Analysis of Geographical and Seasonal Variation of Dengue Fever in Nepal Based on EWARS Line Listing from 2017 to 2019

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Abbreviations

AMR	Antimicrobial Resistance
CIAT	Capacity Improvement and Advancement
DALY	Disability Adjusted Life in years
DF	Dengue Fever
DHF	Dengue Hemorrhagic Fever
DoHS	Department of Health Services
DPR	Democratic People's Republic
DSS	Dengue Shock Syndrome
EBV	Epstein Bar- Virus
EDCD	Epidemiology and Disease Control Division
EWARS	Early Warning and Reporting System
FCHV	Female Community Health Volunteer
GDP	Growth Domestic Product
HIV	Human Immune deficiency Syndrome
IHR	International Health Regulation
JE	Japanese Encephalitis
KoICA	Korea International Cooperation Agency
MoHP	Ministry of Health and Population
NCD	Non Communicable Disease
NPHL	National Public Health Laboratory
RoK	Republic of Korea
SEAR	South East Asia Region

SEARO	South East Asia Regional Office
SPSS	Statistical Package for Social Science
VBD	Vector Borne Disease
WHO	World Health Organization

Abstract

Background: Dengue is a mosquito-borne viral disease; rapidly spreading in many countries worldwide in recent years. Dengue has been identified as one of the youngest emerging infectious diseases in Nepal, the first case reported in 2004. In 2006, 32 laboratory-confirmed cases were reported across hospitals in central and western Terai and Kathmandu during the post-monsoon season. The trend for increased magnitude has been continued with the number of outbreaks reported each year in many districts in two to three years intervals. Since 2010, dengue epidemics have continued to affect lowland districts and mid-hill areas. These all reflected need of study on geographical and seasonal variation of dengue fever and many more.

This study analyzed the geographical and seasonal variation of Dengue fever in Nepal based on EWARS line listing 2017-2019 and provides recommendations for improvement of the dengue control program in Nepal.

Methodology: Quantitative analysis of key variables from the Early Warning and Reporting System (EWARS) line list was applied. EWARS line listing data from 2017to 19 was received from the department of health service, epidemiology and disease control division (EDCD), Nepal and analyzed. Published literature and articles were reviewed to discuss and triangulate the findings. Microsoft excels and SPSS20 software was used for data analysis, and Mendeley software was used for referencing and citations.

Based on the line listing data from EDCD, last three years dengue situation, age, gender, seasons, geography and department of registration in the sentinel sites were analyzed and discussed. The Chi-square test in 95 % confidence interval was applied to test hypothesis assessing the relationship of age group and geographical belt on the dengue cases reported in the studied years.

Results: Entirely of 2273 individual cases were verified and updated by EDCD; among these 1.32 % of received data were excluded and a total of 2243 samples were analyzed and studied.

The male population of the age group 20 to 40 was observed at higher risk of dengue with the infant proportion of 1.43% in Nepal. The notable infant case showed the urgency of actions needed to address this issue. Most of the dengue cases were found registered in from IPD, emergency, OPD and laboratory departments.

The geographical distribution of dengue cases reflected the higher case in Terai low land districts with massively escalating in the hill, Kathmandu valley and Mountain belts. The clusters of cases to outbreak situation of dengue suggest diversity and uncertainty of dengue incidence. In the study period, the highest cases were found in Lumbini province followed by Province 01and significance cases were reported from Province 02 and Bagmati province. In contrast, the Sudurpaschim, Gandaki and Karnali provinces reported a minimum number of cases. Mountain district Dhading had reported one of the top five reporting districts in the study period. Similarly, dengue cases fluctuated based on the seasons, predominantly in the monsoon and post-monsoon season in Nepal.

The test statistics, Chi-square test suggested a significant association between age group and geographical belts to the year wise dengue cases.

Conclusion: Thus Dengue has been tough public health problem with a rising burden and wider geographical and seasonal coverage resulting in a frequent outbreak in Nepal. The changing disease patterns with an uncertainty of prediction increases challenge. It is strongly recommended strategic preparedness and research and developmental works to improve dengue control program for the betterment of the population's health.

CHAPTER ONE: INTRODUCTION

1.1 Background

Vector-borne diseases are one of the furthermost causes of human death and ill health in tropical settings and recently extending geography. Although considerable achievement is being made in the disease containment for malaria, lymphatic filariasis and Chagas disease but other diseases such as dengue continue to spread and raise their number of cases at alarming rate.(1)

Dengue is a viral disease transmitted by mosquito of *Aedes* family and spread throughout the tropical world since the mid-twentieth century.(2) Even though the fatality of dengue fever (DF) is not high, the higher non-fatal cases impose a serious burden of morbidity and make dengue an increasing priority over 120 affected countries in the world.(3) In 2012, DF took the first position among mosquito-borne viral disease in the world.(2) Severe cases may require longer hospitalization, with potential long-term side-effects resulting to complications or death. Clinical DF cases can occupy health facilities and sub-clinical infections may disturb regular work schedules or school; similarly, latent infections represent as a reservoir for infection challenging surveillance and control efforts.(3) After the World War II, the problem of dengue became greater than before leading to DHF and DSS as one of the giant health problem in many parts of the tropics. With its development DHF is a top reason of hospitalization and fatality among children in many states of Southeast Asia.(5) Although the global burden of the DF remains in question, the burden and trends are alarming for both human health and the economy. In the past five decades, the incidence of DF has increased by 30 times.(2)

Dengue may manifest in various forms; viz; DF, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) have become major global health problems; among these DHF and DSS are considered as more serious. Some supporting statistics include estimated 2.5 billion people (two fifths of the world's population) in tropical and subtropical regions are at risk of DF. Similarly estimated 50 million dengue new infections reported each year and estimated 500,000 people with DHF require hospitalization yearly in the world. Among these; larger proportions (approximately 90%) are less than five years children, and about 2.5% of those affected may lose their life.(6) Dengue has been listed as ninth-ranked top ten global health threats in the world by World Health Organization (WHO), 2019. The other nine global health threats are air pollution and climate change, Non Communicable Diseases (NCDs), global influenza pandemic, fragile and vulnerable setting, Antimicrobial Resistance (AMR), Ebola and other threatening pathogens, weak Primary Health Care (PHC), vaccine hesitancy and Human Immunodeficiency Virus (HIV), hence dengue and other Vector Borne Diseases (VBD) are also associated with air pollution and climate change and fragile and vulnerable setting directly two out of top five threats and indirectly with some of other the top ten global health threats by WHO 2019.(7)

An estimation predicted that dengue transmission is everywhere globally in tropical region, with the Americas and Asia as maximum risk zones.(8) Dengue poses a considerable fiscal and health related burden in South East Asia Region (SEAR) with a Disability Adjusted Life of Years (DALYs) per million population in the region, which is higher than that of 17 other conditions, including Japanese Encephalitis (JE), Hepatitis B (HPB) and Upper Respiratory Tract Infections.(9) As there may be a higher proportion of dormant dengue cases like other community health problems; the global disease burden is terrible and evident a mounting challenge to public health professional, global health leaders and authorities.(8) The reported cases in SEA region was found 386,000 patients in the first decade of 21st century (2001–2010) with 2,126 deaths. With overall annual financial pressure due to dengue of US$950 million (m) (US$610m–US$1,384m) with average annual direct costs amounted to US$451m (US$289m– US$716m) and the indirect costs were US$499m (US$290m– US$688m) in this region. Among 12 countries of SEA region; Bhutan, Brunei, Cambodia, East-Timor, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Viet Nam with Indonesia as the most economic burden of dengue in the region, followed by Thailand, representing about 34% and 31% of the total financial burden of dengue, respectively.(9)

Dengue is transmitted by mosquitoes (*Aedes aegypti and Aedes albopictus*)(10) and reported in most of the districts of Nepal. The earliest cases were detected in 2005 in Chitawan district in a foreign citizen. Since 2010, dengue outbreaks have continued to affect lowland districts as well as mid-hill areas in diverse geography over Nepal. This trend of enlarged extent of disease coverage has continued with number of outbreaks reported each year in many districts; Chitwan, Jhapa, Parsa (2012-2013), Jhapa, Chitawan(2016), Rupandehi, Jhapa, Mahottari(2017), Kaski (2018) and Sunsari, Kaski, Chitwan (2019).(11) This trend of Dengue has been identified as one of the youngest emerging infectious diseases in Nepal. In 2006, a large number of probable cases and 32 laboratory-confirmed cases were reported across hospitals in central and western Terai region and Kathmandu during the post monsoon season. Most cases were indigenous and confirmed the presence of all 4 serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) with historically contributing the highest burden in Nepal.(12)

From the reported cases and outbreak status since 2005, most widely affected districts are Chitwan, Kanchanpur, Kailali, Banke, Bardiya, Dang, Kapilbastu, Rupandehi, Rautahat, Sarlahi, Saptari and Jhapa, reflecting the burden of the disease all over the Terai plains from west to east and gradually increasing in the Kathmandu valley and mountainous districts. From the years 2007 to 2009, sporadic clinical cases and outbreaks were reported. Since 2010, dengue outbreak have continued to affect lowland districts as well as mid-hill areas.(9)(12) In Nepal, dengue is a rapidly troubling disease and endemic across most provinces, dengue incidence has increased in recent years primarily due to expansion of the vector *Aedes aegypti* and *Aedes albopictus*, as well as the movement of people and the extensive imported cases.(12)

Many findings including annual incidence, reported outbreak, Early Warning and Reporting System (EWARS) data, research and study finding, experts observation robustly recommended that the trend of DF has been increasing as well as the geographical and seasonal distribution has been widening and shifting all over Nepal. That's why; there is a strong need to have study of the geographical and seasonal variation of dengue fever in Nepal.

1.2 Research Question(s)

- Does the magnitude of DF have been related with age group in Nepal?
- Does the problem of DF have been related with geography in Nepal?

1.3 Hypothesis

Set1:

- Null Hypothesis (H0): There is no association between age groups and DF cases in study years.
- Alternative Hypothesis (H1): There is association between age groups and DF cases in study years.

Set 2:

- Null Hypothesis (H0): There is no relation between geographical belts and DF cases in study years.
- Alternative Hypothesis (H1): There is relation between geographical belts and DF cases in study years.

