Multi-Drug Resistant Pathogens of Pneumonia: Our Stance

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Declaration

It is here by declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
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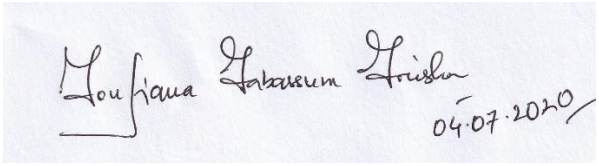

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Approval

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

As one of the preeminent causes of death, pneumonia is causing more harm than anticipated. Especially, the accompanying horror of antibiotic resistance is adding up into the pile of misery and the emergence of multidrug resistance, the evolution of all drug resistant ‘superbug’ is the final nail in the coffin. Here, in this review, the recent scenarios of multidrug resistance of pneumonia pathogens have been discussed about. Also, analysis of the articles related to the topic has been done along with thorough assessment of the local data collected which ultimately provided us with some solutions that will aid to explore future paths.

Keywords:

Pneumonia; Microorganisms; Resistance; Multidrug Resistance; Mechanism

Dedication

Dedicated to my parents and my respected supervisor

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This research would not have been possible without the help of numerous individuals who are gratefully acknowledged here.

As a matter of first importance, I would like to offer my most profound thanks and immense gratitude toward my research supervisor Dr. Md Abul Kalam Azad for his unwavering support and insight. From introducing me to the topic to guiding me write the thesis paper, his continuous guidance has helped me a lot in my quest and inspired me to evolve as a researcher. Also, his dynamism, vision and sincerity has deeply motivated me in every steps. It was a great privilege and honor to study and work under his guidance. No amount of words put together will be enough to express how grateful I am for his encouragement and supervision.

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ARTI	Acute Respiratory Tract Infection
CAP	Community Acquired Pneumonia
HAP	Hospital Acquired/ Healthcare Associated Pneumonia
VAP	Ventilator Associated Pneumonia
COPD	Chronic Obstructive Pulmonary Disorder
MRSA	Methicillin Resistant *Staphylococcus aureus*
MDR	Multi Drug Resistance

Chapter 1

Introduction

1.1 Background

Acute Respiratory Tract Infections (ARTIs) in infants and young children, mostly under 5 is one of the most distinct and dominant causes of worldwide mortality. Evidently, a significant portion of these casualties is caused by pneumonia which is a lower respiratory tract infection. According to a recent estimation, approximately 2 million children die every year globally (Levine et al., 2011) on account of this detrimental condition which is almost 19% of total children mortality rate (Figure 1). Nevertheless, this enumeration is more protrusive for Sub-Saharan Africa and South Asia (Tong et al., 2013).

