pilot survey was done with 50 people as a pre-test in the Jhapa district. A total of 826 questionnaires were administered and 818 complete questionnaires were used for data analysis and discussion, including the 50 used in the pilot survey (Table 5.2). Incomplete questionnaire were not included in the study. The questionnaires were administered by face-to-face personal interview.[1] A total of 15 local survey assistants were hired to conduct the survey. All the survey assistants had experience with survey work through their job or training. One adult individual from each household answered the questions and the interviewer filled out the questionnaire. Interviews were generally 30-45 minutes in length.

Both English and Nepali questionnaires were used while converting the data into electronic format. Bilingual undergraduate researchers converted information into an electronic format after the survey.

[1]The Institutional Review Board (IRB) at Kansas State University approved this study. A written statement about the study was attached to each questionnaire and the interviewer read the statement to respondents before each interview. Respondents were assured their answers would be anonymous and confidential and that they had right to withdraw from the survey at any time. Respondents provided verbal consent before filling out the questionnaire.

Table 5.2: Survey numbers, by district.

District	Number of households surveyed	Completed questionnaires used for analysis
Jhapa	300	295
Kanchanpur	115	115
Chitwan	180	179
Panchthar	70	70
Nuwakot	90	90
Dailekh	70	69
Total	825	818

5.4.4 Data analysis

Survey data were analyzed using a variety of descriptive and inferential statistics, including measures of central tendency (mean and median), percentage measures, and relative frequencies. Categorical variables were expressed as percentages, while means and standard deviations were used for continuous variables. Spearman rank correlation coefficients were calculated to assess the relationships between the disease, vector, and prevention and treatment knowledge with the socio-economic, demographic, and geographic variables. Spearman rank correlation was used because some of the variables under consideration are not normally distributed; this approach is used as a non-parametric alternative to linear regression when variables under study are not normally distributed (Corder and Foreman, 2014; Bonett and Wright, 2000). All the statistical analyses were performed using the open source statistical program, *R Studio* (R Core Team, 2015). In this paper, only the results of overall analysis is presented, comparison among the districts is not included.

5.5 Results

5.5.1 Epidemiological and geographical profiles

Of 818 responses included in analysis, 50% were from high risk regions, 26% were from medium risk regions, and 24% lived in low risk regions (Table 5.3). Most of the respondents were residing in rural areas (70%). About 46% of the respondents had permanently migrated from other districts to the district where they were currently living. The amount of time of residence in the area varies from less than 5 years to 65 years for these migrants. About 45% of the surveyed households had one or more household members currently away for employment, both within the country (33%) and outside the country (67%). The popular foreign destinations for employment-related migration were India, Bangladesh, Qatar, Saudi Arabia, United Arab Emirates, Malaysia, Afghanistan, and Israel. Among these countries, India, Bangladesh, Afghanistan, and Malaysia are malaria-endemic countries.

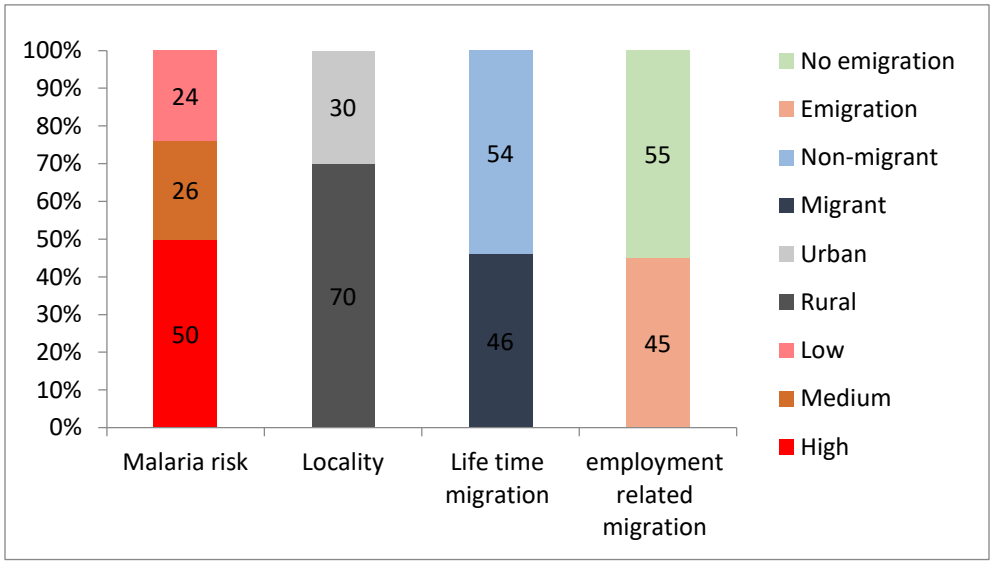

Figure 5.2: Epidemiological and geographic profile of the respondents (N=818)

5.5.2 Demographic and socio-economic profiles

The respondents were mostly male (65%) (Table 5.3). The age of respondents ranged from 18 to 85 years. Mean age of the study cohort was 39 with a standard deviation of 12.4. The minimum household size was one and the maximum household size was 22; the mean household size was 5.7 (standard deviation 2.3). Altogether, 22 different ethnic groups were recorded during the study, with Brahmin (32%), Janajati (21%), and Chhetri (16%) as the dominant ethnic/caste groups. Among the study districts, Jhapa is the most ethnically diverse district, representing 22 ethnic groups, followed by Chitwan with ten different ethnic groups in this study. The remaining four districts were represented by respondents from six different ethnic groups each. Educational status also varied widely among the respondents: 8% of the respondents were illiterate, 7% of the respondents had higher education, 17% were literate, 25% had elementary school education, 12% had middle school education, and 31% had graduated high school. The major primary occupation of the respondents were agriculture (51%), business (19%), laborer (13%), and homemaker (8%); other included students, those in public service positions, and those employed in the private sector. Monthly income varied widely among the respondents. Twenty percent of the respondents did not have any regular monthly income; the highest monthly income was Nepali Rupees (NPR) 150,000. The median income of the survey sample was NPR 10,000 (approximately $110) (Table 5.3).

Table 5.3: Demographic and socio-economic characteristics of the respondents (N=818).

Parameters	n	%		Parameters	n	%
Gender				**Education**		
Male	535	65		Illiterate	68	8
Female	283	35		Literate	135	17
Age group				Elementary School	206	25
less than 20 years	39	2		Middle School	102	12
21-30 years	182	22		High School	251	31
31-40 years	243	30		College	56	7
41-50 years	208	25		Occupation		
51-60 years	104	13		Agriculture	416	51
More than 60 years	42	5		Business	158	19
Household size				Laborer	104	13
1 to 3	90	11		Homemaker	63	8
4 to 6	509	62		Others	193	23
7 to 9	169	21		**Income**		
10 or more	50	6		None	160	20
Ethnicity				1000 - 5000	159	19
Brahmin	260	32		5001-10000	160	20
Chhetri (Kshatriya)	131	16		10001-15000	148	18
Newar	22	3		15001-20000	97	12
Dalit	51	7		20001-25000	27	3
Janajati	180	21		More than 25000	67	8
Adibashi	79	10				
others	95	11				

5.5.3 Malaria-related knowledge

Assessment of malaria-related knowledge of the study sample was done by investigating respondents' knowledge of three major aspects of malaria. The first part consisted of knowledge related to the biomedical concepts of the disease, the second category focused on knowledge related to the disease vector, and the third category consisted of knowledge related to prevention and control of the disease. The assessment is based on answers to the questions related to each of the three categorizes during the closed questionnaire survey.

