Climate change and childhood diarrhoea in Kathmandu, Nepal: a health risk assessment and an exploration of surveillance capacity

Dinesh Bhandari, MSc

School of Public Health
Faculty of Health and Medical Sciences
The University of Adelaide
Australia

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

August 2021

Table of Contents

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Signed: ……………………………………………………………………….

Dinesh Bhandari

Date: 2/8/2021

Acknowledgements

First and foremost, I would like to thank my principal supervisor Dr Scott Hanson-Easey, and my co-supervisors Prof Peng Bi, Dr Meghnath Dhimal and Emeritus Prof Jeevan Bahadur Sherchand. Dr Scott and Prof Peng have been amazing professional, scientific and personal mentors to me for the past three and half years, and I couldn't have asked for any better. This PhD journey wouldn't have been possible had it not been for Prof Peng, who in April 2017 Skype interviewed and accepted a mediocre health graduate from Nepal as one of his PhD students. Dr Scott Hanson-Easey, thank you for being a cool advisor. I am extremely grateful to you for encouraging me to design a research project addressing urgent yet unexplored public health problems of my home country Nepal. This thesis would not have been possible without the support and expert guidance from you and Prof Peng. I will continue to rely on the advice and wisdom you have given to me for the rest of my life. I am thankful to my local supervisors Dr Meghnath Dhimal and Emeritus Prof Jeevan Sherchand, for sharing datasets and supporting me during the field work in Nepal.

Second, thank you to my family for your constant support and encouragement. This PhD is dedicated to my dear wife, my mom and dad. My mom and dad, thank you for everything you have given me in this life. Thank you for all the hardship you have gone through to educate me and help me chase my dream. I will be grateful to god if I can provide my kids with the life that you have given to me. Thanks to my wife Pratigya Thapa — whom I married in the final year of my PhD candidature — for being my strength and inspiration to embark on this journey. Thank you Pratigya, for sacrificing your dreams and allowing me to pursue PhD in Australia. The mid-night Viber and Messenger calls and daily calls from Nepal during the lunch hours in Australia never made me feel away from home. Thank you dear, for lifting my spirit during hard times and being my rock. Thank you to my relatives, the Bhandari family, the Parajuli family and the Thapa family for bearing me and supporting me throughout my PhD journey. Thanks to my friends in Adelaide the Adhikari family, the Sivakoti family, and Roshan Nepal for your care.

To my university friends, Dr Blesson Varghese, Ms Maha Laka, Dr Magdalena Moshi, Dr Mumtaz Begum and Miss Jingwen Liu (Jasmine), thank you for the shared lunch, laughter and fun, encouragement and support, and the unforgettable weekends we spent together outside the university. Thanks to companions Dr Rahul Nair (ARCPOH), Dr Pedro Riberio Santiago (ARCPOH), Mi Du, Dr Mathew Borg and Ryan Pham, I will miss tossing beer and wine glasses with you guys. Thanks to Dr Michael Tong, Dr Rezanur Rahaman, Berhanu Wondmagegn, Dr Engida Yisma, Harshani Jayasinghe, Hira Fatima, Laressa Ryan, Neha Lalchandani, and Dr Sagufta Parveen for normalizing PhD. Thanks to Dr Zidong Liu, a visiting scholar from Shandong University, China in our research group for guiding me through quantitative data analysis in the early days.

Finally to the postgraduate coordinators A/Prof Jaklin Elliot and Dr Afzal Mahmood for their continued support during my PhD journey. I am extremely grateful to Prof Jaklin Elliot for supporting me during every major milestone of my candidature, starting from the Skype interview in 2017 (my scholarship application assessment) till my thesis submission in 2021. To the head of the school Prof Tracey Merlin, all the administrative staffs — school of public health, Isabel Mason, Daphne Georgaras, and the staffs of the graduate centre— I thank you all for your support. Thanks to the Australian public and the University of Adelaide for the Adelaide Scholarship International, that supported my PhD training.

Thank you Bhagwan Pashupati Nath, for this magical journey from a high school graduate in Sinamangal, Nepal to a PhD graduate in Medicine from Australia.

Publications contributing to this thesis

1. **Bhandari D**, Bi P, Sherchand JB, Dhimal M, Hanson-Easey S. Assessing the effect of climate factors on childhood diarrhoea burden in Kathmandu, Nepal. *International Journal of Hygiene and Environmental Health*. 2020; 223(1):199-206. doi:10.1016/j.ijheh.2019.09.002 (Impact factor: 5.84)

2. **Bhandari D**, Bi P, Dhimal M, Sherchand JB, Hanson-Easey S. Non-linear effect of temperature variation on childhood rotavirus infection: A time series study from Kathmandu, Nepal. *Science of the Total Environment*. 2020; 748:141376. doi:10.1016/j.scitotenv.2020.141376 (Impact factor: 7.96)

3. **Bhandari D**, Bi P, Sherchand JB, Dhimal M, Hanson-Easey S. Climate change and infectious disease research in Nepal: Are the available prerequisites supportive enough to researchers? *Acta Tropica*. 2020; 204:105337. doi:10.1016/j.actatropica.2020.105337 (Impact factor: 3.11)

4. **Bhandari D**, Bi P, Sherchand JB, von Ehrenstein OS, Dhimal M, Hanson-Easey S. A qualitative exploration of the socio-cultural, political and institutional factors associated with the surveillance of infectious diseases in the context of a changing climate in Nepal (Finalized and preparing for submission)

Presentations arising from this thesis

Oral presentations (International)

1. **Dinesh Bhandari**, Peng Bi, Meghnath Dhimal, Jeevan Bahadur Sherchand and Scott Hanson Easey. Temperature dependent transmission of rotavirus infection in Kathmandu, Nepal. Sixth Annual Summit of Health and Population Scientist in Nepal, 6-7th July 2020, Virtual Conference

2. **Dinesh Bhandari**, Peng Bi, Meghnath Dhimal, Jeevan Bahadur Sherchand and Scott Hanson Easey. Impact of meteorological factors on rotavirus infection among children below 5 years of age in Kathmandu, Nepal. 31st Annual conference of the International Society for Environmental Epidemiology, 25-28 August 2019, Utrecht, Netherlands

Poster presentations (International)

1. **Dinesh Bhandari**, Peng Bi, Jeevan Bahadur Sherchand, Ondine S. von Ehrenstein, Meghnath Dhimal, Scott Hanso-Easey. Infectious diseases surveillance in the context of climate change: assessment of public health surveillance capacity in Nepal. 32nd Annual conference of the International Society for Environmental Epidemiology, 24-27 August 2020, Virtual Conference.

2. **Dinesh Bhandari,** Peng Bi, Jeevan Bahadur Sherchand, Meghnath Dhimal and Scott Hanson Easey. Modelling the effect of climate variability on childhood diarrhea in Kathmandu Nepal. 31st Annual conference of the International Society for Environmental Epidemiology, 25-28 August 2019, Utrecht, Netherlands

Other presentations

Invited guest lecture (International)

- Climate change and child health: Understanding the impacts of climate change on diarrhoeal among children below 5 years of age living in Kathmandu, Nepal
  Virtually presented among faculties and PhD students in a seminar at the Fielding School of Public Health, the University of California, Los Angeles (UCLA), 21st May 2021
  Nominator: Associate Professor Ondine S. von Ehrenstein, Department of Community Health Science, Fielding School of Public Health, UCLA

Media coverage (International)

The findings from study 1 (chapter 4) of this thesis was covered by three different web based science news outlets:

1. Science and Development Network: **'Nepal exposed to climate-sensitive disease outbreaks'**
   https://www.scidev.net/asia-pacific/news/nepal-exposed-to-climate-sensitive-disease-outbreaks/
2. Medical Xpress: **Nepal exposed to climate-sensitive disease outbreaks**
   https://medicalxpress.com/news/2020-03-nepal-exposed-climate-sensitive-disease-outbreaks.html
3. News Medical Life sciences: **Nepal is highly prone to climate-sensitive infectious disease outbreaks**
   https://www.news-medical.net/news/20200311/Nepal-is-highly-prone-to-climate-sensitive-infectious-disease-outbreaks.aspx

Awards and achievements

1. June 2020: **ISEE 2020 Travel grant**, awarded by the International society for Environmental Epidemiology to support my participation at the 32st annual conference of the International society for Environmental Epidemiology. 24-27 August 2020, Virtual Conference.
2. May 2019: **Walter and Dorothy Duncan Trust travel award**, awarded by the Walter and Dorothy Duncan Trust to support participation at an international conference held outside Australia.
3. May 2019: **ISEE 2019 Travel grant**, awarded by the International society for Environmental Epidemiology to support my participation at the 31st annual conference of the International society for Environmental Epidemiology. 25-28 August 2019, Utrecht, Netherlands
4. Nov 2017: **Adelaide Scholarship International (ASI)**, awarded by the University of Adelaide, Australia; Covers full tuition fee to pursue PhD degree in Public Health, basic living expense for three years and a standard OSHC (Oversea Student Health Cover) for 45 months

List of figures

List of tables

Abbreviations

AFP	Acute Flaccid Polio
AGE	Acute Gastro Enteritis
AIC	Akaike Information Criteria
ARIMA	Autoregressive Integrated Moving Average
ASI	Adelaide Scholarship International
BRACE	Building Resilience Against Climate Change Effects
CBS	Central Bureau of Statistics
CDC	Centers for Disease Control and Prevention
CDD	Control of Diarrheal Diseases
CI	Confidence Interval
CR	Critical Realism
df	Degrees of Freedom
DLNM	Distributed Lag Non-linear Model
DoHS	Department of Health Services
eCI	Empirical Confidence Interval
EDCD	Epidemiology and Disease Control Division
E^3	European Environment Epidemiology Network
ELISA	Enzyme-Linked Immuno Sorbant Assay

EWARS	Early Warning and Reporting System
GCM	General Circulation Model
HDI	Human Development Index
HMIS	Health Management Information System
IMCI	Integrated Management of Childhood Illness
IPCC	Intergovernmental Panel on Climate Change
IPD	Immunisation Preventable Diseases
LMICs	Low-and Middle-Income Countries
NAPA	National Adaptation Program of Action
NHRC	Nepal Health Research Council
NS	Natural Cubic Spline
PIF	Potential Impact Fraction
qAIC	Quasi Akaike Information Criteria
RCMs	Regional Climate Models
RCPs	Representative Concentration Pathways
RR	Relative Risk
RT-PCR	Reverse-Transcriptase Polymerase Chain Reaction
SDGs	Sustainable Development Goals
SIR	Susceptible-Infected-Recovered

SRES	Special Report on Emissions Scenarios
UI	Uncertainty Interval
VBDs	Vector Borne Diseases
WHO	World Health Organization
YLD	Years Lived with Disability

Abstract

There is substantial evidence that the onset and transmission of infectious diseases, particularly vector-borne diseases and diarrheal diseases, are influenced by many factors including climate change. Improving the understanding of the impacts of climate change on infectious diseases is important to inform policy decision making on disease control and prevention, as well as predicting the trends in the infectious diseases burden. Epidemiological analysis of long-term surveillance data on infectious diseases and meteorological factors are instrumental in establishing the association between infectious disease incidence and climate change. Advanced epidemiological techniques are now available to precisely estimate the nature of association (linear, non-linear) as well as the delayed effect: this means that it is possible to plan and design climate-based early warning systems to predict conditions that are likely to be favourable for an outbreak of climate-sensitive infectious disease. However, the association between infectious diseases and climate change varies, depending upon the pathogens responsible for infection. Similarly, the ability of infectious disease surveillance systems or disease control divisions to generate this evidence and utilise the knowledge to cope or adapt to the impacts of climate change is contingent upon the social, economic, political and other contextual problems. In the Nepalese context, the impacts of climate change on infectious diseases, in particular diarrheal disease, remains unknown: similarly, there has been no exploration of the contextual factors associated with the integration of climate change-related risk in Nepalese infectious diseases surveillance systems.

Given this background, the first aim of this PhD thesis is to characterize the association between diarrhoea among children below five years of age and climate variables in Kathmandu, Nepal and then project the future burden of diarrhoea due to climate change. The second aim is to understand the association between rotavirus infection among children below five years of age

and temperature variability in Kathmandu and compute the fraction of rotavirus infection that is attributable to temperature. The third aim is to explore the extant research on climate change and infectious diseases in Nepal and to identify the reasons behind sparse evidence on the topic. The final aim is to explore social, economic and cultural factors associated with infectious diseases surveillance in Nepal in the context of climate change.

A mixed method study design was employed to achieve the goals of this project. There are four analytical chapters in this thesis: two quantitative studies; a study that reviews evidence of the impacts of climate change on infectious disease and policy documents related to infectious disease control and prevention in Nepal; and a qualitative study. Two quantitative studies were carried out to estimate the association between climate variability and childhood diarrhoea, and childhood rotavirus infection in Kathmandu. Study 1 and study 2 utilised time series design involving Poisson regression equations fitted with distributed lag models to characterise exposure-response and possible lagged association between climate variables and diarrhoea, and rotavirus infection. A qualitative research study was undertaken to explore the social, economic, cultural and political factors associated with infectious diseases surveillance in the context of climate change in Nepal. In study 4, semi-structured interviews were conducted with key informants and stakeholders from the Department of Health Services Nepal, World Health Organization Nepal, the Department of Hydrology and Meteorology Nepal and infectious disease experts working in both public and private sectors in Nepal. The interviews and subsequent thematic analysis of data were conducted from a critical realist perspective.

Study 1 established a significant positive association between childhood diarrhoea and temperature, and rainfall. A 1°C increase in maximum temperature above the monthly average was found to be associated with 8.1% (RR: 1.081; 95% CI: 1.02-1.14) increase in the monthly count of diarrhoea among children below five years of age living in Kathmandu, Nepal.

Similarly, a 10mm increase in monthly cumulative rainfall above the mean value was associated with 0.09% (RR: 1.009; 95% CI: 1.004-1.015) increase in childhood diarrhoea. It was further projected that 1357 (UI: 410–2274) additional cases of childhood diarrhoea could be experienced by 2050 given the projected change in climate under low-risk scenario (0.9°C increase in maximum temperature).

Study 2 established a nonlinear negative association between temperature (maximum, mean and minimum) and weekly rotavirus infection cases among children below five years of age in Kathmandu. Compared to the median value of mean temperature, an increased risk (RR: 1.52; 95% CI: 1.08–2.15) of rotavirus infection was detected at the lower quantile (10th percentile) and a decreased risk (RR: 0.64; 95% CI: 0.43–0.95) was detected at the higher quantile (75th percentile). Similarly, an increased risk [(RR: 1.93; 95% CI: 1.40–2.65) and (RR: 1.42; 95% CI: 1.04–1.95)] of infection was detected for both maximum and minimum temperature at their lower quantile (10th percentile). It was further estimated that 47.01% of the rotavirus infection cases reported between 2013 and 2016 in Kathmandu could be attributed to minimum temperature.

Study 3 identified that there was little evidence describing the impacts of climate change on infectious diseases and no evidence describing the projected burden under climate change scenarios. I explored the reasons behind paucity in the evidence and challenges faced by epidemiologists in Nepal. The challenges identified included poor quality infectious disease datasets, shortage of trained human resources, inadequate funding and political instability. As such, it was recommended that an integrated digital network of interdisciplinary experts be established and increased collaboration among different stakeholders be promoted to advance the evidence base on the impacts of climate change on infectious diseases in Nepal.

The fourth and final study outlined that climate change and its impacts on infectious disease surveillance is treated as a less serious issue than other more ‘salient’ public health risks in the context of Nepal. The study further illustrates how climate change is variably constructed as a contingent risk for infectious diseases transmission and public health systems. The analysis exposes a weaker alliance among different stakeholders, particularly policymakers and evidence generators that leads to the continuation of traditional practices of infectious diseases surveillance without consideration of the impacts of climate change.

In summary, this thesis brings to prominence important progress in understanding the link between climate change and infectious diseases, in particular childhood diarrhoea, in a subtropical highland climate from a low and middle income South Asian country. So far, we have not found any other study that explores the contextual factors (social, economic, cultural and political) that impede the integration of climate change-related risk in the disease surveillance systems. Therefore, this thesis illustrates a novel facet of infectious disease surveillance and climate change. This thesis makes an important contribution to address the gap on information related to climate change and infectious diseases in Nepal and can have significant implications towards building a climate-resilient public health system in Nepal.

Chapter 1: Introduction

1.1 Background

The climate crisis has continued unabated over the past decade (2010-20). Prominent manifestations of the climate crisis during this period include the past six years were documented to be the hottest years since the pre-industrial era of 1850-1900; and there were record wildfires in both the Northern and the Southern Hemisphere and several devastating tropical storms in the Atlantic Ocean and the Pacific Ocean (1-3). Climate change has been recognised as an important health issue since the mid-1990s (4), however extant research on climate change and health has yet to establish adequate adaptation and mitigation measures to circumvent the global impacts of climate change on human health, particularly for low-and middle-income countries (LMICs) (5). Based upon the causal pathways, the impacts of climate change on human health is categorised into three different risk categories i.e., the primary, secondary and tertiary risk (6). The primary risk is considered to be the direct biological consequences of heat-waves and extreme weather events; secondary risk is mediated through changes in biophysically- or ecologically-based processes or systems; and tertiary risk is the remaining diffuse effects (mental health, tension and conflicts due to decline in basic needs such as water and food) (6).

The important secondary risk of climate change on human health includes the risk of change in transmission dynamics of infectious diseases. Evidence suggests that climate change influences the increased transmission of infectious diseases — especially vector-borne diseases and food- and water-borne diarrheal diseases — through changes in biological and ecological characteristics of host-pathogen interaction (7). However, historical epidemiological studies investigating the association between climate change and infectious diseases were predominantly from high-income countries: the few studies that utilised data from LMICs were led by the experts from high income countries (7, 8). Consequently, local stakeholders and authorities from

LMIC may lack the knowledge and privilege resulting from such collaborations, due to the potential inequity and disproportionate inclusion of partners from LMICs (9, 10). Although LMICs, like Nepal, share a higher burden of infectious diseases (11), and its people are highly vulnerable to climate change, there remains little evidence on the impacts of climate change on infectious diseases transmission in Nepal (12). Only crude estimates on the association between climate change and some infectious diseases, deduced from simple correlational studies, are available for Nepal (13, 14). A dearth of good quality datasets on infectious diseases in Nepal means that the magnitude and extent of the risk of pathogen-specific diarrheal burden in the context of changing climate remains unquantified (12, 15). Specifically, there is no information on the estimates for the future burden of diarrhoea caused by various etiological agents (bacteria, viruses and protozoan parasites), under different climate change scenarios for Nepal (13, 15). Given that the key government department concerned with public health in Nepal, the Epidemiology and Disease Control Division (EDCD), has yet to institutionalize climate change as a public health problem, it has also not yet gathered information on the socio-economic and political barriers of integrating climate change as an important risk factor for infectious diseases surveillance within the EDCD. Thus, this chapter is organised to reflect on the knowledge on climate change, the burden of climate-sensitive infectious diseases and their surveillance practices in Nepal, to highlight the research gaps and to shed light on the need to strengthening Nepalese infectious diseases surveillance systems in the context of climate change.

1.2 Climate change in Nepal

Nepal is a small, landlocked country in South Asia, situated between India in the south and China in the north. Nepal has a highly variable land topography that extends from the elevation of 300m (from sea level) in the south-eastern plain to the elevation of 8848m in the north-eastern region (16) and that has a significant influence on climate variability across the country. A recent analysis of local data, for the period 1979-2016, suggested that temperature and precipitation will continue to rise throughout the 21st century in Nepal: this data was based on the observed annual increase in mean temperature for the study period by 0.03°C/year and precipitation by 8.7mm/year (17). Similarly, the 2019 national report on climate change assessment in Nepal reports that, compared to the baseline period 1981-2010, the future mean temperature in Nepal is expected to increase by 0.92°C and 1.07°C by the mid-term period (2016-2045) and 1.3°C and 1.82°C by the long-term period (2036- 2065), respectively under the intermediate and high emission scenarios i.e., Representative Concentration Pathway (RCP) 4.5 and RCP 8.5 (18). The projected scenarios are likely to cause scarcity of food and water in the harsh terrains, particularly the Himalayas and rural villages of Nepal that will risk the livelihood and the health of thousands of people in these regions. For people in these regions, their hygiene practices and eating behaviour becomes compromised, exposing them to food-and water-borne infectious diseases. Alternatively, the local residents may get pushed out of their native village and be forced to seek refuge in the capital city and other big towns to earn a living. In reality, the Himalayan exodus has already begun and people are now abandoning their native lands and relocating to densely populated valleys and towns, as climate-change migrants (19). This raises further concern over the increased burden of climate-sensitive infectious diseases, such as food-and water-borne diarrheal diseases, under the influence of future climate change, which is likely to put extra strain on the already overwhelmed EDCD.

1.3 Climate sensitive infectious diseases in Nepal and their surveillance

Nepal still experiences, although the trend is decreasing, a significant burden of various climate sensitive infectious diseases that are broadly categorized under vector borne diseases (VBDs) and food-and water-borne diseases (20). Nepal has been utilizing its network within EDCD to conduct surveillance of several notifiable diseases including vector borne diseases and food-and water-borne diseases (21). The burden of vector borne diseases that are endemic to Nepal are uniquely reported based on their aetiology but the food-and water-borne diseases are pooled under a common heading of acute gastroenteritis (AGE) and aggregately reported, except for the cases of cholera caused by *Vibrio cholerae* (21).

1.3.1 Climate sensitive vector-borne diseases

Vector-borne diseases such as malaria, visceral leishmania, Japanese encephalitis and lymphatic filarial that were historically known to be endemic in Nepal are now in a decreasing trend (14, 22). However, over the past decade, dengue fever has emerged as one of the most significant vector-borne diseases with increased public health concerns (23). Concurrently, the Lancet countdown for health and climate change reports over the past few years have raised the alarm about the increased risk of transmission of dengue fever and other vector-borne diseases due to the impacts of climate change (24-26). Yet few epidemiological and entomological studies have been undertaken in Nepal to estimate the impacts of climate change on vector-borne diseases, and so there remains limited evidence on their association (14, 27). Comparatively, more studies have been conducted on dengue fever (28-31). Although insufficient, some initiatives have been useful in increasing the information on the impacts of climate change on vector-borne diseases in Nepal.

1.3.2 Climate sensitive food-and water-borne diseases

Diarrhoea is the classical manifestation of food-and water-borne diseases, which persists as the leading cause of death among children below five years of age in LMICs like Nepal (32). Diarrhoea is caused by a wide variety of entero-pathogens including several bacteria (*Salmonella, Shigella, Campylobacter, Escherichia coli, Vibrio cholerae*), viruses (rotavirus, norovirus, adenovirus, astrovirus) and protozoa (*Giardia, Cryptosporidium, Cyclospora*) (32), and is highly sensitive to increase in temperature, decrease in humidity and change in rainfall intensity (33, 34). Diarrhoea caused by bacterial pathogens is known to be positively associated with an increase in temperature and rainfall, showing increased incidence during the summer months (35-38). On the other hand, diarrhoea caused by viruses are known to be negatively associated with an increase in temperature, showing increased incidence during the winter months (39, 40) Although Nepal has a very high prevalence of most of the pathogens causing diarrhoea (41), EDCD does not report disaggregated information on the pathogen-specific burden of diarrheal diseases, except for cholera (21). Consequently, there is limited epidemiological evidence on the impacts of climate change on food- and water-borne diarrheal diseases in the Nepalese context (13, 15). Given the aggregated nature of the dataset on diarrheal diseases reported by the EDCD (21), there remains little information on the impact of climate change on pathogen-specific diarrhoea in Nepal. Due to the differential nature of the response of a particular etiological agent of diarrhoea to climate change, it is important to ascertain the association between pathogen-specific diarrhoea and climate change(38).

1.3.3 Infectious diseases surveillance systems in Nepal and climate change

The Health Management Information Section (HMIS), within the Department of Health Services does collect information on community-level burden of ailments, such as unconfirmed acute gastroenteritis and uncharacterized febrile illnesses, through a network of female child health care volunteers. Beyond this, infectious diseases surveillance in Nepal is predominantly overseen by EDCD under the guidance of the Department of Health Services (DoHS), Ministry of Population and Health, Nepal (21). EDCD has a specialized hospital-based sentinel surveillance system called Early Warning and Reporting Systems (EWARS) that reports weekly cases of six priority infectious diseases, namely malaria, kalazar, dengue, acute gastroenteritis, cholera, severe acute respiratory infections and other diseases with epidemic potential (leptospirosis, enteric fever, hydrophobia and chikungunya) (21). In addition to EWARS, EDCD oversees monitoring and surveillance of water quality and acute surveillance of infectious diseases during the outbreaks. Also in existence are the Vector Borne Disease Research and Training Centre (VBDRT) which operates closely with EDCD for control and management of vector-borne diseases and the World Health Organization- Immunization Preventable Diseases (WHO-IPD) that supports surveillance and management of immunization preventable childhood diseases. However, the current surveillance structures and practices managed by EDCD are ill-prepared to cope with the future impacts of climate change on infectious diseases transmission, given that Nepal is yet to even integrate climate change-related threats in its surveillance practices (12, 42). As such, it is important to explore the socio-economic, institutional and political aspects of infectious diseases surveillance in the context of climate change, to guide the integration of climate change threats in the infectious diseases surveillance systems of Nepal.

1.4 Aims of this thesis

The overall aim of this thesis is to contribute towards an improved understanding of the association between climate change and selected infectious diseases in Nepal and to strengthen the capacity of infectious diseases surveillance systems in the context of climate change, with the ultimate aim being to enhance human health. Accordingly, the specific aims of this thesis are to undertake the following.

- Analyse the available data on non-viral diarrhoea among children under five years of age in Kathmandu, to estimate the impact of climate change on childhood diarrhoea and project future burden under different climate change scenarios. I specifically focus on diarrhoea among children below five years of age in Kathmandu because diarrhoea remains an important cause of childhood mortality in Nepal. Also, historical datasets collected at a shorter periodicity required for estimating future projection were not available for other infectious diseases.
- Estimate the association between temperature variation and rotavirus infection among children below five years of age living in Kathmandu, Nepal. Rotavirus has been chosen to estimate pathogen-specific association between temperature and diarrhoea due to the

availability of a good quality dataset from a member lab of the Asian Rotavirus Surveillance Network based in Kathmandu, Nepal.

- Explore the extant research on climate change and infectious diseases in Nepal and identify the reasons behind the scarce evidence on this topic.
- Explore contextual factors affecting the surveillance of infectious diseases in Nepal in the context of climate change. Since climate change-related risk is yet to be integrated into the infectious diseases surveillance practices in Nepal, this research is likely to support future endeavours to build a climate-resilient health system in Nepal by identifying social economic, institutional and political barriers of integrating climate change threats in disease surveillance.

In summary, I pay specific attention in this thesis to use state of the art techniques to generate high quality evidence on the association between climate change and selected infectious diseases (food- and water-borne diarrhoea) in Kathmandu, Nepal (based on the availability of surveillance datasets) and highlight problems associated with the integration of climate change threats in disease surveillance.

1.5 The structure and outline of this thesis

This thesis is formatted as a thesis by publication and consists of eight chapters. Three of the result chapter included in this thesis (chapters 4, 5 and 6) are already published in highly esteemed peer-reviewed journals in the field of environmental epidemiology. The final chapter in the result section (chapter 7) will soon be submitted to a suitable journal for publication. This particular format of the thesis was chosen over the traditional format due to the advantages offered by this format over the traditional format. Firstly, the rigorous peer review process for our papers prior to publication allowed me to improve the quality of this thesis by incorporating feedback and suggestions from the global experts in the field of environmental epidemiology.

Secondly, this format allowed early sharing of research findings to a larger audience through scientific journals and digital media coverage, which would not have been possible with the traditional format.

Following this chapter, which outlines the background information on the research project and the research rationale and aims, *Chapter 2* provides a detailed and comprehensive literature review on the important aspects of this thesis. The chapter reviews the literature on the mechanical pathways of the interaction between climate change and infectious diseases, aspects of infectious disease surveillance in the context of climate change. It also includes a comprehensive synthesis of epidemiological studies that have examined the effects of climate change on diarrheal diseases as well as the effects of meteorological variation on rotavirus diarrhoea, in particular.

Chapter 3 covers the overall methodological framework and data analysis approach undertaken to achieve the aims of this research project. Although each of the result chapters defines a specific methodology and analytical framework used to answer the research questions, this chapter provides details of the overarching methodology applied in this PhD project.

The subsequent chapters in the result section cover the outcomes of studies 1 to 4 of this PhD project (chapters 4, 5, 6 and 7) represent the bulk of analytical work conducted. Three out of the four result chapters (chapters 4 to 6) are already published in peer reviewed journals.

Chapter 4 is titled "Assessing the effect of climate factors on childhood diarrhoea burden in Kathmandu, Nepal", and is published in the *International Journal of Hygiene and Environmental Health*. It explores the impacts of climate change on childhood diarrhoea in Kathmandu, Nepal and projects the potential future burden of childhood diarrhoea under different climate change scenarios in Nepal.

Chapter 5, entitled as "Non-linear effect of temperature variation on childhood rotavirus infection: a time-series study from Kathmandu, Nepal", estimates the impact of temperature variation on rotavirus infection among children below five years of age in Kathmandu, Nepal. It is published in the journal *Science of Total Environment*.

Chapter 6 explores the extent of evidence on climate change and infectious diseases in Nepal and highlights the potential reasons for the scarce evidence on climate change and infectious diseases in Nepal. The chapter is an outcome of a critical qualitative analysis of experts' views on the barriers hindering the progress of climate change and infectious diseases research and action in Nepal and is published in the journal *Acta Tropica*.

Given that the climate change-related risk is not yet integrated into the disease surveillance systems of Nepal, *Chapter 7* explores the socio-economic, institutional and political factors associated with infectious diseases surveillance in the context of climate change in Nepal. It builds on the findings of the first three analytical studies, where I identified problems with infectious diseases surveillance datasets and insufficient epidemiology evidence on climate change and infectious diseases. The findings from this study support future attempts to integrate climate change-related risk in infectious disease surveillance systems and build a climate-resilient public health system in Nepal.

Finally, *Chapter 8* covers the conclusions of the research project. It brings together the empirical findings of the four studies to discuss the potential implications of these findings and outlines areas that require future investigation for building a climate-resilient infectious diseases surveillance system in LMICs like Nepal.

Chapter 2: Literature review

This chapter offers a broad narrative review of the literature covering three major aspects of this thesis work. The first section reviews the literature on the mechanism of interaction between climate change and infectious diseases, with a specific focus on food-and water-borne diarrheal diseases. The second section provides a detailed review of epidemiological studies that have examined the association between climate change and diarrheal diseases in general, and rotavirus diarrhoea in particular. The final section of this chapter relates to the social, economic and cultural aspects of infectious diseases surveillance in the context of climate change. In sum, this chapter aims to synthesise and critique the existing evidence on climate change and infectious diseases, with particular emphasis on diarrheal diseases. The chapter specifically aims to identify gaps in knowledge of the impacts of climate change on infectious diseases transmission in the Nepalese context, to set up a rationale for investigating the impacts of climate change on selected food-and water-borne diarrheal diseases and to support policymakers to strengthen infectious diseases surveillance capacity in the context of climate change.

2.1 The influence of climate change on infectious diseases transmission

"*Whoever studies medicine aright must learn the following subjects. First he (sic) must consider the effect of seasons of the year and the differences between them. Second he must study warm and cold winds, both those which are common to every country and those peculiar to a particular locality. Lastly, the effect of water on health must not be forgotten*."

(Hippocrates Air, Water and Places)

Changes in seasons and weather have been believed to cause several ailments including the onset of infectious diseases epidemics ever since the dawn of medical science (43). Infectious diseases causation is a complex phenomenon however, for simplicity, epidemiologists have relied on a traditional yet popular and succinct model of disease causation called the epidemiological triad or epidemiological triangle (44). According to the model, the onset of an infectious disease is contingent upon the interaction between an etiological agent or a pathogen and a susceptible host in an environment that supports transmission of the pathogen from a source to the host (45). As such, many etiological agents or pathogens causing communicable diseases, as well as their interaction with a host, are highly sensitive to change in environmental conditions such as temperature, precipitation and humidity: these, in turn, are influenced by climate change (46). Climate change exacerbates the overall interaction between host and etiological agents beyond the direct impact of meteorological factors on the survival of pathogens (46, 47), as illustrated in figure 2.1. The figure shows the relationship between climate change, infectious disease and human society through the lens of the epidemiological triad. Climate change-related migration and urbanisation drives change in social activities such as increases in travel and trade, increased land use, deforestation and unregulated agricultural activities: these, in turn, may lead to increased proximity between human and zoonotic hosts, thereby favouring rapid transmission of infectious diseases and spillage of zoonotic diseases to human host (48). Meanwhile, it is important to acknowledge that our knowledge on the impacts of climate change on infectious diseases transmission is always compromised by several research challenges related to studying linkages between ecosystem, socio-economic determinants, climate and infectious diseases (49). As such, climate-related impacts on infectious diseases in humans must be comprehended in relation to other forces driving infectious disease dynamics such as globalisation, change in human behaviour, antimicrobial resistance and disruption in public health services during conflict and war (48, 50).

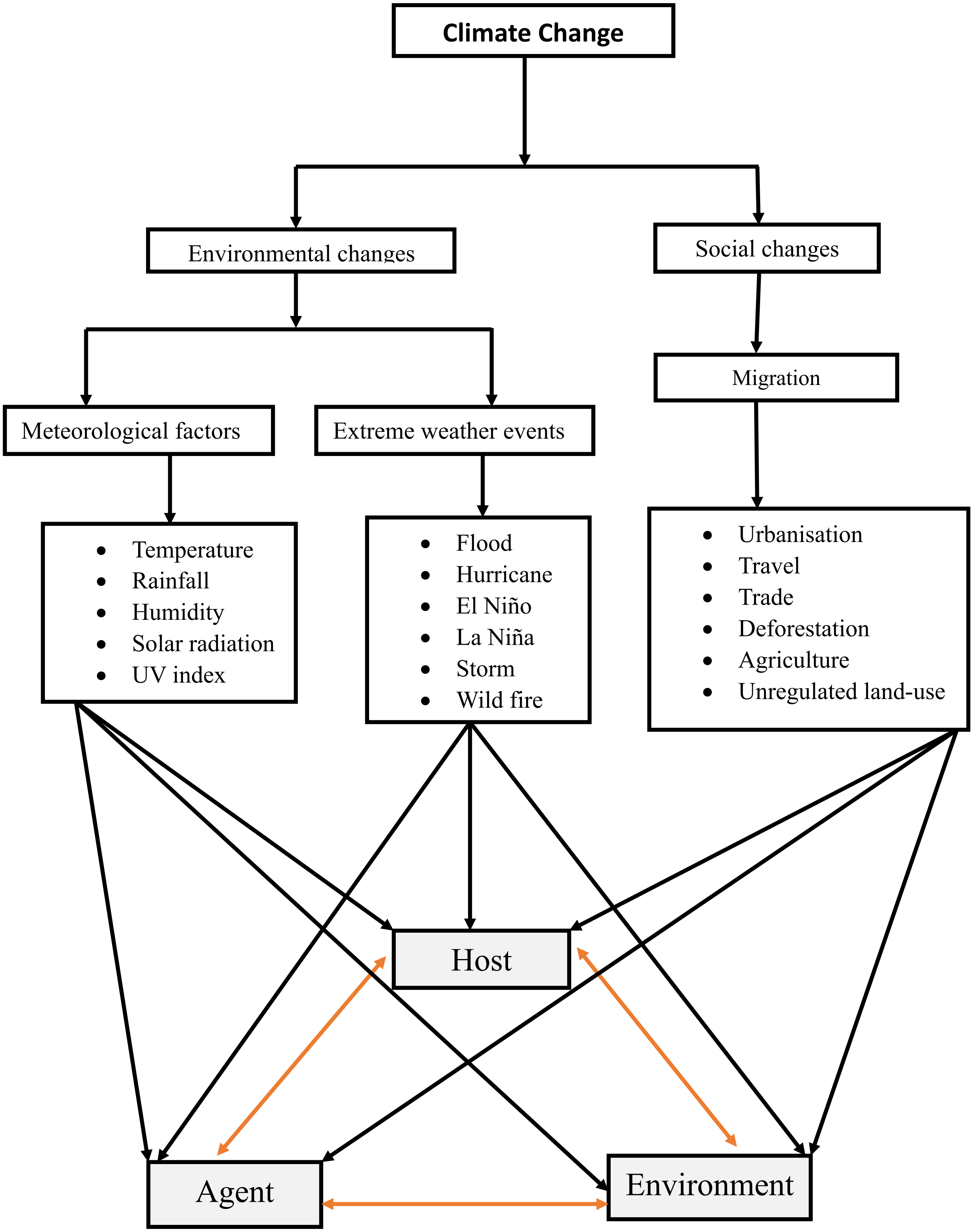


Figure 2. 1 Schematic diagram on the direction of interaction between climate change and infectious disease causation.

It is clear from figure 2.1, that the effects of climate variability on infectious diseases transmission are partly determined by the interference of climate change in the transmission cycle of a pathogen. Based on the transmission cycle and the potential influence of climate change, infectious diseases can be broadly categorised into two distinct categories:

- Directly transmitted diseases: Diseases that are transmitted between a reservoir and a susceptible host via direct physical contact or a droplet exposure are categorised as directly transmitted diseases (7). Diseases like tuberculosis and HIV are examples of diseases that get transmitted between humans (anthroponoses) via direct contact. Both of these diseases are classical examples of diseases that were historically transmitted among animals (zoonosis) but at some point in time spilled over from their zoonotic reservoir to a human host and became established in humans (7).
- Indirectly transmitted diseases: Diseases that are transmitted between two humans via, a biological vector (e.g., mosquito, sand-fly and tick) or a physical vehicle (e.g., soil, food and water) are categorised as indirectly transmitted diseases (7, 46). Typical examples of indirectly transmitted diseases are vector-borne diseases like malaria, dengue and food-and water-borne illnesses like diarrhoea (7, 48). While a major proportion of enteric diseases transmit via, a physical or a biological vector, some enteric pathogens like *Salmonella* can get transmitted from person to person by direct contact via saliva or touch of unhygienic hands.

Infectious diseases for which the pathogens are least exposed to the external environment, or spend less time outside the host body, are less likely to be affected by climate change; but diseases for which the etiological agents are more exposed to environmental conditions during their life cycle are more likely to be affected by climate change (7). As such, indirectly transmitted diseases, such as vector-borne diseases and food-and-water borne diseases, are widely studied due to the direct impacts of climate change on the transmission of these diseases. Although climate change interferes with other aspects of disease causation such as human behavioural changes, and access to health services and socio-economic vulnerability to diseases (6), these aspects are less investigated due to the difficulties associated with their attribution and quantification (50).

2.1. 1. How climate affects vector-borne diseases transmission

An increasing body of research evidence documents the impact of climate change on transmission and distribution of vector-borne diseases such as malaria, dengue, Ross River fever, chikungunya, Japanese encephalitis, West Nile fever and eastern equine encephalitis (51-56). Climate change can influence the complex mechanism involved in the transmission and geographical expansion of vector-borne diseases by affecting several factors, including survival and reproduction rate of disease vectors, intensity and temporal pattern of vector activities (especially the biting rate) and the survival and reproduction of pathogens within the vectors (57, 58). In general, climate change is likely to bring changes to ecosystems and food availability — that, in turn, can interfere with the dynamics of host population and pathogen as well as vectors — by making the habitat either more or less hospitable (58). The usual mode of transmission of vector-borne diseases to humans is through the bite of an infected vector to a susceptible host, which is regulated by vectorial capacity. Vectorial capacity is defined as the number of future infections resulting from a bite taken on one infected person in one day: this depends upon the density of a vector in relation to human, number of bites per vector per day, daily survival probability of the vector and number of days required for the development of pathogen inside the vector (59). Since, all the components of vectorial capacity are highly sensitive to climatic factors, climate change can influence the overall incidence and geographical distribution of vector-borne diseases (57).

2.1.1.1 How temperature variation influences VBD transmission

In general, epidemiological studies assessing the relationship between climate change and vector-borne diseases have reported a positive association between temperature and the disease burden (56, 60). Physiologically, increases in temperature surge the growth rate of a vector population, increases the biting rate, decreases the incubation period of agent/pathogen inside the vector and improves the rate of development of pathogen within the vector (58, 61). However, the relationship between temperature and vector survival or biting rate is not linear in all cases. In the case of a dengue vector *Aedes aegypti,* the development of egg into adult progresses from 0% at 15°C to about 90% at 20°C and then drops to 60% at 35°C (62). Since, humans regulate their body temperature, an increase in temperature does not change attributes of the host in this type of transmission cycle. Overall, warmer temperatures are more favourable to the increased transmission of a vector-borne disease compared to cooler temperatures.

2.1.1.2 How rainfall variation influences VBD transmission

The impact of rainfall on vector-borne disease transmission is complex and contextual (58). Similar to temperature, the impact of rainfall on vector-borne disease transmission is reported to be non-linear (63). Evidence suggests that increases in rainfall favours the growth of vectors, such as mosquitoes, by expanding the breeding habitat of larvae (54). Increases in rainfall can support growth in food supplements, which may lead to an increase in population of a vertebrate host of both the vectors or the pathogens (7). However, drought events are reported to cause outbreaks of West Nile virus infection in New Jersey, USA during the period 2002-2011, indicating the association between rainfall and vector-borne disease transmission to be non-linear and context-specific (63). It is hypothesised that drought may lead to an increase in the proximity of zoonotic host and disease vectors during the drying of water sources in wetlands, consequently favouring the transmission of pathogen from the zoonotic host to the vector (54). In the context of an urban habitat, drought is likely to provide more breeding sites for vectors, due to the increasing use of containers for rainwater collection or storage and stagnation of rainwater in plant pots and abandoned tyres of automobiles (58).

2.1.1.3 How humidity variation influences VBD transmission

Humidity (absolute humidity) depends on temperature and rainfall and therefore humidity is reported to be an important predictor for the transmission of vector-borne diseases (64-66). Epidemiological studies have reported a positive association between all three forms of humidity (relative humidity, absolute humidity and specific humidity) and incidence of dengue fever and West Nile fever (54, 64, 66). The effect of humidity on the transmission of vector-borne diseases is mediated through the development process of the arthropod vector. Both absolute humidity and specific humidity are high when temperature and the amount of rainfall are high, hence rises in both of them are conducive for improved survival and breeding of vector population (64). Increases in relative humidity are reported to increase the hatching percentage of dengue vectors *Aedes agypti* and *Aedes albopictus* (67).

2.1.1.4 How extreme weather events influence VBD transmission

Climate change-related hydro-meteorological disasters, or extreme weather events, refer to unexpected or severe weather phenomena such as floods, storms, hurricanes, typhoons, wildfires and heat waves. Extreme weather events affect the transmission of vector-borne diseases through impacts on both hosts as well as pathogens. Events such as storms and hurricanes may help with the dispersal of vectors in the direction of wind to facilitate the transmission of vector-borne diseases to previously non-endemic areas (68). The ecological changes brought about by extreme rainfall or hurricane can provide breeding sites for disease vectors like mosquitoes. Similarly, disasters like floods and hurricanes can destroy the habitat of a host and make them vulnerable to the bite of disease-carrying vectors (69). Furthermore, disasters like floods or hurricanes may lead to the collapse of health facilities and disruption of public health programs — such as immunisation or vector surveillance and control — to lead to the increased vulnerability of humans to vector-borne diseases (69). Conversely, heat-waves can have a negative effect on the transmission of vector-borne diseases like dengue and malaria (70). As mentioned earlier, the effect of temperature on the survival and breeding of arthropod vectors, like mosquitoes, is non-linear. As such, increases in temperature beyond a certain threshold shows a detrimental effect on the development of larvae of certain vectors (70). Hence, during heat wave events (when the temperature exceeds 35°C), the development of mosquitoes will be greatly reduced and the transmission rate of vector-borne diseases, like malaria and dengue, will also be reduced.

2.1. 2. How climate affects food-and water-borne diarrheal diseases transmission

There is a growing body of literature on the effects of climate change on food-and water-borne diseases, although the detection and attribution of climate change impact on diarrheal diseases remains challenging (71, 72). As discussed in Chapter 1, diarrhoea is the classical manifestation of food- and water-borne diseases: numerous pathogens (bacteria, virus and protozoa) are implicated behind their occurrence (41, 73). Although the mechanism of interaction between specific diarrhoea-causing pathogens and hydro-meteorological factors may be common (except for enteric viruses), as illustrated in figure 2.2 (33), the impact of climate change on diarrhoea caused by specific pathogens is unique (35, 38, 39, 74-77). Climate change-related extreme rainfall and increases in temperature is likely to increase the occurrence of diarrheal diseases (bacterial and protozoan) via different mechanisms. Increase in temperature favours the replication and survival of pathogens in the intermediate substrate (soil, food and water) or their zoonotic hosts and causes overexpression of a virulence gene. However, increase in precipitation flushes pathogens into the waterways during rainfall events or concentrates pathogens in groundwater reservoirs or surface water bodies during droughts (35, 78-81). Climate change is likely to increase the number of warmer days in tropical and subtropical regions and therefore, prolong the number of days conducive for transmission of diarrheal diseases (26). Furthermore, habitat destruction or displacement of humans during extreme weather events — such as floods, cyclones and hurricanes — is likely to compromise hygiene, sanitation and living condition of people, deteriorate their social economic circumstances, disrupt health service delivery, disrupt food supplies and thereby increase the chances of transmission of food-and water-borne diarrheal disease (35, 74, 82).

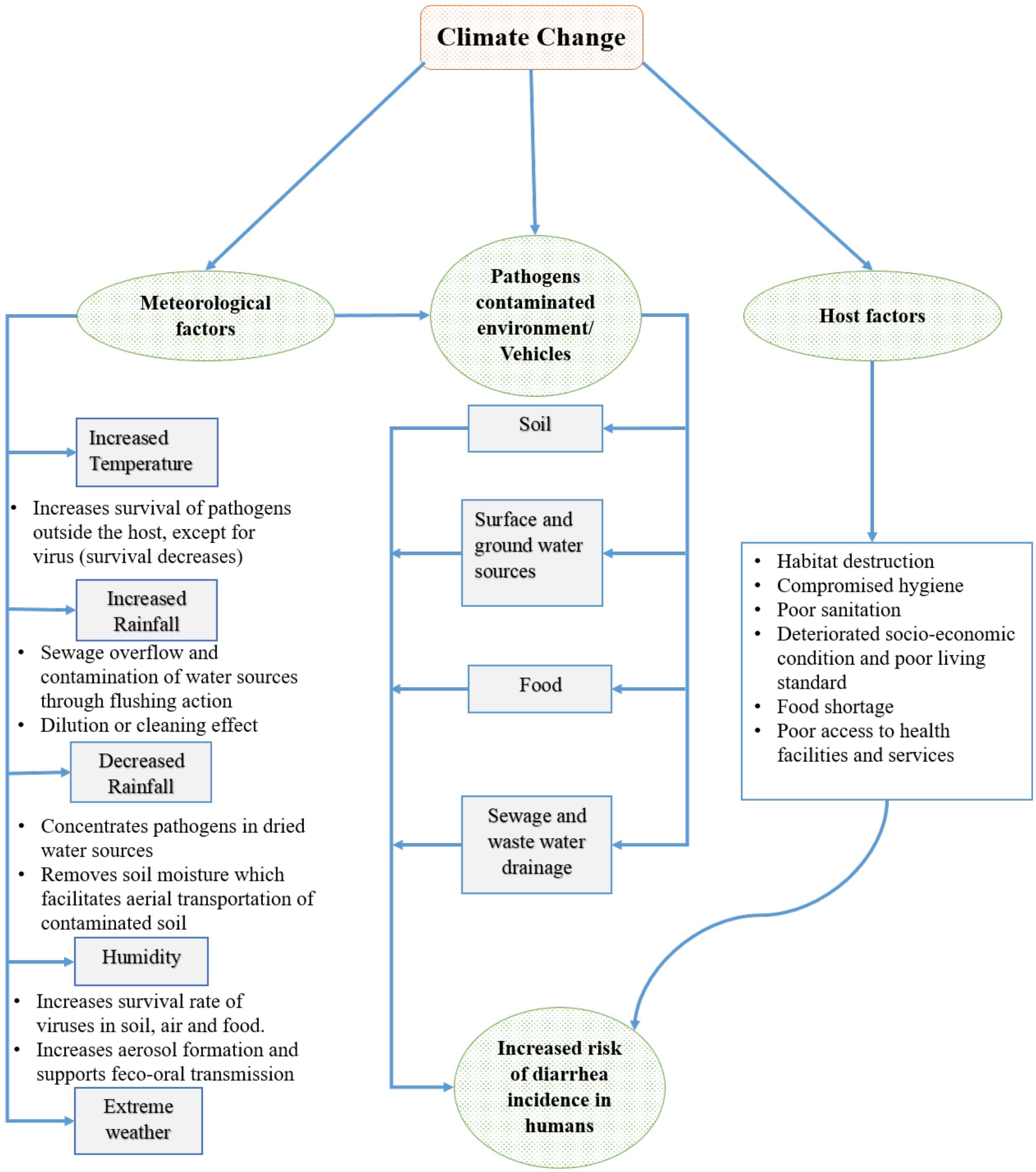


Figure 2. 2 Conceptual diagram representing mechanisms by which climate change is expected to increase the risk of diarrheal diseases transmission, modified from Moors et al. (83).

2.1.2.1 How temperature variation influences the transmission of diarrheal diseases

Generally, increases in temperature have a positive influence on the survival of enteric pathogens (bacteria and protozoa) outside the living host, except for the viral pathogens causing diarrhoea (35). As such, increases in temperature could increase the risk of transmission of diarrhoea caused by bacteria and protozoa because the longer a pathogen survives outside the host, the greater are its chances of transmission through various contaminated vehicles or routes including water, food and other fomites (84). For viral enteric pathogens — such as rotavirus, norovirus and adenoviruses — increases in temperature beyond a certain threshold, decreases the survival of pathogens by decreasing the stability of viral proteins and their genomic materials (85). Experimental studies have reported a faster rate of decline in viral load from groundwater sources at 23°C compared to 7°C (86). For the bacterial pathogen *Vibrio cholerae*, increases in sea surface temperature and increases in salinity favours the survival of the pathogen by improving the nutrient content of water. Resulting from increases in global temperatures over the past two decades, an increased risk of transmission of cholera has been recorded for the inhabitants of the Baltic and US northeast coastlines, compared to the reference period of 2003-2005 (26). Increase in temperature results in the decreased shelf-life of food products and results in higher probability of spoilage of food products, which means there is higher incidence of food poising and subsequent diarrhoea in warmer weather (87). For a diarrheal pathogen *Shigella dysenteriae*, increases in temperature from 30°C to 37°C results in the increased expression of virulent gene encoding the shiga-toxin, which causes inflammation of intestinal tissue linings resulting in the excessive loss of body fluid (80). Similarly, increases in temperature due to climate change is likely to lengthen the seasonality of diarrheal diseases by increasing the load of diarrheal pathogens in a zoonotic host for a prolonged time: consequently, there is an increase in the seasonal and geographic distribution of the disease. Apart from these, changes in human behaviours — such as food storage and consumption practices, increased consumption of water (increases the probability of pathogen ingestion in regions with poor quality drinking water), compromised hygienic practices (due to scarcity of water in hot and dry regions) — during warmer weather creates a favourable environment for the transmission of diarrheal pathogen (7, 87).

2.1.2.2 How rainfall variation influences the transmission of diarrheal diseases

Rainfall shows a differential impact on the transmission of diarrheal diseases depending upon the intensity of rainfall and antecedent conditions (88). Heavy rainfall following a dry run can lead to the flushing of diarrheal pathogens excreted in soil from animal and human sources into groundwater and surface water sources and contaminate the water bodies and result in subsequent diarrheal outbreaks (35, 89, 90). In contrast, continuous rainfall following a wet period could dilute the concentration of pathogens already present in the water bodies and reduce the risk of transmission of water-borne diarrhoea (33, 35, 88). In regions with poor drainage or defective faecal disposal systems, increased rainfall may cause overflow of sewage or leakage of septic tanks and contaminate water sources increasing the risk of diarrhoea transmission (91). Meanwhile, a decrease in rainfall and dry condition could also increase the risk of transmission of diarrheal disease, especially from zoonotic sources, due to the increased concentration of pathogens (absence of cleaning effect) in small water bodies that are shared by humans and animals (33, 92, 93). Similarly, shortage of water for domestic use, due to decreases in rainfall, may lead to change in human behaviours — such as compromised hygienic practices, poor sanitation — and increases their vulnerability to diarrheal diseases (33, 74). Indirect effect of water shortages, or decreased rainfall, can produce malnutrition due to food shortages or reduced agricultural productivity, which could further increase susceptibility towards diarrheal diseases (94). The effect of these biophysical phenomena on rainfall and on the risk of diarrhoea may be confounded by changes in social structure and cultural practices of the host: these could include housing practices (type of building materials used for construction) and use of faecal sludge as a manure in agricultural fields (95, 96).

2.1.2.3 How humidity variation influences the transmission of diarrheal diseases

The effect of humidity on the risk of diarrheal diseases onset and transmission is the least established relationship among the meteorological drivers of diarrheal diseases. Although humidity is identified to be an important driver of airborne pathogens such as influenza viruses and tuberculosis bacilli (97, 98), the influence of humidity on diarrheal pathogens remains poorly understood. Relative humidity can modulate the risk of diarrhoea transmission in a human host by directly affecting the survival of pathogens (particularly viruses) or indirectly via a food-borne route. Relative humidity has been reported to show a positive association with the survival of bacterial pathogens like *Listeria* and *Salmonella* in fresh produce and dried food products such as walnuts (99, 100). As such, increases in humidity is likely to increase the count of diarrheal pathogens (bacteria) in food products and thereby increases the risk of food-borne transmission of diarrheal diseases when optimum requirements for long term food storage are compromised (101) . On the other hand, the survival of viral pathogens, like rotavirus, are reported to be negatively associated with relative humidity (33, 39). When viral pathogens are excreted out into the environment from the infected host, low relative humidity prolongs the survival of the virus outside the host by controlling the amount of water retained, the concentration of solutes in the virus surface and its pH (102). Low relative humidity or dry conditions cause the formation of virus ladened dust particles or droplets nuclei (33, 102), favouring faecal-oral transmission of rotavirus infection, which is the predominant mode of rotavirus transmission (103, 104).

2.1.2.4 How extreme weather events influence the transmission of diarrheal diseases

The effect of extreme weather events on the transmission of diarrheal diseases is mediated indirectly through several factors likely to be conducive to increased survival and transmission of diarrheal pathogens. These include the displacement of human habitat, disruption of electricity supply, disruption of health service delivery (vaccination program disrupted), deterioration in sanitary practices, poor hygienic condition, decreased access to piped water and deterioration in social-economic conditions following extreme weather events such as flood, hurricane and cyclones (35, 105-107). The periodic weather phenomenon like El Niño Southern Oscillation, a major driver of global inter-annual variation, increases the risk of diarrhoea transmission by affecting local weather patterns and triggering heavy floods, droughts, temperature extremes and storms (34, 93, 108). With regard to heat waves, the mechanism driving diarrheal diseases outbreaks during heat waves is less established. Heat-waves are likely to influence the transmission of food-borne diarrhoea by affecting food production, distribution and altering the behaviours of consumers (109, 110).

2.2 Overview of epidemiological studies on climate variability and non-rotavirus diarrhoea

A comprehensive search of electronic databases PubMed, Scopus, Web of Science and Google Scholar was conducted to review existing literature exploring the association between climate variability and diarrheal diseases. Only the epidemiological studies that investigated the short-term and long-term association between climate variability and diarrhoea were included in the final analysis and outbreaks or case studies were excluded. A total of 140 epidemiological studies (including 20 studies on rotavirus diarrhoea) were reviewed and the summary of the studies are synthesised on the basis of exposure variables in the following subheadings, the details of the search strategy are available in Appendix 1.

2.2.1 Temperature and diarrhoea

As summarized in Table 2.1, 79 studies have reported the association between temperature and diarrheal diseases. The studies included data collected between 1965 and 2018 and a wide variety of diarrheal pathogens comprising bacteria (*Salmonella*, *Shigella*, *Campylobacter*, *Escherichia coli* and *Vibrio*), protozoa (*Cryptosporidium*, *Entamoeba histolytica* and *Giardia*) and all cause infectious diarrhoea or acute gastroenteritis. Most of the studies used mean temperature as an exposure variable (37, 111-113), while some used maximum temperature

(114-116) and a few used minimum temperature (78, 117-119). Difference in daily temperature measures, like diurnal temperature, is also used as an exposure variable in a handful of studies (120, 121). The periodic resolution of data used in these studies varies between daily, weekly and monthly, see Table 2.1. A variety of study designs and statistical techniques, ranging from ecological time series regression to case-crossover design, are used to estimate the association, the details of which are covered in Chapter 3. These studies were conducted in a wide variety of settings covering all inhabited continents across the globe. Despite the heterogeneity in study design, exposure variables (different temperature indices) and geographic locations, a positive association is reported between temperature variability and non-rotavirus diarrhoea in almost all the cases. The majority of the studies report the association or impact of temperature variability on all forms of diarrhoea (unclassified), followed by the bacterial cause and, to a lesser extent, the protozoan agent. In general, the reported positive association holds true for all forms of infectious diarrhoea irrespective of the causative agent (bacterial or protozoan). These studies report the increase in the risk of diarrhoea burden ranging from 0.3% to 29%, for every 1°C increase in the exposure temperature (87, 122).

2.2.1.1 Nature of association between temperature and diarrhoea

Although studies consistently report a positive association between temperature variability and all forms of diarrhoea (excluding viral), the nature of this association remains inconsistent. Checkley et al. (111), in early 2000, reported that the association between daily hospitalisation among Peruvian children and maximum temperature is non-linear (inverted U-shape for dehydrating diarrhoea). Consistent with the Peruvian study, Onozunka et al. (123), and Wang et al. (124) more recently have used non-linear regression models to show that the association between temperature and diarrhoea is non-linear across multiple cities in Japan and China respectively. However, most studies assume a linear association and report a constant increase in diarrhoea incidence for each one unit increase in temperature along the entire temperature scale (112, 113, 115, 125-127). Meanwhile, very few studies examine the threshold temperature beyond which the risk of diarrhoea burden is higher. Notably, Rosenberg et al. (128), fitted two piece-wise linear regression models and identified a threshold temperature of 27^{o}C beyond which the risk of Campylobacter incidence in Israel increased by 16.1%, compared to 0.6% increment below the threshold temperature, for every 1^{o} C increase in temperature. Similarly, Zhang et al. (114) and Li et al. (129) in two separate studies use hockey stick models to estimate the threshold temperature beyond which the risk of transmission of bacillary dysentery was higher in China.

2.2.1.2 Lag effects of temperature on diarrhoea incidence

Given the effect of temperature on diarrhoea incidence is not immediate, a wide variety of lag values are used in existing epidemiological studies, depending upon the periodic resolution of exposure and response variables. Usually, the incubation period of a diarrheal pathogen is shorter and does not extend beyond one week, and as such, a majority of studies report that the delayed effect of temperature on diarrhoea does not persist beyond 7-14 days (37, 110, 120, 130). The studies that use monthly data to estimate the association between temperature and diarrhoea have tested the effect of up to one month lag and ended up reporting no significant effect to a diminishing lag effect beyond the first month (113, 115). D'Souza et al. (131) however, reports a significant lag effect of one month on *Salmonella* incidence in Australia. This finding could be explained by the differences in transmission pathways of diarrheal pathogens between food-borne and water-borne diarrhoea. While D'Souza exclusively analysed food-borne pathogen *Salmonella*, the majority of articles using monthly reported diarrhoea cases have included all forms of pathogens without specific distinction on the type, see Table 2.1. Meanwhile, two studies from Africa (sub-Sahara and central Africa) used monthly reported diarrhoea counts and monthly average temperatures but do not include a lag effect in their final models (132, 133). In summary, the lag effect of temperature on the incidence of diarrhoea may differ, based upon the type of pathogens involved and exposure sources (food or water). It thus important to collate information on the lag effects to better understand the causative mechanisms between temperature and diarrheal disease incidence.