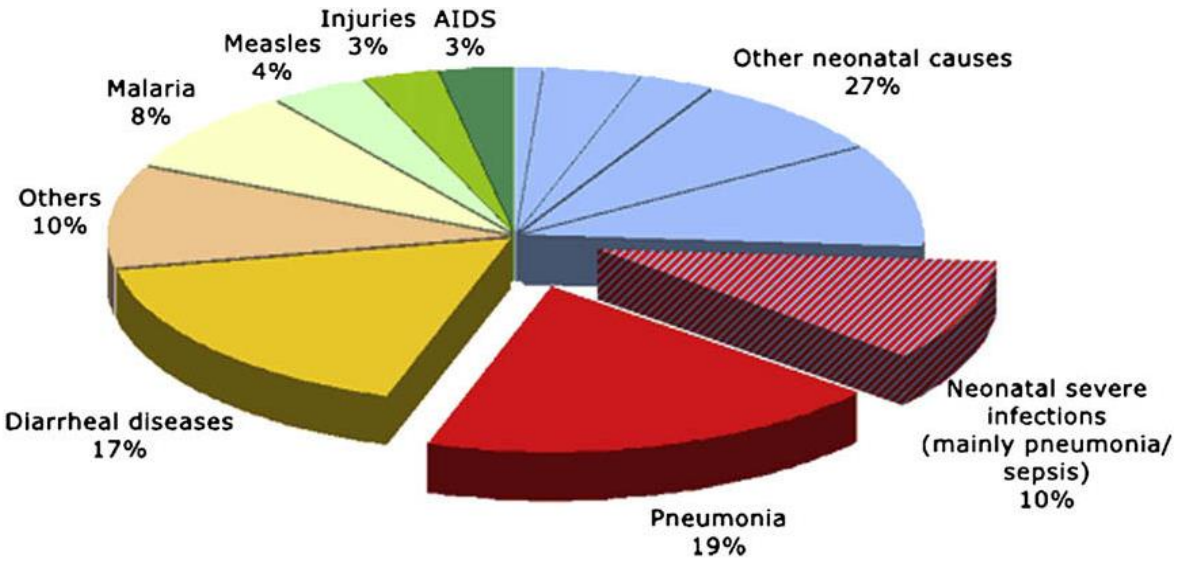


Figure 1: Global distribution of cause-specific mortality in children (Ranganathan & Sonnappa, 2009)

Pneumonia generally occurs in the lungs and it is basically the inflammation of the lungs sac due to infection. A person having pneumonia suffers from relentless chest pain while breathing or coughing. Also, fluid or pus builds up in alveoli of the lungs and causes some complications including limitations in oxygen intake which originates shortness of breath followed by fever,

chills, and fatigue. However, more severe and life threatening conditions include bacteremia (when the bacteria causes pneumonia to move into bloodstream and travel to affect other organs), hypoxia, sepsis, meningitis, empyema –formation of abscess and pleural effusion or para-pneumonic effusion etc.

1.2 Types of Pneumonia Infection

Pneumonia is primarily categorized either as community or nosocomial pneumonia. The community acquired pneumonia is the most common one and it generally occurs in the non-hospital patients. On the other hand, nosocomial infection is contracted by hospitalized patients in healthcare settings which involves 'Ventilator acquired pneumonia (VAP)' and 'Hospital Acquired Pneumonia (HAP)'. Pneumonia is also classified based on the affected area and the way through which the inflammation occurs. These usually comprise of – bronchopneumonia (develops in bronchi), lobar pneumonia (emanates intra-alveolar space), interstitial pneumonia (permeate interstitial tissue in alveoli), lipoid pneumonia (augmentation of fat or lipid particles into the lungs) and aspiration pneumonia (due to insufflating toxic substances). Notably, a broad range of microbes including bacteria, viruses, and fungi are held accountable for varying types of pneumonia and on this ground, pneumonia are of three types- bacterial, viral and fungal pneumonia.

1.2.1 General Classification

The most typical classification of Pneumonia is based on exposure to pathogens which involves Community acquired and Nosocomial Pneumonia (Arshad et al., 2016).

1.2.1.1 Community Acquired Pneumonia

CAP is an acute infection of pulmonary parenchyma and commonly occurs in patients not residing in a hospital facility. It is the most prevailing form of pneumonia and incurred from

the community. A current assessment shows that every 40 out of 1000 cases of pneumonia infection is caused by CAP (McIntosh,2002). Patients develop CAP mostly because of bacterial infection. However, apart from bacteria and viruses, some atypical pathogens also give rise to CAP (Table 1).

Table 1: Microbial pathogens responsible for CAP (Adapted from Bartlett et al. 1995 and McIntosh, 2002)

Microbial agents/ Cause	**Prevalence (%) North American Studies**	**Prevalence (%) British Thoracic Society Studies**
Bacteria		
S. pneumoniae	20–60	60–75
H. influenzae	3–10	4–5
S. aureus	3–5	1–5
Gram-negative bacilli	3–10	Rare
K. Pneumoniae	15-20	—
Miscellaneous	3–5	—
Atypical agents	10–20	—
Legionella	2–8	2–5
Mycoplasma pneumoniae	1–6	5–18
Chlamydia pneumonia	4–6	—
C. trachomatis		
Coxiella brunette		
Chlamydia psittaci		
Viruses	2-15	8-16
Ureplasma urealyticum		
Herpes Simplex virus		
Rhinovirus		
Hantavirus		
Pnumocistic carinii		
Adenovirus		
Respiratory syncytial virus		
Haemophilus influenza type B		
Aspiration	6-10	—

1.2.1.2 Nosocomial Pneumonia

Nosocomial pneumonia infection, on the other hand, is caused by residence in long term care hospital facility. Patients generally get contracted by nosocomial infection within 48-72 hours after being admitted. Nosocomial pneumonia infection is of two types – Ventilator Associated Pneumonia (VAP) and Hospital Acquired/ Healthcare Associated Pneumonia (HAP) and both the types are generally caused by bacteria.