Knowledge scores − disease knowledge score (DKS), vector knowledge score (VKS), and prevention and treatment knowledge score (PTKS) − were calculated for each respondent. Calculating the knowledge score based on the respondent's answer is an established practice in this kind of study (Ul Haq et al., 2012). The criteria used by Ul Haq et al. (2012) were used in this analysis. Each response was scored as "correct" or "incorrect". A score of 1 was given for each correct answer and 0 was assigned for incorrect answers. The DKS was calculated based on respondents' answers regarding knowledge of biomedical concepts of malaria, such as knowledge of its basic signs and symptoms, consequences, and knowledge about susceptibility to the disease. The VKS was calculated based on respondents' answers about perceived the time of the mosquito abundant season, perceived habitat of the vector, and perceived and practiced mosquito bite prevention activities. The PTKS was calculated based on respondents' answers regarding various preventive measures, prevention practices they have adopted, and knowledge related to anti-malarial drugs and access to the treatment. The maximum possible scores for DKS, VKS, and PTKS were 8, 16, and 13, respectively. A cut-off level, 50% of maximum possible score for each category, was considered to categorize the knowledge scores into poor and adequate. The minimum adequate knowledge score for DKS was 4, and those for VKS and

PTKS were 8 and 7 respectively. Any scores equal to or more than the cut-off level were considered adequate; and those less than the cut-off score were considered poor (Figure 5.3).

5.5.3.1 Disease knowledge

During the study period (2012-2013), government reports recorded a total of 861 malaria cases from the study districts (DoHS, 2013; DoHS, 2014). In 2012, 475 cases were reported, and 386 cases were reported in the year 2013. Our study recorded incidence of malaria from 17 out of 818 households. The majority of participants (81%) had heard of malaria (Table 5.4). Approximately 3% of all respondents said that malaria was one of the common illnesses in their neighborhood. Only 2% mentioned either themselves or their family members being infected and treated for malaria in recent months (Table 5.4).

Table 5.4: Disease knowledge profile of the respondents.

	n	%
Heard of malaria		
Yes	*660*	*81*
No	158	19
Mention malaria in neighborhood	24	3
Mention malaria in households	17	2
Cause of malaria		
Mosquito bites	*562*	*69*
Malnutrition	25	3
Drinking contaminated water	25	3
Other	8	1
Do not know	212	26
Basic symptoms of malaria		
Headache and fever	*597*	*73*
Chills	*491*	*60*
Bad stomach and vomiting	39	5
Body rashes	30	4
Joint pain	9	1
Yellow eyes and skin	26	3
Do not know	166	21
Consequences of malaria		
Anemia	*130*	*16*
Physical weakness	*302*	*37*
Death	*204*	*25*
Do not know	237	29

	n	%
Malaria susceptibility		
Who can be infected		
Everyone	*580*	*71*
Only male	16	2
Only female	8	1
Only children	16	2
Only female and children	16	2
Only male and children	8	1
Do not know	172	21
Disease Knowledge Score (DKS)	n	%
0	136	17
1	29	3
2	26	3
3	44	5
4	41	5
5	152	19
6	355	43
7	31	4
8	4	1

Correct answers are italicized in the table.

Percentages do not add up to 100 as there were multiple responses

Mosquito bite was listed as the major cause of malaria by a majority of respondents (69%). Sixty-five percent of participants could name more than one symptom of malaria; 9%

named just one symptom. The most recognized malaria symptoms, physical manifestation of disease, were headache and fever (73%), followed by chills (60%). A low proportion of respondents identified stomach pain and vomiting (5%). Some participants recognized physical weakness (37%), anemia (16%), and death (25%) as major consequences, outcome of disease, of malarial infection. Seventy-one percent mentioned that everyone, regardless of gender or age, is susceptible to malaria infection (Table 5.5). However, a significant portion of the respondents had not heard of malaria (19%), could not name any symptoms (21%), did not know the consequences (29%), and did not know who could be infected from malaria (21%).

There were altogether eight correct answers to items related to disease, whether the respondent had heard of malaria and whether he/she could identify the cause (vector), symptoms, consequences, and what type of individual is susceptible to the disease (shown in italics in Table 5.4), yielding 8 as the maximum possible DKS. The mean DKS for the study sample was 4.3 (standard deviation 2.32). The median score was 5, with the minimum score 0 and maximum score 8. A score of <4 was considered poor, whereas ≥ 4 (50% of the maximum possible score) was considered adequate knowledge for DKS. Of 818 respondents, 235 (28%) were within the poor knowledge range, whereas 583 (72%) showed adequate knowledge about the biomedical concepts of the disease (Table 5.3; Figure 5.3).

5.5.3.2 Vector knowledge

As mentioned above, 69% correctly associated mosquitoes as a major cause of malaria (Table 5.5). The incorrect causes listed were drinking contaminated water, malnutrition, smoking cigarettes, and drinking alcohol. The survey revealed that mosquitoes are abundant in the study area throughout the year. However, the intensity of abundance as perceived by the respondents, varies among the districts of the Terai and Hill regions. The pre-monsoon season was listed as

the mosquito-abundant season by 51% of respondents, followed by the monsoon (41%); 17% said they have noticed mosquito nuisances in winter months as well, and 3% of the respondents did not know anything about the mosquito season. Stagnant water was listed as the common habitat by the majority of respondents (72%), followed by animal sheds (16%), gardens (4%), and forest (4%). Other habitats listed were rivers and streams, agriculture fields, and inside the house. A moderate proportion (15%) of the respondents did not know anything about mosquito habitat.

Table 5.5: Vector knowledge profile of the respondents.

	n	%			n	%
Mosquito-abundant season						
Summer	418	51		**Vector Knowledge Score**		
[1]Winter	147	18		0	15	2
Monsoon	335	41		1	12	1
Do not know	24	3		2	96	12
[2]**Mosquito habitat (where it is seen/ found)**				3	380	47
Stagnant Water	605	72		4	159	19
Animal shed	131	16		5	90	11
Garden	33	4		6	33	4
Forest	33	4		7	15	2
Rivers and streams	8	1		8	10	1
Agriculture field	9	1		9 to 13	5	1
Inside the house	8	1				
Do not know	122	15				
[3]**Mosquito bite prevention**						
Use of door/windows screen	98	12				
Using fan while sleeping	65	8				
Insecticides spray	73	9				
Use repellent coils	163	20				
Sleep inside the house	196	24				
Sleep inside the bed nets	605	74				
Do not know	33	4				

[1] winter as a mosquito abundant season was not correct for some survey clusters, and this fact was considered while scoring the individual response from the particular clusters.

[2/3] Only correct answers are listed in the table, incorrect answers are included in the attached questionnaire (appendix)

Percentages do not add to 100 as multiple answers were possible. N=818

Respondents had good knowledge about various preventive measures to protect themselves from mosquito bites. A majority (74%) stated that sleeping inside bed nets is the best way to prevent mosquito bites, followed by sleeping inside the house (24%), using mosquito

repellent coils (20%), and use of screens in doors and windows (12%). The other prevention methods mentioned were use of ceiling or table fans while sleeping and insecticide sprays. Four percent of the respondents reported that they did not know anything about prevention methods.

There were altogether 16 correct answers, making 16 the maximum possible VKS. The mean VKS for the study sample was 3.08 (1.69 standard deviation). The median score was 3, with 0 being the minimum score achieved and 13 the maximum (Table 5.6). None of the respondents had VKS score 16. Score of less than 8 was considered as poor score whereas ≥ 8 (50% of the possible maximum score) was considered adequate knowledge about the malaria vector. Out of 818 respondents, 803 (98%) fell within the poor knowledge range, whereas 15 (2%) showed adequate vector-related awareness (Figure 5.3).

5.5.3.3 Prevention and treatment knowledge

References to several malaria prevention practices were recorded during the survey (Table 5.8). The most popular prevention were sleeping under bed nets (57%), cleaning around home (53%), draining stagnant water around the house (28%), insecticide spray around home (15%), use of mosquito repellant (11%), and use of anti-malarial drugs (6%). Percentages do not add up to 100% as multiple responses were possible. Other preventive activities mentioned were healthy eating and drinking clean water, but these are not effective against malaria.