2.2.1.3 Projection of diarrhoea under future climate change scenarios

As mentioned earlier, despite heterogeneity in the nature of the diarrhoea-temperature relationship (linear, non-linear or threshold effect), there is a positive overall association between diarrhoea and temperature (127). As such, if other risk factors remain unchanged, the burden of diarrheal disease is likely to increase under future climate change scenarios, where temperatures are expected to increase between 1.5 – 3^{o}C by the end of this century (134). Seven different studies, out of the total 79, that investigated the association between temperature and diarrhoea have projected a future burden of diarrhoea under different climate change scenarios (83, 123, 125, 135-138). Moors et al. (83) and Kolstad et al. (125) used secondary estimates (regression coefficients) derived by other researchers to make future projection for North India and global scale, respectively. Kolstad et al. (125), report a high level of uncertainty in the projected increase in diarrhoea burden under different climate change scenarios and time slices ranging from 8–11% (with SDs of 3–5%) by 2010–2039 and 22–29% (SDs of 9–12%) by 2070–2099. On the other hand, Moors et al. (83), report a precise estimate of approximately 10% increase in the future burden of diarrhoea by 2040s under the future climate change scenario of 1.8^{o}C increase in ambient temperature. While five studies have assumed a linear association between temperature and diarrhoea for making future projections, two nationwide studies (each from China and Japan) have used non-linear regression models to make future projection of bacillary dysentery and all cause infectious gastroenteritis, respectively (123, 136). While the study from China reports a future nationwide increase (ranging from 11% to 20% across different regions) in the burden of bacillary dysentery under different climate changes scenarios (RCP 2.6, RCP 4.5, and RCP 8.5) by 2090, the study from Japan reports a net reduction (-0.8% to – 9.1%) in the burden of acute gastroenteritis under different climate change scenarios (RCP 2.6, RCP 4.5, RCP 6.0 and RCP 8.5) by 2090s.

Table 2. 1 Epidemiological review of studies that explored the association between diarrhoea and temperature.

Reference	Location	Period	Age group	Pathogen	Exposure definition	Outcome definition	Statistical method	Result and conclusion
Delahoyo et al. 2021 (139)	195 provinces in Peru	2005-2015	Less than five years	All cause	Weekly mean temperature	Weekly counts of clinic visit for diarrhoea	Time series, Negative binomial generalised estimating equation with autoregressive correlation	For each 1ºC increase in the mean temperature across three prior weeks, diarrhoea incidence risk increased by 3.8%.
Wang et al. 2021 (140)	Four cities in China	2014-2016	All ages	*Shigella*	Mean temperature (weekly average)	Weekly bacillary dysentery cases	Boosted regression tree with Poisson link function	Weekly mean temperature was an important predictor for weather attributable bacillary dysentery transmission.
Wang et al. 2020 (124)	270 cities in China	2014-2016	All ages	Infectious diarrhoea	Daily mean temperature	Daily infectious diarrhoea cases reported to national diseases surveillance system	Quasi-Poisson regression equation fitted with distributed lag nonlinear model	Compared to the 50th percentile of daily mean temperature, the risk of diarrhoea cases increased by 7.2% at the 81st percentile.
Oberhiem et al. 2020(141)	Germany	2001-2014	All ages	*Campylobacter*	Weekly average of daily mean temperature	Weekly counts of *Campylobacter*	Time series, Sigmoid logistic regression model	Incidence of weekly *Campylobacter* infection increased by 0.52 cases per 100,000 population per every 5°C increase in ambient temperature.
Kuhn et al. 2020 (142)	Europe (Nordic countries)	2000-2015	All ages	*Campylobacter*	Weekly average of mean temperature	Weekly cases of *Campylobacter*	Poisson regression models	The number of *Campylobacter* cases in any week during the summer increased significantly with increasing temperature, precipitation and number

					(two weeks lag)			of heavy precipitation events in the previous week.
Alemayehu et al. 2020 (133)	Southwestern Ethiopia	2007-2017	Less than five years	All cause	Monthly average of mean temperature	Monthly count of diarrhoea cases extracted from HMIS	Time series, Negative binomial regression	The risk of childhood diarrhoea increased by 16.66% (RR: 1.1666; 95% CI: 1.164–1.168) per increase in 1°C temperature.
Galanis et al. 2020 (143)	British Columbia, Canada	1992-2017	All ages	*Vibrio*	Average sea surface temperature	Weekly number of Shell fish associated Vibrio parahaemolyticus cases reported to BC Centre for Disease Control	Poisson regression models	A significant correlation was reported between annual Vibrio incidence and sea surface temperature.
Liu et al. 2020 (136)	China	2014-2016	All ages	*Shigella*	Daily mean temperature	Daily surveillance data on bacillary dysentery reported to Chinese CDC	Two stage time-series design, fitted with distributed lag nonlinear models	For each 1ºC rise in mean temperature, daily count for bacillary dysentery increased by 1.7 %.
Aik et al. 2020 (101)	Singapore	2005-2018	All ages	All cause	Weekly average temperature	Weekly surveillance diarrhoea cases reported to Ministry of Health	Negative binomial regression models	There was a weak evidence on the association between mean temperature and diarrhoea incidence [IRR: 1.013, 95% CI: 0.998–1.027].
Daisy et al. 2020 (144)	Dhaka, Bangladesh	2000-2013	All ages	*Vibrio cholerae*	Monthly average of mean temperature	Monthly count of Vibrio cholera cases reported to icddr,b	SARIMA model	A 1°C increase in maximum temperature at one-month lead time showed a 7% increase of cholera incidence.

Fang et al. 2020 (145)	Jiangsu, China	2013-2017	All ages	Infectious diarrhoea	Monthly mean temperature	Monthly count of laboratory confirmed infectious diarrhoea	Cross correlation analysis, Generalised additive models	Mean temperature and rainfall showed U-shape associations with disease risk (with threshold 15°C and 100mm per month, respectively).
Asadgol et al. 2019 (135)	Qom city, Iran	1998-2016	All ages	Cholera	Monthly mean temperature	Daily cholera cases	Artificial neural network	A significant correlation was reported between low precipitation and cholera infection.
Anwar et al. 2019 (146)	Afghanistan	2010-2016	All ages	All cause	Mean daily temperature	Monthly count of diarrhoea cases reported to the Ministry of Public Health	Spatial-temporal Bayesian hierarchical model and Poisson regression models	Mean daily temperature were positively associated with diarrhoea incidence; every 1°C increase in mean daily temperature and 0.01-unit change in the aridity index were associated with a 0.70% (CI: 0.67%, 0.73%) increase and a 4.79% (CI: 4.30%, 5.26%) increase in the risk of diarrhoea, respectively
Onozuka et al. 2019 (123)	Japan	2005-2015	All ages	All cause	Weekly mean temperature	Weekly count of infectious diarrhoea extracted from National Institute of Infectious Diseases	Two stage time-series design, fitted with distributed lag nonlinear models	The overall cumulative risk for infectious gastroenteritis showed generally a unimodal distribution at lower temperature and tended to increase at higher temperature. Japan may experience a net reduction in temperature-related excess morbidity due to infectious gastroenteritis in higher emission scenarios.
Mertens et al. 2019 (147)	Tamil Nadu, India	2008-2009	Less than five years	All cause	Weekly average of mean temperature	Diarrhoea related symptoms seven days prior to clinic visit	Generalised additive models, binomial regression models	Prevalence of diarrhoea for seven days prior to clinic visit was 2.95 (95% CI: 1.99- 4. 39) times higher when the mean temperature in prior week was in the hottest quartile vs. the lowest quartile for the week.

Djennad et al. 2019 (148)	England and Wales	1989-2014	All ages	*Campylobacter*	Monthly average of mean temperature	Monthly count of laboratory confirmed *Campylobacter* reported to Public Health England	Time series analysis with negative binomial distribution, wavelets and cluster analysis	Generalised structural time series model revealed that changes in temperature accounted for 33.3% of the expected cases of campylobacteriosis,
Lake et al. 2019 (149)	Europe	2008-2016	All ages	*Campylobacter*	Weekly mean temperature	Weekly counts of laboratory confirmed *Campylobacter* cases	A two-stage multivariate meta-analysis methodology was used to explore associations with temperature and precipitation.	Campylobacteriosis cases were positively associated with temperature and, to a lesser degree, precipitation.
Rushton et al. 2019 (150)	Northern England	2004-2009	All ages	*Campylobacter*	Monthly average temperature	Monthly counts of *Campylobacter* cases	Time series analysis using harmonic regression models	De-seasonalised counts of *Campylobacter* cases were not significantly related to de-seasonalised temperature after also adjusting for autocorrelation ($t = 0.212$, $P = 0.230$) or rainfall ($t = -0.119$, $P = 0.906$).
Alexander et al. 2018 (78)	Chobe, Botswana	1998-2017	Less than five years	All cause	Weekly minimum temperature	Weekly counts of diarrhoea cases	Negative binomial regression models	Differential impacts of predictors were observed on diarrhoea incidence during dry and wet seasons. In dry season river height and maximum temperature were significantly associated with diarrhoea incidence.
Morral-Puigmal et al. 2018 (151)	Spain	1997-2013	All ages	All cause	Daily mean temperature	Daily count of hospitalisation	Time series regression fitted with	Both high and cold temperatures increased the risk of gastroenteritis hospitalisations (RR = 1.21, 95% CI:

						for acute gastroenteritis	distributed lag nonlinear models	1.09, 1.34; and RR = 1.07, 95% CI: 1.00, 1.15, respectively).
Song et al. 2018 (152)	South Korea	2002-2010	All ages	*Shigella*	Weekly mean temperature	Weekly count of *Shigella* cases	Generalised additive models, fitted with weekly lag up to six weeks	A 1°C increase in temperature is expected to increase the incidence of shigellosis by 13.6%.
Wang et al. 2018 (153)	Hong Kong	2002-2011	All ages	Salmonella	Daily mean temperature	Daily count of non-typhoidal salmonella cases	Generalised additive models fitted with distributed lag nonlinear models	Relative to 13°C, there was a 6.13 (95% CI: 3.52–10.67) times the risk at a temperature of 30.5°C.
Alik et al. 2018 (154)	Singapore	2005-2015	All ages	Salmonella	Weekly mean temperature	Weekly count of laboratory confirmed *Salmonella* cases	Time series, negative binomial regression models	A 1°C increase in mean ambient air temperature was associated with a 4.3% increase (IRR): 1.043, 95% CI = 1.003, 1.084) in reported *Salmonella* infections in the same week and a 6.3% increase (IRR: 1.063, 95% CI = 1.022, 1.105) three weeks later.
Horn et al. 2018 (155)	Mozambique	1997-2014	All ages	All cause	Weekly maximum temperature	Weekly diarrhoea count	Time series, Generalised linear models	We estimated a 3.64% (95% CI: 3.35, 3.93) increase in diarrheal disease for each 1°C increase in the hottest day of the concurrent week.
Rosenberg et al. 2018 (128)	Israel	1999-2010	All ages	*Campylobacter*	Weekly mean temperature	Weekly count of *Campylobacter* cases	Generalised additive models, Poisson regression model	For each 1°C increase in weekly mean temperature above the threshold of 27°C risk of *Campylobacter* infection increased by 15.4% (95% CI: 6.7–24.1%).

Azage et al. 2017 (156)	Northwest Ethiopia	2013-2015	Less than five years	All cause	Monthly mean temperature	Monthly count of diarrhoea reported to HMIS	Correlation, negative binomial regression	There was a significant positive association between monthly average temperature (IRR = 1.019; 95% CI 1.0034, 1.0347) and the rate of childhood diarrhoea.
Semenza et al. 2017 (137)	Baltic sea, Sweden	2006-2014	All ages	*Vibrio* species	Weekly mean of sea surface temperature	Laboratory confirmed *Vibrio* cases (Weekly)	Time stratified case cross over, conditional logistic regression models	The estimated exposure–response relationship for *Vibrio* infections at a threshold of 16°C revealed a relative risk (RR) = 1.14 (95% CI: 1.02, 1.27; p = 0.024) for a lag of two weeks.
Thiam et al. 2017 (157)	Mbour, Senegal	2011-2014	Less than five years	All cause	Monthly average day temperature and night temperature	Monthly count of diarrhoea	Time series, negative binomial regression models	High Day Temp ≥ 32°C and high Night Temp ≥ 26°C showed a significant negative association with diarrheal incidence of the following month (IRR: 0.78, 95% CI: 0.66–0.91; IRR: 0.76, 95% CI: 0.66–0.87, respectively).
Yan et al. 2017 (158)	Beijing, China	1970-2012	All ages	*Shigella*	Monthly average of mean temperature	Monthly count of bacillary dysentery	Time series, Autoregressive integrated moving average models	Temperature with two month and seven month lags and rainfall with a 12 month lag were positively correlated with the number of BD cases in Beijing.
Wangdi et al. 2017 (159)	Bhutan	2003-2013	All ages	All cause	Monthly average temperature	Monthly average diarrhoea cases	Time series, Poisson regression models	Diarrhoea incidence increased by 0.6% (95% CrI: 0.5–0.6%) for every degree increase in maximum temperature.
Cheng et al. 2017 (160)	Hefei, China	2006-2012	All ages	*Shigella*	Daily mean temperature	Daily count of bacillary dysentery cases	Time series, negative binomial models fitted with	The risk of bacillary dysentery increased with the temperature rise above a threshold (18·4°C), and the temperature effects appeared to be acute. The RR associated with a 1°C

							distributed lag nonlinear models	increase in temperature was 1·04 (95% CI; 1·00–1·07).
Musengimana et al. 2016 (161)	Cape town, South Africa	2012-2014	Less than five years	All cause	Weekly average of mean temperature	Weekly count of diarrhoea cases	Mixed effects over-dispersed Poisson regression model	A 5°C increase in minimum and maximum temperature led to 15% (IRR: 1.46, 95% CI: 1.09–1.20) and 6% (IRR: 1.06, 95% CI: 1.01–1.12) increase in diarrhoea cases, respectively
Mclver et al. 2016 (117)	11 districts of Cambodia	1997-2012	All ages	All cause	Monthly minimum temperature	Monthly cases of diarrhoea	Generalised linear model with negative binomial distribution	Differential impacts of predictors were observed on diarrhoea incidence across different districts in Cambodia.
Philipsborn et al. 2016 (162)	Global	1975-2012	All ages	Diarrhoeagenic *Escherichia coli*	Monthly mean temperature	Monthly count of *E. coli* diarrhoea	Generalised log linear Poisson regression models	A 1°C increase in mean monthly maximum temperature was associated with 8% (CI: 5%-11%) increase in incidence of diarrhoeagenic *E. coli.*
Stephen et al. 2016 (163)	Queensland, Australia	2004-2013	All ages	*Salmonella*	Daily mean temperature	Daily count of Salmonellosis	Poisson regression models with distributed lag nonlinear models, Switching models	A 5°C increase in mean temperature was associated with increases in salmonellosis cases of 45.4% (95% CrI 40.4%, 50.5%).
Lal et al. 2016 (164)	New Zealand (Auckland, Wellington and Christchurch)	1997-2007	All ages	*Salmonella*	Weekly mean temperature	Weekly count of *Salmonella* cases	Time series, Poisson regression models fitted with distributed nonlinear lag	High temperatures were associated with increased risk of *Salmonella* in Christchurch and Auckland but not in Wellington.

Carlton et al. 2016 (127)	Global	Till 2013	All ages	All cause	Maximum, minimum and mean temperature	All cause diarrhoea reported in the studies included	Meta-analysis	A positive association between ambient temperature and all-cause diarrhoea (IRR) 1.07; 95% CI; 1.03, 1.10).
Milazzo et al. 2015 (109)	Adelaide, Australia	1990-2012	All ages	*Salmonella*	Daily maximum temperature	Daily *Salmonella* cases (laboratory confirmed)	Time-series, Poisson regression model fitted with distributed lag non-linear models	Daily *Salmonella spp*. counts increased by 1·3% (IRR) 1·013, 95% CI; 1·008–1·019] per 1°C rise in temperature.
Jinag et al. 2015 (165)	Maryland, USA	2002-2012	All ages	*Salmonella*	Extreme temperature (above 95th percentile of historical daily temperature data) and Extreme precipitation (above 90th percentile of historical daily rainfall data)	Culture confirmed *Salmonella*	Negative binomial generalised estimating equations	A 4.1% increase in salmonellosis risk associated with a one unit increase in extreme temperature events (IRR: 1.041; 95% CI: 1.013–1.069).
Wen et al. 2015 (121)	Hefei, China	2006-2012	Less than 14 years	*Shigella*	Daily diurnal temperature	Daily *Shigella* cases	Poisson generalised linear models with distributed lag nonlinear model	For each 5°C increment of DTR daily bacillary dysentery cases increased by 8% (95% CI = 2.9–13.4 %).

Li et al. 2015 (129)	Beijing, China	2007-2012	All ages	*Shigella*	Daily mean temperature	Daily *Shigella* cases	Time series, Generalised additive model, Quasi-Poisson regression	For each 1°C increase, bacillary dysentery increased by 1·06%, [95% CI: 0·63–1·49 on lag day three].
Phung et al. 2015 (166)	Mekong delta, Vietnam	2004-2011	All ages	All cause	Weekly average temperature	Weekly diarrhoea count	Time series, Generalised linear model, Poisson regression	A 1°C increase in temperature at lag of two and four weeks was associated with a 1·5% (95% CI 0·3−2·7) and 1·1% (95% CI 0·1−2·3) increase in diarrheal risk, respectively.
Phung et al. 2015 (167)	Mekong delta, Vietnam	2004-2011	All ages	All cause	Weekly average temperature	Weekly diarrhoea count	Time series, Generalised linear model, Poisson regression	A 1°C increase in average temperature four weeks prior significantly increased the weekly number of diarrhoea visits by 1 % (95% CI = 0.9–2.6, $p < 0.01$).
Akil et al. 2014 (168)	USA (Mississippi, Alabama, Tennessee)	2022-2011	All ages	*Salmonella*	Monthly mean temperature	Monthly count of *Salmonella*	Time series analysis, including the Mann–Kendall test and a Seasonal trend test	A 1°F increase in temperature will result in 3% increase of the current average of *Salmonella* infections in Mississippi.
Li et al. 2013 (169)	Wuhan, China	2006-2011	All ages	*Shigella*	Daily mean temperature	Daily counts of *Shigella*	Time series, Generalised additive model, Poisson regression	For each 1°C increase in average temperature, excess risk of dysentery incidence increased by 0.94% (CI: 0.46%-1.43% at lag 2).
Wu et al. 2014 (170)	Matlab, Bangladesh	2000-2006	Less than five years	All cause	Monthly average extreme temperature	Monthly counts of diarrhoea	Multivariate logistic regression	The number of hot days (NHD15) have positive effects on the risk of diarrhoea, OR 1.018 (95% CI: 1.011–1.025, p<0.001).

					(above 90th percentile of observed temperature over 30 years).			
Moors et al. 2013 (83)	North India		All ages	All cause	Projected change in average temperature	Projected increase in diarrhoea burden	Multiplication of coefficients with future change in climatic variables	On average, a 1.8°C increase future temperature in the Ganges basin is expected to increase the burden of diarrhoea in north India by 10% by the 2040s.
Grjibovski et al. 2013 (171)	Kazakhstan (Astana, Almaty, North and South Kazakhstan)	2000-2010	All ages	*Salmonella*	Mean monthly temperature	Monthly counts of laboratory confirmed *Salmonella*		In Astana an increase of 1°C in temperature was associated with an increase in the monthly number of cases by 5·5% (95% CI 2·2–8·8). Similar results were obtained for other regions.
Alexander et al. 2013 (118)	Botswana	1974-2003	All ages	All cause	Monthly minimum temperature	Monthly diarrhoea cases reported to government health facilities	Autoregressive analysis of covariance models	Temperature positively associated with diarrhoea in dry seasons and negatively associated in wet seasons.
Ali et al. 2013 (119)	Matlab, Bangladesh	1998-2001	All ages	*Vibrio cholerae*	Monthly minimum temperature	Monthly cholera incidence	Seasonal Autoregressive Moving Average Model	For each 1°C increase in minimum temperature, monthly cholera incidence increased by 6%.
Zhou et al. 2013 (172)	Shanghai, China	2008-2010	All ages	All cause	Daily mean temperature	Daily counts of infectious diarrhoea	Time series, Generalised additive model, Poisson regression	A 1°C increase in the six day moving average of temperature was associated with a 2.68% (95% CI: 1.83%, 3.52%) increase in outpatient visits for diarrhoea.

Xu et al. 2013 (120)	Brisbane, Australia	2003-2009	Less than five years	All cause	Daily diurnal temperature	Daily visit to emergency department for diarrhoea complaints	Time series, Poisson generalised linear equation fitted with distributed lag nonlinear models.	For each 1°C increment in diurnal temperature, emergency hospital visit for diarrhoea-related complaints increased by 3% (95% CI: 2%-5%).
Zhang et al. 2013 (173)	China (Jinan and Baoan)	2000 chosen as baseline	All ages	*Shigella*	Projected change in average temperature	Projected year lost due to disability		The YLDs for bacillary dysentery may increase by up to 75%- 80% by 2020 and 147%- 174% by 2050.
Bhandari et al. 2012 (13)	Jhapa, Nepal	1999-2008	All ages	All cause	Monthly average maximum and minimum temperature	Monthly diarrhoea cases reported to government health facilities	Correlation	No significant association between diarrhoea and temperature.
Bandyopadhya y et al. 2012 (132)	14 African countries (sub-Sahara)	1991-200	Less than three years	All cause	Monthly maximum and minimum temperature	Self-reported diarrhoea from DHS	Ordinary Least Square method	Diarrhoea cases were positively associated with monthly average maximum temperature and negatively associated with monthly average minimum temperature in dry seasons.
Traeup et al. 2011 (122)	Tanzania	1998-2004	All ages	*Vibrio cholerae*	Monthly maximum temperature	Monthly reported cholera cases	Time series, Negative binomial regression	For each 1°C increase in monthly average of maximum temperature, relative risk cholera cases increased by 29%.
Reyburn et al. 2011 (174)	Zanzibar, Tanzania	2002-2008	All ages	*Vibrio cholerae*	Monthly mean temperature	Monthly count of clinically diagnosed cholera cases	Time series, Seasonal Autoregressiv e Moving Average Model	A 1°C increase in temperature at four months lag resulted in a 2-fold increase of cholera cases.

Kolstad and Johansson 2011 (125)	Global	Projection 2010-2099	All ages	All cause	Projected change in average temperature	Projected increase in diarrhoea burden	linear multiplication	The associated mean projected increases of relative risk of diarrhoea in the six study regions were 8–11% (with SDs of 3–5%) by 2010–2039 and 22–29% (SDs of 9–12%) by 2070–2099.
Allard et al. 2011 (175)	Montreal, Canada	1990-2006	All ages	*Campylobacter*	Monthly average temperature	Monthly count of *Campylobacter* cases	Time series, negative binomial regression models	A 1°C increase in temperature above 10°C during any of weeks −1 to −6 was associated with a 0.8% (95% CI: 0.3% to 1.3%) increase in the current count
Onozuka et al. 2010 (176)	Fukuoka, Japan	1999-2007	All ages	All cause	Weekly average temperature	Weekly cases of gastroenteritis	Generalised linear Poisson regression models.	For each 1°C increase in mean temperature, weekly cases of acute gastroenteritis increased by 7.7%.
Britton et al. 2010 (177)	New Zealand	1965-2006	All ages	*Salmonella*	Monthly average temperature	Monthly count of *Salmonella*	Negative binomial regression models	A 1°C increase in monthly average ambient temperature was associated with a 15% increase in salmonellosis notifications within the same month (IRR 1.15; 95% CI 1.07 – 1.24).
Chou et al. 2010 (115)	Taiwan	1996-2007	All ages	All cause	Monthly maximum temperature	Monthly incidence of hospitalised diarrhoea		Monthly temperature was positive associated with hospitalisation due to diarrhoea (IRR: 1.01, 95% CI: 1.00-1.03).
Hashizume et al. 2010 (178)	Dhaka, Bangladesh	1983-2008	All ages	*Vibrio cholerae*	Weekly average temperature	Weekly cholera counts	Time series, Poisson regression models	57% (52.4%- 60.8%) of the cholera cases detected during the study period were attributed to temperature with lag week between 0-4.
Zhang et al. 2010 (179)	Brisbane, Australia	1990-2005	All ages	*Salmonella*	Weekly maximum and minimum temperature	Weekly count of *Salmonella* cases	Time series, Seasonal Autoregressive Moving	Maximum and minimum temperature were both associated with salmonella incidence.

							Average Model	
Patz et al. 2009 (180)	South-East Africa	1971-2006	All ages	*Vibrio cholerae*	Annual mean temperature (Sea surface and air)	Annual count of Cholera	Time series, Poisson regression	For an annual mean temperature increases by 0.1°C, the expected annual number of cholera cases will be multiplied by 1.87 for that year and by 2.78 for the previous year.
Islam et al. 2009 (181)	Matlab, Bangladesh	1989-2005	All ages	*Vibrio cholerae*	Monthly average temperature	Monthly cholera counts	Classification and regression tree, Principal component analysis	Monthly mean temperature positively associated with monthly cholera count.
Lake et al. 2009 (182)	England and Wales	1974-2006	All ages	*Salmonella* and *Campylobacter*	Weekly average temperature	Weekly count of foodborne pathogens (*Salmonella* and *Shigella*)	Least squared regression	Food poisoning, campylobacteriosis, salmonellosis, *Salmonella typhimuriu m* infections and *Salmonella Enteritidis* infections were positively associated (P<0·01) with temperature in the current and previous week.
Bi et al. 2008 (126)	Australia (Brisbane and Adelaide)	1990-2005	All ages	*Campylobacter*	Weekly maximum temperature (average)	Weekly count of laboratory confirmed *Campylobacter* cases	Ecological time series, Poisson regression models	Weekly maximum and minimum temperatures were inversely associated with the weekly number of cases in Adelaide, but positively correlated with the number of cases in Brisbane, with relevant lagged effects.
Fernandez et al. 2008 (183)	Lusaka, Zambia	2003-2006	All ages	*Vibrio cholerae*	Weekly average maximum temperature	Weekly count of Cholera cases	Generalised linear model, Poisson auto regressive model	An ambient temperature increase of 1°C six weeks before the beginning of the outbreaks explained 5.2% of the weekly augmentation of cholera cases observed.
Zhang et al. 2008 (184)	Jinan, China	1987-2000	All ages	*Shigella*	Monthly average	Monthly cases of bacillary dysentery	Seasonal Autoregressiv e Moving	For each 1°C increase in maximum temperature, bacillary dysentery cases increased by 11%.

					maximum temperature		Average Model	
Hashizume et al. 2007 (37)	Dhaka, Bangladesh	1996-2002	All ages	All cause	Weekly average temperature	Weekly count of non-cholera diarrhoea	Time series, Poisson regression	An average 1°C increase in temperature over the past 4 weeks was associated with 6.5% (95% CI: 3.5–9.5) increase in non-cholera and non-rotavirus diarrhoea.
Naumova et al. 2007 (185)	Massachusetts, USA	1992-2001	All ages	*Salmonella, Shigella, Campylobacter, Cryptosporidium* and Giardia	Daily average temperature	Daily reported cases of six enteric pathogens	Generalised linear models	Bacterial diarrhoea peaked with temperature whereas parasitic peaked in fall.
Zhang et al. 2007 (186)	Adelaide, Australia	1990-2004	All ages	*Salmonella*	Weekly average maximum temperature	Weekly counts of *Salmonella*	Poisson regression, autoregressive adjusted Poisson regression, multiple linear regression and the SARIMA model	Maximum temperature with two week lags was significantly related to the number of salmonellosis cases.
Kovats et al. 2005 (187)	Six European countries	1989-2002	All ages	*Campylobacter*	Weekly average temperature	Week with maximum number of *Campylobacter* cases	Time series, Poisson regression	Timing of annual peak was not associated with temperature at lag 0-4 weeks.
Lama et al. 2004 (112)	Lima, Peru	1991-1998	Less than 13 years	All cause	Monthly average temperature	Monthly number of patients visiting emergency department for	Multiple regression models	For each 1°C increase in monthly average temperature, acute diarrheal cases increased by 11.3%, in the months where cholera outbreaks didn't occur.

						diarrhoea complaints		
Kovats et al. 2004 (87)	10 European countries	1983-2003	All ages	*Salmonella*	Weekly average temperature	Weekly Salmonella count	Time series, Poisson regression	A 1°C increase in temperature above the threshold of 6°C, cases of *Salmonella* increased between 0.3% - 12.5%.
D'Souza et al. 2004 (131)	Five Australian cities	1991-2001	All ages	*Salmonella*	Monthly average temperature	Monthly count of *Salmonella*	Time series, negative binomial regression models	Significant association between monthly Salmonella incidence (IRR between 1.04 - 1.10) and monthly mean temperature lagged by one month.
Singh et al. 2001 (113)	Fiji	1978-1998	Infants	All cause	Monthly average temperature	Monthly count of infantile diarrhoea	Time series, Poisson regression models	Positive association between diarrhoea and temperature with one month lag.
Checkley et al. 2000 (111)	Lima, Peru	1993-1998	Less than 10 years	All cause	Daily average temperature	Daily admission for diarrhoea	Time series, Generalised additive model with Poisson distribution	For each 1°C increase in mean temperature in pre-El Niño era, the risk of diarrhoea hospitalisation increased by 1.08.

2.2.2 Rainfall and diarrhoea

Twenty-nine epidemiological studies report on the association between rainfall and diarrhoea (summarised in Table 2.2). These articles include data collected between 1977 and 2017 and cover all five inhabited continents with comparatively lesser representation from Europe, see Table 2.2. These articles predominantly evaluate the impact of rainfall on bacterial diarrhoea, excluding a systematic review on protozoan parasite *Cryptosporidium* (188) and a study on norovirus from Australia (189). To estimate the association between rainfall and diarrhoea, studies predominantly use the cumulative amount of rainfall (weekly or monthly) as exposure value, while few use extreme rainfall or number of wet days as the exposure value (155, 189-191). Despite the heterogeneity in the exposure variable, a significant positive association is reported between rainfall and diarrhoea in the majority of studies, see Table 2.2. Most of the studies [Ecuador (191, 192), Bangladesh (37) and Botswana (78)] report increased cases of diarrhoea following a heavy rainfall event after a dry period. Meanwhile, a study from Bangladesh reports a U-shaped association (increase in rainfall above and below a given value) between weekly cumulative rainfall and the number of children hospitalised for diarrhoea (37). Kraay et al. (190) systematically evaluated and meta-analysed evidence on the association rainfall and diarrhoea, and reports that impact of rainfall on diarrhoea depends on the antecedent condition i.e., a heavy rainfall following a dry period increases the risk of diarrhoea, whereas a heavy rainfall following a wet period reduces the risk of diarrhoea. Intriguingly, a study from Spain (151) reports that heavy precipitation was found to be protective against diarrhoea-related hospitalisation during the study period. Contrary to the majority of findings, a study from the Guam Island in the West-Pacific reported no significant association between rainfall and food-borne diarrhoea caused by *Salmonella* species (193). Rainfall affects the transportation of diarrheal pathogens and so heavy rainfall can disrupt the sanitation infrastructure, increasing the risk of human exposure. Confirming the theoretical assumptions, a review of this evidence suggests that the impact of rainfall on diarrhoea outbreak is contextual and depends upon the definition of exposure value (whether the rainfall data included in the models were collected following a wet period or a dry run).

2.2.2.1 Nature of association between rainfall and diarrhoea

Almost 72% of the reviewed studies report a linear association between rainfall intensity and the risk of diarrhoea, see Table 2.2. Nearly 50% of these studies identified a rainfall threshold beyond which the risk of diarrhoea is higher compared to the rainfall intensity below the identified threshold (165, 183, 192, 194-196). Only a handful of studies report a non-linear association between rainfall and diarrhoea, with a non-identical nature of the rainfall-diarrhoea curve (37, 192). One exception is a study from Bangladesh (37) that reports clear U-shaped association. This contrasts with most of the studies that report a non-linear association between rainfall and diarrhoea and that report an inverted quadratic relationship between rainfall and diarrhoea i.e., the risk of diarrhoea increases with increase in rainfall up to certain quantity and then starts to decrease as the rainfall intensity grows heavier (190, 192, 197). As such, the nature of association between rainfall and diarrhoea remains non-uniform, warranting more studies from different geographic regions of the world to reach a conclusive agreement.

2.2.2.2 Lag effect of rainfall on diarrhoea

Almost all the articles reviewed report a lag effect of rainfall on diarrhoea, which varies from weekly to monthly based upon the periodic resolution of the data used. Reyburn et al. (174), report the highest risk of cholera in Zanzibar, Tanzania following two months of heavy rainfall (200mm). Drayana et al. (198) on the other hand, report increased risk of acute gastroenteritis in Wisconsin, USA following a shorter lag of four days post rainfall. Meanwhile, a study from Singapore reports increased risk of Salmonellosis two weeks after the rainfall event and decreased risk following the fifth week post rainfall (154). It is likely that the lag effect of rainfall on diarrhoea depends on the nature of flooring materials used in the household of the study region and the drainage systems to manage runoff water following the rainfall events (199).

Table 2. 2 Epidemiological review of studies that explored the association between diarrhoea and rainfall.

Reference	Location	Period	Age group	Pathogen	Exposure definition	Outcome definition	Statistical method	Result and conclusion
Kraaay et al. 2020 (190)	Global	2013-2020	All ages	All cause	Heavy rainfall or flooding or rain and drought	All cause diarrhoea or gastroenteritis	Meta regression models	Extreme rainfall was associated with an increased risk of diarrhoea [IRR: 1.26 (1.05-1.15)] when it followed a dry period.
Deshpande et al 2020 (194)	Esmeraldas Province, Ecuador	2013-2014	All ages	All cause	Heavy rainfall if the value exceeded 90th percentile of daily rainfall across study period	Daily count of diarrheal diseases	Mixed effect-Poisson log linear models	HREs with dry antecedent conditions were associated with elevated incidence by up to 1.35 (IRR, 95% CI: 1.14–1.60) times compared with similar conditions without HREs
Alemayehu et al. 2020 (133)	Southwestern Ethiopia	2007-2017	Less than five years	All cause	Monthly average of mean temperature and total rainfall	Monthly count of diarrhoea cases extracted from HMIS	Time series, Negative binomial regression	Rainfall was found to be a significant risk factor of childhood diarrhoea, with 0.16% (RR: 1.00167; 95% CI: 1.001306–1.001928) per 1mm increase in rainfall.
Lee et al. 2019 (200)	Georgia, USA	1997-2016	All ages	*Salmonella*	Weekly rainfall condition	Weekly *Salmonella* counts	Time series, Negative binomial regression	Extreme rainfall was associated with a 5% increase in salmonellosis risk (95% CI: 1%, 10%) compared with weeks with no extreme rainfall.
Lal et al. 2019 (188)	Global	1960-2014	Less than 15 years	*Cryptosporidium*	Monthly average precipitation	Monthly count of laboratory confirmed *Cryptosporidium* infection	Mixed effect-Spatial temporal models	Local rainfall and population density were related with cryptosporidiosis with differential impacts across the latitudes.
Alexander et al. 2018 (78)	Chobe, Botswana	1998-2017	Less than five years	All cause	Weekly maximum and minimum temperature,	Weekly counts of diarrhoea cases	negative binomial	Differential impacts of predictors were observed on diarrhoea incidence during dry and wet

					rainfall and river height		regression models	seasons. In the wet season, rainfall (eight week lag) had a significant influence on under five diarrhoea, with a 10-mm increase in rainfall associated with an estimated 6.5% rise in the number of cases.
Puigmal et al. 2018 (151)	Spain	1997-2013	All ages	All cause	Daily rainfall	Daily count of hospitalisation for acute gastroenteritis	Time series regression fitted with distributed lag nonlinear models	Heavy precipitation was found protective for those hospitalisations (RR = 0.74, 95% CI: 0.63, 0.86).
Wang et al. 2018 (153)	Hong Kong	2002-2011	All ages	*Salmonella*	Daily rainfall	Daily count of non-typhoidal *Salmonella* cases	Generalised additive models fitted with distributed lag nonlinear models	More hospitalisations were observed for small amounts of rainfall relative to none, with 0.02mm and 0.14mm associated with 1.30 (95% CI 1.01–1.67) and 1.34 (95% CI 0.98–1.84) times the risk of hospitalisations, respectively. However, hospitalisations declined with heavier rainfall.
Aik et al. 2018(154)	Singapore	2005-2015	All ages	*Salmonella*	Weekly cumulative rainfall	Weekly count of laboratory confirmed *Salmonella* cases	Time series, negative binomial regression models	A 10mm increase in weekly cumulative rainfall was associated with a 0.8% increase (IRR: 1.008, 95% CI = 1.002, 1.015) in cases two weeks later but a 0.9% decrease (IRR: 0.991, 95% CI = 0.984, 0.998) in cases five weeks later.
Horn et al. 2018(155)	Mozambique	1997-2014	All ages	All cause	Number of wet days per week (rainfall > 1mm)	Weekly diarrhoea count	Time series, generalised linear models	A 1.04% (95% CI: 0.42, 1.66) increase in diarrheal disease counts was estimated for each additional wet day considered over

								a consecutive four week period, controlling for time, average high temperature.
Azage et al. 2017 (156)	Northwest Ethiopia	2013-2015	Less than five years	All cause	Monthly mean rainfall	Monthly count of diarrhoea reported to HMIS	Correlation, negative binomial regression	There was a significant association between monthly average rainfall (IRR = 1.0004; 95% CI 1.0001, 1.0007) and the rate of childhood diarrhoea.
Thiam et al. 2017 (157)	Mbour, Senegal	2011-2014	Less than five years	All cause	Monthly average rainfall	Monthly count of diarrhoea	Time series, negative binomial regression models	Moderate and high rainfall showed a significant positive association with diarrheal incidence in the same month (IRR: 1.23, 95% CI: 1.08–1.42; IRR: 1.34, 95% CI: 1.16–1.56, respectively).
Wangdi et al. 2017 (159)	Bhutan	2003-2013	All ages	All cause	Monthly average rainfall	Monthly average diarrhoea cases	Time series, Poisson regression models	Diarrhoea incidence increased by 5% (95 Cr I: 4.9–5.1%) for a 1mm increase in rainfall.
Mukabutera et al. 2016 (199)	Rwanda	2009-2011	Less than five years	All cause	Total monthly rainfall, monthly rainfall intensity, runoff water and anomalous rainfall	Monthly count of diarrhoea	Multivariate logistic regression models	Higher levels of runoff were protective against diarrhoea compared to low levels among children who lived in households with unimproved toilet facilities (OR = 0.54, 95% CI: [0.34, 0.87] for moderate runoff and OR = 0.50, 95% CI: [0.29, 0.86] for high runoff) but had no impact among children in household with improved toilets.
Soneja et al. 2016 (195)	Maryland, USA	2002-2012	All ages	*Campylobacter*	Extreme precipitation (above 90th percentile of daily precipitation	Monthly count of *Campylobacter* cases	Multivariate negative binomial regression	A one day increase in exposure to extreme precipitation events was associated with a 3% increase in risk of campylobacteriosis in coastal areas of Maryland (IRR:

					between years 1960 and 1989), El Niño and La Niña			1.03, 95% CI: 1.01, 1.05), but such an association was not observed in noncoastal areas. The risk associated with extreme precipitation events was considerably higher during La Niña periods (IRR: 1.09, 95% CI: 1.05, 1.13), while there was no evidence of elevated risk during El Niño or ENSO Neutral periods.
Stephen et al. 2016 (163)	Queensland, Australia	2004-2013	All ages	*Salmonella*	Daily precipitation	Daily count of Salmonellosis	Poisson regression models with distributed lag nonlinear models, Switching models	A 10 mm precipitation were associated with increases in salmonellosis cases of 24.1% (95% CrI 17.0%, 31.6%).
Jinag et al. 2015 (165)	Maryland, USA	2002-2012	All ages	*Salmonella*	Extreme precipitation (above 90th percentile of historical daily rainfall data)	Culture confirmed *Salmonella*	Negative binomial generalised estimating equations	A 5.6% increase in salmonellosis risk (IRR: 1.056; CI: 1.035–1.078) associated with a one unit increase in extreme precipitation events.
Carlton et al. 2014(192)	Ecuador	2004-2007	All ages	All cause	Heavy rainfall event (above 90th percentile (56mm) in a given seven days /one week period).	Weekly diarrhoea count	Random effect Poisson regression models	Heavy rainfall events were associated with increased diarrhoea incidence following dry periods (IRR = 1.39, 95% CI: 1.03, 1.87) and decreased diarrhoea incidence following wet periods (IRR = 0.74, 95% CI: 0.59, 0.92).
Li et al. 2013(169)	Wuhan, China	2006-2011	All ages	*Shigella*	Daily rainfall	Daily counts of *Shigella*	Time series, generalised	For each 1mm increase in rainfall excess risk of dysentery decreased

							additive model, Poisson regression	by −0.23% (95% CI: −0.37% to −0.09%).
Wu et al. 2014 (170)	Matlab, Bangladesh	2000-2006	Less than five years	All cause	Monthly average extreme rainfall (above 90th percentile of observed rainfall over 11 year period).	Monthly counts of diarrhoea	Multivariate logistic regression	The number of heavy rain days (NHR15) have positive effects on the risk of diarrhoea, OR 1.031 (95% CI: 1.019–1.044, ($p<0.001$).
Eisenberg et al. 2013 (191)	Haiti	2010-2011	All ages	*Vibrio cholera*	Daily rainfall	Daily cholera counts	Case cross over, distributed lag nonlinear models	Increased rainfall was significantly correlated with increased cholera incidence 4–7 days later. The odds ratio (OR, ratio of odds of cholera with exposure to a particular level of rainfall at a given lag vs. without exposure) for cholera 4–7 days after rainfall was 1.46 (95% CI: 1.32, 1.61).
Grjibovski et al. 2013 (201)	Kazakhstan (Astana, Almaty, North and South Kazakhstan)	2000-2010	All ages	*Salmonella*	Monthly cumulative rainfall	Monthly counts of laboratory confirmed *Salmonella*		In Astana, an increase in precipitation by 1 mm was associated with a 0·5% (95% CI 0·1–1·0) increase in salmonellosis with a lag of two months. Similar results were obtained for other regions.
Reyburn et al. 2011 (174)	Zanzibar, Tanzania	2002-2008	All ages	*Vibrio cholera*	Monthly average rainfall	Monthly count of clinically diagnosed cholera cases	Time series, Seasonal Autoregressive Moving Average Model	An increase of 200mm of rainfall at two months lag resulted in a 1.6-fold increase of cholera cases.
Bruggink et al. 2010(189)	Victoria, Australia	2002-2007	All ages	Norovirus	Monthly rainfall	Monthly count of norovirus cases	Time series, correlation	There was a statistically significant ($p < 0.05$) correlation between monthly NAGO

								incidence and average monthly rainfall.
Dryana et al. 2010 (198)	Wisconsin, USA	2002-2007	Less than 18 years	All cause	Daily rainfall	Daily emergency visit for AGI	Autoregressive moving average model	Any rainfall four days prior was significantly associated with an 11% increase in AGI visits
Fernandez et al. 2008 (183)	Lusaka, Zambia	2003-2006	All ages	*Vibrio cholera*	Weekly average rainfall	Weekly count of *cholera* cases	Generalised linear model, Poisson auto regressive model	An increase of 50mm in rainfall three weeks earlier explained 2.5%, increase in cholera cases during the study period.
Hashizume et al. 2008 (202)	Dhaka, Bangladesh	1996-2002	All ages	*Vibrio cholera*	Weekly rainfall	Weekly *cholera* count	Time series, Poisson regression models	The weekly number of cholera cases increased by 14% (95% CI = 10.1% - 18.9%) for each 10mm increase above the threshold of 45mm for the average rainfall, over lags 0−8 weeks.
Hashizume et al. 2007 (37)	Dhaka, Bangladesh	1996-2002	All ages	All cause	Weekly rainfall	Weekly count of non-cholera diarrhoea	Time series, Poisson regression	A u-shaped association was observed between weekly diarrhoea count and weekly rainfall with weekly count of diarrhoea cases increasing below and above the threshold of 52mm for every 10mm change.
Haddock et al. 1986 (193)	Guam, Western Pacific	1977-1984	All ages	*Salmonella*	Monthly rainfall	Monthly *Salmonella* counts	Linear regression	No significant association was observed between *Salmonella* and rainfall.

2.2.3 Humidity and diarrhoea

The impact of humidity on diarrhoea is the least studied relationship among the meteorological variables. As shown in Table 2.3, eight studies report the effect of humidity on diarrhoea burden (101, 115, 129, 153, 154, 156, 169, 203). Except for a study from Ethiopia (156), all other studies were conducted in Asia and evaluated the impact of humidity on bacterial and all cause diarrhoea. It is argued that effect of humidity on diarrhoea cannot be studied independently of temperature or rainfall (83, 111, 115). In line with this argument, the reviewed articles report inconsistent findings on the impact of humidity (101, 115). Three studies from Southeast Asia [Singapore (101), Hong Kong (153) and Beijing (129)] report a positive association between relative humidity and diarrhoea, while a study from Africa (156) and two studies from Asia [Singapore (154) and China (169)] report a negative association between humidity and diarrhoea. Meanwhile, the remaining two studies from Asia do not report the direction of the association (115, 203). There are three different hypotheses behind this inconsistency in the findings:

I. The differences in the definition of exposure variables used across these studies.
II. The differences in the outcome variables included in the study.
III. The differences in geographic locations and socioeconomic contexts of the studies.

Two studies conducted in China used the same outcome definition (*Shigella*) but have used a different exposure definition, i.e., the study reporting an increment in diarrhoea with the increment in relative humidity used a threshold value (>40%), whereas, the one reporting a negative association does not mention any threshold value for relative humidity (129, 169). Meanwhile, the other articles reporting negative association with humidity included all forms of diarrhoea including viral diarrhoea and were conducted in Africa (156). Viral diarrhoea is reported to show a negative association with humidity (204).

Table 2. 3 Epidemiological review of studies that explored the association between diarrhoea and humidity.

Reference	Location	Period	Age group	Pathogen	Exposure definition	Outcome definition	Statistical method	Result and conclusion
Aik et al. 2020 (101)	Singapore	2005-2018	All ages	All cause	Weekly average humidity	Weekly surveillance diarrhoea cases reported to Ministry of Health	Negative binomial regression models	Diarrhoea incidence increased by 3% for every 10% increment in relative humidity with a lag effect of one week.
Wang et al. 2018 (153)	Hong Kong	2002-2011	All ages	*Salmonella*	Daily mean relative humidity	Daily count of non-typhoidal *Salmonella* cases	Generalised additive models fitted with distributed lag nonlinear models	Relative to 60%, 85% (75th percentile) RH was associated with 1.45 (95% CI 1.13–1.87) times the risk of hospitalisations for a duration of 17 days.
Aik et al. 2018 (154)	Singapore	2005-2015	All ages	*Salmonella*	Weekly mean relative humidity	Weekly count of laboratory confirmed *Salmonella* cases	Time series, negative binomial regression models	A 1% increase in the mean relative humidity was associated with a 1.3% decrease (IRR: 0.987, 95% CI = 0.981, 0.994) in cases six weeks later.
Azage et al. 2017 (156)	Northwest Ethiopia	2013-2015	Less than five years	All cause	Monthly mean relative humidity	Monthly count of diarrhoea reported to HMIS	Correlation, negative binomial regression	There was a significant inverse relationship between relative humidity and rate of childhood diarrhoea (IRR = 0. 3915; 95% CI 0.2721–0.5631).
Li et al. 2015 (129)	Beijing, China	2007-2012	All ages	*Shigella*	Daily mean relative humidity	Daily *Shigella* cases	Time series, generalised additive model, Quasi-Poisson regression	For relative humidity >40%, 1% increase in RH resulted in 0·18% [95% CI 0·12–0·24 at lag day 4] excess risk of bacillary dysentery.
Li et al. 2013 (169)	Wuhan, China	2006-2011	All ages	*Shigella*	Daily mean relative humidity	Daily counts of *Shigella*	Time series, generalised	For each 1% increase in relative humidity, excess risk of

							additive model, Poisson regression	bacillary dysentery decreased by −0.21% (95% CI: −0.34% to −0.08%).
Rajendran et al. 2011 (203)	West Bengal, India	1996-2008	All ages	*Vibrio cholera*	Monthly mean relative humidity	Monthly count of cholera	Time series, Seasonal Autoregressive Moving Average Model.	Monthly average RH was consistently linear related to V. cholera infection during monsoon season.
Chou et al. 2010 (115)	Taiwan	1996-2007	All ages	All cause	Monthly average relative humidity	Monthly incidence of hospitalised diarrhoea		Humidity significantly contributed to diarrhoea morbidity in adults.

2.2.4 Extreme weather and diarrhoea

Twenty-nine studies (shown in Table 2.4) report the impacts of extreme weather on diarrhoea. The articles analysing short-term or long-term impacts of extreme weather on diarrhoea were included in the review, while and those analysing outbreaks or case studies were excluded. These articles analysed data from 1893 to 2017 and investigated the impacts on diarrhoea from various extreme weather events including floods, droughts, El Niño Southern Oscillation, hurricanes, typhoons, tropical cyclones, heat-waves and Indian Ocean dipole (109, 111, 205-207). These articles report the effects of extreme weather events on infectious diarrhoea (208, 209), all cause diarrhoea (210, 211), *Shigella* (212-214), *Vibrio cholerae* (196, 206, 215), *Escherichia coli* (205), *Campylobacter* (205), *Salmonella* (205), *Cryptosporidium* (205) and *Giardia (205)*.

Despite the use of heterogeneous exposure definitions, almost all the studies report an increased risk of diarrhoea following an extreme weather event (207, 215, 216). The effects of extreme weather events on diarrhoea incidence are reported to be acute and linear. Nearly 60% of the articles reviewed reported the differential impacts of floods on diarrhoea (see Table 2.4). Compared to non-flooded days, the odds of diarrhoea during flooded days is reported to be about 6.75 in the study from Anhui, China (217). Depending upon the periodic resolution of the data analysed, a significant lag effect of flood on diarrhoea is reported after two days to three weeks following the flooding event (210, 218). The only study that estimated the impact of drought on diarrhoea reported an increased risk (RR: 4.3, CI: 2.9 – 7.2) of cholera burden during the drought periods compared to drought-free periods (207). Similarly, the only study to analyse the effect of heat waves on Salmonellosis reported 34% increase in daily Salmonellosis cases compared to non-heat wave days (109). A study from South Korea reported a 3.1-fold increase in bacillary dysentery cases following hydro-meteorological disasters (typhoons) compared to pre-typhoon periods (213).

Almost 24% of the studies estimate the association between the periodic oceanic climate pattern (El Niño Southern Oscillation (111, 205, 216), Indian Ocean Dipole (206) and Northern Atlantic Oscillation(219)) and diarrhoea across Asia and America. The increased risk of diarrhoea incidence is reported to be between 2.6% to 200% during the immediate periods (days or weeks) following ENSO and Indian Ocean Dipole, compared to the periods without ENSO or Indian Ocean Dipole in Matlab, Bangladesh and Lima, Peru, respectively (111, 206). Rodo et al.(220), in one of the pioneering studies investigating the impacts of climate change on diarrhoea, analysed a cholera dataset spanning more than six decades. The study reports that cholera incidence in Bangladesh, Dhaka in the earlier half of the century (1893-1940), is uncorrelated or weakly associated with ENSO, whereas the incidence of cholera towards the end of the century (1980-2001), is strongly and consistently related to ENSO (220). Hulland et al. (215), utilised interrupted time series study design to estimate the impacts of hurricanes on cholera incidence in Haiti between the periods 2013 to 2016 and reported an immediate surge (statistically significant) in cholera cases following Hurricane Matthews and a gradual decline in cases 46 days after the storm.

Section 2.2 has provided a background underpinning the second analytical study of this thesis. As the strength of association between diarrhoea and climate change is found to vary among different climatic zones and aetiological agents, it is important to estimate the relation from previously unexplored regions to improve our understanding of the link between diarrhoea and climate change. Given the dearth of literature on the future burden of climate attributable diarrhoea, especially from endemic countries, the review implies that future research on climate change and diarrhoea from low-and middle-income countries should calculate the climate attributable fraction of diarrheal diseases as well as projected future burden of diarrhoea under different climate change scenarios.

Table 2. 4 Epidemiological review of studies that investigated the impacts of extreme weather on diarrhoea.

Reference	Location	Period	Age group	Pathogen	Exposure definition	Outcome definition	Statistical method	Result and conclusion
Colston et al. 2020 (205)	Loreto province, Peru	2011-2012	Less than two years	*Campylobacter*, *E. coli* (EAEC), *E. coli* (EPEC), *E. coli* (LT/ST-ETEC), *Salmonella*, *E. coli* (EIEC), *Cryptosporidium* and *Giardia*	Flood (El Niño period vs. non- El Niño)	Laboratory confirmed cases of diarrhoea caused by one of the enteric pathogens)	Interrupted time series, Poisson regression model	Risk of diarrhoea incidence caused by specific pathogen varied during early and late flood periods.
Heaney et al. 2019 (216)	Chobe district, Botswana	2007-2017	Less than five years	All cause	El Niño-Southern Oscillation	Monthly count of diarrhoea	Time series, negative binomial regression models	At a five month lag, a 1K increase in El Niño 3.4 was associated with a 30.5% (95% CI: 3.8%, 49.8%) decrease in total December, January and February under-five diarrhoea cases.
Zhang et al. 2019 (208)	Anhui, China	2013-2017	All ages	All cause	Flood	Weekly count of infectious diarrhoea	Interrupted time series, Poisson regression model	A significant increase in infectious diarrhoea risk (RR = 1.11, 95% CI: 1.01, 1.23) after the flood event was found in flooded area, while there was no increase in non-flooded areas.
Gong et al. 2019 (209)	Anhui, China	2013-2017	All ages	All cause	Flood	Daily count of diarrhoea cases reported to NDSS, China	Quasi Poisson generalised linear models	The impact of flood on diarrhoea risk was differential based on the different magnitudes of flood (moderate floods had a RR of 1.05 (95% CI: 1.02–1.09) and severe floods RR = 1.04 (95% CI: 1.01–1.08) controlling for population size, temperature and relative humidity).

Hulland et al. 2019 (215)	Haiti	2013-2016	All ages	Cholera	Hurricane	Daily reported cholera cases	Interrupted time series, Poisson regression model	A significant increase in reported cholera cases after Hurricane Matthew, suggesting that the storm resulted in an immediate surge in suspect cases, and a decline in reported cholera cases in the 46 day post-storm period, after controlling for rainfall and seasonality.
Longar-Henderson et al. 2019 (219)	United States	1997-2014	All ages	Non-cholera *Vibrio*	El Niño-Southern Oscillation and Northern Atlantic Oscillation	Monthly counts of non-cholera Vibrio	Negative binomial regression models	The overall effect of combined ENSO coefficients significantly increased vibriosis risk (combined IRR 1.145, 95% CI 1.064–1.231, P < 0.001). The overall effect of NAO was non-significant (IRR 1.064, 95% CI 0.983–1.151, P = 0.12).
Liu et al. 2019 (210)	Guangxi, China	2006-2010	All ages	All cause	Flood	Daily counts of laboratory confirmed diarrhoea cases	Log linear mixed effect regression models	Flood caused a significant risk of diarrhoea after controlling for all confounders with the highest effect seen at lag of two days (RR: 1.24, CI: 1.11- 1.40).
Wu et al. 2018 (196)	Matlab, Bangladesh	1983-2009	All ages	Cholera	Heat-wave (two or more consecutive days with mean temperature above the 95th percentile of temperature recorded over past 30 years)	Daily cholera count	Case-cross over design, conditional logistic regression	The effect of heat-wave on cholera was differential for dry and wet period (rainfall>0 mm) with wet period showing a significant positive association between the risk of cholera and heat-wave after a two day lag (OR=l .53, 95% CI: 1.07 – 2.19).

Hu et al. 2018 (212)	Zhengzhou, China	2005-2009	All ages	*Shigella*	Flood	Monthly count of *Shigella*	Time series, Poisson regression models	Floods were significantly associated with an increased risk of bacillary dysentery in Zhengzhou with a RR of 2.80 (95% CI: 2.56–3.10) for the whole population.
Saulnier et al. 2018 (211)	Cambodia	2008-2013	All ages	All cause	Flood	Monthly diarrheal count	Time series, Poisson regression models	Moderate increases in the incidence rate of diarrhoea of between 5% (95% CI: 1.00, 1.09) and 17% (95% CI: 1.05, 1.29) in four districts was reported for every $10km^2$ increase in flood water.
Rieckmann et al. 2018 (207)	Sub-Sahara Africa	1990-2010	All ages	*Vibrio cholerae*	Flood and drought	Monthly cholera cases	Self-controlled case series design, conditional logistic regression	An increased incidence rate of cholera outbreaks was estimated during drought periods (IRR= 4.3, 95% CI = 2.9–7.2) and during flood periods (IRR = 144, 95% CI = 101–208) when compared with drought/flood-free periods.
Liu et al. 2018 (221)	Hunan, China	2004-2011	All ages	All cause	Flood	Weekly count of infectious diarrhoea	A two-stage statistical model, Quasi-Poisson models fitted with distributed lag nonlinear models	Floods were significantly associated with infectious diarrhoea in the provincial level with a cumulative RR of 1.22 (95% CI: 1.05, 1.43) with a lagged effect of 0–1 week.
Liu et al. 2017 (222)	Guangxi, China	2004-2010	All ages	*Shigella*	Flood	Monthly count of bacillary dysentery cases	Poisson regression with generalised additive models	The relative risks (RR) of moderate and severe floods on the morbidity of bacillary dysentery were 1.17 (95% CI: 1.03–1.33) and 1.39 (95% CI: 1.14–1.70), respectively.
Liu et al. 2017 (223)	Guangxi, China	2004-2010	All ages	*Shigella*	Flood	Monthly count of bacillary dysentery cases	Mixed generalised additive models, Poisson regression models	The relative risks (RR) of moderate and severe floods on the incidence of bacillary dysentery were 1.40 (95% CI: 1.16–1.69) and 1.78 (95% CI: 1.61–1.97), respectively.

Xu et al. 2017 (224)	Dalian, China	2004-2010	All ages	*Shigella*	Flood	Weekly laboratory confirmed *Shigella*	Time series nonlinear regression, Generalised additive mixed models	The RR of flood impact on bacillary dysentery was 1.17 (95% CI: 1.03-1.33).
Na et al. 2016 (213)	South Korea	2001-2009	All ages	*Shigella*	Flood and typhoon	Weekly count of *Shigella*	Multivariate log linear model with Poisson distribution	Compared with pre-disaster incidences, the incidences shigellosis was 3.10-fold (95% CI, 1.21-7.92) higher, and the second week after the disaster.
Liu et al. 2016 (218)	Huaihua, China	2005-2011	All ages	*Shigella*	Flood	Weekly count of *Shigella*	Time series Poisson regression models fitted with distributed lag nonlinear models.	The effects of floods on bacillary dysentery continued for approximately three weeks with a cumulative risk ratio equal to 1.52 (95% CI: 1.08–2.12).
Milazzo et al. 2016 (109)	Adelaide, Australia	1990-2012	All ages	*Salmonella*	Heat-wave (three or more consecutive days where maximum temperature exceeds 35°C)	Daily laboratory confirmed *Salmonella*	Generalised estimating equation, Poisson regression models fitted with distributed lag nonlinear models	Heat-wave intensity had a significant effect on daily counts of overall salmonellosis with a 34% increase in risk of infection (IRR 1.34, 95% CI 1.01–1.78) at >41 °C.
Zhang et al. 2016 (225)	Zibo, China	2007	All ages	*Shigella*	Flood	Daily cases of bacillary dysentery	Case-cross over design, conditional logistic regression	Flood was associated with an increased risk of bacillary dysentery, with the largest OR of 1.849 (95% CI 1.229–2.780) at 2-day lag.
Ramirez et al. 2016 (226)	Piura, Peru	1991-2001	All ages	*Vibrio cholerae*	El Niño	Weekly count of cholera cases	Wavelet analysis	The effects of El Niño 3.4 SST (β = 0.674, P value = 0.000), Niño 1+2 SST (β = 0.620, P value = 0.000), and Paita SST (β = 0.673, P value = 0.000)

								on cholera were significant and positive.
Liu et al. 2015 (214)	Nanning, China	2004-2010	All ages	*Shigella* and *Entamoeba histolytica*	Flood	Monthly count of dysentery cases	Generalised additive models, Poisson regression models	The relative risk (RR) of floods on the morbidity of dysentery was 1.44 (95% CI = 1.18–1.75). The models suggest that a potential one day rise in flood duration may lead to 8% (RR = 1.08, 95% CI = 1.04–1.12) increase in the morbidity of dysentery.
Kang et al. 2015 (227)	Guangdong, China	2005-2011	All ages	All cause	Tropical cyclone	Daily count of infectious diarrhoea	Case-cross over design, conditional logistic regression	Infectious diarrhoea significantly increased after tropical cyclones with the strongest effect were shown on lag 1 day (HRs = 1.95, 95% CI = 1.22, 3.12).
Cash et al. 2014 (228)	Matlab and Dhaka, Bangladesh	1983-2010	All ages	*Vibrio cholerae* and *Shigella*	El Niño and Flood	Monthly count of cholera and *Shigella*	Spectral analysis and Spearman's rank correlation	The monsoon floods and post-monsoon disease outbreaks of both cholera and Shigella are significantly correlated with ENSO activity in the preceding winter.
Ni et al. 2014 (229)	Xinxiang, China	2004-2010	All ages	*Shigella* and *Entamoeba histolytica*	Monthly flooding events (severe and moderate)	Monthly dysentery count	Generalised linear model, Poisson regression	The risk of moderate and severe floods on the morbidity of dysentery was 1.55 (95% CI: 1.42–1.670) and 1.74 (95% CI: 1.56–1.94), respectively.
Ni et al. 2014 (230)	Henan, China	2004-2009	All ages	*Shigella* and *Entamoeba histolytica*	Monthly flooding events	Monthly dysentery count	Generalised additive models, Poisson regression models	The overall RR on dysentery in the whole region was 1.66 (95% CI: 1.52–1.82).
Ding et al. 2013 (217)	Anhui, China	2007	All ages	All cause	Flood	Daily diarrhoea cases	Time stratified case-cross over, conditional logistic regression	Positive association between flooding and diarrhoea in both cities Fuyang (OR=3.175, 95%CI: 1.126–8.954) and Bozhu (OR=6.754, 95%CI: 1.954–23.344).