1.2.1.2.1 Ventilator Acquired Pneumonia (VAP)

VAP- the patients admitted into the Intensive Care Unit (ICU) are at great risk for acquiring VAP. Depending on the ICU setting, etiology varies from patient to patient. Nonetheless, demographics show that almost 28% of patients receiving Mechanical Ventilation (MV) or any other respiratory support including endotracheal intubation and nasogastric tubes are contracted with VAP frequently (Asensio et al., 2000 and Fagon, 2002).

1.2.1.2.2 Hospital Acquired Pneumonia (HAP)

HAP is the highest leading cause of death among the other nosocomial infections – Urinary Tract Infection (UTI), Blood Stream Infection (BSI) and Surgical Site Infection (SSI), etc. (Gaynes et al., 2011). Several factors are associated with HAP, including, invasive medical or surgical procedures, peripheral venous catheterization, single-room stay of patients of multiple pathological conditions, roll boards, contact with healthcare workers etc. (Asensio et al., 2000, Gaynes et al., 2011, and Lautenbach et al., 2001).

1.2.2 Anatomical Classification

Considering the location of the infection, pneumonia is subdivided into three categories- lobar pneumonia, bronchopneumonia, and interstitial pneumonia.

1.2.2.1 Lobar Pneumonia

Lobar Pneumonia is characterized by the accumulation of exudates in the intra-alveolar space, especially in one distinct lobe. It is also recognized as non-segmental pneumonia or focal non-segmental pneumonia. The most probable causative agent of lobar pneumonia is *Streptococcus pneumonia* known otherwise as pneumococcus. In lobar pneumonia, fluid-filled spaces travel from alveoli to alveoli until it take possession of the whole lobe essentially. Therefore, starting distally it spreads all over the lobe. The progression of lobar pneumonia occurs in four stages- first congestion- which is alveolar edema followed by bacterial proliferation, then red hepatization- inflation of hemorrhagic exudates, grey hepatization- that is the accretion of suppurative alveolar exudates containing fibrin and finally resolution which is the processing of residual exudates. Severe complications of this class of pneumonia include bacteremia and multi-organ infection (Thomas et al., 1930).

1.2.2.2 Bronchopneumonia

The term bronchopneumonia is generally used for the pneumonia infection that is significantly located in bronchi. It can infect in patches throughout the respiratory tract. Here, the congestion begins proximally from bronchioles and move toward the alveoli. Due to the pathophysiological similarities of bronchopneumonia with lobar pneumonia, it often leads to misdiagnosis or a significant error in the treatment plan (Gallagher, 1933).

1.2.2.3 Interstitial Pneumonia

Interstitial pneumonia is characterized by progressive scarring in the lungs. It permeates interstitial tissue in alveoli. The symptoms of infection include fibrosis and inflammation. It is also termed as ‘cryptogenic fibrosing alveolitis’ (Warwick et al., 1980). Interstitial pneumonia is only diagnosed when more acute disease supervenes and bring the patient to medical attention (Inoue et al., 2003).

1.2.3 Etiological classification

Etiologically pneumonia is classified into – bacterial, viral and fungal pneumonia depending on the causative agents. However, bacterial infections are more prevalent.

1.2.3.1 Bacterial Pneumonia

In bacterial pneumonia, the air sacs of lung's become inflated and suffused with pus, fluid, and cellular debris. Bacterial pneumonia can be both mild and serious and it can eventually lead to total respiratory failure and even death. The asperity of this type of pneumonia depends on the strength of the bacteria and how quickly the patient is diagnosed and treated. Cough with thick yellow, green or blood tinged mucus, severe chest pain along with fever can be the primary symptoms suggestive to bacterial infection (Virkki et al., 2002).