Table 5.6: Prevention and treatment knowledge profile of the respondents.

	n	%
Malaria Medication Knowledge		
[1]*Yes* (Chloroquine (CQ))	25	2
No	793	98
Malaria treatment		
Private clinics	171	21
Government hospital	580	70
Local healthcare providers	54	7
Volunteers	16	2
Others	31	4
Do not know	62	8
Malaria spread prevention		
Sleeping under bed net	608	57
Insect repellant	166	11
Cleaning around home	434	53
Anti-malarial drug	49	6
Insecticide spray	125	15
Draining stagnant water	229	28
Drinking clean water	33	4
Healthy eating	28	3
Do not know	80	9

Prevention and Treatment Knowledge Score			
	n	**%**	
0	26	3	
1	78	10	
2	296	36	
3	162	20	
4	124	15	
5	89	10	
6	35	4	
7	5	1	
8	3	1	

[1]The questionnaire did not provide the name of the medication, 2% of the respondent voluntarily named the medicine

Percentages do not add up to 100% as multiple responses were possible.

Correct answers italicized

The respondents demonstrated poor knowledge of malaria medication. Almost none of the respondents (98%) knew any medications for treating malaria. The questionnaire did not provide the name of the medication, only 2% of the respondent voluntarily mentioned chloroquine (CQ) as a treatment for malaria (Table 5.6). In Nepal, CQ was used as first line of treatment for malaria patients. It is also used as prophylaxis in other parts of the world. None of the respondents mentioned the use of any herbal or homeopathic medicines and other malaria treating drugs. There was no record of prophylaxis use to prevent infection, either.

Although the respondents did not know much about malaria treatment medication, a significant portion knew where to go for a treatment. Seventy percent mentioned that a

government hospital and 21% mentioned that private clinics are the places they would go to get medication in case of fever or other illness. The other sources of treatments mentioned were local healthcare providers (7%), traditional healers (4%), and volunteers working for health care projects (2%). Eight percent of the respondents did not know where to go for treatment (Table 5.6).

There were altogether 10 correct answers for malaria treatment and prevention. Therefore, the maximum possible PTKS score was 10. The mean PTKS for the study cohort was 2.9 (standard deviation 1.69). The median score was three, with the minimum score received was 0 and the maximum score was 8. None of the respondents had a PTKS of 10. A score less than 5 was considered as a poor score, whereas 5 or more was considered adequate knowledge about the prevention and treatment of malaria. Of 818 respondents, 564(69%) had poor prevention and treatment knowledge; the remainder had adequate prevention and treatment related knowledge (Table 5.6; Figure 5.3).

Radio and television were the most prevalent sources of malaria information (41%), followed by health care providers (14%), schoolteachers (11%), and posters (9%). Most of the information disseminated through radio and television were delivered in Nepali language. Only one respondent mentioned that his information source was textbooks.

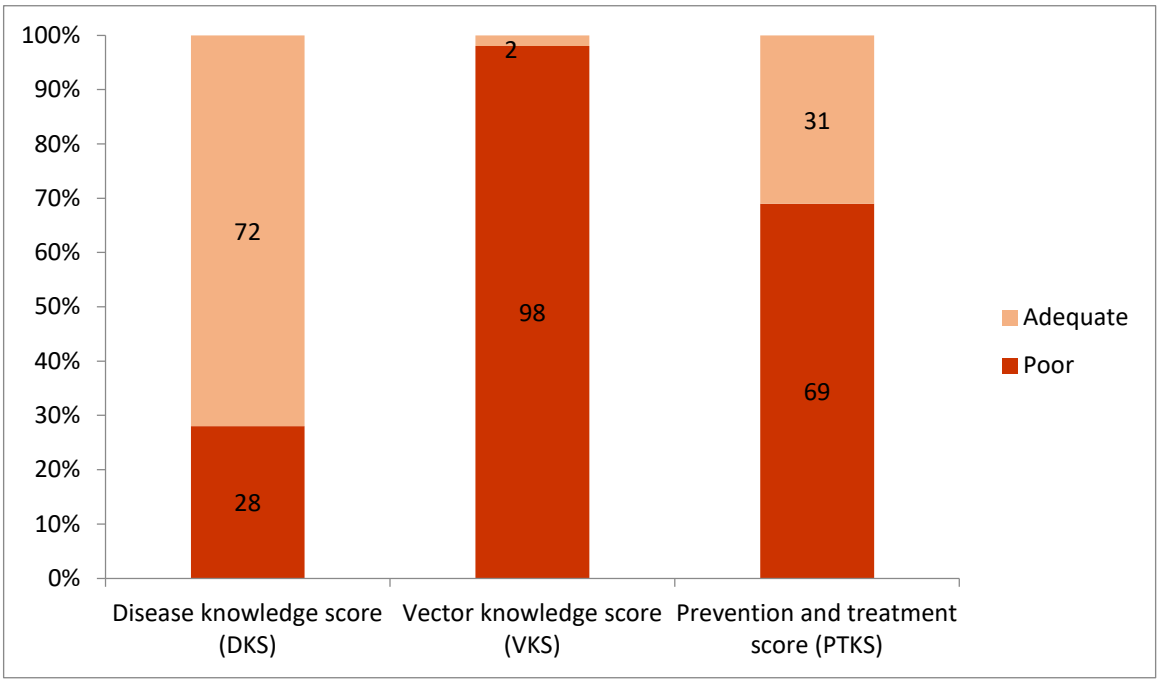

Figure 5.3: Distribution of malaria related knowledge among the respondents

5.5.4 Association of knowledge scores with epidemiological, geographic demographic and socio-economic characteristics

Spearman rank correlations revealed significant relationships between DKS, VKS, PTKS, and many epidemiological, geographical, and socioeconomic characteristics of the respondents. DKS was significantly correlated (α 0.05) with endemicity, locality, migration status, years lived in the district, gender, ethnicity, household size, education, occupation, income, and landholdings (Table 5.7). Similarly, more significant correlates with VKS included endemicity, locality employment related migration, gender), age, ethnicity, household size, and income (Table 5.7). PTKS also showed significant correlation with endemicity, migration status, and years lived in the district, household size, education, occupation, and landholdings (Table 5.7).

Table 5.7: Spearman's Rank Correlation between Malaria Knowledge Scores (DKS, VKS and PTKS) and characteristics of the respondents.

Parameters	**DKS**		**VKS**		**PTKS**	
	Spearman's rho	**p**	Spearman's rho	p	Spearman's rho	p
District	-0.092	0.008**	-0.082	0.018**	0.325	0.001**
Malaria risk	-0.073	0.037**	-0.243	0.001**	0.347	0.001**
Locality	0.152	0.000**	0.226	0.001**	0.033	0.003**
Migrant	-0.098	0.004**	0.035	0.315	0.204	0.000**
Employment-related migration	0.035	0.314	0.081	0.019**	-0.041	0.245
Years lived	-0.097	0.005**	0.056	0.104	0.089	0.011**
Gender	-0.073	0.036**	-0.113	0.001**	0.007	0.825
Age	-0.062	0.077**	0.095	0.006**	-0.080	0.021**
Ethnicity	-0.091	0.008**	-0.130	0.000**	0.043	0.217
Ethnicity	-0.091	0.008**	-0.130	0.000**	0.043	0.217
Household size	-0.064	0.066**	-0.066	0.056**	-0.086	0.013**
Education	0.160	3.834	0.0250	0.474	0.087	0.012**
Occupation	0.127	0.002**	0.0570	0.102	-0.105	0.002**
Landholdings	0.073	0.036**	-0.038	0.265	-0.071	0.041**
Income	0.172	6.967	0.090	0.009**	0.008	0.799