1.4 Objectives

1.4.1 Overall Objective

- To analyze the geographical and seasonal variation of Dengue fever in Nepal based on EWARS line listing 2017-2019.

1.4.2 Enabling Objectives

- To describe the last three years of the burden of dengue fever in Nepal.
- To explore the seasonal and geographical variation of Dengue fever in Nepal.

- To provide potential recommendations for a dengue control program in Nepal.

1.5 Significance of the Study

Dengue is a newer and rising disease in Nepal. It is observed that there have been recurring outbreaks of dengue within a few (2/3-5) years the last two decades. Recently after 2015, the trends of disease magnitude and outbreaks have been shifting towards the Kathmandu valley, hill and mountainous districts of Nepal. Many studies have explored the trend of dengue fever and its associated factors, mostly climatic factors in Nepal. Most of those studies and articles were found concentrated in certain localities, Chitawan district, and Kathmandu valley.

Since the disease burden is increasing with widespread geographical coverage, the whole country looks at higher risk. Therefore there is a scrupulous need to assess and analyze the geographical and seasonal variation of DF in Nepal and provide generous recommendations to the concerned authorities and other stakeholders. Furthermore it will be useful for planning dengue control activities in different territory of Nepal.

1.6 Limitations of the Study

This study may be subjected to some limitations. Considerable limitations of this study are declared below;

- As EWARS captured mostly the hospital data from listed sentinel sites, the other health facility and outbreak data were missed in the study.
- Many dengue cases may not be recorded and reported by the physician in the EWARS sites, which may miss certain eligible cases of study.
- During line listing by the clinician and EWARS focal person, the complete information may not be collected. This will make it difficult for complete analysis of data.

- Due to minimum cases in certain seasons, the seasonal distribution cannot be applied for testing hypotheses.
- Only the reported cases during study years were used instead of incidence rate and other calculated statistics to test hypothesis.
- The hospital services availability in different parts and its association with the dengue reported cases cannot be evaluated.

1. CHAPTER TWO: LITERATURE REVIEW

2.1 General Overview of Dengue

Dengue fever mostly represents severe signs and symptoms, flu-like illness and is characterized by high fever, severe headaches, muscle and joint pains, nausea, vomiting, swollen glands or rash. Dengue itself is not often lethal, but severe dengue mostly develops fatal complication, with symptoms including low temperature, severe abdominal pains, rapid breathing, bleeding gums and blood in vomit.(1) The factors causative to the amplified incidence of dengue and emergence of dengue hemorrhagic fever are increasing and becoming complex, which would be continued until the *Aedes* mosquito can be effectively controlled and cost effective vaccine developed. (13) Among four serotypes, recovery from infection by one confers lifetime immunity against specific serotype; however, succeeding infections of other serotype raise the risk of severe dengue.(1)

2.2 Epidemiology of Dengue

Agent: Dengue viruses are members of the *Flavivirus* genus and *Flaviviridae* family. The small (50 nm) viruses contain single-strand RNA as genome, with four serotypes as DEN-1, DENV-2, DENV-3, and DENV-4, all types are associated with epidemics, cross immunity is not secured.(6)

Vector: The most common two vectors of dengue virus are mosquitoes; *Aedes aegypti (Ae. aegypti) and Aedes albopictus (Ae. albopictus).* The vectorial capacity is governed by the environmental and biological characteristics of the species; two species are different in their vectorial capacity.(6)

Host: Evolved from mosquitoes, adapted to non-human primates and later to humans in an evolutionary process, viremia among humans builds up high titers two days before the onset of fever (non-febrile) and lasts 5–7 days after the onset of fever (febrile). Both monkeys and humans are amplifying hosts and the mosquitoes maintain the virus via eggs.(6)

Environmental Conditions: Climate Change, weather characteristics, altitude, Sanitation practices, precautions taken, urbanization and global travel etc.(6)

Transmission of dengue virus: There are three cycles are of transmission;

I. **Enzootic cycle:** According to cases reported from South Asia and Africa, the monkey-Aedes-monkey cycle maintains a primitive syllabic cycle. Viruses are not found pathogenic to monkeys, and viremia lasts 2–3 days. Viruses are not found pathogenic to monkeys and viremia lasts 2–3 days. (14) All the four dengue serotypes (DENV-1 to -4) have been isolated from monkeys.(6)

II. **Epizootic cycle*:*** The dengue virus crosses over to non-human primates from adjoining human epidemic cycles by bridging vectors. In Sri Lanka, the epizootic cycle was observed with toque macaques (*Macaca sinica)* during 1986–1987 in a study area on a serological basis. Within the study area (three kilometers), 94% macaques were found affected.(15)

III. **Epidemic cycle:** The epidemic cycle is maintained by human-*Aedes aegypti*-human cycle with periodic/cyclical epidemics. Generally, all serotypes circulate and give rise to hyperendemicity. *Ae. aegypti* generally has low susceptibility to oral infection but it is strong anthropophilic with multiple feeding activities, and high domestic habitats makes it an efficient vector. Therefore, the perseverance of dengue virus depends on the improvement of high viral titers in the human host to make certain transmission in mosquitoes.(16)

Features of dengue viral infection in the community: The cases of DF/ DHF mostly represent in the "iceberg" or pyramid model. The majorities of cases remain asymptomatic and lie in the base of the pyramid followed by DF, DHF, and DSS. Clusters of cases occurred in the specific household or social setting or neighborhood due to the feeding habit of vector.(17) Population affected varies from outbreak to outbreak; only 2% to 4% of individuals develop severe disease during sequential infections.(18)

Spread is caused by human movement, receptivity (high-breeding potential for *Ae. aegypti)* and vulnerability in predominant cases. Any congregation at receptive areas will transmit from infected mosquito to human or from viraemic human to the uninfected mosquito. Hospitals, schools, religious institutions and entertainment centers where people congregate become the focus of transmission on account of high receptivity and vulnerability for DF/DHF. Further human movement spreads the infection to larger parts of the urban areas.(19)

2.3 Risk factors associated with Dengue Fever

The Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever (WHO, SEARO, 2011) enlisted various risk factors associated with DF and DHF as;

- **Demographic and societal changes:** Demographic and societal changes leading to unplanned and uncontrolled urbanization has put severe constraints on civic amenities, particularly water supply and solid waste disposal, thereby increasing the breeding potential of vector species.
- **Water supply:** Insufficient and inadequate water distribution.
- **Solid waste management:** Insufficient waste collection and management.
- **Mosquito control infrastructure:** Lack of mosquito control infrastructure.
- **Consumerism:** Consumerism and introduction of non-biodegradable plastic products, paper cups, used tires, etc, that facilitate increased breeding and passive spread of the disease to new areas (such as via the movement of incubating eggs because of the trade in used tires).

- **Increased air travel and globalization of trade:** Increased air travel and globalization of trade have significantly contributed to introducing all the DENV serotypes to most population centers of the world.
- **Microevolution of viruses**: The use of the most potent molecular tools has revealed that each serotype has developed many genotypes due to microevolution. There is increasing evidence that virulent strains are replacing the existing non-virulent strains. The introduction of Asian DENV-2 into Cuba in 1981, which coincided with the appearance of DHF, is a classic example.

2.4 Diagnostic tests and Differential Diagnosis

Along with clinical assessment and presentation of the cases, the following laboratory tests are commonly used for the confirmation of DF and DHF;(6)

- Virus isolation: serotype/genotypic characterization
- Viral nucleic acid detection
- Viral antigen detection
- Immunological response based tests: IgM and IgG antibody assays
- Analysis for hematological parameters.

WHO classification for dengue consist of three categories of dengue fever (2)

- Dengue without warning signs,
- Dengue with warning signs and
- Severe Dengue.

Sets of differential diagnosis for suggestive dengue cases may occur in the clinical setting. So the dengue case should be rule out not a case of following infections.(13)

- Arboviruses: Chikungunya virus (often been misdiagnosed in SEARO).
- Other viral diseases: Measles; rubella and other viral exanthems; Epstein - Barr virus (EBV); enter viruses; influenza; hepatitis A; Hantavirus.

- Bacterial diseases: Meningococcemia, leptospirosis, typhoid, melioidosis, rickettsial diseases, scarlet fever.
- Parasitic diseases: Malaria.

2.5 Disease Burden of Dengue Fever

Over the past three decades, there has been a dramatic global increase in the frequency of DF, DHF and DSS and their epidemics, with a concomitant increase in disease incidence. Dengue is found in tropical and subtropical regions around the world, predominantly in urban and semi-urban areas. The disease is caused by a virus belonging to the family *Flaviviridae* spread by *Aedes (Stegomyia)* mosquitoes. There is no specific treatment for dengue, but appropriate medical care frequently saves the life of patients with the more severe dengue hemorrhagic fever. The most effective way to prevent dengue virus transmission is to combat the disease-carrying mosquitoes. (6) The effects of climate variability have been observed to exaggerate and control DF outbreaks through effective vector management and community education. Based on the quantitative assessment of climate-DF relationship, projected climate change might increase mosquito abundance, activity and DF incidence Asia pacific region.(20)

2.5.1 Global Burden

Dengue epidemics are known to have occurred regularly over the last three centuries in tropical, subtropical and temperate areas worldwide. The first dengue epidemic was recorded in 1635 in the French West Indies, although a disease outbreak compatible with dengue had been reported in China as early as 992 AD. During the 18th, 19th and early 20th centuries, epidemics of dengue-like diseases were observed and reported globally, both in tropical as well as some temperate regions. Rush was probably describing dengue when he wrote of “break-bone fever” occurring in Philadelphia in 1780. During the epidemics of that time, most of the cases mimicked clinical DF, although some displayed characteristics of the hemorrhagic form of the disease.(6)

In most Central and South American countries, effective disease prevention was achieved by eliminating the principal epidemic mosquito vector, *Ae aegypti*, during the 1950s and 1960s. In Asia, however, effective mosquito control was never achieved. A severe form of hemorrhagic fever, most likely akin to DHF, emerged in some Asian countries following the World War II. From the 1950s through 1970s, this type of dengue was reported as epidemics periodically in a few Asian countries such as India, Philippines and Thailand.