Hashizume et al. 2011 (206)	Dhaka and Matlab, Bangladesh	1993-2007	All ages	*Vibrio cholerae*	Monthly change in Dipole moment index (Indian Ocean Dipole)	Monthly cholera cases	Time series, negative binomial regression models	A 0.1-unit increase in average DMI during the current month through 3 months before was associated with an increase in cholera incidence of 2.6% (95% CI, 0.0–5.2; p = 0.05) in Dhaka and 6.9% (95% CI, 3.2–10.8; p < 0.01) in Matlab.
Rodo et al. 2002 (220)	Dhaka, Bangladesh	1893-1940	All ages	*Vibrio cholerae*	Periodic change in ENSO	Annual cholera reports	Time series, Single Spectrum Analysis, Maximum Entropy Method	The association of cholera incidence in the earlier half of the century (1893–1940) is weak and uncorrelated with ENSO, whereas late in the century (1980–2001), the relationship is strong and consistent with ENSO. Past climate change, therefore, may have already affected cholera trends in the region through intensified ENSO events.
Checkley et al. 2000 (111)	Lima, Peru	1993-1998	Less than 10 years	All cause	El Niño index	Daily admission for diarrhoea	Time series, Generalised additive model with Poisson distribution	Mean ambient temperature in Lima during El Niño period increased up to 5°C above normal, and the number of daily admissions for diarrhoea increased to 200% of the previous rate.

2.3 Overview of epidemiological studies on climate variability and rotavirus infection

Twenty studies estimate the association between climatic factors and rotavirus infection (shown in Table 2.5). These studies analyse data on rotavirus infection from across all five inhabited continents in the world, with the study periods extending between the years 1966 – 2018 (39, 231, 232). These articles pre-dominantly used time series regression models to estimate the association between various climatic variables (temperature- mean, maximum and minimum, relative humidity and rainfall) and rotavirus diarrhoea, except for the three studies [India (233), Indonesia (234) and Burkina Faso (235)] that used simple correlation analysis (see Table 2.5). Nearly 60% of the studies include rotavirus cases among children as their outcome variable and the remaining 40% include rotavirus cases from all age groups. The periodic resolution of data analysed in the articles vary from daily (231, 236) and weekly (204, 237) to monthly (238, 239). All of the reviewed studies exclusively included temperature as one of their response variables with a varying definition for temperature as an exposure variable i.e., daily, weekly or monthly average maximum, mean and minimum temperature and threshold maximum or minimum temperature (> 90^{th} percentile) (see Table 2.5). The summary of reviewed articles are synthesised on the basis of exposure variables in the following subheadings.

2.3.1 Temperature and rotavirus

A majority of the reviewed articles used average mean temperature as the exposure variable (39, 197, 204, 232, 236-238, 240-242), while a study from India used average minimum temperature as the exposure variable (239). Except for a study from Bangladesh (204), all other studies report a negative association between temperature and rotavirus infection (See Table 2.5). While a correlation study from India reports simply a significant association between rotavirus infection and temperature, but does not report the direction of the association (233). Two systematic reviews and a meta-analysis from a tropical region (39) and

South Asia (232) report a 10% and 1.3% decrease in rotavirus incidence for each 1°C rise in monthly average temperature, respectively. Contrary to the findings of previous studies, Hashizume et al. (204), report that rotavirus incidence increased by 42% for every 1°C rise in mean temperature above the threshold of 29°C. The study reports possible interaction between high temperature and heavy rainfall, which could have modified the effect of temperature on rotavirus incidence and resulted in positive association beyond the given threshold.

2.3.1.1 Nature of association between rotavirus and temperature and the delayed effect

The majority (80%) of reviewed articles assume a linear association between temperature and rotavirus infection, except for the two studies from the Netherlands (237, 243), a multi-country study (231), a study from Hong Kong (197) and the study from Bangladesh which reported a U-shaped association between rotavirus and temperature (202). A delayed effect of temperature up to four weeks on rotavirus case count is reported by a study from Great Britain and the Netherlands (237). Similarly, a delayed effect up to three weeks is reported by a study from Dhaka, Bangladesh, although the nature of the association is found to be discordant to findings from the other articles (204). Meanwhile, the articles that used simple correlation analysis, as well as those using monthly data, do not report the delayed effect of temperature on rotavirus infection (233-235).

2.3.2 Rainfall and rotavirus

Of the 20 studies reviewed, 50% used rainfall as one of the exposure variables and most of them report a negative association between rotavirus and rainfall (39, 197, 232, 240). Where a correlational study from Indonesia (234), reported a significant positive association between monthly rainfall and rotavirus diarrhoea, the study from Burkina Faso reported no significant association between rainfall and rotavirus diarrhoea (235). The two systematic reviews and the meta-analysis from a tropical region (39) and South Asia (232) report a 1% and 0.3% increase in rotavirus incidence for each 10mm decrease in rainfall intensity, respectively. The association between rotavirus infection and rainfall in most of the cases is reported to be linear, except for the study from Hong Kong (197) and Costa Rica that report a threshold rainfall amount (99th percentile) beyond which the risk of rotavirus infection decreased linearly. The delayed protective effect of increased rainfall on rotavirus incidence is reported in the study from Costa Rica (240) that found a strong negative association between rotavirus infection and rainfall below the threshold of 26.8 mm at the two month lag period. Similarly, the study from Hong Kong reported a delayed protective effect of increased rainfall against rotavirus infection between the lag periods two to seven days in summer, and a delayed increase in risk with the reduction in rainfall between the lag periods three to 16 days in winter (197).

2.3.3 Humidity and rotavirus

Of the 20 studies reviewed, 70% estimated the impact of humidity on rotavirus incidence and reported inconsistent findings on the association between humidity and rotavirus infection. Studies conducted across different countries, including Australia (242), India (238), Bangladesh (204), Singapore (197), tropical region (39) and Burkina Faso (235), reported a significant negative association between rotavirus incidence and relative humidity. A systematic review of articles investigating the impact of climate variables on rotavirus incidence in tropical countries reports a 3% decreased in rotavirus cases for every 1% increase in relative humidity (39). While the studies from most of the European countries [Spain (244), Great Britain (237), the Netherlands (237, 243) and Turkey (245)] did not find any significant association between humidity and rotavirus infection. Contrary to the findings from most of the Asian and Tropical studies, a study from India (233) and the one from Indonesia (234), report a significant positive association between rotavirus incidence and relative humidity. These studies used a simple correlational analysis without adjusting for the effect of other meteorological factors and possible confounders.

2.3.3.1 Nature of the association between humidity and rotavirus and the delayed effect

Among the studies that report a significant negative association between rotavirus and humidity, the majority of the articles report a linear association (39, 204, 242). Meanwhile, two studies [Singapore (197) and a multicounty study (231)] report a non-linear association between relative humidity and rotavirus infection. The study from Singapore reports an increased risk of rotavirus infection below the reference value of 80% and a decrease in risk above the reference value (197). A multi-country study [representing major cities from countries across South America (Brazil and Peru), South Asia (Bangladesh, Pakistan, India and Nepal) and Africa (South Africa and Tanzania)] reports an inverse U-shaped association between rotavirus infection and relative humidity above the site-specific mean value for relative humidity (231). Similar to the nature of the exposure-response curve, findings for the delayed effect of humidity on rotavirus infection are also non-consistent: they range from a prolonged sustained delayed effect up to the lag period of 30 days, to acute and immediate effect (197). Where the study from Singapore (197) reports a significant delayed effect of humidity variation on rotavirus infection up to the lag period of 30 days, the study from Bangladesh (204) reports an immediate effect of relative humidity on weekly rotavirus count, which didn't persist beyond the lag 0.

In summary, this Section 2.3 provides a background underpinning the third analytical study conducted in this thesis. Although previous studies from South Asia have established a link between rotavirus and temperature, none of them calculated the meteorological factors or climate attributable fraction of rotavirus, which is an important epidemiological measure to manage the disease burden in the community. Furthermore, there is no literature on the association between temperature and rotavirus from a subtropical highland climate. More, importantly, the previous study from India (233), which reported a significant positive association between humidity and rotavirus infection, is considered unreliable as it did not adjust for the potential confounding effects of other meteorological variables. Also, it contrasts with previous findings on the association between temperature and rotavirus infection from the bordering countries, India (246) and Bangladesh (204). Therefore, it is imperative that additional and rigorous studies are conducted in this region to establish a conclusive link between rotavirus and meteorological variables.

Table 2. 5 Epidemiological studies that explored association between rotavirus and climate variability.

Reference	Location	Period	Age group	Exposure definition	Outcome definition	Statistical method	Result and conclusion
Ghoshal et al. 2020 (247)	Eastern India	2016-2018	Less than five years	Maximum temperature, minimum temperature, relative humidity, rainfall (average)	Association with laboratory confirmed rotavirus cases	Independent t-test	The maximum, minimum temperature, average rainfall, and average humidity of 83.4 mm, 79.2%, 28.1, and 21.9, respectively, were significantly associated with positive rotavirus cases.
Colston et al. 2019 (231)	Multi-country (Bangladesh, Nepal, India, Pakistan, Peru, Brazil, South Africa, Tanzania)	2009-2014	Less than two years	Daily average temperature, daily total precipitation volume, daily total surface runoff, surface pressure, wind speed, relative humidity, soil moisture, solar radiation and specific humidity	Daily rotavirus count	Time series, modified Poisson regression models	All nine hydro meteorological variables were significantly associated with rotavirus infection after adjusting for seasonality and between-site variation over multiple consecutive or non-consecutive lags, showing complex, often non-linear associations that differed by symptom status and showed considerable mutual interaction.
Urena-Castro et al. 2019 (240)	Costa Rica	2010-2015	Less than 13 years	Monthly average temperature and cumulative rainfall	Monthly rotavirus counts	Time series, Negative binomial regression	A strong negative association was detected between rotavirus case and temperature below the threshold of 16.2º C as well as precipitation below the threshold 26.8 mm at two months lag period.
Alsova et al. 2019 (236)	Russia (three cities)	2005-2011	All ages	Daily average temperature	Daily count of rotavirus	Time series, Poisson Polyharmonic Regression model	Rotavirus incidence was negatively associated with mean temperature in all three cities, showing a lagged effect [(RR: 0.995, 95% CI: 0.992-0.998), (RR: 0.996, 95% CI: 0.993-0.999) and (RR: 0.989, 95% CI: 0.985-0.994)].

Wang et al. 2018 (197)	Hong Kong	2002-2011	Less than five years	Extreme precipitation (99.5 mm, 99th percentile), daily mean temperature, relative humidity.	Daily count of hospitalisation due to rotavirus and norovirus	Time series Generalised additive models, Distributed lag nonlinear models	Extreme precipitation (99.5 mm, 99th percentile) shown to be associated with 0.40 (95% CI: 0.20–0.79) and 1.93 (95% CI 1.21–3.09) times the risk of hospitalisation due to rotavirus and norovirus infection respectively, relative to trace rainfall. Negative association reported between rotavirus incidence and temperature above 17 °C.
Hasan et al. 2018 (248)	Bangladesh	2003-2015	All ages	Composite indices for monthly rainfall, daily maximum and minimum temperature, composite indices for monthly maximum and minimum temperature	Rotavirus case counts	Spatial analysis	Lower number of wet days with suitable cold temperatures for an extended time accelerates the onset and intensity of the outbreaks.
Van Gaalen et al. 2017 (243)	Netherlands	1997-2015	All ages	Weekly mean temperature, relative humidity and rainfall	Weekly rotavirus count	Time series regression models	Relatively mild temperatures combined with the low proportion of susceptible individuals contributed to lower rotavirus transmission in the Netherlands.
Prasetyo et al. 2015 (234)	Bandung, Indonesia		Less than five years	Monthly average temperature, humidity and rainfall	Monthly rotavirus counts	Correlation study	Rotavirus incidence was negatively correlated with temperature and positively correlated with rainfall and humidity (r = -0.427, r = 0.101, r = 0.536).
Ouedraogo et al. 2017 (235)	Ouagadougou, Burkina Faso	2011-2012	All ages	Monthly average temperature, humidity and rainfall	Rotavirus case counts	Chi-square test, Correlation	Rotavirus cases in children were negatively correlated with temperature (r = −0.68, p = 0.01) and humidity (r = −0.61, p = 0.04).
Celik et al. 2015 (245)	Turkey	2006-2012	Less than five years	Monthly average temperature, humidity and rainfall	Monthly rotavirus counts	Time series, Negative binomial regression	A 1°C decrease in average temperature increased the ratio of rotavirus cases in those with diarrhoea by 0.523%.

Hervas et al. 2014 (244)	Mallorca, Spain	2000-2010	Less than five years	Weekly mean temperature, relative humidity, atmospheric pressure, wind speed, and global solar radiation	Weekly rotavirus counts	Time series regression, multivariate regression models	Rotavirus activity was negatively associated to temperature and positively associated to atmospheric pressure, solar radiation, and wind speed. Weekly rotavirus activity could be explained in 82% of cases ($p < 0.001$) with a one-week lag model.
Sarkar et al. 2013 (246)	South India	2002-2003	Less than five years	Weekly mean temperature, relative humidity and cumulative rainfall	Weekly rotavirus count	Time series, Poisson harmonic regression models	Rotavirus incidence showed biannual peaks, each in winter and summer.
Sumi et al. 2013 (238)	Kolkata, India	2007-2009	All ages	Monthly average temperature	Monthly rotavirus counts	Time series, Maximum entropy and Least square regression	Higher proportion of rotavirus positive samples were detected at low temperature.
Chan et al. 2013 (241)	Hong Kong	1995-2009	Less than five years	Weekly mean air temperature and relative humidity	Weekly rotavirus counts	Time series, Poisson generalised additive model	Air temperature was negatively associated with rotavirus incidence (IRR: 0.95, 95% CI: 0.937–0.979).
Jagai et al. 2012 (232)	South Asia	1966-2010	All ages	Monthly average temperature and cumulative rainfall	Monthly rotavirus counts	Linear mixed effect models	A 1°C decrease in monthly ambient temperature and a decrease of 10 mm in precipitation are associated with 1.3% and 0.3% increase above the annual level in rotavirus infections, respectively.
Atchison et al. 2010 (237)	England, Wales, Scotland and the Netherlands	1993-2007	Less than five years	Weekly mean temperature, rainfall and relative humidity	Weekly rotavirus counts (laboratory confirmed)	Time series regression, multivariate regression models	For each 1°C increase in weekly mean temperature above the threshold of 5°C, rotavirus cases decreased by 13%.
Levy et al. 2009 (39)	Global Tropics	1974-2005	All ages	Monthly average temperature, rainfall and relative humidity	Total number of monthly rotavirus cases	Generalised estimating	A 1°C increase in monthly average temperature was associated with 10%

						equation, Poisson regression model	decrease in rotavirus cases across the tropics.
Hashizume et al. 2008 (249)	Dhaka, Bangladesh	1996-2001	All ages	Weekly average temperature and relative humidity	Weekly rotavirus count	Time series, Generalised Poisson regression	For each 1°C increase above a threshold (29°C), rotavirus diarrhoea risk increased by 40·2% (95% CI: 19.4 % - 64.6%).
D'Souza et al. 2007 (242)	Brisbane, Melbourne and Canberra, Australia	1993-2003	Less than five years	Weekly average temperature and relative humidity	Weekly rotavirus count	Time series, Negative binomial regression	Negative association between rotavirus incidence and mean temperature lagged by one week.
Purohit et al. 1998 (239)	Pune, India	1992-1996	Less than two years	Monthly average minimum temperature	Monthly rotavirus counts	Autoregressive Integrated Moving Average Models	Negative association between monthly rotavirus cases and minimum temperature.

2.4 Infectious diseases surveillance in a changing climate and associated social considerations

As climate change is shown to affect the transmission of infectious diseases, in order to protect public health from the consequential impacts, it is important to strengthen the capacity of public health systems to conduct climate change-related public health surveillance (250). Public health surveillance is defined as an ongoing systematic process of collection, analysis and interpretation of health-related data needed for planning, implementation, and evaluation of public health (251). Furthermore, it comprises a holistic practice that aims to explore the determinants of disease and health, identify disease pattern, risk factors and vulnerable populations to inform evidence-based policy for disease prevention and health promotion. However, changing dynamics of infectious disease transmission under a range of factors — the influence of climate, ecological changes, increased travel and trade, urbanisation, population growth and increased immigration trend in bigger cities — is challenging the conventional approach of disease surveillance and so highlights the need for inter-sectoral participation and interdisciplinary collaboration (252-254). As such, the current surveillance practices designed for detection of outbreaks and risk mitigation, rather than early prevention of potential epidemics, are ill-equipped to respond to the shifting dynamics of infectious diseases under the influence of future climate change (250, 255, 256). Therefore it is important that climate change-related risks be integrated into public health surveillance systems to move from a detection and response strategy to an early warning and prevention approach for controlling infectious diseases (256, 257).

The burgeoning literature on climate change and infectious diseases has so far focused on understanding the effect of climate change on infectious diseases transmission, while little work has been done to explore adaptive interventions, such as strengthening public health surveillance systems in response to climate change (250). Frumkin et al. (258), developed a roadmap in 2008, utilising the 10 essential public health services (with pertinent examples), to integrate climate change-related risk in public health action including disease surveillance.

Box 1: The 10 essential public health services include:
• Monitoring health • Diagnosing and investigating health problems • Informing and educating the public about health • Mobilizing community partnership to promote health • Developing health policies and plans • Enforcing laws to protect health • Providing health care • Assuring a competent workforce • Evaluating health services, and • Conducting research to develop new insights of health

The 10 essential public services are inherently exhaustive within the three core public health functions of assessment, policy development and assurance (259). These core functions and essential services are used as a framework to guide the integration of climate change-related policies and planning in public health systems (258, 259). In 2010, the French Institute for Public Health Surveillance conducted a workshop on public health surveillance and climate change. The workshop concluded that the expected impact of climate change does not justify the establishment of new surveillance systems but warrants strengthening of existing surveillance systems by integrating climate change-related risk (254). The workshop further proposed that, apart from the routine activities, the existing surveillance systems in the context of climate change should adopt an additional set of activities including: detecting trends in epidemiological patterns and unexpected events in relation to climate, identifying vulnerable population and risk factors, proposing and evaluating adaptation measures and evaluating the health impacts of adaptation and mitigation strategies (253, 254). Building upon the foundation laid by Frumkin et al. (258), and embracing the tenets of the core functions and essential services, Centres for Disease Control and Prevention (CDC), in 2014 the USA developed a framework, called Building Resilience Against Climate Change Effects (BRACE), to assist public health authorities in the development of specific programs and strategies to protect health of people from the adverse impacts of climate change (260). The BRACE framework consists of five sequential steps (vulnerability assessment, projection of disease burden, assessment of public health interventions, development and implementation of adaptions plans and impact evaluation of interventions), which are perfectly aligned to the definition of public health surveillance (251, 260). Realising the importance of strengthening infectious disease surveillance systems to cope against the impacts of climate change, surveillance networks across the globe (Integrated Circumpolar Surveillance Network in Canada and The European Environment and Epidemiology Network in European Union) have already established specialised units within their infectious diseases surveillance systems (261, 262).

Given the relatively recent experience of strengthening of public health surveillance systems to cope against the effects of climate change, there is little information available on the factors associated with infectious disease surveillance in a changing climate. In 2017, a team from CDC, USA reviewed the efforts to strengthen the capacity of public health surveillance systems in USA to support health-related adaptation of climate change (250). The team reported that efforts from concerned authorities have, so far, focused on identifying suitable indicators and data sources and has ignored the other core components of surveillance capacity (database systems and analytical tools, workforce capacity and execution of pertinent policies) (250). In a similar effort, Sawatzky et al. (261) in 2018, reviewed integrated surveillance systems in Circumpolar Arctic and sub-Artic regions to identify enabling components of integrated surveillance systems to monitor public health impacts of climate change. The researchers reported three major components including structural components (logistic, organisational and operational aspects of the system), procedural components (collection, analysis, management and interpretation of surveillance data) and relational or interpersonal components (building and maintaining connections between stakeholders, understanding the needs and priorities of stakeholders) that were salient to the effectiveness of the integrated surveillance systems (261). Within the structural components, the authors mention of socio-economic and institutional issues such as provision for long-term funding sources, defining clear roles and responsibilities to public health officers as imperatives for successfully attaining goals of the surveillance systems. Similarly, a synthesis of the literature on the efforts to strengthen infectious diseases surveillance systems in the context of changing climate in Europe has exclusively emphasised the quality of datasets and their availability (263).

2.5 Gaps in evidence

Diarrhoea remains an important cause of childhood mortality and morbidity in sub-Sahara Africa and South Asia (32), yet there is limited evidence on the impact of climate change on diarrheal diseases in these regions, except for Bangladesh (37, 119, 178, 204, 206, 220, 248, 264). To manage the future burden of diarrheal disease, which is expected to increase due to climate change, it is important to understand the future burden of diarrhoea under different climate change scenarios. So far, only seven studies project the future burden of diarrhoea under different climate change scenarios: the only study to do so from South Asia extrapolated data from other regions of the world, instead of using locally available data (83).

In summary, this chapter shows that there is little evidence on the impact of climate change on infectious diseases in Nepal and there are knowledge gaps on the association between food-and water-borne diarrheal diseases and climate change. First, only one study has assessed the association between diarrhoea and climate change in Nepal (13), and the study only reports correlation coefficients. Although it mentions the ARIMA model in the method section, it does not report the estimated change in risk of diarrhoea in response to temperature or rainfall variation. As such, the estimated association from the study conducted in Jhapa, Nepal is biased and considered unreliable. It is necessary to apply advanced statistical methods that account for seasonality and long-term variation along with the lagged effect of exposure variables (temperature, rainfall and relative humidity) on diarrheal outcome in Kathmandu, Nepal. Second, the projected burden of childhood diarrhoea under different climate change scenarios in the context of Nepal is completely unknown because no studies have investigated the climate attributable burden of infectious disease in the Nepalese context.

Third, the relationship between climate change and diarrhoea caused by different pathogens is reported to vary, as the exposure pathway and environmental survival can vary considerably among different pathogens (265). Hence, it is important to estimate the association between rotavirus, the leading cause of diarrhoea related morbidity and mortality among children below five years of age in Nepal (266, 267), and climate change to both inform infection control planning and understand the epidemiology of rotavirus infection in response to climate change.

Finally, and most importantly, climate change-related risk has not been integrated in the Nepalese infectious disease surveillance systems. As such, the socio-economic, institutional and political factors associated with infectious disease surveillance remains unknown. Understanding the social and political aspects of infectious disease surveillance in Nepal will enhance the country's surveillance systems to enable effective prediction and future prevention of outbreaks of climate-sensitive epidemics such as vector-borne and food/water-borne diseases.

Chapter 3: Methodological and theoretical approaches

This chapter provides an overarching summary of the methodological and theoretical approaches employed in the thesis. To avoid redundancy, the methodology section in each of the result chapters (Chapters 4, 5, 6 and 7) has been shortened intentionally and does not contain the actual elaborated methodology section published in the peer reviewed papers. As described earlier in the introduction chapter, this thesis is composed of two different parts to cover an ecological aspect and a social aspect of the research problems. Hence, as shown in the figure 3.1, a mixed method study design is employed to address the two key research problems that comprise this thesis. First is quantifying the association between climate factors and diarrhoea as well as rotavirus infection among children below five years of age in Kathmandu, Nepal. Two studies used quantitative methods for the purpose. Second is the social aspect of infectious disease surveillance in the context of climate change in Nepal. Hence, the study addressing the social aspect uses qualitative methods to explore the socio-economic, institutional and political aspects of infectious disease surveillance in Nepal in a changing climate. These two aspects of the thesis has been linked by an opinion article apprising evidence on climate change and infectious disease research in Nepal. The following sub-sections describe in detail the methodology used in each part.

3.1 Quantitative study design

Two studies i.e., study 1 and study 2 use quantitative time series regression methods. Time series data are the series of data collected at a regular time interval such that the observations follow a temporal order that are equally spaced at discrete time points (268). An ecological time series study design was used in both the studies due to the ease of measurement of the exposure-response relationship at population level. Given the unavailability of disaggregated dataset on study variables at the individual level, the ecological time series methods best suited my purpose. Since the individual level characteristics — such as age, sex, gender and other relevant factors —are unlikely to be associated with the change in environmental exposures, the inherent disadvantage of ecological study (possible bias due to the absence of measurement at individual level) is less likely to affect the overall findings of our studies.

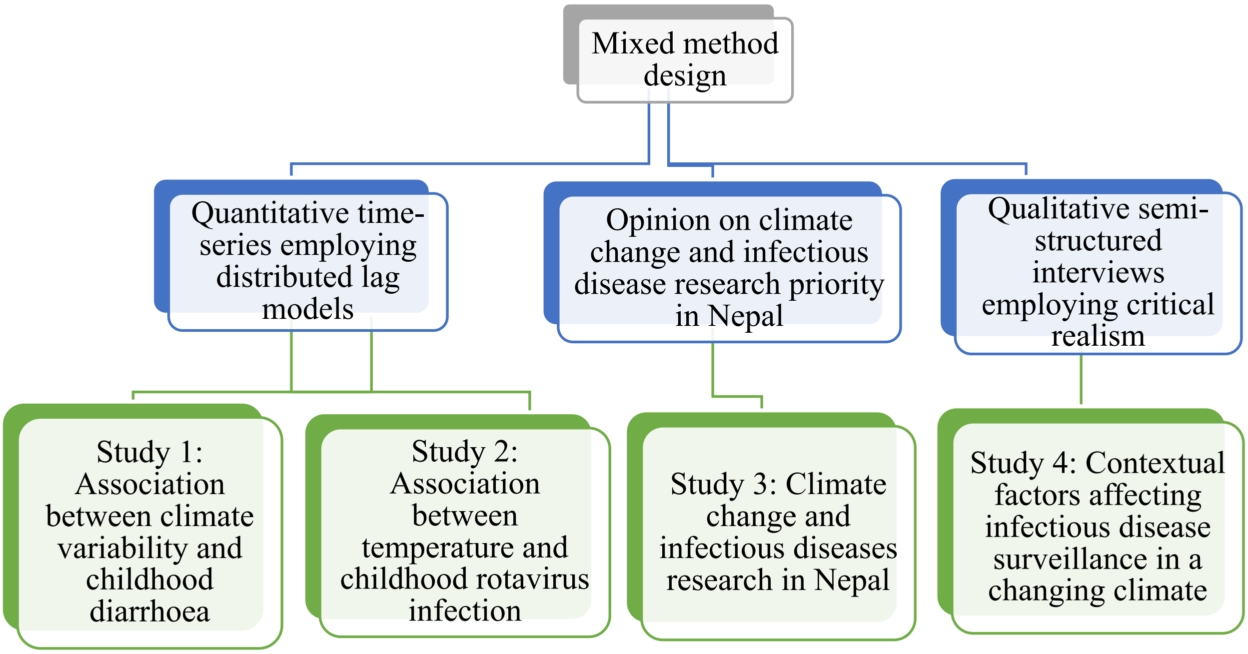


Figure 3. 1 Study design showing the methodology used in the analytical studies of the thesis

In Study 1, the association between climate factors and diarrhoea among children below five years of age is estimated using a generalised linear regression equation, accounting for over-dispersion (quasi-Poisson distribution). Estimated risk ratios from the regression equation was used to estimate potential impact fraction of diarrhoea to assess the proportional reduction in childhood diarrhoea burden under the counterfactual scenario of minimum exposure to maximum temperature (269). Finally, the estimated association between maximum temperature and diarrheal count was used to project the future burden of childhood diarrhoea in Kathmandu under different climate change scenarios, using the method adapted by WHO (270).

Similarly, Study 2 utilises a generalised linear regression equation fitted with distributed lag non-linear models (271), to estimate the association between three different temperature indices (maximum, mean and minimum temperature) and rotavirus diarrhoea among children below five years of age living in Kathmandu, Nepal. Concurrently, to estimate the burden of rotavirus that are attributable to different temperature indices, backward attributable risk was calculated utilising estimates from DLNM models (272). The distributed lag models used in these studies allow simultaneous exploration of exposure-lag-response between the predictor and outcome along a two-dimensional array of exposure and lag relationship. Based upon the functions used, these models allow estimation of both linear and non-linear association between the exposure variable and the response variables.

3.1.1 Study setting

Kathmandu district, the capital city of Nepal is situated at an average elevation of 1,400 metres (4,600 ft.) above sea level and lies in a warm, temperate zone characterised by a subtropical highland climate (Figure 3.1). Based upon the Köppen-Geiger climate classification, the climate of Kathmandu is better described by the sub-category Cwb or subtropical highland type. The subtropical highland type of climate is characterised by a mild summer and relatively cooler winter, with a heavy rainfall during the monsoon season. The average annual temperature of Kathmandu is nearly 16.1°C and it receives an average annual rainfall of about 1343mm. According to the 2011 national census, the total population of Kathmandu district was 1,744,240 with a population density of 4,416 persons per square kilometre (273), which was 30 times higher than the total population density of the country at that time. Based upon the National Census of 2011, and data from the 2011 National Living Standard Survey, the Human Development Index (HDI) for Kathmandu district was estimated to be 0.632, which is below the average value of living standards of South Asian countries (274).

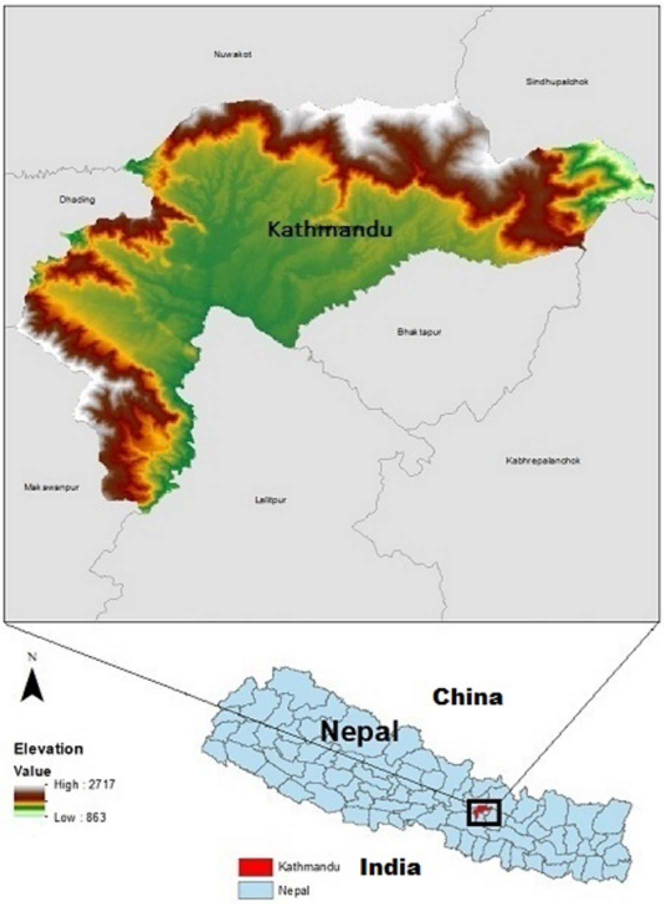


Figure 3. 2 Map of Nepal showing the study site Kathmandu district

3.1.2 Data sources

The clinical data used in study 1 and study 2 were obtained from separate sources and the time period as well as periodic resolution of the data varied accordingly. In study 1, monthly reported infectious diarrhoea cases among the children under 5 years of age living within Kathmandu district, over a 10 year period (2003–2013), were included as the primary outcome variables. Data on the monthly count of diarrheal disease were obtained from the Health Management Information Section (HMIS), Department of Health Services (DoHS), Ministry of Health and Population, Nepal. HMIS was established in 2000 and has been effectively managing health service information from all levels of health service delivery, including services provided by Female Community Health Volunteers and community level health workers to the tertiary care hospitals in Nepal. Clinical facilities in Nepal adhere to the operational definition of diarrhoea as the passage of three or more liquid stools per day (or more frequent passage than is normal for the individual) as a result of an infection in the intestinal tract caused by bacterial, parasitic or viral organisms. The HMIS dataset does not record details of the specific diarrheagenic pathogens by which population members (children under five years of age) have been infected. As such, our analysis included the aggregated monthly diarrhoea count as the outcome variable in our regression model during the data analysis.

In study 2, the weekly reported counts of laboratory-confirmed rotavirus cases among children under five years of age attending Kanti Children Hospital, Kathmandu, were used as the primary outcome variable, based on the illness onset date across a four year period (2013–2016). Surveillance data on the weekly count of laboratory-confirmed rotavirus cases were obtained from the Public Health Research Laboratory, Institute of Medicine, Tribhuvan University, Nepal (275), a member site of the Asian Rotavirus Surveillance Network (276). All participants enrolled in the surveillance program were screened for the presence of rotavirus antigen in their stool samples using Enzyme-linked immune sorbent assay (ELISA) kits (ProSpecT^{TM}Rotavirus, Oxoid Ltd, UK), followed by confirmation via reverse-transcription polymerase chain reaction (RT-PCR) (275).

Meteorological data used in both the studies were obtained from the Department of Hydrology and Meteorology, Nepal, although their periodic resolution varied between the studies. Daily climate data from Kathmandu district were obtained for the study duration (2003-2013) and monthly means for maximum and minimum temperature, relative humidity and rainfall were calculated from the daily records for the study 1. However, for study 2, daily climate data from Kathmandu district were obtained for the study duration (2013-2016) and weekly means were calculated for temperature variables (maximum, minimum and mean) and relative humidity. Weekly cumulative rainfall totals for the study were calculated from daily records. Data from Kathmandu Airport station were used for their completeness and to obtain a wider range of coverage for the study location. Demographic data for Kathmandu district was obtained from the central Bureau of Statistics, Nepal. Data from the last census (2011) were used in both the studies.

3.1.3 Statistical analysis

Descriptive statistics were used to calculate the summary of study variables in the form of measures of central tendency, range, and standard deviation. Following the descriptive analysis, correlation analysis of study variables was carried out to ascertain correlation among study variables and determine the variables that were strongly associated with the primary outcome variables. Finally, a time-series Poisson regression models fitted with distributed lags were defined to quantify the association between the primary outcome variables and other predictors. The final regression models were adjusted for possible confounders, long term trend and seasonality using appropriate techniques. The details of statistical analysis used in each study has been further elaborated in the methodology sections of Chapter 4 and Chapter 5.

Following the two quantitative studies (study 1 and study 2) is study 3, an opinion article on climate change and infectious diseases research priority in Nepal. This chapter critically appraises existing evidence on climate change and infectious diseases, and explains the rationale for the qualitative study. It links the quantitative and qualitative studies and maintains the flow of the thesis.

3.2 Qualitative study design

The original plan for my PhD candidature, was to collaborate with the authorities from EDCD and HIMS, Nepal and obtain disaggregated data sets on different food-and water-borne diarrheal diseases to estimate the effects of climate change on diarrheal diseases caused by various pathogens. As the project developed, apart from significant COVID-related disruption, I had to address several unanticipated problems, including reluctance to share datasets, poor data quality, absence of disaggregated dataset on diarrhoea based on pathogens, sub-standard institutional infrastructure and scant literature on climate change and infectious diseases from Nepal. These challenges exposed the problems within infectious diseases surveillance systems in Nepal, which have been documented in the first three studies of this thesis, particularly in Chapter 6. As such, the Chapter 7 of this thesis builds upon the findings of preceding three studies and takes a critical social scientific approach to the research questions. Analysis specifically focuses on social and institutional dimensions influencing the surveillance of infectious diseases in the context of climate change in Nepal. Hence, I employ semi-structured interviews embedded in critical realism paradigm to explore social, economic and institutional factors associated infectious disease surveillance in Nepal. Semi-structured interviews were conducted with key informants from the Department of Health Services (Epidemiology and Disease Control Division, Health Information Management System), Department of Hydrology and Meteorology, WHO-Nepal and experts working on infectious disease and climate change in Nepal.

I argue that to effectively examine the functioning of public health surveillance systems in the context of climate change may not be justifiable by solely employing a positivist epistemological approach that relies on statistical methods that can decontextualise the role of social, cultural and political factors (277). Moreover, I posit that use of quantitative survey tools in organisation research may fail to reveal the unique socio-political context of the system, as the survey response may lack sufficient depth to capture the complexity of what is going on socially. At the core of a health system are individuals or groups of people whose behaviours are influenced by their belief systems and role positions. These must be appreciated and described to understand functionality of a system. Thus, I chose a semi-structured interview method embedded in critical realism to answer the final question of my project: how do social and institutional factors, observable within the talk of respondents, play a role in infectious disease surveillance in Nepal in the context of climate change? The details of methods used in data collection and analysis is further elaborated in the methodology section of chapter 7.

3.2.1 Qualitative theoretical perspective

For the fourth and final study, I draw from critical realism (CR) (278). CR is a theoretical research approach that lies between realism and relativism on epistemological spectrum, and is of growing interest among health system researchers (279, 280). Critical realism is ontologically realist, taking the position that reality exists independent of human perception, yet is epistemologically constructionist in that our knowledge of reality is created and shaped by human experiences with the natural and social world (278). CR researchers conceive language to be the architect of social reality, which itself is theorised to be shaped by human interaction with the natural and social world (281). Put another way, as social reality is constrained within a material dimension that exists independent of discursive practices, the material constraints impact on the meaning of the social reality constructed out of the discourse utilised by the actors (281, 282).

Critical realism is the best suited philosophical position because it theoretically orients to infectious diseases surveillance systems as 'real', in the sense that these systems aim to prevent infectious diseases epidemic or outbreaks by performing standard set of activities — including timely collection of data on spatial-temporal pattern of infectious diseases, identifying associated risk factors and monitoring intervention measures (251). On the other hand, these systems are bounded by material and structural dimensions that exist independently of discursive practices. As such, these material constraints interact with socially constructed realities that are fundamentally drawn from discourses available in social milieus (281, 282). According to Carla Willig (282), the discourses employed by actors are constrained by underlying structures such as biochemical, social or economic structures, thus, ontological reality cannot be directly accessed but can only be inferred by analysing discourse in relation to these structures (page 45).

Critical realism has widely been utilised in climate change and public health research including climate change mitigation, vulnerability assessment, energy technology debates, stakeholders perception assessment and various other social aspects of climate change related outcomes (280, 283). A CR approach to qualitative data in this study enables us to take account of the fact that potential problems within a disease surveillance system are both socially constructed and influenced by structural factors independent of individuals or groups. For example, the ability of a surveillance system to map vulnerability of a population towards infectious disease exposure due to change in climatic conditions may be contingent upon data availability and societal need or expectations (284). Hence, a CR approach can incorporate influence of material — (e.g. budget), institutional (epidemiological and diagnostic capacity of health service providers) and discursive factors that may transform the significance of a problem being studied — when exploring the contextual issues of a disease surveillance systems in response to environmental stressors such as climate change.

3.2.2 Reflexivity

The term reflexivity is widely used in system and organisational research with varying meanings. In the context of this thesis, reflexivity is defined as an attempt to consciously reflect on my role as a researcher in defining the phenomenon under investigation, collecting and analysing data, and inferring findings from the analysis (286). In articulating my reflexivity, I reveal the assumptions that underpin my research process and the knowledge produced in the context of my professional experience and the philosophical background driving my research process (287).

I identify myself as a trainee infectious disease epidemiologist with a strong background in clinical microbiology and fairly experienced with the operational mechanism of infectious disease surveillance systems in Nepal. After completion of my postgraduate degree in clinical microbiology in 2015, I joined the Public Health Research Laboratory in the Institute of Medicine, Tribhuvan University Nepal and was trained in laboratory based molecular research techniques. During my tenure in the Institute of Medicine, I was a member of an international rotavirus surveillance network and was exposed to several international researcher groups. As I embarked on the journey of bio-medical research and had increased exposure to global health research, I realised the importance of translational research and felt an urgency to move to population-based research. Hence, with the aspiration to learn data analysis techniques and become a competent public health researcher specialising in infectious disease epidemiology I joined this PhD program in epidemiology. This aspiration has helped me to overcome technical challenges that I have encountered in my PhD candidature.

My postgraduate training in clinical microbiology, and professional experience as a research officer in the national rotavirus surveillance program in Nepal, provided the opportunity to learn about the standard operating practices of a diagnostic facility and the attributes of an ideal infectious disease surveillance system. As such, I have employed my priories, as well as knowledge gained during my PhD training in infectious disease epidemiology, to reflect upon the research process undertaken in study 4. Throughout the research process — i.e. identifying the research question, designing the research, interview taking, transcription and data analysis — I linked my priories to explore participants understanding of the problems associated with the infectious disease surveillance systems and construct meaning out of participants’ response.

3.3 Ethics approval

The project was granted ethical approval by the Human Research Ethics Committee (HREC) of The University of Adelaide (H-2018-236), and Ethical Review Board of the Nepal Health Research Council (Reg. no. 560/2018). Data related to human participants used in the study were non-identifiable and were analysed anonymously.

Chapter 4 Study 1: Assessing the effect of climate factors on childhood diarrhoea burden in Kathmandu, Nepal

Statement of Authorship

Title of Paper	Assessing the effect of climate factors on childhood diarrhoea burden in Kathmandu, Nepal
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Bhandari, D., Bi, P., Sherchand, J. B., Dhimal, M. and Hanson-Easey, S. (2020). "Assessing the effect of climate factors on childhood diarrhoea burden in Kathmandu, Nepal." International Journal of Hygiene and Environmental Health 223(1): 199-206

Principal Author

Name of Principal Author (Candidate)	Dinesh Bhandari		
Contribution to the Paper	Conceptualization ,research design, data curation, data analysis and manuscript preparation, revision and editing		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	25/6/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Peng Bi		
Contribution to the Paper	Conceptualization, overall supervision and manuscript revision and editing		
Signature		Date	25/6/2021

Name of Co-Author	Jeevan Bahadur Sherchand		
Contribution to the Paper	Overall supervision and manuscript revision and editing		
Signature		Date	25/6/2021

Name of Co-Author	Meghnath Dhimal		
Contribution to the Paper	Overall supervision and manuscript revision and editing		
Signature		Date	25/6/2021

Name of Co-Author	Scott-Hanson Easey		
Contribution to the Paper	Conceptualization, overall supervision and manuscript revision and editing		
Signature		Date	25/6/2021

Abstract

Introduction: This study was undertaken to assess the effect of climate variability on diarrheal disease burden among children under 5 years of age living in Kathmandu, Nepal. The researchers sought to predict future risk of childhood diarrhoea under different climate change scenarios to advance the evidence base available to public health decision-makers, and the Nepalese infection control division, in planning for climate impacts.

Methods: A time series study was conducted using the monthly case count of diarrheal disease (2003- 2013) among children under 5 years of age living in Kathmandu, Nepal. A quasi Poisson generalized linear equation with distributed lag linear model was fitted to estimate the lagged effect of monthly maximum temperature and rainfall on childhood diarrhoea. The environmental framework of comparative risk assessment was used to assess the environmental burden of diarrhoea within this population.

Results: A total of 219,774 cases of diarrheal disease were recorded during the study period with a median value of 1286 cases per month. The results of a regression model revealed that the monthly count of diarrhoea cases increased by 8.1% (RR: 1.081; 95% CI: 1.02-1.14) per 1 ^{o}C increase in maximum temperature above the monthly average recorded within that month. Similarly, rainfall was found to have significant effect on the monthly diarrhoea count, with a 0.9% (RR; 1.009; 95% CI: 1.004-1.015) increase in cases for every 10 mm increase in rainfall above the monthly cumulative value recorded within that month. It was estimated that 7.5% (95% CI: 2.2% - 12.5%) of the current burden of diarrhoea among children under 5 years of age could be attributed to climatic factors (maximum temperature), and projected that 1357 (UI: 410-2274) additional cases of childhood diarrhoea could be climate attributable by the year 2050 under low-risk scenario (0.9 ^{o}C increase in maximum temperature).

Conclusion: It is estimated that there exists a significant association ($p<0.05$) between childhood diarrhoea and an increase in maximum temperature and rainfall in Kathmandu, Nepal. The findings of this study may inform the conceptualization and design of early warning systems for the prediction and control of childhood diarrhoea, based upon the observed pattern of climate change in Kathmandu.

Key words: Diarrhoea, Children, Climate variability, Nepal

4.1 Introduction

Diarrhoea remains a leading cause of death among children under 5 years of age. In 2015, 1.31 million diarrhoea-related deaths were reported globally, and diarrheal disease represents the second major cause of death among children under 5 years in low and middle-income countries (285, 286). The average total societal cost of diarrheal disease treatment in low and middle-income countries has been estimated to be as high as US$101 per episode in Rwanda, and US$ 67.81 in Bangladesh (287, 288). In the context of Nepal, the financial burden borne by a family due to childhood diarrhoea is undetermined but can be speculated to be calamitous.

Evidence suggests that the onset and transmission of diarrheal disease can be influenced by many factors including climatic parameters such as rainfall and temperature (34, 37, 112, 176, 289). During extreme weather events such as floods and hurricanes, water sources can become contaminated with micro-organisms including bacteria (e.g.: Salmonella, *Shigella, Escherichia coli*, *Campylobacter, Vibrio Cholerae),* viruses (e.g.: Rotavirus, Norovirus, Adenovirus) and protozoa (e.g.: *Giardia*, *Cryptosporidium*, *Cyclospora*) that are capable of causing gastro-intestinal infections (290, 291). An increase in temperature is likely to have a direct effect on the spread of diarrheal diseases by altering their geographical distribution and encouraging bacterial growth (7).

A national report on climate change vulnerability in Nepal projects that the mean annual temperature of Nepal will increase by 0.5 ^{o}C to 2.0 ^{o} C with a multi-model mean of 1.4 ^{o} C by the 2030s, and 1.7- 4.1 ^{o} C with a multi-model mean of 2.8 ^{o} C by the 2060s, under a high emission scenario (the ‘A2 scenario’ used in the third assessment report by the Intergovernmental Panel on Climate Change (IPCC) (292). Indeed, the 5th assessment report of the IPCC has predicted an increase in the magnitude of extreme weather events (including flood, drought and heat-waves) due to the effect of anthropogenic and natural climate change, which in turn is likely to result in an increased prevalence of diarrheal disease (134).

Kathmandu city has a high population density (4,416 people per square kilometre) (273) and faces an acute shortage of potable water during hot and dry summer months owing to the water demands of the increasingly populated Kathmandu valley (293). According to Nepalese Government estimates, in 2014, 83.59% of the total population in Nepal had access to basic water supply services, and 70.28% had access to basic sanitation facilities (294), although data specific to Kathmandu city were not available . Under such conditions, people are compelled to consume unsafe water leading to an increased susceptibility to diarrheal diseases (81). Rutkowski et al. (95) have reported a widespread use of pathogen-contaminated wastewater for irrigation purposes in Kathmandu city and its outskirts during dry seasons of low rainfall. Residents' consumption of vegetables and crops irrigated with waste water can pose a potential risk factor for infective gastroenteritis (295). Moreover, for developing countries like Nepal, climatic variations and employment opportunities are likely to drive migration of people into urban centres (296). Internal migration can lead to an increase in urban density, exacerbating already poor living conditions and the risk of transmission of diarrheal diseases among vulnerable populations (81).

Compared to the adult population, children are more vulnerable to the effect of adverse environmental challenges caused, or aggravated by, climate change (297). During the aftermath of hurricane Maria in Puerto Rico in 2017, for instance, an upsurge of infective gastroenteritis was reported among children (297). Musengimana et al. (161), reported a 32% increase in diarrhoea among children under five years of age in Cape Town, South Africa for every 5 ^{o}C increase in maximum temperature. Given the higher vulnerability of children to the effects of global climate change, and susceptibility to diarrheal diseases (298), there remains an increasing concern over the endemicity of diarrheal diseases in low income countries like Nepal.

In light of these concerns, the current study was undertaken to assess the effect of climate variability on diarrheal diseases among children under 5 years of age living in Kathmandu

Nepal and to predict future climate-attributable diarrhoea burden. The study seeks to advance the evidence for health policy decision-makers by assessing the risk of childhood diarrhoea under current and future climate change scenarios in Kathmandu.

4.2 Methods

As mentioned earlier in chapter 3, the methodology section in this chapter has been deliberately shortened to avoid redundancy between chapter 3 and the methods sub-section in each result chapters. Hence, this section as presented here, differs from the original methods section as published in the peer reviewed paper. A complete detail of methodology has been presented in chapter 3 and only the statistical analysis section, which is unique to this chapter has been presented here.

4.2.1 Statistical analysis

4.2.1.1 Modelling the relationship between maximum temperature, rainfall and childhood diarrhoea

Pearson's correlation analysis was carried out to assess the association between monthly diarrheal count and climate variables including monthly minimum temperature, maximum temperature, mean temperature, relative humidity and rainfall. Monthly maximum temperature and rainfall were used to estimate the relationship between temperature variability and diarrhoea count due to the positive correlation of these factors with diarrhoea. We conducted a time series analysis to examine the relationship between monthly diarrheal count, monthly average maximum temperature and total monthly rainfall using a generalized linear Poisson regression model, allowing for over-dispersion. Seasonality and long term effects not directly related to weather were adjusted in the model using natural cubic splines with four knots per year (degree of freedom (df)=40) (Supplementary Figure S4.1). A linear relation was assumed between the maximum temperature and diarrheal disease above its monthly average temperature, and the lag effect was modelled using unconstrained distributed lag linear model using the DLNM package in software R (271). Guided by the prior research on the effect of climate variability on diarrheal diseases, and based upon the result of correlation analysis at different lag periods (Table 4.1), we set a lag period up to 1 month to assess the delayed effect of maximum temperature and rainfall (34, 37, 289). The confounding effect of relative humidity was adjusted in the model by including a natural cubic spline (df=3). In summary, the final model took the following form:

Log [E(y)] = $\alpha + \beta_1$ (cbo_max_temp) + β_2 (cbo_rainfall) + NS (mean_rh, df=3) + NS (time, df=40)

where [E(y)] is the expected monthly case count, cbo_max_temp is the cross basis matrix for mean monthly maximum temperature, cbo_rainfall is the cross basis matrix for mean monthly rainfall, β1 & β_2 are their respective regression coefficients, NS (mean_rh) is the monthly mean relative humidity with natural cubic spline of 3 degree of freedom, and NS (time) is the natural cubic spline of time with 4 degree of freedom per year.

4.2.1.2 Calculating climate-attributable risk for diarrhoea and projecting the future attributable burden

Firstly, we calculated the potential impact fraction (PIF) to assess the proportional reduction in childhood diarrhoea burden, assuming a counterfactual situation in which the study population experience the least exposure to increased temperature under the current climate scenario. We used the environmental framework of comparative risk assessment developed by World Health Organization (WHO) for assessing the environmental burden of diseases to compute PIF(269).

$$\textbf{PIF} = (\sum P_i RR_i - \sum P_i^* RR_i) / \sum P_i RR_i$$

where P_i is the proportion of the population in exposure group i, P_i^* is the proportion of the population in the exposure group under a counterfactual situation, RR_i is the relative risk for the exposure group.

Assuming the counterfactual situation of least exposure, the above PIF can be calculated using a simplified formula,

$$\mathbf{PIF} = \sum P_i RR_i - 1 / \sum P_i RR_i$$

We then estimated the future climate change-attributable increase in diarrhoea burden for Kathmandu district using the formulae adapted by the WHO for their climate-related quantitative risk assessment of disease morbidity study (270).

$$\mathbf{n = N\,(exp^{(\beta * \Delta T)} - 1) / exp^{(\beta * \Delta T)}}$$

where n is the number of climate change-attributable average annual cases of diarrhoea, N is the total average annual baseline (current) diarrheal count, Δ T is the future change in temperature for various climate change scenarios, and β is the log linear increase in diarrhoea per 1 ^{o}C rise in temperature.

4.2.1.3 Sensitivity Analysis

Sensitivity of the model was analysed by changing the degree of smoothing (knots per year), in time splines and lag periods (0, 1 and 2 months) for both rainfall and maximum temperature. The model with lowest qAIC value was selected as the robust model (Supplementary Table S4.1) and used to project the climate-attributable increase in diarrhoea under future climate change scenarios. Further, the robustness of the model was tested by checking the residual autocorrelation plot and distribution of the residuals (Supplementary Figures S4.2 and S4.3).

4.3 Results

A total of 219,774 cases of diarrhoea were recorded among the children under 5 years of age living in Kathmandu district during the study period from 2003 to 2013. The monthly average diarrheal case-count for this population reported during the study period was 1,665 (Table

4.2). Seasonal distribution of the diarrheal cases showed a higher burden between the months of June-August (Figure 4.1).

Table 4. 1 Pearson's correlation coefficient of the diarrhoea and maximum temperature at different lag periods.

Climate variables	Pearson's correlation coefficient (r)	p-value
Maximum temperature (Lag 0)	0.7591	<0.001
Maximum temperature (Lag 1)	0.5465	<0.001
Maximum temperature (Lag 2)	0.2795	<0.001
Rainfall (Lag 0)	0.6832	<0.001
Rainfall (Lag1)	0.3169	<0.001
Rainfall (Lag 2)	-0.1124	0.199

Table 4. 2 Distribution of meteorological data (monthly average) and diarrheal count in children under 5 years in Kathmandu district 2003-2013.

Study variables	Lowest	1^{st} quartile	Median	Mean	3^{rd} quartile	Highest
Maximum temperature (^{o} C)	17.46	23.28	28.08	26.33	29.25	31.91
Rainfall (mm)	0	15.45	73.05	149.94	261.52	735.70
Relative humidity (%)	58.03	72.75	78.72	76.73	82.40	90.21
Under 5 Diarrheal count	100	621	1286	1665	2676	4232

4.3.1 Relationship with maximum temperature

We estimated an 8.1% (RR: 1.081; 95% CI: 1.02-1.14) increase in risk of diarrhoea cases among children under 5 years of age per 1 ^{o}C increase in maximum temperature above the monthly average recorded within that month. (Figure 4.2). The effect of maximum temperature on diarrhoea was not significant at the lag period of 1 month (refer to Supplementary Figure S4.4 for the estimated relationship between mean temperature and diarrhoea).

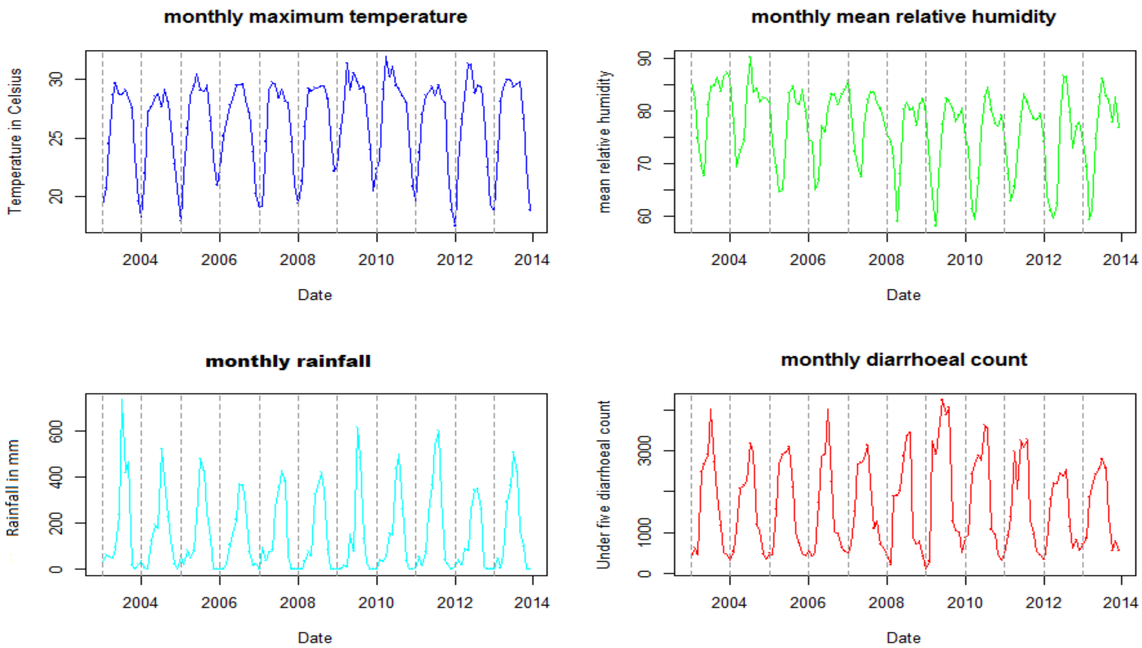
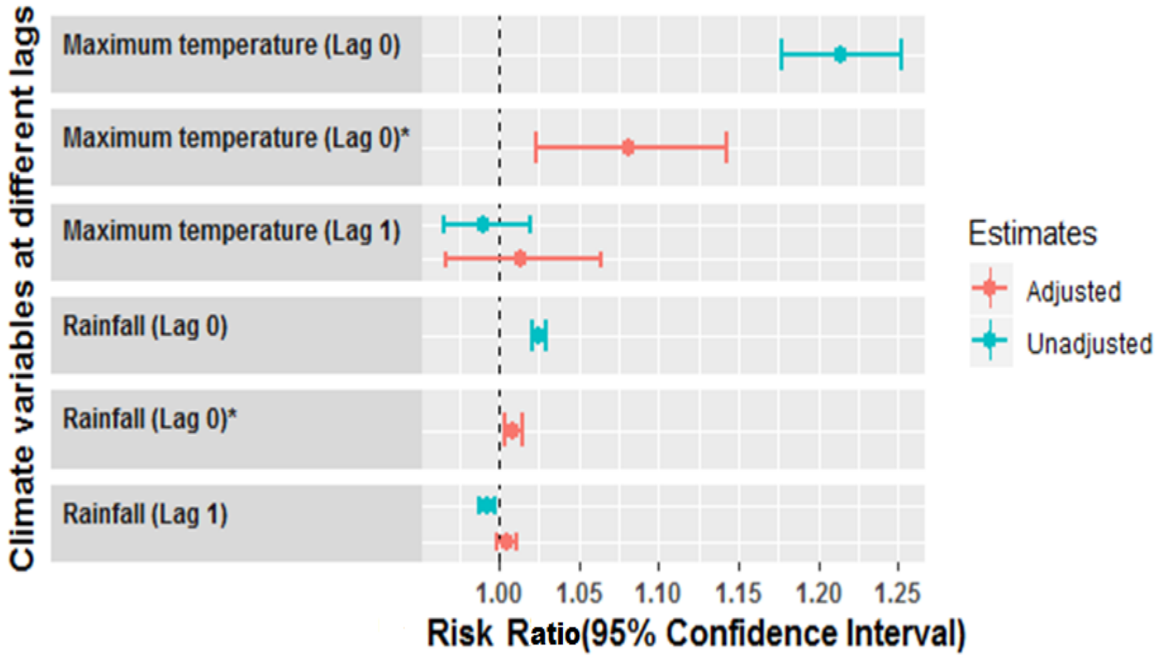


Figure 4. 1 Trend of meteorological data and monthly diarrheal count in children under 5 in Kathmandu district 2003-2013.



Note:Adjusted relation indicates all the climate variables that were included in the model and adjusted for seasonality, long term variation and the effect of relative humidity; CI: confidence interval; *p value siginificant at <0.05.