Staphylococcus aureus, Streptococcus pnemoniae, Mycobacterium tuberculosis, Haemophilus influnzae (type B) and *Klebsiella pneumoniae* are some of the common bacterial causative agents (McIntosh, 2002) and among them pathogen with the highest invading rate is *Streptococcus pnemoniae (Table 2).*

Table 2: Invading bacteria rate (Adapted from Jones, 2010)

Rank	**Pathogen Rate (%)**
1	*S. pneumoniae* (41.8)
2	*Mycoplasma pneumoniae* (19.1)
3	*Chlamydophila pneumoniae* (10.1)
4	*H. influnzae* (8.6)
5	*S. aureus* (5.5)
6	*Haemophilus parainfluenzae* (4.4)
7	*Legionella pneumophila* (3.5)

8	*Klebsiella pneumoniae* (3.3)
9	*Moraxella catarrhalis* (2.0)
10	*E. coli* (1.8)

1.2.3.2 Viral Pneumonia

According to a recent study, about 200 million cases of viral pneumonia occur every year (Ruuskan et al.,2011). Viral pneumonia as suggested by the name is caused by a virus. It occurs mostly in immune-compromised patients. Viral pneumonia is induced by, rhinovirus, influenza virus (A and B), parainfluenza viruses1, 2, 3, and respiratory syncytial virus mostly (McIntosh, 2002). However, some other significant agents include-

Table 3: Virus responsible for pneumonia (Adapted from Virkki et al., 2002 & Ruuskanen et al., 2011)

• Human meta-pneumovirus
• Human bocavirus
• Coronavirus types 229E, OC43, NL63, HKU1, SARS
• Enteroviruses
• Human herpesvirus 6 and 7
• Herpes simplex virus
• Cytomegalovirus
• Epstein-Barr virus
• Varicella-zoster virus
• Hantavirus
• Mimivirus
• Parechoviruses

• Measles etc.

1.2.3.3 Fungal Pneumonia

Fungal pneumonia is mediated by fungus. In people having a normal immune system, fungi are a rare cause of pneumonia and often it's regional. It is induced by Cryptococcus, Histoplasma, and coccidioides predominantly.

1.3 Clinical Symptoms and Risk Factors of Pneumonia

Usually, the symptoms of pneumonia include cough with or without bloody sputum which is the colored mucus. Again, as lungs are filled with exudates due to fluid buildup, oxygen intake by the lungs becomes significantly lower which ultimately causes dyspnea-shortness of breath followed by chest pain. Also, often there are systematic symptoms including fever and fatigue. Some generalized and well known risk factors of pneumonia are- being hospitalized, having a history of smoking and also, the use of proton pump inhibitors has been recently associated with the development of pneumonia (Gulmez et al., 2007). Additionally, having a pulmonary diagnosis such as COPD (Chronic Obstructive Pulmonary Disorder) is a big risk factor. Impaired immune system, alcohol abuse, IV drug use, and some neurological injuries also have a great impact (Table 4).

Table 4: Modifying factors that increase the risk of infection (Adapted from Dupont et al., 2001)

Multiple medical comorbidities
Residence in a nursing home
Immune-suppressive illness (including therapy with corticosteroids)
Enteric gram-negatives
Exposure in a day care center
Structural lung disease (bronchiectasis)
Underlying cardiopulmonary disease
Malnutrition
Smoking

Age
Alcoholism

1.4 Diagnosis of Pneumonia

Entrenched upon the symptoms, a general diagnosis of pneumonia is usually done. The patient who develops typical pneumonia usually shows signs like- increased respiratory rate, use of accessory muscles (sternocleidomastoid, PEC major, minor, etc.) and intercostal retraction (a contraction of the intercostal muscle) due to heavy and interrupted breathing. Conventional ways of diagnosis are- chest radiograph or x-ray, differential diagnosis, having an ultrasound of lungs, microbiological or etiological diagnosis through blood culture, etc. (Dupont et al.,2001). The most trivial form of diagnosis is the chest x-ray and a usual chest x-ray of bronchopneumonia typically shows patchy areas throughout the lungs. In atypical or interstitial pneumonia the pattern is also often quite similar in a sense that it spreads throughout the lungs. However, in this case, it is often condensed in the perihilar region of lungs and looks reticular. That means, there will be more line shaped cloudy areas visible in a chest x-ray. In lobar pneumonia, the fluid is confined within a single lobe or a set of lobes. There is also tactile vocal fremitus which means, every time patients repeat certain phrases a typical sort of vibrations can be felt from their chest because sound travels better through the fluid filled consolidate tissue than air-filled healthy tissues.