During the 1980s, incidence increased markedly, and distribution of the virus expanded to the Pacific islands and tropical America. In the latter region, the species re-infested tropical countries in the 1980s on account of disbanding of the *Ae aegypti* eradication program in the early 1970s. Increased disease transmission and frequency of epidemics were also the result of circulation of multiple serotypes in Asia. This brought about the emergence of DHF in the Pacific Islands, the Caribbean, and Central and South America. Thus, in less than 20 years by 1998, the American tropics and the Pacific Islands went from being free of dengue to having a serious dengue/ DHF problem.(6)

Every ten years, the average annual number of cases of DF/DHF cases reported to WHO continues to grow exponentially. From 2000 to 2008, the average annual number of cases was 1 656 870, or nearly three-and-a-half times the figure for 1990–1999, which was 479 848 cases. In 2008, a record 69 countries from the WHO regions of South-East Asia, Western Pacific and the Americas reported dengue activity.(6)

Geographical extension of the areas with dengue transmission or resurgent dengue activity has been documented in Bhutan, Nepal, Timor-Leste, Hawaii (USA), the Galapagos Islands (Ecuador), Easter Island (Chile), and the Hong Kong and Macao (special administrative regions of China) between 2001 and 2004. Nine outbreaks of dengue occurred in north Queensland, Australia, in four years from 2005 to 2008.(6)

All four dengue viruses are circulating in Asia, Africa and the Americas. Due to early detection and better case management, reported case-fatality rates have been lower in recent years than in the decades before 2000. Countries at risk of dengue transmission in 2008 are mostly located in the coastline and tropical areas in the southern hemisphere.(6)

2.5.2 SEARO Regional Burden

Among 2.5 billion people around the world living in dengue endemic countries and at risk of contracting DF/DHF, 1.3 billion live in 10 countries of the WHO South-East Asia (SEA) Region which are dengue endemic areas. Till 2003, only eight countries in the Region had reported dengue cases. By 2009, all Member countries except the Democratic People's Republic (DPR) of Korea reported dengue outbreaks. Timor-Leste reported an outbreak in 2004 for the first time. Bhutan also reported its first dengue outbreak in 2004. Similarly; Nepal too reported its first indigenous case of dengue in November 2004.(6)

The reported dengue cases and deaths between 1985 and 2009 in 10 countries of the WHO SEA Region (all Member States except DPR Korea) underscore the public health importance of this disease in the Region.(6)

Table 1 Variable endemicity of DF/DHF in countries of the SEA Region

Category A	Category B	Category C
• Major public health problem. • Leading cause of hospitalization and death among children. • Hyper endemic, all four serotypes occurring in urban areas and spreading to rural areas. • Countries (9): Bangladesh, India, Indonesia, Maldives, Myanmar, Sri Lanka, Thailand and Timor-Leste.	• Endemicity uncertain. • Countries (2) Bhutan and Nepal • Bhutan reported first outbreak and Nepal reported first dengue case in 2004.	• No evidence of Endemicity • Country (1): DPR Korea

The number of dengue cases has increased over the last three to five years, with recurring epidemics. Moreover, there has been an increase in the proportion of severe dengue cases, particularly in Thailand, Indonesia and Myanmar.(6)

DF/DHF is endemic in most countries of the SEA Region and detection of all four serotypes has now rendered these countries hyperendemic. However, the endemicity in Bhutan and Nepal is uncertain. (6)

2.5.3 National Burden

Dengue is occurring in most of the districts of Nepal in recent years. After the first case detected in 2004, sporadic cases and outbreaks were occurred in 2006 and 2010. Initially most cases had travelled to the neighboring country (India), although indigenous cases have also been reported lately.(6)

The affected districts are Chitwan, Kanchanpur, Kailali, Banke, Bardiya, Dang, Kapilbastu, Parsa, Rupandehi, Rautahat, Sarlahi, Saptari and Jhapa, reflecting the spread of the disease throughout the Tarai plains from west to east. In 2011, 79 confirmed cases were reported from 15 districts with the highest number in Chitwan. During 2012 -15, the dengue cases still continued to be reported from several districts but the number fluctuated between the years. *Ae. aegipti* was identified in five peri-urban areas of the Tarai (Kailali, Dang, Chitwan, Parsa and Jhapa) during entomological surveillance by EDCD during 2006–2010, demonstrating the local transmission of dengue.(11)

The number of reported dengue cases has decreased significantly since 2010 but cases of dengue were increased in recent years. In FY 2074/75 (2018), total 2111 cases were reported from 28 districts. The majority of cases have been reported from Rupandehi (32%), Jhapa (25%), Mahottari (20%) and Sarlahi (6%). There were three confirmed deaths due to Dengue, one each from Chitwan, Jhapa and Arghakhanchi district.(11)

Studies carried out in collaboration with the Walter Reed/AFRIMS Research Unit (WARUN) in 2006 by EDCD and the National Public Health Laboratory (NPHL) found that all four sub-types of the Dengue virus (DEN-1, DEN-2, DEN-3 and DEN-4) were circulated in Nepal. Those findings concluded dengue as public health problem spreading throughout the country, the activities should focus the goal of national Dengue control program; reduce the morbidity and mortality due to DF, DHF DSS.(11)

2.6 Dengue Control Policy in Nepal

The national dengue control policy includes one goal, four objectives and four strategies for prevention, control and treatment of dengue in Nepal.(11)

Goal: To reduce the morbidity and mortality due to DF, DHF and DSS.

Objectives:

- To develop an integrated vector management (IVM) approaches for prevention and control.
- To develop capacity on diagnosis and case management of dengue fever, DHF and DSS.
- To intensify health education and Information Education Communication (IEC) activities.
- To strengthen the surveillance system for prediction, early detection, preparedness and early response to dengue outbreaks.

Strategies:

- Early case detection, diagnosis, management and reporting of dengue fever
- Regular monitoring of dengue fever surveillance through the EWARS
- Mosquito vector surveillance in municipalities
- The integrated vector control approach where combinations of several approaches are directed towards containment and source reduction.

2.7 Early Warning and Reporting System (EWARS)

The international health regulation (IHR) 2005 suggests having clear structures for surveillance, preferably through public health policy and legislation, with definite roles and responsibilities for each organization and authorities in each state. For the surveillance system there should be specific unit with the ability to monitor public health risks, verify alerts and respond to public health emergencies.(21)

EWAR is the "mechanism to detect as early as possible any abnormal occurrence or any divergence from the usual or normally observed frequency of phenomena"(21) The national EWAR should incorporate information from sources beyond the routine health system data. An effective early warning system ascertain quick response to acute public health events of all origins, resulting in mitigation of the public health impact.(22)

In Nepal, EWARS is a hospital-based sentinel surveillance system of collecting and communicating immediate and weekly reports (including zero reports) on six priority diseases and outbreaks of any diseases from selected and authenticated hospitals. Focus of this system is to provide timely report of selected epidemic prone, vector-borne, water and food borne diseases, for the early detection of outbreaks. EWARS was initiated in 1997 from eight sentinel sites and has been gradually expanded to 118 sentinel sites by 2019 including all the federal (central) hospitals, provincial hospitals, district hospitals, medical colleges and selected private hospitals.(23)

2.7.1 Mechanism of EWARS in Nepal

Currently, six diseases are reported in EWARS, three epidemic prone diseases; Acute Gastroenteritis (AGE) cholera and Severe Acute Respiratory Infection (SARI) and three vector borne disease; malaria, dengue and Kala- azar. Scrub typhus and Influenza like illness (ILI) cases have also been reported for few years. These two diseases are in process of incorporating in the EWARS. Beyond these prioritized diseases, other infectious diseases also need to be reported in EWARS in case of their outbreaks. There is an established system for the collection, reporting, publication, communication of EWARS bulletin. (23)

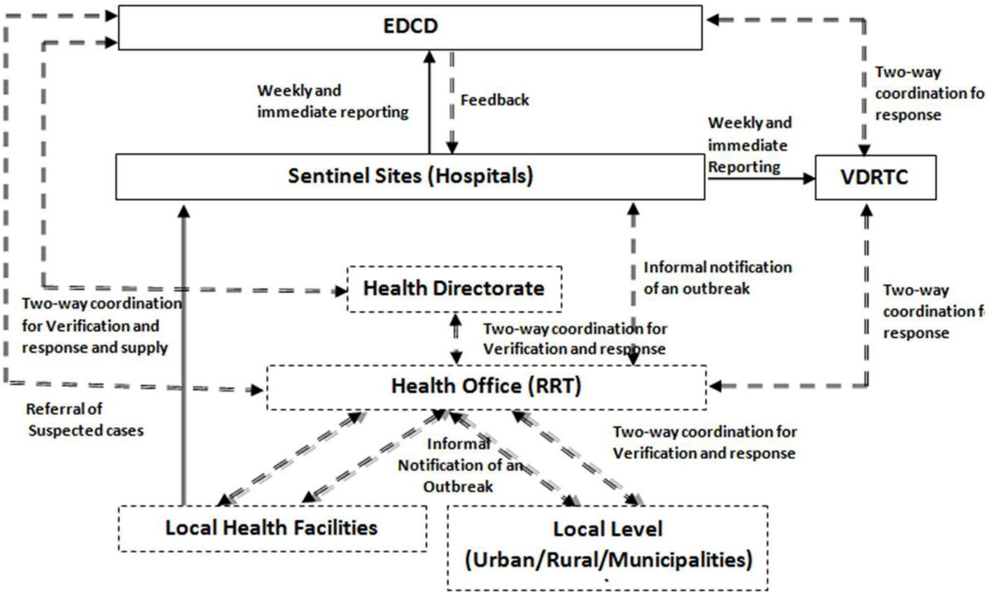


Figure 1 Mechanism of EWARS in Nepal

Similarly the sentinel hospitals should prepare weekly report based on the epidemiological week calendar which starts on the first week of January (Epidemiological Week 1) and ends on lasts week of December (Epidemiological Week 52). Each week starts on Sunday and ends on Saturday. Consolidated weekly reports should be prepared for the epidemiological week and sent to EDCD and VBDRTC by Friday of the subsequent week.(23)