** Significant at 95% confidence Interval (α-level 0.05)
Degree of freedom = 816

5.6 Discussion and Conclusion

The general perception among the people in Nepal is that malaria has already been eradicated, following massive deforestation coupled with an intense malaria eradication campaign carried out during the 1970s and 1980s. Malaria risk is perceived to be low and not a common health problem. Today the disease is believed to occur mostly in the Terai region, the humid plains in the south. During the study period (2012-2013), government reports recorded a total of 861 malaria cases from the study districts (DoHS, 2013; DoHS, 2014). In 2012, 475 cases were reported, and 386 cases were reported in the year 2013. Our study recorded incidence of malaria from 17 out of 818 households. Malaria occurrence during the study period was reported from only 2% of the study households. Only 3% of all respondents stated that malaria is one of common illnesses in their neighborhood. The self-reporting of malaria occurrence from high-risk districts is relatively low in this study. A similar study done in Jhapa, Kailali, and Kanchanpur districts reported 7.4% of households with malaria occurrence during the study period 2004-5 (Joshi and Banjara, 2008). The results of this study confirm a number of factors related to malaria knowledge among respondents. Though a significant portion of the respondents have heard about malaria, there was a wide range of variation among the respondents in specific and detailed knowledge. The percentage of respondents with knowledge related to the biomedical concepts of the disease was higher than the respondents with knowledge related to vectors and prevention and treatment (Figure 5.3). Respondents identified mosquitoes as the major cause of malaria. This result was similar to reporting from Dhanusha district (Sherchand et al. 1996). Other researchers have also shown that people of malaria-risk countries are aware that malaria is caused by mosquito bites (Ahmed et al. 2009). Sleeping under bed nets to protect from mosquito bites, thus preventing or protecting from malaria

infection is a widely accepted practice throughout Nepal. Knowledge about malaria medication was poor among respondents, however. Only 2% of the respondents voluntarily mentioned chloroquine (CQ), a medicine which treats malaria. CQ was the first line drug for malaria treatment from the 1950s through 1988, and is still used in many districts (Chand et al., 2003; DoHS, 2014). This study is consistent with other findings that there is limited knowledge specific to treatment than the knowledge about the biomedical concept, sign and symptoms of the disease (Nonaka et al., 2012). Poor content of malaria-related information in school textbooks in Nepal was found by Nonaka et al. (2012). Only one respondent in this study mentioned that the source of his malaria-related knowledge came from textbooks. Locality, age, household size, education, and income were significantly associated with malaria-related knowledge.

The involvement of civil society is a must if a malaria-free future is to be realized in Nepal. This study revealed that malaria knowledge varied widely among respondents. Malaria is recognized as a significant disease; however, its prevalence is highly underestimated. Efforts to increase malaria-related knowledge among the population from all geographic regions needs to be continued: providing correct and adequate information is the key to changing understanding and practices related to malaria. Since television and radio are the most common sources of malaria information, increasing the frequency of awareness campaigns via these media is recommended. Special attention should be given to treatment procedures, location of treatment facilities, and cost associated with treatment, as the knowledge related to treatment was very poor. Delivering malaria information in local languages is highly recommended, as the population of the study area is multilingual and multiethnic. Incorporating malaria-related

information in textbooks at various levels (elementary, middle, and high schools) thus is recommended.

This study provides scientific clues and information for policy makers to design targeted anti-malarial campaigns so that the population has access to correct information. Greater resource allocation and broadening of intervention policies in low-risk districts, especially the Hill region, is recommended because this research recorded higher malaria reporting from low risk districts.

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Chapter 6 - Summary of Major Findings and Future Work

6.1 Background

Nepal is one of the 99 countries identified by the World Health Organization (WHO) where malaria transmission occurs. WHO has classified its malaria prevention and control program into four distinct phases: control, pre-elimination, elimination, and prevention of re-introduction. Nepal is one of the eight countries categorized in malaria elimination phase. Malaria elimination is defined as the permanent interruption of vector-borne malaria transmission in a given geographic region. The government of Nepal is committed to meet all the criteria of malaria elimination. The nation, along with partner organizations, is working to create a malaria-free future by 2026. However, challenges exist in completely eradicating the disease from the country.

This research attempts to realistically create beneficial information that can be used to develop effective intervention programs during elimination phase for the government and WHO related to malaria in Nepal.This research identified four major themes related to malaria research in Nepal between 1950 -2013. The four themes were geographic or spatio-temporal studies, social (economic, demographic, behavioral), biomedical, and ecological studies. Geographic studies have tended to focus on investigations of the spatial and temporal distribution of malaria in the country. Social research has focused more on the behavioral aspects of people living in the endemic zones. Social-science based studies also measured the cost-effectiveness of malaria control programs, and examined malaria related awareness and treatment-seeking patterns. The biomedical research concentrated on understanding the sero-epidemiology of malaria, development and efficacy of diagnostic tests, and the life cycles of pathogens. It has also investigated drug resistance patterns of various pathogen strains and complications associated

with malaria infection. Ecological studies have identified vectors and their habitat, stratified the country into various endemic zones based on the biophysical aspects of the country, and assessed the relationships among the spatio-temporal distribution of malaria and climatic factors, such as temperature and precipitation.

The depth and breadth of malaria research has increased since the 1990s. However, it has been restricted to selected districts of the Terai region. A very limited number of have been done in malaria endemic districts in the Hill and the Mountain region. For most of the studies done during the last 10-15 years, sample sizes were small, and the studies were limited to one or two districts, with almost no follow up studies conducted in most cases. The topic and problems addressed in these publications are very genuine and important. The literature suggests that underlying biophysical, socioeconomic, and behavioral factors influence malaria transmission and create region-specific patterns. Each geographic setting is unique, therefore to generate meaningful outcomes this research employs methods that use various concepts from the discipline of geography, landscape ecology, climatology, epidemiology, and sociology to understand the geographic distribution of malaria in a specific geographic region, Nepal. Understanding local epidemiological patterns is important for sustainable malaria management.

My research brings together theoretical, conceptual and technical aspects of existing research from multiple disciplines and investigated malaria related problem from multiple perspectives. Geospatial techniques, such as GIS, remote sensing, advanced spatial statistics, and qualitative methods were used to tie different components of the research together (epidemiological, climatic and socio-cultural) and develop models to identify the geographic pattern of malaria in Nepal. This research identifies malaria hotspots and provides valuable, complete and detailed information regarding stable, emerging, reemerging, intermittent and

disappearing malaria hot spots in Nepal. It provides the scientific assessment of climatic factors and these hot spots in relation to malaria transmission. The research also provides assessment of knowledge and practices related to malaria among a sample of those living in high, medium and low malaria-risk regions of Nepal. My research is valuable in providing scientific evidences in understanding the geographic extent of malaria in Nepal. It also informs policy makers about where the nation stands in achieving its goal of malaria elimination and whether the country is ready to fulfill its ambitious vision of malaria eradication by 2026.

The research advances knowledge and understanding within the sub-fields of medical geography and human-environment interactions. Multi-scale approaches highlight the importance of scale in infectious disease study in similar geographic regions of the world. The potential broader impacts of the research are substantial. The results of this research will help the Nepal government and agencies such as WHO to establish a national campaign to educate people about basic public health measures and access to health care related to malaria. The research has also address the important public health concept, status of health equity to malaria based on individual's income, occupation and social status. The research also helps public health scientists to understand the disease from geographic perspective.

6.2 Summary of major contributions

Through this dissertation, I made few major contributions in malaria related research in Nepal, in particular and infectious disease studies, in general. Identification of malaria hotspots and providing details of spatio-temporal distribution of these hotspots is one of the major contributions (Figure 6.1). This section of the research, identifies malaria hot spots, describes their characteristics and examines if there have been shifts in malaria hot spots between 1988 through 2013. In 26 years, altogether, 39 out of 75 districts were identified as malaria hot spots

in Nepal. The identified hot spots were grouped into five different categories: stable, disappearing, reemerging, emerging, and intermittent, based on the frequency, persistence, and proportion of caseloads each year (Figure 6.1). The location, size, and magnitude of these hot spots varied overtime. None of the previous studies looked into the temporal shift of geographic distribution of malaria in Nepal at this spatio-temporal scale.