Figure 4. 2 Effect estimates of maximum temperature and rainfall on monthly diarrhoea cases at different lag periods showing crude and adjusted relationship.

4.3.2 Relation with rainfall

We estimated a 0.9% (RR; 1.009; 95% CI: 1.004-1.015) increase in risk of diarrhoea cases among children under 5 years of age per 10 mm increase in rainfall above the monthly cumulative value recorded within that month (Figure 4.2). Similar to the effect of maximum temperature, the effect of rainfall was not significant at the lag period of 1 month.

4.3.3 Estimation of current potential impact fraction (PIF) and climate attributable diarrhoea burden

According to the National Census carried out in the year 2011, the total population of Kathmandu district was 1,744,240 and the population of children under five years of age was 111,600 (273). We assumed all children under 5 years of age were exposed to the risk factor (maximum temperature), and estimated the potential impact fraction to be 0.075. We estimated, 7.5% (95% CI: 2.2% - 12.5%) of the current burden of diarrhoea among children under 5 years of age to be attributable to the climatic factor (maximum temperature).

4.3.4 Projection of climate-attributable diarrhoea count in future climate change scenarios

We conducted a literature search to identify studies that have projected future increases in maximum temperature for Kathmandu district under different climate change scenarios (Supplementary Table S4.2), and used the estimated increase in temperature range (0.5 ^{o}C to 3.7 ^{o}C) for different time slices under future climate change scenarios (Table 4.3). We calculated the mean annual count of diarrhoea in children under 5, taking the summation of monthly diarrhoea counts for each year (2003 to 2013), and estimated the baseline diarrheal count to be 20,019. Due to the unavailability of data on the projected population of children under 5 years of age in the Kathmandu district, we assume no significant change in study population when projecting the future burden. Under the low risk scenario and the most conservative estimate, we projected 766 (228 to 1297) (refer to Supplementary Table S4 for calculation details) additional annual diarrhoea cases attributable to climate change by the year 2020 (Figure 4.3).

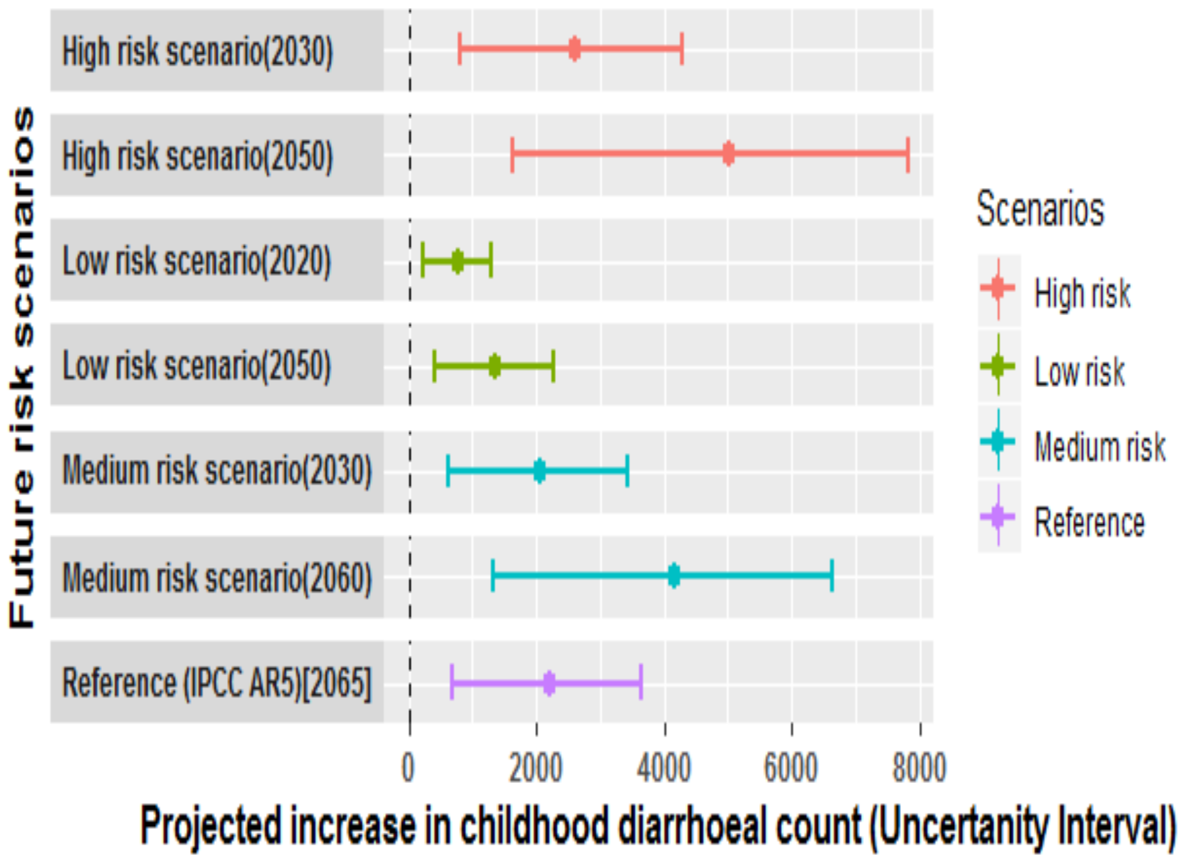


Figure 4. 3 Projected increase in diarrheal count attributable to climate change in children below 5 years of age. * Baseline annual count of diarrhoea used for prediction was 20,019 [calculated by summation of monthly diarrhoea count for each year (2003-2013)].

Table 4. 3 Estimates of predicted temperature increase for Kathmandu valley informing projection of future increase in climate-attributable childhood diarrhoea under different climate change scenarios.

Study	Projection coverage	Climate model used	Scenarios	Baseline data used (years)	Projection years	Projected increase in temperature (ΔT in ºC)		Remarks	Risk category
Babel et al. 2014 (299).	Kathmandu district (Baghmati river Basin)	5 GCM tested and HadCM3 was selected because of best fit	A2 based on SRES	1970-1999	2020s	0.5		Projection made for maximum temperature and GCM was downscaled	Low risk
				1970-1999	2050s	1.1			
				1970-1999	2080s	2.1			
			B2 based on SRES	1970-1999	2020s	0.5			
				1970-1999	2050s	0.9			
				1970-1999	2080s	1.5			
NCVST 2009 (292).	Nepal (central Nepal, which includes Kathmandu district)	15 GCMs with details of name of all the models used in projection and 2 RCM models (PRECIS and RegCM3)	A2 based on SRES, due to closest match to observe emission for region since 2000.			Nepal	Central Nepal	RCM model used to make projection for central Nepal, which includes Kathmandu district.	Medium risk
				1970-1999	2030s	1.4 (0.5-2)	1.4 (0.9-2)		
				1970-1999	2060s	2.8 (1.7-4.1)	3.0 (1.7-4.1)		
				1970-1999	2090	4.7 (3-6.3)	4.9 (3.0-6.3)		
Jha 2012 (300).	Kathmandu valley	21 GCMS available in SimCLIM software and IPSL-CM40 used for projection	A1F1 based on SRES	1980-2009	2030s	1.8 – 1.9	1980-2009	Temperature type not mentioned	High risk
				1980-2009	2050	3.7 – 3.8	1980-2009		
				1980-2009	2100	9.3 – 9.7	1980-2009		

4.4 Discussion

This study is one of the few epidemiological studies conducted in Kathmandu, Nepal that uses the national disease surveillance dataset to comprehensively quantify the association between childhood diarrhoea and climate variability after adjusting for the long-term effects and seasonal pattern of the disease. The findings of our study showed that the onset and distribution of diarrhoea among children under 5 years of age in Kathmandu, Nepal is highly associated with climate variability. We estimated that an increase in both maximum temperature and rainfall intensity is likely to increase the burden of climate change-attributable childhood diarrhoea in Kathmandu for different projected time slices in future.

The positive association between diarrhoea incidence and temperature observed in our study mirrors the findings of similar studies conducted in Asia, Pacific islands and Latin America, which have reported a 5% to 13% increase in diarrhoea cases per 1 ^{o}C increase in ambient temperature (34, 37, 71, 176, 289, 301). These studies, however, used weekly or daily mean temperature as a predictor variable, compared to maximum temperature as used in our study. We used daily maximum and minimum temperature data to compile monthly average temperature measures, which may fail to capture the discrete effect of extreme short-term variability in temperature, and may harmonize the effect of diurnal or weekly variability in the maximum temperature measure. Despite the use of a different temperature index, the significant association observed between maximum temperature and diarrhoea count in our study resonates with findings of studies from Pacific islands, Latin America and other Asian countries (34, 37, 176, 289). Along with mean temperature, maximum temperature is also considered a suitable index of temperature exposure, and has been increasingly used as the index of choice by epidemiologists in recent years (36, 302). Barnett et al. (303), in their seminal paper entitled “What measure of temperature is the best predictor of mortality?” have concluded that the choice of temperature measure between mean and maximum temperature can be made on the basis of practical concern as these indices have the same predictive ability in terms of exposure risk estimation. We observed an immediate effect of temperature increase on childhood diarrhoea in our study, which can be explained by the fact that the incubation period for most of the entero-pathogens is under a few weeks (304). Our findings indicate a low risk effect of maximum temperature on diarrhoea incidence beyond the lag period of 1 month, which is consistent with the findings of previous works from Bangladesh, Japan and Australia (37, 305, 306). Our study did not include the adult population, however a study from Bangladesh has reported a lack of evidence on the differential effects of temperature on diarrhoea incidence by individual characteristics such as age and gender (37). Although an overall non-significant effect of diarrhoea risk and age was reported in the study, their age-stratified analysis did show a significant increment in risk of diarrhoea among children in the age group <14 years compared to the age group >30 years. Compared to the adult population, children can be assumed to be more vulnerable to diarrheal risk under climate change owing to their comparatively weaker immune system and lack of control over their exposure to contaminants, potential pathogens and other risk factors (297)

Several plausible explanations have been proposed to elucidate the underlying mechanisms affecting the association between an increase in temperature and higher onset and transmission of diarrhoea (35). Diarrhoeagenic pathogens such as *Shigella,* spp. have been reported to express virulent gene coding for toxin-causing inflammation of intestinal linings resulting in fluid loss in response to the increase in temperature from $30\ ^{o}C$ to $37\ ^{o}C$ (80). Likewise, an increase in temperature may result in higher survival and increased load of diarrhoeagenic pathogens (especially, bacteria and protozoa) in their zoonotic host, facilitating the prolonged transmission of the pathogens (79). In addition, scarcity of water during dry summer months has been reported to facilitate transmission of waterborne diarrhoeagenic pathogens due to the compromised hygiene and altered feeding behaviours of the human host (35). Chronic scarcity of water in Kathmandu district during the dry summer seasons (293) could be therefore be one factor contributing to the higher risk of diarrhoea during the period of increased maximum temperatures (81). Likewise, compromised hygienic practice among the parents and care-givers during Kathmandu's dry and hot conditions might have favoured the increased transmission of pathogens to the children in our study. Although data on specific pathogens causing diarrhoea among children were not available, children below the age of 5 years have been reported to be more prone to infection with foodborne bacterial pathogens such as *Salmonella* spp., *Escherichia coli, Norovirus* genogroup I (GI) and II (GII) and *Campylobacter* when the ambient temperature is high (307-309), leading to increased hospitalization due to diarrhoea. In the context of Nepal, the diagnostic laboratories at public hospitals and community health care centres are generally not funded financially to test the viral aetiology of diarrhoea on a routine basis. Nor are pathology labs at community health care centres well equipped to carry out routine analysis of stool samples for the viral aetiology of diarrhoea. As such, cases of Rotavirus, Norovirus and other viruses causing childhood diarrhoea are under reported, which might have resulted in the distinct summer peak (Figure 4.1) of diarrhoea in our study compared to the bimodal distribution (summer and winter peak) of diarrhoea reported in some other studies analysing the effect of climate variation on paediatric diarrhoea (305).

In addition to maximum temperature, our findings also revealed a significant association between monthly average rainfall and diarrhoea burden among the children in Kathmandu district, Nepal with an estimated, 0.9% increase in diarrhoea burden for every 10 mm increase in rainfall within the same month. This result is in concordance with studies conducted in Bangladesh and Mozambique which have reported 5.1%, and 1.04 % increases in diarrhoea within four weeks of a heavy rainfall (37, 310). Our estimate of a 0.9% increase with each 10 mm increase in rainfall is slightly lower than the findings of a study in Bangladesh (37). This may be explained by the fact that Dhaka has been reported to have experienced several diarrheal epidemics during flooding episodes caused by excessive rainfall in the context of a monsoon (311). Regular flooding in Dhaka plays an important role in the contamination of water sources with pathogenic bacteria, giving rise to a higher incidence of diarrhoea during heavy rainfall events when compared to Kathmandu district, which has not recorded severe flooding for over 30 years. Rainfall can cause a flushing action, sending pathogens into surface and ground water sources through the infiltration of bacteria and protozoan oocysts deposited in soil by their zoonotic hosts and flushing out bacteria from fertilizers, leading to the contamination of water sources (35). This phenomenon has been previously reported for Kathmandu where, in addition to zoonotic sources, the seepage of waste water and the leakage of sewers from improperly constructed septic tanks have resulted in increased microbial contamination of water sources following the events of heavy rainfall (312).

We sought to quantify the burden of climate-attributable childhood diarrhoea in Nepal under future climate change scenarios for various time slices in the near (2030) and far future (2050). The outcomes of this study will serve to inform mitigation and adaptation policy in the management of the projected additional burden of childhood diarrhoea in Kathmandu under future climate change scenarios, as well as to inform strategies for resilience against the impacts of climate change. For the purposes of projecting climate change-attributable diarrhoea, we selected 3 different studies that have predicted the future increase in maximum temperature, under different climate change scenarios (Table 4.3), for Kathmandu district (292, 299, 300). These studies were classified as low, medium and high risk based upon the results of the future climate projections for the study site. We also included the 50th percentile of the climate projection for the South Asian region (1.5 ^{o}C; 0.5-2 ^{o}C) under the Representative Concentration Pathway 2.6 (RCP), reported in the IPCC 5th assessment report (134), as a standard reference for the study region. To the best of our knowledge this is the first study that has attempted to project the future burden of climate-attributable diarrhoea among children. Our study estimated a substantial increase of 700 to 5000 cases of climate-attributable diarrhoea among children in the Kathmandu district in the near (2030) and longer-term (2050) future. This finding highlights the imperative that the infection control and prevention division in Nepal prepare and enhance their capacity to respond to the increased prevalence of diarrhoea, whilst underscoring the risk of future climate change-related health impacts on children (298). The United States Centre for Disease Control and Prevention (CDC) has developed the Building Resilience Against Climate Effect (BRACE) framework to assist health officials in the development of strategies and programs to protect public health against the adverse effects of climate change (260). Out of the five sequential steps advocated by the BRACE framework (vulnerability assessment, projection of disease burden, assessment of public health interventions, development and implementation of adaptation plans, and evaluation of the impact of interventions), 'projection of the disease burden' is key. We anticipate that our childhood diarrhoea burden projection estimates will facilitate health officials in Nepal to design the subsequent phases of BRACE framework for the control of climate-attributable childhood diarrhoea.

Our findings can be utilized to inform the conceptualization and design of early warning systems for the prediction and control of childhood diarrhoea in Kathmandu based upon the observed variation in climate patterns in this area. These results can support evidence-based decision-making around the existing childhood diarrhoea control program via the inclusion of climate change adaptation perspective. The inclusion of climate change adaptation measures can further improve the efficacy of the Control of Diarrheal Disease (CDD) program, implemented under the Integrated Management of Childhood Illness (IMCI) by the Child Health Division of Ministry of Health and Population, Nepal.

At the same time, these findings should be interpreted with caution given the caveats associated with the study. Firstly, data used in this study was monthly-aggregated data on diarrhoea among children under 5 years of age, which limits the possibility of estimating the precise short-term effect of the exposure-response relationship that may vary within the span of a day or a week. Secondly, weak surveillance systems in low and middle-income countries like Nepal can lead to an under-estimation of the burden of disease due to under-reporting of cases, as well as a lack of the resources required to diagnose the precise aetiology of diarrhoea at the community level. Finally, the projection of diarrhoea counts was based on data published in peer reviewed studies that have made predictions with regard to future temperature changes, which might limit our ability to endorse their findings. In addition, these studies have used obsolete scenarios (SERS) in projecting future temperature increases, instead of the RCP-based scenarios endorsed by IPCC's 5th assessment report. Also, our assumption of no significant change in the study population during the estimation of disease projection may fail to reflect the role of change in population size, especially considering the massive demographic changes and mobility of people due to climate change.

In conclusion, our analysis demonstrated a strong association between diarrheal disease among children under 5 years of age and increases in maximum temperature and rainfall in Kathmandu, Nepal. Although these findings highlight the effect of regional climate impacts on childhood diarrhoea in Kathmandu, the precision of future predictions can be improved by analysing the short-term association between climate and disease data collected on a daily or weekly basis. Future research in environmental and infectious disease epidemiology in Nepal will produce impactful outcomes if disease morbidity and mortality data are reported on time, and systematically centralized in an electronic database and shared among researchers and policy makers.

Ethical consideration

The study was granted ethical approval by the Human Research Ethics Committee (HREC) of the University of Adelaide (H-2018-236), and the Nepal Health Research Council (Reg. no. 560/2018). Data related to human participants used in the study were non-identifiable and were analysed anonymously.

Conflict of Interest

We declare no conflict of interest.

Author's contribution

D.B: Research design, data curation, data analysis and manuscript preparation, P.B, J.B.S and S.H.E: Conceptualization, overall supervision and manuscript preparation; M.D: Data curation, conceptualization, manuscript preparation and overall supervision,

Acknowledgements

We would like to acknowledge the Department of Health Services Nepal and Department of Hydrology and Meteorology Nepal for providing the disease and climate datasets respectively. In addition, many thanks to Ms Susanne Edwards, Senior Statistician at the University of Adelaide for her guidance with statistical analysis and Ms Syeda Hira Fatima for her contribution in preparation of the study site map. Thanks to the anonymous reviewers for their insightful and detail comments. D.B is supported by Adelaide Scholarship International (ASI), provided by the University of Adelaide for his PhD study.

Supplementary materials

Supplementary table S4. 1 Model sensitivity testing for different lag periods and degree of freedom.

Model description	df.	estimates (β)	p value	qAIC
Model with lag of 1 month for both maximum temperature and rainfall.	3	0.09	0.006	21109.7
	4	0.08	0.022	21066.6[a]
	5	0.09	0.037	22920.2
	6	0.08	0.142	24373.5
	7	0.06	0.424	26373.5
Model with lag of 2 months for maximum temperature and lag 1 for rainfall.	3	0.08	0.011	21464.1
	4	0.09	0.025	22032.8
	5	0.10	0.031	22077.0
	6	0.09	0.147	22868.7
	7	0.15	0.089	23096.9
Model with lag of 2 months for both maximum temperature and rainfall.	3	0.11	0.092	21291.2
	4	0.10	0.075	21377.1
	5	0.10	0.034	21818.3
	6	0.03	0.563	22778.1
	7	0.11	0.213	22740.0

[a] Model with the lowest qAIC value was selected as the best fit and used for projection of climate attributable future increase in diarrhoea count.

Supplementary table S4. 2 Results of the literature search of the research work that have projected future increase in temperature for Kathmandu valley under different climate change scenarios.

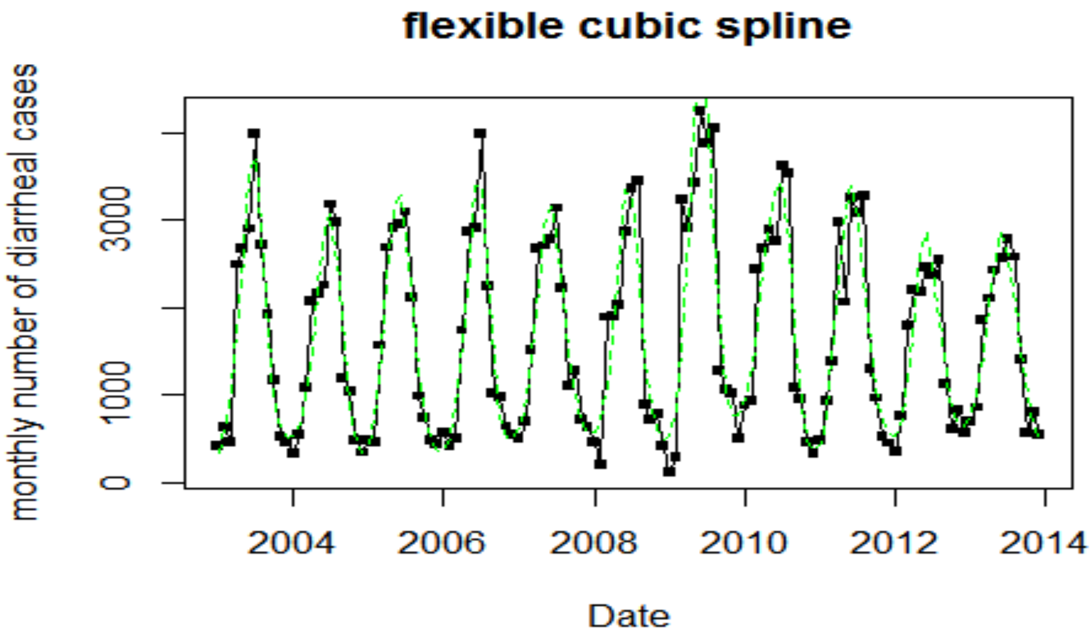
Study	Projection coverage	Climate model used	Scenarios	Projection years	Projected increase in temperature (ΔT in °C)	Remarks
Babel et al. 2014.	Kathmandu district (Baghmati river Basin)	5 GCM tested and HadCM3 was selected because of best fit	A2 based on SRES	2020s	0.5	Projection made for maximum temperature and GCM was downscaled
				2050s	1.1	
				2080s	2.1	
			B2 based on SRES	2020s	0.5	
				2050s	0.9	
				2080s	1.5	
Jha 2012.	Kathmandu valley	21 GCMS available in SimCLIM software and IPSL-CM40 used for projection	A1F1 based on SRES	2030s	1.8 – 1.9	Temperature type not mentioned.
				2050	3.7 – 3.8	
				2100	9.3 – 9.7	
McSweeney et al. 2006	Nepal	15 GCMs used to pool the estimates	A2	2030s	0.8-1.9	Mean annual temperature
				2060s	1.8-3.8	
				2090s	3.4-5.8	
			A1B	2030s	0.9-2.2	
				2060s	2.0-3.7	
				2090s	2.9-5.2	
			B1	2030s	0.8-1.7	
				2060s	1.3-2.8	
				2090s	1.8-3.9	
			A2	2030s	0.7-2.8	
				2060s	1.8-4.3	
				2090s	3.6-6.5	

WHO 2015	Nepal	GCMs from CMIP3 ensemble used to pool the estimate for 2 different scenarios under IPCC 5th assessment report.	RCP 8.5	2100	6		Mean annual temperature
			RCP 2.6	2100	1.6		
IDS-Nepal et al. 2014.	Kathmandu	9 models using downscaled data by climate system analysis group university of cape town	A2	2050	2-3		Mean annual temperature
NCVST 2009	Nepal	15 GCMs with details of name of all the models used in projection and 2 RCM models (PRECIS and RegCM3)	A2 based on SRES, due to closet match to observe emission for region since 2000	Years	Nepal	Central Nepal	RCM model used to make projection for central Nepal that includes Kathmandu district.
				2030s	1.4(0.5-2)	1.4 (0.9-2)	
				2060s	2.8(1.7-4.1)	3.0 (1.7-4.1)	
				2090	4.7(3-6.3)	4.9 (3.0-6.3)	

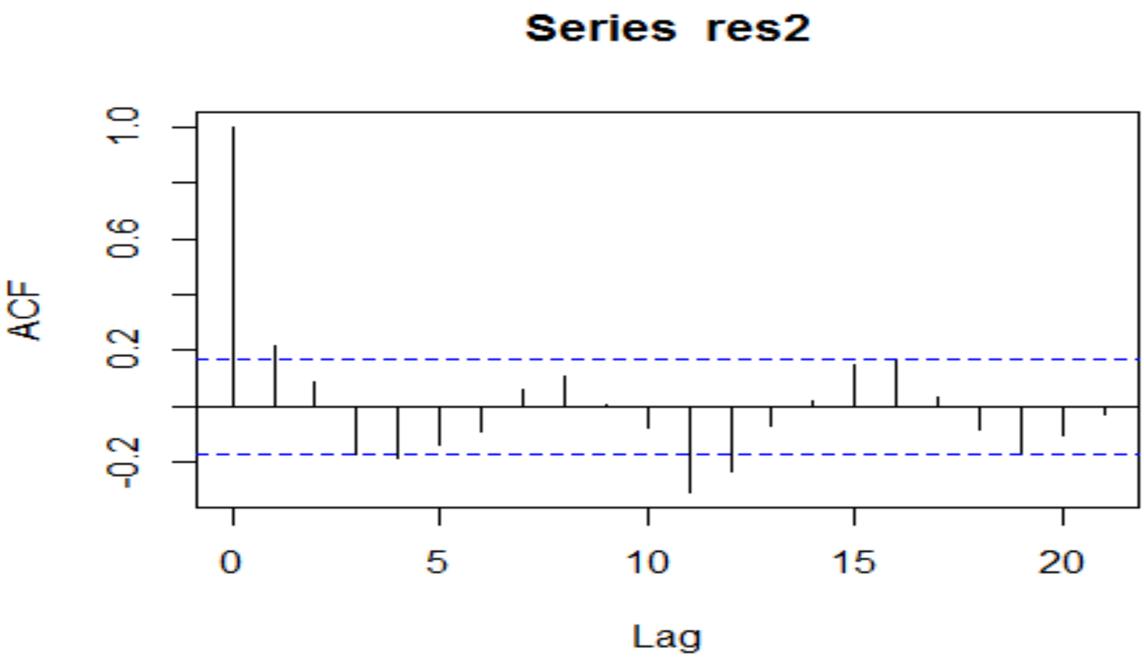
Supplementary table S4. 3 Calculation of projected increase in climate attributable diarrhoea burden among children under 5 years of age.

Risk scenarios	Projection by year	Δ T (projected temperature increase)	Lower estimate (β =0.023)			Projected count (β =0.078)			Upper count (β =0.134)			Count = $N (e^{(\beta * \Delta T)} - 1) / e^{(\beta * \Delta T)}$		
			A	B	C	A	B	C	A	B	C	Lower estimate	Projected count	Upper count
Low risk scenario	2020	0.5	1.012	0.012	0.011	1.040	0.040	0.038	1.069	0.069	0.065	228	766	1297
	2050	0.9	1.021	0.021	0.020	1.073	0.073	0.068	1.128	0.128	0.114	410	1357	2274
Medium risk scenario	2030	1.4	1.033	0.033	0.032	1.115	0.115	0.103	1.206	0.206	0.171	634	2071	3424
	2060	3.0	1.071	0.071	0.067	1.264	0.264	0.209	1.495	0.495	0.331	1335	4177	6627
High risk scenario	2030	1.8	1.042	0.042	0.041	1.151	0.151	0.131	1.273	0.273	0.214	812	2622	4290
	2050	3.7	1.089	0.089	0.082	1.335	0.335	0.251	1.642	0.642	0.391	1633	5019	7826
Reference	2065	1.5	1.035	0.035	0.034	1.124	0.124	0.110	1.223	0.223	0.182	679	2210	3645

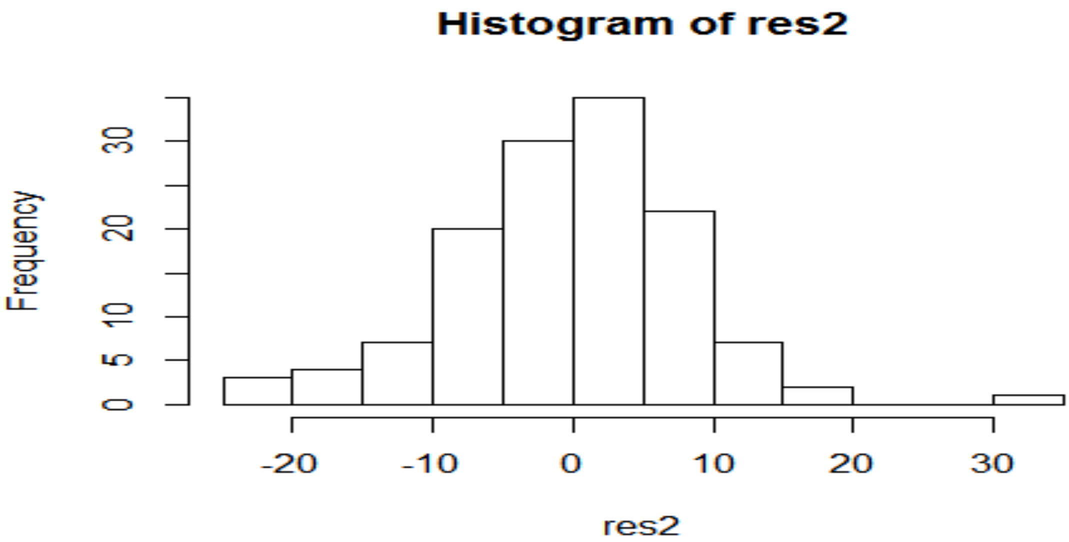
Where, N= 20,019; A= $e^{\wedge(\Delta T * \beta)}$; B= $(e^{(\beta * \Delta T)} - 1)$ and C= $(e^{(\beta * \Delta T)} - 1) / e^{\wedge(\Delta T * \beta)}$



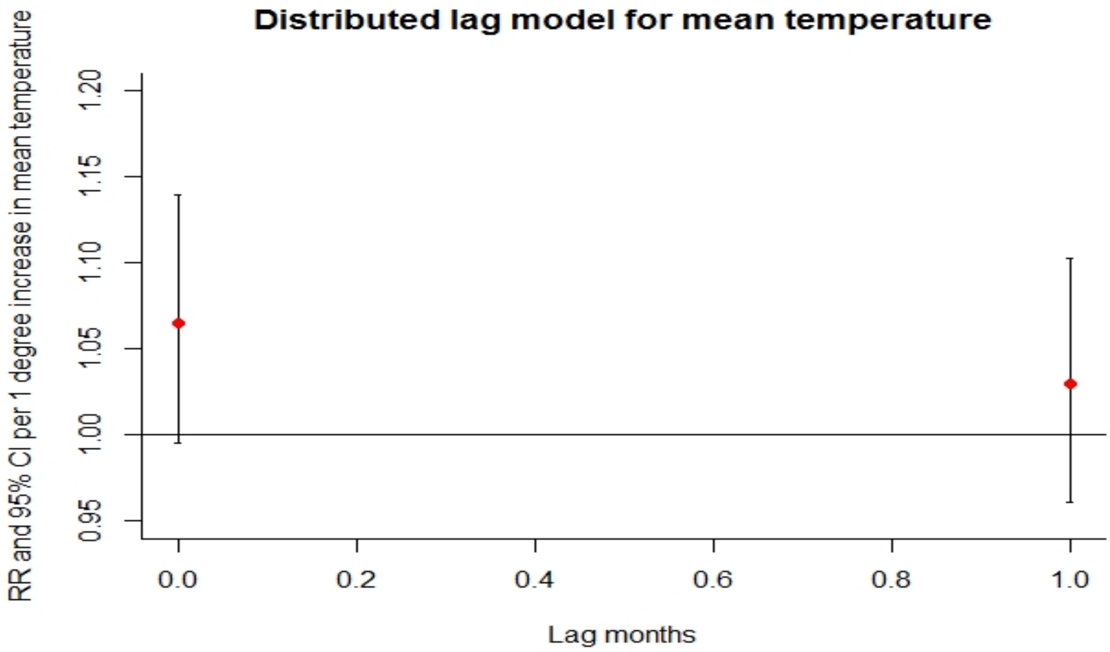
Supplementary Figure S4. 1 Smoothing the diarrheal diseases time series using natural cubic spline of 4 knots per year (df =4/year).



Supplementary Figure S4. 2 Autocorrelation plot of the residuals of the final model showing no positive residual autocorrelation.



Supplementary Figure S4. 3 Histogram of the residuals of the final model shows normal distribution.



Supplementary Figure S4. 4 Effect estimates for mean temperature and monthly childhood diarrhoea cases at different lag periods/months (Lag 0 and Lag 1), with reference to monthly average value of mean temperature.

Chapter 5 Study 2: Non-linear effect of temperature variation on childhood rotavirus infection: A time series study from Kathmandu, Nepal

Statement of Authorship

Title of Paper	Non-linear effect of temperature variation on childhood rotavirus infection: A time series study from Kathmandu, Nepal
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Bhandari, D., Bi, P., Dhimal, M., Sherchand, J. B., & Hanson-Easey, S. (2020). Non-linear effect of temperature variation on childhood rotavirus infection: A time series study from Kathmandu, Nepal. The Science of the total environment, 748, 141376.

Principal Author

Name of Principal Author (Candidate)	Dinesh Bhandari		
Contribution to the Paper	Conceptualization, Methodology, Data curation, Software, Formal analysis, Visualization, Writing - original draft, revision and editing		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	25/6/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Peng Bi		
Contribution to the Paper	Conceptualization, Resources, Validation, Supervision, Writing - review & editing		
Signature		Date	25/6/2021

Name of Co-Author	Meghnath Dhimal		
Contribution to the Paper	Data curation, Supervision, Writing - review & editing.		
Signature		Date	25/6/2021

Name of Co-Author	Jeevan Bahadur Sherchand		
Contribution to the Paper	Data curation, Supervision, Writing - review & editing.		
Signature		Date	25/6/2021

Name of Co-Author	Scott-Hanson Easey		
Contribution to the Paper	Conceptualization, Resources, Validation, Supervision, Writing - review & editing		
Signature		Date	25/6/2021

Abstract

Introduction: This study aimed to investigate the effects of temperature variability on rotavirus infections among children under five years of age in Kathmandu, Nepal. Findings may inform infection control planning, especially in relation to the role of environmental factors in the transmission of rotavirus infection.

Methods: Generalized linear Poisson regression equations with distributed lag non-linear model were fitted to estimate the effect of temperature (maximum, mean and minimum) variation on weekly counts of rotavirus infections among children under five years of age living in Kathmandu, Nepal, over the study period (2013 to 2016). Seasonality and long-term effects were adjusted in the model using Fourier terms up to the seventh harmonic and a time function, respectively. We further adjusted the model for the confounding effects of rainfall and relative humidity.

Results: During the study period, a total of 733 cases of rotavirus infection were recorded, with a mean of three cases per week. We detected an inverse non-linear association between rotavirus infection and average weekly mean temperature, with increased risk (RR: 1.52; 95% CI: 1.08-2.15) at the lower quantile (10^{th}percentile) and decreased risk (RR: 0.64; 95% CI: 0.43-0.95) at the higher quantile (75^{th} percentile). Similarly, we detected an increased risk [(RR: 1.93; 95%CI: 1.40-2.65) and (RR: 1.42; 95%CI: 1.04-1.95)] of rotavirus infection for both maximum and minimum temperature at their lower quantile (10^{th} percentile). We estimated that 344 (47.01%) cases of rotavirus diarrhoea among the children under five years of age were attributable to minimum temperature. The significant effect of temperature on rotavirus infection was not observed beyond lag zero week.

Conclusion: An inverse non-linear association was estimated between rotavirus incidence and all three indices of temperature, indicating a higher risk of infection during the cooler times of the year, and suggesting that transmission of rotavirus in Kathmandu, Nepal may be influenced by temperature.

Key words: Rotavirus, Environmental factors, Epidemiology, Children, Nepal

5.1 Introduction

Rotavirus infection was globally responsible for 29.3% (146,500 deaths) of all diarrhoea-related deaths among children below five years of age in 2015 (313), and 128,500 deaths among the same population in the following year (266). In the context of Nepal, rotavirus infection has been estimated to cause 50-100 deaths per 100,000 infection cases reported each year among children under five years of age (267). The worldwide distribution of rotavirus infection, regardless of the hygiene levels, socio-economic status, and food and air quality, highlights the important role of weather factors in the transmission of rotavirus diarrhoea (237, 314, 315). Rotavirus infection has been reported to show distinct seasonality with a winter peak in temperate regions, while a less pronounced seasonality has been observed in tropical regions where the infection prevails all year round (316) . In addition to tropical countries, year-round prevalence of rotavirus infection has been reported in several South Asian countries, including Bangladesh (316-319).

Kathmandu city lies in a warm, temperate zone, situated at an average elevation of 1,400 metres above sea level, and is characterised by a subtropical humid to subtropical highland climate. The annual average summer temperature varies from 28 °C to 30 °C, with the average winter temperature varying between 8 °C and 10 °C. The city receives monsoon rainfall with an average of 1,407 mm of rain per annum. According to the census of 2011, the total population of Kathmandu district was 1,744, 240 with a population density of 4,416 per sq. km. The population of the under five year age group was 111, 600 (320). With a low Gross National income of around US$2,472 and a lower Human Development Index (0.578), the socioeconomic development status of people living in this region is below the average value for South Asia countries (321). It is estimated that nearly 350 MLD (million litre per day) of waste water is produced in Nepal, of which only 5% is being treated currently (322). Direct discharge of untreated waste water and sewage into the water bodies is a common practise in Kathmandu that has led to transformation of water bodies into open sewage with contaminant and entero pathogens. In context of Kathmandu, a waste water treatment plant of capacity 17.3 MLD is partially in operation to clean up a major water body i.e., Bagmati river (322).

A hospital-based program of rotavirus infection surveillance was initiated in 2005 at Kanti Children Hospital, Kathmandu, through a collaboration between the Institute of Medicine, Tribhuvan University, Nagasaki University, and the University of Liverpool (323). This program was later integrated into the Asian Rotavirus Surveillance Network to continue rotavirus monitoring in Kathmandu, Nepal(276). Over the last decade, the annual prevalence of rotavirus infection among children under five years in Kathmandu has been reported to be between 22.2% and 33%. Infections occur year-round, with a higher incidence during the winter months (275, 323-325). A number of studies have used rigorous statistical methods to estimate the effects of climatic factors on rotavirus infections, while controlling for confounding variables and seasonal and long-term variation (103, 204, 237, 242, 243, 326, 327). However, few studies have been carried out in a warm, temperate region like Kathmandu city.

Given the lack of a unifying explanation for varying degrees of rotavirus seasonality across the world (328), investigating the role of local climatic conditions may provide insights into the transmission and epidemiology of rotavirus infection for a given location (314), especially for the city of Kathmandu with its unique climatic and socioeconomic characteristics. Although rotavirus burden has been consistently substantial over the past few decades, a rotavirus vaccine has not been introduced into the National Immunization Program of Nepal(275). As such, better understanding of the role of climatic factors and seasonal patterns in the spread of rotavirus in Kathmandu may support the implementation of effective vaccine intervention programs in the future(242). Discerning the role of environmental factors in virus transmission may help public health authorities design a more systematic plan for the prevention of rotavirus infection in Kathmandu during high risk periods. Furthermore, it may facilitate exploration of the broader effects of climate variation and climate change on rotavirus transmission in the Nepalese context (315). Thus, this study aims to explore the association between climatic factors and rotavirus infections among children younger than five years in the warm temperate zone of Kathmandu, Nepal, and to provide scientific evidence to local health authorities to support the design of an appropriate intervention program for the prevention of rotavirus infections in the context of a changing climate.

5.2 Methods

As mentioned earlier in Chapter 3 and Chapter 5, the methodology section in this chapter has been deliberately shortened to avoid redundancy between Chapter 3 and the methods sub section in each result chapters. Hence, this section as presented here, differs from the original methods section as published in the peer reviewed paper. A complete detail of methodology has already been discussed in the chapter 3 and only the statistical analysis section, which is unique to this chapter has been presented here.

5.2.1 Statistical analysis

Spearman's correlation analysis was carried out to assess the association between weekly rotavirus infections and climatic variables including temperature (maximum, mean and minimum), mean relative humidity and rainfall over the study period (*Supplementary figure S5.1*). We conducted a time series regression analysis to examine the relationship between the weekly average of climate variables and rotavirus infection count using a generalised Poisson regression model. We first checked the distribution of the weekly rotavirus count for over-dispersion using a regression-based test for the Poisson regression model (329) to ensure the data were not over-dispersed (*Supplementary figure S5.2*). We then carried out the univariate regression analysis for all climatic variables against the outcome variable i.e., total weekly count of rotavirus infection among children (<5 years). Three different indices of temperature (mean, maximum, and minimum) were the only variables significantly associated with rotavirus infection in the univariate models. Hence, to avoid multicollinearity, we finally defined three separate multivariable regression models for each temperature index by adjusting the possible confounding effects of relative humidity and rainfall. Seasonality and long-term effects were also adjusted in the model using Fourier terms up to the seventh harmonic and a function of time, respectively. We used distributed lag non-linear models using the DLNM package in software R (271) to model the non-linear and possible lagged effects of temperature on rotavirus infection. The DLNM model facilitates simultaneous exploration of the exposure-lag-response relationship between the predictor and outcome along a two-dimensional array of exposure and lagged effect (271). Using the DLNM package we modelled the effect of temperature with natural cubic splines of 3 degrees of freedom. Guided by previous research on the effect of climate variation on rotavirus infection (204, 237, 242), we set a lag period of 4 weeks to model the delayed effect using natural cubic splines of 3 degrees of freedom. The selection of spline type for both exposure and lag function was based upon the Akaike Information Criterion (AIC). The confounding effects of both rainfall and humidity were adjusted using the natural cubic spline of 3 degrees of freedom. Risk ratios of rotavirus infection in response to temperature variation were estimated with reference to the weekly median temperature value. In summary, the final model took the following form:

Log [E(y)] = α + (cbo_temperature) + time (Fourier, 7 harmonics/year) + NS (mean_rh, df=3) + NS (rainfall, df=3) + f (time)

where, E(y) is the expected weekly case count, cbo temperature is the cross basis matrix for three different indices of temperature, Fourier represents the Fourier (trigonometric) terms, NS (mean_rh) and NS (rainfall) are the weekly average humidity level and weekly cumulative rainfall total with natural cubic splines of 3 degrees of freedom, and time is the linear function of time.

The sensitivity of the model was analysed by changing the number of Fourier harmonics from 3 to 9 harmonics per year. The model with lowest AIC value and low (partial) autocorrelation was selected as the robust model (*Supplementary table S5.1 and figure S5.3)*.

5.2.1.1 Attributable risk estimation for rotavirus infection cases

We calculated the attributable risk of rotavirus infection against temperature exposure (maximum, mean and minimum) from risk estimates of a distributed lag non-linear model, using "attrdl.R" function in software package R, as previously described (272). Briefly, the backward attributable fraction and attributable number were calculated using risk estimates obtained from the dlnm model with reference to a counterfactual scenario of minimum exposure, indicated by the lowest relative risk, for maximum temperature, mean temperature and minimum temperature respectively.

5.3 Results

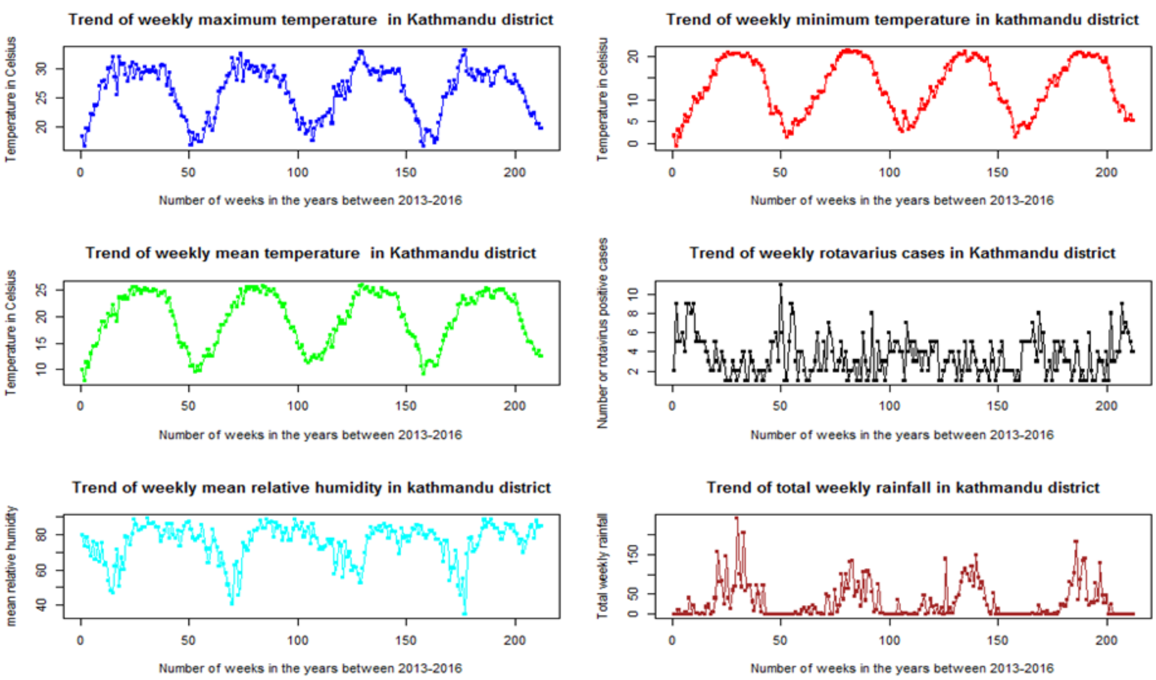
During the study period (2013-2016), a total of 733 cases of rotavirus infection were recorded among children under five years of age attending Kanti Children's Hospital, Kathmandu, Nepal. The average weekly number of cases of rotavirus infection among children younger than five years reported during the study period was three (Table 5.1).

Table 5. 1 Distribution of weekly average of meteorological data and Rotavirus infections among children under five years of age in Kathmandu, Nepal (2013-2016).

Study variables	Lowest	1st quartile	Mean	Median	3rd quartile	Highest
Maximum temperature (^{o} C)	16.50	22.25	26.07	27.70	29.52	33.10
Mean temperature (^{o} C)	7.90	14.80	19.52	20.40	24.30	26.10
Minimum temperature (^{o} C)	-0.80	7.675	12.957	12.95	19.40	21.20
Relative humidity (%)	34.80	71.50	75.61	78.10	83.60	89.10
Rainfall (mm)	0	0	31.18	7.40	47.40	239.20
Rotavirus count	1	2	3	3	5	11

The overall distribution pattern of rotavirus infection cases during the four year period showed year-round prevalence with a minimum of one case and a maximum of 11 cases reported during the total 212 weeks included in study (Figure 5.1). Age-specific distribution patterns of the cases and different variables recorded during the study period have been published elsewhere (275).

Figure 5. 1 Trend of meteorological data and weekly Rotavirus infection among children under five years of age in Kathmandu, Nepal



5.3.1 Relationship with maximum temperature

We estimated an inverse nonlinear association between rotavirus infection among children (<5 years) and maximum temperature, with an increased risk (RR: 1.93; 95% CI: 1.40-2.65) at the lower quantile (10th percentile) and decreased risk (RR: 0.95; 95% CI: 0.84-1.11) at the higher quantile (75th percentile) (Figure 5.2 & 5.3). The risk of rotavirus infection appears to increase at the 99th percentile of the temperature data, but the effect was not significant (Figure 5.2). The effect of maximum temperature on rotavirus was not significant beyond the lag period of zero weeks (*Supplementary figure S5.4*).

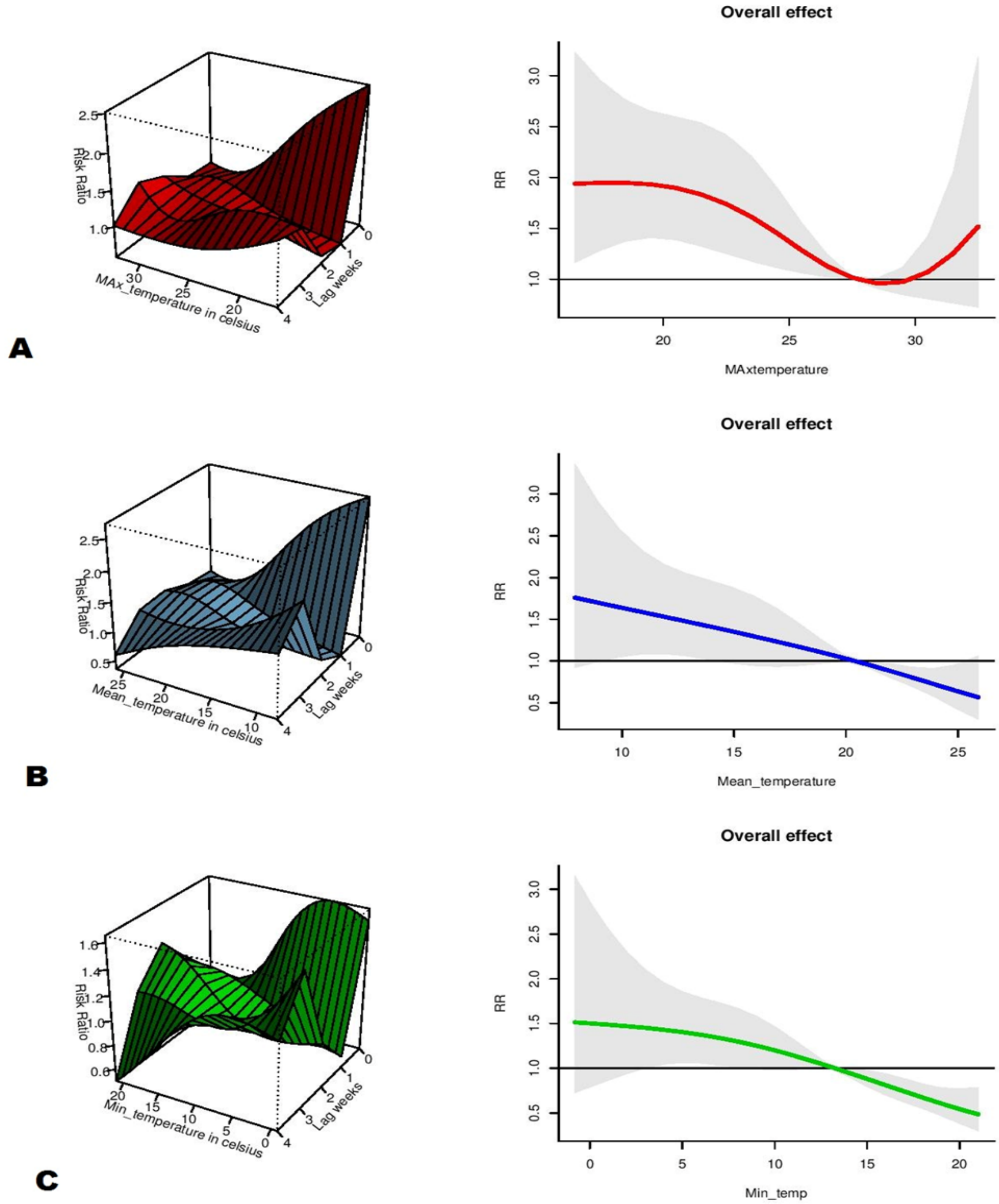


Figure 5. 2 Three dimensional plot and overall cumulative plot of risk ratio of rotavirus for maximum temperature (A), mean temperature (B) and minimum temperature (c).

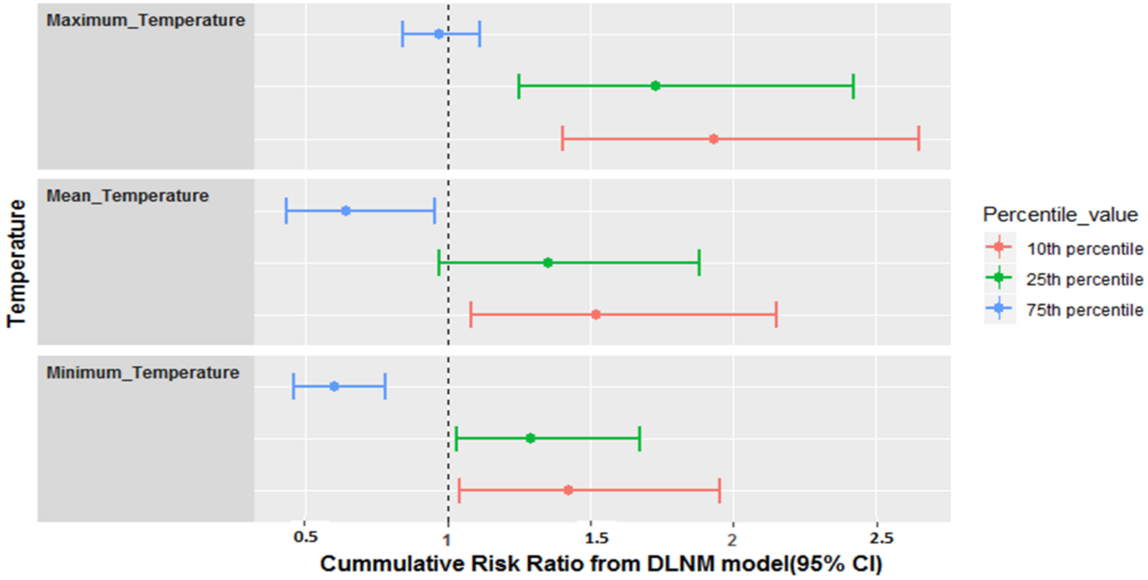


Figure 5. 3 Cumulative Risk Ratio of Rotavirus at different percentiles of temperature.

5.3.2 Relationship with mean temperature

As per the effect of maximum temperature, we also observed an inverse nonlinear relationship between mean temperature and rotavirus infections, with an increased risk (RR: 1.52; 95% CI: 1.08-2.15) at the lower quantile (10^{th} percentile) and decreased risk (RR: 0.64; 95% CI: 0.43-0.95) at the higher quantile (75^{th} percentile) (Figure 5.3). Akin to the effect of maximum temperature, the effect for mean temperature did not persist beyond the lag period of zero weeks *(Supplement figure S5.4).*

5.3.3 Relationship with minimum temperature

There was an inverse relationship between minimum temperature and rotavirus infection among children (<5 years), with increased risk (RR: 1.42; 95% CI: 1.04-1.95) at the lower quantile (10^{th} percentile) and decreased risk (RR: 0.60; 95% CI: 0.46-0.78) at the higher quantile (75^{th} percentile). Unlike maximum temperature, the protective effect of increased temperature against rotavirus infection continued beyond the 99^{th} percentile (Figure 5.2). Similarly, the effect of minimum temperature on rotavirus infection was also not observed beyond the lag period of zero week (*Supplementary figure S5.4*).

Overall, an inverse nonlinear association was detected between all three indices of temperature and rotavirus infection, with an increased risk of infection at the lower quantile and decreased risk at the higher quantile (Figure 5.2). Relative humidity and rainfall were not found to be associated with rotavirus infection among children (<5 years).

5.3.4 Rotavirus infection risk attributable to temperature

The estimates of total backward attributable risk (attributable number and attributable fraction) of rotavirus infection specific to different temperature indices are reported in Table 5.2. As outlined in the table, 47% (eCI: 24-60) of cases of rotavirus diarrhoea among the children under 5 years of age were attributable to minimum temperature.

Table 5. 2 Attributable risk (backward) of rotavirus infection among children (<5 years), specific to maximum temperature, mean temperature and minimum temperature, reported as attributable number and attributable fraction.

Temperature indices	Total attributable number	Attributable Fraction [%] (eCI)
Maximum temperature	131	17.86(3.44 -27.62)
Mean temperature	319	43.59(13.62-64.80)
Minimum temperature	344	47.01(26.66-61.05)

6.4 Discussion

We have used the state of art modelling technique (distributed lag nonlinear model), widely used in environmental epidemiology, to assess the short-term effect of temperature variability on the risk of rotavirus infection in Kathmandu, Nepal, while adjusting for seasonality, long-term variation, lag-effect and other possible meteorological factors such as rainfall and humidity. Despite the year-round detection of rotavirus infection, our study has found that lower temperature poses a higher risk of rotavirus diarrhoea incidence among children under 5 years of age in Kathmandu, demonstrating an inverse non-linear relationship with all three indices of temperature. Our findings with regard to the increased risk of rotavirus transmission on colder days of the year in Kathmandu supports public health practitioners and health policy-makers to design and deploy effective intervention programs for the prevention of rotavirus infection in Nepal, considering the climatic aspect of virus transmission. The Epidemiology and Disease Control Division of Nepal, in coordination with electronic and print media, might usefully broadcast special alerts to promote precautionary measures during winter high-risk periods, such as improved hygiene practices (e.g., hand washing, proper dispensing of baby diapers), and advice to reduce unnecessary physical interaction with children to prevent rotavirus transmission form carrier to susceptible children (104). In the absence of mandatory rotavirus vaccinations in Nepal, these findings further highlight the importance of identifying specific pathways (interactions between host and environmental factors) through which a higher risk of rotavirus transmission is mediated during colder days in Kathmandu.

Apart from the increased survival duration of viral particles at low temperatures, the biological reasons behind the higher transmission rate of rotavirus infection at lower temperature remains unclear (328). A plausible explanation for the increased risk of rotavirus infection at lower temperatures could be a due to poorer hygienic practices in cooler conditions, for example, reduced hand washing frequency during cold weather, which may increase chances of faecal-oral transmission of rotavirus (330). We speculate that the reluctance of people to leave a warm place, or the irregular availability of warm water in high-risk areas of sub-Saharan Africa and South Asia, may compromise the hand hygiene practices of mothers and caregivers during cold weather. In the context of Kathmandu district, 58.7% of households live in rental housing (331), and the average number of rooms per household in Nepal is 4.4 (332). Given the higher population density (4,416 person per sq.km) of Kathmandu district (320), and the lower number of rooms per household, it is highly likely that residents living in rented houses are living in overcrowded conditions. Indeed, an increased risk of rotavirus transmission in cold weather due to the overcrowding of people in rented households has been previously reported in England and Wales (237, 333). Hence, increased proximity among people living in overcrowded conditions is likely to cause more frequent physical interaction between individuals, especially between susceptible children and their caregivers, which may be a key facilitator of the transmission of rotavirus in Kathmandu city during cold weather. Similarly, the increased physical interaction between children and their caregivers during cold weather, facilitating airborne droplet-mediated transmission of rotavirus from asymptomatic adults to children, could be another plausible cause of virus transmission during these conditions (330). Meanwhile, some research has indicated that the higher transmission of rotavirus in colder conditions may not be directly related to lower temperatures *per se*, but rather, be the result of unfavourable conditions for rotavirus transmission during hot summer days, given the lower survival rate of rotavirus at higher temperatures and in higher humidity (314, 334).

The inverse association between rotavirus infection and temperature observed in our study is consistent with previous studies conducted in the Netherlands and Great Britain (237, 243), Spain(326), Australia (242), Turkey (245), Hong Kong (327) and Indonesia (234). These studies were conducted in a diverse climatic zones, ranging from cool temperate, dry temperate, sub-tropical coastal to a humid tropical, and spanned diverse socio-economic contexts, yet have reported similar findings to our results recorded in a sub-tropical highland climate, strengthening evidence for the negative association between rotavirus infection and temperature irrespective of the climate type. A multisite study including Bhaktapur city, Nepal, also reported an inverse association between rotavirus infection and temperature (103). Bhaktapur city shares its boundary with Kathmandu city, and both cities have similar climatic characteristics. Colston et al, (103), however, have adjusted for additional variables including soil moisture, solar radiation and specific humidity in their final model while estimating the effect of daily mean temperature on rotavirus infection in Bhaktapur city.

Two separate systematic reviews and meta-analyses on the seasonality of rotavirus in South Asian and Tropical countries have reported a 1.3% and 10% (95% CI: 6-13%) decrease in rotavirus infection respectively, with a 1°C increase in mean temperature (232, 314). These studies have only used mean temperature as the primary exposure variable, but we have used all three temperature indices to measure the exposure-response relationship between temperature and rotavirus incidence in our study. In addition, most of these studies have assumed a linear relationship between rotavirus and temperature except for one study in the Netherlands (243, 314). In contrast, we have used a distributed lag non-linear model to estimate non-linear and possible lag association between temperature exposure and risk of rotavirus infection, as the use of conventional modelling strategy using splines and an unconstrained distributed lag model to account for non-linearity may result in imprecise estimates with wider confidence intervals due to a higher correlation between lag terms used in the model (268).