2.8 Review of Related Studies

An entomological study in Nepal, 2014 explored that DENV vectors *Ae aegypti* and *Ae albopictus* were found from the lowlands up to the Middle Mountain region (1,310 m as of sea level) in central Nepal.(24) An ecological Niche Model analysis in Nepal, for mapping dengue cases from 1993- 2013 showed that about one quarter area of Nepal, mainly in the southern lowland Tarai, is currently suitable for dengue fever. This will expand northwards in the future in response to climate change. The same study estimated that 70% of the total population is at risk of dengue fever and will further increase (up to 90%) in the future due to climate change impacts.(25)

A study analyzing meteorological factors in upland hilly and low land Terai region done in Nepal, 2015/16 found that temperature and rainfall contribute to the vector indices in the upland hilly region while relative humidity contributes in the lowland plains. Since vector prevalence is not only linked to meteorological factors, other factors such as water storage practices, waste disposal, sanitary conditions and vector control strategy should also be considered. This study recommend strengthening and scaling up dengue vector surveillance and control programs for monsoon season in both upland and lowland regions in Nepal.(26)

A recent publication from Nepal concluded higher risk of dengue outbreak especially in the Terai region with increasing spread towards the mid-mountains and beyond, and there is higher risk of Chikungunya and Zika viral infections due to the similar vector *Ae. aegypti and Ae. albopictus* associated with the transmission of these vector borne disease.(27)

An eco-epidemiological prospective study done in India, 2005 highlighted rain, temperature and relative humidity as the considerable climatic factors, which could alone or collectively be responsible for an outbreak of DF. More studies could further reveal the correlation between the climatic changes and dengue outbreaks, which would help in making the strategies and plans to forecast any outbreak in future well in advance.(28)

A recent longitudinal study done in Rajasthan, India explained dengue as the new emerging disease in 2001, with increasing disease trend. Conversely the CFR is below one after 2010. The same study revealed a fourfold more cases (>4000 cases/year) during 2013 and 2015, despite of increasing dengue trend few districts have Zero reporting of dengue suggested the need for improvement in reporting system.(19)

A recent study done in Bangladesh suggests that relatively low case numbers indicate the potential of active transmission of the disease in a district which is crucial in the absence of information regarding the mosquito vector population, which indicates increased transmission risk across the neighboring districts resulting from inter-district movements of viraemic individuals. The assumption that transmission is governed by climatic suitability is reasonable, especially in the absence of effective public health strategies including mosquito control program.(29)

A study done on temporal distribution of dengue incidence using GIS in 2016 in Sri Lanka explained the association of geographical and climatic risk factors with dengue incidence. This study further suggested a combination of the environment, changing climatic conditions and the extreme appearances of the climate change, the growing DENV, and the highly adaptive vectors and their spread results the ever-increasing dengue incidence. For this instance, health authorities must eliminate or minimize the contributing factors to reduce the dengue burden.(30)

An epidemiological study of dengue in Khon Kaen Province, Thailand between 2006 and 2016 shows that rainfall and temperature has significant relation with dengue transmission. Spatial clustering of cases is partly associated with urban areas closer to Khon Kaen city and rural areas in the southwest of the province. The same analysis was not able to detect a close proxy factor to quantify a relationship between urbanization and dengue incidence.(31)

A similar study done in Vietnam in 2010 suggested domination of *Ae aegypti* in the low altitude area and other mosquito including *Ae albopictus* in the higher altitude area. *Ae Albopictus* was dominant, in the northern part of Vietnam and its magnitude gradually reduced toward the south. *Ae aegypti* was dominant in the southern area, whereas in the coastal areas far south of Khanh Hoa province, most of the larvae collected were those of *Ae aegypti*. At the same time, the proportion of *Ae albopictus* was found higher in the mountainous areas with forest vegetation. Ae *albopictus* were collected from used tires in Ho Chi Minh City and Vinh Long, Soc Trang, and Ca Mau provinces in the southern Vietnam.(32)

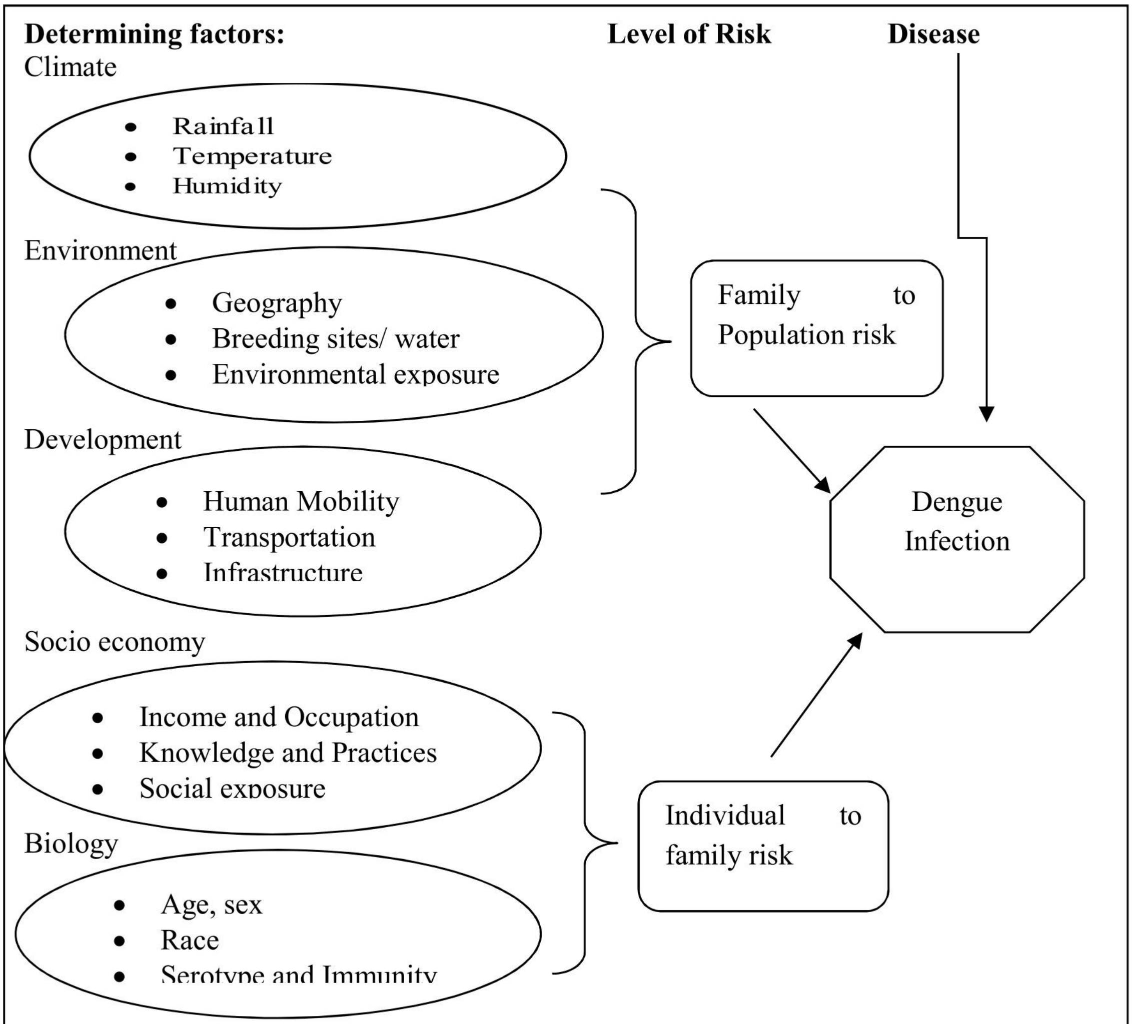
A study for spatial analysis of monthly variations to analyze the vulnerability of dengue fever in Jamaica implied a change in the climatic factors that support the dengue spread at high altitudes. In the spring and autumn seasons, there was moderate vulnerability in rural areas. In contrast high to very high vulnerability was illustrated in urban areas especially is spring and even in the winter, summer and autumn, showing an evidence that moderate vulnerability increases in summer, especially in rural areas.(33)

A systematic review done in 2019 indicated that the risk zone for dengue transmission may vary due to the impact of climate change. Some of the non-climatic drivers behind the existence of dengue vectors and the crucial factors activating dengue transmission in such climatically suitable areas were important. The future projections accounting for alternative climate change scenarios, the benefit might come from considering different control scenarios, all of these suggesting further studies on this matter. (34)

3. CHAPTER THREE: METHODOLOGY

3.1 Conceptual framework

Figure 2: Conceptual framework of Risk Factors of Dengue Fever(35)



Adapted from Lance Sese, Gabriel Castillo, Angelica Ermino, Abigail Juat, and Rexelle Piad, " Dengu end is Near: An Unmatched Case Control Study on the Dengue Vaccine Efficacy and Its Association between Dengue Cases among Children Ages 9-12 in Pasig City." American Journal of Epidemiology and Infectious Disease, vol. 6, no. 1 (2018): 1-6.

3.2 Selection of Study Topic

After the nomination by the Government of Nepal in 2019, the Korea international Cooperation Agency (KoICA) country office Kathmandu instructed us about the admission criteria and study plan. After that this thesis journey started. Informal discussion with related stakeholders in Nepal, Ministry of Health Officials, WHO officials and previous batch fellows was done informally for selecting thesis topic.

Further discussion and presentation with the research methodology subject professors and program director in the Graduate School of Public Health, Yonsei University facilitated the selection of thesis topic. After the thesis advisor's assignment, reviewing literature and data, coordination and series of meetings with the thesis advisor, the thesis topic was concluded. For the initial discussion, different topic was proposed as "the sensitivity analysis of the EWARS system in Nepal to detect disease of public health importance malaria, dengue etc", later after the professor's and my colleagues recommendation the thesis topic is finalized.

3.3 Selection of Study Area

Study area; Nepal was selected purposively for this study. As researchers represented the Government of Nepal for this KoICA Capacity Improvement and Advancement for Tomorrow (CIAT) program, exploration of global health issues especially for dengue prevention and control would be valuable. Due to limitation of 1.5 yrs course duration and COVID19 pandemic, it became difficult to collect primary data from Nepal. Similarly due to language and disease-related issues, collecting primary data in Korea was not practical. The Republic of Korea (RoK) is free from vector borne diseases like malaria and dengue for a long time. For my convenience to collect secondary data from different authorities of Nepal, Nepal has preferred the study area. Thus from the intensity of problem, convenience to perform and application point of view, the study area was selected.