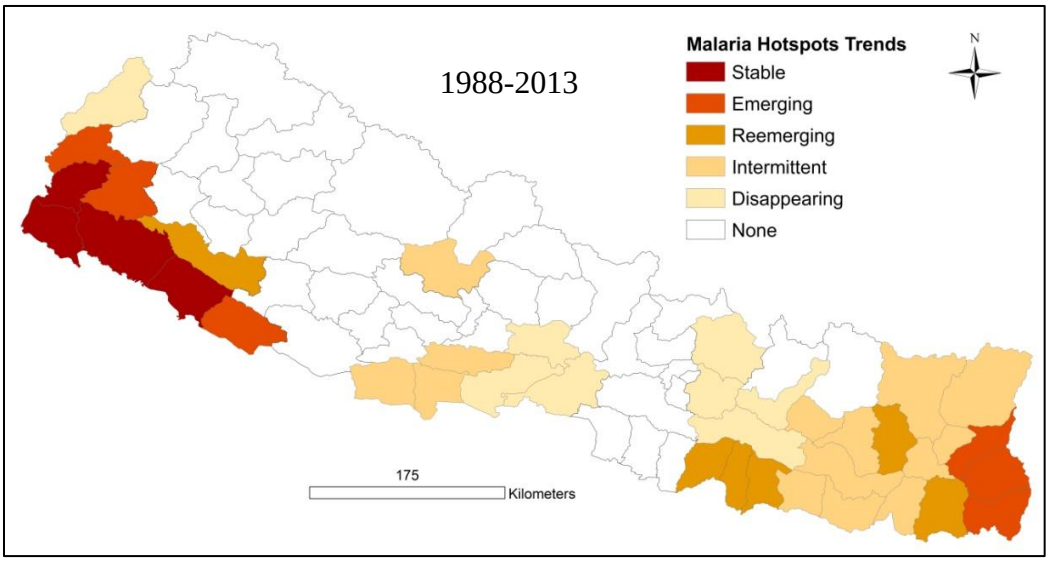


Figure 6.1: Stable, emerging, reemerging, intermittent, and disappearing malaria hot spots in Nepal, 1988-2013.

The research has highlighted the fact that epidemiological, geographic and public health risks associated with malaria are unevenly distributed within the country. Year to year reporting differs geographically and varies in number of positive cases and intensity of infection. The malaria patterns in a few endemic districts have not changed, and new patterns have emerged in districts which otherwise are categorized as low risk or new risk districts. The malaria burden in Nepal is underestimated due to the presence of more cases of *P. vivax,* less severe form of malaria as compared to *P. falciparum*, resulting less death. As a result, there has been considerable decline in resources to support control programs, leading to a situation where malaria in Nepal would be in the verse of being neglected tropical disease.

Second major contribution of this research is, it investigated the relationship between the climate variables, during the Monsoon and non-monsoon seasons, and malaria disease frequency in Nepal at the district level during 1988 through 2013 using panel data models based regression analysis. The study is the adaptation of an analysis technique that, up to now, had not been commonly used for analyzing environment-disease interaction. This investigation has, for the first time, adopted panel data models to explore the relationship between the climate variables and malaria disease frequency across a 26 year time span including all the 75 districts in Nepal. The method was appropriate for the analysis because the longitudinal data were available for multiple spatial units and the spatial autocorrelation existed. Panel data analysis considers both spatial and temporal heterogeneity, which is not addressed by the traditional linear model.

The first panel analysis tested if the presence and absence of malaria is related to climatic factors. The monsoon maximum temperature, monsoon minimum temperature, non-monsoon minimum temperature, and monsoon precipitation showed significant positive relationship with malaria frequency. The second analysis tested the relationship between the climatic factors and the low and high frequency of malaria. Out of six predictors only three variables, monsoon maximum temperature, monsoon and non-monsoon precipitation have shown significance in the model. The second analysis identified maximum temperature during monsoon season is the likely predictor of high and low frequency of malaria along with both Monsoon and non-monsoon precipitation. The results of the panel data analysis suggest that between 1988 and 2013, climatic factors did play a significant role in the distribution of malaria in Nepal. The most influential climatic factors in determining the presence and absence of malaria in a district were minimum temperatures of both monsoon and non-monsoon seasons.

Finally, the research looked into the public awareness of malaria symptoms, mosquito ecology, preventive measures, and cure availability for the six selected districts of Nepal. None of the studies in the past included the population from the low risk districts. The study revealed that self reporting of malaria cases were higher from the low risk districts as compared to the high risk districts. This study examines knowledge and practices related to malaria among adults in Nepal and revealed that significant portion of the population did not have adequate malaria related knowledge. Though a significant portion of the respondents have heard about malaria there was a wide range of variation among specific and detailed knowledge. The results of this study confirm that a combination of determinants influence malaria related knowledge among the respondents. Locality, age, household size, education, and income were significantly associated with malaria-related knowledge.

During the research, various databases are created, including district-wise demographic database, district-wise monthly/yearly climate database, and malaria-climate geodatabase for Nepal (figure 6.2). The databases have wide applicability. The databases are archived in the Remote Sensing Laboratory (RSL) at the department of geography, Kansas State university which, is available for research purposes upon request.

