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Antibiotic Resistance and Environmental Factors:
Focusing on the Situation in Odisha, India

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ABSTRACT

Background: The rise of antibiotic resistant bacteria is a major challenge to global public health. The environment has a significant impact on health and infectious diseases; however, there is a lacuna of information on the relationship between the environment and antibiotic resistance.

Aim: The overall aim of this thesis was to explore the relationship between antibiotic resistance and environmental components.

Methods: This study was conducted in Odisha, India. In Paper I, eight focus group discussions and ten individual interviews among community members without any healthcare background, and in Paper II, 24 interviews among healthcare professionals: allopathic doctors, veterinarians and drug dispensers from two different environmental settings were conducted. In Paper III, studies were conducted to investigate the antibiotic resistance pattern of *Escherichia coli* isolated from samples of children's stool, cow-dung and drinking water from two geographical regions: non-coastal (230 households) and coastal (187 households). Paper IV investigated the association of temperature and relative humidity with occurrence of skin and soft-tissue infections (SSTIs, n=590), *Staphylococcus aureus* associated skin infections (SA-SSTIs, n=387) and methicillin-resistant *S. aureus* (MRSA, n=251) during a period of 18 months in case of outpatients in a tertiary care hospital in Bhubaneswar.

Findings: Participants perceived a relationship between environmental factors, infectious diseases and antibiotic use and resistance. It was perceived that behavioural and social environmental factors, i.e. patients' non-compliance with antibiotic use, irrational prescription by informal as well as trained healthcare providers and over-the-counter availability of antibiotics are the major contributors for antibiotic resistance development. It was also perceived that natural and physical environmental factors are associated with the occurrence and prevalence of infectious diseases and antibiotic resistance (Paper I & II). When quantitative studies were conducted, it was found that the overall prevalence of antibiotic resistance in *E. coli* isolated from children's stool, cow-dung and drinking water was higher in the non-coastal than the coastal environment (Paper III). In Paper IV it was revealed that the maximum temperature above 33°C and minimum temperature above 24°C coinciding with relative humidity between 55% to 78% is a favourable combination for the occurrence of SSTIs, SA-SSTIs and MRSA infections; this combination of temperature and relative humidity is observed during late summer in Odisha.

Conclusions: Although behavioural and social environmental factors are major contributors to resistance development; natural and physical environmental factors also influence antibiotic resistance development. There was geographical variation in antibiotic resistance. It was also evident that climatic factors have influence on skin and soft-tissue infections and resistant bacteria. There is a need for further research on the influence of natural and physical factors on antibiotic resistance development and for education, information dissemination and proper implementation and enforcement of legislation at all levels of the drug delivery and disposal system in order to improve antibiotic use and minimise resistance development.

Key words: environment, antibiotic use, antibiotic resistance, coastal, non-coastal, skin and soft-tissue infections, qualitative studies, climate, temperature, humidity, *E. coli*, *S. aureus*, MRSA, behavioural, social, biophysical, time-series, Orissa, Odisha, India

LIST OF PUBLICATIONS

I. Sahoo KC, Tamhankar AJ, Johansson E, Stålsby Lundborg C. Community perceptions of infectious diseases, antibiotic use and antibiotic resistance in context of environmental changes: a study in Odisha, India. *Health Expectations* 2012. doi: 10.1111/j.1369-7625.2012.00789.x.

II. Sahoo KC, Tamhankar AJ, Johansson E, Stålsby Lundborg C. Antibiotic use, resistance development and environmental factors: a qualitative study among healthcare professionals in Orissa, India. *BMC Public Health* 2010; 10: 629.

III. Sahoo KC, Tamhankar AJ, Sahoo S, Sahu PS, Klintz SR, Stålsby Lundborg C. Geographical Variation in Antibiotic-Resistant *Escherichia coli* Isolates from Stool, Cow-Dung and Drinking Water. *Int. J. Environ. Res. Public Health* 2012; 9: 746-759.

IV. Sahoo KC, Tamhankar AJ, Marrone G, Sahoo S, Pathak A, Stålsby Lundborg C. Climatic factors and *Staphylococcus aureus* associated skin and soft-tissue infections in Odisha, India (Manuscript).

These papers will be referred to in the text by their Roman numerals (I-IV). Previously published papers were reproduced with permission from the publisher.

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LIST OF ABBREVIATIONS

ARIMA	Auto Regressive Integrated Moving Average
ASHA	Accredited Social Health Activist
AYUSH	Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy
B. Pharm.	Bachelor of Pharmacy
BVSc	Bachelor of Veterinary Science
CLSI	Clinical and Laboratory Standards Institute
Dip. Pharm.	Diploma of Pharmacy
ESBL	Extended-Spectrum Beta-Lactamase
IDSP	Integrated Disease Surveillance Programme
IIMAR	Indian Initiative for Management of Antibiotic Resistance
MBBS	Bachelor in Medicine and Bachelor in Surgery
MD	Master in Medicine
MDR	Multidrug-Resistance
MS	Master in Surgery
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MVSc	Master of Veterinary Science
NRHM	National Rural Health Mission
SSTI	Skin and soft-tissue infection
SA-SSTI	*S. aureus* associated skin and soft-tissue infection
USEPA	United States Environmental Protection Agency
WHO	World Health Organisation

DEFINITIONS

Antibiotic resistance: Antibiotic resistance is the ability of certain strains of bacteria to develop a tolerance to specific antibiotics to which they once were susceptible.
Climate change: Climate change refers to a statistically significant variation in either the mean state of the climate or in its variability, persisting for an extended period (operates over decades or longer).
Climate variability: Climate variability refers to variations in the mean state and other statistics (such as standard deviations, the occurrence of extremes, etc.) of the climate on all temporal and spatial scales beyond that of individual weather events (short-term fluctuations around the average weather).
Coastal region: Ten kilometres of the landside of coastal structures.
Healthcare professionals: The health care professionals are educated, trained, certified, or licensed to provide healthcare.
Highest temperature: The highest maximum air temperature observed at the site, calculated over all years on record.
Household or family: A group of persons who commonly live together and would take their meals from a common kitchen unless the exigencies of work prevented any of them from doing so.
Lowest temperature: The lowest recorded temperature observed at the site, calculated over all years on record.
Relative humidity: The ratio of the actual vapour pressure to the saturation vapour pressure expressed as a percentage.
Time-series: An ordered sequence of values of a variable at equally spaced time intervals.
Trend: A trend is a long-term movement in a time-series without calendar-related and irregular effects.

PREFACE

As I look back on my life so far, some pleasant memories come to mind. Of all those pleasant memories, the achievements that I have obtained are the most valuable to me. I owe gratitude to all those who have been my strength through various trials and tribulations.

"If I have seen further than others, it is by standing upon the shoulders of giants"
Sir Isaac Newton

My current environment stems from my roots back in Odisha, India, where I was born and brought up in a middle-class family, moulded by the harsh conditions of rural India. My father earned a basic living by selling sweets and tea in his small shop, while my mother continues to be a dedicated homemaker. Educating and supporting four demanding children was no easy task, however, they still managed to provide us with the basic education. Although my parents had a plan for me in the business field, it was not my destiny. Instead, my true potential unfolded in the field of sciences under the guidance of my guru, who convinced my parents of my interests. A career in medical sciences was far-fetched for me, due to the limited number of medical seats, the huge number of applicants and the highly competitive placements at Indian universities. However, I was still able to pursue a career in biological sciences, obtaining a Masters degree in zoology in Odisha. This was a difficult time for us, as my father was affected by filariasis and we had lost our income source.

"Struggle for existence is the survival of fittest"
Charles Darwin

My passion for social work was recognised by the university and the state government, in the form of awards and accolades. Teaching and learning also appealed to me early on in my academic career. My dreams of studying abroad became a reality, when I was accepted into the Masters programme in applied ecology, at Halmstad University, Sweden. The reason for choosing Sweden was due to the high standards and free education policy of the Swedish government, to which I am grateful. My Masters study in Sweden, with superb guidance of my supervisors became the building block for my doctoral thesis. The supervision that I received is the backbone of my success.

I was warmly accepted as part of the 'Medicines in the health system - focusing antibiotics' research group at the Division of Global Health, Karolinska Institutet. My research theme included the integration of the environment and antibiotic resistance, which is a global concern. However, the research setting of my project was Odisha, India. The findings of this study contribute to new knowledge in environmental health, infectious diseases and antibiotic resistance, and could possibly reflect similar trends in other parts of the globe with similar environments. For me, this process will not end here, with the knowledge gained, but will be explored further in a new dimension.

" Arise! Awake! And stop not till the goal is reached"
Swami Vivekananda

"It is not difficult to make microbes resistant to penicillin, ……"

"……The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

Alexander Fleming Nobel Speech 1945

"We may not be able to control the environment fully
But
We may become wise
And
Manage antibiotic resistance better
If we know
What`s the relationship of environment with antibiotic resistance"

A. J. Tamhankar, National Coordinator, IIMAR

1 BACKGROUND

1.1. ENVIRONMENT AND ITS COMPONENTS

The environment is a ubiquitous and invincible factor that governs all activities of living beings on earth. Four major components constitute the environment: physical, natural, social and behavioural (Figure 1.1) [1, 2]. The physical environment is described as the external surroundings that include air quality, weather and climatic conditions. Temperature, humidity and rainfall form part of these climatic factors. The natural environment encompasses the geographical areas in association with living and non-living components of the ecosystems. An ecological system (ecosystem) is a natural system, which involves the interaction of living beings with their natural environment. The natural and physical environments in combination are referred to as the biophysical environment. The components of the biophysical environment have a significant impact on the properties and functioning of the ecosystem [3]. The social aspects concerning the environment involve a social system which is dependent on culture, population size, ethnicity, educational level, socioeconomic factors, urbanisation, policies and legislation in communities [4]. The behavioural aspects concerning the environment involve individual perceptions and knowledge [5], for example personal hygiene, infection control practices, compliance with medical use and lifestyle. The social and behavioural environmental components however, are interrelated and complement one another, and are often confused when used in isolation.

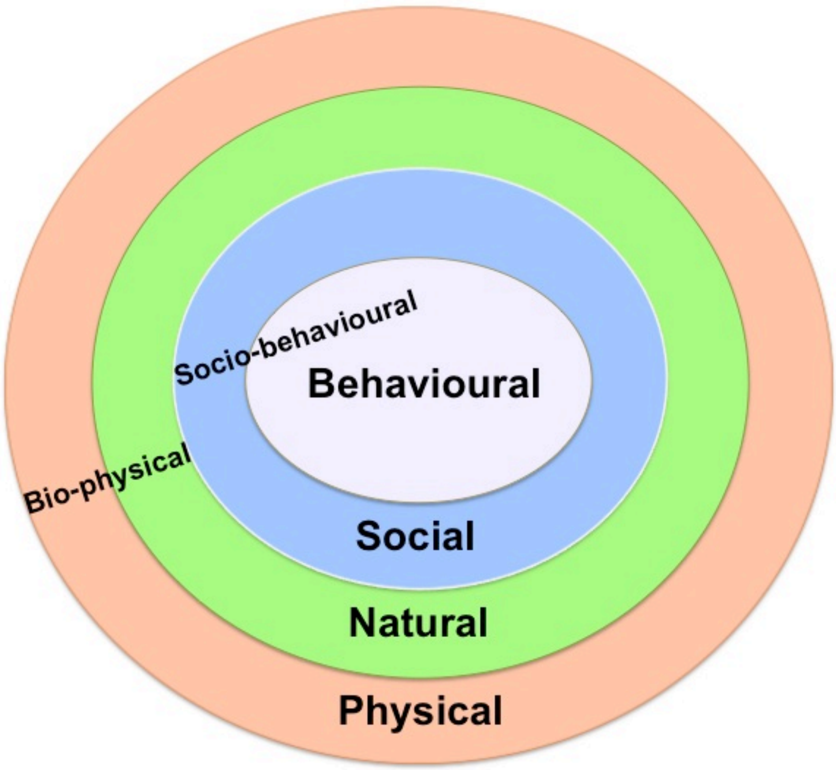

Figure 1.1: Components of the environment

1.2. INFLUENCE OF ENVIRONMENT ON HEALTH AND INFECTIOUS DISEASES

All the environmental components interact with each other and, independently and/or in combination, influence human health. According to the World Health Organisation (WHO), health is a state of complete physical, mental and social well being and not merely the absence of disease or infirmity [6]. The connection between environment and health is clear-cut. Good health begins with a good environment. The environmental components directly or indirectly determine the health and well being of individuals or a community. The direct impacts are associated with extreme weather events, pollution, nutrition, etc. The indirect impacts are caused by contaminated food, water, air or by vectors, etc. Figure 1.2 shows the relationship between environmental components, health and infectious diseases. The environment influences health and infectious diseases either by ecological or social processes. These processes involve climate variability, cataclysmic events, natural perturbations, deforestation, water use, urbanisation, agricultural intensification, migration, trade and travel, sanitation and hygiene, hospitalisation and antibiotic usage etc. as described by Eisenberg *et al.* [7]. Both ecological and social processes influence health, directly or indirectly affecting the transmission pathways of infectious diseases [3, 8, 9]. The various transmission pathways are: human-human, human-vector-host, human-environment, human-environment-host, host-vector-human and host-environment-human [7].

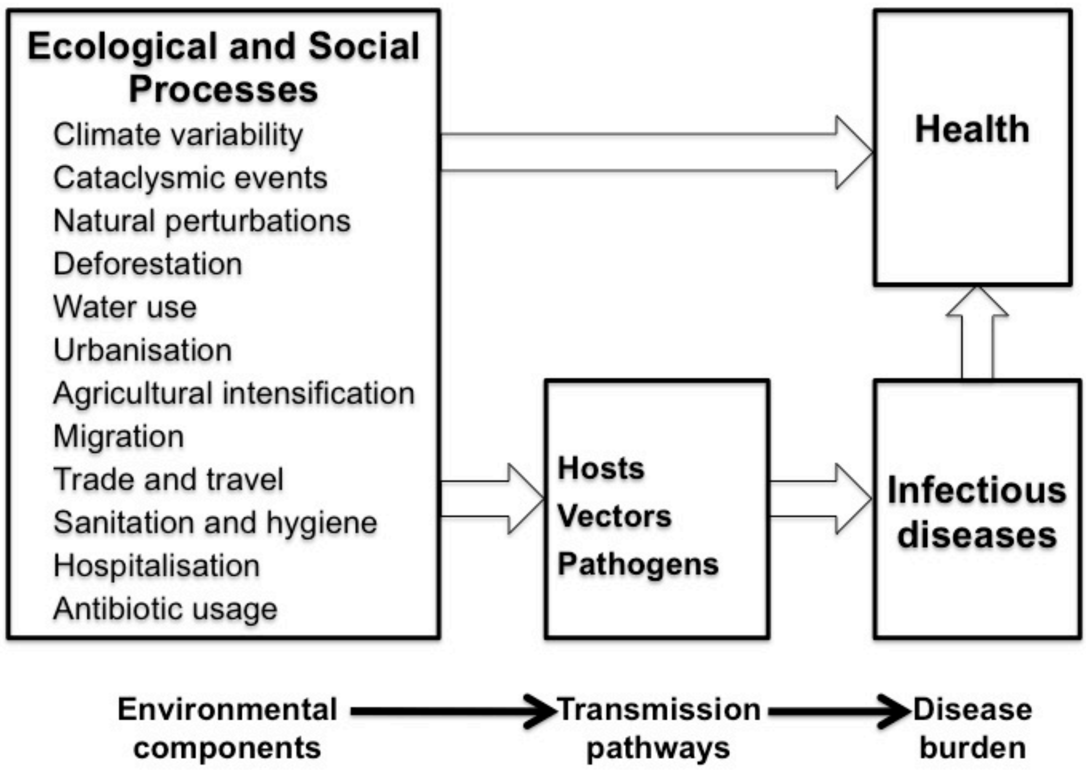

Figure 1.2: Relationship between environmental components, health and infectious diseases

1.2.1. Environment and Infectious Diseases

The environment plays a key role in the occurrence and spread of infectious diseases. Almost every human disease is influenced or caused by exposure to some adverse aspect of the environment [8, 10, 11]. The relationship between environmental components and the emergence of infectious diseases has historical transitions [12]. According to the WHO, over the past two decades, at least thirty new diseases have emerged [13]. The emergence and resurgence of infectious diseases is directly or indirectly linked with behavioural, social and biophysical environmental components [9, 11, 14-16]. Alternations in the environment [7, 17-20] contribute to the occurrence, transmission and spread of infectious diseases. Various studies have reported on association between incidence of new and previously suppressed infectious diseases with environmental changes [12, 17-21].

The impact of environmental change on health depends on the exposure, sensitivity and adaptive capacity of the population of a specific region [22]. India is very diverse: geographically, climatically and culturally. More than 70% of the Indian population lives in rural areas and agriculture is their main source of income. Furthermore, in India, increasing population and rate of urbanisation, trade, travel, migration, agricultural intensification, inadequate infrastructure and weak implementation of existing policies are causing environmental degradation, and contemporary spread and increased liability of various infectious diseases [23-25].

Odisha is amongst the poorest and most vulnerable states in India and faces all the inadequacies mentioned earlier for India. Besides, due to its geographical location and tropical climate, Odisha is vulnerable to natural disasters. It has 480 km of coastline, which is subjected to climate-mediated cyclones and coastal erosion. Furthermore, extreme weather events, inconsistent rainfall, drought and frequent occurrence of floods, combined with extreme poverty, poor rural infrastructure and lack of resources create an unhygienic environment and a higher infectious disease burden [26-28].