3.4 Description of Study Area

Nepal is situated in South Asia. It is also known as the land of Mt. Everest, the highest peak of the world and the birth place of Lord Buddha, Lumbini. Nepal is a land locked country, which occupies 0.03 % and 0.3% land area of the World and Asia respectively. It has diverse topography and climate. It stretches from east to west with an average length of 885 kilometers and widens from north to south with an average breadth of 193 kilometers.(36)

Geographically, Nepal lies in between Latitude of 26, 22' north to 30, 27' North Longitude 80, 04' east to 88, 12' East with an area 147181 Square kilometer area with surrounded by China in the North and by India in the East, West and South. (36)

According to the National Population Census 2011, the annual growth rate of population is 1.35 percent and the total population has recorded about 26.5 millions with gender ratio 94.2 male per 100 female. The preliminary estimate of GDP per capita at current price stands at NRs. 117455 (US$ 1034) for the fiscal year 2018/19. Growth rate of GDP at basic price is estimated to be 6.81% for the same fiscal year. About one fourth of the population (25.16%) lives below poverty line.(37)

Nepal has three clear east-to-west elongated ecological belts. The northern mountain belt is naturally decorated by an unbroken range of Himalayas, which contains eight peaks higher than 8,000 meters, including the Mt. Everest (8848 meters). The Middle hilly belt is enriched by gorgeous hills, valleys and lakes. Kathmandu, the capital city of Nepal is situated in this belt. Terai belt is the plain area situated in southern part of Nepal, which is usually known as the country's grain house.(38) The Constitution of Nepal (2015) has declared the Federal Democratic Republic with seven provincial and 753 local level governments. There are 77 administrative districts in Nepal. (39)

Currently Nepal is further divided into five geographical belts; Mountain, Hill, Kathmandu Valley, Inner Terai and Terai (in past it has been considered as *Himal, Pahad and Terai* as

3 belts) from higher altitudes toward lower altitude. The seven provinces; Province 01, Province 02, Bagmati, Gandaki, Lumbini, Karnali and Sudurpaschim Province are located from east to west.(39)(40)

3.5 Study Design

A quantitative, non-experimental, retrospective study based on time series analysis was done to look at the geographical and seasonal variation of dengue fever in Nepal. The EWARS line listing data from 2017 to 2019 were analyzed in 2020, and drawn conclusions and recommendations provided accordingly.

3.6 Study Population and Unit of Analysis

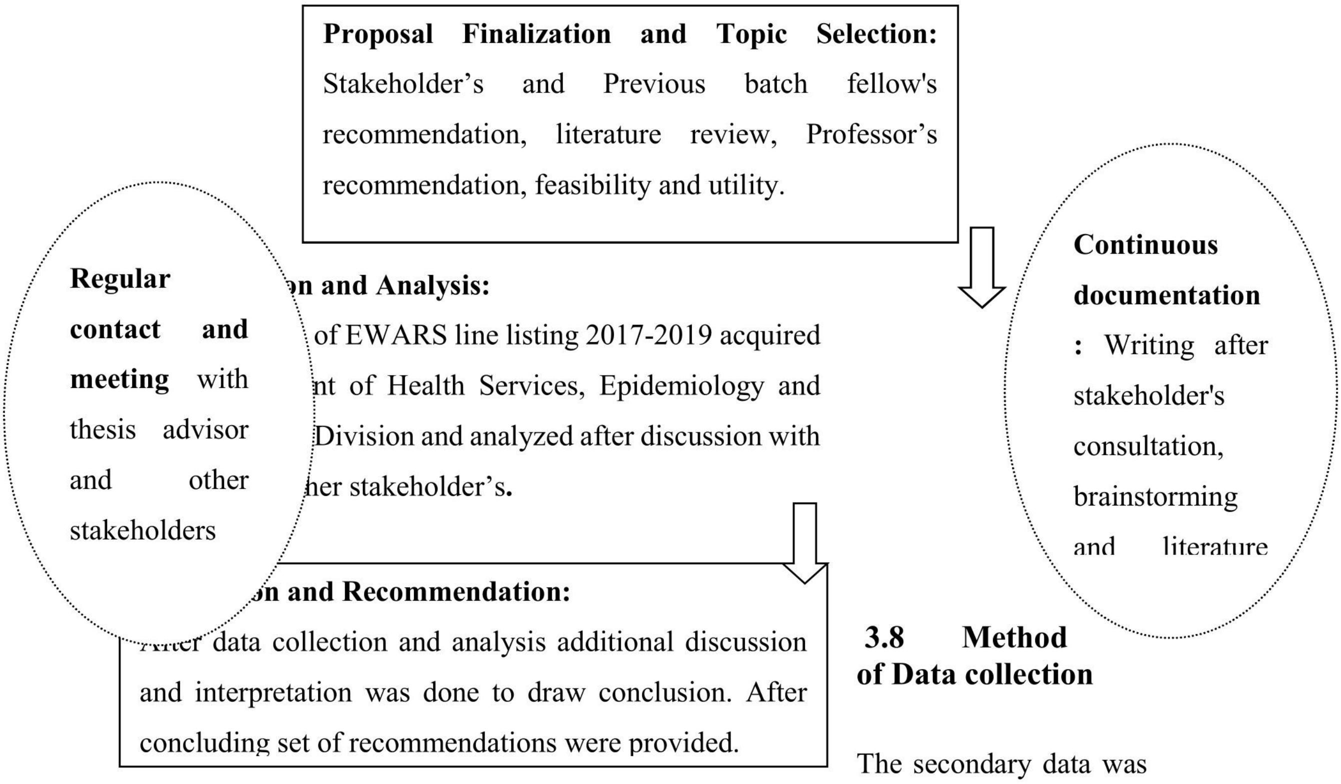
All the EWARS registered line lists for confirmed DF cases from 2017-19 in Nepal (N=2273) were the population under study, among these some were found from out of the study area, and some found with incomplete study variables. So the final population under study was fixed to 2243. The individual line listing information was expressed and analyzed during study.

3.7 Study Variables

Although various variables were observed and discussed from the collected data, the age, gender, geographical belts and provinces (set of various districts) as geographical unit and reporting weeks and seasons were considered as predictor variables while dengue case line listed were considered as response variables.

The detail of geographical belts, provinces and seasons are enlisted in the Appendices.

Figure 3: Overall Process and Methods of Thesis



3.8 Method of Data collection

The secondary data was collected in an authorized way. Three years (2017-19) EWARS line listing data were obtained from the DoHS, EDCD Nepal via email. The official permission for the use of data during my thesis work was received.

3.9 Tools for Data collection

A formal request letter prepared from the University was sent through email to the EDCD and contact person to obtain the required data set. Before and after sending the email the researcher himself performed regular communication with the contact point in EDCD.

3.10 Data analysis methods and tools

After obtaining the data through email from the EDCD contact point, the completeness and any observable errors were inspected thoroughly. Regular communication with EDCD through the contact person has been establishing through the email.

Further organization and analysis of received data was completed through a computerized system. A review of published articles, reports and guidelines was done to discuss and triangulate the findings. The list of reviewed secondary literatures were cited and listed in the references section of this thesis report.

Microsoft Excel and Statistical Packages for Social Science (SPSS 20) software were used to analyze the data.

The Mendeley desktop software was used to cite and referencing various bibliographic sources.

3.11 Hypothesis Testing

The Chi Square test was done to test the hypothesis at 95 % CI,

Two sets of hypothesis; the relationship of dengue cases in different years with age group and geographical belts were tested with the computation of Chi- square test (test of goodness).

Chi-square (χ2) test

A chi-square test for independence, also called Pearson's chi-square test of association is used to see whether distributions of categorical variables differ from each other.

The chi-square test statistic is calculated by using the formula:

$$\chi^2 = \frac{\Sigma(O_i - E_i)^2}{E_i} \quad \text{With K-1 dif (K is categories)}$$

Where, O_i represents the observed frequency

E_i is the expected frequency under the null hypothesis and computed by

$$E = \frac{\text{row total X column total}}{\text{sample size}}$$

It is recommended to compare the value of the test statistics to the critical value of χ^2_α with the degree of freedom= (r-1) (c-1), and reject the null hypothesis if $\chi^2 > \chi^2_\alpha$

r = number of rows and c= number of column.

3.12 Ethical Consideration

The researcher has taken both the online and offline course as per the university requirement to conduct the thesis related work following bioethics and publication ethics. Letter of permission is received on 2nd November 2020 from the DoHS, EDCD Nepal binding with the ethical issues to use and not to explore data for other than this thesis purpose.

3.13 Inclusion and Exclusion criteria

All the EWARS line listing cases with complete information were included and the cases from out of the study area and with incomplete information were excluded in this study.

4. CHAPTER FOUR: RESULTS

4.1 Completeness and Exclusion status of data

The three years reported cases, included cases and excluded cases are discussed in the tabular and diagrammatic way.