Although there are no accepted diagnostic criteria for Hospital Acquired Pneumonia (HAP) and Ventilator Acquired Pneumonia (VAP), bacteria may be cultured by sputum or lower respiratory tract secretions. Then, in both HAP and VAP, the following criteria will determine whether the patient has pneumonia - (Fàbregas et al., 1999, and Potgieter & Hammond, 1992)

i. New, progressive or persistent infiltrate

ii. Body temperature greater than 38 Degree Celsius

iii. Neutropenia/ Neutrophilia

iv. Increased sputum or Lower Respiratory Tract Secretions and

v. Decreased Gas Exchange which may be evidenced by decreased oxygen saturation.

1.5 Pathophysiology of Pneumonia Infection

Customarily, pneumonia infection occurs in two main ways, either by inhalation or aspiration. In the case of inhalation, the invasion of pathogens (either bacteria or viruses) occurs in the airway because of constant exposure to contaminated air. On the other hand, pneumonia due to aspiration occurs when food or stomach acid enters the lungs and particles remains there which allows bacterial growth and allows infection. However, in both cases, upon entry, pathogens attach with the airway and start colonizing to the mucous and cells of the nasopharynx which results in the infiltration of the pathogen in the bronchial tree and gradually defect the host defense mechanisms. Subsequently, damage to the surface cells causes the accumulation of fluid and also helps the fluid to enter the alveoli. As a result, parenchymal and alveolar sacs tend to consolidate (Singh, 2012).

1.6 Prevention and Treatment of Pneumonia

Pneumonia can somewhat be prevented through the use of vaccines. For example, there is pneumococcal vaccine specified as PPSV 23 where 23 stands for 23 polysaccharide antigens that are present on *Streptococcal pnemoniae* bacteria which accounts for 85-90% invasive *Streptococcal pnemoniae*. This vaccine is generally given to patients who are 19 years old with a history of asthma or smoking, patients over 65 years old and (2-64) years old only when they have underlying comorbidities like HIV, diabetes mellitus, malignancy, hemolytic disorders like sickle cell anemia (Pilishvili & Bennett, 2015). Another vaccine called PCV 13 which is a

pneumococcal conjugate vaccine is also given. Here, 13 stands for 13 different polysaccharide antigens and it is given to children under 2 years old specially to 2, 4, 6 and 12 months old (Tomczyk et al., 2011).

Owing to the sluggish improvement in the discovery of new drugs, treatment of pneumonia comprises only a meager range of antimicrobials including beta lactams, macrolides, and aminoglycosides (Gleason et al., 1999). Majority of the patients who get contracted by lower respiratory tract infection or pneumonia often are provided a course of antibiotics as a first line treatment. Whereas it is absolutely correct for a superior number of patients, it might not be eligible for patients who are sick enough to warrant hospital admission. In that case, the prognosis and treatment decision is often made considering a whole different approach where there is a formal assessment which includes the assessment of clinical history to find out or understand the sequence of events that led the condition. Then, the required tests are performed. For example, firstly, the imaging tests are taken to confirm pneumonia, and then secondly a variety of blood tests and sputum tests are done to assess the severity of illness, it's impact on other organ systems and the causative organism. If the patient is believed to have a viral cause, the tests, the kits will allow pinpointing exactly what virus has caused the infection and the anti-viral medications are given accordingly. For example, it might be one of the subtypes of influenza, and then we will consider anti-influenza medication e.g. Tamiflu. If however it is believed to be a bacterial infection, then the approach of treatment will be primarily antibiotics, and the type of antibiotics would be in part determined by the severity of illness and in part by what information we have initially as to the potential cause. Along with the antibiotics, cough medicine is sometimes given to calm the cough and to help cough up mucus and a fever medicine as well to reduce the temperature.