Sanitation and infectious diseases

According to WHO, around 1.1 billion people do not have access to safe drinking water and about 2.4 billion people lack access to any type of improved sanitation [29, 30]. Diarrhoeal diseases cause two million deaths every year and most of them are under five years of age [29]. Inadequate water supply, unprotected drinking water sources and unhygienic sanitation practices contribute to the above problem [31]. In low and middle-income countries, poor socioeconomic conditions further enhance the infectious disease burden. For prevention of infectious diseases, behavioural aspects of infection prevention related to hygiene, food handling and cleaning practices are important [11, 32, 33].

The quality of water supply and facility for proper disposal of waste, are indispensable for improvement of sanitation and hygiene [34]. Over-crowding, inadequate water supply and poor sewage management are the barriers to improved sanitation practices in India [35]. It was reported that in India about 28% of rural and 10% of urban population lack access to safe drinking water facilities [36]. In rural India, open-air defecation is still a common practice and more than76% of the rural population does not have access to proper sanitary disposal of human excreta [36]. It was also reported that in India, about 60% of illnesses in communicable diseases are associated with faecal contamination of drinking water, as a result of poor sanitation practices [37].

In Odisha, about 38% of the rural population lack access to safe drinking water and over 88% do not have adequate sanitation facilities [36]. The above factors might contribute to infectious disease burden in Odisha [38].

1.2.2. Environmental Factors, Infectious Diseases, Antibiotic Use and Antibiotic Resistance

Environmental factors directly or indirectly modify antibiotic use and resistance. The alternation in environmental factors affects the incidence and prevalence of infections and projected increase in the distribution and prevalence of infectious diseases. The distribution of infectious diseases has links with antibiotic use and resistance. The association of antibiotic use and resistance with behavioural and social environmental factors is well documented [39, 40]. Although antibiotic resistant bacteria are found in the natural environment [41-44], still there is a paucity of information on how antibiotic resistance varies in different natural environments and the reasons for geographical difference in resistance. Physical environmental factors such as temperature, humidity, rainfall, etc., play an important role in the distribution and prevalence of infectious diseases [17, 20]. Climate variability may exacerbate infectious disease occurrence. As antibiotics are used to manage infectious diseases, it is possible that antibiotic use also varies with climate variability. The same may be true for antibiotic resistance. However, not much is known about this and therefore the association of climatic factors with antibiotic use and antibiotic resistance is an issue that warrants further studies. Figure 1.3 presents the possible relationship of various environmental factors with infectious diseases, antibiotic use and antibiotic resistant bacteria.

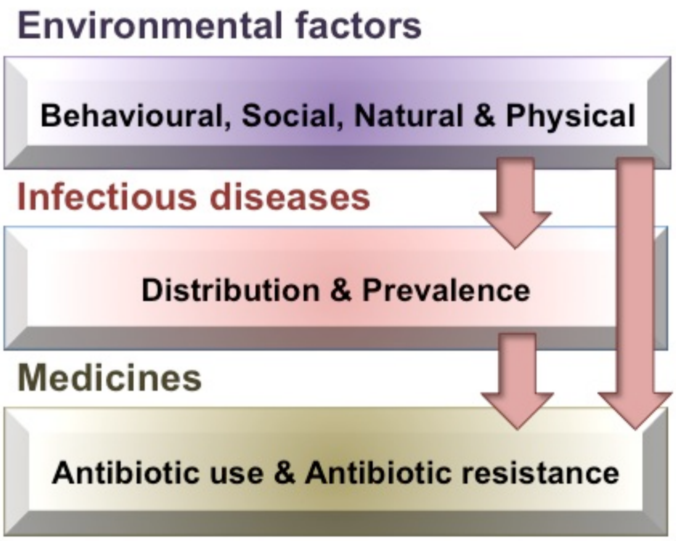

Figure 1.3: Relationship between environmental factors, infectious diseases, and antibiotic use and antibiotic resistance

1.3 ANTIBIOTIC RESISTANCE

1.3.1 Antibiotic Resistance - Global Scenario

Mortality as a result of infectious diseases represents one-fifth of global deaths [45, 46]. The success of antibiotics against diseases caused by bacteria is a great achievement in modern medicine. However, bacteria are becoming resistant and less responsive to antibiotic treatment when it is really needed [47-50]. Antibiotic resistance is the ability of certain strains of bacteria to develop a tolerance to specific antibiotics to which they were once susceptible [51]. The rise of antibiotic resistant bacteria is a major public health problem as infections from resistant bacteria are becoming increasingly difficult and expensive to treat [52-56]. Hospital-acquired infections, medical tourism and extensive personal travel are posing new threats in the spread of antibiotic resistant bacteria across the world [57-60]. The emergence of multi-drug resistant *Salmonella enterica* serotypes *Choleraesuis* and *Typhi*, extensively drug-resistant *Mycobacterium tuberculosis* (XDR-TB) [61, 62], community and hospital acquired methicillin-resistance in *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Staphylococcus aureus* (VRSA) [63, 64], extended-spectrum beta-lactamase (ESBL) producing *Klebsiella pneumoniae* and New Delhi metallo lactamase 1 (NDM-1) producing *Enterobacteriaceae* [65] are current issues which give reason for global health concern on antibiotic resistance [48, 49, 66]. Taking into account the severity of the problem as a global concern, WHO declared 'Antimicrobial Resistance' as a theme of the World Health Day, on 7^{th} April 2011.

1.3.2 Antibiotic Resistance - Situation in India

In general in Asia, the uneven antibiotic use policies and poor standards of public hygiene are resulting in an increasing resistance burden [48]. Antibiotic resistance is a growing problem in India also [67-71]. A few examples that threaten public health are: Multidrug-resistant typhoid fever (MDRTF) [72, 73], epidemic Shigellosis dysentery [74], sepsis in neonates due to imipenem-resistant *Klebsiella* [75], rapid increase in rate of MRSA [76-79], emergence of NDM-1, spread of NDM-1 among *Enterobacteriaceae* [80, 81], ESBL producers [82-85], carbapenemase New Delhi metallo-β-lactamase 1 (NDM-1) producers [86-88]. It may however be noted that there are instances of false alarms also, for example a recent report on outbreak of totally drug-resistant tuberculosis (TDR-TB) [62, 89-91].

In India, the major factor responsible for antibiotic resistance development is the widespread use of antibiotics and over-the-counter availability of antibiotics for human, animal and industrial consumption. There is a need for regulation of antibiotic use and also monitoring of antibiotic resistance at national and state level. In India, the manufacture, sale and distribution of medicines is primarily regulated by the State Drug Control Authorities. In 2011, Government of India has come out with a policy on antibiotic resistance to rationalise the usage of antibiotics [92]. However, implementation of the policy at field level is not an easy task.

In India, a list of 536 drugs has been notified (Drug and cosmetics act, Government of India, schedule H) [93] with certain conditions stipulated therein such as: drugs can be dispensed only on the prescription of a registered medical practitioner; the prescription of a registered medical practitioner should be effected only by or under the personal supervision of a registered pharmacist; the supply of any drug on the prescription of a registered medical practitioner should be recorded at the time of supply in a prescription register and it is suggested that incentives should be given to pharmacies for not selling antibiotics without prescription [92]. Antibiotics are included in this list. Antibiotic consumption data in general is lacking in India [92].

In India, as elsewhere, antibiotics are used in food animals, as growth promoters, especially in poultry and to prevent and treat infections. There is no regulatory provision regarding the use of antibiotics in livestock [92].

1.3.3 Antibiotic Use and its Consequences on the Ecosystem

Injudicious and indiscriminate use of antibiotics in humans and non-humans is one of the major reasons for the development of resistance in bacteria [50]. The WHO reported, that about half of the total antibiotics produced globally are for non-human use [94]. These include veterinary, agriculture, aquaculture and as growth promoters in pig and poultry production.

It is frequently recognised that the widespread use of antibiotics in human health, for veterinary use, in aquaculture and agriculture, in itself represents an important reason for the increase in antibiotic resistance [50, 94-97]. The widespread use of antibiotics in non-humans also contributes to development of resistance and has implications for humans, as we share the same environment. Recently, the so-called 'one health concept' emerged. The objective of the one health concept is to understand the interface of human-animal-environment. To combat antibiotic resistance, combined efforts of human and animal healthcare professionals, as well as environmentalists along with policy makers, are necessary. Therefore, an overall concept of 'One World-One Health-One Medicine' is promoted, to foster collaborative efforts of multiple disciplines, working locally, nationally and globally, to reach a goal of optimal health for people, animals and a clean environment [98-100]. Resistance to antibiotics is the link between animals and humans in the natural ecosystem. Resistant bacteria may spread from animals to the environment (water/soil) to humans [101, 102].

Around the world, thousands of tonnes of pharmaceuticals are used annually but little is known about the potential after-effects of their use. Recently some studies have demonstrated that antibiotics are found in waste water and surface water [41, 96, 103]. A major concern has been that antibiotics found in the aquatic environment may cause increased resistance among natural bacterial populations, as antibiotics remain biologically active even at low levels. The pollution of natural ecosystems due to antibiotics and resistance genes has consequences for human health, as antibiotic resistance is generated due to antibiotics' selective pressure [104]. Antibiotic resistance can be acquired either by mutation or by horizontal gene transfer (HGT) [104-106]. In the natural ecosystem antibiotic concentrations are usually low. The low antibiotic concentrations in natural environments are important for enrichment and maintenance of resistance in bacterial populations [107].

1.3.4. Bacteria Selected for Antibiotic Sensitivity Study in this Thesis

Escherichia coli are Gram-negative bacteria, having both commensal and pathogenic strains. These are the most common enteric bacteria present in the intestinal tracts of both humans and animals. They are released into the environment through faecal material and are therefore used as an indicator of faecal contamination [108]. *E. coli* is the ideal indicator organism because it can be detected easily and affordably. It is the only faecal coliform bacterium of true faecal origin, present in large numbers in faeces of warm-blooded animals [109]. It is one of the United States Environmental Protection Agency (USEPA) recommended indicator bacteria for fresh water ecosystems. It is also considered as a reservoir for antibiotic resistance genes [110].

Staphylococcus aureus are facultative anaerobic Gram-positive bacteria. *S. aureus* are the most common bacteria causing SSTIs. They occur, as commensals on skin and about 15 to 40% of healthy humans are carriers of *S. aureus*. Currently, community-acquired methicillin-resistant *S aureus* (CA-MRSA) have emerged as an epidemic [77]. MRSA is one of the most frequently occurring antibiotic-resistant bacteria [64]. They are climate sensitive bacteria. SA-SSTIs are more common in tropical settings [111-113].

1.4 HEALTHCARE SYSTEMS IN INDIA AND ODISHA

The healthcare systems in India consist of public sector, private sector and an informal network of providers. The organisation at national level consists of the Union Ministry of Health and Family Welfare. The Ministry has the following departments: Health and Family Welfare, AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy), and Health Research and AIDS Control [114]. Private healthcare hospitals, dispensaries, and clinics are more common in urban areas than in rural areas. About 88% of the urban areas have a health facility compared to 24% of rural areas. Informal networks of providers are more common in urban areas and nearly two-thirds of doctors are concentrated in urban areas [115]. The following description of the healthcare system in Odisha further elucidates the healthcare structure in the country.

Healthcare system in Odisha

The healthcare systems in Odisha are under the supervision of the Health and Family Welfare Department, Government of Odisha in line with the National Health Policy of India [116]. Healthcare is provided by public, private and non-profit organisations and includes providers from allopathic and the AYUSH system. The Government of Odisha has recognised AYUSH systems of medicine and encourages the promotion and utilisation of these systems among community members. In Odisha, there are three medical college hospitals (MCH), 32 district headquarter hospitals (DHH), 22 sub-divisional hospitals (SDH), 231 community health centres (CHC), 117 primary health centres (PHS), 1162 new primary health centres (single doctor PHC), 120 other hospitals, 14 mobile health units (MHU) and 6688 sub-centres (SC). There are 1188 AYUSH dispensaries (619 Ayurvedic, 9 Unani and 560 Homeopathic) covering 30 districts in the state [116]. There are also informal healthcare providers (untrained allopathic prescribers) generally referred to as ‘quacks’ and local traditional faith healers.

Like elsewhere in India, private healthcare facilities are more available in the urban areas of Odisha. More than 85% of the population lives in rural areas in Odisha. The rural people depend on CHC, PHC, SC for their healthcare. One CHC serves for every 80,000 to 120,000 population and it provides the basic specialty services in general medicine, paediatrics, surgery, and obstetrics and gynaecology. One PHC covers a population of about 30,000 and it has 15 to17 staff members including one medical officer. The most peripheral healthcare facility is the sub-centre, which is run by an Auxiliary Nurse Midwife (ANM). The ANMs are interacting directly with the community and they are the central focus of all the reproductive child health programmes. At village level an Accredited Social Health Activist (ASHA) is posted under the National Rural Health Mission (NRHM). They are the female community health activists, trained to work as an interface between the community and the public health system [116]. Due to lack of healthcare facilities and insufficient staff at the above health centres most of the rural people are dependent on informal healthcare providers. However, in some areas informal healthcare providers are not even available.

1.5 RATIONALE OF THE STUDY

The rise of antibiotic resistant bacteria is a major global public health problem [52, 54, 117]. Infections from resistant bacteria are becoming increasingly difficult and expensive to treat. The environment has a significant impact on human health. It also plays a key role in the distribution and prevalence of infectious diseases. There is a multi-faceted inter-relationship between the environment, health, infectious diseases, antibiotic use and resistance. However, there is a gap in information regarding the relationship between antibiotic resistance and environmental components. In community environmental health research, qualitative methods are essential for understanding community perceptions of specific or unknown issues [118]. Therefore, this study was undertaken among communities to find out their perceptions regarding the relationship between antibiotic resistance and environmental components, which were then further explored quantitatively.

2 AIMS AND OBJECTIVES

2.1. OVERALL AIM

To explore the relationship between antibiotic resistance and environmental components.

2.2. RESEARCH QUESTIONS

The following was explored by taking Odisha, India as a study setting:

- How do lay people and professionals perceive the association between environmental factors and antibiotic use and resistance development?
- Are natural and physical environmental factors associated with antibiotic resistance? If so how?

2.3. SPECIFIC OBJECTIVES

1. To explore the community perceptions on human health, infectious diseases, antibiotic use and antibiotic resistance development in the context of environmental changes (Paper I).
2. To explore the healthcare professionals' perceptions on infectious diseases, antibiotic use and resistance development in relation to environmental factors (Paper II).
3. To investigate the association of antibiotic resistance pattern of *E. coli* isolated from children's stool, cow-dung and drinking water with natural environment i.e. non-coastal and coastal (Paper III).
4. To investigate the association of climatic factors i.e. temperature and relative humidity with skin and soft-tissue infections, *S. aureus* associated skin and soft-tissue infections and methicillin-resistant *S. aureus* (Paper IV).

3 METHODS

3.1. OVERVIEW OF THE STUDY DESIGN

Both qualitative and quantitative approaches were used for the studies in this thesis. The studies are presented as four papers (I-IV). The subject matter of the four papers is 'the relationship of antibiotic resistance with the four major environmental factors: behavioural, social, natural and physical'. Papers I and II are qualitative studies. Paper I explores the perceptions of community members (without any healthcare background) regarding the relationship between environmental factors and infectious diseases, antibiotic use and antibiotic resistance development. Paper II explores the perceptions of healthcare professionals on infectious diseases, antibiotic use and resistance development in relation to environmental factors. Papers III and IV are quantitative studies. Paper III is a cross sectional study, which investigates the association of natural environmental factors with the prevalence of antibiotic resistance. Paper IV is a cross sectional study with prospective data collection, which investigates the association of physical environmental factors, i.e. temperature and relative humidity, with infectious diseases and antibiotic resistant bacteria.

Details of environmental factors focused upon in each study, study type, data collection methods, study participants and data analysis are given in Table 3.1.

Why both Qualitative and Quantitative Approaches?

The combination of qualitative and quantitative methods in a research framework can increase the validity of research findings, as research triangulation is a powerful technique that facilitates the application of different methodologies in the study of a single phenomenon [119]. In community environmental health research, qualitative methods are essential for understanding of community perceptions [118, 120, 121]. The objective of a qualitative study is to explore the issues/problems/unknown, to understand the phenomenon and gain insight into peoples' attitudes, beliefs, preferences and behaviours about the underlying concepts [122], which can provide a way forward for further quantitative studies. Quantitative research is concerned with testing hypotheses derived from theory and/or being able to estimate the size of a phenomenon of interest [119].

In this thesis, the qualitative approaches were used as a preliminary inquiry for the quantitative work. As there is little information available on the association of environmental factors with antibiotic resistance, qualitative studies were conducted to explore the perceptions of lay people as well as professionals, which were further tested quantitatively. Qualitative studies were used in conjunction with quantitative studies in order to enhance the validity of the findings through research triangulation.

Table 3.1: Summary of the study type, data collection methods, study participants and data analysis

Paper/ Study	**Environmental factors focussed**	**Study type**	**Data collection methods and Study participants**	**Data analysis**
I.	Behavioural Social Natural Physical	Qualitative Study	8 Focus group discussions (FGDs) and 10 Individual Interviews ▪ 63 Community members of different sex, age, educational background and occupation without any healthcare background	Content analysis
II.	Behavioural Social Natural Physical	Qualitative Study	24 Interviews (Healthcare Professionals) ▪ 8 Allopathic doctors ▪ 8 Veterinarians ▪ 8 Drug dispensers	Content analysis
III.	Natural	Quantitative Study	Questionnaires and samples ▪ 417 households: 230 from non-coastal and 187 from coastal region ▪ 1251 Samples of children's stool, cow-dung and drinking water, 417 of each type ▪ 696 isolates of *E. coli* obtained from: children's stool (277), cow-dung (268), and drinking water (151) Testing for antibiotic sensitivity	Descriptive statistics Regression analysis
IV.	Physical	Quantitative Study	Prospective data (July 2009 to December 2010) ▪ 590 skin and soft-tissue infections (outpatients), ▪ 387 *S. aureus* associated skin and soft-tissue infections Testing for antibiotic sensitivity ▪ 251 MRSA infections ▪ Daily climate data: Temperature and Relative humidity	Descriptive statistics Time-series analysis

3.2. STUDY SETTINGS

Odisha, India

India is located in the Southern part of Asia. There are 28 states and seven Union territories. Odisha (Orissa) is one of the states located on the east coast of India. Figure 3.1 shows the map of the study areas.