Contrary to the findings of a majority of previous studies, a study from Bangladesh reported that a higher temperature (mean temperature) above a threshold (29 °C) was positively associated with an increased risk of rotavirus infection (204). For this reason, most of the high-temperature weeks coincided with heavy rainfall in the study site (Dhaka), a complex interaction of several climatic factors which might have driven the temperature-dependent effect modification on rotavirus infection in this study (237) . Intriguingly, in our study, the risk of rotavirus infection appeared to increase with the increase in maximum temperature towards the 99th percentile; however, the result was not statistically significant and showed a very wide confidence interval, which could have stemmed from the relatively smaller sample size of rotavirus positive cases. Consequently, we checked for the weeks with a maximum temperature above 31 °C in our dataset, and discerned that mean relative humidity during these weeks was below the first quantile and that these weeks were dry with low rainfall (10 weeks out of the 14 weeks had cumulative rainfall <2.5 mm), suggesting that dry weather conditions with low humidity could have been responsible for the observed pattern of increased risk towards the higher percentile of maximum temperature. Several epidemiological and laboratory based studies have reported that low relative humidity and dry conditions can be conducive for insitu survival and higher transmission rate of rotavirus (232, 314, 334), which may explain the aberrant observation of an increased slope of exposure risk curve for maximum temperature, towards the 99th percentile in our study.

Besides the use of a distributed lag non-linear model, another strength of our study is the inclusion of minimum temperature as an exposure variable. Given the observed negative association between temperature and the winter peak of rotavirus infection in Kathmandu over the past decade (243, 275, 323, 325), it is essential to identify the minimum temperature range that poses a higher risk of infection among the exposed population. As observed in our findings, the risk of developing rotavirus infection is significantly higher at the lower quantiles (10th percentile as well as the 25th percentile) of the minimum temperature with reference to its median value. This observation implies that days with a minimum temperature between 4.2 °C to 7.8 °C represent high risk days for rotavirus infection among children in Kathmandu. Following this observation, to quantify rotavirus infection cases that could have been reduced with reference to the counterfactual scenario of lowest risk exposure (specific to minimum temperature), we used a backward attributable risk perspective and calculated attributable risk. From among the estimates of "dlnm" model, the lowest risk i.e., RR: 0.48 (95% CI: 0.29-0.78), corresponding to 21 °C (minimum temperature) was used as a reference value. We observed that the attributable fraction of rotavirus infection specific to minimum temperature exposure was 47.01%, which means that nearly half of the cases of rotavirus infection can be attributed to minimum temperature. This finding implies that, among the temperature indices used in our study, minimum temperature is an important predictor of rotavirus infection in Kathmandu. This information is crucial in minimizing the risk of rotavirus infection among children through the adoption of safe food handing and hand hygiene practices (104).

We observed an acute effect of temperature variation on rotavirus infection among children at different percentiles of all three indices of temperature. This finding may be related to the fact that rotavirus is a self-limited diarrheal illness (among immune competent hosts) that lasts only a few days and has a relatively short incubation period i.e., approximately 2 days, and usually less than 48 hours (104). Due to the unavailability of daily count data, we only used the weekly count of rotavirus infection cases, and the risk of rotavirus infection for different percentiles of temperature indices in our study was not significant at lag one or at subsequent weeks up to the fourth week (*Supplement figure S5.4*). Similar results indicating the acute effect of temperature on rotavirus infection have been reported in previous studies, including one from Nepal (103, 204, 237, 242). Atchison et al. (237), however, reported a lag effect of up to four weeks for the reported count of rotavirus, and an immediate effect for infection-rate parameters in their study conducted in the Netherlands and Great Britain. This prolonged lag effect could have been due to patients' inaccurate recall, or recall bias, regarding the precise date of diarrhoea onset when attending clinical facilities for treatment of diarrhoea (335). However, the biological plausibility (if any exists) behind the prolonged lag effect of temperature in their study remains unexplained.

Apart from temperature, we did not find a significant association between rotavirus infection and other meteorological variables i.e., mean relative humidity and total weekly rainfall. These findings mirror the results of studies from Great Britain, the Netherlands and Turkey (237, 245), and resonate with the findings of other epidemiological studies and laboratory based evidence (232, 314, 334). However, our findings did differ from those conducted in Australia (242), Bangladesh (204) and Hong Kong (327). Such differences could be due to geographical location, heterogeneities in socioeconomic conditions, demographic factors, behavioural factors or other environmental factors that may interact with climatic factors, complicating the dynamics of disease epidemiology at a local level (336).

The use of data from a single sentinel surveillance site may be a limitation of our study, as surveillance data only captures the proportion of cases seeking medical attention at the given facility. Hence, it is highly likely that rotavirus burden in Kathmandu is much higher, and the data analysed in our study may not necessarily represent all cases. Likewise, the use of weekly data spanning the period of four years for the purpose of a time series analysis may be another limitation of our study. We carried out subgroup analysis for gender, different age groups (stratified by months) and degree of dehydration to see if they are differentially associated with the exposure variables. Probably, due to the small sample size of our study, we could not find a significant association among gender, age groups and degree of dehydration with any of the exposure variables (maximum, minimum and mean temperature) used in the multivariate analysis (results not shown). Ideally, for trend analysis on the short-term effect of exposure-response relationships in environmental epidemiology, daily data for a considerably longer time period is desired. Rotavirus is a highly contagious disease with an increased likelihood of transmission from person-to-person contact. As such, failure to include a Susceptible-Infected-Recovered (SIR) model in our analysis may undermine the influence of host immunity on rotavirus transmission in our ecological model (337). A common problem associated with conducting epidemiological studies in low- and middle-income countries is the unavailability of updated information on demographic characteristics of the study population. The unavailability of this data, and other relevant health information, constrained us from conducting regression analysis using SIR parameters in our time series model. Despite these limitations, the major strengths of our study are the use of laboratory-confirmed cases on rotavirus infections furnished by a member laboratory of the Asian Rotavirus Surveillance Network, and the use of a distributed lag non-linear model for estimation of the exposure-response relationship.

In conclusion, our analysis demonstrated an inverse non-linear association between rotavirus incidence and all three indices of temperature, indicating a higher risk of infection during the cooler times of the year, and lower risk during the hotter times, in Kathmandu, Nepal.

Ethical consideration

The study was granted ethical approval by the Human Research Ethics Committee (HREC) of The University of Adelaide (H-2018-236), and Ethical Review Board of the Nepal Health Research Council (Reg. no. 560/2018). Data related to human participants used in the study were non-identifiable and were analysed anonymously.

Conflict of Interest

We declare no conflict of interest.

Abbreviations

AIC: Akaike Information Criterion; CI: Confidence Interval; DLNM: Distributed Lag Nonlinear Model; eCI: Empirical Confidence Interval; ELISA: Enzyme-linked immune sorbent assay; NS: Natural Cubic Spline; RR: Relative Risk; RT-PCR: reverse-transcription polymerase chain reaction; SIR: Susceptible-Infected-Recovered; WHO: World Health Organisation

Acknowledgements

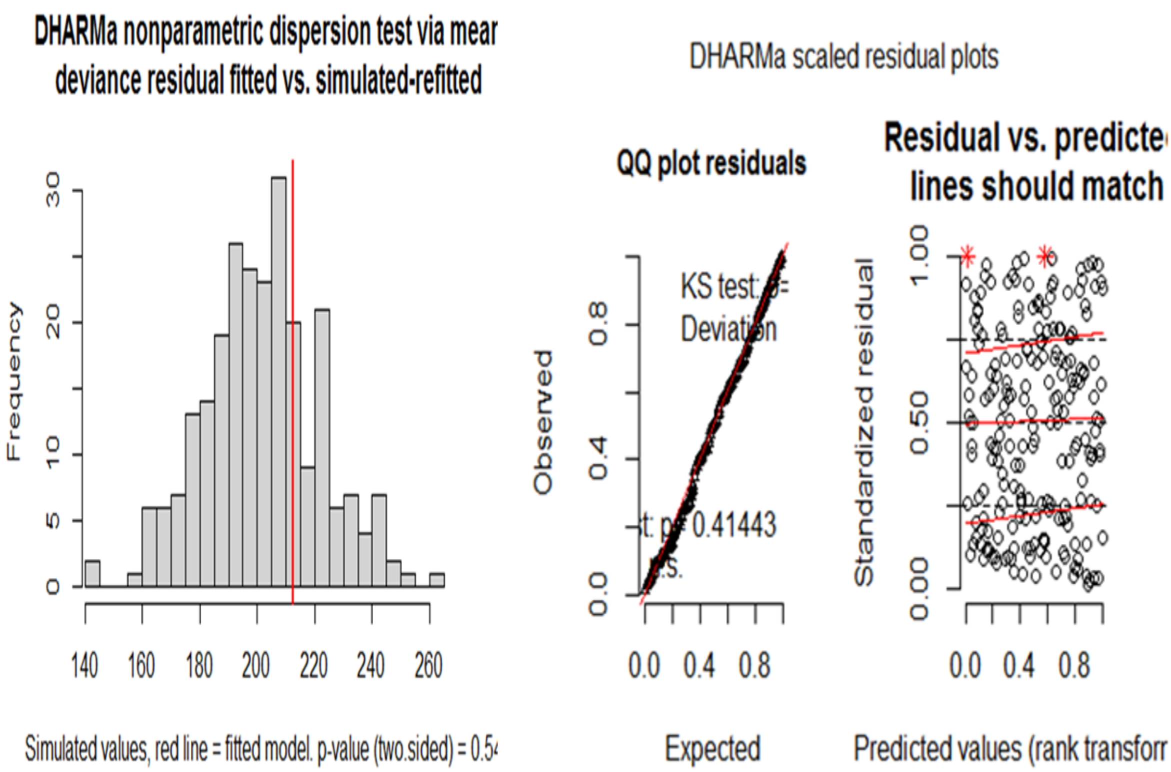
We would like to acknowledge all the members of the rotavirus surveillance team in Kathmandu, Nepal involved in data collection and the laboratory analysis of collected samples. The authors would like to acknowledge Department of Hydrology and Meteorology Nepal for providing climate dataset. In addition, many thanks to Ms Susanne Edwards (senior statistician), the University of Adelaide for her guidance with statistical analysis. D.B is supported by Adelaide Scholarship International provided by the University of Adelaide for his PhD study.

Supplementary materials

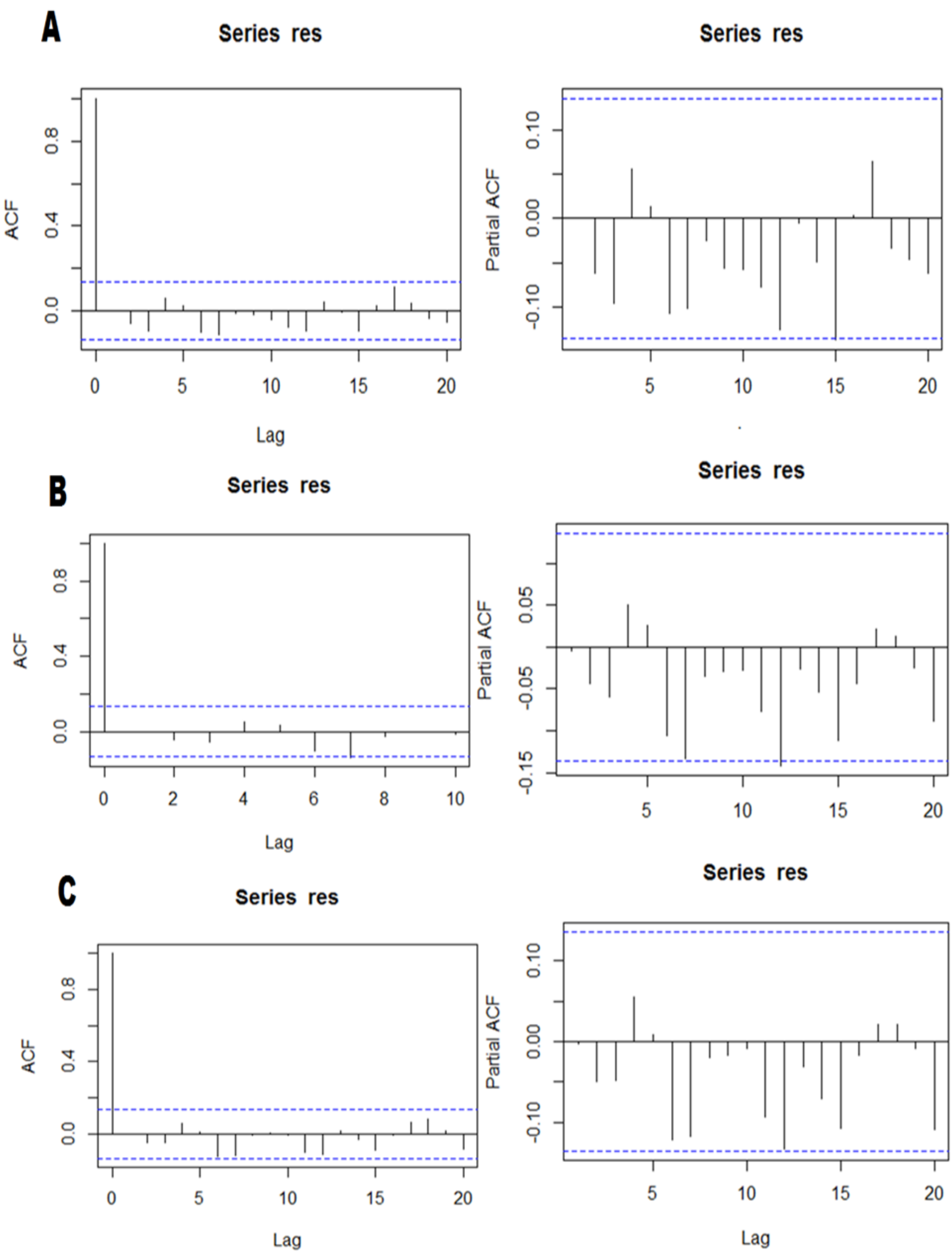
Supplementary table S5. 1 Model sensitivity test with different pair of harmonics.

Predictor variable	Number of Harmonics	Cumulative RR for 10th percentile of temp.	Cumulative RR for 25th percentile of temp.	Cumulative RR for 75th percentile of temp.	AIC
mean_temp	3	1.35(0.97-1.88)	1.24(0.90-1.70)	0.64(0.44-0.93)	844.2
mean_temp	4	1.44(1.02-2.02)	1.29(0.93-1.78)	0.59(0.40-0.86)	842.6
mean_temp	5	1.45(1.03-2.04)	1.31(0.95-1.82)	0.64(0.43-0.95)	844.4
mean_temp	6	1.47(1.04-2.07)	1.30(0.94-1.81)	0.65(0.43-0.97)	846.0
mean_temp	7	1.52(1.08-2.15)	1.35(0.97-1.88)	0.64(0.43-0.95)	841.1
mean_temp	8	1.53(1.08-2.15)	1.35(0.97-1.88)	0.63(0.42-0.94)	844.8
mean_temp	9	1.53(1.08-2.16)	1.35(0.97-1.88)	0.64(0.43-0.95)	848.3
max_temp	3	1.66(1.24-2.24)	1.64(1.12-2.13)	0.94(0.83-1.06)	847.5
max_temp	4	1.80(1.30-2.57)	1.61(1.16-2.22)	0.95(0.80-1.04)	847.5
max_temp	5	1.78(1.31-2.43)	1.62(1.17-2.24)	0.95(0.83-1.08)	846.3
max_temp	6	1.87(1.36-2.56)	1.69(1.22-2.36)	0.98(0.86-1.13)	846.9
max_temp	7	1.93(1.40-2.65)	1.73(1.25-2.42)	0.97(0.84-1.11)	844.0
max_temp	8	1.94(1.41-2.67)	1.74(1.25-2.42)	0.97(0.84-1.11)	847.3
max_temp	9	1.94(1.41-2.67)	1.73(1.24-2.41)	0.97(0.84-1.12)	851.0
min_temp	3	1.27(0.94-1.71)	1.20(0.95-1.52)	0.61(0.47-0.78)	842.1
min_temp	4	1.38(1.01-1.88)	1.31(1.02-1.68)	0.57(0.44-0.74)	840.9
min_temp	5	1.36(0.99-1.85)	1.29(1.01-1.66)	0.59(0.45-0.76)	841.8
min_temp	6	1.36(0.99-1.18)	1.28(0.99-1.64)	0.59(0.46-0.77)	843.1
min_temp	7	1.42(1.04-1.95)	1.29(1.03-1.67)	0.60(0.46-0.78)	839.2
min_temp	8	1.42(1.04-1.95)	1.29(1.02-1.72)	0.60(0.37-0.76)	842.6
min_temp	9	1.42(1.04-1.95)	1.30(1.01-1.67)	0.59(0.46-0.77)	846.6

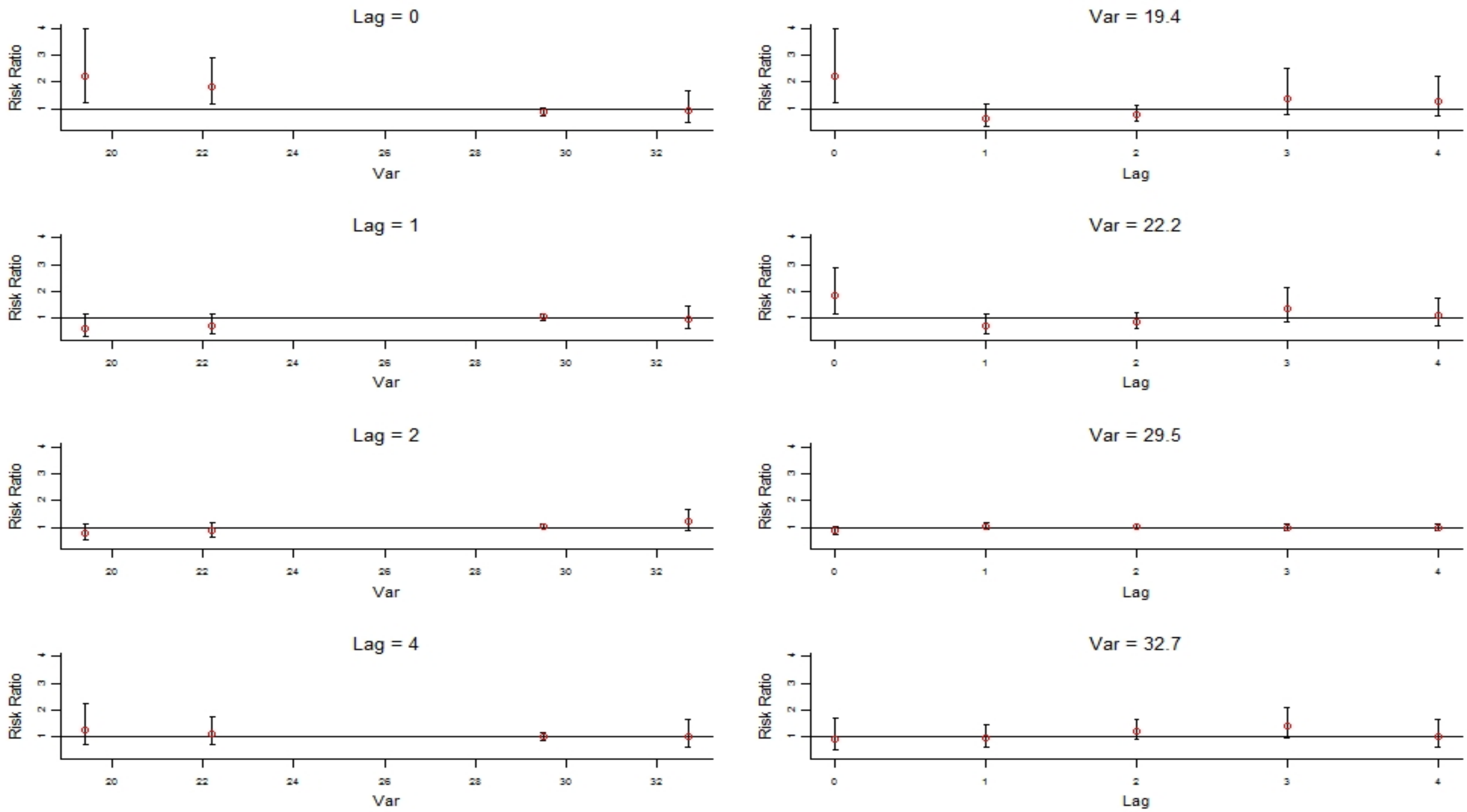
Supplementary Figure S5. 1 Spearman's correlation plot of the study variables.



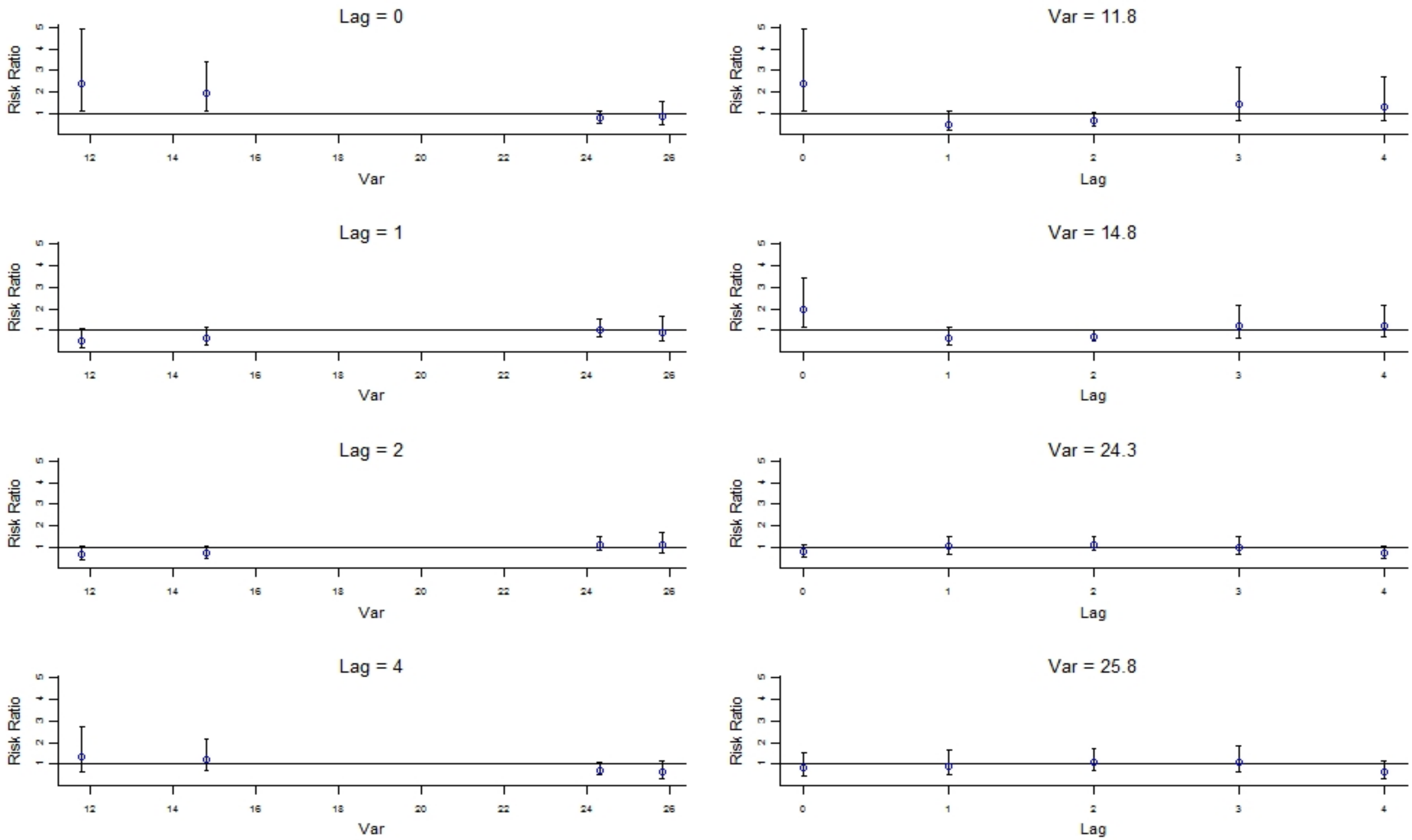
Supplementary Figure S5. 2 Histogram and QQ plot of the residual vs. simulated distribution shows data are not over dispersed.



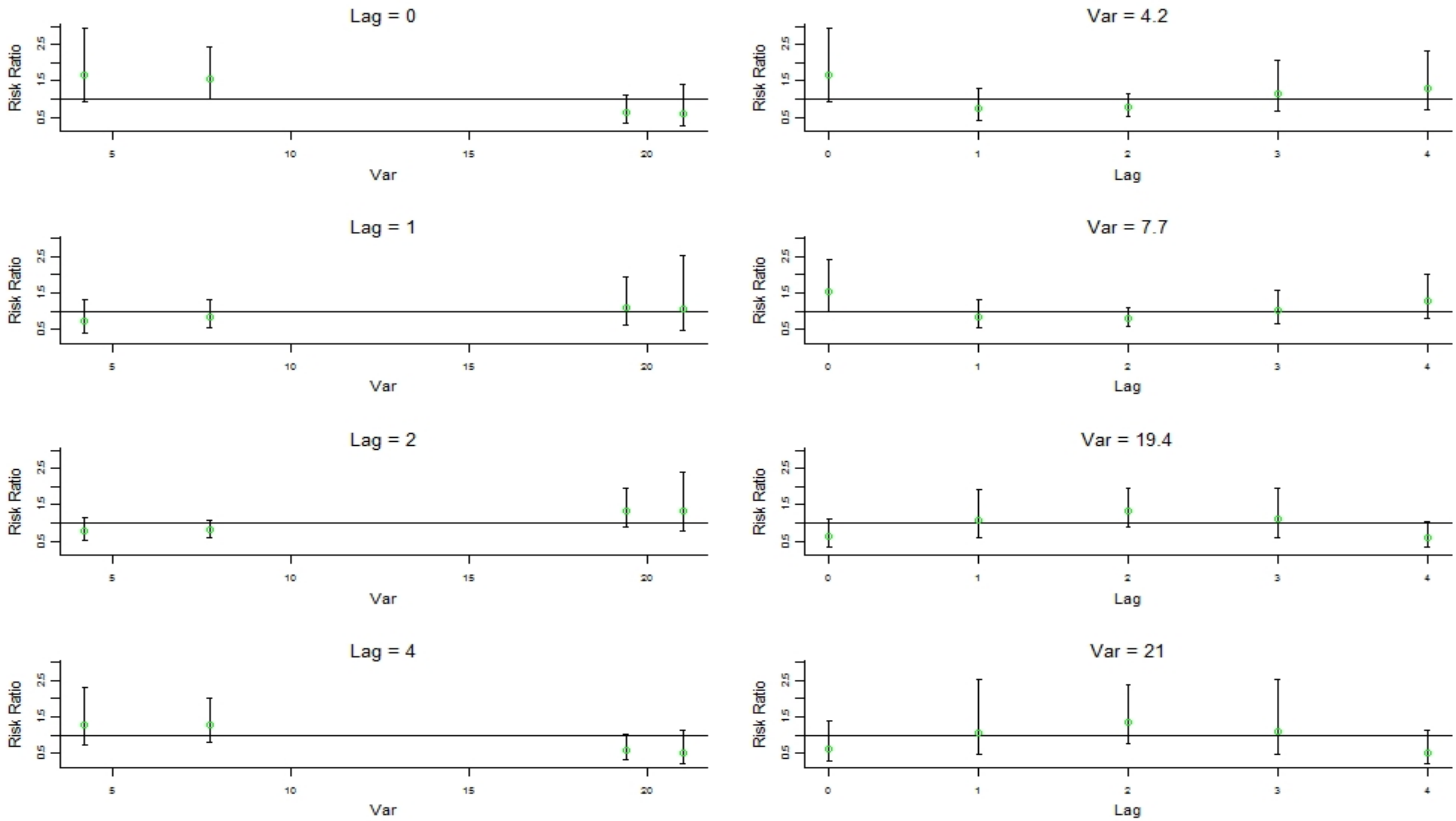
Supplementary Figure S5. 3 Autocorrelation and partial autocorrelation plots of model for maximum temperature (A), mean temperature (B) and minimum temperature (c



Supplementary Figure S5. 4 Lag specific effects of rotavirus risk at 10th, 25th, 75th and 99th percentiles of maximum temperature with reference to the median value.



Supplementary Figure S5. 5 Lag specific effects of rotavirus risk at 10th, 25th, 75th and 99th percentiles of mean temperature with reference to the median value



Supplementary Figure S5. 6 Lag specific effects of rotavirus risk at 10th, 25th, 75th and 99th percentiles of minimum temperature with reference to the median value

Chapter 6 Study 3: Climate change and infectious disease research in Nepal: Are the available prerequisites supportive enough to researchers?

Statement of Authorship

Title of Paper	Climate change and infectious disease research in Nepal: Are the available prerequisites supportive enough to researchers?
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Bhandari, D., Bi, P., Sherchand, J. B., Dhimal, M. and Hanson-Easey, S. (2020). Climate change and infectious disease research in Nepal: Are the available prerequisites supportive enough to researchers? Acta Tropica, 204, 105337

Principal Author

Name of Principal Author (Candidate)	Dinesh Bhandari		
Contribution to the Paper	Conceptualization, Methodology, Writing - original draft, review and editing.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	25/6/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Peng Bi		
Contribution to the Paper	Supervision, Writing - review & editing		
Signature		Date	25/6/2021

Name of Co-Author	Jeevan Bahadur Sherchand		
Contribution to the Paper	Supervision, Writing - review & editing		
Signature		Date	25/6/2021

Name of Co-Author	Meghnath Dhimal		
Contribution to the Paper	Supervision, Writing - review & editing		
Signature		Date	25/6/2021

Name of Co-Author	Scott-Hanson Easey		
Contribution to the Paper	Supervision, Writing - review & editing		
Signature		Date	25/6/2021

Abstract

Although Nepal has been identified as a country highly vulnerable to adverse health and socioeconomic impacts arising from climate change, extant research on climate sensitive infectious diseases has yet to develop the evidence base to adequately address this threat. In this opinion paper, I identify and characterise basic requirements that are hindering the progress of climate change and infectious disease research in Nepal. My considered view is that immediate attention should be given to strengthening Nepal's public health surveillance system, promoting inter-sectoral collaboration, improving public health capacity, and enhancing community engagement in disease surveillance. Moreover, I advocate for greater technical support of public health researchers, and data sharing among data custodians and epidemiologists/researchers to generate salient evidence to guide relevant public health policy formulation aimed at addressing the impacts of climate change on human health in Nepal. International studies on climate variability and infectious diseases have clearly demonstrated that climate sensitive diseases, namely vector-borne and food/water-borne diseases, are sensitive to climate variation and climate change. This research has driven the development and implementation of climate-based early warning systems for preventing potential outbreaks of climate-sensitive infectious diseases across many European and African countries. Similarly, I postulate that Nepal would greatly benefit from a climate-based early warning system, which would assist in identification or prediction of conditions suitable for disease emergence and facilitate a timely response to reduce mortality and morbidity during epidemics.

Key words: climate change, infectious diseases, public health, Nepal

6.1 Introduction

Although the role of climatic variables and associated environmental factors in exacerbating the spread of infectious diseases has been known for centuries, extensive research investigating the impacts of climate variability on infectious diseases soared towards the end of the twentieth century (51, 338, 339). Abundant literature on climate variations and infectious diseases published over the last two decades has clearly demonstrated that climate-sensitive diseases, namely vector-borne and food/water-borne diseases, are highly affected by climate variability and climate change (47, 340, 341). Based on the evidence generated from extensive epidemiological studies, several American, European and some of the African countries have envisaged and implemented climate-based early warning systems for preventing potential epidemics of infectious diseases in the near future (342-345).

In the context of Nepal, despite a high prevalence of climate sensitive infectious diseases, limited evidence is available on the effect of climate change on infectious diseases transmission. A systematic review on climate change and vector borne disease in Nepal published in 2015 identified eight studies that have examined the association between vector borne diseases and climate variables (14). However, most of these studies were entomological studies that explored spatiotemporal distributions of disease vectors and offer little epidemiological insights on the risk of infectious disease incidence in changing climate. Although the primary objective of this paper is not to synthesise current evidence on climate variability and infectious disease in Nepal, a brief summary of updated evidence is presented in table 6.1.

In this opinion paper, we identify challenges with basic prerequisites that might be hindering the progress of climate change and infectious disease research in Nepal. We highlight key problems in the public health agency that need immediate attention, to support public health researchers in generating evidence to guide relevant public health policy formulation for mitigating the impacts of climate change on human health in Nepal.

6.2 Climate change vulnerability in Nepal

The land topography of Nepal is highly variable, ranging from high altitudes in the Himalaya Mountains in the north-western border area, to the low south-eastern plain at around 300 metres above sea level (16). This range of altitudes strongly influences climate variability across the country, which has a total surface area of 14,7181km^2 and extends across a narrow latitudinal distance, an average north–south width of 140km (Figure 6.1). The lowland region of the south-eastern plains has a warm and humid subtropical climate with summer temperature between 22–27°C, dropping to 10–15°C in winter. The high hills in the northern belt are considerably colder, ranging between 5–15°C during the summer with winter temperature dropping below zero (346). A vulnerability assessment report on climate change effects in Nepal suggests that mean annual temperature of Nepal will increase by 0.5°C to 2.0°C by the 2030s and 1.7°C to 4.1°C by the 2060s, under a high emission scenario (292). The rate of warming in the Himalayan region has been reported to be greater by 0.06°C per year than the average warming rate at global scale (347). A recent landmark report on the assessment of climate change impacts on the Hindu Kush Himalaya region has highlighted that the livelihood of almost two billion people (including 30 million Nepali people) inhabiting this region is under serious threat as a consequence of natural and anthropogenic climate change (348). The report highlighted increased environmental, social and economic vulnerability among people living in this region. In the context of Nepal, issues like rapid melting of the Himalayan glacier, poor nutrition, food insecurity and increased frequency of extreme rainfall events (an increment of 31% by 2021-2050 for Representation Concentration Pathway 4.5 and 88% by 2071-2100 for Representation Concentration Pathway 8.5, for Langtang basin of Nepal) were identified a major concerns (348).

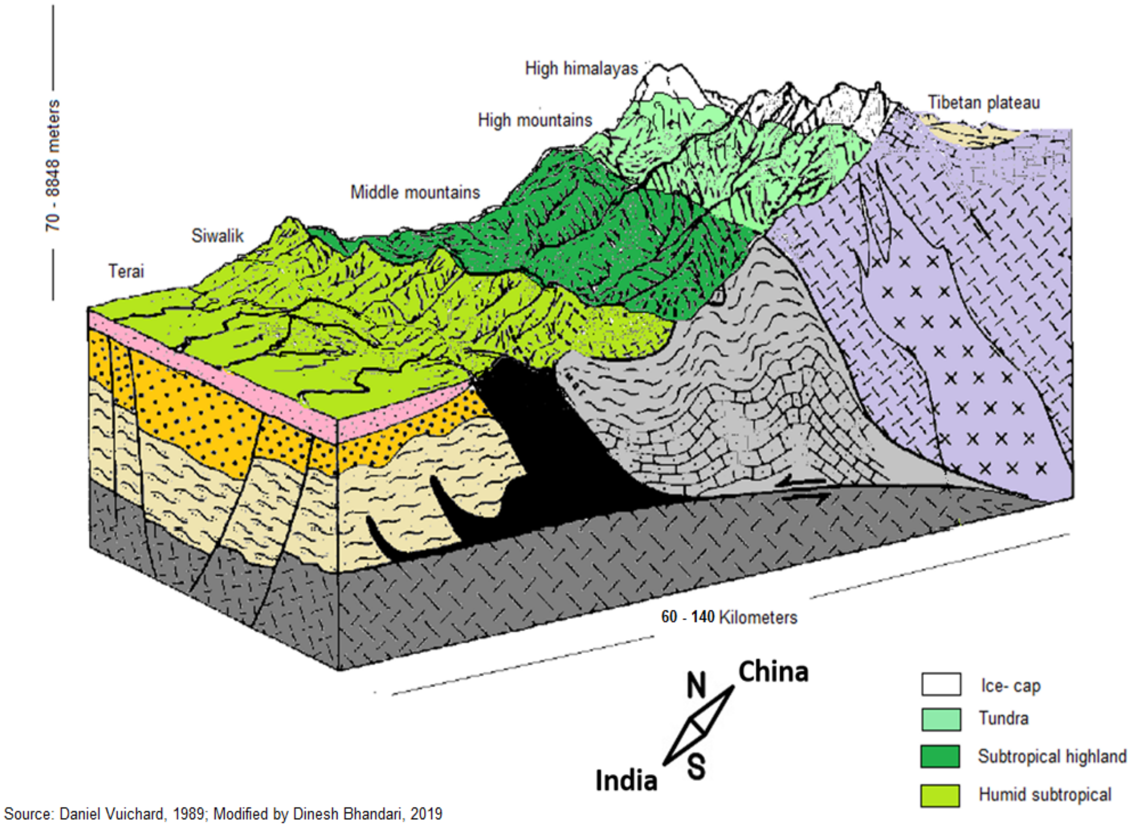


Figure 6. 1 Cross-section of Nepal's topography with corresponding climate types.

With a Human Development Index (HDI) score of 0.578 and a Gross National Income of US$2,472 per capita, the socioeconomic development status of Nepal is below the average value for South Asian countries (HDI= 0.638) and only above Pakistan (HDI= 0.562) and Afghanistan (HDI = 0.498) among countries in the Hindu Kush Himalaya region (321). Given the unique geophysical condition of Nepal in the Hindu Kush Himalaya region (the so called 'third pole' of the planet), its highly diverse climatic conditions (tropical to tundra), rapid population growth, unplanned migration to urban cities and a high level of poverty, climate change is likely to exacerbate the burden of climate-sensitive infectious diseases in Nepal (274, 349).

Table 6. 1 Summary of updated evidence on the impacts of climate change on infectious disease in Nepal.

Study	Study site	Study period	Disease	Methods	Evidence on climate change impacts
Bhandari et al. 2012 (13)	Jhapa district	1999-2008	Diarrhoea	Time series (ARIMA model)	Despite a significant correlation, temperature was not found to be a predictor for diarrhoea incidence.
Acharya et al. 2018 (31)	Nepal	Not mentioned	Dengue	Spatiotemporal analysis (maximum entropy ecological niche modelling)	Under the different climate change scenarios, dengue in Nepal is likely to shift towards higher elevation region.
Tuladhar et al. 2019b (28)	Chitwan district	2010-2017	Dengue	Time series (negative binomial models)	The incidence rate ratio of dengue cases was found to rise by more than 1% for every 1°C increase in minimum temperature.
Tuladhar et al. 2019a (29)	Upland hilly and lowland terai	2015-2016	Dengue vectors	Entomological survey (gamma regression)	Temperature and rainfall effect showed a more significant influence on vector indices compared to humidity.
Bhandari et al. 2020 (350)	Kathmandu district	2003-2013	Under 5 diarrhoea	Time series (Quasi-Poisson regression with distributed lag linear model)	Maximum temperature and rainfall were found to be significantly associated with childhood diarrhoea, with an additional 1357 (UI: 410-2274) climate attributable diarrhoea cases projected by the year 2050 under low-risk scenario of climate change.

6.3 Climate sensitive infectious disease: knowledge gaps

Nepal is afflicted by various climate-sensitive infectious diseases including malaria, dengue, visceral leishmaniasis, Japanese encephalitis and infectious diarrhoea caused by pathogens including bacteria, parasites and viruses (22). Although Nepal's National Adaption Programme of Action to Climate Change in 2010 (349) highlighted inadequacy of research on the impacts of climate change on infectious diseases transmission to inform evidence-based decision making, no significant progress has been achieved over last eight years (20). The National Adaption Programme of Action identified the public health sector as one of the sectors vulnerable to future climate change related events. In an effort to promote climate change research in Nepal, the National Adaption Programme of Action recognised the importance of an integrated network of resources and links to meteorological databases from various sources, and this led to the establishment of the Nepal Climate Change and Development portal. However, the portal in its current configuration may support environmental aspects of climate change research, but does not offer the necessary support to epidemiologists and public health researchers, as it does not include links to major infectious diseases databases and demographic data sets in Nepal (351). The recent unprecedented outbreak of dengue fever in Nepal, killing six people and hospitalising more than 8,000 (between June–September 2019), demonstrated that Nepal lacks preparedness and resources to manage the threat of climate-sensitive infectious diseases (352). Dengue fever was reported in Nepal for the first time in 2004, and since then it has been reported every year during the monsoon season, which indicates that rainfall can be an important predictor for dengue infection. The existing infectious diseases control approach in Nepal focuses on disease-specific vertical programs, and has ignored the opportunity to design and utilise a climate-based early warning system for prevention and control of infectious diseases. Hence, it is important to conduct public health research to assess the health risk of climate change on vector-borne and food/water-borne diseases in Nepal, identify the attributable contributions from climate change, project the future challenges due to climatic and demographic changes, and improve the capacity of existing health care system in Nepal to deal with such challenges.

6.3.1 Infectious diseases data sources

The Nepalese Department of Health Services, under the Ministry of Health and Population, has dedicated divisions to collect infectious diseases data and maintain a national registry of infectious diseases in Nepal (353). The Integrated Health Management Information Section and the Epidemiology and Disease Control Division work in tandem to collect data and relevant information on infectious diseases from public health facilities and some private facilities (<50% coverage) across the nation. The Epidemiology and Disease Control Division in particular is responsible for carrying out routine hospital-based sentinel surveillance of major notifiable diseases (malaria, kala azar, dengue, scrub typhus, acute gastroenteritis, cholera, and severe acute respiratory infection), across public health facilities participating in the surveillance system through a weekly reporting mechanism (average coverage rate is above 80%). Besides this, an Early Warning and Reporting System and active syndromic surveillance of diseases are deployed after disaster events by the Epidemiology and Disease Control Division (354). In addition to these potential sources of infectious diseases data that are gathered by Epidemiology and Disease Control Division, several vertical surveillance programmes especially for immunization preventable diseases are in operation, mainly regulated by the World Health Organisation Immunization Preventable Disease division. Likewise, vertical surveillance of several other diseases of interest (i.e. of interest to funding agencies) are carried out, mainly regulated by research and academic institutes in collaboration with external donor/funding agencies or foreign universities (10).

6.4 Challenges for public health researchers

Unlike in developed nations, epidemiologists and public health researchers in low-income countries like Nepal face several challenges when conducting studies related to climate change and human health (355). Besides the underperforming economy, inadequate funding, political instability, shortage of trained staff and inadequate provision of capacity-building opportunity for public health researchers, there is an additional barrier — poor quality infectious diseases datasets — that epidemiologists and public health researchers in Nepal have to overcome (355).

6.4.1 Infectious diseases data–related challenges: In order to shift from a surveillance and response strategy to a prevention strategy through establishment of a climate-based early warning system, an effective mechanism to systematically collect, analyse and interpret infectious disease data is indispensable (256). Among several intrinsic challenges commonly experienced in low and middle-income countries, public health data quality-related issues are a major hindrance to the progress of climate change and human health research in Nepal. Moulton et al. (250), in their recent assessment of the strengths of public health agencies in the United States, identified four core components of public health surveillance systems, which support climate change and health-related research and, adaptation to climate change. These are: appropriate indicators and data availability; an electronic system or network for data sharing and analysis; a skilled workforce; and supportive policies. They regarded good quality public health data to be the back bone of an effective public health system. In the context of Nepal, several aspects of a utilitarian public health database are substandard or missing in certain cases. Environmental epidemiologists and researchers utilising these datasets for research and health intervention purposes have to contend with issues such as: a lack of a centralised electronic database on infectious disease burden (which is routinely collected and dis-aggregated, daily or weekly); the unavailability of long-term historical data on infectious diseases epidemiology; poor quality existing health data; a lack of spatial data on disease incidence cases; and a lack of data linkage and sharing among data custodians and researchers (356, 357).

The Epidemiology and Disease Control Division regularly dispatches reports on infectious disease epidemiology in the form of weekly bulletins with an objective to support decision-makers in identifying public health priorities and resource allocation. However, data made available through these reports are of limited use for secondary analysis by public health researchers and environmental epidemiologist, as the reports simply mention aggregated counts on disease burden. They have insufficient information on: disease onset dates, socio-economic and demographic characteristics, detailed spatial information, and the water quality or hygiene status of disease incidence locations. The best approach to identify climatic drivers of infectious diseases and estimate the effects of climate change on infectious diseases dynamics is epidemiological studies using empirical or mechanistic (process-based simulation) statistical models (255, 358). However, the publicly available information on infectious diseases in Nepal does not support sophisticated statistical analysis of infectious disease patterns in relation to climatic drivers, to generate sufficient evidence and to guide climate change and human health-related policy formulation. Similarly, sources of data on immunisation coverage, vector density, and rodent density surveillance are limited to ad hoc surveys and research work carried out by the private sector, and are not easily accessible by public health researchers and policy makers.

6.4.2 Financial/Economic Challenges: Nepal has been heavily dependent on international donor agencies and philanthropic organisations for the conduct of health research since the commencement of the first-ever health research undertaken in Nepal in 1952 (10). In the fiscal year 2018–19, the cluster-wise allocation of budget in the health sector for the Health Management Information System, disease survey/surveillance, and health research combined was 1% of the total NPR56.41 billion (1 NPR~ 0.0091 USD) budget allocated for the Ministry of

Health and Population (359). Given the low financial capacity of the state to invest in health research and given also the absence of adequate research-based evidence on the health impacts of climate change in Nepal, Nepalese researchers are forced to try to attract international donors to invest in climate health research, which is challenging (355).

6.4.3 Public health capacity-related challenges: Public health professionals in Nepal are deprived of knowledge related to recent advancements in techniques and skills in the environmental health sector due to the lack of opportunity to upgrade their skills through appropriate training, including by attending international conferences (360). Institutions in Nepal only offer general public health training, so that professionals and researchers interested in a specific field of public health, such as environmental epidemiology, will have to partially rely on the free sources of information, such as internet, in their attempt to compensate for inadequate training opportunities (360). In addition, Nepal faces a shortage of skilled researchers capable of carrying out trans-disciplinary public health research (355), primarily due to the preference of highly trained native researchers to settle in developed countries (361).

6.4.4 Political challenges: Like any other aspect of the health sector, promotion of public health research in Nepal has been impeded by Nepal's ever changing political landscape (362). Frequent changes in government have interfered with several national priorities, including public health policies such as promotion of the Planetary health in Nepal program established after the 2015 Gorkha earthquake (that resulted in 9000 deaths and left 18,000 injured) (363). Although the Nepalese government has recognised the potential impacts of climate change on health in developing several policies and plans such as the NAPA, the Climate Change policy in 2011, and several other documents (20), implementation of these policies remains uncertain given that the country has continued to grapple with political uncertainties and frequent changes in government over the past two decades.

Despite these challenges, a handful of entomological and time series studies have attempted to estimate the association between climate change and infectious diseases in Nepal (13, 364, 365). These studies have clearly demonstrated that vector-borne diseases such as malaria, lymphatic filariasis, and dengue, as well as food and waterborne diarrheal diseases, are highly associated with climate change (28, 350, 364, 365). However, attribution of these observations to climate change is still awaiting confirmation, which can only be achieved by carrying out well-designed epidemiological studies utilising long-term surveillance data. Furthermore, the compounding effect of demographic changes and other non-climatic factors (social, economic and other environmental factors), along with climatic variation are likely to play important roles in future transmission of these diseases. Hence, future studies estimating the projected burden of these climate-sensitive diseases are necessary to allocate adequate resources for infection control and planning effective adaptation policy.

6.5 Future directives and priorities to promote climate change and infection disease research in Nepal

The latest Lancet countdown report (2019) on health and climate change reported future climate scenarios to be more conducive and suitable for transmission of climate sensitive infectious diseases like dengue, malaria and cholera (26). Given, the increasing threat of climate sensitive infectious disease and a paucity of epidemiological evidence to support public health decision makers in Nepal, we argue that following priorities should be addressed within next five to ten years to support public health researchers in generating evidence to guide relevant public health policy formulation in the context of climate change on human health.

6.5.1 Strengthen Public Health Surveillance systems: We believe evaluation of the infectious diseases surveillance system, as well as a relevant public health data collection system, is necessary. Stakeholders, including the infection control division, the environmental health division, the national planning commission, researchers, and policy makers working in the public health sector of climate change and human health, should be consulted to identify their needs from the surveillance systems. Particularly, the quality of surveillance data and periodicity of data collection should be revised such that data available from these sources meets the minimum requirements for exploring attributable risk of infectious diseases to climate change, projection of future burden of diseases attributable to climate change, and the establishment of a climate-based early warning systems. Apart from disease surveillance, the system should extend its service to routine surveillance of arthropod vectors and effective vector control program to check spatiotemporal distribution of vectors. The public health division should encourage inter-sectoral collaboration and linkage of data from various sources to share information and data (health, meteorological, demographic, and socioeconomic data) between the data custodians, researchers, and policy makers.

6.5.2 Inclusion of additional climate sensitive infectious disease under the notifiable disease category: Given that it is feasible from a financial and technical point of view, we believe it is desirable to include information on additional epidemic-prone and climate-sensitive diseases such as salmonellosis, campylobacteriosis, meningococcal meningitis, enterohemorrhagic *E. coli*, shigellosis and viral causes of diarrheal and respiratory infections, in the routine surveillance system in order to better understand the impacts of climatic factors on infectious disease in Nepal.

6.5.3 Establishment of an integrated digital network of interdisciplinary experts to support data sharing and inter sectoral collaboration for public health research on climate change: In 2009, the European Centre for Disease Prevention and Control proposed an integrated network of epidemiologists, meteorologists, remote sensing experts, and entomologists to facilitate public health research in the climate change and human health sectors, and this led to the formation of the European Environment and Epidemiology (E^3) Network (342). Similarly, the US Center for

Disease Control and Prevention set up the National Environmental Public Health Tracking Network to support environmental health researchers by providing access to health data and environment data through a single platform (366). Establishment of such a network in Nepal could promote environmental health research and generate key evidence to guide policy on climate change and human health. As the Nepal Climate Change and Development portal is already in existence, linking data from Epidemiology and Disease Control Division, Integrated Health Management Information Section and the Central Bureau of Statistics to the portal could be a viable solution to some of the problems faced by public health researchers.

6.5.4 Public health capacity building, international co-operation and aid, and increasing funding sources: We believe public health courses in Nepalese academic institutions should switch their focus from a general Masters in Public Health programme to more specific fields such as environmental and occupational health, biostatistics and epidemiology, and health promotion to institutionalise climate change and human health adaptation research (360). Provision of adequate training (for faculty staff from major health institutes of Nepal, for public health professionals and researchers from the Department of Health Services and the Nepal Health Research Council) should be arranged on a regular basis through faculty exchange programs with reputable universities in developed countries. Budget allocations for health research need a significant boost and the health sector budget allocation needs to be prioritised similarly to that of programs including environmental health research and infectious diseases surveillance. Inadequate funding from the state for research on environmental health and diseases surveillance can be compensated for to some extent by planning collaborative studies with universities in other countries on relevant climate change and human health projects based in Nepal.

6.5.5 Engaging community in infectious disease surveillance and climate change research programs: Evidence from previous studies on community engagement in public health surveillance and climate change research programs has highlighted the importance of social and cultural factors along with local knowledge in disease detection/reporting and adaptation strategies to deal with the effects of climate change (367, 368). Nepal has a strong community health volunteer network that has been successfully used to achieve several public health goals, including: improved maternal and child health outcomes; effective implementation of immunisation programs and; control of non-communicable diseases. This existing network of community health workers can be trained and deployed in surveillance of infectious diseases, in conjunction with epidemiologists. In our opinion, involvement of community members who are directly bearing the health effects of climate change in research can help generate enhanced localised evidence to improve adaptation policy in a specific context

6.6 Concluding perspective

As envisioned in the 2013 World Health Report by the World Health Organisation, in order to achieve health goals and sustainable development goals, particularly the goal to take action to combat climate change and its impacts (Sustainable Development Goal 13), all countries including low and middle-income countries should be both consumers and producers of research (369). Given a quarter of the global burden of diseases can be attributed to various environmental risk factors (370), and given also the vulnerability of the Nepalese population to adverse impacts of climate change, promotion of epidemiological studies assessing the impacts of climate change on infectious diseases in Nepal is urgently needed. The difficulty of generalising about health outcomes from one setting to another, when many diseases have important local transmission dynamics that cannot easily be represented in simple relationships, further highlights the importance of conducting such studies in vulnerable countries like Nepal.

Impediments to the conduct of environmental health research in Nepal, such as political instability, can be expected to be overcome by the establishment of a stable government under the recently adopted federal system. Meanwhile, issues related to public health agencies, health care workforce capacity, and funding agencies need to be addressed urgently, to foster climate change and health research in Nepal and generate sufficient and updated evidence to guide health policy, which accounts for the impact of climate change. To reiterate, evaluation of current notifiable diseases surveillance practice is desirable to improve the quality of infectious disease data so that this rich data source can be used by public health researchers and stakeholders. It would be advisable to also review: the frequency of reporting (preferably daily); completeness of reporting; inclusion of more public and private health service providers; and the possibility of collection of dis-aggregated data on the socio-economic, spatial, and demographic characteristics of cases.

South Asia (Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan and Sri Lanka) bears a significant proportion of the global burden of infectious diseases, which can be attributed to factors such as: a weaker health system capacity, rapid urbanization and land use, poor sanitation and hygiene, high population density, low socioeconomic status and a higher vulnerability to climate change (371, 372). The institutional capacity of this region, including its diagnostic laboratories and surveillance systems, are under resourced and often fragmented; hence they are less organised to support the establishment of early warning systems for epidemic-prone and climate-sensitive infectious diseases(371, 372). Advancement in epidemiological techniques (in statistical and mathematical models) have led to optimism about holistic investigation and prediction for climate-sensitive infectious diseases, by making use of high quality observational data on climatic variables, disease incidence, spatial distribution, hygiene coverage, socio-economic status, land coverage, disease susceptibility, and the vulnerability index (373, 374). Improved disease intelligence collection (integrated surveillance system), as well as cross-disciplinary and trans-border collaboration among South East Asian countries will be needed in future to curb the threat of climate change on infectious diseases transmission in this region.

Conflict of Interest

We declare no conflict of interest.

Acknowledgements

D.B. is supported by Adelaide Scholarship International (ASI), provided by the University of Adelaide for his PhD Study. Thanks to the anonymous reviewers for their insightful and detail comments.

Chapter 7 Study 4: A qualitative study on the social, cultural, political and institutional factors associated with the surveillance of infectious diseases in the context of a changing climate in Nepal

Statement of Authorship

Title of Paper	A qualitative exploration of the socio-cultural, political and institutional factors affecting the surveillance of infectious diseases in the context of a changing climate in Nepal		
Publication Status	☐ Published ☐ Submitted for Publication	☐ Accepted for Publication ☑ Unpublished and Unsubmitted work written in manuscript style	
Publication Details	Bhandari, D., Bi, P., Sherchand, J. B., von Ehrenstein S.O, Dhimal M& Hanson-Easey, S. (unpublished). A qualitative exploration of the socio-cultural, political and institutional factors affecting the surveillance of infectious diseases in the context of a changing climate in Nepal.		

Principal Author

Name of Principal Author (Candidate)	Dinesh Bhandari		
Contribution to the Paper	Conceptualization, Methodology, Data collection, Software, Formal analysis, Interpretation, Writing - original draft, revision and editing		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	25/6/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Peng Bi		
Contribution to the Paper	Conceptualization, Resources, Validation, Supervision, Writing - review & editing		
Signature		Date	25/6/2021

Name of Co-Author	Jeevan Bahadur Sherchand		
Contribution to the Paper	Supervision, Writing - review & editing.		
Signature		Date	25/6/2021

Name of Co-Author	Ondine S von. Ehrenstein		
Contribution to the Paper	Critical interpretation, Writing - review & editing.		
Signature	Ondine von Ehrenstein Digitally signed by Ondine von Ehrenstein DN: cn=Ondine von Ehrenstein, o=UCLA, ou, email=ovehren@ucla.edu, c=US Date: 2021.06.29 18:31:43 +02'00'	Date	25/6/2021

Name of Co-Author	Meghnath Dhimal		
Contribution to the Paper	Resources, Validation, Supervision, Writing - review & editing		
Signature		Date	25/6/2021

Name of Co-Author	Scott Hanson-Easey		
Contribution to the Paper	Conceptualization, Methodology, Resources, Supervision, Validation, Interpretation, Writing - revision and editing		
Signature		Date	25/6/2021

Abstract

The dynamics of infectious disease transmission is changing under the influence of climate change, urbanisation, population growth and increasing trends of travel and migration. This is challenging the conventional approach of disease surveillance and highlights the need for inter-sectoral participation and interdisciplinary collaboration. In this study, semi-structured interviews are conducted in Nepal amongst key informants from the Department of Health Services, Health Information Management System, Department of Hydrology and Meteorology, World Health Organization (WHO), and experts working on infectious disease and climate change in the country. Interviews explored socio-cultural, political and institutional issues associated with infectious diseases surveillance in the context of a changing climate. A critical realist theoretical lens is used to analyse how climate change has been variably constructed as a contingent risk for infectious diseases transmission and public health systems. More specifically, this analysis articulates how climate change and its impact on infectious diseases surveillance is treated less seriously than other 'more salient' public health risks. Consequently, resources are invested in addressing public health threats considered to be more urgent. Our findings expose a weak alliance among different stakeholders, particularly policy makers and evidence generators, that results in the continuation of traditional practices of infectious diseases surveillance without consideration of the impacts of climate change. I argue that, along with strengthening systemic issues (epidemiological capacity, data quality and inter-sectoral collaboration), it is necessary to have a strong political commitment by the nation and prioritisation of climate change as an urgent public health issue by the stakeholders: this may then support the integration of climate change as a present and growing factor in infectious diseases surveillance in Nepal.

Key words: Climate change, infectious diseases surveillance, qualitative, Nepal, medical hegemony

7.1 Introduction

Climatic factors were believed to play a crucial role in determination of health and wellbeing of humans as early as 400 B.C., evident in the treatise titled *On Airs, Waters and Places* in which Hippocrates indicated a probable causal relationship between seasonal change, temperature variation, and disease (43). According to ancient writings and artefacts — even before the establishment of the notion of infectious agents — Roman aristocrats were believed to have practised seasonal migration to high areas such as hills during summer months to avoid malaria (7). By the end of the 20th century, scientific insights into the relationship between climate and infectious diseases had become increasingly concerned about unprecedented environmental changes (7, 50). This alarm drove epidemiologists, and the broader public health community, to undertake extensive research on climate change and health that demonstrated that infectious diseases, particularly vector-borne and food/water-borne diseases, are highly sensitive to climate change (341, 375).

By the end of 20th century, there had been a significant reduction in global mortality attributed to infectious disease. Yet continued surveillance of infectious diseases remains a high priority due to its important role in reducing morbidity and mortality due to infectious diseases, both across the globe and more specifically in low-and middle-income countries (376). Evidence from continuous surveillance of infectious disease supports public health authorities to design, refine and target specific intervention measure or guide strategic action to control and monitor disease burden across populations, whilst striving to realise Sustainable Development Goal 3 (Good Health and Well-Being).

Higher incidence of infectious diseases are frequently documented following extreme weather events such as flood, hurricane, drought and heatwaves (105). Such events, and subsequent disease outbreaks, are predicted to increase in magnitude due to the effects of anthropogenic climate change (377). More recently, the *2020 Report of The Lancet Countdown on Health and Climate*, noted that one impact of climate change is an increase in climate suitability for transmission of infectious diseases like dengue, malaria and cholera (24). As such, the World Health Organization has identified surveillance of infectious disease as an urgent priority in the context of a changing climate (375). Regular surveillance of infectious diseases helps to understand the change in disease patterns and trends in response to climate change: this information can contribute to better management or prevention of such disease outbreaks.

Effective surveillance of infectious diseases in a changing climate is reported to be contingent on multiple factors including data availability, nature of surveillance system in place, work force capacity, stakeholder knowledge and implementation of well-informed policies (250, 255). Moreover, there is significant influence of social, cultural and political factors on surveillance practices. To date, there has been very little research of this facet of surveillance systems, mainly due to their complex nature (250, 255, 259, 261, 262). This current study aims to address this gap and explore contextual issues of public health surveillance systems in Nepal in a changing climate. We aim to glean insights from participants on how socio-economic, cultural, and political issues are interacting with disease surveillance in Nepal in the context of a changing climate. In so doing, we suggest potential enhancements to infectious diseases surveillance systems of Nepal in the context of climate change.