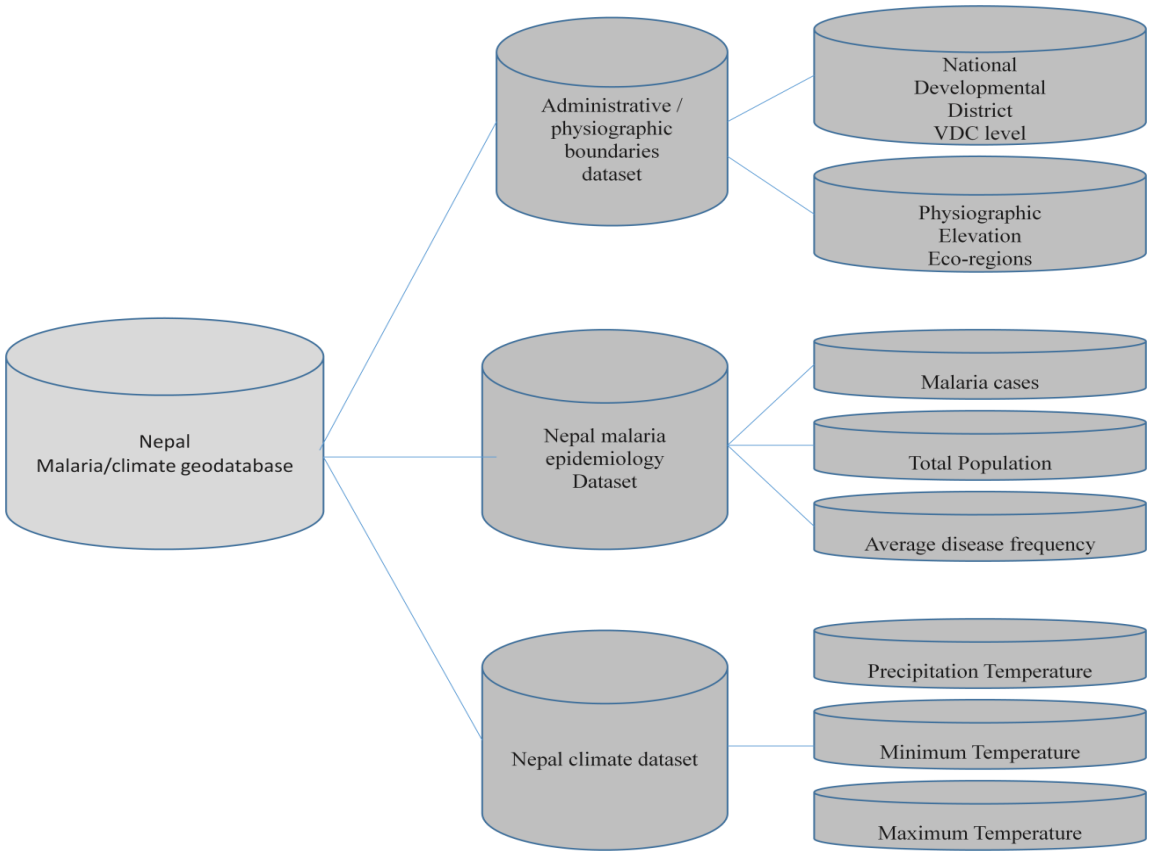


Figure 6.2: District-wise Malaria, Climate, Demography geodatabase for Nepal

6.3 Future work

The cases reported from the Mountain region were based on passive surveillance, suggesting incomplete and inadequate reporting from the area. This study identifies the need for independent studies focusing just on the Mountain region with the aims of understanding the occurrence and distribution patterns specific to the region and investigating the reasons behind the occurrence of malaria. Five of the 75 districts, three from the Mountain region and 2 from the Kathmandu Valley in the Hill region did not record any malaria cases throughout the study period. Kakchapati and Ardkaew (2011) reported six districts without malaria between 1998 and 2009. In the last few decades, there has been significant population growth in the two districts

from the Kathmandu valley, Kathmandu and Bhaktapur, identified as no malaria risk districts during the study period (CBS, 1992, 2002, 2012). The demographic change within the valley, with the majority of migrating populations coming from high endemic regions and a noticeable increase of mosquitoes in the area suggest the potential existence of malaria transmission in the valley. A recent independent study also suggests the presence of malaria in the Kathmandu valley (Singh et al., 2006). Therefore, independent studies need to be conducted in the valley to identify the current malaria situation as the environmental and socioeconomic conditions of the valley are favorable for malaria occurrence and transmission. The population of the districts has increased more than 60% in the last decade, the influx of travelers in the valley from within the country and outside the country is very high. The country's only international airport is located in the valley and is the only entry and exit point for all the international travelers, both local and foreigners, traveling by air.

This dissertation identifies the geographic distribution of malaria hotspots at the district level in Nepal or periods of single years and beyond. Identification of malaria hotspots at a finer scale, both spatial and temporal, (monthly, weekly) needs to be conducted to further understand the patterns within the five identified malaria hot spot categories. The microclimate, the land use practices, medical infrastructure presence, and population distribution varies significantly within these hotspot regions. Identifying the hotspots at finer scales will help identify the priority areas and prime time of malaria occurrence and facilitate the efficient allocation of limited malaria control and prevention resources within the districts. This will also help identify and isolate the areas of frequent epidemics, which was not visible at the scale of the analysis done in this paper. Separating the cases by infection types (pathogen specific) and differentiating indigenous cases

versus imported cases while identifying the local scale hot spots will also help provide specific details of the disease patterns, ultimately contributing to the overall goal of malaria eradication.

Understanding the factors that are associated with the distribution of malaria is crucial for decision making and designing a policy to control and eventually eradicate malaria. Keeping the complexity of malaria-climate relationship in mind, it would be beneficial to investigate the relationship further using disaggregated data at the finer scale. The finer scale study would be looking into the relationship at the VDC/municipality level, lowest administrative unit, with monthly and weekly climate variables considering the monthly and weekly malaria frequency. The effect of climate covariates on malaria distribution was assumed to be uniform for all the districts in this paper. Malaria distribution may not always be and only be a function of climatic factors. Many other confounding factors contribute in malaria distribution dynamics. The paper did not consider other underlying biophysical, socio-economic and public health factors. The factors such as deforestation, drug resistance among pathogen and vectors, population growth, limited access to the healthcare facilities and failure of the malaria control programs, are known to influence malaria transmission. Therefore, there is a need for further study considering multiple factors that are associated with malaria prevalence in Nepal.

References

Kakchapati, S., and Ardkaew, J. (2011). Modeling of malaria incidence in Nepal. *Journal of Research in Health Sciences*, *1*(1), 7–13.

Singh, S. B., Chaudhary, D., Neupane, A., and Karki, D. B. (2006). Two cases of severe falciparum malaria in KMCTH. *Kathmandu University Medical Journal*, *4*(1), 86–88.

Appendix A : Project geodatabase diagram

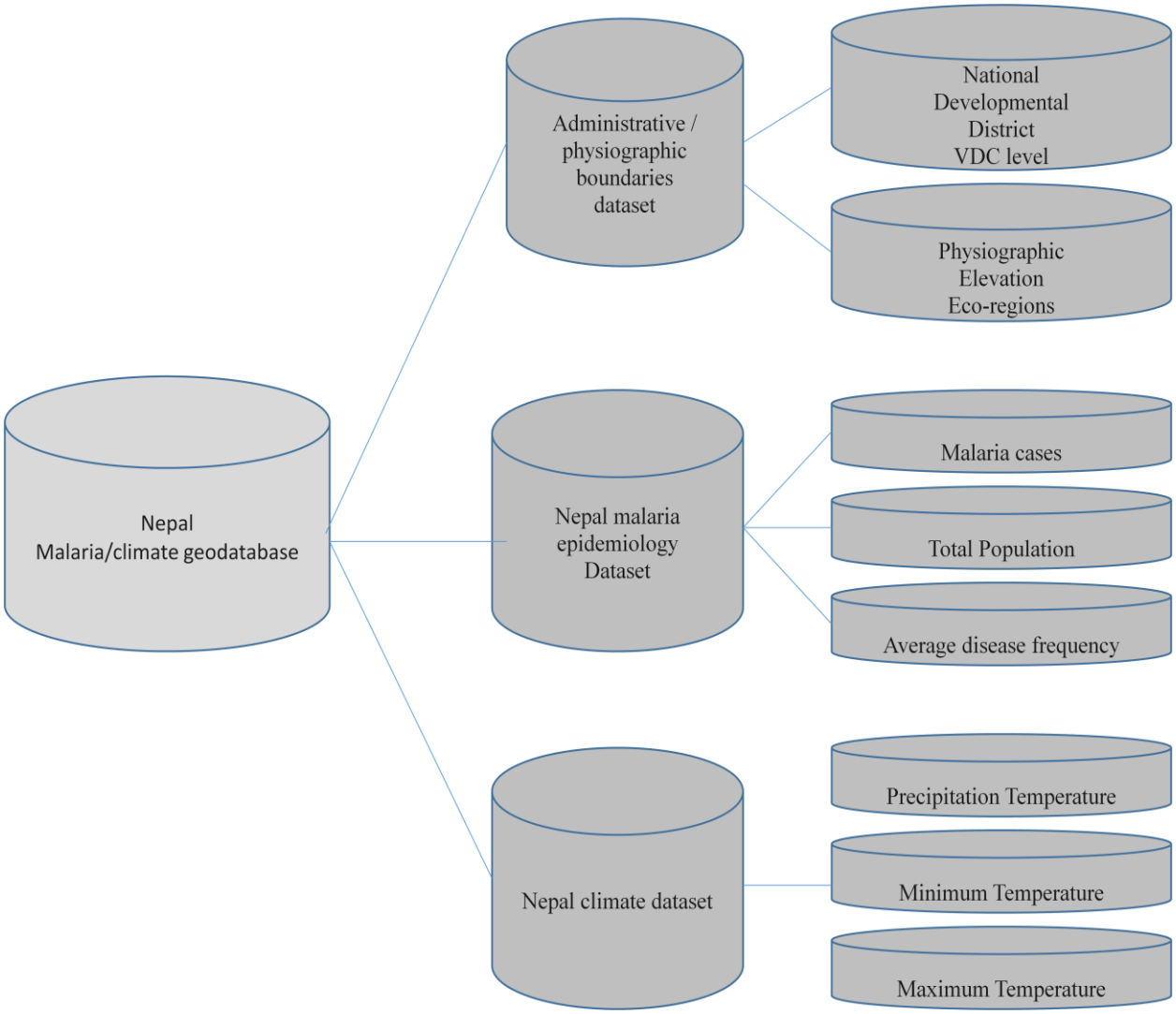


Figure Appendix A.1 : Project geodatabase diagram

Appendix B: Oden's I pop statistics details

Oden's I pop Statistics (Biomedware, 2015; Oden, 1995)

H_o Variation in disease rates is related to variation in population size of the spatial unit.