Figure 3.1: Map of study areas

Odisha is by the Bay of Bengal and has a coastline of about 480 kilometres. It extends over an area of 155,707 square kilometres, accounting for 4.9% of the total area of India. It has a population of 41 million, which is 3.5% of the population of India. The population density of Odisha is 269 persons per square kilometre. More than 85% of the population lives in villages and about 25% are tribal. Out of the 30 districts of Odisha, five (Khurda, Puri, Cuttack, Koraput and Malkangiri) were included in the study based on their distinct environmental features such as climate, geography, social factors and health indicators. Table 3.2 gives details regarding the environmental components and health indicators of the study areas and India.

A special mention must be made here about the 'Malkangiri' district of Odisha. The Malkangiri district has above 57% tribal population, the lowest literacy rate and the highest maternal and infant mortality rates (IMR) compared to other districts of Odisha. The IMR is the second worst in the world; next only to Afghanistan. In addition, malaria is endemic and healthcare, communication and transportation facilities are inadequate. Furthermore, there is internal violence due to the Naxal problem. Naxalites are considered as a terrorist organisation under the Unlawful Activities (Prevention) Act of India (1967). Their strongholds are in the poorest areas of India, particularly the tribal belts. They are causing insecurity and instability, which discourages both governmental and non-governmental organisations, severely restricting development work in the areas. It was therefore of interest to collect data from such an area, although the process of data collection was difficult.

Table 3. 2: Description of study areas (environmental components and health indicators)

	Country	**State**	**Study Districts**				
	India	Odisha	Khurda	Puri	Cuttack	Koraput	Malkangiri
Studies districts are involved in			I, II, IV	III	II	II	I, II, III
Physical components							
Temperature in °C							
Average high			33	33	33	31	32
Average low			23	23	23	18	20
Highest recorded			45	45	45	47	47
Lowest recorded			10	13	8	3	11
Average Relative humidity in %			73	73	73	68	67
Average rainfall in mm	1200	1489	1664	1586	1587	1334	1465
Climatic conditions	Tropical						
Natural components							
Above mean sea level in metres	1 to 8848	1 to 1672	75	3	36	870	178
Physiography			Coastal	Coastal	Coastal	Highlands	Highlands
Forest cover in %	22	31	13	3	16	18	38
Social components							
Population Density per Sq. Km	382	269	799	488	666	156	106
Literacy Rate in %	74.0	73.4	87.5	85.4	84.2	49.9	49.5
Tribal population %	8.2	22.2	5.2	0.30	3.6	49.6	57.4
Health indicators							
Infant Mortality Rate (SRS 2008)	53	69	57	73	63	136	151
Maternal mortality ratio (SRS 2004-06)	254	303	-	-	-	-	-
Life expectancy at birth in years (2011)	63.5	59.6	-	-	-	-	-

Data Sources:

http://www.census2011.co.in/ , http://malkangiri.nic.in/Climate.htm

http://saipdata.awardspace.com/orissa_district-wise_st_population.htm

http://www.123orissa.com , http://www.weatherreports.com/India

www.odisha.gov.in/p.../2011-12/Annual_Plan_2011_12_Vol_I.pdf

Note- The Government of Orissa changed the name of the State 'Orissa' and the name of the state language 'Oriya', to 'Odisha' and 'Odia' respectively, with effect from November 2011. Therefore, in Paper II, which was published before this date, the name of the state appears as 'Orissa' and the language spoken as 'Oriya'. In Papers I, III and IV, the new name 'Odisha' is mentioned.

3.3. DATA COLLECTION

The qualitative data were collected using Focus Group Discussions (FGDs) and individual interviews. The quantitative data gathering strategies included face-to-face questionnaire based interviews, prospective and retrospective information and laboratory test results.

Focus Group Discussions and Interviews (Study I and II)

Both Focus Group Discussions (FGDs) and individual interviews were used for data collection. In Study I, eight FGDs were conducted among the community members of different sex, age, educational background and occupation. Four homogeneous FGDs with (i) illiterate females, (ii) illiterate males, (iii) literate females and (iv) literate males were conducted in each of the two districts. For each FGD, eight to ten participants were contacted with the help of the local authority (village or ward head). Five to seven persons participated in each FGD as per their availability and willingness to participate. In order to bring out the views of the laypeople, community members having any kind of healthcare provider background were not included in the study.

In Study I, after the preliminary analysis of the FGDs, individual open-ended interviews were conducted among the community members in order to obtain more in-depth information. Participants of the FGDs were asked to suggest suitable informants for the individual interviews. After seven to eight interviews saturation of data was reached, as no new information emerged.

In Study II, 24 individual interviews were conducted among healthcare professionals, defined for this study as registered allopathic doctors, veterinarians and drug dispensers. Four participants from each category of healthcare professionals were selected from the two environmental regions to ensure diverse viewpoints.

The participants were selected purposively, based on the objective of the study, from both the environmentally different districts. The participants from two different environmental contexts were selected with the assumption that their perceptions might differ. All the participants were contacted in person or by telephone before the FGDs/interviews. Participation was voluntary. All the FGDs and interviews were carried out at a place convenient for both participants and the moderator/interviewer (residence of a participant, open ground or the school). Specific discussion/interview guides (Appendices I & II for study I & II) were used for data collection. All the FGDs and interviews were conducted in the local language, in this case Odia (Oriya). The interviews were conducted and the FGDs moderated by the author except one FGD in conducted in tribal language. The FGDs were conducted in the presence of an observer, a sociologist who took notes during the discussions. The FGDs were audiotaped and video recorded to facilitate transcription, whereas the interviews were only audiotaped.

Face-to-Face Questionnaire Based Interviews (Study III)

In Study III, a pre-designed questionnaire (Appendix III) was used for the collection of information regarding the participating households, children and cows. The information included the socioeconomic status of the family, source of drinking water, defecation practices of household members, and age and sex of the participating child.

Kuppuswamy's socioeconomic status scale [123] was modified and used for socioeconomic classification of the household. The socioeconomic classes lower middle, upper-lower and lower from the scale were put together to form the lower-economy group, and upper and upper middle classes were put together to form the upper economy group. Antibiotic treatment history of the participating children and cows was also collected. Information about reported antibiotic use during the two previous weeks and last year was obtained. As children in a good state of health (as reported by the head of the family) were included in the study, very few had used medicine during the preceding weeks. Therefore, in the final analysis, the previous year's antibiotic treatment history was used.

Two geographical regions (coastal and non-coastal) were selected for study III. The regions were selected based on the difference in environmental features. One census block was chosen from each geographical region, based on distance from the seacoast, vehicular accessibility and feasibility of transportation of samples to the microbiology laboratory. The villages in coastal census block were within 10 kms from the coast, while the average distance for the non-coastal census block was 120 kms. Each selected census block consisted of about 120 villages. Fifteen to twenty villages were selected from each census block. Within each village, all households having at least one cow and at least one child between three to nine years of age in a good state of health (as reported by the head of the family) were selected for sampling. From each selected household the samples collected were: child stool, cow-dung and drinking water (from storage container). The sample size was calculated conventionally by assuming that resistance is 50% in each comparison group, with power 80% and minimum difference of proportion 20%. Children and cows are both commonly present in both areas. Thus, children's stool and cow-dung samples were chosen as they reflect the respective communities. The study design is given in Figure 3.2.

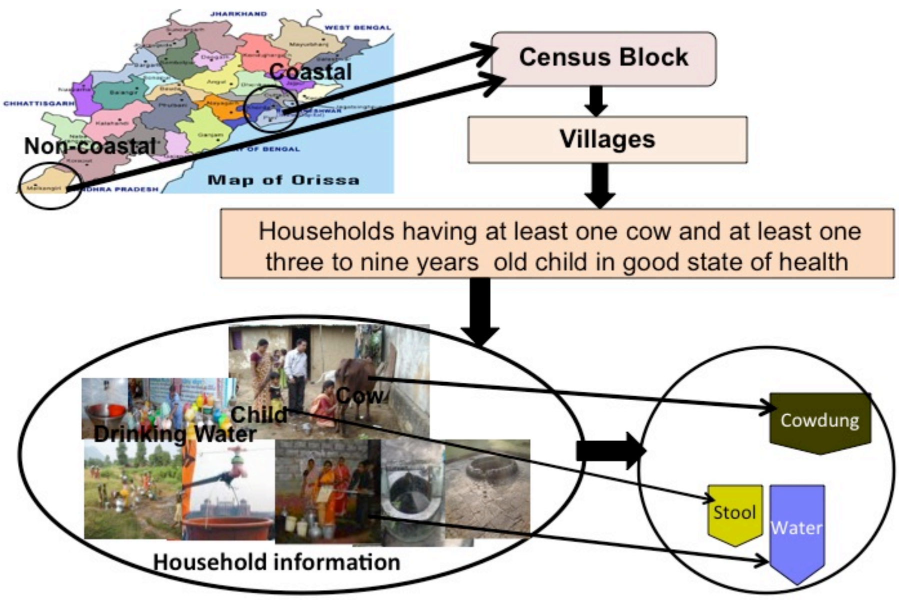

Figure 3.2: Study III design and sampling

Note: The author took the pictures in the figure and consent was taken from the participants for their use.

Prospective and Retrospective Data (Study IV)

In Study IV, all prospectively enrolled consecutive patients diagnosed to have SSTIs from the outpatient clinics of the departments of dermatology and surgery of Kalinga Institute of Medical Sciences (KIMS) from 1st July 2009 to 31st December 2010 were included. The following SSTIs were included in the study: impetigo, furuncle, carbuncle, cellulitis, pyoderma and erythrasma. The physicians made the diagnosis of SSTIs clinically. Assumed fungal or viral SSTIs and patients having a SSTI severe enough to require hospitalisation were not included in the study. The study assistants collected the samples daily in the form of a single pus swab from the SSTI site of consecutive patients. From each patient, a sample was taken only once. The detailed study design is given in Figure 3.3.

The retrospective records of climatic factors i.e. temperature in degree Celsius (°C) and relative humidity in percentage (%) of Bhubaneswar, were obtained from the local meteorological station on a monthly basis from January 1987 to December 2010 and on a daily basis from 1st July 2009 to 31st December 2010. The records of temperature and relative humidity were considered, as these climatic factors were most likely to be associated with occurrence of infectious diseases [124-126].

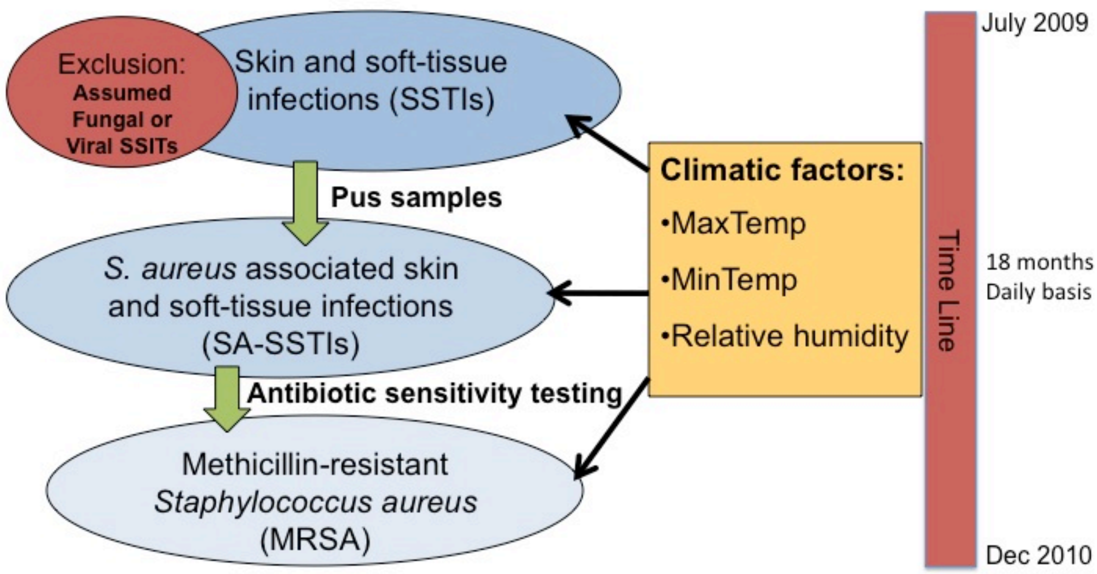

Figure 3.3: Study IV design and sampling

Microbiological Data Collection and Analysis (Study III and IV)

In Study III, three types of samples were collected from the selected households. These were, stool from a child aged three to nine, cow-dung and drinking water (500 mL from the household drinking water storage container). All the samples were collected in sterile containers in a single sampling time in the morning. For Study III, all samples were transported to the microbiology laboratory - Super Religare Laboratories Limited, Kalinga Hospital, Bhubaneswar - for analysis. In Study IV, pus swab samples were collected and transported in Amies transport media with charcoal at a temperature of 4°C to 8°C to the Microbiology laboratory at KIMS hospital for culture. Both the laboratories are accredited laboratories. The bacterial culture and isolation were carried out following standard procedures as described by the Clinical Laboratory Standards Institute (CLSI) guidelines [127, 128].

Modified Kirby-Bauer disk diffusion method was used for antibiotic sensitivity testing [128]. The antibiotic disk strengths were according to the CLSI guidelines [128]. The panel of antibiotics was selected based on the antibiotic prescription patterns in local hospitals and the CLSI guidelines [128].

The antibiotic sensitivity testing of *E. coli* isolates was done for the following antibiotics: tetracycline (30 μg), ampicillin/sulbactam (10 μg/10 μg), cefuroxime (30 μg), cefotaxime (30 μg), cefixime (5 μg), cotrimoxazole (1.25 μg/23.75 μg), amikacin (30 μg), ciprofloxacin (5 μg) and norfloxacin (10 μg). *E. coli* ATCC 25922 was used as control strain.

The antibiotic sensitivity testing of *S. aureus* isolates was done for the following antibiotics: oxacillin (1 μg), ampicillin/sulbactam (10/10 μg), ceftriaxone (30 μg), erythromycin (15 μg), amikacin (30 μg), ciprofloxacin (5 μg), vancomycin (30 μg), and linezolid (30 μg). The cefoxitin disk screen test and 6 μg/ml of oxacillin in Mueller-Hinton agar supplemented with 4% NaCl were used for screening of methicillin resistance. The *S. aureus* ATCC 25923 was used as a control strain.

3.4. DATA ANALYSIS

Qualitative Data Analysis

The audio and video recorded interviews were transcribed verbatim in Odia and then translated into English. For both the qualitative studies (Study I & II) content analysis was applied for analysing the data.

Why content analysis?

The objective in using content analysis is to describe the phenomenon of interest for a particular purpose. This deals with subjective interpretation of the content of the data. It provides a systematic and objective means to make inference from the data, in order to describe the specific phenomenon. The main objective of content analysis is to provide knowledge and understanding of the phenomenon under study [129]. The manifest content analysis describes only the visible or obvious components of the data i.e. what the text says. The latent content analysis coding interpretation of underlying meaning focuses on the tone or implied feelings i.e. what the text talks about [130]. According to Downe-Wamboldt, it is wise to use both manifest and latent content analysis whenever there is a dilemma between level of understanding and specificity [130]. Both manifest and latent content analysis were used for analysis of transcripts.

One of the most basic decisions when using content analysis is selecting the unit of analysis. Meaning units were selected from the transcripts. A meaning unit is the constellation of words or statements that relates to the same central meaning; it can be called coding unit or content unit. From the meaning units, condensed meaning units, i.e. condensed of the underlying meaning or description close to the text, were generated. A code (label of meaning unit) was formulated from a condensed meaning unit. In Table 3.3, examples of coding are given. Similar codes were clustered together and collapsed into sub-sub categories, subcategories and categories. A category is a group of content that shares a commonality; it is the descriptive level of the content. The main themes, i.e. emergent concepts, were based on the similarities between categories. A theme is a thread of underlying meaning through condensed meaning units, codes or categories on an interpretative level. A theme can be seen as expression of latent content of the text. A category answers the question 'what'; whereas a theme answers the question 'how' [129, 130].

Table 3. 3: Examples of coding in content analysis

Meaning unit	Condensed meaning unit	Codes
People are not taking medicines completely; poor people, no money for rice and salt, how will they buy full course of medicine; some people when cured a little, they think, they are well, no need to take full medication.	Financial problem causes incomplete course of medicine	Incomplete course, Poverty, Non-compliance
Heat is increasing and cold is decreasing day by day. In our childhood, we were feeling severe cold in the winter. Nowadays no more cold, and also rain is not in time; during winter and the rainy seasons, we feel like summer. We destroyed lots of forests, so no rain and cold. If all the three seasons are in time, we feel happy and no more diseases will occur; there is no cold and more heat, that's why diseases are occurring.	Change in climate and irregularity in occurrence of seasons which is the result of deforestation, causes health consequences	Climate variability, Irregularity in seasonality, Deforestation, Health consequences,
Out-of-date medicine, if thrown outside, will impact the environment. What we throw away, it will mix with water, again when we drink that water, that water again enters into the blood and obviously it will have an impact. Environmental law is essential.	Antibiotics in the environment and effect of presence of antibiotics in the environment	Antibiotics in the environment, Impact of presence of antibiotics in the environment, Environmental law

Quantitative Data Analysis

In Study III, descriptive statistics and logistic regression, and in Study IV, descriptive statistics and time series analysis was used for data analysis. Frequencies, proportions, mean, median, minimum and maximum were used for the descriptive analyses. Usually, 95% confidence limits were used. $P < 0.05$ was considered statistically significant. In study IV, p-values between 0.05 and 0.10 were considered as of 'borderline significant'. The data were entered in Excel version Office 2007. In Study III and IV analyses were performed using Stata 10.1 software (Stata Corp. College Station, Texas, USA).