Infectious diseases surveillance and climate change

Public health surveillance is defined as an ongoing systematic process of collection, analysis and interpretation of health-related data needed for planning, implementation, and evaluation of public health (251). It comprises a holistic practice that aims to explore the determinants of disease and health, identify disease pattern, risk factors and vulnerable populations to inform evidence-based policy for the detection of epidemics and its prevention and control, and promotion of health. However, the conventional approach of disease surveillance is being challenged by the changing dynamics of infectious disease transmission under the influence of climate change, ecological change, increased travel and trade, urbanisation, population growth, and increased immigration trends in cities and regions, which highlights the need for inter-sectoral participation and interdisciplinary collaboration (252-254).

In a changing climate, infectious disease surveillance requires the establishment of an expanded set of activities that are characterised by the Building Resilience Against Climate Effects (BRACE) framework (260). The BRACE framework is a process of five sequential steps: vulnerability assessment, projection of disease burden, assessment of public health interventions, development and implementation of adaptions plans and impact evaluation of interventions. The BRACE framework was developed by the United States Centers for Disease Control and Prevention (CDC) to assist public health authorities to design specific programs and strategies to protect health of people from the adverse impacts of climate change (260).

Other literature on climate change and public health surveillance underscore the critical importance of efficient data sharing amongst public health agencies and divisions to determine climate attributable risk, make projections on future health burdens, predict probable climate sensitive epidemics in future, and guide decisions on infection control programs (250, 254, 255, 260). In recognition, disease control divisions in the US, Canada and European Union have established specialised networks (e.g. Environmental Public Health Tracking Network, Integrated Circumpolar Surveillance Network and The European Environment and Epidemiology Network) within their public health surveillance systems to track the changing dynamics and distribution of infectious disease under the influence of climate change (261, 262, 366). Evidence from a decade-long operation of these surveillance networks has enabled these countries to establish climate-based early warning systems for prediction and control of infectious diseases, with data sharing underpinning the effectiveness of these systems (378).

Infectious disease surveillance in Nepal

The history of infectious disease surveillance in Nepal dates back to 1996, marked by the establishment of a hospital-based passive surveillance system called the Early Warning and Reporting System (EWARS), under the control of the Epidemiology and Disease Control Division (EDCD), Ministry of Health and Population, Government of Nepal (379). In addition to EWARS, active surveillance of infectious diseases during outbreaks included water quality monitoring and surveillance (carried out by EDCD) to analyse and prevent potential epidemics. Following the elimination of polio, the Nepalese Acute Flaccid Polio (AFP) surveillance system was expanded in 2005 to integrate several vaccine-preventable diseases (like measles, rubella, Haemophilus influenza b and rotavirus) and to continue surveillance under the support of WHO Immunization Preventable Disease (IPD) (380). Collectively these surveillance systems complement the Nepalese Health Management Information system and they collect, analyse and use this data to inform the design of necessary interventions, as well as the policies that aim to control infectious diseases in Nepal.

However, conventional surveillance practices and policies designed to minimise risk to public health from infectious diseases epidemics are, by themselves, ill-suited to respond to the shifting epidemiological dynamics of infectious diseases under the influence of future climate change (255). A limited number of studies on climate change and infectious diseases in Nepal provide evidence that diseases such as malaria, dengue and diarrhoea are highly influenced by the natural variation in the climate and anthropogenic changing climate (14, 350). For example, the unprecedented outbreak of dengue fever in Nepal — that also affected the historically less-prone Kathmandu city area (September – October, 2019) — killed six people and hospitalised nearly

8000 people. This suggests that surveillance systems in Nepal are unprepared for climate sensitive epidemics like dengue fever and respiratory virus illnesses (352). Meanwhile, it is also likely that Nepal's public health surveillance systems lack the necessary resources and capacity, or a strong political will, to conduct and fund effective surveillance and attribution of infectious disease in a changing climate (381).

Previous experience of working on climate sensitive infectious diseases in Nepal (350, 382), identified that current infectious diseases surveillance systems do not collect disaggregated datasets required to understand the impacts of climate change on infectious diseases transmission. We further realised that existing datasets on infectious diseases in Nepal are not analysed or interpreted by EDCD to reflect the trend or incidence pattern of infectious diseases in relation to climate change (12). Given these infectious diseases surveillance systems are not considering diseases affected by climate change, there is a need to better understand social and structural factors that may affect the integration of climate change-related threats in disease surveillance. Findings of this research could help to direct the future integration of climate change components in disease surveillance systems and guide change in policy and practices across these surveillance systems to enable effective prediction and prevention of outbreak of climate-sensitive epidemics.

7.2 Methods

The study of complex health surveillance systems requires an approach that acknowledges the dynamic and complex nature of the social, political and cultural contexts of the system being studied (250, 255, 259, 279). As the father of modern pathology, Rudolf Virchow, stated: "medicine is a social science, and politics is nothing but medicine at large scale," (383). Similarly, public health problems are embedded in society and are influenced by the social, cultural and political environment (383). These socio-cultural forces shape contemporary health problems as well as our approach to address them (384). Thus, we argue, the study of a public health surveillance systems in the context of climate change requires more than the traditional positivist inquiry that depends upon experimental or statistical approaches that fail to account for the context or complexity of the role of social, cultural and political factors (277). Moreover, we argue that use of quantitative survey instruments in organisational research can oversimplify complex and dynamic social reality. A set of standard survey questions validated at a given setting or a population cohort may invoke simplistic responses that fail to capture the nuance of social systems, when used in a different social setting. At the core of a health system are individuals or groups of people whose behaviour is influenced by the unique culture of the individuals and the organisation: to understand the functionality of the system this culture must be appreciated and described (279).

Hence, we use a qualitative research technique that employs critical realist (CR) epistemology to explore the socio-cultural and political problems associated with infectious diseases surveillance in the context of climate change for a low-and middle-income country like Nepal (279). CR uses social discourse as the starting point for systems research, but does not limit its inquiry to the interpretation of talk and text. It encompasses the broader elements of the systems such as the physical, environmental, socio-economic and political context, which intrinsically regulates the operation of the system (385). This approach enables us to gain insights into the views and beliefs of stakeholders associated with the system, but also supports exploration of structural and contextual factors interacting with the system.

Theoretical perspective

We used a CR approach to study infectious diseases surveillance systems of Nepal and, understand the factors associated with infectious diseases surveillance in the context of climate change (386). CR is positioned between realist and relativist paradigms and is of growing interest among health system researchers. It is ontologically realist in that it adopts the position that reality exists independent of human perception: while epistemologically, it takes a social constructionist view that our knowledge of the reality can only be created and shaped by human experiences with the natural and social world (278). The CR approach has been used recently in the evaluation of integrative care initiatives in Australia (387), as well as in health policy and systems research elsewhere in the world (388). CR researchers conceive language to be the architect of social reality that itself is theorised to be shaped by human interaction with the natural and social world (281). Put another way, as social reality is constrained within the material dimension that exists independent of discursive practices, the material constraints impact on the meaning of the social reality constructed from the discourse utilised by the actors (281, 282). According to Carla Willig (282), the discourses employed by actors are accommodated within the underlying structures such as biochemical, social or economic structures, hence the ontological reality cannot be directly accessed, but can be inferred by interpreting the discourse in relation to these structures (p. 45).

CR is widely used in climate change and public health research including climate change mitigation, vulnerability assessment, energy technology debates, stakeholders perception assessment and various other social aspects of climate change related outcomes (280, 283). Using a CR approach to qualitative data in this study enables us to consider that problems within a disease surveillance system are both socially constructed and influenced by material factors that are independent of the perceptions of an individual or a group. For example, the ability of a surveillance system to map vulnerability of a population towards infectious disease exposure, due to change in climatic conditions, can be contingent upon the very real problem of data availability *and* perceived societal need or expectations (284). Hence, a CR approach can incorporate the influence of material (e.g. budget), institutional (epidemiological and diagnostic capacity of health service providers) and discursive factors that may transform the significance of a problem being studied when exploring the contextual issues of a disease surveillance systems in response to environmental stressors such as climate change.

Data collection and data treatment

Sixteen semi-structured interviews were conducted with key informants from the Department of Health Services (Epidemiology and Disease Control Division, Health Information Management System), Department of Hydrology and Meteorology, WHO-Nepal and experts working on infectious disease and climate change in Nepal. Participants were recruited by employing a purposive sampling technique, and included epidemiologists, infectious disease experts (physicians), public health administrators, surveillance officers, data managers, a focal person on climate change and health from WHO-Nepal and the Department of Hydrology and Meteorology, and academic researchers. Interview questions and preliminary codes were informed by the BRACE framework and other basic principles of public health surveillance as discussed in section 1.1 (260). All interviews were audio recorded, transcribed into Nepali by myself and then translated into English. Transcripts were analysed using thematic analysis (389), an iterative process of reading and re-reading data to identify common patterns across the dataset, and generate overarching themes and subthemes. Coding of the interviews was done using NVivo 12. Both inductive and deductive coding techniques were employed in the analysis process. Themes generated from the reflexive analytic process were then subjected to an interpretive analysis to identify factors associated with infectious disease surveillance in the context of a changing climate.

7.3 Analysis

Three key themes were constructed from the interview data: 1) climate change and health is a less important public health priority; 2) medical reductionism; and 3) science policy interaction in climate change and health. These themes are discussed in subsections below.

7.3.1 Climate change and health: a less important public health priority

Several participants emphasised a lack of sufficient empirical evidence to support the link between climate change and infectious diseases transmission: this served to characterise climate change as a lesser threat to public health problem than other well-known risks. This is exemplified in the extract below from an epidemiologist from the EDCD.

> *We get (a) few cases of malaria, dengue and kala-azar in high altitude regions, but we don't know why. There are few correlational studies and anecdotal accounts…. Mostly likely we cannot say anything without analysing temperature data over past 20-30 years.*
>
> *That's why I personally say… Is climate change responsible for these disease and conditions? I mean a strong causality, highly proved causality… is it due to climate change? Is climate change a determinant of these disease and their geographical expansion? I am not sure if we have ~~a~~ very strong evidence….*
>
> *Let's say an article has been published… a correlational study but it cannot benefit policy makers, to convince policy makers, the ingredients required to claim it to be evidence, we don't have all these ingredients…*
>
> *(Epidemiologist, EDCD, QSNP01).*

This account from a senior epidemiologist suggests that the absence of strong local evidence on the impacts of climate change in disease transmission from Nepal is constraining public health officials from considering climate change as a determinant of infectious diseases transmission. In this account, the epidemiologist argues that random observations can't be considered to guide policy decision-making on a complex public health problem like the impacts of climate change on infectious disease transmission. Indeed, attribution of climate change to public health problems like infectious disease transmission remains challenging and there remains little evidence for Nepal (12). How public health authorities consider climate change to be relevant as a global health issue can support the framing of policy and actions to mitigate the impacts of climate change on emergence and transmission of infectious diseases (5).

Further to a lack of empirical evidence, in the extract below, a stakeholder expresses the view that making climate change a public health priority is contingent upon whether it receives funding from external sources.

> *In our context, climate change is a donor-driven issue. If WHO announces some funding support for climate change, it becomes a hot issue, an urgent issue. Not only WHO, we have some other donors like DFID, USAID and some other UN agencies. When they are ready to support climate change (it) becomes the biggest health issue.*
>
> *However, once the funding agency discontinues the support... It is all over. Do we have any information on the budget allocated by our government for climate change in health sector? No… not at all…. We have other important things to take care of!!!!*
>
> *(Senior Public Health Administrator, Ministry of Health and Population, QSNP03)*

This account from a senior public health administrator describes the Ministry of Health as prioritising — through the practical means of investing its resources and expertise — other public health issues that are represented as more important than the health impacts of climate change. Interestingly, climate change and health are portrayed to be issues of more interest to foreign donor agencies than the Nepalese government.

This quote from a senior government bureaucrat further supports the case that Nepal has not yet succeeded in mainstreaming climate change into the national planning and budgetary system (390). According to the most recent report from the Ministry of Finance, the Government of Nepal (390), over the past five years only 5% of the total national budget has been allocated to developmental programmes that address climate change, that too not specifically allocated to the cluster, climate change and health (359). A review of previous work on public health aspects of climate change in Nepal reveals that most have been initiated and supported by international non-governmental organisations (20). The failure of the state to take ownership of the issue may undermine how climate change is discerned as a driver of infectious diseases transmission, subordinating it as a priority in the public health system.

In the next extract, responsibility for funding an infectious disease alert system in the context of climate change is placed at the feet of much larger neighbouring countries. In this way, climate change is attributed to increasing industrial activities in China and India.

> *The country which does not have industry, can it emit carbon? We are victims of emission from China and India…. victims of fossil fuel consumption by these countries. They need to do that, they are a booming economy… but we are victims …*
>
> *The next thing we should do is claim with them that we are victimised due to them… we should ask them to support us, we should lobby them that they should support us to contain this outbreak…*
>
> *If this is an actual variation due to climate change, we should ask them to build an alert system for us. Our people should not die (…) I feel it that way!!!*
>
> *(Senior authority, EDCD, QSNP02)*

In the above extract, the senior authority from EDCD contends that Nepal does not contribute to climate change ('emit carbon'), chiefly because its economy is not industrialised or 'booming' like economies of India and China. With this logic, adverse impacts experienced by Nepal are singularly caused by neighbouring countries. In other words, Nepal is positioned to bear no moral or pragmatic responsibility for building resilience and adaptation capacity within the state. While Nepal's greenhouse gas emissions are comparatively lower than neighbouring nations, its 0.027% contribution to total global emission is not insignificant, even for a small country (20). Thus, characterising Nepal as a climate change 'victim' and eschewing responsibility for — rather than making proactive attempts to address — climate change-related impacts on health serves to relieve government agencies obligation to commit funding and act to strengthen and adapt infectious diseases surveillance systems in response to climate change.

Although the National Adaptation Program of Action to Climate Change (NAPA) 2010 for Nepal identified health as one of the key sectors vulnerable to climate change, the implementation of NAPA remains uncertain (20). By shifting the blame to larger countries, the construction of climate change as 'someone else's' responsibility could be perceived to reduce or avoid accountability for failure to implement activities identified by NAPA and other national policies and plans on climate actions in Nepal.

7.3.2 Marginalisation of the preventive medicine: a barrier to including climate change in infectious disease surveillance

The discipline of public health is concerned with the protection of health of an entire population by preventing diseases, promoting health and curing diseases through organised efforts of society (391). These three pillars of public health — health promotion, disease prevention and protection — are hallmarks of a good health system and are essential to effective public health goals i.e., the improvement of the health of people (392). Imbalance in these three pillars can have consequences such as low quality of health services, inefficiency in the monitoring and control of diseases, and difficulty in the management of acute and chronic health conditions. One instance of imbalance of the ideal health care model is the dominance of a biomedical model over the disease prevention and health promotion model, otherwise known as medical hegemony (393). Medical hegemony refers to when a biomedical model of healthcare, or curative medicine, dominates, leading to the active suppression of alternative forms of healthcare and excessive practice of clinical medicine such as reliance on pharmaceutical interventions and hospital-centred treatment (393). Medical hegemony in a public health system may underutilise the power of preventive medicine or health promotion and under value the role of social and behavioural science in public health (393).

A consultant from the WHO country office Nepal describes his experience with EDCD and public health systems in Nepal and emphasises the marginalisation of health prevention and other public health principles.

> *In the context of Nepal, public health as a subject is not specialised, environmental health has not received much attention. Public health in our context operates under the shadow of medicine. The overall, public health sector in Nepal seems to be giving priority to outbreak detection, outbreak control and treatment.*
>
> *In general, (the) preventive aspect of public health has been ignored. Climate change and disease surveillance comes under preventive aspect of public health so, this mindset is the biggest constraint. So this mindset needs to change from the very top level.*
>
> *(Consultant, WHO country office Nepal, QSNP09)*

This extract was elicited when the stakeholder was asked about constraints faced by his team through their efforts to strengthen surveillance systems in Nepal. The speaker indicates that public health systems in Nepal have not utilised health prevention, but instead focus on disease detection and treatment. Effective surveillance of infectious diseases and early warning or forecasts in response to variation in climatic parameters is an important aspect of preventive health, yet preventive aspects of health are given low priority. This disregard of basic principles of public health seems to be more prominent in the discipline of disease surveillance and outbreak management, where the primary aim is to prevent epidemics or mitigate the impacts of unavoidable disasters. According to this view, infectious diseases surveillance in Nepal operates with a selective goal of diseases or outbreak detection, remediation, or damage control rather than the identification of associated risk factors or causes of future outbreaks.

In the extract below, an academic from a public health university reiterates the view that, in contrast to the identification and treatment of disease or ailments, health prevention is given lower priority, and the major focus of surveillance systems in Nepal is detection and treatment of diseases.

> *If there are infected cases, we treat them (…) whenever there are outbreaks our main priority is to control these outbreaks (…) once they are under control, we completely forget them.*
>
> *No one bothers (about) why these outbreaks happened? We don't pay attention to find out the reason behind (an) outbreak to prevent such (an) outbreak in future. If we get them again in future, we will cure the cases and control the outbreaks and forget it again.*
>
> *(Senior academic from a public university, QSNP06)*

A focus on treatment and containing the spread of infectious disease are key facets of the medical and epidemiological practices dominated by a biomedical model. The above extract suggests a disregard towards preventive health by public health practitioners in Nepal. It further strengthens the argument that surveillance systems in Nepal undervalue the significance of epidemiological modelling for disease forecasting. One of the key facets of modern epidemiology is unravelling the potential causal mechanism of disease outbreaks, such that an effective intervention measure can be designed to prevent similar outbreaks in future. This narrative suggests that surveillance systems in Nepal operate with non-holistic or a selective goal of diagnosis or disease detection and treatment with little focus on disease prevention. At the structural level, it can be argued that the low funding capacity of the state, as discussed in the previous theme, has limited the scope and functioning of infectious disease surveillance systems in Nepal. Alternatively, this approach of disease cure rather than outbreak prevention may be related to the preference for medical graduates (rather than public health graduates and a diverse range of other relevant disciplines) to fill influential positions in public health divisions (360). Consequentially, the decision-making process within the public health division is strongly influenced by the mindset of professionals trained for curing disease rather than for health promotion and disease prevention.

In the extract below, an epidemiologist from a private institution suggests that scholars from a medical science background exercise a strong grip within the public health sector in Nepal.

Respondent: There is nothing you can do when you don't have database… It is a big problem and there isn't much we epidemiologists can do about it.

Researcher: You pointed database as a major problem, what else would you like to add?

Respondent: Well planners and policy makers!!! People who are accountable for public health in Nepal…. I think public health sector in Nepal is over medicalised … It is like a norm in Nepal that only medicine graduates should do public health…

They think everything is drugs, medicine is everything, as if medicine can solve all health-related issues. If there is a health problem they opt for medicine and do not bother other interventions like behaviour modification, environment manipulation…. They have pills for every health problem (…) so environment health is a distant topic for them.

(Epidemiologist from a private institution, QSNP05)

In the above extract, the stakeholder also makes the claim that public health sector in Nepal does not have proper databases to support researchers. Professionals with expertise in database management are suggested to be underrepresented in the public health sector of Nepal due to the preference for medical graduates within public health departments. Furthermore, the use of term 'medicalised' following the statement about the database suggests that medical graduates in the public health department of Nepal may have greater influence on the decision-making process.

The stakeholder also further attributes the medical hegemony in Nepal's public health systems of Nepal to the health education system in Nepal e.g. "What qualifies to be a public health professional in Nepal?" This has always been a contentious issue, especially the eligibility requirements for public health training and education. High school graduates with a background in biological sciences or health sciences are eligible to pursue a career in health sector (medicine, paramedicine and other non-clinical specialities related to health sciences) and those with background in social sciences or other faculties are not permitted to pursue a career in health sciences, including public health and epidemiology. Traditionally, public health in Nepal has been a career goal for medicine graduates who are better incentivised or preferred for influential positions, compared to students from a basic science background (360). Consequently, the field of public health and epidemiology in Nepal predominantly employs medical graduates. Yet, to cope with the challenges of emergence and re-emergence of infectious diseases posed by climate change, infectious disease surveillance systems need strong cadres of personnel with interdisciplinary expertise in a range of disciplines including environmental health, epidemiology, social and behaviour science, meteorology, science communication, health policy and health promotion (259, 263) .

7.3.3 Science-policy interaction in climate change and public health surveillance

In the absence of a shared consensus among stakeholders and decision makers on what constitutes important considerations for disease surveillance, it becomes very challenging to integrate climate change as a risk factor. Scientists are trained to generate knowledge for scientific audiences but have little if any training in communicating science to the general public and policymakers. Hence, the effective delivery of timely and accessible science information to policy makers is of paramount importance for effective decision-making in an interdisciplinary health system, like infectious diseases surveillance systems (259). However, science alone cannot provide policy solutions to many problems faced by society because of the complicated path of evidence into policy. Lack of trust and mutual respect between the science and the policy domains may lead to underutilisation of the evidence generated or may prompt questioning of the usefulness of the research undertaken (394). In practice, to serve the public interest, policy makers should arrange for support systems to rigorously evaluate scientific evidence and consider scientifically informed suggestions backed up by the best available evidence for decision-making (395).

A focal person on climate change from the Department of Hydrology and Meteorology, when asked about the implications of climate change and support systems available for the health sector within her department, expressed her discontent on the failure to communicate scientific information effectively with policy makers and other stakeholders in the following extract.

> *If only government would listen to our demand and prioritise our needs, it would have a wide range of impact in different sectors. The biggest problem with meteorological division in Nepal, is (that) we have not been able to explain our potential to government or EDCD and they do not have capacity to understand it.*
>
> *(Focal person on climate change, Department of Hydrology and Meteorology, QSNP08)*

This extract represents a theme that was observed across numerous interviews. Policymaking is a complex process involving multiple stakeholders, including evidence generators, decision makers and the consumers or end users. If these stakeholders do not align, it makes it difficult to develop and achieve the shared goal of evidence-based decision-making to meet local needs. The speaker in this extract suggests that the government hasn't been interested enough to listen to the needs of the Department of Hydrology and Meteorology. Conversely, it is possible that the department has not been able to effectively communicate their demands to the government. Furthermore, it seems that the EDCD is not aware of the weather forecasting potential of the meteorological department, which is one of the pre-requisites for climate-based disease forecasting outlined in the BRACE framework (260).

Formulation of an effective policy on adaptation measures or mitigation of health effects of climate change, requires that concerned authorities must be educated or made aware of the current state of knowledge by the experts working in the field of public health. While the lack of effective science communication may contribute, the intentional or unintentional exclusion of experts from the process of policy discussion can also disrupt information flow to the relevant authorities. This theme is reiterated in an extract from a senior academic who portrays the government as not being interested in consulting experienced experts in planning surveillance priorities in the context of a changing climate.

No one cares about suggestions of academics in this country. I would say, we are the last person this country would turn into for suggestion. No one values our contribution, no one values our research and evidence generated by us.

Yes, this is the bitter truth… We would be very happy to contribute for (the) nation, to generate evidence for planning and policy formulation, to help government (…) for an instance we prepared training manual for health professionals on climate change without government's support. We conducted training in different districts (…) I was very happy that I could contribute from my personal effort.

But the country barely seeks our support. Government does not encourage and support us to generate evidence. If we do it with our own effort, they don't bother listening to our findings.

(Senior academic from a public university, QSNP07)

National policy, and subsequent efforts for strengthening infectious diseases surveillance systems in response to the potential impacts of climate change, is contingent upon local evidence and the discrete needs of various communities, identified through rigorous scientific inquiry by experts. Evident from the above extract, is that there is a gulf between the public health experts involved in infectious diseases control and the policy makers. This lack of communication amongst stakeholders can reinforce the status quo of infectious diseases surveillance practice, and stop the system from transforming to cope with the future impacts of climate change on diseases transmission.

To accentuate the theme, a freelance infectious disease consultant provided an alternative explanation of how infection control policy development was influenced by experts. In this account, a motivated reasoning on the part of stakeholders is implicated in policy development, to include or exclude particular experts to make the job of the leadership/politicians more convenient or secure their position.

They only invite experts to show the public that they are involving experts in decision making and setting priorities. But (the) reality is different. They only listen to the experts who speak (the) government's language. One who nods yes to everything the government speaks or proposes, their voices get heard. One who *disagrees for a good reason, they are ignored. In doing so, the government is playing a game and telling the public, "We are following experts' suggestion".*

(Freelancer infectious disease expert, QNSP13)

In the above extract, the stakeholder suggests that the government invites experts who will support the government's decision to legitimise preconceived beliefs held by the government rather than support ideas that are generated by the best available evidence (396). He contends that there is a bias in the selection of experts for consultation on public health issues. This practice was further exemplified by the Nepalese government's selection of an expert panel and the resultant decisions and work practices of the Ministry of Health during the early days of the COVID-19 pandemic in Nepal (397). Similarly, a report published in The Lancet in 2010, exposed the temporary disruption in health services in Nepal triggered by corruption and political appointments into influential positions in public health sectors (398). In the Nepalese context, such practices frequently question the legitimacy of experts in policymaking processes. Furthermore, these practices highlight that policymakers need to be more neutral and invite opinions from a range of sources to identify local needs and evaluate and integrate these ideas to formulate policy to strengthen infectious diseases surveillance systems.

7.4 General Discussion

The analysis suggests that EDCD Nepal routinely prioritises imperatives other than the impacts of climate change on infectious disease epidemiology as it grapples with other aspects of regular surveillance practices. The stakeholders interviewed in this study were either involved in infection control, disease surveillance or scientific consultation to EDCD and yet none of them had a remit to act on public health impacts of climate change. Despite being an urgent priority for consideration according to the IPCC and WHO, strengthening early surveillance and response to climate sensitive infectious diseases will only occur when authorities give higher priority to the impacts of climate change on vector-borne and food-and water-borne infectious diseases epidemiology and other public health imperatives (5). Research from China and Western Europe on ways to strengthen infectious disease surveillance in a changing climate highlights the public understanding of risk, and preventing and prioritising the issue of climate and health equally amongst the other public health problems such as control of non-communicable diseases (399, 400). Although chronic diseases replaced infectious diseases as the leading causes of deaths — and shifted the focus of public health towards health promotion programs — there is an impetus for reinforcement of infectious diseases surveillance systems following recent outbreaks of infectious diseases following a series of natural disasters, and emergence of diseases like Middle East Respiratory Syndrome (MERS) and Sever Acute Respiratory Syndrome (SARS).

Citing the absence of convincing local scientific evidence, participants employed a discourse that underplayed climate change as a public health threat. Such discourse may justify that fewer resources are allocated to target the impact of climate change on infectious disease control, and rationalise a focus on public health problems that are perceived to be more compelling and locally salient (359). Public health priority setting is a product of both a situation analysis process to identify public health problems and deliberation by public health authorities of potential approaches to overcome these challenges (401). There are complex links between climate change and other interactions to changing patterns of infectious diseases incidence that make direct attribution difficult: explicit impacts may not be obvious, easily quantifiable or hence prioritised during routine situation analysis exercises (402, 403). Consequently, a government with limited financial capacity and resources may be obliged to consider trade-offs and support community health needs that are construed to be more obvious and pressing needs (401).

Our study identified the marginalisation of preventive medicine in public health decision-making as an important factor that restrains the integration of climate change-related risk in routine surveillance of infectious diseases. Discounting the power of health promotion and disease prevention and excessive focus to hospital centred disease cure model is a major hindrance to progress of several health reform goals, including universal health coverage (404). Investment in preventive public health measures, such as climate-based early warning and infectious diseases forecasting, allows early identification of conditions that may be conducive to a disease outbreak: this can enable effective public health interventions to be deployed in time to mitigate morbidity and mortality if the outbreak occurs (256). Mitigation of the impacts of climate change on infectious diseases transmission patterns requires collaboration across various disciplines to operationalise pertinent practices across the spectrum of public health principles (250). For effective functioning of a public health program, like infectious diseases surveillance, it is important to follow the core principles of public health, acknowledge the local context and understand the social structure of a public health systems. Based on our analysis, we argue that medical hegemony, or the dominance of curative medicine in health systems of Nepal, is entrenched in Nepalese society, which prefers medical graduates — intrinsically trained in individual-oriented medical care — to be the practitioners of public health (360). The discourse used by our participants made evident the colonisation of public health, an interdisciplinary subject, by a highly specialised cadre that is prevalent through the medical hegemony of the health care sector of Nepal.

The Intergovernmental Panel on Climate Change (IPCC), through its practice of releasing summary of Assessment Reports to policy makers, confirms that relevant scientific advice in simple language is imperative to inform decision makers about climate change issues. Unless policy makers are informed of the potential threats of climate change, climate change and health cannot be a public health priority (5, 401). Our findings suggests that there are many barriers for knowledge translation from experts into policy. In theory, public health practice should be driven by scientifically derived policy that, in turn, directs appropriate resourcing of programs and strategies (394). Research doesn't easily move from a journal paper into policy and subsequently into implementation. Successful translation of research findings from evidence to policy and practice is contingent upon four key ingredients: research questions that align with information priorities of decision makers, knowledge about decision-making milieu, effective engagement of key stakeholders and effective science communication (405). However, our study exposes several caveats in the process of evidence-based policymaking to mitigate the impacts of climate change on health in Nepal. Salient issues were ineffective science communication with stakeholders and problems with a bias in the representation of experts in decision-making process on climate change and public health impacts. However, our analysis revealed that the most prominent problem of all was the cultural underpinning of the representation of experts in decision-making process, in which authorities appear to be motivated to invite a particular faction of experts – who supported pre-conceived ideas of leadership – into the decision-making process, while also excluding opposing experts from the process. Moulton et al. (250) have reported that even developed nations like the United States, that has abundant evidence on health impacts of climate change, have struggled to enact appropriate policies for public health surveillance in a changing climate. Hence, for a nation such as Nepal, under the current circumstances it becomes an even greater challenge to align science and policy on climate change and health to integrate climate change-related risks in infectious disease surveillance.

In conclusion, a strong political commitment by the nation and local ownership of the issue — that climate change as an urgent public health priority — is necessary to integrate climate change as an important consideration in the infectious diseases surveillance practices in Nepal. The research findings presented here indicate that long term efforts to strengthen infectious diseases surveillance systems with the integration of climate change-related risks need to address socio-economic, cultural and political dimension of health and climate change simultaneously with the obvious systemic issues.

Ethical consideration

The study was granted ethical approval by the Human Research Ethics Committee (HREC) of The University of Adelaide (H-2018-236), and Ethical Review Board of the Nepal Health Research Council (Reg. no. 560/2018). Interview data analysed in the study were anonymised.

Conflict of Interest

We declare no conflict of interest.

Acknowledgements

We would like to acknowledge all the participants and stakeholders who, despite the public health emergency created by the COVID-19 pandemic, made available their time to speak with us and share their experience. We are also in-depth to Nepal Health Research Council, Epidemiology and Disease Control Division and the Department of Health Services, Nepal for providing space to conduct the interviews. D.B is supported by Adelaide Scholarship International provided by the University of Adelaide for his PhD study.

Chapter 8: Discussion and conclusions

In this final chapter, I provide an overview of the key findings from the four analytical chapters, the general significance of this PhD work and the problems encountered during the project. Furthermore, I discuss the implications of this research for our understanding of the impacts of climate change on infectious disease transmission in Nepal and suggest key recommendations to stakeholders, policy makers and concerned public health authorities. I make suggestions, with special a focus on LMICs, for future research work on climate change and infectious diseases and the integration of climate change-related risk in infectious disease surveillance systems.

8.1 Key findings of this research project

In chapter 4, I analysed the relationship between climate variables and burden of diarrhoea among children below five years of age living in Kathmandu, Nepal and projected the future burden of diarrhoea under different climate change scenarios. A strong positive linear association was estimated between increase in maximum temperature, rainfall and diarrhoea among children below five years of age. The final adjusted model revealed an 8.1% increase in monthly diarrhoea count for every 1 ^{o}C increase in maximum temperature above the monthly average. Similarly, it was estimated that for every 10mm increase in cumulative rainfall the risk of childhood diarrhoea increased by 0.9%. However, humidity was not found to be associated with childhood diarrhoea burden. Based upon the risk assessed from the final adjusted model it was estimated that 7.5% of the total burden of diarrhoea cases recorded during the study period was attributable to the primary exposure variable i.e., the maximum temperature. The final key finding of the study 1 is the projected increase of 2400 additional cases of childhood diarrhoea burden attributable to climate change (under the high risk scenario i.e., 2 ^{o}C increase in temperature) by the year 2030s.

In chapter 5, I analysed the relationship between three different temperature indices (maximum, mean and minimum) and rotavirus diarrhoea among children below five years of age in

Kathmandu, Nepal, and estimated the temperature attributable burden of rotavirus diarrhoea. A nonlinear negative association was estimated between temperature and rotavirus infection among children below five years of age, with the risk of rotavirus infection increasing below the median value of temperature and decreasing above the median value. The effect of temperature on rotavirus infection was immediate and was not significant beyond the lag week zero. Among the three temperature indices used as exposure variables, the temperature-attributable risk of rotavirus infection was found to be highest for minimum temperature (47.01 %). Another key finding of the study 2 was the identification of colder days (minimum temperature 4.2 – 7.8 ºC) as a high-risk period for rotavirus infection.

In chapter 6, I examined the available evidence on the impacts of climate change on infectious disease transmission in Nepal. A comprehensive review of literature was undertaken that analysed the association between climate change and infectious disease in Nepal: I identified 13 relevant papers of which only three studies utilised epidemiological datasets on infectious diseases to estimate the risk of disease onset in the context of climate change. Thus, my study concluded that available evidence on the impacts of climate change on infectious disease and diarrheal disease is scarce in the Nepalese context. Therefore, I explored the reasons behind the paucity in evidence and challenges faced by epidemiologists in Nepal. I argued that poor quality datasets, inadequate funding, poor epidemiological capacity, and political challenges were preventing epidemiologist from developing evidence base on climate change and infectious disease to adequately address the threat. I concluded the study by advocating for strengthening of Nepalese infectious diseases surveillance systems and postulating that Nepal will derive immense benefit from the establishment of a climate based early warning systems for identification and prediction of conditions suitable for outbreaks and emergence of infectious diseases.

In chapter 7, the final analytical chapter, I employed critical realism (278) to explore socio-economic, cultural and institutional factors associated with infectious disease surveillance in Nepal in the context of climate change. Although the assessment of impacts of climate change on human health has received greater attention, social aspects of infectious disease surveillance in a changing climate hasn't been a priority among public health researchers (250, 259). In the preceding analytical chapters of this thesis, it was evident that there was scant information on the impacts of climate change on infectious disease in Nepal and there were several challenges in the public health sector of infectious disease and climate change. As such, this chapter elaborated on the issues related to infectious disease surveillance constructed from the interview data of key informants involved in infectious disease prevention and control in Nepal. Using empirical evidence, I illustrated how climate change and its impact on infectious disease surveillance is considered to be less serious than other salient public health problems. It was exemplified, via the extracts of the interviews, that climate change as a public health priority was contingent upon funding support from external sources. I further posited that the dominance of medical graduates in public health systems of Nepal has resulted in an undervaluation of the role of social and behavioural science from the arena of public health and, furthermore, has led to the underutilization of the power of preventive medicine and health promotion.

Finally, I argued that a weaker alliance among the range of stakeholders and poor science communication, particularly between policy makers and evidence generators, is leading to traditional surveillance practices continuing to operate without consideration of climate change-related risk. I further contend that a strong political commitment by the nation's leaders and stakeholders is necessary to strengthen Nepal's infectious diseases surveillance systems in the context of climate change.

8.2 Significance of this research

In the global context, prior work in the field of climate change and infectious diseases has clearly demonstrated that climate change is having significant effect on infectious disease onset and transmission, particularly for vector borne and food-and water-borne diarrheal diseases (7, 342). However, in the context of Nepal, there is limited evidence available on the impact of climate change on diarrheal diseases. This thesis has made an important contribution to improve our understanding of the impacts of climate change on diarrheal disease and the preparedness of infectious diseases surveillance systems in Nepal. The findings further add to existing body of literature on the impacts of climate change and infectious diseases, particularly diarrheal disease and socio-cultural factors associated with surveillance of infectious diseases in a changing climate.

Firstly, study 1 represents the first attempt to generate quantitative evidence on the impacts of climate change on childhood diarrhoea in Kathmandu, Nepal as well as the projection of a future burden under different climate change scenarios using advanced epidemiological techniques. The findings are significant in the sense that the estimates or projected burden would provide guidance for the adaptation of existing childhood diarrhoea management programs and allocation of additional resources to manage the future additional burden of climate attributable childhood diarrhoea. It is one of the few studies that has projected future burden of diarrhoea under different climate change scenarios.

Secondly, this research identifies the high-risk period for transmission of rotavirus infection in Kathmandu, Nepal. The significance of this finding is that interventions to control burden of rotavirus — such as a vaccination campaign — is likely to provide the best outcome if administered during the high risk period, rather than running a year-round vaccination campaign. In fact, for LMICs, evidence already exists that a vaccine administered during the high risk winter period shows higher efficacy against the Respiratory syncytial virus infection, compared to the year-round vaccination strategy (406). At the global scale, this finding further adds to the existing body of literature on rotavirus seasonality and the association between rotavirus infection and temperature. It strengthens the previous findings from sub-tropical and temperature regions on the strong negative association between rotavirus infection and temperature.

Thirdly, study 3 clearly presents the status quo of climate change and infectious disease research in Nepal and identified associated challenges for epidemiologist and researchers working in this field. The significance of this study is that it is the first of its kind in Nepal and so provides baseline information and a starting point for researchers planning to further explore impacts of climate change on infectious diseases in Nepal. The core recommendations from this study included the establishment of a digital network of interdisciplinary experts to tackle the impact of climate change on infectious disease. This recommendation is broadly applicable throughout the South Asian region, as the institutional capacity of health care structures within this region are similar to Nepal. Furthermore, advocacy for the establishment of climate based early warning systems to identify conditions suitable for emergence and outbreak of infectious diseases, if implemented, is likely to facilitate more timely responses that would reduce morbidity and mortality during the epidemics.

Finally, I am unaware of any study that has explored socio-cultural factors associated with infectious disease surveillance in the context of climate change. Compared to widely studied structural or systemic issues (such as data quality, timeliness, representativeness, and sensitivity etc.) — which are evaluated using standard quantitative tools— socio-cultural factors associated with infectious disease surveillance are complex in nature. Hence, traditional positivist enquiry utilising an experimental or statistical approach is insufficient to capture the role of cultural, political and social factors in the effective functioning of surveillance systems. The use of a qualitative research technique, embedded in critical realist epistemology, in the final study enabled me to explore why climate change and health was constructed as a less important public health priority compared to other issues perceived to be locally more important by public health officials in Nepal. The analysis suggested a weaker alliance between evidence generators and public health authorities, which is an important barrier for translation of scientific evidence into policy. The elucidation of these intangible aspects of infectious disease surveillance systems using a CR approach are the novel findings of this research. Thus, study 4 is novel serves to guide future research on infectious disease surveillance systems in the context of climate change, especially the path finding literature on the extended function of surveillance systems in climate change context and the use of critical realist paradigm for deeper exploration of contextual issues in surveillance systems. Furthermore, this study provides important information in the local context: climate change-related risk has not been integrated in the Nepalese infectious disease surveillance systems and so, by identifying social, institutional and political factors aspects of infectious disease surveillance, this research will help to direct the integration of climate change related- risk components in the surveillance systems and guide change in necessary policy and practices for the nation.

8.3 Limitations of this research

Besides the study-specific limitations mentioned in each chapter, I would like to discuss four general limitations of this thesis.

Firstly, the quality of datasets used in this study is not ideal for the estimation of the impact of climate variability on diarrhoea outcomes. Precise estimation of short-term association between climate variables and diarrhoea outcomes requires daily datasets and yet only weekly or month resolution of datasets were available to be used for this research. Furthermore, the vulnerability of individuals to climate changes and susceptibility to diarrhoea are reported to differ by age groups, living standards, socioeconomic status, access to health care services and nutritional status among other factors. As such, the aggregated nature of dataset didn't allow stratified or sub-group analysis to estimate the effects on the basis of gender, socio-economic status, housing practices, different age groups within under five years populations and other behavioural risk factors (e.g. hygiene status, drinking and feeding practices) likely to affect the strength and direction of the association.

Secondly, the ecological study design used in quantitative part of this study measures the effect at population level. Hence, the findings are prone to ecological fallacy (407). This means that the collected data are analysed at population level, but it is assumed that the results will apply at the individual level that, in reality, is compromised by ecological bias.

Thirdly, the analysis of datasets from a single study site, such as Kathmandu city, does not reflect the true nature of the problem within the entire nation. Although Kathmandu is the most densely populated city in Nepal, children living in rural areas are more vulnerable to diarrhoea (due to poor sanitation, no access to toilet facilities, low literacy rate, no provision of processed drinking water supply), plus the people of rural Nepal are more vulnerable to overall impacts of climate change (408, 409).

Finally, the findings of qualitative study in this research project should be interpreted with reference to social, political, economic and institutional context of the study setting. I chose a mixed method design because the purpose of the qualitative research study is to offer in-depth explanations on contextual factors associated with infectious diseases surveillance systems in a changing climate in Nepal: hence to better understand this specific context with the generalizability of the findings not the main objective. In using this qualitative approach to explore the social aspects of infectious disease surveillance in the context of climate change, my hope was to inspire fellow epidemiologists to also use similar tools to explore similar research questions in the future.

8.4 Challenges faced during the research

For a scientist trained in laboratory medicine, it was itself a huge challenge to embark on a PhD journey that is not in my primary areas of expertise but in the field of epidemiology. With the support of an excellent supervisory team, a supportive post graduate coordinator and necessary resources made available by the university, I was able to overcome all technical challenges. However, this project was not free of unanticipated challenges, including being conducted amidst the COVID pandemic in collaboration with an LMIC like Nepal, with poor public health infrastructure and with a poor health registry and health database. Some of the noteworthy challenges faced during the research are described briefly in the following subsection.

8.4.1 Challenges related to public health datasets

A primary challenge was the identification of authentic sources of public health related datasets in Nepal. As discussed in chapter 4 and chapter 6, the Department of Health Services and its specialised units maintain databases related to infectious diseases in Nepal. However, the datasets are not publicly available and are only available in the form of annual health report. Having worked with the rotavirus surveillance program among children in Nepal, I was aware of several disease specific vertical surveillance programs in Nepal that are supported by international donor agencies and are not under direct control of EDCD. These surveillance programs are better regulated and maintain far superior datasets compared to the one maintained by HMIS or EDCD. As such, I wrote several times to country coordinators of these programs, specifically to the Japanese encephalitis surveillance program, dengue surveillance program and enteric fever surveillance programs but without success. The data custodians were reluctant to share database with a PhD scholar because they had existing reservations and demands (intellectual and financial) that were impossible to meet. After several months of efforts and several rounds of emails, I finally had collaborators who were willing to share the datasets with some minor conditions and restrictions. However, these datasets had limitations. The data on diarrhoea obtained from HMIS was aggregated and only available at the monthly resolution. Similarly, the data on rotavirus, though a better quality dataset compared to the diarrhoea dataset, was only available for a short period of four years. Due to the poor quality datasets, I spent longer than I had anticipated cleaning and preparing the data. Similarly, an updated dataset on population was unavailable, which results in my use of the 2011 census population dataset for both the studies. Fortunately, routine meteorological datasets, with some missing values for rainfall, were available from the Department of Hydrology and Meteorology. On the other hand, data on projected temperature for Kathmandu under different climate change scenario were not available from the Department of Hydrology and Meteorology and so I used secondary estimates from published research work for our projection study.

8.4.2 Methodological challenges

As discussed in chapter 3, time-series regression models fitted with distributed lag were used in the quantitative analysis. Time series analysis ideally requires a denominator to calculate incidence rate, however, no data were available on exposed population, apart from the monthly count of cases. Thus, I had to model diarrhoea count against the exposure variables and consequently report relative risk instead of absolute risk, which is the better estimates of the two. Apart from that, the potential lag effect of temperature on diarrhoea incidence couldn't be ascertained with absolute precision because of the monthly resolution of outcome database available in our study. In general, diarrheal diseases have a very short incubation period of less than a week, so using monthly data means it is not possible to ascertain the effect that may not persist beyond few days.

Further to the methodological data limitations, there were also challenges with the qualitative study. I am unaware of any prior study that has used a qualitative approach to explore the contextual factors associated with infectious disease surveillance systems in the context of climate change. As such, I had to build a conceptual framework and research methodology from scratch, which was quite a challenge without guidance from the literature.

8.4.3 Challenges posed by Coronavirus pandemic

My research was heavily impacted by the COVID-19 pandemic and the challenges it posed have still not abated even now, as I draft the final chapter of my thesis. As outlined in earlier chapters, for the final study of my research project, I needed to interview key informants and stakeholders from EDCD, Department of Health Services and the Ministry of Health, Nepal. To conduct these face to face interviews, I travelled to Nepal in mid-January 2020 and was supposed to return to Adelaide in early April 2020. I planned to interview at least 20 participants and hence, I spent the first two weeks of February meeting with stakeholders and identifying key informants, with the support from my local supervisors. As I began my data collection, the first global wave of the COVID-19 pandemic became more serious and I had to stop my data collection in late March 2020, after interviewing eight participants, due to the first lockdown implemented by the government of Nepal. As all my potential research participants were directly involved in management and containment of the coronavirus pandemic in Nepal, I couldn’t resume my interviews until late June 2020.

My personal circumstances also deteriorated in the following months, as my wife tested positive for COVID-19 in October 2021 and I had to cease work for three weeks until she recovered from the disease. In May 2021, I also tested positive for COVID-19 and had to remain in isolation for 15 days until my symptoms receded. Furthermore, for past 16 months, I have been stranded in Nepal, away from the University of Adelaide due to COVID-related travel restrictions imposed by the Australian government. As such, the past year and a half of my PhD journey has been very challenging as I work to complete my thesis from Nepal. There were many inherent challenges such as irregular supply of electricity, low internet connectivity, recurrent COVID waves and subsequent lockdowns. It has been a difficult year and half with losing close friends and relatives to COVID and then refocusing on my thesis has not been easy.

8.5 Recommendations

Based on the findings of the research project, the implications for advancing evidence for policy makers to control and manage childhood diarrhoea in a changing climate, and strengthening of Nepalese infectious diseases surveillance system in the context of climate change, are elaborated in the following subsections.

8.5.1 Evidence generation and public health advocacy against the impacts of climate change

In chapter 4, a significant association was established between maximum temperature, rainfall and under five diarrhoea. It is thus recommended that potential be explored for the establishment of climate-based early warning systems to predict future outbreaks of climate sensitive infectious diseases. Given the projected future increment in the burden of climate attributable diarrhoea, it is recommended that climate change adaptions measures be included in national programs for controlling diarrheal diseases.

Chapter 5 identified a high-risk period for increased transmission of rotavirus infection. Based on these findings, it is recommended that public health authorities through local media broadcast cautionary information to the general population about the increased risk of rotavirus transmission during cold weather. In communicating this risk, they could also include practical tips, such as dos and don’ts, in their messages.

Rotavirus vaccination was not included in the routine immunisation schedule when we conducted this study, but was added to the routine schedule in mid-2020. Hence, the findings from study 2 have implications for the implementation of effective rotavirus vaccination program in Nepal. It has been reported that, for viral infections with strong seasonality, a strategy of vaccination during a high risk period shows greater efficacy compared to a strategy of year-round vaccination (406). Since rotavirus shows a strong seasonality, and increased risk during colder days, it is recommended that similar clinical trials be designed and tested in the context of Nepal to evaluate if rotavirus vaccination during high risk colder periods would be more effective than an all year-round vaccination strategy.

The findings of chapter 4, 5 and chapter 6 clearly highlight the absence of sufficient evidence on the impacts of climate change on infectious diseases, including diarrheal diseases. It is thus recommended that more epidemiological analysis is undertaken to assess the impacts of climate change on infectious diseases to support public health policy for mitigating health impacts of climate change. Estimation of the impacts of climate change on infectious diseases and mapping the vulnerability requires expertise from multiple disciplines, including epidemiologists, statisticians, meteorologists, and social scientists. Therefore, and based upon the findings from chapter 6, it is recommended that an integrated network of interdisciplinary experts be established to support evidence generation on the health impacts of climate change.

As mentioned in the chapter 6, Female Community Health Volunteers form the primary source of health-related events information and reporting within the Nepalese public health systems. The absence of quality surveillance datasets was identified as a major challenge for evidence generation and therefore, in order to cater the need of a quality surveillance datasets on different infectious diseases, it is recommended that this existing network of volunteers be trained and utilised for infectious disease surveillance and reporting.

8.5.2 Strengthening infectious diseases surveillance systems

Based on the findings of this research project, it is recommended that infectious diseases surveillance systems in Nepal collect and report disaggregated information on pathogen specific diarrheal disease instead of ongoing syndromic surveillance on acute gastroenteritis. Although the analytical chapters of this research project clearly demonstrate a significant association between climate change and food-and water-borne diarrheal disease, climate change-related risk is yet to be integrated in the Nepalese disease surveillance systems. It is hence, recommended that Nepalese infectious disease surveillance systems address the social, political and institutional factors associated with infectious disease surveillance identified in study 4 and take an important stride towards integrating climate change-related risk in infectious disease surveillance systems.

It is also argued that the dominance of graduates from medical science in the Nepalese public health sector, has resulted in the undervaluation of the power of preventive public health and health promotion in the design of public health programs and interventions. As such, it is recommended that public health sectors in Nepal encourage the inclusion of the graduates of multiple disciplines that can contribute to the improvement of health sector. This could include graduates from information technology, social and behavioural science, environmental science, life science, geographical information systems, epidemiology and statistics etc.

In study 4 it was argued that an absence of science communication between evidence generators and policy makers was thwarting the consideration of climate change related threats in infectious disease surveillance. Thus, it is recommended that effective science communication be established among authorities and different stake holders.

Similarly, the analysis in chapter 7 shows that there are divisions within and across the public health sectors and these tend to work in silos. To break down these barriers and strengthen infectious disease surveillance systems of Nepal in the context of climate change, it is also recommended that inter-sectoral collaboration be established between public health sector and other concerned sectors (e.g. Department of Hydrology and Meteorology, the Central Bureau of Statistics, and the Department of Environment).

8.6 Future research direction

In this thesis, particularly chapters 4 and 5, I estimated the impacts of climate change on food-and water-borne diarrhoea and rotavirus infection among children under five years of age living in the Kathmandu district and projected future burden of diarrhoea under different climate change scenarios, using advanced state of the art techniques in environmental epidemiology. Therefore, future research in this sector should focus on estimating the impacts of climate change on diarrhoea at the national level in Nepal. Having said that, climate change is one of the drivers of infectious diseases and its impact on infectious diseases transmission cannot be ascertained with absolute certainty unless other key factors are identified and are accounted properly. Hence, future work on climate change and infectious diseases, in particular food-and water-borne diarrheal disease, should consider the impacts of other key drivers such as hygiene status, social-economic characteristics, land use, access to drinking water and population growth, when estimating the effect of climate change on infectious disease transmission. Epidemiological studies that analyse the impacts of climate change on infectious diseases should move towards more sophisticated investigation: for instance, to investigate that proposed causal pathways are clearly defined and that the intervention efforts to reduce the risk (i.e., mitigation and adaptation measures) can be evaluated.

Recently, a team of researchers estimated the global burden of temperature related mortality attributable to human induced climate change (410). The methodology used by Vicedo-Cabrera et al. (410) can be adapted to conduct similar research to estimate the temperature related diarrhoea burden attributable to human induced climate change. Such efforts will contribute to develop an evidence base towards the formulation of regional climate change mitigation and adaptation policy: it could also support mandating of legislation to reduce greenhouse gas emissions. In the context of Nepal, more research should be conducted to examine the association between climate change and other infectious diseases such as dengue, malaria, Japanese encephalitis etc. Future research should include a range of sub-groups in their analysis to identify more vulnerable groups and to understand the differential impacts of climate change among various age groups and gender. More studies projecting the future burden of infectious diseases under different climate change needs to be carried out to assist policy makers and resource allocation in the health sector.

As demonstrated in this research, the impacts of climate change, particularly increases in temperature and rainfall, on diarrhoea varies by pathogens: there is a positive association with all cause diarrhoea and negative with rotavirus infection. Future research on this topic should evaluate the differential impacts of climate change on food-and water-borne diarrhoea for different causative pathogens. As there is variation in the survival of the pathogens outside the host and their exposure pathways, future research should go beyond all cause diarrhoea to evaluate the impacts of climate change on specific pathogens whenever possible (265).

Finally, future efforts to build a climate resilient public health system should aim to identify ways to overcome institutional, technical and other systemic barriers along with social-economic and political factors to make an important stride towards the integration of climate change-related risk in infectious diseases surveillance systems.

8.7 Concluding remarks

The findings of this thesis will contribute to improve our understanding on the impacts of climate change on childhood diarrhoea in a metropolitan city of a Himalayan country—one of the most vulnerable countries, yet the least explored climatic zone. This thesis includes the first study in a LMIC to project the future climate attributable burden of childhood diarrhoea under different climate change scenarios. The findings of these studies are important to support health service providers and policy makers to allocate necessary resources and design appropriate diarrhoea control program by anticipating the potential health impacts of climate change. Similarly, the findings of our research serves as a starting point to explore the potential of establishing a climate based early warning systems for childhood diarrhoea and other climate sensitive diseases in Nepal. In addition, the results of this work on rotavirus suggests that lower temperature poses higher risk for the incidence of rotavirus infection among children. Hence, it is important that precautionary measures, such as improved hand hygiene practices by care takers or parents, be practiced. This thesis further underscores the importance of developing appropriate adaption measures, considering the behavioural changes and increased access to basic health care service, to cope against and mitigate the health impacts of climate change in an already overburdened health system and vulnerable ecosystem. Considering the status quo of infectious diseases surveillance systems in the various climate change scenarios, it is argued that there is a lower priority to the impacts of climate change on infectious diseases transmission compared to other salient public health problems. Furthermore, a weaker alliance among stakeholders is leading to the established practices of infectious disease surveillance without any consideration of climate change related threats.

To conclude this thesis, I want to reiterate that climate change is affecting the transmission of infectious diseases in Nepal. I argue that effective science communication between evidence generators and policy makers is imperative and I suggest there be institutionalisation of climate - related risk in public health systems of Nepal to strengthen infectious disease surveillance in the context of climate change.

References

1. IPCC. Global Warming of 1.5°C. An IPCC Special Report on the impacts of global warming of 1.5°C above pre-industrial levels and related global greenhouse gas emission pathways, in the context of strengthening the global response to the threat of climate change, sustainable development, and efforts to eradicate poverty. Geneva, Switzerland: Intergovernmental Panel on Climate Change; 2018.
2. Thoman RL, Richter-Menge J, Druckenmiller ML. NOAA Arctic Report Card 2020 Executive Summary. 2020.
3. Xu R, Yu P, Abramson MJ, Johnston FH, Samet JM, Bell ML, et al. Wildfires, Global Climate Change, and Human Health. 2020;383(22):2173-81.
4. McMichael AJ, Haines JA, Slooff R, Sari Kovats R, World Health Organization. Office of G, Integrated Environmental H, et al. Climate change and human health : an assessment / prepared by a Task Group on behalf of the World Health Organization, the World Meteorological Association and the United Nations Environment Programme ; editors : A. J. McMichael ... [et al.]. Geneva: World Health Organization; 1996.
5. Costello A, Abbas M, Allen A, Ball S, Bell S, Bellamy R, et al. Managing the health effects of climate change: Lancet and University College London Institute for Global Health Commission. The Lancet. 2009;373(9676):1693-733.
6. McMichael AJ. Globalization, Climate Change, and Human Health. New England Journal of Medicine. 2013;368(14):1335-43.
7. Patz J, Githeko A, McCarty J, Hussein S, Confalonieri U, de West N. Climate Change and Infectious Diseases. In: Mc Michael A, Campbell-Lendrum D, Corvalan C, Ebi K, Githeko A, Scheraga J, et al., editors. Climate Change and Human Health: Risks and Responses. Geneva, Switzerland: World Health Organization; 2003.
8. McMichael AJ, Woodruff RE, Hales S. Climate change and human health: present and future risks. The Lancet. 2006;367(9513):859-69.
9. Abimbola S, Pai M. Will global health survive its decolonisation? The Lancet. 2020;396(10263):1627-8.
10. Sharma JR, Khatri R, Harper I. Understanding Health Research Ethics in Nepal. Developing world bioethics. 2016;16(3):140-7.
11. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1204-22.
12. Bhandari D, Bi P, Sherchand JB, Dhimal M, Hanson-Easey S. Climate change and infectious disease research in Nepal: Are the available prerequisites supportive enough to researchers? Acta Tropica. 2020;204:105337.
13. Bhandari GP, Gurung S, Dhimal M, Bhusal CL. Climate change and occurrence of diarrheal diseases: evolving facts from Nepal. Journal of Nepal Health Research Council. 2012;10(22):181-6.
14. Dhimal M, Ahrens B, Kuch U. Climate Change and Spatiotemporal Distributions of Vector-Borne Diseases in Nepal – A Systematic Synthesis of Literature. PLOS ONE. 2015;10(6):e0129869.
15. Dhimal M, Karki K, Aryal K, Shrestha S, Pradhan B, Khanal M. Effects of climate change on diarrheal diseases at national and sub-national levels in Nepal. National Conference on Climate Change and Health; April 2018; Kathmandu2018.
16. World Atlas. Nepal Geography [Available from: https://www.worldatlas.com/webimage/countrys/asia/nepal/npland.htm.
17. Shrestha UB, Shrestha AM, Aryal S, Shrestha S, Gautam MS, Ojha H. Climate change in Nepal: a comprehensive analysis of instrumental data and people's perceptions. Climatic Change. 2019;154(3):315-34.
18. MoFE. Climate change scenarios for Nepal for National Adaptation Plan (NAP). Kathmandu, Nepal: Ministry of Forest and Environment; 2019.

19. Sharma B, Schultz K. As Himalayas Warm, Nepal's Climate Migrants Struggle to Survive. The New York Times. 2020 20/04/2020.
20. Dhimal M, Dhimal M, Pote-Shrestha R, Groneberg D, Kuch U. Health-sector responses to address the impacts of climate change in Nepal. WHO South-East Asia journal of public health. 2017;6(2):9-14.
21. EDCD Nepal. Surveillance of Communicable Disease Program Kathmandu, Nepal: Ministry of Health and Population; 2020 [Available from: https://www.edcd.gov.np/section/surveillance-of-communicable-disease-program.
22. Ministry of Health and Population DoHS. Annual report 2073/74 (2016/17). Kathamndu, Nepal: Government of Nepal, Ministry of Health and Population, Department of Health Sevices N; 2018 04/2018.
23. Rijal KR, Adhikari B, Ghimire B, Dhungel B, Pyakurel UR, Shah P, et al. Epidemiology of Dengue viral infection in Nepal: 2006-2019. 2020:2020.08.27.269720.
24. Watts N, Amann M, Arnell N, Ayeb-Karlsson S, Beagley J, Belesova K, et al. The 2020 report of The Lancet Countdown on health and climate change: responding to converging crises. The Lancet. 2020.
25. Watts N, Amann M, Arnell N, Ayeb-Karlsson S, Belesova K, Berry H, et al. The 2018 report of the Lancet Countdown on health and climate change: shaping the health of nations for centuries to come. The Lancet. 2018;392(10163):2479-514.
26. Watts N, Amann M, Arnell N, Ayeb-Karlsson S, Belesova K, Boykoff M, et al. The 2019 report of The Lancet Countdown on health and climate change: ensuring that the health of a child born today is not defined by a changing climate. The Lancet. 2019;394(10211):1836-78.
27. Dhimal M, Ahrens B, Kuch U. Malaria control in Nepal 1963–2012: challenges on the path towards elimination. Malaria Journal. 2014;13(1):241.
28. Tuladhar R, Singh A, Varma A, Choudhary DK. Climatic factors influencing dengue incidence in an epidemic area of Nepal. BMC research notes. 2019;12(1):131-.
29. Tuladhar R, Singh A, Banjara MR, Gautam I, Dhimal M, Varma A, et al. Effect of meteorological factors on the seasonal prevalence of dengue vectors in upland hilly and lowland Terai regions of Nepal. Parasites & Vectors. 2019;12(1):42.
30. Acharya BK, Cao C, Lakes T, Chen W, Naeem S. Spatiotemporal analysis of dengue fever in Nepal from 2010 to 2014. BMC Public Health. 2016;16(1):849.
31. Acharya BK, Cao C, Xu M, Khanal L, Naeem S, Pandit S. Present and Future of Dengue Fever in Nepal: Mapping Climatic Suitability by Ecological Niche Model. International journal of environmental research and public health. 2018;15(2).
32. Troeger C, Blacker BF, Khalil IA, Rao PC, Cao S, Zimsen SRM, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Infectious Diseases. 2018;18(11):1211-28.
33. Moors E, Singh T, Siderius C, Balakrishnan S, Mishra A. Climate change and waterborne diarrhoea in northern India: Impacts and adaptation strategies. Science of The Total Environment. 2013;468-469:S139-S51.
34. Checkley W, Epstein LD, Gilman RH, Figueroa D, Cama RI, Patz JA, et al. Effects of EI Niño and ambient temperature on hospital admissions for diarrhoeal diseases in Peruvian children. The Lancet. 2000;355(9202):442-50.
35. Levy K, Woster AP, Goldstein RS, Carlton EJ. Untangling the Impacts of Climate Change on Waterborne Diseases: a Systematic Review of Relationships between Diarrheal Diseases and Temperature, Rainfall, Flooding, and Drought. Environmental Science & Technology. 2016;50(10):4905-22.
36. Milazzo A, Giles LC, Zhang Y, Koehler AP, Hiller JE, Bi P. The effect of temperature on different Salmonella serotypes during warm seasons in a Mediterranean climate city, Adelaide, Australia. Epidemiology and Infection. 2015;144(6):1231-40.