H_a Variation in disease rate is not related to variation in population size of the spatial unit.

Test Statistic

Moran's I, Moran, 1950) is a weighted correlation coefficient used to detect departures from spatial randomness. Oden (1995) adjusted Moran's I (Ipop) is a modified Moran's I which account for differences in population size across the spatial units under study. Ipop statistics is given by :

$$Ipop = \frac{N^2 \sum_{i=1}^{m} \sum_{j=1}^{m} w_{ij}(e_i - d_i)(e_j - d_j) - N(1-2\bar{b}) \sum_{i=1}^{m} w_{ij} e_i - N\bar{b} \sum_{i=1}^{m} w_{ii} d_i}{S_o \bar{b}(1-\bar{b})}$$

- m represents the number of locations or areas
- N is the total number of cases in all of the areas
- n_i is the total number of cases in area i
- e_i is the proportion of cases in area i ($e_i = n_i/N$).
- X is the total size of the risk population in all areas
- x_i is the size of the risk population in area i
- d_i is the proportion of the population in area i, $d_i = x_i/X$
- $e_i - d_i$ is the difference between the proportion of cases in area i and the number of cases expected given the area's population size.
- b is the average prevalence, b = N/X, b2 = 1/b(1-b) -3.
- $S_0 = X^2A-XB$, $S_1 = X^3E-4X^2F+4XD$
- w_{ij} is a weight denoting the strength of connection between areas i and j, developed from neighbor information.

$$A = \sum_{i=1}^{m}\sum_{j=1}^{m} d_i d_j w_{ij}$$

$$B = \sum_{i=1}^{m} d_i w_{ii}$$

$$C = \sum_{i=1}^{m}\sum_{j=1}^{m} d_i d_j \left(w_{ij} + w_{ji}\right)^2$$

$$D = \sum_{i=1}^{m} d_i w_{ii}^2$$

$$E = \sum_{j=1}^{m} d_i \left[\sum_{j=1}^{m}\left(w_{ij} + w_{ji}\right)\right]^2$$

$$F = \sum_{j=1}^{m} d_i w_{ii} \sum_{j=1}^{m} d_j \left(w_{ij} + w_{ji}\right)$$

$$G = \sum_{i=1}^{m} e_i w_{ii}$$

$$H = \sum_{i=1}^{m}\sum_{j=1}^{m} w_{ij}\left(e_i - d_i\right)\left(e_j + d_j\right)$$

The expectation of Ipop under the null hypothesis (no clustering) approaches zero for large total population:

$$E(Ipop) = \frac{-1}{(X-1)}$$

The range of Ipop depends on population size, therefore t can be useful to standardize the statistic using the average prevalence, for comparison among different study areas.

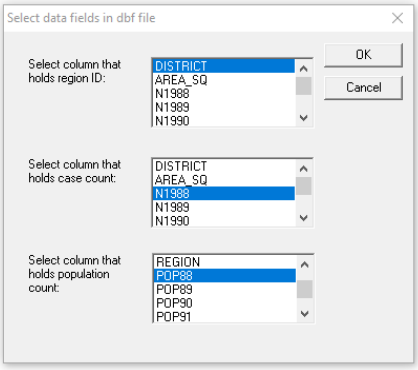
$$Ipop' = \frac{Ipop}{\bar{b}}$$

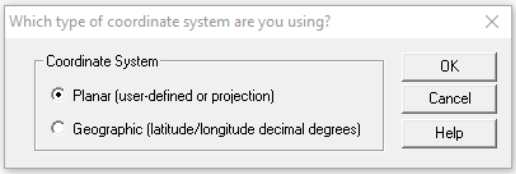
The variance of Ipop can be written as:

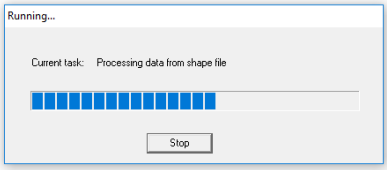
$$Var_R(Ipop) = \frac{X\left[\left(X^2 - 3X + 3\right)S_1 - XS_2 + 3S_0^2\right] - b_2\left[X^{(2)}S_1 - 2XS_2 + 6S_0^2\right]}{(X-1)^{(3)}S_0^2} - E(Ipop)^2$$

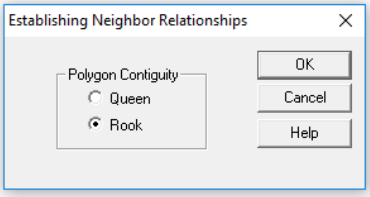
The significance of Ipop using three approaches: using the z-scores and variance calculated in each way and through Monte Carlo randomization, using multinomial randomization.

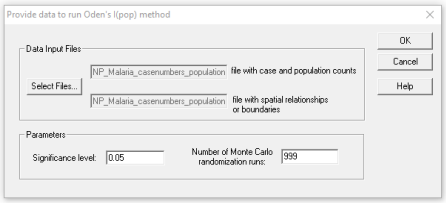
Workflow screen shots and results of Oden's I pop analysis in ClusterSeer











Welcome to ClusterSeer (Copyright: TerraSeer 2002)
January 26, 2015 Dataset source:

Dataset source:
D:\NP_Malaria_Epidemiology_June2015\ClusterSeer\Clusterseer_Feb2015\NP_Malaria_casenumbers_population.dbf 02/27/2015 06:46 PM
D:\NP_Malaria_Epidemiology_June2015\ClusterSeer\Clusterseer_Feb2015\NP_Malaria_casenumbers_population.shp 02/27/2015 06:46 PM

Oden's Ipop method (Year 1988)

****

Results:

Ipop = 0.00193556

Ipop' = 1.37595

E[I] = -5.73046e-008

Alpha level = 0.050000

% within = 73.618235

% among = 26.381765

Approximation:

Variance = 9.8131e-014

z-score = 6178.98

Significance = 0.000000

Randomization Assumption:

Variance = 9.81269e-014

Appendix C:Kulldorff's Spatial Scan Statistics details

Welcome to ClusterSeer (Copyright: TerraSeer 2002)

February 27, 2015 08:04 PM

Dataset source:

C:\Users\Kabita\Desktop\NP_Malaria_Epidemiology_Feb2015\ClusterSeer\Clusterseer_Feb2015\NP_Malaria_casenumbers_population.shp 02/27/2015 05:46 PM

Total number of regions = 75; Total number of cases = 24548.00; Total population-at-risk size = 17450607.00; Average disease frequency = 0.00140671

Kulldorff's Scan Method - Spatial

****

Variable Analyzed: Case count: N1988

Population count: POP88

Maximum spatial population radius analyzed (50% of total population) = 8725304

Number of Monte Carlo simulations performed = 999

First Most Likely Cluster:

Regions Included: KANCHANPUR, DADELDHURA

Average disease frequency: 0.0122498

Log likelihood ratio: 5460.04

Upper-tail P-value: 0.001000

Second Most Likely Cluster:

Regions Included: SINDHULI, MAHOTTARI, RAMECHHAP, DHANUSA,

Average disease frequency: 0.00391756; Log likelihood ratio: 2234.31; Upper-tail P-value: 0.001000

Third Most Likely Cluster:

Regions Included: SURKHET

Average disease frequency: 0.00903817; Log likelihood ratio: 1961.83; Upper-tail P-value: 0.001000

Appendix D: IRB approval, Consent letter and Questionnaire

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203 Fairchild Hall
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Manhattan, KS 66506-1103
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TO: Douglas Goodin
Geography
Seaton 118

Proposal Number: 5864

FROM: Rick Scheidt, Chair
Committee on Research Involving Human Subjects

DATE: May 5, 2011

RE: Proposal Entitled, "Landscape Epidemiology of Malaria in Nepal"

The Committee on Research Involving Human Subjects / Institutional Review Board (IRB) for Kansas State University has reviewed the proposal identified above and has determined that it is EXEMPT from further IRB review. This exemption applies only to the proposal - as written – and currently on file with the IRB. Any change potentially affecting human subjects must be approved by the IRB prior to implementation and may disqualify the proposal from exemption.