In Study III, since the outcome variables were categorical and independent chi-square tests were performed to examine the difference between proportions. Multivariate logistic regression analysis was used to investigate the associations of resistance, co-resistance and multi-resistance with geographical region and the households' information. Odds ratios (OR) with 95% confidence intervals were determined.

Why time-series analysis?

A time-series is a collection of observations of well-defined data items obtained through repeated measurement over time. It is helpful to obtain an understanding of the underlying structure of the observed data and fit a model, and proceed to forecasting. The basic data requirements for time-series analyses are: repeated measurement of an outcome variable at equal time intervals, number of occurrences of an event must be in successive time periods of equal duration, data must be intensive (at least 50 to100 data points needed) and data must be stationary [131, 132].

In Study IV, weekly data were analysed. The Auto-Regressive Integrated Moving Average (ARIMA) model [132] was used to investigate the potential associations of climatic factors with SSTIs, SA-SSTIs and MRSA. The ARIMA model was identified and fitted according to Box and Jenkins methodology [132] (Appendix IV). The model identified by determining the ARIMA model orders (p, d, q) with p representing the autoregressive, 'd' non-seasonal difference and 'q' moving average parameters using autocorrelation and partial autocorrelation. To check the stationary (points) in data scatter plot, autocorrelation plot and lag plot were used. Smoothing, curve fitting and autocorrelation were used for identifying the patterns, and autoregressive (AR) and moving average (MA) models were used for prediction of time-series [131, 132]. An autoregressive model is a linear regression of the current value of the series against one or more prior values of the series. A moving average is a set of numbers, each of which is the average of the corresponding subset of a larger set of data points. It is the linear regression of the current value of the series against the random shocks of one or more prior values of the series. Random shocks are the variables that affect the series of observations [131, 132].

Two-way line plots, uniformly weighted moving average (using two lagged terms, two forward terms, and the current observation) and order 4 polynomial trends were used to estimate the general trend of the considered outcomes i.e. SSTIs, SA-SSTIs and MRSA over the study period. Lag is a fixed time displacement. A trend is a long-term movement in a time-series without calendar-related and irregular effects. Seasonality is the periodic fluctuation by regular peaks and troughs. Restricted cubic splines with three knots and 95% confidence intervals (CI) were used to study the potential associations of climatic factors (weekly average maximum temperature, minimum temperature, and relative humidity) with the study outcomes.

Three regression models with Newey-West standard errors and coefficients estimated by ordinary least squares (OLS) regression, assuming a heteroskedastic error structure and a maximum lag to be considered in the autocorrelation structure equal to 2, were used to study the relationship between the outcomes and the cubic splines of independent variables. The cubic splines knots were chosen on the basis of the cut-off evident from the graphs.

3.5. ETHICAL CONSIDERATIONS

Ethical approval for the studies was obtained from the ethical review committee of Kalinga Institute of Medical Sciences, Odisha, India. Local authorities in all settings gave permission to conduct the studies. The purpose of the study was explained in local language to the participants. The participants were informed that they could withdraw from the study at any time without any implications, although none of the participants withdrew during the course of the studies. Informed consent from the participants was obtained for the interviews, FGDs and collection of samples. Thumb impressions from the illiterate and written consent from the literate participants were taken. The participants in the study and the local authorities were/will be informed regarding the outcome of the studies.

4 MAIN FINDINGS

4.1. BEHAVIOURAL AND SOCIAL ENVIRONMENTAL FACTORS AND ANTIBIOTIC RESISTANCE

4.1.1. Community Perception of relation of Behavioural and Social Environment with Antibiotic Resistance (Paper I)

What were the community members' perceptions of infectious diseases? Community members' perceptions of infectious diseases and antibiotics varied according to their educational level and social environment i.e. rural or urban. The literate participants of both the districts had a common view. The perceptions of the illiterate participants of Khurda differed from the views of the illiterate participants of Malkangiri.

The community members perceived that most of the infectious diseases are either waterborne or airborne, and contaminated water or food were major factors for the spread of infectious diseases. All participants perceived that infectious diseases are transmitted from human to human, environment to human, animal to human, and by physical contact with infected persons or animals.

Did they know what antibiotics are?
Most of the educated participants were familiar with the term antibiotics. According to some of the participants, antibiotics were powerful medicines, used for quick or instant relief of any kind of disease. Some of the participants viewed antibiotics as necessary medicines to avoid serious disease. Some educated participants of Khurda district stated that antibiotics are used to kill bacteria or germs and some of them also used the terms high antibiotic, high dose and side effect. They had heard the names of antibiotics from doctors, informal healthcare providers, medicine shops and neighbours. The illiterate participants of Malkangiri were not at all able to understand the term antibiotics. The illiterate participants of Khurda were also not able to understand the term antibiotics but they had heard the term. They viewed penicillin as 'fever injection'.

> *"We have heard the word antibiotics from hospitals, village doctors (quacks) and medicine shop when we feel fever, doctors prescribe antibiotics and another tablet…Penicillin injection is good for wounds" (FGD, illiterate males, Khurda).*

What did they understand from the term 'antibiotic resistance'?
None of the participants understood the meaning or concept of antibiotic resistance. However, after a brief description of the term, some of the educated participants and a few illiterate participants of Khurda were of the view that, given that some of the previously used medicines are no longer prescribed nowadays, this must mean that those medicines are not working. So for them, non-functioning of medicines implicitly meant resistance.

> *"Previously, penicillin was working well, now doctors are not giving penicillin…." (FGD, illiterate females, Khurda).*

What did they see as possible factors responsible for resistance development?
The participants viewed that noncompliant behaviour of community members, irrational prescriptions by trained and untrained prescribers and availability of fake and low quality medicines were probably factors for some medicines being ineffective.

The participants (except illiterate participants of Malkangiri) perceived that an incomplete course of antibiotics, self-medication, medicine sharing, and use of leftover medicines were common practices among most of the community members. This happens because of poverty, high costs of medicines and lack of awareness of appropriate use of medicine.

> *"People are not taking medicines completely; poor people, no money for rice and salt, how will they buy a full course of medicine; some people when cured a little, they think, they are well, no need to take full medication" (FGD, illiterate females, Khurda).*

According to some of the educated participants, availability of fake and low quality medicines was also a factor responsible for non-functioning of some of the medicines. Most of the educated participants viewed that improper diagnosis, irrational prescription by trained prescribers due to high load of patients in hospitals and lack of trained prescribers, were also reasons for non-functioning of some the medicines. The mercenary nature of some of the trained and untrained prescribers and frequent changes in prescriptions of some of prescribers were other factors for irrational prescription. Most of the participants viewed that the untrained prescribers, so called 'quacks' (informal healthcare providers), were prescribing erratically.

Did they think it is possible to reduce antibiotic use?
Educated participants understood the consequences of antibiotic resistance. They perceived that there is a need for improved hygiene, medication by herbal treatment instead of unnecessary antibiotic treatment, rational antibiotic use practices and awareness among the public to reduce the use of antibiotics.

The participants perceived that antibiotic use can be avoided by improving personal hygiene like cleanliness, hand hygiene and good sanitation practices. Some educated participants suggested high quality water supply, education and awareness about hygiene as being essential in the community. Although some participants emphasised antibiotic treatment for the common cold, some disagreed and suggested traditional treatment, such as basil (*Ocimum sanctum*) leaf with honey for treatment of the common cold. Some informants highlighted yoga (exercise, breathing, and meditation) and pranayam (breathing exercises) as a preventive method to improve health and reduce the need for medicines.

The participants viewed that although untrained prescribers or informal healthcare providers were giving irrational treatment; they were still helping people in remote areas. They suggested that supportive training and orientation on appropriate treatment for common diseases might benefit. Some of the participants also suggested that there is need for law to restrict the 'quacks' to carry out only primary treatment or first aid, followed by referral to local trained prescribers.

"There is a need for rules and regulations for quacks. They should be permitted for only first aid. They are providing saline without knowing the diseases; that is wrong. They are injecting intravenously without justification, they should be limited in their treatment to first aid level, just take care of the patients until they reach a hospital. Anyhow, they are helping people in emergencies; we should verify their knowledge and train them" (FGD, literate males, Malkangiri).

Most of the participants viewed that by creating proper awareness among the community members through health missions or by mass media, misuse of antibiotics can be prevented. They suggested that awareness can be created by healthcare providers, health workers, teachers, NGOs and neighbours.

4.1.2. Healthcare Professionals' Perceptions of relation of Behavioural and Social Environment with Antibiotic Resistance (Paper II)

Antibiotic prescription/use and resistance

According to healthcare professionals, the major social and behavioural factors influencing antibiotic prescription/use and resistance were patients' behaviour, providers' or prescribers' behaviour, and policy and regulatory issues.

The healthcare professionals viewed that patients' noncompliance with prescribers' instructions, self-medication, poverty and ignorance about antibiotic use were the possible contributors to the development of resistance. The major reasons behind the incomplete courses of antibiotics were poverty in rural areas and self-medication in urban areas.

"If patients have taken incorrect medicine, they will develop resistance and due to resistance to previously prescribed antibiotics, the doctor will prescribe new, more expensive antibiotics. Because of the high price involved, the patient is unable to buy the full course, which will once again create resistance to the new antibiotics, so public awareness is essential" (Drug dispenser, Dip.Pharm., 12 years experience).

They perceived that inadequate prescription, i.e. insufficient dose or too short a course, of antibiotics by some of the prescribers was also responsible for improper use of antibiotics. They reported that sometimes, because of an improper diagnosis, antibiotics were used for a disease condition that might not need antibiotic treatment. This happened because there is lack of laboratories for culturing and sensitivity testing.

According to the healthcare professionals, before visiting an authorised medical practitioner, most of the patients take earlier treatment from informal healthcare providers (quacks). They viewed that the quacks were prescribing incomplete courses and doses of antibiotics and some of them suggested training for quacks, as there is lack of trained healthcare providers in Odisha.

"Doctors are not available, quacks are helping the patients…in my view we have to give training to them and license them, something that has recently been done in Kolkota [a city in India], and we have to train them as paramedical practitioners" (Registered allopathic doctor, MS, 40 years experience).

According to drug dispensers' views, sometimes doctors are influenced by a particular pharmaceutical company and prefer to prescribe that company's medicine. Such factors were also influencing antibiotic prescriptions.

The registered allopathic doctors viewed that weak implementation of prevailing legislation was one of the possible contributors to resistance development. They reported that many patients buy medicines directly from the drug store on the advice of drug dispensers or based on their own knowledge. According to them weak implementation of prevailing legislation is the reason for availability of fake and low quality antibiotics as well as over-the-counter sale of antibiotics. Some of the drug dispensers admitted recommending antibiotics themselves even for the common cold.

> *"If the patients say that they have a sore throat, we prescribe five tablets of roxithromycin. We force them to take [buy] the full course, but they often just take for one day or one to two tablets. The common cold is very common here and people usually take anticold tablets with antibiotics. We prescribe lower antibiotics like cefadroxil for colds. If they aren't cured, we prescribe higher antibiotics like cefixime" (Drug dispenser, B.Pharm., 34 years experience).*

According to the views of the participants, antibiotics are also commonly prescribed by some of the homeopathic and ayurveda healthcare providers even though they are not supposed to do so.

> *"Unauthorised medical practice should be banned, either they are quacks or homeopathic or ayurvedic doctors, they should prescribe their own medicine, the majority of them are prescribing antibiotics, they don't have enough knowledge about dosage, course" (Registered allopathic doctor, MS, 21 years experience).*

According to the veterinarians, antibiotics were used both for prophylactic purposes and as growth promoters in feeds in poultry; which they disliked and suggested the use of probiotics instead of antibiotics for growth promoters.

> *"In poultry, antibiotics are generally used as growth promoters in feeds, e.g. tetracycline and lincomycine. Non-human use of antibiotics definitely creates resistance problems in humans" (Veterinarian, MVSc, 10 years experience).*

Measures to prevent resistance development

They suggested a need for information, education, dissemination and proper implementation and enforcement of legislation at all levels of the drug delivery system in order to improve antibiotic use and prevent resistance development. They viewed that there is lack of awareness about the consequences of improper use of antibiotics, which causes resistance development.

4.2. NATURAL ENVIRONMENT AND ANTIBIOTIC RESISTANCE

4.2.1. Community Members' Views on Natural Environment and Antibiotic Resistance (Paper I)

Natural environment and pharmaceutical waste

Educated participants viewed that improperly disposed pharmaceutical waste from households got mixed in ponds or rivers through rainwater. The chemicals present in those wastes polluted the natural environment which affected microorganisms, aquatic organisms and polluted drinking water. The participants mentioned that they were not aware of any policy for proper disposal of household pharmaceutical waste. They suggested that there is a need for policy and awareness on proper management and disposal of unused pharmaceuticals from households.

Geography and infectious diseases

According to most of the literate participants, geography influenced occurrence and prevalence of infectious diseases. For example, there is a geographical difference in disease patterns between coastal and non-coastal environment.

> *"In coastal areas lots of filariasis patients are there as coastal climate is suitable for survival of filaria and non-coastal for malaria mosquitoes" (FGD, literate males, Khurda).*

4.2.2. Healthcare Professionals' Views on Natural Environment and Antibiotic Resistance (Paper II)

The healthcare professionals perceived that antibiotic use differed between geographical regions. In their opinion, there was geographical variation in antibiotic consumption. According to the healthcare professionals, in coastal areas higher antibiotics (i.e. high dose, new generation, broad spectrum, or high-price antibiotics) were prescribed, whereas traditional herbal treatment was more common in hilly regions. They thought that antibiotic prescription rates were lower in the non-coastal region.

> *"In my view rampant use of antibiotics for minor infections is one cause of resistance in coastal areas; they are prescribing higher antibiotics unnecessarily." (Registered allopathic, MBBS, 2 years experience).*

Management of pharmaceutical wastes

According to the healthcare professionals, antibiotics are contaminating the aquatic and the terrestrial environment due to improper disposal of pharmaceuticals. They stated that the hospital waste, out-of-date medicines from shops and unwanted household pharmaceuticals were not disposed properly. The improperly disposed antibiotics, affected the aquatic organisms, grazing animals and also human beings, especially those using river/pond water for drinking and cooking purposes. They suggested that properly implemented and enforced environmental law was essential for the proper disposal of pharmaceutical waste.

"If pharmaceutical wastes are disposed improperly, it will affect the environment. Expired medicine loses its efficacy, but not toxicity...if we throw these wastes outside they will mix with water; if that water is taken by humans or animals it may create problems; what happened recently at Cuttack, some cattle died by taking expired medicine including some antibiotics which were thrown improperly in to the river. Some aquatic organisms also died. Every drug in its proper dose is medicine, and in improper dose is poison" (Registered allopathic doctor, MD, 41 years experience).

Some of them perceived that antibiotics in the environment had a significant impact on microorganisms, for example if waterborne bacteria are exposed to low doses of antibiotics in water they might develop resistance. Some of them thought that there was not much research on the environmental aspects of antibiotic resistance and they suggested further research in this area for proper solutions.

"If waterborne diseases causing bacteria are exposed to low doses of antibiotics every day, they gradually become tolerant to that particular drug and resistance will develop…Antibiotic resistance in relation to the environment is a research question" (Veterinarian, MVSc, 10 years experience).

"Antibiotic resistance in relation to the environment is a research question, further study is essential in this field" (Veterinarian, MVSc, 27 years experience).

4.2.3. Observations on Quantitative Association between Natural Environment and Antibiotic Resistance (Paper III)

Table 4.1 presents the information on household characteristics of selected children and cows. Antibiotic resistance patterns of *E. coli* isolates from various sources i.e. children's stool, cow-dung and drinking water from the two different natural environments are presented in Table 4.2. Overall, the findings showed that the prevalence of antibiotic resistance was higher in the non-coastal than the coastal environment. *E. coli* isolates from all the three sources of the non-coastal region showed significantly higher resistance to both second and third generation cephalosporins. Norfloxacin and ciprofloxacin resistance was significantly higher in non-coastal cow-dung and drinking water. Amikacin resistance among *E. coli* isolates from children's stool was higher in the coastal region; however, this was not statistically significant.

The odds ratios for occurrence of resistance in *E. coli* isolates from children's stool (OR = 3.1, 95% CI 1.18–8.01), cow-dung (OR = 3.6, 95% CI 1.59–8.03, P = 0.002) and drinking water (OR = 3.8, 95% CI 1.00–14.44, P = 0.049) were higher for the non-coastal compared to the coastal region. Similarly, the odds ratios for occurrence of co-resistance in cow-dung (OR = 2.5, 95% CI 1.39–4.37, P = 0.002) and drinking water (OR = 3.2, 95% CI 1.36–7.41, P = 0.008), and multi-resistance in cow-dung (OR = 2.2, 95% CI 1.12–4.34, P = 0.022) and drinking water (OR = 2.7, 95% CI 1.06–7.07, P = 0.036) were higher in the non-coastal compared to the coastal region.