37. Hashizume M, Armstrong B, Hajat S, Wagatsuma Y, Faruque AS, Hayashi T, et al. Association between climate variability and hospital visits for non-cholera diarrhoea in Bangladesh: effects and vulnerable groups. International journal of epidemiology. 2007;36(5):1030-7.
38. Philipsborn R, Ahmed SM, Brosi BJ, Levy K. Climatic Drivers of Diarrheagenic Escherichia coli Incidence: A Systematic Review and Meta-analysis. The Journal of Infectious Diseases. 2016;214(1):6-15.
39. Levy K, Hubbard AE, Eisenberg JN. Seasonality of rotavirus disease in the tropics: a systematic review and meta-analysis. International journal of epidemiology. 2009;38(6):1487-96.
40. Atchison CJ, Tam CC, Hajat S, van Pelt W, Cowden JM, Lopman BA. Temperature-dependent transmission of rotavirus in Great Britain and The Netherlands. Proceedings of the Royal Society B: Biological Sciences. 2010;277(1683):933-42.
41. Cardemil CV, Sherchand JB, Shrestha L, Sharma A, Gary HE, Estivariz CF, et al. Pathogen-Specific Burden of Outpatient Diarrhea in Infants in Nepal: A Multisite Prospective Case-Control Study. Journal of the Pediatric Infectious Diseases Society. 2017;6(3):e75-e85.
42. Dhimal M, Pradhan B, Dahal S, Sah A, Gautam I, Dhimal ML, et al. Review of Existing Diseases Surveillance System in Nepal from Climate Change Perspective. Kathmandu: Nepal Health Research Council; 2019.
43. Lloyd GER. Hippocratic Writings. Harmondsworth, England: Penguin; 1978.
44. Morabia A. Snippets From the Past: The Evolution of Wade Hampton Frost's Epidemiology as Viewed From the American Journal of Hygiene/Epidemiology. American Journal of Epidemiology. 2013;178(7):1013-9.
45. Frost WH. Some conceptions of epidemiology in general. American Journal of Epidemiology. 1976;103(2):141-53.
46. Harvell CD, Mitchell CE, Ward JR, Altizer S, Dobson AP, Ostfeld RS, et al. Climate Warming and Disease Risks for Terrestrial and Marine Biota. Science. 2002;296(5576):2158-62.
47. Wu X, Lu Y, Zhou S, Chen L, Xu B. Impact of climate change on human infectious diseases: Empirical evidence and human adaptation. Environment international. 2016;86:14-23.
48. Altizer S, Ostfeld RS, Johnson PT, Kutz S, Harvell CD. Climate change and infectious diseases: From evidence to a predictive framework. Science. 2013;341:514-9.
49. Martens P, Moser SC. Health Impacts of Climate Change. Science. 2001;292(5519):1065-6.
50. National Research Council. Under the weather: Climate, Ecosystems, and Infectious Disease. Washington DC: National Academy Press; 2001.
51. Hay SI, Cox J, Rogers DJ, Randolph SE, Stern DI, Shanks GD, et al. Climate change and the resurgence of malaria in the East African highlands. Nature. 2002;415:905.
52. Campbell LP, Luther C, Moo-Llanes D, Ramsey JM, Danis-Lozano R, Peterson AT. Climate change influences on global distributions of dengue and chikungunya virus vectors. Philos Trans R Soc Lond B Biol Sci. 2015;370(1665):20140135.
53. Messina JP, Brady OJ, Golding N, Kraemer MUG, Wint GRW, Ray SE, et al. The current and future global distribution and population at risk of dengue. Nature Microbiology. 2019;4(9):1508-15.
54. Paz S. Climate change impacts on West Nile virus transmission in a global context. Philos Trans R Soc Lond B Biol Sci. 2015;370(1665):20130561.
55. Tong S, Bi P, Donald K, McMichael AJ. Climate variability and Ross River virus transmission. 2002;56(8):617-21.
56. Githeko AK, Lindsay SW, Confalonieri UE, Patz JA. Climate change and vector-borne diseases: a regional analysis. Bulletin of the World Health Organization. 2000;78(9):1136-47.
57. Kovats RS, Campbell-Lendrum DH, McMichael AJ, Woodward A, Cox JS. Early effects of climate change: do they include changes in vector-borne disease? Philos Trans R Soc Lond B Biol Sci. 2001;356(1411):1057-68.
58. Rocklöv J, Dubrow R. Climate change: an enduring challenge for vector-borne disease prevention and control. Nature Immunology. 2020;21(5):479-83.

59. Garrett-Jones C. Prognosis for Interruption of Malaria Transmission Through Assessment of the Mosquito's Vectorial Capacity. Nature. 1964;204(4964):1173-5.
60. Campbell-Lendrum D, Manga L, Bagayoko M, Sommerfeld J. Climate change and vector-borne diseases: what are the implications for public health research and policy? Philosophical Transactions of the Royal Society B: Biological Sciences. 2015;370(1665).
61. Liu-Helmersson J, Stenlund H, Wilder-Smith A, Rocklöv J. Vectorial Capacity of Aedes aegypti: Effects of Temperature and Implications for Global Dengue Epidemic Potential. PLOS ONE. 2014;9(3):e89783.
62. Morin CW, Comrie AC, Ernst K. Climate and Dengue Transmission: Evidence and Implications. 2013;121(11-12):1264-72.
63. Johnson BJ, Sukhdeo MVK. Drought-Induced Amplification of Local and Regional West Nile Virus Infection Rates in New Jersey. Journal of Medical Entomology. 2013;50(1):195-204.
64. Hales S, de Wet N, Maindonald J, Woodward A. Potential effect of population and climate changes on global distribution of dengue fever: an empirical model. The Lancet. 2002;360(9336):830-4.
65. Paz S. The West Nile Virus outbreak in Israel (2000) from a new perspective: the regional impact of climate change. International journal of environmental health research. 2006;16(1):1-13.
66. Xu H-Y, Fu X, Lee LKH, Ma S, Goh KT, Wong J, et al. Statistical Modeling Reveals the Effect of Absolute Humidity on Dengue in Singapore. PLOS Neglected Tropical Diseases. 2014;8(5):e2805.
67. Dickerson CZ. The effects of temperature and humidity on the eggs of Aedes aegypti (L.) and Aedes albopictus (Skuse) in Texas. Texas, USA: Texas A&M University; 2007.
68. Kay BH, Farrow RA. Mosquito (Diptera: Culicidae) Dispersal: Implications for the Epidemiology of Japanese and Murray Valley Encephalitis Viruses in Australia. Journal of Medical Entomology. 2000;37(6):797-801.
69. Kouadio IK, Aljunid S, Kamigaki T, Hammad K, Oshitani H. Infectious diseases following natural disasters: prevention and control measures. Expert review of anti-infective therapy. 2012;10(1):95-104.
70. Jia P, Liang L, Tan X, Chen J, Chen X. Potential effects of heat waves on the population dynamics of the dengue mosquito Aedes albopictus. PLOS Neglected Tropical Diseases. 2019;13(7):e0007528.
71. Kolstad EW, Johansson KA. Uncertainties Associated with Quantifying Climate Change Impacts on Human Health: A Case Study for Diarrhea. Environmental health perspectives. 2011;119(3):299-305.
72. Lo Iacono G, Armstrong B, Fleming LE, Elson R, Kovats S, Vardoulakis S, et al. Challenges in developing methods for quantifying the effects of weather and climate on water-associated diseases: A systematic review. PLOS Neglected Tropical Diseases. 2017;11(6):e0005659.
73. Kotloff KL, Platts-Mills JA, Nasrin D, Roose A, Blackwelder WC, Levine MM. Global burden of diarrheal diseases among children in developing countries: Incidence, etiology, and insights from new molecular diagnostic techniques. Vaccine. 2017;35(49 Pt A):6783-9.
74. Levy K, Smith SM, Carlton EJ. Climate Change Impacts on Waterborne Diseases: Moving Toward Designing Interventions. Current environmental health reports. 2018.
75. Zhang Y, Bi P, Hiller JE, Sun Y, Ryan P. Climate variations and bacillary dysentery in northern and southern cities of China. Journal of Infection. 2007;55(2):194-200.
76. Mellor JE, Levy K, Zimmerman J, Elliott M, Bartram J, Carlton E, et al. Planning for climate change: The need for mechanistic systems-based approaches to study climate change impacts on diarrheal diseases. Science of The Total Environment. 2016;548-549:82-90.
77. Mellor J, Kumpel E, Ercumen A, Zimmerman J. Systems Approach to Climate, Water, and Diarrhea in Hubli-Dharwad, India. Environmental Science & Technology. 2016;50(23):13042-51.
78. Alexander KA, Heaney AK, Shaman J. Hydrometeorology and flood pulse dynamics drive diarrheal disease outbreaks and increase vulnerability to climate change in surface-water-dependent populations: A retrospective analysis. PLOS Medicine. 2018;15(11):e1002688.
79. Lal A, Hales S, French N, Baker MG. Seasonality in Human Zoonotic Enteric Diseases: A Systematic Review. PLOS ONE. 2012;7(4):e31883.

80. Konkel ME, Tilly K. Temperature-regulated expression of bacterial virulence genes. Microbes and Infection. 2000;2(2):157-66.
81. Boithias L, Choisy M, Souliyaseng N, Jourdren M, Quet F, Buisson Y, et al. Hydrological Regime and Water Shortage as Drivers of the Seasonal Incidence of Diarrheal Diseases in a Tropical Montane Environment. PLOS Neglected Tropical Diseases. 2016;10(12):e0005195.
82. Kang R, Xun H, Zhang Y, Wang W, Wang X, Jiang B, et al. Impacts of different grades of tropical cyclones on infectious diarrhea in Guangdong, 2005-2011. PloS one. 2015;10(6):e0131423-e.
83. Moors E, Singh T, Siderius C, Balakrishnan S, Mishra A. Climate change and waterborne diarrhoea in northern India: impacts and adaptation strategies. The Science of the total environment. 2013;468-469 Suppl:S139-51.
84. Rzeżutka A, Cook N. Survival of human enteric viruses in the environment and food. FEMS Microbiology Reviews. 2004;28(4):441-53.
85. Tang JW. The effect of environmental parameters on the survival of airborne infectious agents. 2009;6(suppl_6):S737-S46.
86. John DE, Rose JB. Review of Factors Affecting Microbial Survival in Groundwater. Environmental Science & Technology. 2005;39(19):7345-56.
87. Kovats RS, Edwards SJ, Hajat S, Armstrong BG, Ebi KL, Menne B. The effect of temperature on food poisoning: a time-series analysis of salmonellosis in ten European countries. Epidemiology and Infection. 2004;132(3):443-53.
88. Kraay ANM, Man O, Levy MC, Levy K, Ionides E, Eisenberg JNS. Understanding the Impact of Rainfall on Diarrhea: Testing the Concentration-Dilution Hypothesis Using a Systematic Review and Meta-Analysis. 2020;128(12):126001.
89. Auld H, MacIver D, Klaassen J.

Heavy rainfall and waterborne disease outbreaks: the Walkerton example. Journal of Toxicology and Environmental Health, Part A. 2004;67(20-22):1879-87.
90. Carlton EJ, Eisenberg JNS, Goldstick J, Cevallos W, Trostle J, Levy K. Heavy Rainfall Events and Diarrhea Incidence: The Role of Social and Environmental Factors. American Journal of Epidemiology. 2014;179(3):344-52.
91. El-Fadel M, Ghanimeh S, Maroun R, Alameddine I. Climate change and temperature rise: Implications on food- and water-borne diseases. Science of The Total Environment. 2012;437:15-21.
92. Moran P, Nhandara C, Hove I, Charimari L, Katito C, Bradley M, et al. Contamination of traditional drinking water sources during a period of extreme drought in the Zvimba communal lands, Zimbabwe. The Central African journal of medicine. 1997;43(11):316-21.
93. Heaney AK, Shaman J, Alexander KA. El Niño-Southern oscillation and under-5 diarrhea in Botswana. Nature Communications. 2019;10(1):5798.
94. Guerrant RL, Schorling JB, McAuliffe JF, de Souza MA. Diarrhea as a cause and an effect of malnutrition: diarrhea prevents catch-up growth and malnutrition increases diarrhea frequency and duration. The American journal of tropical medicine and hygiene. 1992;47(1 Pt 2):28-35.
95. Rutkowski T, Raschid-Sally L, Buechler S. Wastewater irrigation in the developing world—Two case studies from the Kathmandu Valley in Nepal. Agricultural Water Management. 2007;88(1):83-91.
96. Benjamin-Chung J, Crider YS, Mertens A, Ercumen A, Pickering AJ, Lin A, et al. Household finished flooring and soil-transmitted helminth and Giardia infections among children in rural Bangladesh and Kenya: a prospective cohort study. The Lancet Global Health. 2021;9(3):e301-e8.
97. Paynter S. Humidity and respiratory virus transmission in tropical and temperate settings. Epidemiology and Infection. 2015;143(6):1110-8.
98. Marr LC, Tang JW, Van Mullekom J, Lakdawala SS. Mechanistic insights into the effect of humidity on airborne influenza virus survival, transmission and incidence. 2019;16(150):20180298.
99. BLESSINGTON T, MITCHAM EJ, HARRIS LJ. Growth and Survival of Enterobacteriaceae and Inoculated Salmonella on Walnut Hulls and Maturing Walnut Fruit. Journal of Food Protection. 2014;77(9):1462-70.

100. Likotrafiti E, Smirniotis P, Nastou A, Rhoades J. Effect of Relative Humidity and Storage Temperature on the Behavior of Listeria monocytogenes on Fresh Vegetables. 2013;33(4):545-51.
101. Aik J, Ong J, Ng LC. The effects of climate variability and seasonal influence on diarrhoeal disease in the tropical city-state of Singapore - A time-series analysis. Int J Hyg Environ Health. 2020;227:113517.
102. Sattar SA, Ijaz MK, Johnson-Lussenburg CM, Springthorpe VS. Effect of relative humidity on the airborne survival of rotavirus SA11. Appl Environ Microbiol. 1984;47(4):879-81.
103. Colston JM, Zaitchik B, Kang G, Peñataro Yori P, Ahmed T, Lima A, et al. Use of earth observation-derived hydrometeorological variables to model and predict rotavirus infection (MAL-ED): a multisite cohort study. The Lancet Planetary Health. 2019;3(6):e248-e58.
104. Center for Disease Control and Prevention. Rotavirus 2018 [updated 23/04/2018; cited 2019 26/02/2019]. Available from: https://www.cdc.gov/rotavirus/index.html.
105. McMichael AJ. Extreme weather events and infectious disease outbreaks. Virulence. 2015;6(6):543-7.
106. Kim S, Shin Y, Kim H, Pak H, Ha J. Impacts of typhoon and heavy rain disasters on mortality and infectious diarrhea hospitalization in South Korea. International journal of environmental health research. 2013;23(5):365-76.
107. Natuzzi ES, Joshua C, Shortus M, Reubin R, Dalipanda T, Ferran K, et al. Defining Population Health Vulnerability Following an Extreme Weather Event in an Urban Pacific Island Environment: Honiara, Solomon Islands. The American journal of tropical medicine and hygiene. 2016;95(2):307-14.
108. Bennett A, Epstein LD, Gilman RH, Cama V, Bern C, Cabrera L, et al. Effects of the 1997-1998 El Niño episode on community rates of diarrhea. American journal of public health. 2012;102(7):e63-e9.
109. Milazzo A, Giles LC, Zhang Y, Koehler AP, Hiller JE, Bi P. Heatwaves differentially affect risk of Salmonella serotypes. The Journal of infection. 2016;73(3):231-40.
110. Milazzo A, Giles LC, Zhang Y, Koehler AP, Hiller JE, Bi P. The effects of ambient temperature and heatwaves on daily Campylobacter cases in Adelaide, Australia, 1990–2012. Epidemiology and Infection. 2017;145(12):2603-10.
111. Checkley W, Epstein LD, Gilman RH, Figueroa D, Cama RI, Patz JA, et al. Effect of El Niño and ambient temperature on hospital admissions for diarrhoeal diseases in Peruvian children. Lancet (London, England). 2000;355(9202):442-50.
112. Lama JR, Seas CR, Leon-Barua R, Gotuzzo E, Sack RB. Environmental temperature, cholera, and acute diarrhoea in adults in Lima, Peru. Journal of health, population, and nutrition. 2004;22(4):399-403.
113. Singh RB, Hales S, de Wet N, Raj R, Hearnden M, Weinstein P. The influence of climate variation and change on diarrheal disease in the Pacific Islands. Environmental health perspectives. 2001;109(2):155-9.
114. Zhang Y, Bi P, Hiller JE, Sun Y, Ryan P. Climate variations and bacillary dysentery in northern and southern cities of China. The Journal of infection. 2007;55(2):194-200.
115. Chou WC, Wu JL, Wang YC, Huang H, Sung FC, Chuang CY. Modeling the impact of climate variability on diarrhea-associated diseases in Taiwan (1996-2007). The Science of the total environment. 2010;409(1):43-51.
116. Milazzo A, Giles LC, Zhang Y, Koehler AP, Hiller JE, Bi P. The effect of temperature on different Salmonella serotypes during warm seasons in a Mediterranean climate city, Adelaide, Australia. Epidemiol Infect. 2016;144(6):1231-40.
117. McIver LJ, Imai C, Buettner PG, Gager P, Chan VS, Hashizume M, et al. Diarrheal Diseases and Climate Change in Cambodia. Asia-Pacific journal of public health. 2016;28(7):576-85.
118. Alexander KA, Carzolio M, Goodin D, Vance E. Climate change is likely to worsen the public health threat of diarrheal disease in Botswana. International journal of environmental research and public health. 2013;10(4):1202-30.
119. Ali M, Kim DR, Yunus M, Emch M. Time series analysis of cholera in Matlab, Bangladesh, during 1988-2001. Journal of health, population, and nutrition. 2013;31(1):11-9.

120. Xu Z, Huang C, Turner LR, Su H, Qiao Z, Tong S. Is diurnal temperature range a risk factor for childhood diarrhea? PLoS One. 2013;8(5):e64713.
121. Wen LY, Zhao KF, Cheng J, Wang X, Yang HH, Li KS, et al. The association between diurnal temperature range and childhood bacillary dysentery. International journal of biometeorology. 2016;60(2):269-76.
122. Trærup SL, Ortiz RA, Markandya A. The costs of climate change: a study of cholera in Tanzania. International journal of environmental research and public health. 2011;8(12):4386-405.
123. Onozuka D, Gasparrini A, Sera F, Hashizume M, Honda Y. Modeling Future Projections of Temperature-Related Excess Morbidity due to Infectious Gastroenteritis under Climate Change Conditions in Japan. Environmental health perspectives. 2019;127(7):77006.
124. Wang H, Liu Z, Xiang J, Tong MX, Lao J, Liu Y, et al. Effect of ambient temperatures on category C notifiable infectious diarrhea in China: An analysis of national surveillance data. The Science of the total environment. 2021;759:143557.
125. Kolstad EW, Johansson KA. Uncertainties associated with quantifying climate change impacts on human health: a case study for diarrhea. Environmental health perspectives. 2011;119(3):299-305.
126. Bi P, Cameron AS, Zhang Y, Parton KA. Weather and notified Campylobacter infections in temperate and sub-tropical regions of Australia: an ecological study. The Journal of infection. 2008;57(4):317-23.
127. Carlton EJ, Woster AP, DeWitt P, Goldstein RS, Levy K. A systematic review and meta-analysis of ambient temperature and diarrhoeal diseases. International journal of epidemiology. 2016;45(1):117-30.
128. Rosenberg A, Weinberger M, Paz S, Valinsky L, Agmon V, Peretz C. Ambient temperature and age-related notified Campylobacter infection in Israel: A 12-year time series study. Environ Res. 2018;164:539-45.
129. Li ZJ, Zhang XJ, Hou XX, Xu S, Zhang JS, Song HB, et al. Nonlinear and threshold of the association between meteorological factors and bacillary dysentery in Beijing, China. Epidemiol Infect. 2015;143(16):3510-9.
130. Aik J, Ong J, Ng L-C. The effects of climate variability and seasonal influence on diarrhoeal disease in the tropical city-state of Singapore – A time-series analysis. International Journal of Hygiene and Environmental Health. 2020;227:113517.
131. D'Souza RM, Becker NG, Hall G, Moodie KB. Does ambient temperature affect foodborne disease? Epidemiology (Cambridge, Mass). 2004;15(1):86-92.
132. Bandyopadhyay S, Kanji S, Wang L. The impact of rainfall and temperature variation on diarrheal prevalence in Sub-Saharan Africa. Applied Geography. 2012;33:63-72.
133. Alemayehu B, Ayele BT, Melak F, Ambelu A. Exploring the association between childhood diarrhea and meteorological factors in Southwestern Ethiopia. The Science of the total environment. 2020;741:140189.
134. Hartmann D, Klein Tank A, Rusticucci M, Alexander L, Bronnimann S, Charabi Y, et al. Observations: Atmosphere and Surface. Climate Change 2013 the Physical Science Basis: Working Group I Contribution to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. 9781107057999.

: Cambridge Univeristy Press. 2013, p. 159-254; 2013.
135. Asadgol Z, Mohammadi H, Kermani M, Badirzadeh A, Gholami M. The effect of climate change on cholera disease: The road ahead using artificial neural network. PLoS One. 2019;14(11):e0224813.
136. Liu Z, Tong MX, Xiang J, Dear K, Wang C, Ma W, et al. Daily Temperature and Bacillary Dysentery: Estimated Effects, Attributable Risks, and Future Disease Burden in 316 Chinese Cities. Environmental health perspectives. 2020;128(5):57008.
137. Semenza JC, Trinanes J, Lohr W, Sudre B, Löfdahl M, Martinez-Urtaza J, et al. Environmental Suitability of Vibrio Infections in a Warming Climate: An Early Warning System. Environmental health perspectives. 2017;125(10):107004.

138. Zhang Y, Bi P, Sun Y, Hiller JE. Projected Years Lost due to Disabilities (YLDs) for bacillary dysentery related to increased temperature in temperate and subtropical cities of China. Journal of environmental monitoring : JEM. 2012;14(2):510-6.
139. Delahoy MJ, Cárcamo C, Huerta A, Lavado W, Escajadillo Y, Ordoñez L, et al. Meteorological factors and childhood diarrhea in Peru, 2005-2015: a time series analysis of historic associations, with implications for climate change. Environmental health : a global access science source. 2021;20(1):22.
140. Wang S, Liu Z, Tong M, Xiang J, Zhang Y, Gao Q, et al. Real-time forecasting and early warning of bacillary dysentery activity in four meteorological and geographic divisions in China. The Science of the total environment. 2021;761:144093.
141. Oberheim J, Höser C, Lüchters G, Kistemann T. Small-scaled association between ambient temperature and campylobacteriosis incidence in Germany. Sci Rep. 2020;10(1):17191.
142. Kuhn KG, Nygård KM, Guzman-Herrador B, Sunde LS, Rimhanen-Finne R, Trönnberg L, et al. Campylobacter infections expected to increase due to climate change in Northern Europe. Sci Rep. 2020;10(1):13874.
143. Galanis E, Otterstatter M, Taylor M. Measuring the impact of sea surface temperature on the human incidence of Vibrio sp. infection in British Columbia, Canada, 1992-2017. Environmental health : a global access science source. 2020;19(1):58.
144. Daisy SS, Saiful Islam AKM, Akanda AS, Faruque ASG, Amin N, Jensen PKM. Developing a forecasting model for cholera incidence in Dhaka megacity through time series climate data. Journal of water and health. 2020;18(2):207-23.
145. Fang X, Ai J, Liu W, Ji H, Zhang X, Peng Z, et al. Epidemiology of infectious diarrhoea and the relationship with etiological and meteorological factors in Jiangsu Province, China. Sci Rep. 2019;9(1):19571.
146. Anwar MY, Warren JL, Pitzer VE. Diarrhea Patterns and Climate: A Spatiotemporal Bayesian Hierarchical Analysis of Diarrheal Disease in Afghanistan. The American journal of tropical medicine and hygiene. 2019;101(3):525-33.
147. Mertens A, Balakrishnan K, Ramaswamy P, Rajkumar P, Ramaprabha P, Durairaj N, et al. Associations between High Temperature, Heavy Rainfall, and Diarrhea among Young Children in Rural Tamil Nadu, India: A Prospective Cohort Study. Environmental health perspectives. 2019;127(4):47004.
148. Djennad A, Lo Iacono G, Sarran C, Lane C, Elson R, Höser C, et al. Seasonality and the effects of weather on Campylobacter infections. BMC Infect Dis. 2019;19(1):255.
149. Lake IR, Colón-González FJ, Takkinen J, Rossi M, Sudre B, Dias JG, et al. Exploring Campylobacter seasonality across Europe using The European Surveillance System (TESSy), 2008 to 2016. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2019;24(13).
150. Rushton SP, Sanderson RA, Diggle PJ, Shirley MDF, Blain AP, Lake I, et al. Climate, human behaviour or environment: individual-based modelling of Campylobacter seasonality and strategies to reduce disease burden. Journal of translational medicine. 2019;17(1):34.
151. Morral-Puigmal C, Martínez-Solanas È, Villanueva CM, Basagaña X. Weather and gastrointestinal disease in Spain: A retrospective time series regression study. Environment international. 2018;121(Pt 1):649-57.
152. Song YJ, Cheong HK, Ki M, Shin JY, Hwang SS, Park M, et al. The Epidemiological Influence of Climatic Factors on Shigellosis Incidence Rates in Korea. International journal of environmental research and public health. 2018;15(10).
153. Wang P, Goggins WB, Chan EYY. Associations of Salmonella hospitalizations with ambient temperature, humidity and rainfall in Hong Kong. Environment international. 2018;120:223-30.
154. Aik J, Heywood AE, Newall AT, Ng LC, Kirk MD, Turner R. Climate variability and salmonellosis in Singapore - A time series analysis. The Science of the total environment. 2018;639:1261-7.

155. Horn LM, Hajat A, Sheppard L, Quinn C, Colborn J, Zermoglio MF, et al. Association between Precipitation and Diarrheal Disease in Mozambique. International journal of environmental research and public health. 2018;15(4).
156. Azage M, Kumie A, Worku A, A CB, Anagnostou E. Effect of climatic variability on childhood diarrhea and its high risk periods in northwestern parts of Ethiopia. PLoS One. 2017;12(10):e0186933.
157. Thiam S, Diène AN, Sy I, Winkler MS, Schindler C, Ndione JA, et al. Association between Childhood Diarrhoeal Incidence and Climatic Factors in Urban and Rural Settings in the Health District of Mbour, Senegal. International journal of environmental research and public health. 2017;14(9).
158. Yan L, Wang H, Zhang X, Li MY, He J. Impact of meteorological factors on the incidence of bacillary dysentery in Beijing, China: A time series analysis (1970-2012). PLoS One. 2017;12(8):e0182937.
159. Wangdi K, Clements AC. Spatial and temporal patterns of diarrhoea in Bhutan 2003-2013. BMC Infect Dis. 2017;17(1):507.
160. Cheng J, Xie MY, Zhao KF, Wu JJ, Xu ZW, Song J, et al. Impacts of ambient temperature on the burden of bacillary dysentery in urban and rural Hefei, China. Epidemiol Infect. 2017;145(8):1567-76.
161. Musengimana G, Mukinda FK, Machekano R, Mahomed H. Temperature Variability and Occurrence of Diarrhoea in Children under Five-Years-Old in Cape Town Metropolitan Sub-Districts. International journal of environmental research and public health. 2016;13(9).
162. Philipsborn R, Ahmed SM, Brosi BJ, Levy K. Climatic Drivers of Diarrheagenic Escherichia coli Incidence: A Systematic Review and Meta-analysis. The Journal of infectious diseases. 2016;214(1):6-15.
163. Stephen DM, Barnett AG. Effect of temperature and precipitation on salmonellosis cases in South-East Queensland, Australia: an observational study. BMJ open. 2016;6(2):e010204.
164. Lal A, Hales S, Kirk M, Baker MG, French NP. Spatial and temporal variation in the association between temperature and salmonellosis in NZ. Australian and New Zealand journal of public health. 2016;40(2):165-9.
165. Jiang C, Shaw KS, Upperman CR, Blythe D, Mitchell C, Murtugudde R, et al. Climate change, extreme events and increased risk of salmonellosis in Maryland, USA: Evidence for coastal vulnerability. Environment international. 2015;83:58-62.
166. Phung D, Huang C, Rutherford S, Chu C, Wang X, Nguyen M, et al. Temporal and spatial patterns of diarrhoea in the Mekong Delta area, Vietnam. Epidemiol Infect. 2015;143(16):3488-97.
167. Phung D, Huang C, Rutherford S, Chu C, Wang X, Nguyen M, et al. Association between climate factors and diarrhoea in a Mekong Delta area. International journal of biometeorology. 2015;59(9):1321-31.
168. Akil L, Ahmad HA, Reddy RS. Effects of climate change on Salmonella infections. Foodborne pathogens and disease. 2014;11(12):974-80.
169. Li Z, Wang L, Sun W, Hou X, Yang H, Sun L, et al. Identifying high-risk areas of bacillary dysentery and associated meteorological factors in Wuhan, China. Sci Rep. 2013;3:3239.
170. Wu J, Yunus M, Streatfield PK, Emch M. Association of climate variability and childhood diarrhoeal disease in rural Bangladesh, 2000-2006. Epidemiol Infect. 2014;142(9):1859-68.
171. Grjibovski AM, Bushueva V, Boltenkov VP, Buzinov RV, Degteva GN, Yurasova ED, et al. Climate variations and salmonellosis in northwest Russia: a time-series analysis. Epidemiol Infect. 2013;141(2):269-76.
172. Zhou X, Zhou Y, Chen R, Ma W, Deng H, Kan H. High temperature as a risk factor for infectious diarrhea in Shanghai, China. Journal of epidemiology. 2013;23(6):418-23.
173. Zhang Y, Bi P, Hiller JE. Projected burden of disease for Salmonella infection due to increased temperature in Australian temperate and subtropical regions. Environment international. 2012;44:26-30.
174. Reyburn R, Kim DR, Emch M, Khatib A, von Seidlein L, Ali M. Climate variability and the outbreaks of cholera in Zanzibar, East Africa: a time series analysis. The American journal of tropical medicine and hygiene. 2011;84(6):862-9.

175. Allard R, Plante C, Garnier C, Kosatsky T. The reported incidence of campylobacteriosis modelled as a function of earlier temperatures and numbers of cases, Montreal, Canada, 1990-2006. International journal of biometeorology. 2011;55(3):353-60.
176. Onozuka D, Hashizume M, Hagihara A. Effects of weather variability on infectious gastroenteritis. Epidemiol Infect. 2010;138(2):236-43.
177. Britton E, Hales S, Venugopal K, Baker MG. Positive association between ambient temperature and salmonellosis notifications in New Zealand, 1965-2006. Australian and New Zealand journal of public health. 2010;34(2):126-9.
178. Hashizume M, Faruque AS, Wagatsuma Y, Hayashi T, Armstrong B. Cholera in Bangladesh: climatic components of seasonal variation. Epidemiology (Cambridge, Mass). 2010;21(5):706-10.
179. Zhang Y, Bi P, Hiller JE. Climate variations and Salmonella infection in Australian subtropical and tropical regions. The Science of the total environment. 2010;408(3):524-30.
180. Paz S. Impact of temperature variability on cholera incidence in southeastern Africa, 1971-2006. EcoHealth. 2009;6(3):340-5.
181. Islam MS, Sharker MA, Rheman S, Hossain S, Mahmud ZH, Islam MS, et al. Effects of local climate variability on transmission dynamics of cholera in Matlab, Bangladesh. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2009;103(11):1165-70.
182. Lake IR, Gillespie IA, Bentham G, Nichols GL, Lane C, Adak GK, et al. A re-evaluation of the impact of temperature and climate change on foodborne illness. Epidemiol Infect. 2009;137(11):1538-47.
183. Luque Fernández MA, Bauernfeind A, Jiménez JD, Gil CL, El Omeiri N, Guibert DH. Influence of temperature and rainfall on the evolution of cholera epidemics in Lusaka, Zambia, 2003-2006: analysis of a time series. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2009;103(2):137-43.
184. Zhang Y, Bi P, Hiller JE. Weather and the transmission of bacillary dysentery in Jinan, northern China: a time-series analysis. Public health reports (Washington, DC : 1974). 2008;123(1):61-6.
185. Naumova EN, Jagai JS, Matyas B, DeMaria A, Jr., MacNeill IB, Griffiths JK. Seasonality in six enterically transmitted diseases and ambient temperature. Epidemiol Infect. 2007;135(2):281-92.
186. Zhang Y, Bi P, Hiller J. Climate variations and salmonellosis transmission in Adelaide, South Australia: a comparison between regression models. International journal of biometeorology. 2008;52(3):179-87.
187. Kovats RS, Edwards SJ, Charron D, Cowden J, D'Souza RM, Ebi KL, et al. Climate variability and campylobacter infection: an international study. International journal of biometeorology. 2005;49(4):207-14.
188. Lal A, Fearnley E, Wilford E. Local weather, flooding history and childhood diarrhoea caused by the parasite Cryptosporidium spp.: A systematic review and meta-analysis. The Science of the total environment. 2019;674:300-6.
189. Bruggink LD, Marshall JA. The incidence of norovirus-associated gastroenteritis outbreaks in Victoria, Australia (2002-2007) and their relationship with rainfall. International journal of environmental research and public health. 2010;7(7):2822-7.
190. Kraay ANM, Man O, Levy MC, Levy K, Ionides E, Eisenberg JNS. Understanding the Impact of Rainfall on Diarrhea: Testing the Concentration-Dilution Hypothesis Using a Systematic Review and Meta-Analysis. Environmental health perspectives. 2020;128(12):126001.
191. Eisenberg MC, Kujbida G, Tuite AR, Fisman DN, Tien JH. Examining rainfall and cholera dynamics in Haiti using statistical and dynamic modeling approaches. Epidemics. 2013;5(4):197-207.
192. Carlton EJ, Eisenberg JN, Goldstick J, Cevallos W, Trostle J, Levy K. Heavy rainfall events and diarrhea incidence: the role of social and environmental factors. Am J Epidemiol. 2014;179(3):344-52.
193. Haddock RL, Malilay J. The possible role of rainfall in spreading Salmonella on Guam. Journal of diarrhoeal diseases research. 1986;4(4):229-32.
194. Deshpande A, Chang HH, Levy K. Heavy Rainfall Events and Diarrheal Diseases: The Role of Urban-Rural Geography. The American journal of tropical medicine and hygiene. 2020;103(3):1043-9.

195. Soneja S, Jiang C, Romeo Upperman C, Murtugudde R, C SM, Blythe D, et al. Extreme precipitation events and increased risk of campylobacteriosis in Maryland, U.S.A. Environ Res. 2016;149:216-21.
196. Wu J, Yunus M, Ali M, Escamilla V, Emch M. Influences of heatwave, rainfall, and tree cover on cholera in Bangladesh. Environment international. 2018;120:304-11.
197. Wang P, Goggins WB, Chan EYY. A time-series study of the association of rainfall, relative humidity and ambient temperature with hospitalizations for rotavirus and norovirus infection among children in Hong Kong. The Science of the total environment. 2018;643:414-22.
198. Drayna P, McLellan SL, Simpson P, Li SH, Gorelick MH. Association between rainfall and pediatric emergency department visits for acute gastrointestinal illness. Environmental health perspectives. 2010;118(10):1439-43.
199. Mukabutera A, Thomson D, Murray M, Basinga P, Nyirazinyoye L, Atwood S, et al. Rainfall variation and child health: effect of rainfall on diarrhea among under 5 children in Rwanda, 2010. BMC Public Health. 2016;16:731.
200. Lee D, Chang HH, Sarnat SE, Levy K. Precipitation and Salmonellosis Incidence in Georgia, USA: Interactions between Extreme Rainfall Events and Antecedent Rainfall Conditions. Environmental health perspectives. 2019;127(9):97005.
201. Grjibovski AM, Kosbayeva A, Menne B. The effect of ambient air temperature and precipitation on monthly counts of salmonellosis in four regions of Kazakhstan, Central Asia, in 2000-2010. Epidemiol Infect. 2014;142(3):608-15.
202. Hashizume M, Armstrong B, Hajat S, Wagatsuma Y, Faruque AS, Hayashi T, et al. The effect of rainfall on the incidence of cholera in Bangladesh. Epidemiology (Cambridge, Mass). 2008;19(1):103-10.
203. Rajendran K, Sumi A, Bhattachariya MK, Manna B, Sur D, Kobayashi N, et al. Influence of relative humidity in Vibrio cholerae infection: a time series model. The Indian journal of medical research. 2011;133(2):138-45.
204. Hashizume M, Armstrong B, Wagatsuma Y, Faruque A S G, Hayashi T, Sack D A. Rotavirus infections and climate variability in Dhaka, Bangladesh: a time-series analysis. Epidemiology and Infection. 2008;136(9):1281-9.
205. Colston J, Paredes Olortegui M, Zaitchik B, Peñataro Yori P, Kang G, Ahmed T, et al. Pathogen-Specific Impacts of the 2011-2012 La Niña-Associated Floods on Enteric Infections in the MAL-ED Peru Cohort: A Comparative Interrupted Time Series Analysis. International journal of environmental research and public health. 2020;17(2).
206. Hashizume M, Faruque AS, Terao T, Yunus M, Streatfield K, Yamamoto T, et al. The Indian Ocean dipole and cholera incidence in Bangladesh: a time-series analysis. Environmental health perspectives. 2011;119(2):239-44.
207. Rieckmann A, Tamason CC, Gurley ES, Rod NH, Jensen PKM. Exploring Droughts and Floods and Their Association with Cholera Outbreaks in Sub-Saharan Africa: A Register-Based Ecological Study from 1990 to 2010. The American journal of tropical medicine and hygiene. 2018;98(5):1269-74.
208. Zhang N, Song D, Zhang J, Liao W, Miao K, Zhong S, et al. The impact of the 2016 flood event in Anhui Province, China on infectious diarrhea disease: An interrupted time-series study. Environment international. 2019;127:801-9.
209. Gong L, Hou S, Su B, Miao K, Zhang N, Liao W, et al. Short-term effects of moderate and severe floods on infectious diarrheal diseases in Anhui Province, China. The Science of the total environment. 2019;675:420-8.
210. Liu Z, Ding G, Zhang Y, Lao J, Liu Y, Zhang J, et al. Identifying different types of flood-sensitive diarrheal diseases from 2006 to 2010 in Guangxi, China. Environ Res. 2019;170:359-65.
211. Saulnier DD, Hanson C, Ir P, Mölsted Alvesson H, von Schreeb J. The Effect of Seasonal Floods on Health: Analysis of Six Years of National Health Data and Flood Maps. International journal of environmental research and public health. 2018;15(4).

212. Hu X, Ding G, Zhang Y, Liu Q, Jiang B, Ni W. Assessment on the burden of bacillary dysentery associated with floods during 2005-2009 in Zhengzhou City, China, using a time-series analysis. Journal of infection and public health. 2018;11(4):500-6.
213. Na W, Lee KE, Myung HN, Jo SN, Jang JY. Incidences of Waterborne and Foodborne Diseases After Meteorologic Disasters in South Korea. Annals of global health. 2016;82(5):848-57.
214. Liu Z, Ding G, Zhang Y, Xu X, Liu Q, Jiang B. Analysis of Risk and Burden of Dysentery Associated with Floods from 2004 to 2010 in Nanning, China. The American journal of tropical medicine and hygiene. 2015;93(5):925-30.
215. Hulland E, Subaiya S, Pierre K, Barthelemy N, Pierre JS, Dismer A, et al. Increase in Reported Cholera Cases in Haiti Following Hurricane Matthew: An Interrupted Time Series Model. The American journal of tropical medicine and hygiene. 2019;100(2):368-73.
216. Heaney AK, Shaman J, Alexander KA. El Niño-Southern oscillation and under-5 diarrhea in Botswana. Nat Commun. 2019;10(1):5798.
217. Ding G, Zhang Y, Gao L, Ma W, Li X, Liu J, et al. Quantitative analysis of burden of infectious diarrhea associated with floods in northwest of anhui province, china: a mixed method evaluation. PLoS One. 2013;8(6):e65112.
218. Liu ZD, Li J, Zhang Y, Ding GY, Xu X, Gao L, et al. Distributed lag effects and vulnerable groups of floods on bacillary dysentery in Huaihua, China. Sci Rep. 2016;6:29456.
219. Logar-Henderson C, Ling R, Tuite AR, Fisman DN. Effects of large-scale oceanic phenomena on non-cholera vibriosis incidence in the United States: implications for climate change. Epidemiol Infect. 2019;147:e243.
220. Rodo X, Pascual M, Fuchs G, Faruque AS. ENSO and cholera: a nonstationary link related to climate change? Proceedings of the National Academy of Sciences of the United States of America. 2002;99(20):12901-6.
221. Liu Z, Zhang F, Zhang Y, Li J, Liu X, Ding G, et al. Association between floods and infectious diarrhea and their effect modifiers in Hunan province, China: A two-stage model. The Science of the total environment. 2018;626:630-7.
222. Liu X, Liu Z, Zhang Y, Jiang B. The Effects of Floods on the Incidence of Bacillary Dysentery in Baise (Guangxi Province, China) from 2004 to 2012. International journal of environmental research and public health. 2017;14(2).
223. Liu X, Liu Z, Ding G, Jiang B. Projected burden of disease for bacillary dysentery due to flood events in Guangxi, China. The Science of the total environment. 2017;601-602:1298-305.
224. Xu X, Ding G, Zhang Y, Liu Z, Liu Q, Jiang B. Quantifying the Impact of Floods on Bacillary Dysentery in Dalian City, China, From 2004 to 2010. Disaster medicine and public health preparedness. 2017;11(2):190-5.
225. Zhang F, Ding G, Liu Z, Zhang C, Jiang B. Association between flood and the morbidity of bacillary dysentery in Zibo City, China: a symmetric bidirectional case-crossover study. International journal of biometeorology. 2016;60(12):1919-24.
226. Ramírez IJ, Grady SC. El Niño, Climate, and Cholera Associations in Piura, Peru, 1991-2001: A Wavelet Analysis. EcoHealth. 2016;13(1):83-99.
227. Kang R, Xun H, Zhang Y, Wang W, Wang X, Jiang B, et al. Impacts of different grades of tropical cyclones on infectious diarrhea in Guangdong, 2005-2011. PLoS One. 2015;10(6):e0131423.
228. Cash BA, Rodó X, Emch M, Yunus M, Faruque AS, Pascual M. Cholera and shigellosis: different epidemiology but similar responses to climate variability. PLoS One. 2014;9(9):e107223.
229. Ni W, Ding G, Li Y, Li H, Jiang B. Impacts of floods on dysentery in Xinxiang city, China, during 2004-2010: a time-series Poisson analysis. Global health action. 2014;7:23904.
230. Ni W, Ding G, Li Y, Li H, Liu Q, Jiang B. Effects of the floods on dysentery in north central region of Henan Province, China from 2004 to 2009. The Journal of infection. 2014;69(5):430-9.

231. Colston JM, Zaitchik B, Kang G, Peñataro Yori P, Ahmed T, Lima A, et al. Use of earth observation-derived hydrometeorological variables to model and predict rotavirus infection (MAL-ED): a multisite cohort study. The Lancet Planetary health. 2019;3(6):e248-e58.
232. Jagai JS, Sarkar R, Castronovo D, Kattula D, McEntee J, Ward H, et al. Seasonality of Rotavirus in South Asia: A Meta-Analysis Approach Assessing Associations with Temperature, Precipitation, and Vegetation Index. PLOS ONE. 2012;7(5):e38168.
233. Ghoshal V, Das RR, Nayak MK, Singh S, Das P, Mohakud NK. Climatic Parameters and Rotavirus Diarrhea Among Hospitalized Children: A Study of Eastern India. Frontiers in pediatrics. 2020;8:573448.
234. Prasetyo D, Ermaya Y, Martiza I, Yati S. Correlation between climate variations and rotavirus diarrhea in under-five children in Bandung. Asian Pacific Journal of Tropical Disease. 2015;5(11):908-11.
235. Ouedraogo N, Ngangas SMT, Bonkoungou IJO, Tiendrebeogo AB, Traore KA, Sanou I, et al. Temporal distribution of gastroenteritis viruses in Ouagadougou, Burkina Faso: seasonality of rotavirus. BMC public health. 2017;17(1):274-.
236. Alsova OK, Loktev VB, Naumova EN. Rotavirus Seasonality: An Application of Singular Spectrum Analysis and Polyharmonic Modeling. International journal of environmental research and public health. 2019;16(22).
237. Atchison CJ, Tam CC, Hajat S, van Pelt W, Cowden JM, Lopman BA. Temperature-dependent transmission of rotavirus in Great Britain and The Netherlands. Proceedings Biological sciences. 2010;277(1683):933-42.
238. Sumi A, Rajendran K, Ramamurthy T, Krishnan T, Nair GB, Harigane K, et al. Effect of temperature, relative humidity and rainfall on rotavirus infections in Kolkata, India. Epidemiol Infect. 2013;141(8):1652-61.
239. Purohit SG, Kelkar SD, Simha V. Time series analysis of patients with rotavirus diarrhoea in Pune, India. Journal of diarrhoeal diseases research. 1998;16(2):74-83.
240. Ureña-Castro K, Ávila S, Gutierrez M, Naumova EN, Ulloa-Gutierrez R, Mora-Guevara A. Seasonality of Rotavirus Hospitalizations at Costa Rica's National Children's Hospital in 2010-2015. International journal of environmental research and public health. 2019;16(13).
241. Chan MCW, Mok HY, Lee TC, Nelson EAS, Leung TF, Tam WWS, et al. Rotavirus activity and meteorological variations in an Asian subtropical city, Hong Kong, 1995–2009. 2013;85(11):2026-33.
242. D'Souza RM, Hall G, Becker NG. Climatic factors associated with hospitalizations for rotavirus diarrhoea in children under 5 years of age. Epidemiology and Infection. 2007;136(1):56-64.
243. van Gaalen RD, van de Kassteele J, Hahné SJM, Bruijning-Verhagen P, Wallinga J. Determinants of Rotavirus Transmission: A Lag Nonlinear Time Series Analysis. Epidemiology (Cambridge, Mass). 2017;28(4):503-13.
244. Hervás D, Hervás-Masip J, Rosell A, Mena A, Pérez JL, Hervás JA. Are hospitalizations for rotavirus gastroenteritis associated with meteorologic factors? European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2014;33(9):1547-53.
245. Celik C, Gozel MG, Turkay H, Bakici MZ, Guven AS, Elaldi N. Rotavirus and adenovirus gastroenteritis: time series analysis. Pediatr Int. 2015;57(4):590-6.
246. Sarkar R, Kang G, Naumova EN. Rotavirus Seasonality and Age Effects in a Birth Cohort Study of Southern India. PLOS ONE. 2013;8(8):e71616.
247. Ghoshal V, Das RR, Nayak MK, Singh S, Das P, Mohakud NK. Climatic Parameters and Rotavirus Diarrhea Among Hospitalized Children: A Study of Eastern India. 2020;8(716).
248. Hasan MA, Mouw C, Jutla A, Akanda AS. Quantification of Rotavirus Diarrheal Risk Due to Hydroclimatic Extremes Over South Asia: Prospects of Satellite-Based Observations in Detecting Outbreaks. GeoHealth. 2018;2(2):70-86.
249. Hashizume M, Armstrong B, Wagatsuma Y, Faruque AS, Hayashi T, Sack DA. Rotavirus infections and climate variability in Dhaka, Bangladesh: a time-series analysis. Epidemiol Infect. 2008;136(9):1281-9.

250. Moulton AD, Schramm PJ. Climate Change and Public Health Surveillance: Toward a Comprehensive Strategy. J Public Health Manag Pract. 2017;23(6):618-26.
251. World Health Organisation. Public Health Surveillance [Available from: https://www.who.int/topics/public_health_surveillance/en/.
252. Buehler JW. CDC's vision for public health surveillance in the 21st century. Introduction. MMWR Suppl. 2012;61(3):1-2.
253. Pascal M, Viso AC, Medina S, Delmas MC, Beaudeau P. How can a climate change perspective be integrated into public health surveillance? Public Health. 2012;126(8):660-7.
254. Medeiros H, Pascal M, Viso A-C, Medina S. Workshop on Public heatlh surveillance and climate change. 2010.
255. Wilson ML, Martha A. Disease surveillance in the context of climate stressors: needs and opportunities. In: Ebi KL, Smith JB, Burton I, editors. Integration of Public Health with Adaptation to Climate Change Lessons Learned and New Directions. London: Taylor and Francis; 2005.
256. Morin CW, Semenza JC, Trtanj JM, Glass GE, Boyer C, Ebi KL. Unexplored Opportunities: Use of Climate- and Weather-Driven Early Warning Systems to Reduce the Burden of Infectious Diseases. Current environmental health reports. 2018;5(4):430-8.
257. Ebi K, Boyer C. Building resilience of health systems to climate change in Pacific Least Developed Countries: implementation science. The Lancet Planetary Health. 2019;3:S6.
258. Frumkin H, Hess J, Luber G, Malilay J, McGeehin M. Climate change: the public health response. American journal of public health. 2008;98(3):435-45.
259. Fox M, Zuidema C, Bauman B, Burke T, Sheehan M. Integrating Public Health into Climate Change Policy and Planning: State of Practice Update. International journal of environmental research and public health. 2019;16(18):3232.
260. Marinucci GD, Luber G, Uejio CK, Saha S, Hess JJ. Building Resilience against Climate Effects—A Novel Framework to Facilitate Climate Readiness in Public Health Agencies. International journal of environmental research and public health. 2014;11(6):6433.
261. Sawatzky A, Cunsolo A, Jones-Bitton A, Middleton J, Harper SL. Responding to Climate and Environmental Change Impacts on Human Health via Integrated Surveillance in the Circumpolar North: A Systematic Realist Review. International journal of environmental research and public health. 2018;15(12).
262. Semenza JC, Sudre B, Oni T, Suk JE, Giesecke J. Linking Environmental Drivers to Infectious Diseases: The European Environment and Epidemiology Network. PLOS Neglected Tropical Diseases. 2013;7(7):e2323.
263. Nichols GL, Andersson Y, Lindgren E, Devaux I, Semenza JC. European Monitoring Systems and Data for Assessing Environmental and Climate Impacts on Human Infectious Diseases. International journal of environmental research and public health. 2014;11(4):3894.
264. Hashizume M, Wagatsuma Y, Faruque AS, Hayashi T, Hunter PR, Armstrong B, et al. Factors determining vulnerability to diarrhoea during and after severe floods in Bangladesh. Journal of water and health. 2008;6(3):323-32.
265. Levy K, Woster AP, Goldstein RS, Carlton EJ. Untangling the Impacts of Climate Change on Waterborne Diseases: a Systematic Review of Relationships between Diarrheal Diseases and Temperature, Rainfall, Flooding, and Drought. Environ Sci Technol. 2016;50(10):4905-22.
266. Troeger C, Khalil IA, Rao PC, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. JAMA Pediatrics. 2018.
267. Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2012;12(2):136-41.
268. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. International journal of epidemiology. 2013;42(4):1187-95.

269. Prüss-Üstün A, Mathers C, Corvalan C, Woodward A. Introduction and methods: assessing the environmental burden of disease at national and local levels. Geneva: World Health Organization. (WHO Environmental Burden of Disease Series, No. 1). . 2003.
270. Kovats RS, Lloyd SJ. Diarrhoeal diseases. In: Hales S, Kovats RS, Lloyd SJ, Campbell- Lendrum D, editors. Quantitative risk assessment of the effects of climate change on selected causes of death, 2030s and 2050s. Geneva: World Health Organisation; 2014. p. 37-50.
271. Gasparrini A. Distributed Lag Linear and Non-Linear Models in R: The Package dlnm. Journal of statistical software. 2011;43(8):1-20.
272. Gasparrini A, Leone M. Attributable risk from distributed lag models. BMC Medical Research Methodology. 2014;14(1):55.
273. Government of Nepal National Planning Comission Secretariat Central Bureau of Statistics. National Population and Housing Census 2011 (National Report). Kathmandu, Nepal, Statistics CBo; 2012.
274. Government of Nepal National Planning Comission. Nepal Human Development report 2014: Beyong Geography, Unlocking Human Potential. Kathmandu, Nepal: Government of Nepal National planning comission; 2014.
275. Sherchand JB, Thakali O, Sherchan JB, Bhandari D, Tandukar S, Paudel KP, et al. Hospital based surveillance and molecular characterization of rotavirus in children less than 5 years of age with acute gastroenteritis in Nepal. Vaccine. 2018;36(51):7841-5.
276. Nelson EAS, Widdowson M-A, Kilgore PE, Steele D, Parashar UD. A decade of the Asian Rotavirus Surveillance Network: Achievements and future directions. Vaccine. 2009;27:F1-F3.
277. Ackroyd S. Critical Realism. Research Techniques, and Research Designs. In: Edwards KP, O'Mahoney J, Vincent S, editors. Studying Organizations Using Critical Realism: A Practical Guide. United Kingdom: Oxford University Press; 2014.
278. Bhaskar R. A Realist Theory of Science: Routledge; 1978. 284 p.
279. Adam T, de Savigny D. Systems thinking for strengthening health systems in LMICs: need for a paradigm shift. Health Policy and Planning. 2012;27(suppl_4):iv1-iv3.
280. Bhaskar R, Frank C, Hoyer KG, Naess P, Parker J. Interdisciplinary and Climate Change: Transforming Knowledge and Practice for Our Global Future. Bhaskar R, editor. London, United Kingdom: Taylor and Francis 2010.
281. Sims-Schouten W, Riley SCE, Willig C. Critical Realism in Discourse Analysis: A Presentation of a Systematic Method of Analysis Using Women's Talk of Motherhood, Childcare and Female Employment as an Example. Theory & Psychology. 2007;17(1):101-24.
282. Willig C. Beyond appearances: A critical realist approach to social constructionist work. In: Cromby J, Nightingale DJ, editors. Social constructionist psychology: A critical analysis of theory and practice. Buckingham/Philadelphia, PA: Open University Press.; 1999. p. 37—52.
283. Navi M, Hansen A, Nitschke M, Hanson-Easey S, Pisaniello D. Developing Health-Related Indicators of Climate Change: Australian Stakeholder Perspectives. International journal of environmental research and public health. 2017;14(5):552.
284. O'Fallon LR, Wolfle GM, Brown D, Dearry A, Olden K. Strategies for setting a national research agenda that is responsive to community needs. Environmental health perspectives. 2003;111(16):1855-60.
285. Troeger C, Forouzanfar M, Rao PC, Khalil I, Brown A, Reiner RC, Jr., et al. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Infectious Diseases. 2017;17(9):909-48.
286. Walker CLF, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. The Lancet. 2013;381(9875):1405-16.
287. Sarker AR, Sultana M, Mahumud RA, Ali N, Huda TM, Salim Uzzaman M, et al. Economic costs of hospitalized diarrheal disease in Bangladesh: a societal perspective. Global health research and policy. 2018;3:1-.

288. Ngabo F, Mvundura M, Gazley L, Gatera M, Rugambwa C, Kayonga E, et al. The Economic Burden Attributable to a Child's Inpatient Admission for Diarrheal Disease in Rwanda. PLOS ONE. 2016;11(2):e0149805.
289. Singh RB, Hales S, de Wet N, Raj R, Hearnden M, Weinstein P. The influence of climate variation and change on diarrheal disease in the Pacific Islands. Environmental health perspectives. 2001;109(2):155-9.
290. Reacher M, McKenzie K, Lane C, Nichols T, Kedge I, Iversen A, et al. Health impacts of flooding in Lewes: a comparison of reported gastrointestinal and other illness and mental health in flooded and non-flooded households. Commun Dis Public Health. 2004;7(1):39-46.
291. Bronstert A. Floods and Climate Change: Interactions and Impacts. Risk Analysis. 2003;23(3):545-57.
292. NCVST. Vulnerability Through the Eyes of Vulnerable: Climate Change Induced Uncertainties and Nepal's Development Predicaments. Kathmandu, Nepal: Institute for Social and Environmental Transition-Nepal (ISET-N, Kathmandu) and Institute for Social and Environmental Transition (ISET, Boulder, Colorado) for Nepal Climate Vulnerability Study Team (NCVST) Kathmandu; 2009.
293. Thapa BR, Ishidaira H, Pandey VP, Shakya NM. A multi-model approach for analyzing water balance dynamics in Kathmandu Valley, Nepal. Journal of Hydrology: Regional Studies. 2017;9:149-62.
294. National Management Information Project (NMIP). Nationwide Coverage and Functionality Status of Water Supply and Sanitation in Nepal. Department of Water Supply and Sewage, Government of Nepal: Kathmandu, Nepal; 2014.
295. Shrestha S, Haramoto E, Shindo J. Assessing the infection risk of enteropathogens from consumption of raw vegetables washed with contaminated water in Kathmandu Valley, Nepal. Journal of applied microbiology. 2017;123(5):1321-34.
296. Bohra-Mishra P, Oppenheimer M, Hsiang SM. Nonlinear permanent migration response to climatic variations but minimal response to disasters. Proceedings of the National Academy of Sciences. 2014;111(27):9780.
297. Stanberry LR, Thomson MC, James W. Prioritizing the needs of children in a changing climate. PLOS Medicine. 2018;15(7):e1002627.
298. Xu Z, Sheffield PE, Hu W, Su H, Yu W, Qi X, et al. Climate change and children's health--a call for research on what works to protect children. International journal of environmental research and public health. 2012;9(9):3298-316.
299. Babel MS, Bhusal SP, Wahid SM, Agarwal A. Climate change and water resources in the Bagmati River Basin, Nepal. Theoretical and Applied Climatology. 2014;115(3):639-54.
300. Jha PK. Climate change: impact, adaptation and vulnerability in the water supply of Kathmandu Valley. WIT Transactions on Ecology and the Environment. 2012;155:563-74.
301. Zhang Y, Bi P, Hiller JE. Weather and the Transmission of Bacillary Dysentery in Jinan, Northern China: A Time-Series Analysis. Public Health Reports. 2008;123(1):61-6.
302. Xiang J, Bi P, Pisaniello D, Hansen A, Sullivan T. Association between high temperature and work-related injuries in Adelaide, South Australia, 2001–2010. Occupational and Environmental Medicine. 2014;71(4):246-52.
303. Barnett AG, Tong S, Clements ACA. What measure of temperature is the best predictor of mortality? Environmental Research. 2010;110(6):604-11.
304. Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;65(12):e45-e80.
305. Onozuka D, Hashizume M. Weather variability and paediatric infectious gastroenteritis. Epidemiol Infect. 2011;139(9):1369-78.