Table 2 Completeness and Exclusion status of data set

Year	2017	2018	2019	Total	%
Number of Reported Cases	1299	236	738	2273	100
Cases from India	4	1	0	5	0.22
Incompletely Reported	12	11	2	25	1.10
Total Excluded	16	12	2	30	1.32
Studied Number of Cases (N)	1283	224	736	2243	98.68
Included Cases among N (%)	57.2	10.0	32.8	100.0	

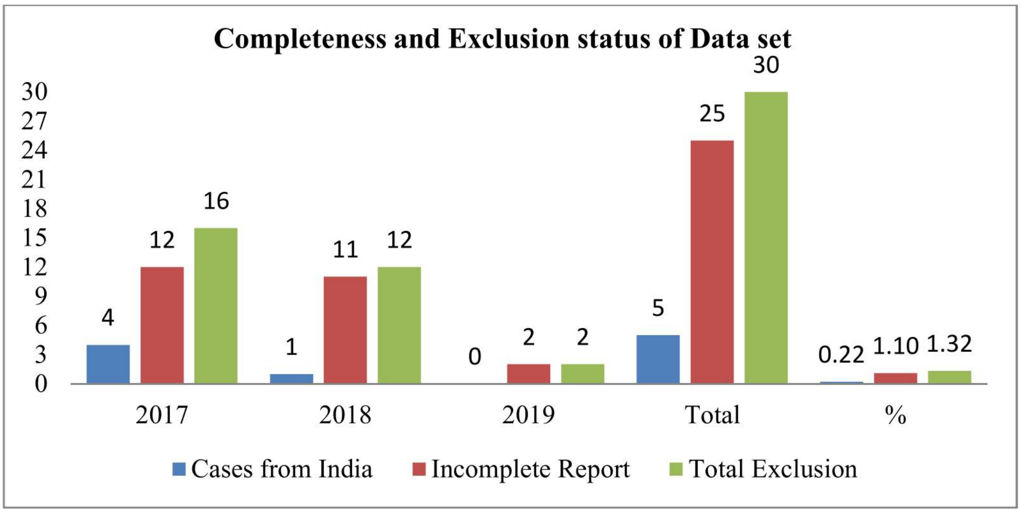


Figure 4 Completeness and Exclusion status of Data set

From the description of above table and figure, it has been found that a total of 2273 individual case based line listing data of 2017 to 2019 were received. Among these data, 0.22% was represented from out of the study area and 1.10 % was found incompletely reported. Thus altogether 1.32 % of received data was excluded and hence 2243 out of 2273 (98.68 %) were analyzed, among these the 2017 data consisted of 57.2 % followed by 2019 32.8% and 2018 by 10 %.

4.2 Gender distribution of Dengue Cases

Table 3 Gender wise distributions of Dengue Cases

Year	Female		Male		Gender ratio
	N	%	N	%	
2017	504	39.28	779	60.72	1.55
2018	84	37.50	140	62.50	1.67
2019	366	49.73	370	50.27	1.01
Total	954	42.53	1289	57.47	1.35

From the gender wise distribution of cases, the first two years dengue cases were found predominantly male 62.50 % in 2018 and 60.72 % in 2017. In contrast in 2019 the gender wise distribution was found nearly equal among male and female. Male: Female gender ratio was 1.55, 1.67 and 1.01 in 2017, 2018 and 2019 respectively with an average of 1.35.

4.3 Age distribution of Dengue Cases

Table 4 Descriptive Information of Scale variable (Age distribution)

Variable	Minimum	Maximum	Mean	Median	Standard deviation	Range
Age(Year)	0.003	99	32.628	30	17.076	98.997

From the age distribution analysis, age range was found 98.98 with minimum 0.003 (1st day of birth) and maximum 99 yrs, average age 32.628 years (median: 30) and standard deviation 17.076.

The relative age distribution of EWARS line listed dengue cases in Nepal was found as below.

Table 5 Age distribution of Dengue Cases

Year	Age Group					
	0-1	1-05	5-20	20-40	40-60	60 and more
2017	2	12	196	714	273	86
2018	11	4	27	85	64	33
2019	19	25	187	264	176	65
Total	32	41	410	1063	513	184
Chi-square test (P- Value)	151.274 (<0.001)					

Among different age groups, it is found that people from age group 20 to 40 are mostly affected by dengue than other age groups with 35.87 % proportion, a higher infant case 4.91 % is found in 2018 followed by 1.43 % in 2019 and 0.16 % in 2017 with combined infant cases 1.43%.

Bivariate analysis was performed to analyze the relationship between age group and year wise dengue cases using chi-square test. The p-value for calculated chi-square is seen to be less than 0.05 indicating that there is a significant impact of age group with a year of occurrence.

4.4 Dengue cases based on registration in Hospital

Table 6 Dengue cases based on department of registration in Hospitals

Year	Registered % in Hospital Department			
	Emergency	IPD	Lab	OPD
2017	7.33	88.07	0	4.60
2018	18.30	65.63	0	16.07
2019	1.49	66.71	30.16	1.63
Total	6.51	78.82	9.90	4.77

Among three years dengue cases line listing the majority of cases, 78.82% (n= 1768) were registered from the IPD department, followed by laboratory 9.9 % (n=222) and emergency 6.51% (n=146). The proportion of registered cases from the OPD was found 4.77 % (n=107); lowest among these four department all of the laboratory registered cases were in 2019.

4.5 Geographical Distribution of Dengue cases

Nepal comprised of variety of geographical structures and belts varied from low land to high mountains and large valleys.

Table 7 Dengue cases by geographical belts

Year	Geographical Belts				
	Mountain	Hill	Valley	Inner Terai	Terai
2017	94	90	3	42	1054
2018	15	59	5	15	130
2019	11	35	6	9	675
Total (N)	120	184	14	66	1858
Total (%)	5.35	8.20	0.62	2.94	82.84

The table 08 described details with majority of dengue cases 82.84 % were from the Terai districts the low land area of Nepal, followed by the hilly districts 8.2 %, mountain districts 5.35 %, inner Terai 2.94 % and least cases 0.62 % from Kathmandu valley. The different belts have different risk population and socioeconomic status which might be related with the different burden of diseases including DF. A higher the dengue cases in mountain districts in 2017 were due to the outbreak in Dhading district.

The geographical belts are merged based on climatic similarity as inner Terai to Terai and Kathmandu valley to hill region for testing the second hypothesis.

Table 8 Dengue cases by revised geographical belts

Year	Geographical Belt			Total
	Hill	Mountain	Terai	
2017	93	94	1096	1283
2018	64	15	145	224
2019	41	11	684	736
Total	198	120	1925	2243
Chi-square (P-value)	157.934 (<0.001)			

Bivariate analysis is performed to analyze the relationship between geographical belt and number of dengue cases of Nepal using chi-square test. The p-value for calculated chi-square is seen to be less than 0.05 which indicates that there is a significant impact of geographical belt with the dengue cases in different years.

4.6 Province wise distribution of Dengue cases

Table 9 Distribution of Dengue cases by Provinces

Year		Provinces						
		Prov. 1	Prov. 2	Bagmati	Gandaki	Lumbini	Karnali	Sudur Paschim
2017		95	118	118	13	922	3	14
2018		19	11	28	30	115	1	20
2019		690	24	14	1	4	0	3
Total	**N**	804	153	160	44	1041	4	37
	%	35.84	6.82	7.13	1.96	46.41	0.18	1.65

Table 9 presented the dengue cases by provinces; it was found that there were clusters of cases to outbreak situations in different districts and provinces in the different years. In 2017 and 2018, 922 and 115 cases were reported respectively from Lumbini province, resulting in 46.41 % of total cases consequential the maximum cases among all provinces in the study period; whereas 690 cases were reported in 2019 from the province 01, resulting in 35.84 % the second most cases in the study period. Totally 4, 37 and 44 cases were reported from Karnali, Sudurpaschim and Gandaki province respectively contributing a total caseload of less than 5%. Province 02 and Bagmati province have contributed 6.82 and 7.13 % of EWARS line listed cases in the study period correspondingly.

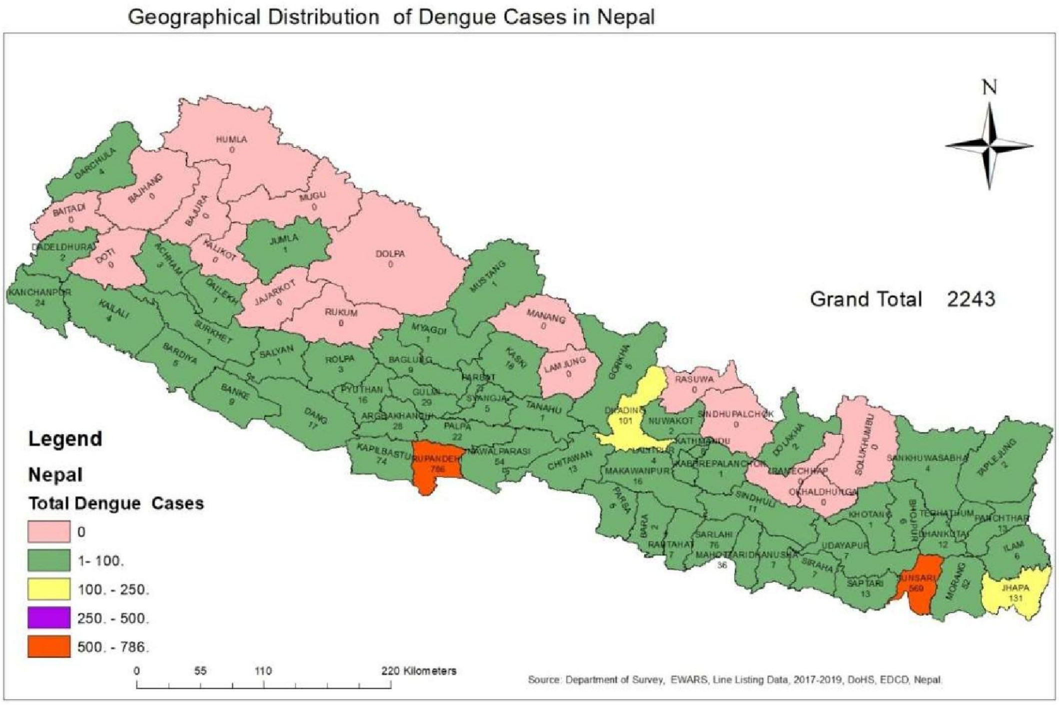


Figure 5 Geographical Distribution of Dengue cases in Nepal 2017 to 2019.

From the combined cases from the line listing data it was found that among 77 districts, 59 districts have reported the dengue cases in 2017-2019 with top five cases in Rupandehi, Sunsari, Jhapa, Dhading, Sarlahi and Kapilbastu contributing 77.44 % of total cases. Similarly, 10 districts (Dailekh, Jumla, Kavrepalanchok, Khotang, Mustang, Myagdi, Salyan, Surkhet, Tanahu, Terhathum) reported only one case in the three years, rest 18 districts (Okhaldhunga, Lamajung, Rukum, East Rukum, Jajarkot, Baitadi, Doti, Solukhumbu, Ramechhap, Sindhupalchowk, Rasuwa, Manang, Dolpa, Humla, Kalikot, Mugu, Bajhang and Bazura) reported zero cases in the study period based on the EWARS line listing data 2017 -2019.