Table 4.1: Characteristics of the households from the non-coastal and coastal environment.

Information on households	**NCE (N = 230) n (%)**	**CE (N = 187) n (%)**	**P-value**
Socioeconomic status			0.080
Lower	197 (86)	148 (79)	
Upper	33 (14)	39 (21)	
Drinking water sources			**<0.001**
Tube well	192 (83)	169 (90)	
Water supply system	28 (12)	5 (3)	
Well	4 (2)	13 (7)	
Pond	6 (3)	0	
Defecation			0.158
Latrine	26 (11)	30 (16)	
Open-air	204 (89)	157 (84)	
Reported antibiotic use in the child, last year^{+}			**<0.001**
Yes	175 (76)	175 (94)	
No	3 (1)	6 (3)	
Not known	52 (22)	6 (3)	
Reported antibiotic use in the cow, last year^{++}			0.604
Yes	11 (5)	7 (4)	
No	219 (95)	180 (96)	

NCE = Non-coastal Environment; CE = Coastal Environment; *N* = Total number of samples; Chi-square test, P <0.05 considered as significant, *n* = Samples with observed variable; $^{+}$In some cases other medicines were named as antibiotics by them; $^{++}$Most of them did not use any kind of medicine in cows.

Table 4.2: Antibiotic resistance patterns of *E. coli* in non-coastal and coastal regions

Antibiotics	Resistance in *E. coli* isolates from various sources					
	Children's stool, n (%)		Cow-dung, n (%)		Drinking water, n (%)	
	NCE N=139	CE N=138	NCE N=140	CE N=128	NCE N=97	CE N=54
Tetracycline	76 (55)	70 (51)	69 (49)	46 (36)*	59 (61)	16 (30)***
Ampicillin/Sulbactam	69 (50)	55 (40)	71 (51)	35 (27)***	46 (47)	16 (30)*
Cefuroxime	88 (63)	70 (51)*	89 (64)	48 (37)***	63 (65)	22 (41)**
Cefotaxime	90 (65)	68 (49)**	82 (59)	39 (30)***	72 (74)	23 (43)***
Cefixime	95 (68)	72 (52)**	86 (61)	49 (38)***	52 (54)	16 (30)**
Cotrimoxazole	79 (57)	52 (38)**	69 (49)	37 (29)**	51 (53)	22 (41)
Amikacin	39 (28)	52 (38)	58 (41)	42 (33)	25 (26)	9 (17)
Ciprofloxacin	60 (43)	56 (41)	43 (31)	33 (26)	40 (41)	11 (20)**
Norfloxacin	70 (50)	59 (43)	71 (51)	43 (34)**	47 (48)	18 (33)
Resistance^{+}	131 (94)	116 (84)**	129 (92)	98 (77)***	92 (95)	44 (81)**
Co-Resistance^{++}	116 (83)	109 (79)	111(79)	76 (59)***	82 (85)	31 (57)***
Multi-Resistance $^{+++}$	33 (24)	33 (24)	35 (25)	16 (12)**	29 (30)	8 (15)*

N=Total number of samples; n=Resistant isolates; NCE=Non-coastal Environment; CE=Coastal Environment; $^{+}$Resistance to at least one of the tested antibiotics; $^{++}$Resistance to two antibiotic groups; $^{+++}$Resistance to at least three different antibiotic groups; Chi-square test: *P <0.05, **P<0.01, ***P<0.001

4.3. PHYSICAL ENVIRONMENTAL FACTORS AND ANTIBIOTIC RESISTANCE

4.3.1. Community Members' Views on Physical Environment and Antibiotic Resistance (Paper I)

Weather and seasons

The participants viewed that of late there was an irregularity in the occurrence of seasons associated with an increase in average temperature. They reported occurrence of excessive heat in the summer and reduced rain, inconsistency in rain patterns, and undue heat in the rainy season. They also viewed that winters were becoming comparatively warmer than previous years, with the exception of occasional severe cold for very short periods occurred during winter. According to them, deforestation, urbanisation, air pollution and agricultural intensification are factors responsible for persistent climate variability experienced nowadays.

> *"Heat is increasing and cold is decreasing day by day. In our childhood, we were feeling severe cold in the winter. Nowadays no more cold, and also rain is not in time; during winter and the rainy seasons, we feel like summer…. We destroyed lots of forests, so no rain and cold…. If all the three seasons [summer, winter and rainy] are in time, we feel happy and no more diseases will occur; there is no cold and more heat, that's why diseases are occurring" (FGD, iliterate males, Malkangiri).*

Climate variability and health

The participants reported that the persistent climate variability is responsible for unpredictable cataclysmic events such as floods, cyclones, droughts and heat waves, which cause direct health consequences. They also perceived that the increase in temperature has caused a decrease in the level of ground water and dryness of surface water sources like ponds, wells and rivers as well as tube-wells, leading to health consequences associated with water scarcity. The climate variability is also indirectly associated with water and food-borne diseases such as acute diarrhoeal disorders, malnutrition due to food scarcity and air pollution-related diseases. According to the participants, the consequent temperature-related health effects were skin infections, measles among children, sunstroke, jaundice, malaria and dengue fever.

Interrelationship between climate, infectious diseases and medicines

The community members perceived an interrelationship between the climate, infectious diseases and medicines. The literate participants viewed that climate variability is responsible for re-emerging outbreaks of chicken pox and chikungunya. They also viewed that variation in climate alters the life cycle of some vectors.

> *"The chicken pox and measles had decreased, now these are again spreading. The environment is getting polluted which results in the rise of new diseases. The climate has a definite impact on diseases" (FGD, literate males, Khurda).*

> *"In heavy rains usually they (mosquitoes) die and their eggs are destroyed. Less rain is providing suitable surroundings for increase of their population; heavy rain*

during rainy seasons is essential to decrease the Kita patanga [insect population]" (Individual interview, literate female 45 years, Khurda).

According to few literate participants, climate variability is contributing to non-functioning of some medicines, including penicillins, spread of drug-resistant malaria and decreased immunity of humans.

"Now penicillin injection is not working, malaria drugs are not functioning…. these medicines' power is not able to kill germ…this may be due to changing climate" (FGD, literate males, Khurda).

"Gradually, immunity power of our body is decreasing; for that reason we are requiring high doses of medicines…. our food habits and climate, both are changing. Due to these reasons body immunity is decreasing and medicines are not working" (Individual interview, literate male 32 years, Khurda).

4.3.2. Healthcare Professionals' Views on Physical Environment and Antibiotic Resistance (Paper II)

Interrelationship between climate, infectious diseases and medicines

The healthcare professionals viewed an interrelationship between climate, infectious diseases and medicines focusing on antibiotic. According to them, each season had its own types of diseases, for example diarrhoea in the rainy season and respiratory tract infections in winter. They also viewed a seasonal pattern of occurrence in skin infections. They reported that high temperatures in the summer and high humidity in the rainy season increases the number of skin infections. According to them, change in climate i.e. temperature, precipitation and humidity, and pollution were responsible for the emergence and the re-emergence of diseases, which in turn influenced antibiotic prescriptions/use. As per the veterinarians, stress-related diseases in animals were more common in high temperatures during the summer.

"When the monsoons start, at that time bacterial disease is more common…there is less infection in winter. In summer, protozoan diseases are more common, due to summer stress. The environment is slowly changing, the temperature is rising" (Veterinarian, BVSc, 25 years experience).

"In most of the cases, high doses of antibiotics are prescribed from the beginning, probably due to the change in climate" (Drug dispenser, B.Pharm., 25 years experience).

4.3.3. Observations on Quantitative Association between Physical Environment and Antibiotic Resistance (Paper IV)

Observation of change in weather/climate

Figure 4.1 presents the climatic record over a period of 29 years (maximum temperature, minimum temperature and relative humidity) of Bhubaneswar (from January 1987 to December 2010). It shows that there was an overall increase in average maximum temperature and decrease in average minimum temperature over time. It also shows a slightly increased trend of average mean temperature and mean relative humidity over time. The temperature and relative humidity of Bhubaneswar from 1st July 2009 to 31st December 2010 is given in Table 4.3.

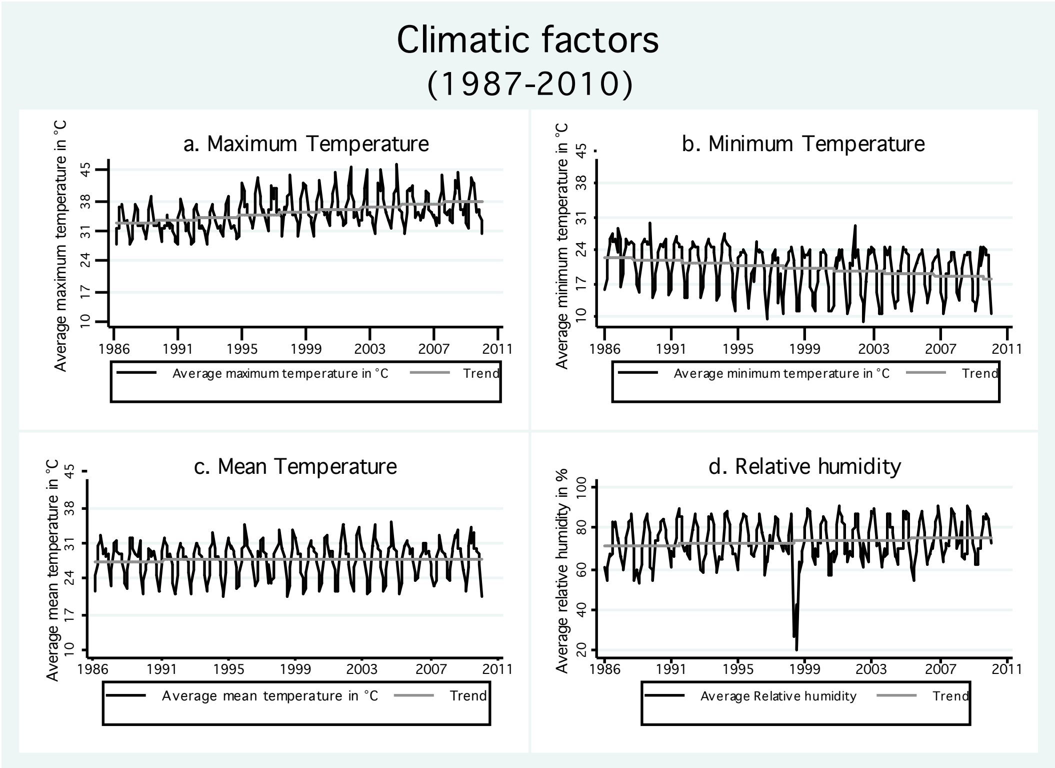

Figure 4.1: Temperature and relative humidity at Bhubaneswar from January 1987 to December 2010

Table 4.3: Description of temperature and relative humidity in various seasons between July 2009 to December 2010 at Bhubaneswar, India

Seasons	Climatic factors (weekly average ranges)		
	MaxTemp	MinTemp	RH
Early summer (mid-February to mid-April)	34-41	18-28	55-76
Late summer (mid-April to mid-June)	33-40	25-29	64-81
Early monsoon (mid-June to mid-August)	29-36	25-27	80-97
Late monsoon (mid-August to mid-October)	30-33	22-27	73-95
Early winter (mid-October to mid-December)	26-33	14-24	63-87
Late winter (mid-December to mid-February)	28-32	13-18	57-74

MaxTemp=Maximum temperature in °C, MinTemp=Minimum temperature in °C, and RH= Relative humidity in %.

Climatic factors and skin and soft-tissue infections

This study found an association between climatic factors i.e. temperature and relative humidity with SSTIs, and SA-SSTIs.

Figure 4.2 shows the observed weekly data, four weeks moving average and the estimated polynomial trend of number of SSTI cases. A high peak of SSTI cases during May-July and a decrease in number of cases during October to December was observed. A higher occurrence of SSTIs during late summer (mid-April to mid-June) and early monsoon (mid-June to mid-August) and lower occurrence during winter (mid-October to mid-February) was also recorded.

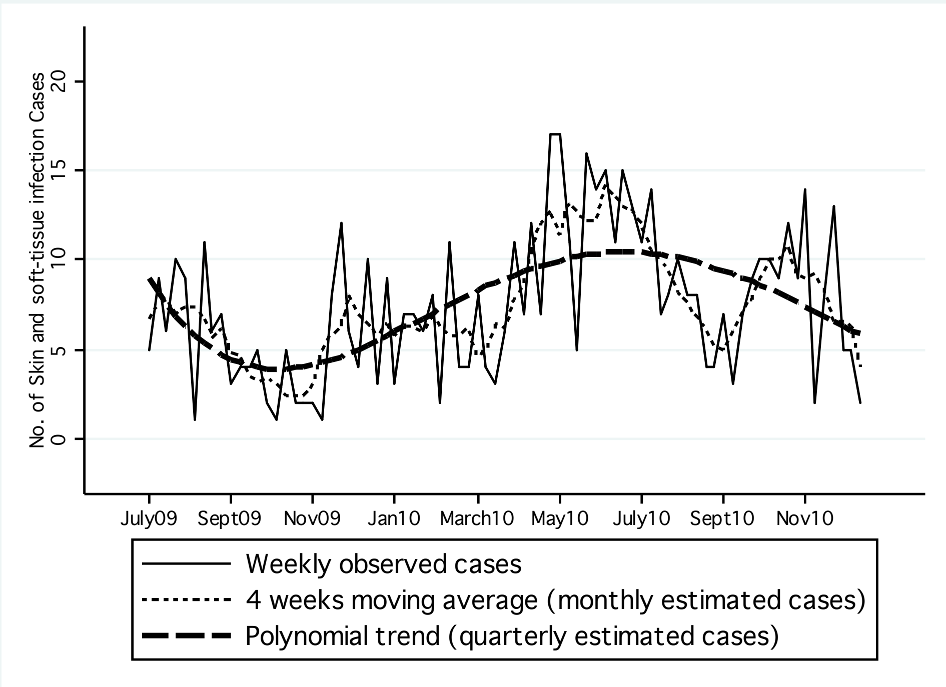

Figure 4.2. Occurrence of skin and soft-tissue infections from July 2009 to December 2010 in Bhubaneswar, Odisha

Table 4.4 shows a fitted regression model for the effect of temperature and relative humidity on the incidence of SSTIs and SA-SSTIs.

Table 4.4: Fitted regression model* for the effect of temperature and relative humidity on the incidence of the skin and soft-tissue infections (SSTIs), skin and soft-tissue infections caused by *S. aureus* (SA- SSTIs)

Climatic factors		Infectious diseases			
	Cut-off values	SSTIs		SA-SSTIs	
		Coefficient	P	Coefficient	P
MaxTemp	Below 33 °C	-0.20	0.600	-0.56	**0.056**
	Above 33 °C	0.60	0.253	0.69	**0.058**
MinTemp	Below 24 °C	-0.48	0.180	0.03	0.919
	Above 24 °C	0.90	**0.040**	-0.12	0.781
RH	Below 78%	0.24	**0.025**	0.10	0.228
	Above 78%	-0.25	**0.065**	-0.17	**0.078**

MaxTemp= Weekly average maximum temperature °C, MinTemp= Weekly average minimum temperature °C, RH= Weekly average relative humidity in %.

* Regression models with Newey-West standard errors and coefficients estimated by ordinary least squares (OLS) regression, assuming a heteroskedastic error structure and a maximum lag 2.

** The cut-off values for temperature and relative humidity were chosen from the graphs of the cubic splines.

Negative sign in the coefficient indicates decreasing number of cases and positive sign indicates increasing number of cases. P-values less than 0.05 were considered as significant and P-values between 0.05 and 0.10 as 'borderline significance'.

Figure 4.3 (a-b) shows the variation in number of SSTI and SA-SSTI cases in relation to weekly average maximum temperature. No significant association was observed between the weekly average maximum temperature and SSTIs. However, a borderline significant negative relationship of SA-SSTI cases (i.e. the number of cases decreased) with weekly average maximum temperature below 33°C (Coef -0.56, P=0.056) and a borderline significant positive relationship (i.e. the number of cases increased) above 33°C (Coef. 0.69, P=0.058) was found.

Figure 4.4 (a-b) shows the variation in number of SSTI and SA-SSTI cases in relation to weekly average minimum temperature. It was found that the number of SSTI cases increased significantly when the weekly average minimum temperature was higher than 24°C (Coef. 0.90, P=0.04). However, no significant association between weekly average minimum temperature and SA-SSTIs was observed.

Figure 4.5 (a-b) shows the association of number of SSTI and SA-SSTI cases with weekly average relative humidity. A significant increase in SSTI cases was found, when the weekly average relative humidity increased from the minimum value of 55% to 78% (Coef. 0.24, P=0.025), and a borderline significant decrease in SSTI cases was found when the weekly average relative humidity increased above 78% (Coef. -0.25, P=0.065). In case of SA-SSTIs a borderline significant negative relationship was observed, when the weekly average relative humidity was higher than 78% (Coef -0.17, P=0.078).