306. Zhang Y, Bi P, Hiller J. Climate variations and salmonellosis transmission in Adelaide, South Australia: a comparison between regression models. International Journal of Biometeorology. 2008;52(3):179-87.
307. Sockett PN, Rodgers FG. Enteric and foodborne disease in children: A review of the influence of food- and environment-related risk factors. Paediatrics & child health. 2001;6(4):203-9.
308. Bentham G, Langford IH. Environmental temperatures and the incidence of food poisoning in England and Wales. Int J Biometeorol. 2001;45(1):22-6.
309. Randazzo W, D'Souza DH, Sanchez G. Chapter Two - Norovirus: The Burden of the Unknown. In: Rodríguez-Lázaro D, editor. Advances in Food and Nutrition Research. 86: Academic Press; 2018. p. 13-53.
310. Horn L, Hajat A, Sheppard L, Quinn C, Colborn J, Zermoglio M, et al. Association between Precipitation and Diarrheal Disease in Mozambique. International journal of environmental research and public health. 2018;15(4):709.
311. Schwartz BS, Harris JB, Khan AI, Larocque RC, Sack DA, Malek MA, et al. Diarrheal epidemics in Dhaka, Bangladesh, during three consecutive floods: 1988, 1998, and 2004. The American journal of tropical medicine and hygiene. 2006;74(6):1067-73.
312. Shrestha S, Nakamura T, Malla R, Nishida K. Seasonal variation in the microbial quality of shallow groundwater in the Kathmandu Valley, Nepal. Water Science and Technology: Water Supply. 2013;14(3):390-7.
313. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016;388(10053):1459-544.
314. Levy K, Hubbard AE, Eisenberg JNS. Seasonality of rotavirus disease in the tropics: a systematic review and meta-analysis. International Journal of Epidemiology. 2009;38(6):1487-96.
315. Martinez PP, King AA, Yunus M, Faruque ASG, Pascual M. Differential and enhanced response to climate forcing in diarrheal disease due to rotavirus across a megacity of the developing world. Proceedings of the National Academy of Sciences. 2016;113(15):4092-7.
316. Cook SM, Glass RI, LeBaron CW, Ho MS. Global seasonality of rotavirus infections. Bulletin of the World Health Organization. 1990;68(2):171-7.
317. Stoll BJ, Glass RI, Huq MI, Khan MU, Holt JE, Banu H. Surveillance of patients attending a diarrhoeal disease hospital in Bangladesh. Br Med J (Clin Res Ed). 1982;285(6349):1185-8.
318. Bresee J, Fang Z-Y, Wang B, Nelson EAS, Tam J, Soenarto Y, et al. First report from the Asian Rotavirus Surveillance Network. Emerging infectious diseases. 2004;10(6):988-95.
319. Nelson EAS, Bresee JS, Parashar UD, Widdowson MA, Glass RI. Rotavirus epidemiology: The Asian Rotavirus Surveillance Network. Vaccine. 2008;26(26):3192-6.
320. Central Bureau of Statistics. National Population and Housing Census 2011 (National Report). Kathmandu, Nepal: Government of Nepal National Planning Comission Secretariat, Statistics CBo; 2012.
321. United Nations Development Programme. Human Development Indices and Indicators: 2018 Statistical Update. Washington DC, USA: Human Develoment Report Office UNDP; 2018.
322. Jha AK, Bajracharya TR. Wastewater Treatment Technologies in Nepal. Proceedings of IOE Graduate Conference,. 2014.
323. Sherchand JB, Nakagomi O, Dove W, Nakagomi T, Yokoo M, Pandey BD, et al. Molecular Epidemiology of Rotavirus Diarrhea among Children Aged <5 Years in Nepal: Predominance of Emergent G12 Strains during 2 Years. The Journal of infectious diseases. 2009;200(Supplement_1):S182-S7.
324. Sherchand J, Tandukar S, Sherchan J, Gurung S, Dhakwa J, Bichha R, et al. Molecular epidemiology of Rotavirus diarrhea among children in Nepal: Emergence of G12 and G9 strains. Journal of Institute of Medicine. 2013;35(2):3-10.
325. Sherchand JB, Schluter WW, Sherchan J, Tandukar S, Dhakwa JR, Choudhary GR, et al. Prevalence of group A genotype human rotavirus among children with diarrhoea in Nepal, 2009-2011. WHO South-East Asia journal of public health. 2012;1(4):432-40.

326. Hervás D, Hervás-Masip J, Rosell A, Mena A, Pérez JL, Hervás JA. Are hospitalizations for rotavirus gastroenteritis associated with meteorologic factors? European Journal of Clinical Microbiology & Infectious Diseases. 2014;33(9):1547-53.
327. Wang P, Goggins WB, Chan EYY. A time-series study of the association of rainfall, relative humidity and ambient temperature with hospitalizations for rotavirus and norovirus infection among children in Hong Kong. Science of The Total Environment. 2018;643:414-22.
328. Patel MM, Pitzer VE, Alonso WJ, Vera D, Lopman B, Tate J, et al. Global seasonality of rotavirus disease. The Pediatric infectious disease journal. 2013;32(4):e134-e47.
329. Cameron AC, Trivedi PK. Regression-based tests for overdispersion in the Poisson model. Journal of Econometrics. 1990;46(3):347-64.
330. European Centre for Disease Prevention and Control. Disease factsheet about rotavirus 2019 [cited 2019 26/02/2019]. Available from: https://ecdc.europa.eu/en/rotavirus-infection/facts.
331. Himalayan News Service. Housing becoming unaffordable for the urban poor, says report. The Himalayan Times. 2018 January 03, 2018.
332. Government of Nepal National Planning Comission. Annual Household Survey 2015/16. Kathmandu; 2016.
333. Sethi D, Cumberland P, Hudson MJ, Rodrigues LC, Wheeler JG, Roberts JA, et al. A study of infectious intestinal disease in England: risk factors associated with group A rotavirus in children. Epidemiology and infection. 2001;126(1):63-70.
334. Sattar SA, Ijaz MK, Johnson-Lussenburg CM, Springthorpe VS. Effect of relative humidity on the airborne survival of rotavirus SA11. Appl Environ Microbiol. 1984;47(4):879-81.
335. Coughlin SS. Recall bias in epidemiologic studies. Journal of Clinical Epidemiology. 1990;43(1):87-91.
336. Pitzer VE, Viboud C, Lopman BA, Patel MM, Parashar UD, Grenfell BT. Influence of birth rates and transmission rates on the global seasonality of rotavirus incidence. J R Soc Interface. 2011;8(64):1584-93.
337. Imai C, Armstrong B, Chalabi Z, Mangtani P, Hashizume M. Time series regression model for infectious disease and weather. Environmental Research. 2015;142:319-27.
338. Linthicum KJ, Anyamba A, Tucker CJ, Kelley PW, Myers MF, Peters CJ. Climate and Satellite Indicators to Forecast Rift Valley Fever Epidemics in Kenya. Science. 1999;285(5426):397.
339. Patz JA, Epstein PR, Burke TA, Balbus JM. Global Climate Change and Emerging Infectious Diseases. JAMA. 1996;275(3):217-23.
340. Shuman EK. Global Climate Change and Infectious Diseases. New England Journal of Medicine. 2010;362(12):1061-3.
341. Lafferty KD. The ecology of climate change and infectious diseases. Ecology. 2009;90(4):888-900.
342. Semenza JC, Menne B. Climate change and infectious diseases in Europe. The Lancet Infectious Diseases. 2009;9(6):365-75.
343. Thomson MC, Doblas-Reyes FJ, Mason SJ, Hagedorn R, Connor SJ, Phindela T, et al. Malaria early warnings based on seasonal climate forecasts from multi-model ensembles. Nature. 2006;439:576.
344. Johansson MA, Reich NG, Hota A, Brownstein JS, Santillana M. Evaluating the performance of infectious disease forecasts: A comparison of climate-driven and seasonal dengue forecasts for Mexico. Sci Rep. 2016;6:33707.
345. Shaman J, Kandula S, Yang W, Karspeck A. The use of ambient humidity conditions to improve influenza forecast. PLoS computational biology. 2017;13(11):e1005844.
346. McSweeney C, New M, Lizcano G. UNDP Climate Change Country Profile-Nepal. 2012.
347. Shrestha UB, Gautam S, Bawa KS. Widespread climate change in the Himalayas and associated changes in local ecosystems. PLoS One. 2012;7(5):e36741.
348. Wester P, Mishra A, Mukherji A, Shrestha AB. The Hindu Kush Himalaya Assessment: Mountains, Climate Change, Sustainability and People: Springer International Publication; 2019.
349. Ministry of Environment. National Adaptation Programme of Action (NAPA) to Climate Change. Kathmandu, Nepal; 2010.

350. Bhandari D, Bi P, Sherchand JB, Dhimal M, Hanson-Easey S. Assessing the effect of climate factors on childhood diarrhoea burden in Kathmandu, Nepal. International Journal of Hygiene and Environmental Health. 2020;223(1):199-206.
351. Ministry of Science Technology and Envrionment. Nepal Climate Change and Development Portal 2014 [14/03/2019]. Available from: http://climatenepal.org.np/main/index.php?p=home.
352. Wallen J. Thousands fall ill as Nepal becomes latest country to be hit by dengue outbreak. The Telegraph. 2019. 11 September 2019;Sect. Science and Disease: Global Health Security.
353. Government of Nepal Ministry of Health. Department of Health services [Available from: http://www.mohp.gov.np/content/department-of-health-services.
354. Government of Nepal Ministry of Health and population. Early Warning and Reporting System (EWARS) Guidelines. Teku, Kathmandu, Nepal: Epidemiology and Disease Control Divison; 2016.
355. Dhimal M. Climate Change and health:research challenges in vulnerable mountaoinous countries like Nepal. Climate change and health: research challenges for vulnerable populations. Geneva: Global Forum for Health Research; 2008.
356. Nori-Sarma A, Gurung A, Azhar G, Rajiva A, Mavalankar D, Sheffield P, et al. Opportunities and Challenges in Public Health Data Collection in Southern Asia: Examples from Western India and Kathmandu Valley, Nepal. Sustainability. 2017;9(7):1106.
357. Gurung A, Bell ML. The state of scientific evidence on air pollution and human health in Nepal. Environmental Research. 2013;124:54-64.
358. Metcalf CJE, Walter KS, Wesolowski A, Buckee CO, Shevliakova E, Tatem AJ, et al. Identifying climate drivers of infectious disease dynamics: recent advances and challenges ahead. Proc Biol Sci. 2017;284(1860).
359. FMoHP, NHSSP. Budget Analysis of Ministry of Health and Population FY 2018/19. Federal Ministry of Health and Population and Nepal Health Sector Support Programme.; 2018.
360. Mahat A, Bezruchka SA, Gonzales V, Connell FA. Assessment of graduate public health education in Nepal and perceived needs of faculty and students. Human Resources for Health. 2013;11(1):16.
361. Kattel RR, Sapkota M. Brain drain of agriculture and veterinary graduates to abroad: evidence from Nepal. Agriculture & Food Security. 2018;7(1):61.
362. Chand P, Kharel R. Politics of Primary Health Care in Nepal. In: Medcalf A, Bhattacharya S, Momen H, editors. Health For All: The Journey of Universal Health Coverage. Hyderabad, India: Orient Blackswan; 2105.
363. Mishra SR, Adhikari B. Planetary health in Nepal's post-earthquake rebuilding agenda: progress and future directions. The Lancet Planetary health. 2019;3(2):e55-e6.
364. Dhimal M, Gautam I, Kreß A, Müller R, Kuch U. Spatio-Temporal Distribution of Dengue and Lymphatic Filariasis Vectors along an Altitudinal Transect in Central Nepal. PLOS Neglected Tropical Diseases. 2014;8(7):e3035.
365. Dhimal M, O'Hara RB, Karki R, Thakur GD, Kuch U, Ahrens B. Spatio-temporal distribution of malaria and its association with climatic factors and vector-control interventions in two high-risk districts of Nepal. Malaria Journal. 2014;13(1):457.
366. Center for Disease Control and Prevention. National Environmental Public Health Tracking Network Georgia, Atlanta [9/04/2019]. Available from: https://ephtracking.cdc.gov/showHome.
367. McClymont Peace D, Myers E. Community-based participatory process--climate change and health adaptation program for Northern First Nations and Inuit in Canada. International journal of circumpolar health. 2012;71(0):1-8.
368. Ndiaye SM, Quick L, Sanda O, Niandou S. The value of community participation in disease surveillance: a case study from Niger*. Health Promotion International. 2003;18(2):89-98.
369. Dye C, Boerma T, Evans D, Harries A, Lienhardt C, McMAnus J, et al. The World Health Report 2013: Research for universal health coverage. Geneva, Switzerland: World Health Organisation; 2013.
370. Prüss-Üstün A, Corvalán C. Preventing disease through healthy environments. Towards an estimate of the environmental burden of disease. Geneva: World Health Organisation,; 2006.

371. Laxminarayan R, Kakkar M, Horby P, Malavige GN, Basnyat B. Emerging and re-emerging infectious disease threats in South Asia: status, vulnerability, preparedness, and outlook. BMJ (Clinical research ed). 2017;357:j1447.
372. Sen B, Dhimal M, Latheef AT, Ghosh U. Climate change: health effects and response in South Asia. BMJ (Clinical research ed). 2017;359:j5117.
373. Parham PE, Waldock J, Christophides GK, Hemming D, Agusto F, Evans KJ, et al. Climate, environmental and socio-economic change: weighing up the balance in vector-borne disease transmission. Philosophical Transactions of the Royal Society B: Biological Sciences. 2015;370(1665):20130551.
374. Harley D, Bi P, Hall G, Swaminathan A, Tong S, Williams C. Climate change and infectious diseases in Australia: future prospects, adaptation options, and research priorities. Asia-Pacific journal of public health. 2011;23(2 Suppl):54S-66.
375. World Health Organisation. Protecting health from climate change global research priorities.; 2009.
376. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392(10159):1789-858.
377. IPCC. Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge, United Kingdom and New York, NY, USA: Cambridge University Press; 2013.
378. Semenza JC. Prototype Early Warning Systems for Vector-Borne Diseases in Europe. International journal of environmental research and public health. 2015;12(6):6333-51.
379. Pyle DF, Nath LM, Shrestha BL, Sharma A, Koirala S. Assessment of Early Waning and Reporting Systems (EWARS) in Nepal. Washington DC: U.S Agency for International Development, Office of Health Infectious Diseases and Nutrition Bureau for Global Health; 2004.
380. World Health Organisation. Joint National/International Review of Acute Flaccid Paralysis (AFP) Surveillance - Nepal. New Delhi: World Health Organisation Regional Office for South-East Asia; 2006.
381. Sekine K, Roskosky M. Lessons Learned from Enhancing Sentinel Surveillance for Cholera in Post-Earthquake Nepal in 2016. The American journal of tropical medicine and hygiene. 2019;100(3):494-6.
382. Bhandari D, Bi P, Dhimal M, Sherchand JB, Hanson-Easey S. Non-linear effect of temperature variation on childhood rotavirus infection: A time series study from Kathmandu, Nepal. The Science of the total environment. 2020;748:141376.
383. Mackenbach JP. Politics is nothing but medicine at a larger scale: reflections on public health's biggest idea. Journal of Epidemiology and Community Health. 2009;63(3):181.
384. Marmot M, Friel S, Bell R, Houweling TAJ, Taylor S. Closing the gap in a generation: health equity through action on the social determinants of health. The Lancet. 2008;372(9650):1661-9.
385. Vincent S, Wapsott R. Critical realism and the organizational case study: A guide to discovering institutional mechanisms. In: Edwards PK, O'Mahoney J, Vincent S, editors. Studying Organizations using Critical Realism: A Pactiocal Guide. Oxford: Oxford University Press; 2014. p. 148-67.
386. Fletcher AJ. Applying critical realism in qualitative research: methodology meets method. International Journal of Social Research Methodology. 2017;20(2):181-94.
387. Tennant E, Miller E, Costantino K, De Souza D, Coupland H, Fotheringham P, et al. A critical realist evaluation of an integrated care project for vulnerable families in Sydney, Australia. BMC Health Services Research. 2020;20(1):995.
388. Dugle G, Wulifan JK, Tanyeh JP, Quentin W. A critical realist synthesis of cross-disciplinary health policy and systems research: defining characteristic features, developing an evaluation framework and identifying challenges. Health Research Policy and Systems. 2020;18(1):79.
389. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77-101.

390. Ministry of Finance. Climate Change Financing Framework: A roadmap to systematically strengthen climate change mainstreaming into planning and budgeting. Kathmandu, Nepal: Ministry of Finance, the Government of Nepal; 2017.
391. Acheson ED. On the state of the public health [The fourth Duncan lecture]. Public Health. 1988;102(5):431-7.
392. Huang WY, Wong SH, Gao Y. Public Health. In: Michalos AC, editor. Encyclopedia of Quality of Life and Well-Being Research. Dordrecht: Springer Netherlands; 2014. p. 5208-11.
393. Coombs M, Ersser SJ. Medical hegemony in decision-making – a barrier to interdisciplinary working in intensive care? 2004;46(3):245-52.
394. Choi BCK, Pang T, Lin V, Puska P, Sherman G, Goddard M, et al. Can scientists and policy makers work together? 2005;59(8):632-7.
395. Schaal B. Informing policy with science. 2017;355(6324):435-.
396. Van Leeuwen T. Legitimation in discourse and communication. Discourse & Communication. 2007;1(1):91-112.
397. Poudel A. Inside the Health Ministry during the pandemic. The Kathmandu Post. 2020 28/06/2020.
398. Sharma SP. Politics and corruption mar health care in Nepal. Lancet (London, England). 2010;375(9731):2063-4.
399. Wei J, Hansen A, Zhang Y, Li H, Liu Q, Sun Y, et al. The Impact of Climate Change on Infectious Disease Transmission: Perceptions of CDC Health Professionals in Shanxi Province, China. PLOS ONE. 2014;9(10):e109476.
400. Akin SM, Martens P, Huynen MM. Climate Change and Infectious Disease Risk in Western Europe: A Survey of Dutch Expert Opinion on Adaptation Responses and Actors. International journal of environmental research and public health. 2015;12(8):9726-49.
401. Terwindt F, Rajan D, Soucat A. Priority-setting for national health policies, strategies and plans. Strategizing national health in the 21st century: a handbook. Switzerland, Zeneva: World Health Organisation; 2016.
402. Metcalf CJE, Walter KS, Wesolowski A, Buckee CO, Shevliakova E, Tatem AJ, et al. Identifying climate drivers of infectious disease dynamics: recent advances and challenges ahead. Proceedings Biological sciences. 2017;284(1860):20170901.
403. McMichael AJ. Impediments to Comprehensive Research on Climate Change and Health. International journal of environmental research and public health. 2013;10(11):6096-105.
404. Coe G, de Beyer J. The imperative for health promotion in universal health coverage. Global Health: Science and Practice. 2014;2(1):10-22.
405. Woolf SH, Purnell JQ, Simon SM, Zimmerman EB, Camberos GJ, Haley A, et al. Translating Evidence into Population Health Improvement: Strategies and Barriers. 2015;36(1):463-82.
406. Li Y, Hodgson D, Wang X, Atkins KE, Feikin DR, Nair H. Respiratory syncytial virus seasonality and prevention strategy planning for passive immunisation of infants in low-income and middle-income countries: a modelling study. The Lancet Infectious diseases. 2021.
407. Sedgwick P. Ecological studies: advantages and disadvantages. 2014;348:g2979.
408. Climate Risk Country Profile: Nepal (2021). The World Bank Group and the Asian Development Bank.
409. Budhathoki SS, Bhattachan M, Yadav AK, Upadhyaya P, Pokharel PK. Eco-social and behavioural determinants of diarrhoea in under-five children of Nepal: a framework analysis of the existing literature. Tropical Medicine and Health. 2016;44:7.
410. Vicedo-Cabrera AM, Scovronick N, Sera F, Royé D, Schneider R, Tobias A, et al. The burden of heat-related mortality attributable to recent human-induced climate change. Nature Climate Change. 2021;11(6):492-500.

Appendix 1: Search strategy for literature review

1. Search strategy for literature review on climate change and diarrhoea or rotavirus infection

("climate change"[All Fields] OR "global warming"[All Fields] OR "climate variability"[All Fields] OR "greenhouse effect"[All Fields] OR "Temperature variation" [All Fields] OR “Humidity” [All Fields] OR “Rainfall" [All Fields] OR "Flood" [All Fields]) AND ("Vibrio"[All Fields] OR "Cholera"[All Fields] OR "Salmonella"[All Fields] OR “Shigella” OR "Campylobacter”[All Fields] OR "Diarrhea"[All Fields] OR "Salmonella Infections"[All Fields] OR "Campylobacter Infections"[All Fields] OR "Enterovirus Infections"[All Fields] OR "Rotavirus"[All Fields] OR "Rotavirus Infections"[All Fields] OR "Norovirus"[All Fields] OR "Dysentery"[All Fields])

2. Search strategy for climate change and infectious disease surveillance

("climate change"[All Fields] OR "global warming"[All Fields] OR "climate variability"[All Fields] OR "greenhouse effect"[All Fields]) AND ("Malaria"[Mesh] OR "Dengue"[Mesh] OR "Encephalitis, Tick-Borne"[Mesh] OR "Tick-Borne Diseases"[Mesh] OR "Chikungunya Fever"[Mesh] OR "West Nile Fever"[Mesh] OR "Rift Valley fever virus"[Mesh] OR "Encephalitis, Japanese"[Mesh] OR "Hemorrhagic Fever with Renal Syndrome"[Mesh] OR "Hantaan virus"[Mesh] OR "Plague"[Mesh] OR "Lyme Disease"[Mesh] OR "Vibrio"[Mesh] OR "Cholera"[Mesh] OR "Salmonella"[Mesh] OR "Campylobacter"[Mesh] OR "Diarrhea"[Mesh] OR "Salmonella Infections"[Mesh] OR "Campylobacter Infections"[Mesh] OR "Enterovirus Infections"[Mesh] OR "Enterovirus"[Mesh] OR "Coxsackievirus Infections"[Mesh] OR "Hand, Foot and Mouth Disease"[Mesh] OR "Rotavirus"[Mesh] OR "Rotavirus Infections"[Mesh] OR "Harmful Algal Bloom"[Mesh] OR "Dysentery"[Mesh] OR "Schistosomiasis"[Mesh] OR “Communicable diseases” [Mesh]) AND (“ Public Health Surveillance” [All Fields] OR “surveillance system” [All Fields] OR “surveillance” [All Fields] OR “Population Surveillance” [All Fields] OR “Epidemiological Monitoring” [All Fields] OR “Environmental Monitoring” [All Fields] OR “Sentinel Surveillance” [All Fields])

Appendix 2: Interview guide

Lead Questions for the Interview

General questions to specific without distinct transition

I. What is your role within the infectious diseases surveillance system?
- ✓ Probe questions to explore: **T**itle (Check full-Time or Part-time), **E**xperience (How long in the system?

II. Could you please walk me through the process of disease surveillance practise within your system?
- ✓ Probe questions to explore: **W**ork flow, **C**overage, **C**ommunication, **R**eporting, **R**ecording

III. Can you share your experience on infectious diseases reporting pattern (transmission pattern) in recent years?
- ✓ Probe questions to explore: **C**hange in seasonal pattern or distribution (geographic, age-groups), **E**mergence or re-emergence of new diseases, **C**hange in risk factors [*if necessary, lead towards* ***Climate*** *as a risk factor*]

IV. Do the system function in a way to allow capturing of information required for generating evidence on the health effects (specifically infectious diseases/diarrhoea) of climate change?
- ✓ Probe questions to explore: **D**ata quality; System: **A**ttributes, **W**eakness, **F**lexibility, **A**daptability

V. If system components are missing, Could you please highlight what components or practises need to be addressed?
- ✓ Probe questions to explore: **L**ogistics and financial resources, **S**upport, **C**hallenges, **E**lectronic database, [*if necessary, lead to* ***D****ata integration concept*]

VI. Is there any specific policy to guide and regulate infectious disease surveillance?
- ✓ Probe to explore:

  If yes, is the policy supportive enough to regulate disease surveillance in changing climate? **R**egulatory act, **S**pecific concern about climate effects in disease transmission

  If no, how can reporting and recording of diseases be regulated (made accountable/information validated), especially with increased threat of changing climate?

VII. Can you share your experience on ability of experts working in the system to assess risk of disease transmission, based on observed pattern of potential risks?
- ✓ Probe to explore: **R**isk assessment (quantitative and qualitative)**, C**limate attribution to observe changing pattern, **V**ulnerability assessment [*if necessary, lead towards training of the epidemiologists, resources availability, government support and opportunity to improve skills*]

VIII. Can you recall any experience of pre-informing public about potential outbreaks of infectious diseases in advance?

- ✓ Probe to explore: **C**apacity for early warning, **P**rospect of climate based early warning system

IX. What measures could improve performance and effectively of the surveillance systems in days to come (meaning in the context of changing climate)?

- ✓ Probe to explore: **B**arriers of timely reporting and recording, **B**arriers that limits coverage of the system, **B**arriers of Data integration and, **F**eedback and **d**issemination mechanism

X. Is there anything further you would like to discuss?

Appendix 3: Information sheet, informed consent and demographic form

THE UNIVERSITY of ADELAIDE

शाहभागी जानकारी पत्र

बिद्यावारिदी अनुसन्धान को बिशय: Climatic and socio-economic determinants of diarrhoea among children under 5 years living in Kathmandu Valley Nepal

यो अध्ययन को बिसय: Assessment of the capacity of Public Health Surveillance systems in Nepal to generate evidence on the impacts of climate change in infectious diseases transmission.

University of Adelaide human research ethics committee approval number: H-2018-236
NHRC approval number: reg. No. 560/2018

आदर्णिये शाहभागी ज्यु,

हजुरलाई निम्न विवरण गरिएको अनुसन्धान मा सहभगिता जनौन आमन्त्रित गरिन्छ ।

यो अनुसन्धान के का लागि हो?

Introduction: Climate change has been feared as the biggest global health threat of the century by experts and public health professionals. Evidence have suggested that infectious diseases like vector borne diseases, food and waterborne diseases are highly affected by climate variability and climate change. Human capacity to mitigate or adapt to future impacts of climate change on infectious diseases transmission is related to knowledge and understanding of present diseases patterns. Public health surveillance system that detects and describes change in the dynamics of infectious diseases under climate stressors will enable the state authority in setting up priority to curb the impacts of climate change on human health. Unfortunately the conventional surveillance systems designed for protection of public health from potential infectious diseases epidemics are ill suited to respond to the shifting epidemiological dynamics of infectious diseases under influence of future climate change related events. Hence, we aim to explore the public health surveillance systems in Nepal to understand their capacity to assess the impacts of climate change on human infectious diseases transmission.

We strive to understand the functional mechanism of ongoing infectious disease surveillance system, particularly Early warning and Response System (EWARS) and WHO-IPD so as to evaluate suitability of the data collected for secondary analysis by public health researchers, epidemiologists and policy makers working in the sector of climate change and human health.

जल्बयु परिवर्तनलाई जन्भ्वासथकर्मी तथा अन्ये बैज्ञानीक समाजले २१ सौ सतब्धिको ठुलो चुनौती को रुप्मा लिएका छन । अध्ययन अनुसन्धानले देखाए अनुसार लम्खुतेबाट सर्ने रोघ तथा पानी बाट सर्ने झाडजन्ये रोघहरु बिशेष गरी जल्बयु परिवर्तनको करणले प्रभाबित छन र यि रोघहरुको सन्क्रमन र प्रकोप बध्दो अवस्थामा देखिएको छ ।

भबिस्येमा जल्बयु परिवर्तनको करणले हुनसक्ने यस्ता स्वस्थ समस्या अवम रोघ्को प्रकोप बाट जोगिनको तयारीका निमित एस्त समस्याको बर्तमन अवस्थाको जानकारी निकै महत्वो पूर्ण हुन्छ । जनश्वासथ सेवा तथा रोघ्नियन्त्रन महसखाले भबिस्येमा जल्बयु परिवर्तनले निम्त्यौन सक्ने सरुवरोघको प्रकोपको बारेमा पूर्व अनुमान लगएत्का यवत सुचन प्रधान गर्न सकेमा ठुलो जन्धन को सुरक्षा गर्न सकिन्छ । तर बिडम्बन बर्तमन जन्भ्वासथ सेवा र रोघ्नियन्त्रन महसख को सम्रचना केवल सन्क्रमन सुरुभएपछी नियन्त्रन र छ्यती नुनिकरन तर्फ बडी कृयाशिल हुने खल्को देखिन्छ । हामीले बिगत्मा गरेक अनुसन्धान हरुले देखए अनुसार काठमाडौं लगएत्क अन्ये भुभग हरुमा जल्बयु परिवर्तन ले झदाजन्ये र कित्जन्ये

रोघको प्रकोप बडौन सक्ने छ । तसर्थ यस् अनुसन्धान को क्रम्मा हामीले नेपालमा सरुवरोघ नियन्त्रनका निमित गरिने तथ्यन्क सन्कलन र सरुवरोघ नियन्त्रन महसखाको कार्यबिधी अवम छ्यमताको जानकारी लिने छौं । भबिश्यमा जल्बयु परिवर्तनले सरुवरोघ्को सन्क्रमन प्रनली मा। पर्न सक्ने असर मापन तथा तेस्बाट हुन सक्ने छ्यती न्युनिकरन गर्न सक्ने छ्यमता रस्ट्रिये जनश्वासथ तथा सरुवा रोघ नियन्त्रन महसखासँग के कस्तो छ भन्ने कुरको को जानकारी लिने छौं ।

यस्क निम्त हामी सम्बन्धित बिग्ये अबम जान्कर हरु सँग अन्तर्वाता लिने छौम।

यो अनुसन्धान कस्ले गर्दैछ?
यो अनुसन्धान अडेलैड बिश्वोबिध्यलयेमा अध्ययनरत नेपाली विद्यार्थी, श्री दिनेश भण्डारी ज्युको बिद्यबारिदी अध्ययनको सिल्सिलामा गर्नलगिएको हो। यस् अनुसन्धानका अन्य अनुसन्धान कर्ता हरुमा अष्ट्रेलियाको तर्फ बाट प्राध्यपक पेङ बि, डक्टर स्कोट हयानसोनएिजी तथा नेपालका तर्फ बाट प्रध्यपक जीवन बहादुर शेर्चन र डक्टर मेघनाथ धिमाल सम्हिलित हुनुहुन्छ ।

यो अनुसन्धानमा सहभगिता जनौन मलाई किन आमन्त्रन गरिन्दै छ?
याँहाले लामो समयए देखी सरुवा रोघ् नियन्र्त्रन, नितिनियम/पारीयोजन निर्माण तथा तथ्यन्क सन्कलन समबन्धित कृयाकलापमा योग्दान पुर्याउनु भएको र सरुवारोघ नियन्त्रन कृयाकलाप सम्बन्धी जान्कार हुनुभएको हुनाले यस् अनुसन्धानमा सहभागि हुन आमन्त्रन गरिअको हो ।

यो अनुसन्धमा मेरो योग्दान के हुने छ अथवा म बाट के अपेक्च्य गरिअको छ?
यस् अनुसन्धानमा हजुरबाट, नेपालमा सरुवरोघ निर्यन्त्रन माहासखले गर्ने कृयाकलाप, माहसखाको कार्येबिधी सम्भन्धी जानकारीको अपेक्च्या गरेअको छ । साथै नेपालमा जल्बयु परिवर्तनले सरुवरोघको प्रकोपमा के कस्तो असर परेको छ र त्यो असर को मापन तथा नियन्त्रन गर्न महसखको श्रोत साधन र छ्यमता के कस्तो छ भन्ने बारेमा जानकारीको अपेक्च्या गरिएको छ ।

यो अनुसन्धान का निमित मैले कती समय दिनुपर्ने छ?
यो अनुसन्धान अन्तर्गात हजुर सँग केवल एक्पतक ४० मिनट देखी ५० मिनट सम्मको अन्तर्वाता गरिने छ । आवसेक परेमा सो अन्तर्वाताको लिखित प्रतीको भेरीफिकेसन गरिन्छ ।

यस् अनुसन्धानमा शाहभागी हुन परेमा जोखिम्हरु के कस्त छन?
यदी तपाईंले यस् किसीम्को अन्तर्वाता पहिलो पटक अनुभव गर्दै हुन्हुन्छ भने सुरुवात्मा केइ असहज महसुश हुनसक्छ। नौलो अनुभव्को करणले हुनसक्ने साधारण असहज्ता बहेक यस् अनुसन्धानमा सहभागि भएर हजुरलाई अरुकुनै जोखिम पर्ने छैन । तपाईंको अन्तर्वाताको अडियो रेकडको लिखित अनुवाद गरिनेछ र अनुसन्धको निम्ती प्रयोग गरिनेछ।

यस् अनुसन्धानबाट प्राप्त हुनसक्ने सम्भाभित फाईदाहरु के कस्ता छन?
ब्यक्तिगत रुप्मा यस् अध्ययन को कुनै तत्कलिन लाभ हुने छैन । यध्यपी यस् अध्ययनको सिल्सिलामा महत्वो पूर्ण जानकारी तथा सुचनहरु हासिल्हुन हुनसक्ने सम्भाबना बलियो छ । जुन सुचन तथा जानकारी कलन्तर्मा सरुवरोघ नियन्त्रन, तथ्याँक सन्कलन सम्भन्धी उचित निती तथा नियम निर्माणमा प्रयोग हुन सक्ने अंभावना बलियो छ ।

के म अनुसन्धानको दैउरान कुनै पनि बेला बहिरिन सक्छु?

यस् अनुसन्धानमा सहभगिता नितान्त स्वैच्छिक हो। यदी तपाईंले अधयनमा सहभागि हुने सुइक्रिती दिनु हुन्छ र करणबश अध्ययन बाट बहिरुनु पर्ने अवस्था आएमा कुनै पनि बेला बहिरिन सक्नु हुने छ ।

मैले प्रधान गर्ने सुचना तथा विवरण हरुलाई कसरी प्रयोग गरिन्छ?
हजुरले दिनु भएको सम्पूर्ण जानकारी र सुचन ब्यग्तिगत बिबरण नखुल्ने तरिकले गोप्ये रुप्मा प्रयोग गरिने छ। अन्तर्वार्ताको दौरान हजुरले दिनु भएको सम्पूर्ण जानकारी को लिखित अनुवादन गरिनेछ र सो जानकारी सुरक्चित कम्प्युटरमा पस्स्वोड लक गरेर केवल अध्ययन टोली ले मात्र प्रयोग गर्नेछन । यस् अनुसन्धान बाट प्राप्त हुने जानकारी तथा पारीनाम बैज्ञानीक सोध पत्र तथा लेखको रुप्मा गररनी प्रकाशन गरिने छ । अध्ययनको कुनै पनि चरन्मा हजुरको ब्यग्तिगत् जानकारी खुल्ने छैन । अध्ययनको सिल्सिलमा सन्कलन गरिएको जानकारी तथा तयान्क ५ बर्ष पछी नस्ट गरिनेछ । हजुरले प्रधान गर्न्एको सम्पूणद जानकारी केबल यस् अनुसन्धान क। लनम्ती मात्र प्रयोग गररने छ र सम्पूणद जानकारी यस् मन्जुररनमा मा दिएको विवरण अनुसार मात्र प्रयोग हुने छ

यस् अनुसन्धानको बारेमा केही प्रश्न तथा जिज्ञासाहरु भएमा मैले कस्लाई संपर्क गर्ने?
यदी तथ्यन्क सन्कलनको दौरन कुनै जिज्ञासा भएमा मलाई संपर्क गर्नु होला,

दिनेश भण्डारी
जनश्वासथ भिभाग, अडेलैड बिशोब्विध्यालये, अष्ट्रेलिया
संपर्क नम्बर: 9861800898
ईमेल: dinesh.bhandari@adelaide.edu.au

यदी तथ्यन्क सन्कलन पस्चात कुनै जिज्ञासा भएमा मलाई संपर्क गर्नु होला,

डक्टर मेघनाथ धिमाल
नेपाल स्वस्थ अनुसन्धान परिषद
सिंहदरबार, काठमाडौं
संपर्क नम्बर:977-1-4254220
ईमेल:meghdhimal@gmail.com

यस् अनुसन्धान सम्बन्दी केही गुनासो भए के गर्ने?

यो अध्ययन अडेलैड बिशोब्विध्यालये, तथा नेपाल स्वस्थ अनुसन्धान महसखा बाट अनुमतिप्रत गरेर मात्र सुरु गरिएको छ । कुनै गुनासो भए गोप्ये रुप्ले कारबाही गरिन्छ र परिणम् जानकारी गरैइने छ ।

संपर्क नम्बर: +61 8 8313 6028
ईमेल: hrec@adelaide.edu.au
पोस्ट्: लेवेल ४, रुन्द्ल मल प्लाजा, ५० रुन्द्ल मल, अडेलैडे, एस् अ, ५०००

स्थानिये संपर्क:
डक्टर मेघनाथ धिमाल
नेपाल स्वस्थ अनुसन्धान परिषद
सिंहदरबार, काठमाडौं
संपर्क नम्बर:977-1-4254220

ईमेल:meghdhimal@gmail.com

मैले यस् अनुसन्धानमा सहभगिता जनौनका निमित के गर्नु पर्छ?

यदी तपाईं यस् अनुसन्धानमा शाहभागी हुन चाहनुहुन्छ भने मन्जुरिनमा मा हस्तर्क्ष् गरेर श्री दिनेश भण्डारी अथवा डक्टर मेघनाथ धिमाल लाई संपर्क गर्नु होल । तत्पस्चात अन्तर्वाताको तलिक निर्धारणा गरेर हजुरलाई संपर्क गरिनेछ।

भवदिये,

दिनेश भण्डारी	विद्यार्थी अनुसन्धानकर्त
डक्टर स्कोट हयानसोनएिजी	प्रमुख सुपरभाइजर
प्राध्यपक पेङ बि	को-सुपरभाइजर
प्रध्यपक जीवन बहादुर शेर्चन	को-सुपरभाइजर
डक्टर मेघनाथ धिमाल	को-सुपरभाइजर

THE UNIVERSITY *of* ADELAIDE

Human Research Ethics Committee (HREC)

मन्जुरी नामा

१। मैले यस् अनुसन्धान सँग सम्बन्धीत लिखीत जानकारी पत्र राम्रो सँग पढेको छु र म यस् अनुसन्धानमा शाहभागि हुन सुइक्रिती प्रधान गर्दछु।

Title:	**Climatic and socio-economic determinants of diarrhoea among children under 5 years living in Kathmandu valley, Nepal**
Ethics Approval	**H-2018-236 and NHRC Reg. no. 560/2018**

२। मैले यस् अनुसन्धान सँग सम्बन्धीत लिखीत जानकारी पत्र राम्रो सँग पढेको छु, यस् अनुसन्धानमा शाहभागी हुँदा पर्न सक्ने जोखिम मलाई स्पर्स्ट तरिकाले सम्झइअको छ। मैले यो मन्जुरिनमा कुनै दबाबमा परेर दिएको हैन ।

३। यस् अनुसन्धान सम्बन्धी जानकारी प्रधान गर्ने क्रममा मलाई मेरो परिवारको सदस्ये अथवा साथी साक्षी राख्ने मौका प्रधान गरिएको थियो ।

४। यस् अनुसन्धानको प्रमुख उद्एशे स्वस्थ सेवाको गुणस्तर सुधारमा टेवा पुरौने भएकोले, यस्मा शाहभागीता। जनाएर ब्यग्तिगत फाईदा नहुने कुरा मलाई स्पर्स्ट जानकारी गराइएको छ ।

५। लिखीत जानकारी पत्रमा जनाअको सम्पूर्ण कृयाकलापमा शाहअभागी हुन, म मेरो मजुरिनमा प्रधान गर्दछु।

६। अनुसन्धान को क्रममा गरिने अन्तर्वाता अडियो रेकर्ड गर्न म सुइक्रिती प्रधान गर्द छु।

७। मलाई जानकारी गराइअको अनुसार मेरो शाहभागीता। गोप्ये रहने छ , साथै अनुसन्धानको दौरान कुनै पनिबेला बहिरिन सकिने मेरो अधिकारको बारेमा मलाई जानकारी गराको छ, त्यस्तो अवस्थामा मलाई प्रधान गरिनी स्वस्थ उपचारमा कुनै कमी औनेछैन ।

८। यस् अनुसन्धान बाट प्राप्त हुने जानकारी तथा पारीनाम बैज्ञानीक सोध पत्र तथा लेखको रुप्मा प्रकाशित गरिनी कुरा मलाई जानकारी गराएको छ ।

९। प्रकाशनमा औने कुनै पनि लेख र पत्रमा मेरो ब्यग्तिगत परिच्ये खुल्ने छैन।

Version I Date: 31/08/2018

१०। यस् अनुसन्धानका निमित मैले प्रधान गरेको जानकारी, भबिस्येमा गरिने यस् किसिम्का अनुसन्धान हरुमा; मेरो ब्यग्तिगत परिचये नखुल्ने तरिकाले प्रयोग गर्न सुइक्रिती प्रधान

गर्दछु ☐ गर्दिन ☐

११। अनुसन्धानका निम्ती मैले प्रधान गरेको जानकारी अन्लाईन बिदुतीय् भन्डारमा जम्मा गर्न सुइक्रिती प्रधान

गर्दछु ☐ गर्दिन ☐

१२। मैले प्रधान गरेको सम्पूर्ण जानकारी केबल यस् अनुसन्धान का निम्ती मात्र प्रयोग गरिने छ र सम्पूर्ण जानकारी यस् मन्जुरिनमा मा देएअको विवरण अनुसार मात्र प्रयोग हुने छ ।

१३। यस् मन्जुरी नामाको एक प्रती साथै लिखित जानकारीको एक प्रती आफ्नो साथ् राख्नु पर्ने बेवोराको बारेमा म सुसिचित छु ।

शाहभागी ले भर्ने:

नाम: ______________________ हस्ताक्चेर: ________________________ मिती:____________

अनुसन्धान कर्ता/ साक्छी ले भर्ने:

मैले यस् अनुसन्धान को विवरण, श्रीमान/ श्रीमती / शुश्री ______________________ स्पर्स्ट तरिकाले सम्झाअको र मेरो बिचारमा श्रीमान/ श्रीमती / शुश्री ले सम्पूर्ण जानकारी स्पर्ट रुप्ले बुझ्नु भएको छ ।

हस्ताक्चेर: ___________________ पद: _____________________________ मिती: ___________

Participant's demographic form

Participant's code:

1.	How old are you?	Age in years	☐				
2.	I am :	Male	☐	Female	☐	Other	☐
3.	I identify myself as a	Surveillance officer (epidemiologist, statistician, data manger)	☐	Laboratory technician	☐	Infectious disease expert	☐
		Policy maker/Senior authority	☐	Administrative staff	☐	Researcher	☐
4.	I am in this role for:	< 1 year	☐	1-3 years	☐	>3 years	☐

Please suggest a pseudo name (optional) ☐

Appendix 4: Ethics approvals

Government of Nepal

Nepal Health Research Council (NHRC)

Estd. 1991

Ref. No.: 689

30 September 2018

Mr. Dinesh Bhandari
Principal Investigator
The University of Adelaide
Australia

Ref: **Approval of thesis proposal** entitled **Climatic and socio-economic determinants of Diarrhoeal diseases among children under 5 Years Living in Kathmandu Valley, Nepal**

Dear Mr. Bhandari,

It is my pleasure to inform you that the above-mentioned proposal submitted on **30 August 2018 (Reg. no. 560/2018)** please use this Reg. No. during further correspondence) has been approved by Nepal Health Research Council (NHRC) Ethical Review Board on **26 September 2018**.

As per NHRC rules and regulations, the investigator has to strictly follow the protocol stipulated in the proposal. Any change in objective(s), problem statement, research question or hypothesis, methodology, implementation procedure, data management and budget that may be necessary in course of the implementation of the research proposal can only be made so and implemented after prior approval from this council. Thus, it is compulsory to submit the detail of such changes intended or desired with justification prior to actual change in the protocol. Expiration date of this proposal is **February 2021.**

If the researcher requires transfer of the bio samples to other countries, the investigator should apply to the NHRC for the permission. The researchers will not be allowed to ship any raw/crude human biomaterial outside the country; only extracted and amplified samples can be taken to labs outside of Nepal for further study, as per the protocol submitted and approved by the NHRC. The remaining samples of the lab should be destroyed as per standard operating procedure, the process documented, and the NHRC informed.

Further, the researchers are directed to strictly abide by the National Ethical Guidelines published by NHRC during the implementation of their project proposal and **submit progress report in between and full or summary report upon completion.**

As per your thesis proposal, the total research amount is **NRs 3,50,000** and accordingly the processing fee amounts to **NRs 10,000.** It is acknowledged that the above-mentioned processing fee has been received at NHRC.

If you have any questions, please contact the Ethical Review M & E Section at NHRC.

Thanking you.

Prof. Dr. Anjani Kumar Jha
Executive Chairperson

Tel: +977 1 4254220, Fax: +977 1 4262469, Ramshah Path, PO Box: 7626, Kathmandu, Nepal
Website: http://www.nhrc.org.np, E-mail: nhrc@nhrc.org.np

RESEARCH SERVICES
OFFICE OF RESEARCH ETHICS, COMPLIANCE AND INTEGRITY
THE UNIVERSITY OF ADELAIDE

LEVEL 4, RUNDLE MALL PLAZA
50 RUNDLE MALL
ADELAIDE SA 5000 AUSTRALIA

TELEPHONE +61 8 8313 5137
FACSIMILE +61 8 8313 3700
EMAIL hrec@adelaide.edu.au

CRICOS Provider Number 00123M

Our reference 33290

02 November 2018

Dr Scott Hanson-Easey
Public Health

Dear Dr Hanson-Easey

ETHICS APPROVAL No:	H-2018-236
PROJECT TITLE:	Climatic and socio-economic determinants of diarrhea among children under 5 years living in Kathmandu Valley Nepal

The ethics application for the above project has been reviewed by the Secretariat, Human Research Ethics Committee and is deemed to meet the requirements of the *National Statement on Ethical Conduct in Human Research (2007)* involving no more than low risk for research participants.

You are authorised to commence your research on: 02/11/2018
The ethics expiry date for this project is: 30/11/2021

NAMED INVESTIGATORS:

Chief Investigator:	Dr Scott Hanson-Easey
Student - Postgraduate Doctorate by Research (PhD):	Mr Dinesh Bhandari
Associate Investigator:	Professor Peng Bi
Associate Investigator:	Jeevan Bahadur Sherchand
Associate Investigator:	Meghnath Dhimal

CONDITIONS OF APPROVAL: Thank you for your emails and responses to the matters raised. The revised application provided on 30.10.18 has been approved. It has been noted that the Applicant will seek an amendment to ethics approval prior to commencing the second phase of the research project involving qualitative interviews.

Ethics approval is granted for three years and is subject to satisfactory annual reporting. The form titled Annual Report on Project Status is to be used when reporting annual progress and project completion and can be downloaded at http://www.adelaide.edu.au/research-services/oreci/human/reporting/. Prior to expiry, ethics approval may be extended for a further period.

Participants in the study are to be given a copy of the information sheet and the signed consent form to retain. It is also a condition of approval that you immediately report anything which might warrant review of ethical approval including:

- serious or unexpected adverse effects on participants,
- previously unforeseen events which might affect continued ethical acceptability of the project,
- proposed changes to the protocol or project investigators; and
- the project is discontinued before the expected date of completion.

Yours sincerely,

Ms Michelle White
Secretary
The University of Adelaide

Our reference 33290

THE UNIVERSITY of ADELAIDE

RESEARCH SERVICES
OFFICE OF RESEARCH ETHICS, COMPLIANCE AND INTEGRITY
THE UNIVERSITY OF ADELAIDE

LEVEL 4, RUNDLE MALL PLAZA
50 RUNDLE MALL
ADELAIDE SA 5000 AUSTRALIA

TELEPHONE +61 8 8313 5137
FACSIMILE +61 8 8313 3700
EMAIL hrec@adelaide.edu.au

CRICOS Provider Number 00123M

27 June 2019

Dr Scott Hanson-Easey
Public Health

Dear Dr Hanson-Easey

ETHICS APPROVAL No: H-2018-236
PROJECT TITLE: Climatic and socio-economic determinants of diarrhea among children under 5 years living in Kathmandu Valley Nepal

Thank you for the amended ethics application provided by D.Bhandari on the 26th of June 2019 requesting an amendment to begin phase two - qualitative interviews. The amended protocol has been approved.

The ethics amendment for the above project has been reviewed by the Low Risk Human Research Ethics Review Group (Faculty of Health and Medical Sciences) and is deemed to meet the requirements of the *National Statement on Ethical Conduct in Human Research 2007 (Updated 2018)* involving no more than low risk for research participants.

You are authorised to commence your research on: 02/11/2018
The ethics expiry date for this project is: 30/11/2021

NAMED INVESTIGATORS:

Chief Investigator:	Dr Scott Hanson-Easey
Student - Postgraduate Doctorate by Research (PhD):	Mr Dinesh Bhandari
Associate Investigator:	Professor Peng Bi
Associate Investigator:	Jeevan Bahadur Sherchand
Associate Investigator:	Meghnath Dhimal

Ethics approval is granted for three years and is subject to satisfactory annual reporting. The form titled Annual Report on Project Status is to be used when reporting annual progress and project completion and can be downloaded at http://www.adelaide.edu.au/research-services/oreci/human/reporting/. Prior to expiry, ethics approval may be extended for a further period.

Participants in the study are to be given a copy of the information sheet and the signed consent form to retain. It is also a condition of approval that you immediately report anything which might warrant review of ethical approval including:

- serious or unexpected adverse effects on participants,
- previously unforeseen events which might affect continued ethical acceptability of the project,
- proposed changes to the protocol or project investigators; and
- the project is discontinued before the expected date of completion.

Yours sincerely,

Miss Sarah Harman
Secretary

The University of Adelaide

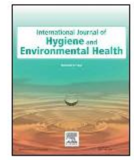
Appendix 5: Abstract of published manuscripts

International Journal of Hygiene and Environmental Health 223 (2020) 199–206

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh



Assessing the effect of climate factors on childhood diarrhoea burden in Kathmandu, Nepal

Dinesh Bhandari[a], Peng Bi[a], Jeevan Bahadur Sherchand[b], Meghnath Dhimal[c], Scott Hanson-Easey[a,*]

[a] *The University of Adelaide, School of Public Health, Adelaide, South Australia, Australia*
[b] *Public Health Research Laboratory, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal*
[c] *Nepal Health Research Council, Kathmandu, Nepal*

A R T I C L E I N F O

Keywords:
Diarrhoea
Children
Climate variability
Nepal

A B S T R A C T

Introduction: This study was undertaken to assess the effect of climate variability on diarrhoeal disease burden among children under 5 years of age living in Kathmandu, Nepal. The researchers sought to predict future risk of childhood diarrhoea under different climate change scenarios to advance the evidence base available to public health decision-makers, and the Nepalese infection control division, in planning for climate impacts.
Methods: A time series study was conducted using the monthly case count of diarrhoeal disease (2003–2013) among children under 5 years of age living in Kathmandu, Nepal. A quasi Poisson generalised linear equation with distributed lag linear model was fitted to estimate the lagged effect of monthly maximum temperature and rainfall on childhood diarrhoea. The environmental framework of comparative risk assessment was used to assess the environmental burden of diarrhoea within this population.
Results: A total of 219,774 cases of diarrhoeal disease were recorded during the study period with a median value of 1286 cases per month. The results of a regression model revealed that the monthly count of diarrhoea cases increased by 8.1% (RR: 1.081; 95% CI: 1.02–1.14) per 1 °C increase in maximum temperature above the monthly average recorded within that month. Similarly, rainfall was found to have significant effect on the monthly diarrhoea count, with a 0.9% (RR; 1.009; 95% CI: 1.004–1.015) increase in cases for every 10 mm increase in rainfall above the monthly cumulative value recorded within that month. It was estimated that 7.5% (95% CI: 2.2%–12.5%) of the current burden of diarrhoea among children under 5 years of age could be attributed to climatic factors (maximum temperature), and projected that 1357 (UI: 410–2274) additional cases of childhood diarrhoea could be climate attributable by the year 2050 under low-risk scenario (0.9 °C increase in maximum temperature).
Conclusion: It is estimated that there exists a significant association ($p < 0.05$) between childhood diarrhoea and an increase in maximum temperature and rainfall in Kathmandu, Nepal. The findings of this study may inform the conceptualization and design of early warning systems for the prediction and control of childhood diarrhoea, based upon the observed pattern of climate change in Kathmandu.

1. Introduction

Diarrhoea remains a leading cause of death among children under 5 years of age. In 2015, 1.31 million diarrhoea-related deaths were reported globally, and diarrhoeal disease represents the second major cause of death among children under 5 years in low and middle-income countries (Troeger et al., 2017; Walker et al., 2013). The average total societal cost of diarrheal disease treatment in low and middle-income countries has been estimated to be as high as US$101 per episode in Rwanda, and US$ 67.81 in Bangladesh (Ngabo et al., 2016; Sarker et al., 2018). In the context of Nepal, the financial burden borne by a family due to childhood diarrhoea is undetermined but can be speculated to be calamitous.

Evidence suggests that the onset and transmission of diarrhoeal disease can be influenced by many factors including climatic parameters such as rainfall and temperature (Checkley et al., 2000; Hashizume et al., 2007; Lama et al., 2004; Onozuka et al., 2010; Singh et al., 2001). During extreme weather events such as floods and hurricanes, water sources can become contaminated with micro-organisms including bacteria (e.g.: Salmonella, *Shigella, Escherichia coli*, *Campylobacter, Vibrio cholerae),*

* Corresponding author.
E-mail addresses: dinesh.bhandari@adelaide.edu.au (D. Bhandari), peng.bi@adelaide.edu.au (P. Bi), jeevanbsherchand@gmail.com (J.B. Sherchand), meghdhimal@gmail.com (M. Dhimal), scott.hanson-easey@adelaide.edu.au (S. Hanson-Easey).

https://doi.org/10.1016/j.ijheh.2019.09.002
Received 11 June 2019; Received in revised form 5 September 2019; Accepted 8 September 2019
1438-4639/

Science of the Total Environment 748 (2020) 141376

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Non-linear effect of temperature variation on childhood rotavirus infection: A time series study from Kathmandu, Nepal

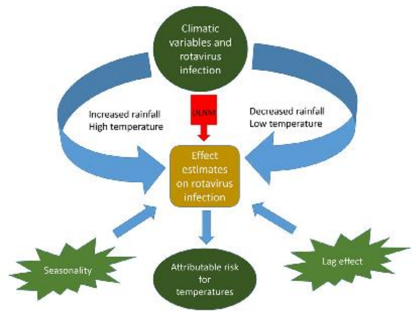
Dinesh Bhandari [a], Peng Bi [a], Meghnath Dhimal [b], Jeevan Bahadur Sherchand [c], Scott Hanson-Easey [a,*]

[a] The University of Adelaide, School of Public Health, Adelaide, South Australia, Australia
[b] Nepal Health Research Council, Kathmandu, Nepal
[c] Public Health Research Laboratory, Institute of Medicine Tribhuvan University, Kathmandu, Nepal

HIGHLIGHTS

- Rotavirus infection risk increased with decreased in all three temperature indices.
- An inverse nonlinear association was observed between rotavirus infection and temperature.
- Relative risk was higher for lower percentiles of temperature.
- 47.01% of cases (<5 years age) were attributable to minimum temperature.
- No significant association was observed with rainfall and relative humidity.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 1 March 2020
Received in revised form 7 July 2020
Accepted 28 July 2020
Available online 30 July 2020

Editor: SCOTT SHERIDAN

Keywords:
Rotavirus
Environmental factors
Epidemiology
Children
Nepal

ABSTRACT

Introduction: This study aimed to investigate the effects of temperature variability on rotavirus infections among children under 5 years of age in Kathmandu, Nepal. Findings may inform infection control planning, especially in relation to the role of environmental factors in the transmission of rotavirus infection.
Methods: Generalized linear Poisson regression equations with distributed lag non-linear model were fitted to estimate the effect of temperature (maximum, mean and minimum) variation on weekly counts of rotavirus infections among children under 5 years of age living in Kathmandu, Nepal, over the study period (2013 to 2016). Seasonality and long-term effects were adjusted in the model using Fourier terms up to the seventh harmonic and a time function, respectively. We further adjusted the model for the confounding effects of rainfall and relative humidity.
Results: During the study period, a total of 733 cases of rotavirus infection were recorded, with a mean of 3 cases per week. We detected an inverse non-linear association between rotavirus infection and average weekly mean temperature, with increased risk (RR: 1.52; 95% CI: 1.08–2.15) at the lower quantile (10th percentile) and decreased risk (RR: 0.64; 95% CI: 0.43–0.95) at the higher quantile (75th percentile). Similarly, we detected an increased risk [(RR: 1.93; 95% CI: 1.40–2.65) and (RR: 1.42; 95% CI: 1.04–1.95)] of rotavirus infection for both maximum and minimum temperature at their lower quantile (10th percentile). We estimated that 344 (47.01%) cases of rotavirus diarrhoea among the children under 5 years of age were attributable to minimum temperature. The significant effect of temperature on rotavirus infection was not observed beyond lag zero week.
Conclusion: An inverse non-linear association was estimated between rotavirus incidence and all three indices of

* Corresponding author.
E-mail addresses: dinesh.bhandari@adelaide.edu.au (D. Bhandari), peng.bi@adelaide.edu.au (P. Bi), scott.hanson-easey@adelaide.edu.au (S. Hanson-Easey).

https://doi.org/10.1016/j.scitotenv.2020.141376

Acta Tropica 204 (2020) 105337

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Climate change and infectious disease research in Nepal: Are the available prerequisites supportive enough to researchers?

Dinesh Bhandari[a], Peng Bi[a], Jeevan Bahadur Sherchand[b], Meghnath Dhimal[c], Scott Hanson-Easey[a,*]

[a] The University of Adelaide, School of Public Health, Adelaide, South Australia, Australia
[b] Public Health Research Laboratory, Institute of Medicine Tribhuvan University, Kathmandu, Nepal
[c] Nepal Health Research Council, Kathmandu, Nepal

ARTICLE INFO

Keywords:
Climate change
Infectious diseases
Public health
Nepal

ABSTRACT

Although Nepal has been identified as a country highly vulnerable to adverse health and socioeconomic impacts arising from climate change, extant research on climate sensitive infectious diseases has yet to develop the evidence base to adequately address these threats. In this opinion paper we identify and characterise basic requirements that are hindering the progress of climate change and infectious disease research in Nepal. Our opinion is that immediate attention should be given to strengthening Nepal's public health surveillance system, promoting inter-sectoral collaboration, improving public health capacity, and enhancing community engagement in disease surveillance. Moreover, we advocate for greater technical support of public health researchers, and data sharing among data custodians and epidemiologists/researchers, to generate salient evidence to guide relevant public health policy formulation aimed at addressing the impacts of climate change on human health in Nepal. International studies on climate variability and infectious diseases have clearly demonstrated that climate sensitive diseases, namely vector-borne and food/water-borne diseases, are sensitive to climate variation and climate change. This research has driven the development and implementation of climate-based early warning systems for preventing potential outbreaks of climate-sensitive infectious diseases across many European and African countries. Similarly, we postulate that Nepal would greatly benefit from a climate-based early warning system, which would assist in identification or prediction of conditions suitable for disease emergence and facilitate a timely response to reduce mortality and morbidity during epidemics.

1. Introduction

Although the role of climatic variables and associated environmental factors in exacerbating the spread of infectious diseases has been known for centuries, extensive research investigating the impacts of climate variability on infectious diseases soared towards the end of twentieth century (Hay et al., 2002; Linthicum et al., 1999; Patz et al., 1996). Abundant literature on climate variations and infectious diseases published over the last two decades has clearly demonstrated that climate-sensitive diseases, namely vector-borne and food/water-borne diseases are highly affected by climate variability and climate change (Lafferty, 2009; Shuman, 2010; Wu et al., 2016). Based on the evidence generated from extensive epidemiological studies, several American, European and some of the African countries have envisaged and implemented climate-based early warning systems for preventing potential epidemics of infectious diseases in the near future (Johansson et al., 2016; Semenza and Menne, 2009; Shaman et al., 2017; Thomson et al., 2006).

In the context of Nepal, despite a high prevalence of climate sensitive infectious diseases, limited evidence is available on the effect of climate change on infectious diseases transmission. A systematic review on climate change and vector borne disease in Nepal published in 2015 identified 8 studies that have examined the association between vector borne diseases and climate variables (Dhimal et al., 2015). However, most of these studies were entomological studies that explored spatio-temporal distributions of disease vectors, and offer little epidemiological insights on the risk of infectious disease incidence in changing climate. Although the primary objective of this paper is not to synthesize current evidence on climate variability and infectious disease in Nepal, a brief summary of updated evidence has been presented in Table 1.

In this opinion paper, we identify challenges with basic

* Corresponding author.
E-mail addresses: dinesh.bhandari@adelaide.edu.au (D. Bhandari), peng.bi@adelaide.edu.au (P. Bi), scott.hanson-easey@adelaide.edu.au (S. Hanson-Easey).

https://doi.org/10.1016/j.actatropica.2020.105337
Received 2 December 2019; Received in revised form 7 January 2020; Accepted 7 January 2020
Available online 10 January 2020
0001-706X/