Antimicrobial therapy is the most complex treatment process and is specific for different conditions. For examples-

For Community Acquired Pneumonia:

- CAP (outpatient) + No comorbidities (other underlying conditions)+ No recent antibiotic therapy : (Rodríguez et al., 2007)
  - Macrolides (inhibit protein synthesis)
    - Azithromycin
  - Doxycycline (a tetracycline- also protein synthesis inhibitor)

- CAP (outpatient setting) + Underlying comorbidity (COPD, asthma, liver diseases, chronic kidney diseases, cancer, any type of immunosuppressive diseases or immunosuppressant therapy, heart failure, diabetes mellitus etc.) + Recent antibiotic therapy (within past 90 days) : (Rodríguez et al., 2007)
  - Respiratory Fluoroquinolone
    - Moxifloxacin
    - Levofloxacin or,
  - Macrolide or Doxycycline + Amoxicillin/ Augmentin/ 3rd Generation Cephalosporins

- CAP + 0 to 1 sign of CURB 65 [Confusion, Uremia, Respiratory rate (increased), Blood pressure (low diastolic), age >65]: (Carratalà et al., 2007)
  - Moxifloxacin
  - Levofloxacin + No Hospital Admission
  - Azithromycin

- CAP + 2 signs of CURB 65 [Confusion, Uremia, Respiratory rate (increased), Blood pressure (low diastolic), age >65]: (Rodríguez et al., 2007)
  - Admission into Hospital
  - Respiratory Fluoroquinolone or,
  - Macrolide or Doxycycline + Ampicillin (penicillin)/Ceftriaxone (3^{rd} Generation Cephalosporin)
  - Duration: minimum 5 days

- CAP + >3 signs of CURB 65 [Confusion, Uremia, Respiratory rate (increased), Blood pressure (low diastolic), age >65]:(Rodríguez et al., 2007 & Dupont et al., 2001)
  - Admission into ICU
  - Ceftrixaone/ Cefotaxime + Azithromycin/ Fluoroquinolone or,
  - Ampicillin + Sulbactam (beta- lactam inhibitor) + Macrolide/ Fluoroquinolone or,
  - In case of penicillin allergy = Aztreonom (Monobactam)
  - Duration: 5days minimum

- In case of *Pseudomonas* infection: (Baddour et al., 2004)
  - Zosyn, Cefepime, Imipenem, Meropenem (Any of these)

    +

    a. Levofloxacin/ Ciprofloxacin or,
    b. Aminoglycosides with a macrolide or,
    c. Aminoglycosides + Levofloxacin

- In case Methicillin Resistant *Staphylococcus aureus (MRSA)* infection, (Neralla & Meyer, 2004)
  - Vancomycin or,
  - Linezolid

For Hospital Acquired Pneumonia: (Friis et al., 1984 and Loeches et al., 2010)

- Early Onset [been in hospital >2days but <5days] or No multi-drug Resistant Pathogen:
  - 3rd Generation Cephalosporin or,
  - Fluoroquinolone or,
  - Etropenem (weaker carbapenem) or,
  - Ampicillin + Sulbactam (beta- lactam inhibitor)

- Late Onset [>5days hospital stay] or Multi-drug Resistant Pathogen:
  - Aminoglycoside or Levofloxacin

    +

    Zosyn/ Powerful Carbapenem (e.g. Imipenem) / Ceftazodine/ Cefepime

1.7 Antimicrobial Resistance

In the early 19th century, the leading cause of death was pneumonia, tuberculosis, diarrhea, and enteritis. Pathogens like *Streptococcus pyogenes* caused half of all post-birth deaths and also *Staphylococcus aureus* wound infection was 80% fatal. These were the scenario of the pre-antibiotic era. However, the innovation of antimicrobials, the wonder drug antibiotics came with a revolution of reduced childhood mortality and increased life expectancy. From the treatment of infections to their compelling role as a chemotherapeutic agent, this phenomenal discovery has saved countless lives. Nevertheless, the conducive use of this miraculous drug is

in jeopardy because of the emergence of resistance (Figure 2) and antibiotic resistance is one of the biggest public health crisis in the world now (Davies & Davies, 2010).