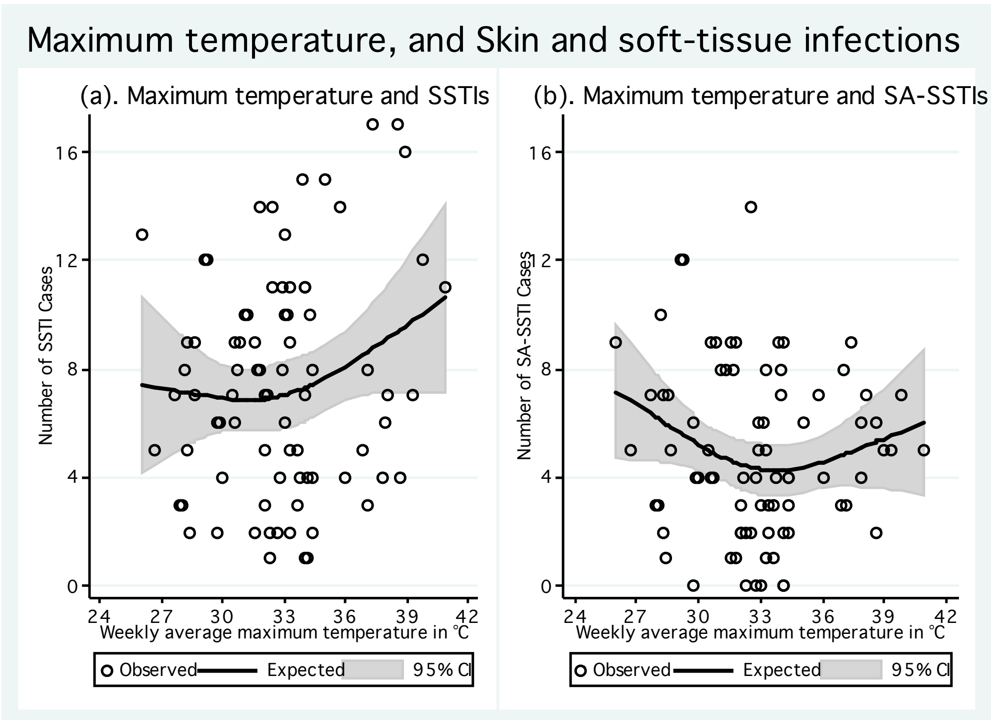

Figure 4.3: Relationships between skin and soft-tissue infections (SSTIs) and skin and soft-tissue infections caused by *S. aureus* (SA-SSTIs) with climatic factors (a). Weekly average maximum temperature and SSTIs (b). Weekly average maximum temperature and SA-SSTIs The centre lines in the graphs show the estimated spline curve, and the upper and lower lines represent the 95% confidence limits

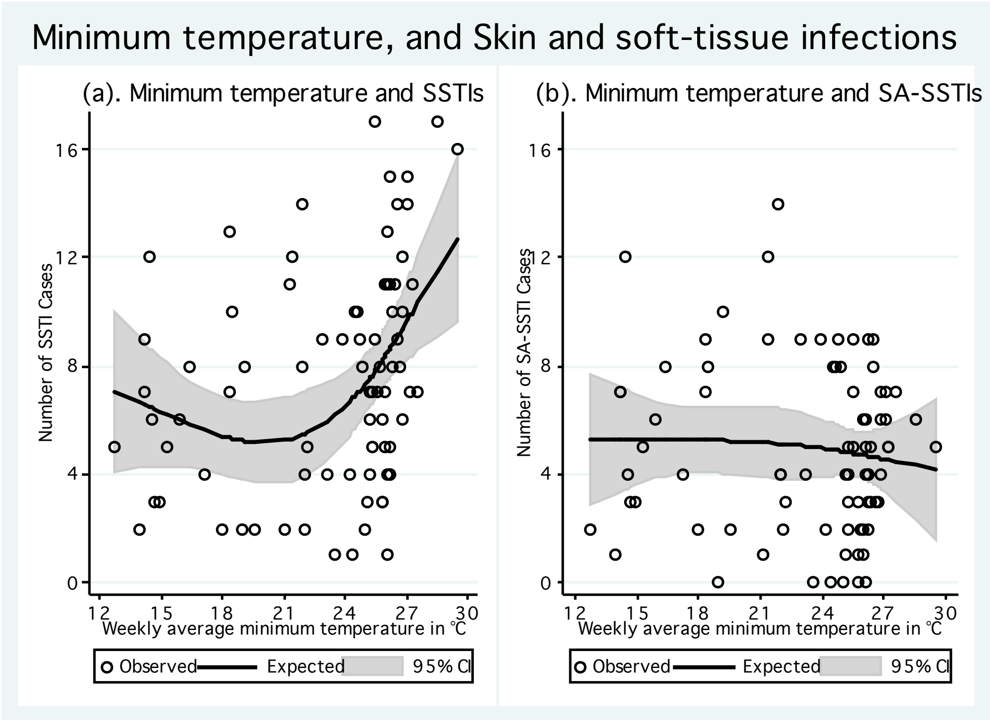

Figure 4.4: Relationships between skin and soft-tissue infections (SSTIs) and skin and soft-tissue infections caused by *S. aureus* (SA-SSTIs) with climatic factors (a). Weekly average minimum temperature and SSTIs (b). Weekly average minimum temperature and SA-SSTIs. The centre lines in the graphs show the estimated spline curve, and the upper and lower lines represent the 95% confidence limits

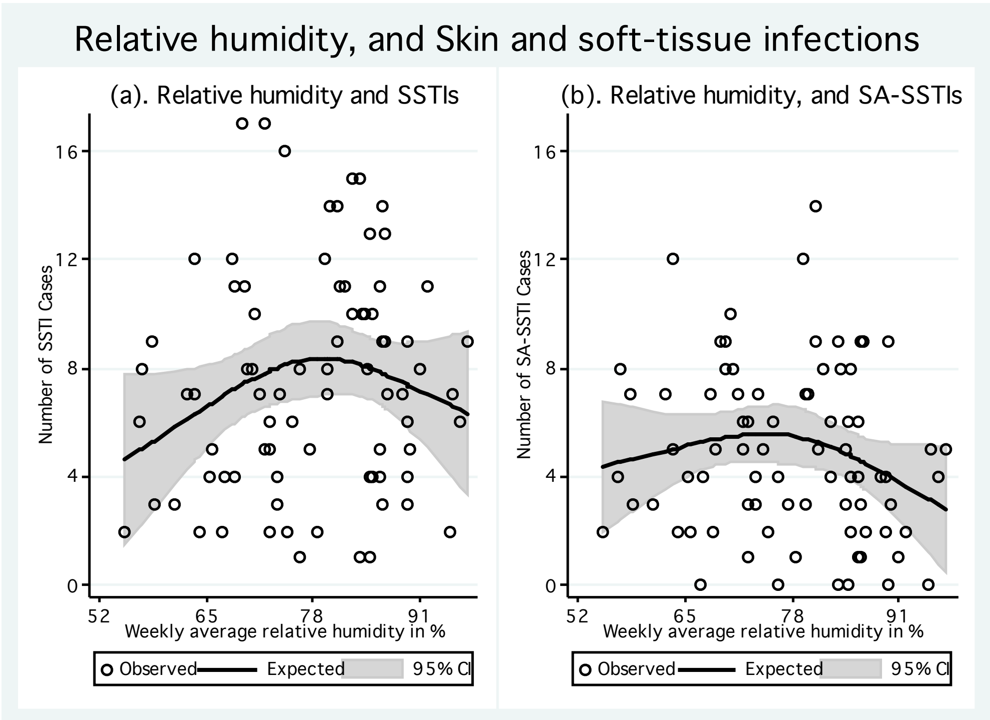

Figure 4.5: Relationships between skin and soft-tissue infections (SSTIs) and skin and soft-tissue infections caused by *S. aureus* (SA-SSTIs) with climatic factors (a). Weekly average relative humidity and SSTIs (b). Weekly average relative humidity and SA-SSTIs. The centre lines in the graphs show the estimated spline curve, and the upper and lower lines represent the 95% confidence limits

Climatic factors and MRSA infections

The association between MRSA infections and climatic factors such as maximum temperature, minimum temperature and relative humidity is given in Figures 4.6 to 4.8 respectively. The fitted regression model for the effect of temperature and relative humidity on the incidence of MRSA is presented in Table 4.5. A borderline significant negative relationship between MRSA and weekly average maximum temperature below 33°C (Coef. -0.42, P=0.066) was observed and the number of cases significantly increased when the weekly average maximum temperature was above 33°C (Coef. 0.57, P=0.044). No significant association between weekly average minimum temperature and MRSA was observed. It was also found that, there was no significant effect of weekly average relative humidity on number of MRSA infections up to a relative humidity of 78%. However, the number of MRSA cases significantly decreased when the relative humidity was above 78% (Coef. -0.18, P=0.012).

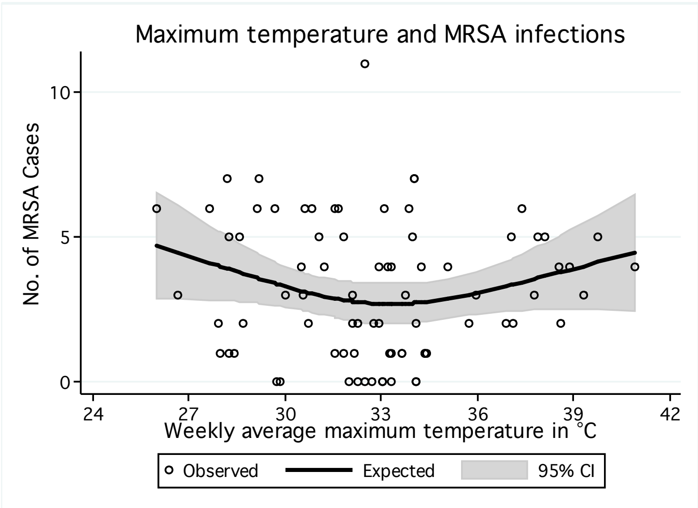

Figure 4.6: Relationships of MRSA with weekly average maximum temperature.
The centre line in the graph shows the estimated spline curve, and the upper and lower lines represent the 95% confidence limits

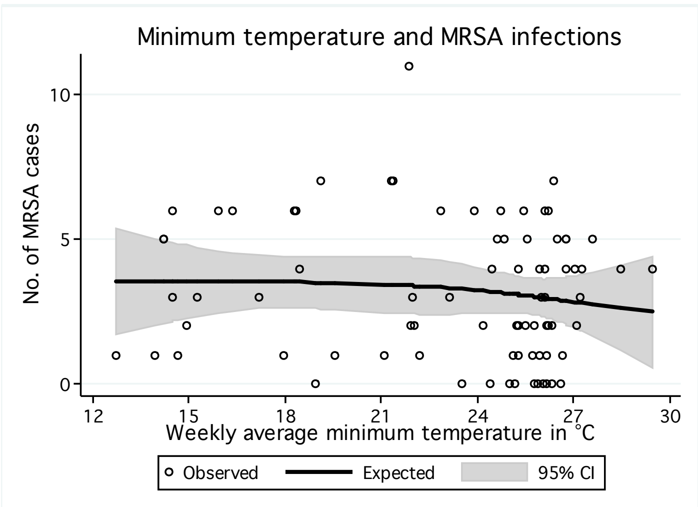

Figure 4.7: Relationships of MRSA with weekly average minimum temperature. The centre line in the graph shows the estimated spline curve, and the upper and lower lines represent the 95% confidence limits

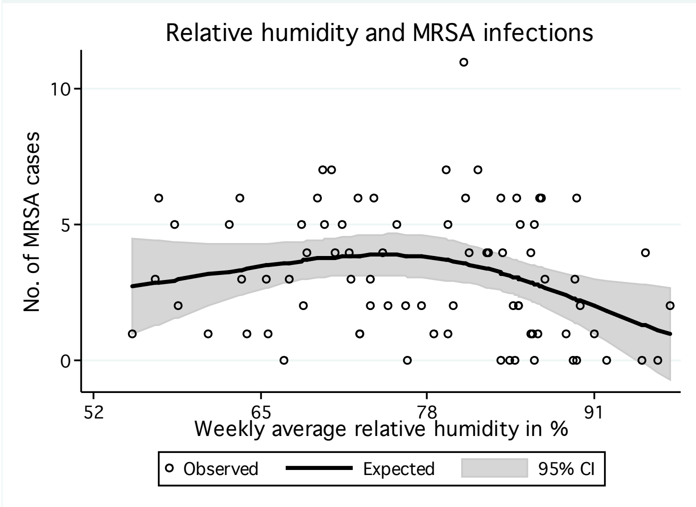

Figure 4.8: Relationship of MRSA with weekly average relative humidity. The centre line in the graph shows the estimated spline curve, and the upper and lower lines represent the 95% confidence limits

Table 4.5: Fitted regression model* for the effect of temperature and relative humidity on the incidence of the methicillin-resistant *Staphylococcus aureus* (MRSA)

Climatic factors	**Cut-off values**	**MRSA**	
(Weekly average)		Coefficient	P
Maximum temperature °C	Below 33 °C	-0.42	**0.066**
	Above 33 °C	0.57	**0.044**
Minimum temperature °C	Below 24 °C	0.03	0.895
	Above 24 °C	-0.11	0.718
Relative humidity in %,	Below 78%	0.10	**0.097**
	Above 78%	-0.18	**0.012**

* Regression models with Newey-West standard errors and coefficients estimated by ordinary least squares (OLS) regression, assuming a heteroskedastic error structure and a maximum lag 2.
** The cut-off values for temperature and relative humidity were chosen from the graphs of the cubic splines.
Negative sign in the coefficient indicates decreasing number of cases and positive sign indicates increasing number of cases. P-values less than 0.05 were considered as significant and P-values between 0.05 and 0.10 as 'borderline significance'.

5 DISCUSSION

5.1. KEY FINDINGS

The community members and healthcare professionals perceived an inter-relationship between environmental factors, infectious diseases and medicines, particularly in relation to antibiotic use and antibiotic resistance. According to them, although behavioural and social environmental factors are the major contributors to antibiotic resistance, natural and physical environmental factors are also associated with occurrence and prevalence of infectious diseases and antibiotic resistance (Papers I & II). Quantitative studies supported the perceptions of the participants involved in the qualitative studies. It was observed that antibiotic resistance pattern varied geographically; the overall prevalence of antibiotic resistance in *E. coli* isolated from children's stool, cow-dung and drinking water was higher in the non-coastal than the coastal environment (Paper III). Furthermore, seasonality in the incidence of SSTIs and MRSA was observed (Paper IV). Time series analysis of data collected in this context over 18 months revealed that average weekly maximum temperature above 33°C and minimum temperature above 24°C coinciding with relative humidity between 55% to 78% is a favourable combination for the occurrence of SSTIs, SA-SSTIs and MRSA infections; this combination of temperature and relative humidity is observed in Odisha during late summer (mid-April to mid-June), when peak incidence of SSTIs, SA-SSTIs and MRSA infections occurred during the study period (Paper IV).

5.1.1. Behavioural and Social Environmental Factors and Antibiotic Resistance

The views put forward by the participants suggest that behavioural and social environmental factors are the major contributors for the development of antibiotic resistance. There is variation in community members' knowledge of infectious diseases, antibiotic use and resistance. The major behavioural and social factors affecting antibiotic resistance seen were, behaviour of patients and professionals, as well as policy and regulatory issues. The participants suggested that antibiotic resistance can be prevented by reducing the need for antibiotic use.

Community members' knowledge of infectious diseases, antibiotic use and antibiotic resistance
Community members' knowledge of infectious diseases and antibiotics varied according to their education and social environment i.e. urbanisation of the community. The literate and urban members were more aware of infectious diseases and they had heard the term antibiotics. The participants were confident in the effectiveness and safety of antibiotic, but unfamiliar with their disadvantages and side effects. They believed that antibiotics were 'quick', 'effective', 'strong', 'safe' and a 'life saver' medicine, similar to the findings of a previous study on community perceptions in the United Kingdom [133]. However, in the present study (Paper I) participants were aware of side effects of antibiotics. The participants perceived that antibiotics were useful for the common cold, which indicates poor knowledge of the appropriate use of antibiotics, similar to other findings. The community members did

not understand the term antibiotic resistance and how resistance develops. However, they were aware of non-functioning of some medicines including antibiotics, for example penicillin. A previous study from India showed that community members perceived that if the same medicine is used repeatedly it might become ineffective after some time [134]. The participants in this study also viewed that use of antibiotics in farm animals may influence antibiotic resistance in humans [134]. According to Hawkings *et al.,* community members do not see bacterial resistance as a personal threat but something that occurs in hospitals [135]. Some community members (Paper I) also thought that excessive use of chemicals in cultivation and climate variability might be contributing factors to non-functioning of medicines.

Health system and policy factors influencing resistance

Three major health system and policy factors were seen as influencing antibiotic use and resistance development. These factors were patients, the health system and prescribers, and policy and regulatory issues. The participants viewed that non-compliance with medicine use, irrational prescription by trained prescribers and informal healthcare providers (quacks), as well as availability of fake and low quality medicines, and over-the-counter antibiotics, are all contributors to antibiotic resistance development. According to Heymann, behaviours such as excessive demand for antibiotics by the community and over- and under-prescription of antibiotics have a "remarkable impact" on selection and survival of resistant bacteria [11]. Siddiqi *et al.* from Pakistan - a neighbouring country with a similar situation - suggest that a combination of non-regulatory (by providing training and information) and regulatory (by implementation of policy) interventions, directed at healthcare providers and community members would be helpful for rational prescription of medicines [136].