4.7 Seasonal distribution of Dengue cases

Table 10 Seasonal Distribution of Dengue Cases (%)

Year	Seasons in Korea				Seasons in Nepal			
	Winter	Spring	Summer	Fall	Winter	Pre Monsoon	Mon soon	Post Monsoon
2017	2.57	0.47	2.26	94.70	2.57	0.47	7.72	89.24
2018	12.50	0.45	29.91	57.14	12.50	0.45	40.63	46.43
2019	0.95	5.57	90.63	2.85	0.95	5.57	93.48	0.00
Total	3.03	2.14	34.02	60.81	3.03	2.14	39.14	55.68

There is common practice of four seasons based on three months in each seasons in many countries. In Nepal, it is quite different. There are revised and recently classified four seasons in Nepal are Winter December, January and February, Pre monsoon March, April and May, Monsoon June, July, August and September and Post monsoon October and November.

From the table 10, the dengue cases were found to fluctuate based on the seasons. The cases reported in the spring (Pre monsoon in Nepal) and winter were found only 2.14 % and 3.03 % respectively, at the same time in maximum cases were found in fall following by summer season. As monsoon is one month longer than summer and post monsoon is one month shorter than fall season, the proportion of cases was seen by 34.02 % in summer and 39.14% in monsoon and 60.81% in fall and 55.68% in the post monsoon season. The test of significance cannot be applied due to data variability among seasons in Nepal.

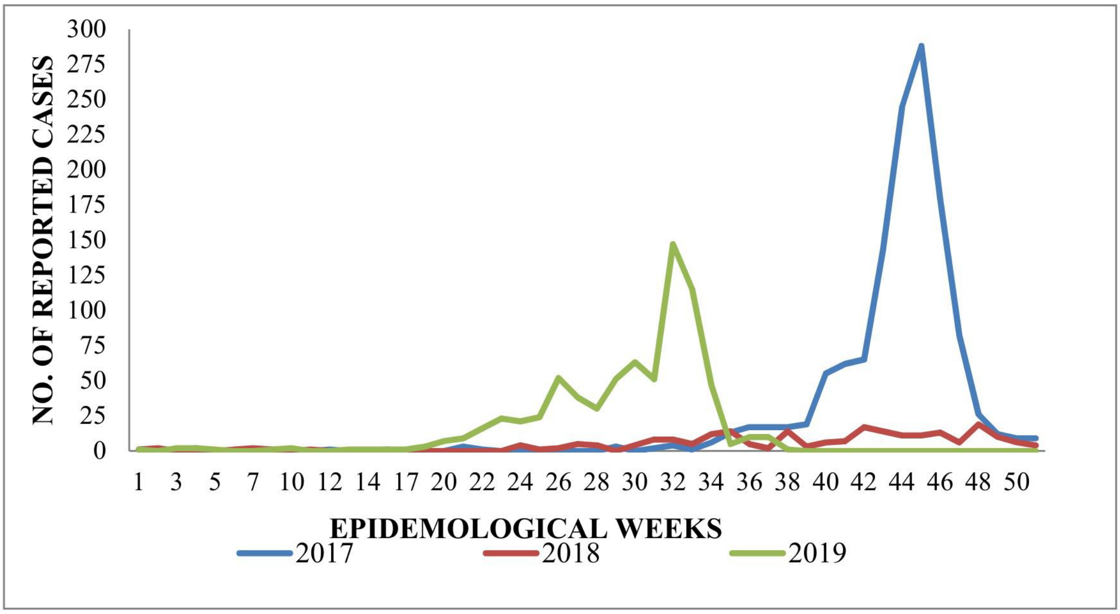


Figure 6 Dengue Cases Distribution by Epidemiological Weeks

Various trends were found from the trend analysis of line listed dengue cases in 2017, 2018 and 2019 in Nepal. Single peaks were observed in the 2017 and 2019 whereas year round cases reported in 2017 and 2018. In 2017, cases were reported from week one to 51, a slow rise in cases suggesting signal of outbreak, started in 34th week which reached peak in 45th week (n= 288), then slowly declined. Dengue incidence in 2018 was flattened curve year-round with scattered cases from week one to 51, maximum cases in 48th week (n=19) showing smaller peak than other two years.

A different type of trend in 2019 with cases reported from week one to 38, with increased cases from week 20 and showed peak of cases in 32nd week (n= 147), suggesting an outbreak situation. The cases were declined in the short time, immediately after the peak with only 26 cases from 35 to 38 weeks then zero cases till 52nd weeks might be due to disease occurring with mild cases and or not captured by EWARS.

5. CHAPTER FIVE: DISCUSSION

Sentinel reporting is a useful early warning system to predict the outbreak in advance. Data from sentinel sites are presumed to be available faster than the data from the routine and integrated reports from districts and health facilities. Thus can be analyzed quickly to assess the possibility of an unusual occurrence, atypical distribution suggesting an outbreak of reportable disease. The reporting health facilities should record the name, personal details such age, gender, sentinel site, type of registered department, complete address, contact number, diagnosis and it's methods, outcome etc based on EWARS software and expected to report the number of cases, as well as weekly zero reports of disease that were diagnosed in specific time period.(23) As far based on the guidelines each part should filled up properly and hence expected to have access of complete profile of the case in EDCD so that it will be easy to perform epidemiological investigation, contact tracing and apply specific interventions. Among 2273 total line listing received in the three years, 2243 line listing were studied. Among different characteristics to be reported in the EWARS line listing data, the epidemiological week, department of case registered, age, gender and districts are essential parts; in the study 1.1 % (n=25) were incompletely reported.

Symmetrical findings were found from the routine data of dengue in 2073/074; 2111, 207/075; 811 and 2075/076; 3424. A total of 6364 dengue cases were reported through health management information system all over the country.(11)

Although there was a massive dengue outbreak in Nepal in 2019 with 17,992 dengue cases and expansion to 68 districts of Nepal,(27) only 4.10 % (n=738) were captured by EWARS line listing.

The incomplete recording and reporting might be due to various reasons such as EWARS focal person's busy schedule, incompletely recorded by service providers, insufficient knowledge and culture of recording reporting system and administrative limitations. Dengue diagnosis and surveillance system review in Nepal also concluded poor surveillance of dengue leading to inappropriate detection and control. Hence, it suggested a need to develop improved, proactive, laboratory-based surveillance systems that can predict future dengue outbreak in Nepal.(41)

The higher the chances of occurrence of vector borne disease to male in low and middle income countries has been expected and observed mostly due to the mobile habit and more outdoor involvement of males than females. In the finding the similar data of gender ratio (M:F) of 1.55 in 2017 and 1.67 in 2018 supports the above statements where as 2019 and combined gender ratio (M:F) was found 1.01 and 1.35, reflect nearly equal gender ratio in 2019 and 1.35 (n; M: 1289, n; F: 954) times higher male proportion of cases in study period were found.

Similarly, the age range was found 98.98 with minimum 1day and maximum 99 yrs, average 32.628 years (median 30) and standard deviation 17.076. The hypothesis testing with Chi square value at 95% CI was found to have a significant association between different age groups and number of dengue cases in the study years.

In the 2016 outbreak of dengue, infection was found higher in males in the 19–41 years age group with a child: adult ratio of 0.3:1 and male: female ratio 6:4. In that outbreak, a mean age of 37.85 and standard deviation of 7.14 years.(42)

Dengue outbreak and epidemiological trend analysis in Nepal, demonstrated the more male susceptibility towards dengue (n = 2248) higher than the female (n = 1086) with gender ratio 2.15 and age group of 15–40 years (median age 27.35) more vulnerable. In the same study age interval of dengue cases was found 2 to 87 years, with range 85 with a higher proportion of below 15 years cases 51.8% (n= 14), in 2007 and 43.3% (n=13) in 2009. (43)

Similar findings were found in a study done in Thailand representing most dengue patients by male (8057; 53.1%) from the hospital data in the Khon Kaen province.(31) A study based on reported dengue cases from national surveillance systems, from different six Asian countries, Lao People's Democratic Republic, the Philippines, Singapore, Sri Lanka and Cambodia and Malaysia, were found a consistent and significant excess among males of more than15 years of age in the former five countries.(44)

It has been observed that there is association of dengue cases and outbreaks with major climatic factors: temperature, rainfall and humidity. These climatic factors are positively related with seasons. Hence there is a practice of risk and vulnerability mapping, disaster preparedness and outbreak prediction based on the seasonal calendar in many reasons of Nepal. In this study; majority of cases were reported in post monsoon season (n=1249, 55.68%) and monsoon season (n=878, 39.14%) from June to November. In contrast only the 5.17 % of cases were reported from the winter and post monsoon seasons from December to April, supporting the higher risk of dengue with seasonal and climatic risk.
Many pieces of literature support these findings with the favorable breeding environment for the *Ae. aegypti and Ae. albopictus* in the monsoon and post monsoon season. The trends of annual seasonal variation of dengue incidence suggest infections emerge rapidly in July, after the beginning of the monsoon and, cases peak in August and September, the late monsoon season with the more favorable climate for mosquitoes breeding.(45) The outbreak of dengue in 2016 get peaked in September, corresponding to the tail end of monsoon season in Nepal, and subsided around the last week of November.(42) The findings have high link with the dengue causing vectors and seasonal association; *Aedes* larval count was peak during the monsoon season when water-holding containers were abundant.(26)(31)
A study done in Thailand suggested that mean rainfall and maximum temperature were positively associated with dengue incidence and minimum temperature was negatively associated. In this point estimates finding supported the higher chance of occurring dengue in monsoon and post monsoon and lower the chances in the winter and pre monsoon seasons.(31)
As dengue has a positive relationship with temperature and other climatic factors, geography is also closely related. As Nepal is a country with vast geographical diversity, the geographical association of dengue incidence has been observed since the first case. It is mostly expanding into new districts and higher altitudes. This studies have got some notable findings including a lower cases reported from the province 02 (n= 153) in

comparison to other similar geography province 01 (n=804) and Lumbini province (n=1041). Although province 02 comprises all 8 Terai districts, are considering more risk for dengue and other vector borne disease due to climatic factors, many open water ponds, dense population and sub standard sanitation practices. The higher the cases in the Lumbini province and Province 01 were linked with the dengue outbreak in 2017, Rupandehi and 2019 in Sunsari district.(11)

A recent epidemiological study of dengue in Nepal described the province wise distribution of dengue cases in 2019 dengue outbreak in Nepal, showed partially similar findings with higher cases in Bagmati province, 40.5% (n=7276) followed by province 01, 24.4% (n=4379), Gandaki province 19% (n=3421) from, Lumbini province 13.4% (n= 2414), province 02, 1.5% (n=276), Sudurpaschim province 0.8% (n= 152) and the lowest in Karnali province 0.4% (n= 74) from Karnali province(27). These findings suggest uncertainty of dengue distribution in different provinces in different years and missing many cases of dengue by EWARS line listing data.