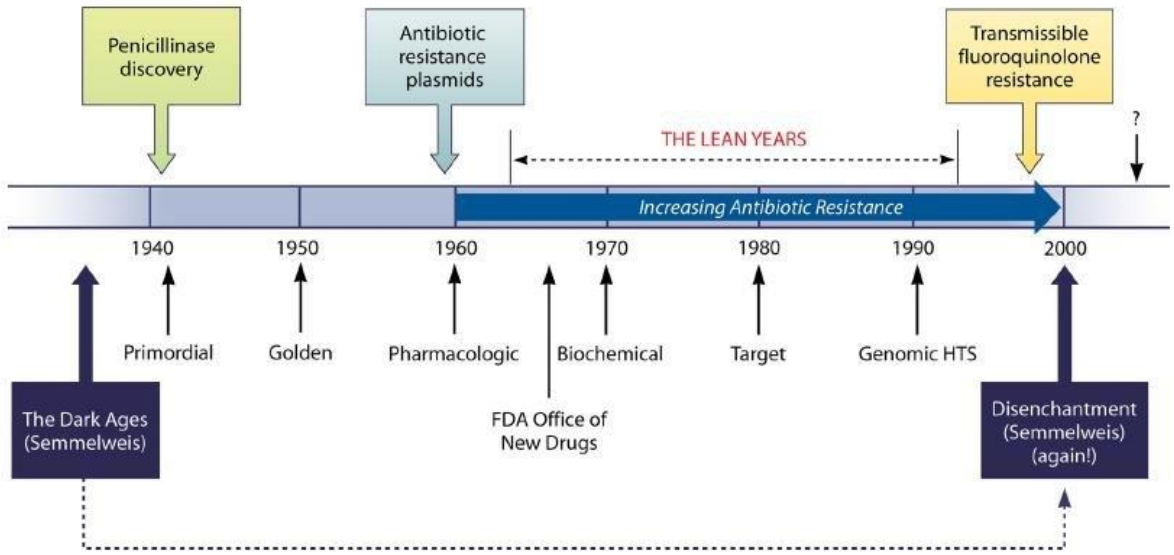


Figure 2: Events in the age of antibiotics (Adapted from Davies & Davies, 2010)

1.8 Multi-drug Resistance (MDR)

Multi-drug resistance occurs due to the resistance of pathogens to multiple antimicrobials. This condition is so severe that sometimes the accurate treatment regimen is harder to be found or no one appropriate antimicrobials are accessible for infections caused by those microorganisms (Magiorakos et al., 2012). Multidrug resistant bacteria are given the term 'superbug' to express them and the emergence of superbugs made the years of research and findings on antibiotics worthless, as we once again stand on the verge of returning to the pre-antibiotic era.

1.9 Multidrug Resistant Pneumonia Pathogens

What makes pneumonia more daunting in the present-day scenario is that these infections seem to be quite indomitable due to the emergence of anti-microbial resistance genes. Especially, if

we contemplate the recently promulgated list of ‘World’s Most Dangerous Superbugs’ by WHO in 2017, it is evident that, our ground against dealing these infections is very substandard as ESBL (Extended Spectrum Beta- Lactamases) producing and Carbapenem resistant *Klebsiella pneumoniae,* methicillin-resistant *Staphylococcus aureus,* penicillin-non-susceptible *Streptococcus pneumoniae,* ampicillin-resistant *Haemophilus influenzae* are all on the list (Asokan et al., 2019).

The occurrence of ‘superbug’ is more alarming in the developing countries including Bangladesh, according to a recent database (Islam et al., 2019). Particularly, there is a significant increase of nosocomial and community based pneumonia and the causative agents are found to be multi-drug resistant. In this paper, we did detailed research about such conditions and also analyzed blood culture reports of different age groups collected from a city of Bangladesh to investigate the threat and to suggest what should be done next.