Patients: In the current study**,** participants perceived that at a patient or consumer level, socioeconomic and behavioural factors (poverty and self-medication) and non-compliance with medicine usage guidance result in inappropriate use of antibiotics and subsequent development of resistance. These finding are consistent with the results of other studies from low- and middle-income countries [40, 137-140]. It is a common observation from many countries that persons discontinue antibiotics, i.e. do not complete the course if they feel symptomatic relief [39, 133, 140, 141]. According to Le *et al.* the factors influencing self-medication are: perception of illness, waiting time, attitudes of public health medical staff, lack of healthcare facility, and poor control of prescribed medicine in the market [141]. A previous study in Nagpur, India [142] found that poverty is the major driving force for self-medication with antibiotics among community members. A previous study in Vietnam also found a significant association between family socioeconomic conditions and medicine use [140]. Self-medication is the selection and use of medicines by individuals to treat self-recognised illness. Those who self-medicate might think that if a doctor has previously recommended a particular medicine for a similar complaint in the past, it is not necessary to get a new prescription and thus pay a consultation fee [142]. A study from the UK found non-compliant behaviour of a community towards antibiotic use to be one of the major determinants for development of resistance [133]. Odisha is socioeconomically more disadvantaged in comparison to other Indian states; the findings of the thesis suggest that poverty is the major driving-force for use of leftover medicines, self-medication with antibiotics and incomplete courses. A comparative study from 11 European countries shows that lack of awareness and an attitude towards situational use of antibiotics are contributors for irrational use of antibiotics [143].

Health system and prescribers: The community members viewed that irrational prescriptions by trained prescribers and informal healthcare providers are responsible for non-functioning of medicines. According to healthcare professionals overcrowding of patients, inadequate prescription, overprescribing and improper selection of antibiotics are the major reasons behind resistance development. Previous studies from India by Basu *et al.* [144] and Patel *et al.* [145] show similar findings.

The healthcare professionals viewed that improper diagnosis and inadequate prescription due to a lack of infrastructure and irrational prescription by unauthorised practitioners are also responsible for resistance development. This finding is similar to the findings of Kumar *et al.* in India [146]. According to Kumar *et al.*, healthcare facilities with better infrastructure and prescribers with higher education and specialisation are associated with low antibiotic prescription [146]. Education regarding antibiotic prescribing and resistance at undergraduate and graduate education level is likely to enhance the quality of antibiotic prescribing [147]. The healthcare professionals also felt a need for information and awareness of what constitutes prudent use of antibiotics should be given to practitioners routinely. They further suggested monitoring of resistance patterns at local level and making the data available to local prescribers so that unnecessary antibiotic use will be reduced and hence resistance development will be minimised. The above findings are similar to other studies from low- and middle-income countries [39, 60].

Antibiotic susceptibility testing is difficult in most areas in Odisha. Often, treatment is based solely on symptoms and suspected bacterial infections. Lack of diagnostic facilities or improper diagnoses indirectly promote the prescription of unnecessary antibiotics.

Policy and regulatory issues: In India, state governments have adopted central government guidelines on policies and programmes for healthcare development, and Odisha adopted a policy on rational drug use in 1997 [148]. In 2011, the Government of India came out with a policy for management of antibiotic resistance to rationalise the usage of antibiotics [92].

In principle, the registered allopathic doctors and veterinarians should prescribe antibiotics for humans and animals respectively, the drug dispensers should dispense antibiotics on prescription, and the Ayurvedic and Homoeopathic providers should prescribe medicines from their own system. However, in practice, in Odisha, allopathic medicines, including antibiotics, are prescribed by some of the Ayurvedic and Homoeopathic providers, drug dispensers and informal healthcare providers (quacks), due to an increase in demand of allopathic medicines and lack of adequate numbers of registered allopathic doctors.

For this reason, participants in the qualitative studies of this thesis reported availability of antibiotics without authorised prescription. In addition to this, there is also a problem of increased availability of fake or substandard medicines in Odisha. This has arisen due to ineffective law enforcement. Similar findings are also obtained from previous studies in India and other countries [142, 149, 150]. The enforcement of the law-forbidding sale of antibiotics without prescription from a qualified allopathic prescriber would probably be helpful for rational use of antibiotics. In India, antibiotics are notified drugs to be dispensed only on the prescription of a registered medical practitioner and the prescription has to be effected only by or under the personal supervision of a registered pharmacist [92]. However, in India there is a need for policy to make the practical implementation of these regulations feasible. A previous study from nine African countries by Viberg *et al.* suggests that, since most people purchase medicines from drug dispensers due to lack of healthcare facilities, educating drug dispensers about rational use of antibiotics would probably be beneficial for public health in low- and middle-income countries [151]. Education for all types of formal and informal healthcare providers is needed in India as they continue to prescribe antibiotics.

According to the WHO, informal health workers are persons who have no formal training in healthcare. However, in some cases they might receive guidance from professional healthcare providers [152]. In remote areas where there is lack of formal healthcare facilities, the informal health worker is the first and most important point of call by people in search of health services. The informal health workers, those who are not breaking any regulations of the health system, are more popular in some settings and they should be acknowledged, encouraged and supported [152]. However, the regulation and supervision of informal health workers is important due to their inappropriate and irrational prescription [153]. When formal health workers operate outside the rules of the health system they are considered as informal health workers [152]. In India, the informal health care providers are untrained providers (they do not have any formal training or education in medicine). Due to lack of trained healthcare prescribers, they are providing healthcare and also prescribing antibiotics irrationally. Both community members and healthcare professionals suggest, that although the informal healthcare providers are prescribing irrational treatment, they serve patients in remote areas, where the availability of trained prescribers is virtually non-existent. Training them might thus benefit public health.

Prevention of antibiotic resistance

The participants viewed that overcrowding in urban areas and unhygienic surroundings due to poor sanitation practices like open-air defecation in rural areas are responsible for occurrence of some of the infectious diseases. They suggested that domestic and personal hygiene is essential for community members in order to prevent infections and reduce antibiotic use, as has previously been documented [11, 32, 154]. The community members also perceived that the choice of herbal treatment, as an alternative to antibiotics for non-severe infections (such as the common cold), might help reduce antibiotic use and thereby help prevent resistance. The community members believed that regular practice of yoga and pranayam can help in strengthening immunity and thus can help in fighting diseases, which has also been mentioned in a review by Arora and Bhattacharjee [155]. The participants also suggested the need for orientation programmes on rational use of antibiotics for trained and untrained prescribers, and community members.

5.1.2. Natural Environmental Factors and Antibiotic Resistance

The participants perceived that infectious diseases, antibiotic use and antibiotic resistance are associated with geographical location. The quantitative finding also shows geographical variation in antibiotic resistance patterns in all the sample sources such as stool, cow-dung and drinking water. According to Marra *et al.,* the use of antibiotics is associated with climatic conditions of particular settings [156]. Geographical variation in infectious diseases and antibiotic resistance is also documented in previous studies [157-159].

A high prevalence of resistance was found in all the sample sources (Paper III). Among *E. coli* isolates from children's faecal flora, it was observed that there was 92% resistance to at least one of the tested antibiotics and there was 24% multi-resistance. A previous study in Tamil Nadu, India, carried out in 2005 on *E. coli* from healthy children's stools, found 63% resistance to at least one antibiotic and 32% multi-resistance [160]. A study in Greece conducted in 1998, reported that 40% of healthy children carried resistant *E. coli* [161]. A high prevalence of resistance in commensal *E. coli* among children was also found in Vietnam [162]. According to Kalter *et al.,* environmental contamination with resistant bacteria significantly contributes to carriage of antibiotic resistance in *E. coli* among healthy children in Peru [163]. Among the *E. coli* isolates from cow-dung, 19% were found to be multi-resistant, although participants informed that only 5% of cows had been given antibiotic treatment (Paper III). Veterinary use of antibiotics results in antibiotic resistance in commensal *E. coli* isolates from farm cattle faeces [164]. A previous study in Pennsylvania, United States, found 40% multidrug-resistance among *E. coli* isolates from cow-dung from healthy lactating cows [165]. It was found that 24% of *E. coli* isolated from drinking water was multi-resistant (Paper III). On the Indian sub-continent, a previous study from Tamil Nadu, India found *E. coli* from eight out of nine drinking water samples to be resistant to at least one tested antibiotic [160] and a study from Hyderabad, Pakistan, found 63% multi-resistance in *E. coli* isolates from drinking water [166]. The emerging pathogens in drinking water is a growing problem [167] and antibiotic resistant bacteria have been documented in the aquatic environment [41]. In countries like India, where water sources are prone to easy contamination due to unhygienic sanitary practices, detection of bacteria, pathogenic and/or resistant bacteria in water can be common.

Antibiotics and antibiotic resistant bacteria are found in soil as well as the aquatic environment [104]. Antibiotic resistant *E. coli* from human and animal sources are also found [168]. The selection of resistant bacteria at very low antibiotic concentrations has also been reported [107]. A previous study in Virginia, USA, showed that faecal pollution in rural water is a source of resistant bacteria in the natural environment [169]. As 80% of households in the present study did not have adequate sanitation facilities, they followed open-air defecation practice, which might spread antibiotic residuals and resistant bacteria in the grassland and aquatic environments, from which run-off water can carry it to water sources.

There are various ways by which antibiotics or resistant bacteria impact humans. It may be through contaminated food, whereby the bacteria might transfer resistance determinants to other bacteria in the human gut by horizontal gene transfer [101, 105, 106]. Antibiotic residues in food products or water may also allow the selection of antibiotic-resistant bacteria after food or water consumption [170]. Through faecal contamination, resistant bacteria might flow from the gut of humans and animals into soil or terrain and water. Therefore, there might be an interaction between *E. coli* from the natural environment (soil or terrain and water) and humans and animals. As most cows generally graze in open fields and drink water from open water sources like ponds, rivulets and stagnant water, it is possible that this might be one of the reasons for development of resistant *E. coli* detected in cow-dung. The high prevalence of resistance obtained in household drinking water may also be through such a route.

In the qualitative study (Paper II), participants perceived that the prevalence of resistance is higher in the coastal compared to the non-coastal environment. The quantitative findings however, showed a higher prevalence of resistance in the non-coastal environment. This apparent contradiction in findings becomes clearer when it is understood that all the participants perceived a higher consumption of antibiotics, owing to a higher infection rate due to over-crowding in the coastal areas, leading to increased antibiotic resistance. In reality however, infection rates were higher in the non-coastal areas.

A higher prevalence of antibiotic resistance was found in *E. coli* isolates from community and environmental sources i.e. children's stools, cow-dung and drinking water, in the non-coastal region compared to the coastal region (Paper III). This regional difference in antibiotic resistance could have resulted from different local co-selective events, dissimilar antibiotic pressure and independent clonal spread in each region [158]. The non-coastal setting in the study reported in Paper III can be characterised mainly as rural, tribal, woodland, with lower literacy rates and which is less developed compared to the coastal setting. Diverse findings have been reported in this context. Previous studies from Tamil Nadu, India [160] and from South Africa [171] found that prevalence of antibiotic resistance among commensal bacteria was higher in a rural population compared to an urban population. By contrast, a study among adults from eight developing countries found that the prevalence of antibiotic resistance in faecal *E. coli* was more common in urban than in rural areas [172]. Parveen *et al.* found that *E. coli* isolates from point sources (industrial and municipal effluents) have higher resistance as compared to non-point sources (land run-off and septic tank seepage) [173].

A significantly higher resistance to tetracycline and quinolones was found in cow-dung and drinking water in the non-coastal compared to the coastal environment. Tetracycline and quinolones have lower degradation rates (half-life more than 100 days in the nature) and high affinity properties [42, 174]. Both are commonly prescribed antibiotics in humans as well as animals [164]. It might be possible that residues of these antibiotics stay in the environment for longer periods in non-coastal regions in comparison to coastal, as in coastal areas there is a greater chance of flow of antibiotic residues into the sea. This may be another reason for the observed higher resistance in the non-coastal than coastal environment.

5.1.3. Physical Environmental Factors and Antibiotic Resistance

Climate variability and health consequences

The participants (Paper I) perceived an irregularity in seasons. They also perceived that, over the years, there has been an increase in average temperature, excessive heat in the summer, inconsistency in rain patterns and comparatively warmer winters with occasional severe cold for very short periods, similar to the findings of community perceptions of climate change and human health reported by Haque *et al.* from Bangladesh [175]. In their study, more than 95% of participants reported that there is an increase in heat during the summers, 80% reported decrease in rainfall and 60% reported warmer winter with an exception of severe cold for about 5-7 days [175]. For this thesis, 29 years of local climate records for Bhubaneswar were analysed, with focus on temperature and relative humidity. It was found that, over the three decades, there was a projected increasing trend in local average maximum temperature and a decreasing trend in average minimum temperature, gradual widening the gap between maximum temperature and minimum temperature over the decades. Whether there were changes in the humidity and rain pattern could not be studied during the period of this thesis. However, information obtained from the analysis supports the community members' perceptions of occurrence of changes in local weather or climate (Paper I).

The participants viewed that changes in the climate had health consequences. The perceptions varied according to the education of the individuals and the educated members were more aware of climate variability and its health consequences (Paper I). However, a study in the USA found that views on climate and health consequences differ according to the income level rather than educational level [176]. The participants were concerned about both the direct and indirect impact of climatic variations on health. According to them, the direct impact includes, lives lost due to extreme weather events such as heat waves, floods and cyclones. The indirect impact includes increase in acute diarrhoeal disorders, vector-borne diseases and malnutrition. The findings are similar to the studies of public perceptions of climate change from Africa, the USA and Europe [177-179]. The participants perceived that climate variability causes inconsistency in rain patterns, drought, floods and ground water depletions, which leads to health consequences. The scarcity of water during summer and excess water due to floods in the rainy season, results in unhygienic surroundings and an increase in infectious diseases. The relationship between drinking water contamination and infectious diseases is well documented [167, 180, 181]. The participants suggested the need for good quality water supply.

Inter-relationship between climate, infectious diseases and medicines

The inter-relationship between the climatic factors, health, infectious diseases and medicine use is complex, which brings new challenges to epidemiology [182]. There are a few empirical studies on the inter-relationship between climate, infectious diseases, and antibiotic use and resistance. This thesis has attempted to explore the perceptions of community members and healthcare professionals on the issue.

The community members perceived that climate variability is changing the life cycle of vectors, which might increase the burden of infectious diseases. They had noticed re-emergence and outbreaks of chickenpox and chikungunya infections and they viewed that this might be due to climate variability. It is documented that the change in climate is increasing the water-borne and vector-borne infectious disease burden [20, 124, 183].

It was perceived that the climate variability results in spread of infectious diseases and increased use of medicines, which might result in development of antibiotic resistance. A previous study in Spain has reported the relationship between social and climatic factors and antibiotic resistance [184]. The healthcare professionals in our study perceived that seasonal changes in weather conditions, such as temperature, precipitation and humidity were responsible for the emergence and the re-emergence of diseases, which in turn influenced antibiotic consumption (Paper II). The seasonality of antibiotic prescriptions has also been documented in India [185].

Improving monitoring and surveillance of infectious diseases is essential in Odisha [28]. Presently, Integrated Disease Surveillance Program (IDSP) under National Rural Health Mission (NRHM) is functioning from the year 2004 and is strengthening surveillance of various infectious diseases in the state [186]. However, there is need for integration of infectious diseases data with climatic records, to understand the impact of climate on occurrence of infectious diseases.

Climatic factors, skin and soft-tissue infections and MRSA

It was observed that the maximum temperature above 33°C and the minimum temperature above 24°C, coinciding with the relative humidity 55% to 78%, is a favourable combination for the occurrence of SSTIs, SA-SSTIs and MRSA infections (Paper IV). This combination of temperature and relative humidity is observed especially during mid-April to mid-June (late summer). A seasonality in the incidence of SSTIs has been observed and the finding is consistent with previous findings from India and elsewhere [111]. It was found that there are a greater number of SSTI cases in the time period between late summer to early monsoon. Previous studies from New Delhi [187] and Varanasi [188] in India have found that at high atmospheric temperature and relative humidity bacterial skin infections are more abundant, which happens from mid-April to mid-August (late summer and early monsoon) in most parts of India. A previous study from Pondicherry, India also found higher rates of SSTIs during the summer [189]. The findings are consistent with other studies [190-192]. However, a previous study among hospitalised patients in Maryland, USA, did not find seasonality in the incidence of *S. aureus* infection, but they found a peak in the incidence of Gram-negative bacterial infection during summer [193].

Presently, MRSA is a growing problem worldwide [64] and also in India [194-196]. In the present study it was found that 65% of SA-SSTIs were caused by MRSA. Previous studies from India, e.g. a study in a tertiary care rural hospital in central India, found that 51.8% of hospital-acquired infections were MRSA positive [79]. Although MRSA prevalence was high, no resistance to vancomycin was found. This finding is similar to other studies from India [69, 194]. It was observed that the incidence of MRSA infections was high during late summer. The previous studies from Iowa [197] and Georgia [198], USA also observed peak incidence of MRSA infections during the summer.

There is a complex relationship between environmental factors and bacterial growth. Survival and growth of *S. aureus* outside a host depends on physical environmental factors such as temperature, humidity, exposure to sunlight, pH and salinity [126]. According to Taplin *et al.,* the colonisation of *S. aureus* increases with hydration of the stratum corneum of the skin [113], and the process of hydration peaks when both atmospheric temperature and relative humidity are high [111]. *S. aureus* require salty and humid conditions for best growth (Mannitol-salt agar is a selective medium for in vitro growth). The combination of high temperature and humidity is essential for sweat production in the body [111].

It was found that the combination of a maximum temperature above 33 °C, a minimum temperature above 24°C and relative humidity about 55% to 78% increases the occurrence of SSTIs, SA-SSTIs and MRSA infections. This combination of maximum temperature (33-40°C), minimum temperature (25-29°C) and relative humidity (64-81%) is only observed from mid-April to mid-June (late summer). Therefore, the colonisation of *S. aureus* in the skin is higher during the late summer. Usually, during winter, the atmospheric temperature is below 33°C and in the rainy season relative humidity was above 78% in Bhubaneswar. These are not suitable environmental conditions for colonisation of *S. aureus,* therefore, the occurrence of SA-SSTIs and MRSA infections are comparatively less during the winter. Along with the hot and humid weather conditions, poor socioeconomic status, overcrowding and poor skin hygiene are also responsible for SSTIs in tropical settings [112]. Similar findings have been demonstrated previously from India [187, 189]. The association of behavioural and social environmental factors was not looked at in the present study, as the intention was to focus on physical environmental factors. However, it was believed that results obtained by the present study may be due to socioeconomic environmental factors.