In 2019, Nepal experienced the outbreak of dengue at Sunsari district (Province 01, Terai), Chitwan (Bagmati province, Inner Terai) and Kaski (Gandaki province, Hill). *Ae. aegypti* , the vector was identified in five peri-urban areas of the Terai (Kailali, Dang, Chitwan, Parsa and Jhapa) demonstrating the evidence of local transmission of dengue in the respective regions and districts. (11)

On the other hand higher cases were found in Mountain districts (n= 120) than the inner Terai (n= 66) and Kathmandu valley (n= 14). This was due to the higher cases reported from Dhading district (n= 105), among these 89 cases were reported in 2017. The hypothesis testing with Chi square test at 95 % CI was found to have a significant association between geographical belts as, Hill, mountain and Terai with the number of dengue cases in the study years.

In 2006, an indigenous case was identified with undetected strain of dengue fever in Dhading district.(46) The Himalayan regions and nations were predicted an increasing risk for future dengue outbreak based on secondary dengue data review in 2016.(42)

An entomological study done in middle region of Nepal demonstrated a higher prevalence and establishment of DENV vectors and DF cases up to the Middle Mountain region (1,310 m as of sea level), with definite increasing risk of dengue in middle mountain and hill districts in Nepal recommending dengue control measures from the lowlands up to the High Mountain regions. (26)

The predominance of registered dengue cases from the inpatient department 78.82% (n= 1768) than other departments signifying more severe cases were sought hospital services for treatment and care instead of diagnosis. The higher the IPD cases were in all three years 2017; 88.07 % (n=1130), 2018; 65.63% (n=147) and 2019; 66.71% (n=491). Among 2243 cases 9.9 % (30.16 % of 2019 cases, n=222) were registered from the laboratory department suggestive of increased trend of self referral for diagnosis for DF in Nepal.

As cases were found registered from different departments, there is strong need of leadership commitment and interdepartmental coordination for complete recording of dengue cases towards successful and functional EWARS system in Nepal.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Although dengue is younger re emerging disease in Nepal with the first reported case in 2004, its problem has been expanding with geography and intensity over time. Only limited studies on this subject matter were done in Nepal.

All the line listed and verified dengue cases, 2273 individual cases were verified and updated by EDCD. Among these only 1.32 % of received data were excluded. Hence a quantitative analysis of age, sex, department of registration, week of reporting (seasons) of occurrence and district (geography) of those cases were studied.

Predominance of male cases was found in 2017 and 2018. The combined gender ratio of 1.35 suggests a higher risk of dengue in male population in Nepal. A diversity of age relationship was found with an average age 32.628 years, range 98 yrs and standard deviation 17.076. The 20 to 40 years age group was affected mainly by dengue with combined infant cases 1.43%. The test statistics; chi-square test in 95 % CI was applied to test the age group relationship with the year wise dengue cases and found significant. Hence, there was significant relationship of age group with the occurrence of dengue fever in 2017 -2019 in Nepal.

Cases were found registered in different hospital departments, in IPD, emergency, OPD and laboratory. The dengue cases were found to fluctuate based on the seasons, predominantly in the monsoon and post monsoon. Cases reported in the spring (Pre monsoon in Nepal) and winters were found minimum. As Nepal has diversity of geography, geographical distribution of dengue cases reflects the higher case in Terai low land districts with a massive expansion in the hill, Kathmandu valley and Mountain districts, Dhading is considered as Mountain district fall in the top five reporting district in the study period.

The clusters of cases to outbreak situations in different provinces in the different year were reported, with highest cases in Lumbini province followed by province 01. All provinces possessed a variety of risk of DF in Nepal. To assess the relationship between geographical belts and the year wise dengue cases, the chi-square test in 95 % CI was applied and found significant. Hence, there was significant relationship of geographical belt with the DF in 2017 -2019 in Nepal.

Thus Dengue has been challenging public health problem with changing burden and pattern of geographical and seasonal varied incidence resulting periodic outbreak situations every 2-3 years, sometimes yearly in Nepal. The changing disease pattern with more extensive geographical and seasonal coverage and uncertainty of outbreak prediction creates challenges. There is a strong need to do research and developmental works to improve of dengue control program to uplift the population's health and mitigate the loss of resources.

6.2 Recommendations

After the study following recommendations are recommended for improving Dengue control program in Nepal.

Table 11 Recommendations on different spheres.

Area of Recommendation	Recommendations
Research and Development	Further studies on the dengue risk mapping, seasonal and geographical variation.
	The national vector borne disease research and developmental capacity should be strengthened.
	The capacity of Vector Borne Disease Research and Training Centers should be expanded up to each province.
Surveillance and Reporting System	Comprehensive orientation and regular follow up of EWARS Sentinel site should be ensured.
	Surveillance of dengue fever should be expanded in all districts.
	The recording and reporting system in health sector should be maintained complete, clear and consistent.
	An external evaluation of EWARS should be done periodically.
Policy and Program Improvement	Each level should consider climate risk and the burden of dengue during policy and programming and preparedness.
	Dedicated hospital for Dengue care and complication management should be developed in each province.
	Required institutional and HR capacity for the prevention and treatment of dengue should be developed.

7. APPENDICES

Appendix 1: Geographical Belts in Nepal

Geographical Belt	Districts	No of Districts
Mountain	Sankhuwasava Solukhumbu, Taplejung, Ramechhap, Dolakha, Dhading, Sindhupalchok, Rasuwa, Gorkha, Manang, Mustang, East Rukum * Dolpa, Humla,, Jumla, Kalikot, Bajura, Darchula	20
Hill	Bhojpur, Dhankuta, Ilam, Khotang, Okhaldhunga, Panchthar, Terhathum, Kavrepalanchok Nuwakot, Baglung, Kaski, Lamjung, Myagdi, Parbat Syangja, Tanahun, Arghakhanchi, Gulmi, Palpa, Pyuthan, Rolpa, Rukum, Salyan, Dailekh, Jajarkot, Achham,Doti, Dadeldhura Baitadi	29
Kathmandu Valley	Kathmandu, Lalitpur, Bhaktapur	3
Inner Terai	Udayapur, Sindhuli, Chitwan, Makwanpur, Nawalpur*, Dang, Surkhet	7
Terai	Jhapa, Morang, Sunsari, Saptari, Siraha, Dhanusa, Mahottari, Sarlahi, Bara, Parsa, Rautahat, Nawalparasi, Rupandehi, Kapilvastu, Banke, Bardiya, Kailali, Kanchanpur.	18

Appendix 2: Provincial Distribution of Districts in Nepal.

Province	Districts	No of Districts
Province 01	Solukhumbu Sankhuvasava, Taplejung Terhathum Bhojpur Khotang , khaldhunga Udayapur Dhankuta Panchthar Ilam, Jhapa, Morang, Sunsari, Jhapa	14
Province 02	Sunsari Saptari Siraha Dhanusa Mahottari Sarlahi Rautahat Bara Parsa.	8
Bagmati Province	Ramechhap Dolakha Dhading Sindhupalchok Rasuwa, Kavrepalanchowk, Nuwakot Kathmandu Lalitpur Bhaktapur Sindhuli Chitawan Makwanpur	13
Gandaki Province	Gorkha Manang Mustang Baglung Kaski Lamjung Myagdi Parbat Syangja Tanahun Nawalpur*	11
Lumbini Province	East Rukum* Arghakhanchi, Gulmi, Palpa, Pyuthan Rolpa Nawalparasi Rupandehi Kapilvastu Dang, Banke Bardiya.	12
Karnali Province	Dolpa Humla Mugu Jumla Kalikot Dailekh Rukum Salyan Jajarkot Surkhet	10
Sudurpaschim Province	Bajhang Bajura Darchula Achham, Doti Dadeldhura Baitadi Kailali Kanchanpur	9

*Two Districts with * sign are newly formed districts after announcement of Constitution of Nepal in 2015.*

Appendix 3: Description of Seasons in Nepal and Korea.

Four Seasons in Korea				
Season	**Winter**	**Spring**	**Summer**	**Autumn**
Months	December – February	March- May	June- August	Sep- Nov
Epidemiological Weeks	49-9	10-22	23-35	36-48
	Revised four Seasons in Nepal			
Season	**Winter**	**Pre-monsoon**	**Monsoon**	**Post Monsoon**
Months	December – February	March- May	June - Sep	Oct- Nov.
Epidemiological Week	49-9	10-22	23-39	40-48

Appendix 4: Data use permission Letter by DoHS, EDCD.

Government of Nepal
Ministry of Health and Population
Department of Health Services
EPIDEMIOLOGY AND DISEASE CONTROL DIVISION

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Kathmandu, Nepal

Ref. No:

Ref. No: 229

Date : 2 Nov,2020

Mr. Keshab Rijal (Student ID No: 2019552016)
Master of Public Health, Global Health Security Response Program,
Graduate School of Public Health,
Yonsei University Seoul, South Korea.

Subject: Permission to use data for completing thesis.

This letter is issued in response to your communication dated on 17th Sep, 2020 requesting data use for your thesis required for the completion of Master of Public Health, Global Health Security Response Program, Graduate School of Public Health, Yonsei University Seoul, South Korea.

I would like to inform you that you are provided the data on dengue cases by location of the cases and date of diagnosis by 2015-2019 as per your request to use for your thesis on "*Analysis of geographical and seasonal variation of Dengue fever in Nepal (2015-2019)*". You are hereby requested to follow all the relevant legal, academic and ethicall requirements related to use the data.
I wish you all the success of completion of your thesis and future progress.

....
Dr. Basudev Pandey (PhD)
Director

CC:
Graduate School of Public Health,
Yonsei University Seoul, South Korea.

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