Based upon information provided to the IRB, this activity is exempt under the criteria set forth in the Federal Policy for the Protection of Human Subjects, **45 CFR §46.101, paragraph b, category: 2, subsection: ii.**

Certain research is exempt from the requirements of HHS/OHRP regulations. A determination that research is exempt does not imply that investigators have no ethical responsibilities to subjects in such research; it means only that the regulatory requirements related to IRB review, informed consent, and assurance of compliance do not apply to the research.

Any unanticipated problems involving risk to subjects or to others must be reported immediately to the Chair of the Committee on Research Involving Human Subjects, the University Research Compliance Office, and if the subjects are KSU students, to the Director of the Student Health Center.

Consent letter

March,26, 2012

Dear respondent:

We are conducting a study to determine the impact of socio-economic characteristics at household level on geographic distribution of malaria in your area. As a part of the study we would ask you or your household members a series of questions and/or your opinions regarding health of you and your family members and other relevant information related to malaria.

We would very much appreciate your collaboration and cooperation in participating in questionnaire survey which will be done by interviewing you or your family members by us or the research assistant appointed by us. All of the information we collect during the survey will be kept anonymous. No one else will have access to the information you provide. Information will be used for academic research purpose.

Your participation in this survey is strictly voluntary and you may not have to answer any of the questions if you do not wish to answer it. You can quit anytime during the interview and there is no foreseeable risk involved because of your participation. If you have any question regarding your rights and about the manner in which you the study is conducted, you may contact Dr. Rick Scheidt, IRB Chair, 203 Fairchild Hall, Kansas State University, Manhattan, Kansas, 66506, USA, phone 0-1-785-532-3224

If you have any questions, please feel free to contact one of us at the address/phone number provided below. Thank you very much for your participation in this important study.

Sincerely,

Douglas G. Goodin, Ph.D
Professor
Department of geography
Kansas State University
Manhattan, Kansas 66506
Ph: 785-532-6727
email: dgoodin@ksu.edu

Kabita Ghimire
Ph.D Candidate
Department of geography
Kansas State University
Manhattan, Kansas
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Household survey to determine the impact of socio-economic characteristics at household level on geographic distribution of malaria in in Nepal

Gender: Age group: Ethnic group: Household size:
Level of education:

1. Where is your place of origin? How long have you been living in this place?

2. Has anybody from your household gone outside of the area for employment? Yes/ No

3. If yes who has gone and where has he/she gone? How long he/she has been gone? Has he/she came back for a visit or returned back?

4. Have you gone anywhere leaving your home in last one year? If Yes, where have you been and for how long?

5. What is your Primary occupation?
   a. Farming and cattle raising b. Civil servants c. School teacher d. Student
   e. House maker f. Private sector worker g. Local business h. Others (specify)

6. What is your monthly income?
7. How much land do you own?
8. How many storey's does your house have?
9. How many rooms do you have in your house?
10. What type materials are used to construct your house walls?
    a. Mud b. Bamboo and mud c. Brick d. Stone
    e. Cement f. Others (specify)
11. What type of materials are used to construct your house floors?
    a. Mud b. Mud and dung c. Cement d. Others (specify)
12. What type of materials are used to construct the roof of your house?
    a. Thatch b. Aluminum Tin c. Tile d. Stone e. Cement f. Others (specify)
13. Do you have electricity at your house? Yes / No
14. What kind of fuel is use for cooking in your house?
    a. Electric heater b. Charcoal c. Fire wood d. Kerosene stove
    e. LPG gas stove e. Others (specify)
15. What are the diseases you have encountered in your household in past few years?
16. What are the other prominent diseases in your neighborhood and area?
17. Do you or any of your family members ever suffered from high fever in last five years? Yes / No
18. If yes, who suffered from it? How long ago was it?
19. What was the age of the person who suffered from the high fever?
20. What time of the year you or your family member had a incidence of high fever?
    a. Winter b. summer c. Monsoon d. Month (Specify)
21. Have you heard of malaria? Yes / No
22. How did you hear about malaria?
    a. Mass media (TV and Radio) b. Posters c. Health care providers d. School teachers e. Change agents (NGO representatives) f. Community leaders g. Others (specify)

23. Do you know what causes malaria?

a. Bites by the infected mosquitoes b. Drinking contaminated water
c. Malnutrition d. Smoking cigarette and drinking alcohol
e. I do not know f. others (specify)

24. Malaria is a disease that can be caused to:

a. Men only b. Women only c. Children only
d. Women and children only e. Men and children only f. everyone

25. What are the symptoms of malaria?

a. Headache b. Chills and fever c. Vomiting
d. Rashes in body parts e. Upset stomach f. Yellow
g. discoloration of the eyes and skin f. Limbs swelling and Joint pain
h. Others (Specify)

26. Do you know what happens when one suffer from malaria?

a. Anemia b. Disability c. Death d. Others (Specify)

27. Where do you go for a treatment when you or your family member has a high fever?

a. Use home remedies (like …) b. Local healers c. Local pharmacy
d. Nearby clinics e. Big hospitals in the nearby city f. Do nothing

28. How much are you willing to pay when you or your family members have a symptoms of malaria?

a. NRS 100 -200 b. NRS 200 -300 c. NRS 300 - 400
d. NRS 400-500 d. More than NRS 500

29.How much are you willing to travel for the malaria treatment?

a. Less than an hour b. 1- 2 hours c.2-5 hours
d. 1 day e. More than a day

30. How far is a nearby city hospital from your home?

31. What time of the year do you see more mosquitoes in your area?

a. Winter b. summer c. Monsoon
d. Month (Specify)

32. Do you know where these mosquitoes breed?

a. Stagnant water b. Cow dung and shed c. Kitchen garden d. River and streams e. Forests f. Paddy fields g. inside the house h. Tree holes i. Others (specify)

33. What kind of preventive measures you use to keep yourself and family members away from mosquito bites?

a. Sleep inside the house b. Use of door/windows screen
c. Using fan while sleeping d. Insecticides spray d. sleep inside the bed nets
e. Use repellant coils f. Others (specify)

34. Do you have bed net in your household? Yes / No (if no, go to question no. 35)

35. If yes, How many bed nets do you have in your household?

a. None b. 1 c. 2 d.3 e. 4 f. 5 or more

36. If yes , Where did you get the bed nets from?

a. Self purchase b. Health professional's c. Others (specify)

37. Who sleeps under the bed nets in your house?

38. Do you use bed nets when you sleep? Yes / No
39. Do you or your family members sleep outside during summer time? Yes/No
40. How can we prevent malaria from spreading?

a. Eating healthy food b. sleeping inside the bed net c. Drinking clean water d. Controlling mosquitoes f. Taking anti-malarial drugs
g. Draining stagnant water
h. Spraying inside and outside of the house with chemicals

41. Do you know what medication will cure malaria?
42. Do you know where to get the medication for malaria treatment?