5.1.4. Dilemma of Desegregating the Influence of Various Environmental Components

In isolation as well as together, all the environmental components influence on human health as well as various facets of human life. It is not easy to differentiate the impact of each component, as most of the times they co-exist making it difficult to desegregate their effect. The geographical variation in antibiotic resistance – higher resistance in the non-coastal than in the coastal area found (Paper III) is an example. In general, higher antibiotic consumption is associated with incidence of higher resistance. According to Marra *et al*. higher antibiotic consumption was associated with a higher proportion of Aboriginals population and lower level of education in British Columbia [156]. In India a previous study has also noted a higher rate of antibiotic prescribing in rural areas than urban areas [146]. The healthcare professionals (Paper II) informed that in the non-coastal region of Malkangiri, which is tribal, less literate and relatively more economically disadvantaged, there is a lack of registered allopathic doctors, hence informal healthcare providers and some of the homeopathic and ayurvedic (Indian system of medicine) healthcare providers commonly prescribe antibiotic treatment. In the coastal region the healthcare facilities are better and there is availability of higher numbers of trained allopathic doctors. The trained healthcare providers could be expected to have comparatively more rational prescribing than the untrained prescribers. So besides the impact of varying geographical conditions, the above factors might also have contributed to the high antibiotic resistance found the in the non-coastal area as compared to the coastal area.

A previous study in tropical South America found that heavy use of chloroquine to treat malaria was a likely factor for selection of ciprofloxacin resistance in *E. coli* [199]. This might also explain for the relatively higher quinolone resistance observed in Malkangiri (non-coastal), as chloroquine has been commonly used medicine due to endemic malaria in this region.

Along with the hot and humid weather conditions, poor socioeconomic status, overcrowding and poor skin hygiene have also been found to be associated with occurrence of SSTIs in tropical settings [112], including India [187, 189]. Such conditions could exist in any setting and put a dilemma as to what is their contribution together and independently.

5.2. METHODOLOGICAL CONSIDERATIONS

The study outline of epidemiological research is as follows: the study is designed, a pilot study is conducted to validate the design or determine the feasibility of the study, and finally, the study is carried out. During the study some unexpected problems may arise, which may bring about limitations on the study. However, some of the problems may be overcome with a robust study design, a major strength of any study.

5.2.1. Trustworthiness (Papers I & II)

Credibility
Credibility refers to the quality of being believable or trustworthy in selection of context, participants and approach to gathering data in relation to the focus of the study [129]. To improve the credibility of the findings, triangulation, peer debriefing and member checks were followed.

Triangulation of data sources, methods, investigators and analysis were used to improve trustworthiness of the study. Both FGDs and interviews were used for data collection. In Paper I, information was collected from various groups of community members, i.e. different sex, age, occupation, socioeconomic status, education and urbanisation levels. In paper II, data were collected from different healthcare professionals including, allopathic doctors, veterinarians and drug dispensers. The informants were from different geographical areas and socioeconomic environments, in this case, coastal or non-coastal areas and urban or rural environments. As the study associates (supervisor and co-supervisors) have different educational backgrounds and are from different countries and cultural settings, the findings were interpreted with both insider and outsider perspectives. The recorded versions, Oriya and English transcripts of data were consulted time and again during coding procedure to avoid misinterpretation of the full meaning of the texts. Both manifest and latent content analysis were used during analysis.

To avoid misinterpretation of the results, the transcripts were checked against both the Odia transcripts and recorded versions by an independent researcher with a background in infection biology and had a command over the Odia language. Cross-checking methods were followed during analysis of transcripts. Formal member check was not done but informal discussions with the study participants (on a revisit after finishing the analysis) suggest that they agreed with our interpretation.

Dependability and confirmability
To exclude bias arising from the researchers' pre-understanding and experiences, open-ended questions were used during data collection. The investigators were from different educational backgrounds and countries, and each one brought a unique perspective to the study, enhancing its conformability. In the analyses, this factor served to broaden the interpretation and the final result is a negotiated outcome. The open-ended nature of the questions also resulted in generating 'thick descriptions' on which the interpretations could be soundly based.

Having been brought-up in the same area, I also have a prolonged engagement with the place and its people and am familiar with the overall social context of the study setting. Moreover, my background in biological and environmental sciences, and social work, together with my knowledge of the local language, has enabled me to gain the trust of the community.

5.2.2. Validity and Reliability (Papers III & IV)

Strengths: To improve the internal validity of the studies, the data collection instruments were developed in consultation with relevant professionals and were carefully field-tested before use. A pilot study was conducted before the main study. All the microbiological analyses were performed in accredited laboratories using standard laboratory methods using CLSI guidelines. All of the entered data were checked against questionnaires and microbiological reports. The main strength of Paper III is that it isolated and compared *E. coli* obtained from three different sources (children's stool, cow-dung and drinking water) from the same household in two contrasting natural environments. Similarly, for Paper IV, data were collected for 79 weeks, which is higher than the minimum 50 data points required for time-series analysis.

Limitations: The limitation for Paper III was that we tested only one isolate per sample. However, in the pilot study, when we tested five isolates per sample, we obtained almost identical resistance patterns for all isolates from the same sample. Thus, due to funding limitations, it was decided to include only one isolate per sample in the main study. For paper IV, the sample size was small, as data were collected only from one centre and we also had limited number of observations during certain weeks. This could have led to missing out on particular trends. The molecular method (test for the *mecA* gene) for MRSA confirmation was not performed; instead a cefoxitin disk-screen test was used.

5.2.3. Generalisability and Transferability

The findings of the qualitative studies can be theoretically generalised to similar settings, both in Odissa and elsewhere. Most of the social and behavioural factors studied are common for India, hence are applicable to several Indian settings too. Thus, any guidelines developed regarding the prescription and sale of antibiotics based on these studies will benefit most of India, not just the study setting. Moreover, in both qualitative studies, we have provided a thick description of the socio-cultural context; selection and characteristics of participants; data collection; and process of analysis to enable the reader to make an informed choice about transferability to other contexts [129, 200]. The quantitative studies however, are generalisable to only the study population. The findings of Paper III may be applicable to similar other settings in India and elsewhere having coastal and non-coastal areas with similar environmental components like Odisha. The findings of Paper IV, while generalisable to the study setting, may be applicable to any tropical environment having similar climatic features like Bhubaneswar.

6 CONCLUSIONS

This thesis highlights the perceptions of the community regarding the contributors for antibiotic resistance development like behavioural, social, natural and physical environmental factors. It specifically demonstrates the influence of the natural and physical environmental factors, like geography and climate, in the development of antibiotic resistance. Thus, it gives credence to the perception through a reality check. Finally, it also underlines the need for awareness and implementation of legislation to prevent resistance development.

The key conclusions of this thesis are:

- Community members as well as health care providers perceived an inter-relationship between environmental factors, infectious diseases, and antibiotics use and resistance. Community members' knowledge and perceptions varied according to their social environment and individual education.

- Behavioural and social environmental factors like patients' non-compliance with antibiotic use, irrational prescription by informal as well as trained healthcare providers and over-the-counter availability of antibiotics were seen as the major contributors to resistance development.

- There is lack of information and awareness about prudent use of antibiotics. There is a need for information, education, dissemination and proper implementation and enforcement of legislation at all levels of the drug delivery and disposal system in order to improve antibiotic use and to prevent pharmaceutical contamination of the environment.

- The prevalence of antibiotic resistance in *E. coli* isolated from both community and environmental sources was higher in the non-coastal than the coastal environment.

- Climatic factors have influence on skin and soft-tissue infections and resistant bacteria, i.e. methicillin-resistant *S aureus.*

7 IMPLICATIONS

The findings obtained from this study suggest the following recommendations and points for further research:

- The community members mentioned the need for the proper use of antibiotics. They also admitted their lack of knowledge about prudent use of antibiotics. This suggests the need for the development of a strategy or action plan for creating awareness about prudent use of antibiotics. There is also a need for education and awareness campaigns among community members on hygiene practices and other measures to minimise spread of infections and thus unnecessary use of antibiotics.

- The healthcare professionals admitted that knowingly or unknowingly they do not prescribe antibiotics rationally either due to demand from patient or as they suspect infection. This suggests that the awareness about antibiotic resistance among healthcare professional is essential. Present results also recommend that a policy is needed to update the knowledge of registered medical practitioners regarding antibiotic use and resistance at regular intervals. There is also a need for availability of laboratories for susceptibility testing in rural settings.

- The participants in this study informed that unauthorised practitioners such as 'quacks' serve patients in remote areas, indicating a lack of well-educated trained healthcare staff in remote areas. Therefore, there is a need to provide supportive training and orientation for 'quacks' on appropriate treatment, since they are the only people providing health services in remote areas where there is lack of trained healthcare providers. However, there is also need for laws to restrict 'quacks' to only carry out primary treatment or first aid, followed by referral to local trained prescribers.

- The findings showed a difference in antibiotic resistance in bacteria from water, stool and cow-dung collected from two different geographical regions; coastal and non-coastal. Further research is needed to find out the reasons for geographical variation in antibiotic resistance to know the actual factors responsible for antibiotic resistance and actions to eliminate those factors.

- It was also observed from the climatic records of Bhubaneswar meteorological centre that, over the decades, there is a trend for increase in ambient air temperature, which the participants in qualitative studies perceived as cause of health consequences and infectious diseases. As a significant association between climatic factors and skin and soft-tissue infections was observed, it may be proposed that studies may be undertaken to explore the relationship between other infectious diseases and climatic factors.

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APPENDICES

APPENDIX I

Interview/discussion guide, showing the introductory questions for each area of discussion for Paper I.

- Introductory questions
- What do you understand by infectious diseases?
- What is your view on change in climate/weather?
- What do you think of impact of change in environment or change in climate on infectious diseases?
- Where and how do you take medicine/treatment?
- Do you know what an antibiotic is? Can you describe more about it?
- What is your view on nonfunctioning of some medicines? Have you heard of antibiotic resistance?
- Do you have any idea about how resistance problems can be controlled?

APPENDIX II

Interview guide including introductory questions and probing areas Paper II

1. What are the common indications of antibiotic prescribing/dispensing and factors influencing these?
   - Common infectious diseases, antibiotics prescription and prior treatments.
2. What is your view on antibiotic resistance?
   - Possible causes, drug quality, human and nonhuman use of antibiotics and their impact.
3. What is your view on environmental issues of antibiotics?
   - Antibiotic use and resistance development in relation to the environment, disposal of pharmaceutical waste and its impact.

APPENDIX III

Paper III Questionnaire

Collection date (dd/mm/yy)……………….................................
Name of the village……………………………………………………………………
I. Socio-economic information of the household
A. Head of the family …………………………………..
B. Education of the head of family 1. Profession/Honors ☐ 2.Graduate/Postgraduate ☐ 3. Intermediate/diploma 4. High school ☐ 5. Middle school ☐ 6. Primary school ☐ 7. Illiterate ☐
C. Occupation of the head 1. Profession ☐ 2. Semi-Profession ☐ 3. Clerical, Shop-owner, farmer ☐ 4. Skilled worker 5. Semi-skilled worker ☐ 6. Unskilled worker ☐ 7. Unemployed ☐
D. Family income per month (in Rs) 1. More or equal 19575/ ☐ 2. 9788/ to 19574/ ☐ 3. 7323/ to 9787/ ☐ 4. 4894/ to 7322/ ☐ 5. 2936/ to 4893/ ☐ 6. 980/ to 2935/ ☐ 7. Less or equal to 979/ ☐
Socioeconomic status: …+…+…=…… (………………………….)
E. Total no of family members……………………….
F. Total no of house…………….
G. Distance between cattle-shed and kitchen………….meters
H. Distance between cattle-shed and bedroom………meters
I. Sources of drinking water 1. Tube-well ☐ 2. Well ☐ 3. Supply water ☐ 4. Pond ☐ 5. Supply water and tube well ☐ 6. Tube well and well ☐ 7. All of the above ☐
J. Defecation practice of family members 1. Latrine ☐ 2. Open air ☐ 3. Both ☐

II. Information on participating child
K. Age………………………………………..
L. Sex 1. Male ☐ 2. Female ☐
M. Defecation practice of the particular child 1. Latrine ☐ 2. Open air ☐ 3. Both ☐

III. History of antibiotic treatment of child
N. Does the child had taken any antibiotics last one year 1. Yes ☐ 2. No ☐ 3. Not known ☐
O. If yes, any antibiotics treatment in the last two weeks 1. Yes ☐ 2. No ☐
P. Name of the antibiotics previously taken. 1. Known ☐ 2. Not known ☐
Q. If known name of the antibiotics taken…………………………………………
R. Duration of the treatment……………….in days

IV. History of antibiotic treatment of cow
S. Have you given any antibiotics treatment to your cow during last one year
1. Yes ☐ 2. No ☐ 3. Not known ☐
T. If yes, any antibiotics treatment in the last two weeks 1. Yes ☐ 2. No ☐
U. Name of the antibiotics previously received 1. Known ☐ 2. Not known ☐
V. If known name of the antibiotics received………………………………………..
W. Duration of the treatment……………….in days

V. Sample Code No.

[A (1.Malkangiri 2.Puri), B (Village 01 to 15), C (Sample type 1.Fecal 2.Cow dung 3.Water), D (Family or household 01to 20)]

FECAL					
A	B		C	D	
			1		

COW DUNG					
A	B		C	D	
			2		

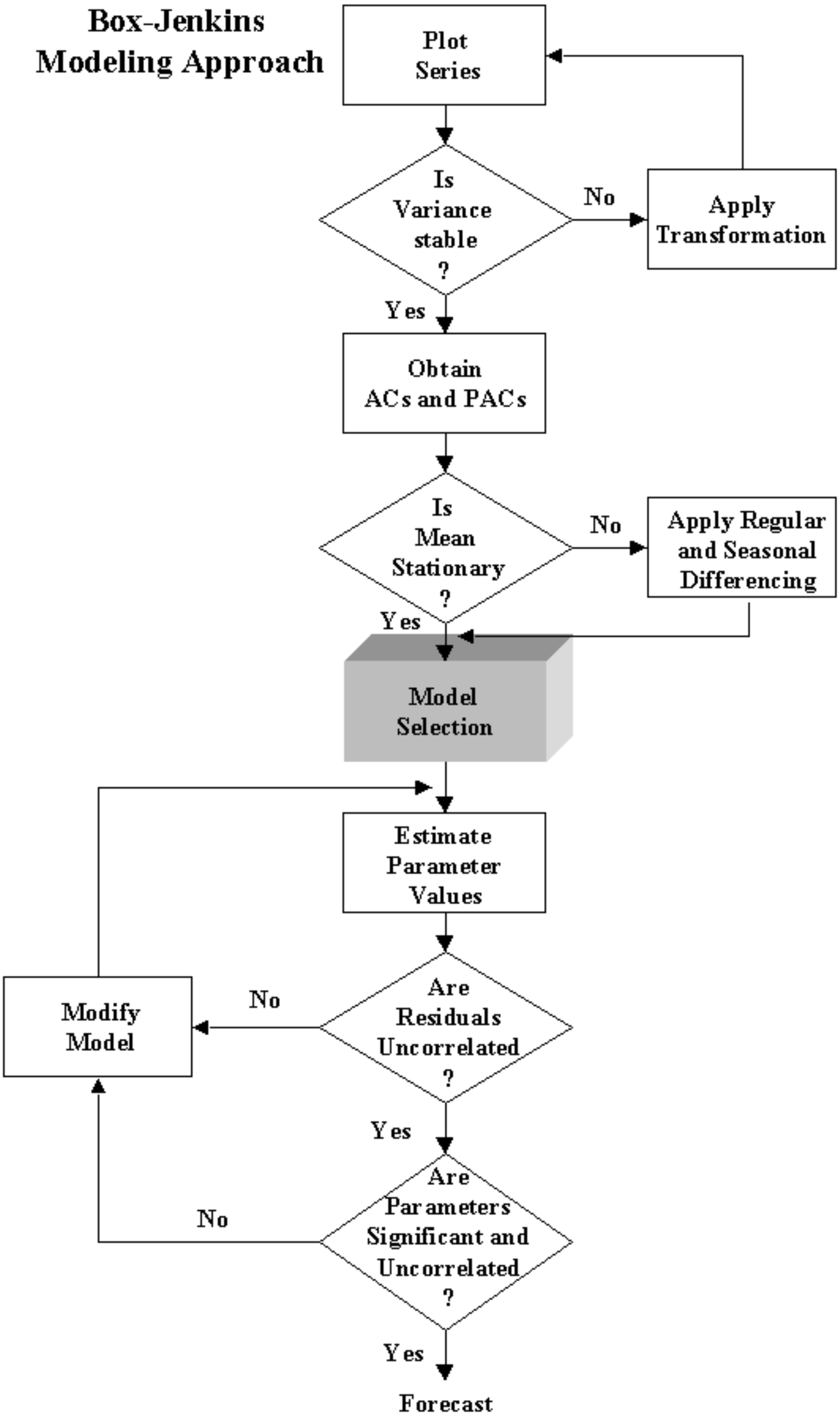
Water Source			
Tube well	Well	Supply water	Pond

WATER					
A	B		C	D	
			3		

Consent: The information provided by the interviewee will keep confidential. The interviewee may not answer a question at his/her discretion; the answer is then ‘no comment’. I have agreed to interview and for giving sample.

Signature of interviewee Signature of Interviewer

APPENDIX IV



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