Chapter 2

Objectives of the study

Given the thought to the scenarios of MDR and emanation of pneumonia superbugs, the purpose of this study is to highlight the current situation of multidrug resistant pneumonia pathogens, their effect in both Bangladesh and worldwide perspective and how to solve the dire consequences. In short, this research is heading to-

i. Confer about all the pathogens involved and their rate of severity in causing pneumonia
ii. Evaluate the available treatment options of pneumonia, scrutinize the ways or mechanisms of antibiotic resistance and pathogens which developed resistance
iii. Explore the topic of Multidrug resistance (MDR), it's ferocity in case of pneumonia pathogens and review the bearings of this calamitous condition in both Bangladesh and worldwide context.
iv. Delve into the challenges, opportunities, solutions and future promises of this appalling matter.

Chapter 3

Methodology

An extensive literature search was performed for extracting all papers related to the topic. Multiple searches were operated on 'Multidrug-resistant pathogens of pneumonia' using PubMed, Science Direct, SCOPUS and Bangladesh Journal Online utilizing appropriate key terms (pneumonia, antimicrobial resistance, multi-drug resistance, etc.). Google scholar was used as well in evocation of data, as it shows literature with a ranking algorithm based on the relevancy of keyword and citation count. Furthermore, 'Mendeley' software was used for managing in-text citations and bibliographies of the research articles for the review. Initially 130 articles were selected based on the title. After reading the abstract, 90 articles were found to be related to the project. After that, all the articles were screened and 50 articles were selected for this review. All selected papers were then assessed to accumulate data. Titles and modified works were screened and all copy and random papers were barred.

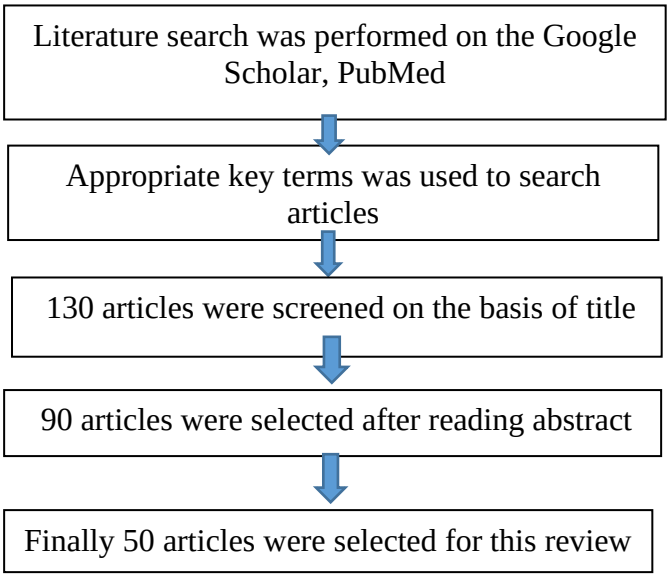


Figure 3: Flowchart of article search process

Besides, quantitative data extraction was done as well. All the numerical data, blood culture and blood susceptibility reports of 30 patients of different age groups were collected from the diagnostic centers of Gazipur, Bangladesh for evaluating the recent scenario of pneumonia infection pattern, types of antibiotics used and antibiotic resistance history.

Chapter 4

Molecular Mechanism of Resistance Methodology

4.1 Mechanism of action of antibiotic resistance

Antibiotic resistance can build up after bacteria have become repeatedly exposed to antibiotics. Overuse, underuse of antibiotics and not abiding by the regimen are some of the major influencers. Also, resistance develops depending on the actual therapeutic mechanisms of antibiotics, as in, how they work in disease control.

Table 5: Modes of action and resistance mechanisms of commonly used antibiotics

(Adapted from Davies & Davies, 2010)

Antibiotic Class	Examples	Target	Mode(s) of action
Beta Lactams	Penicillin (ampicillin), cephalosporins (cephamycin), penems (meropenem), monobactams (aztreonam)	Peptidoglycan biosynthesis	Hydrolysis, efflux, altered target
Glycopeptides	Vancomycin, teicoplanin	Peptidoglycan biosynthesis	Reprogamming peptidoglycan biosynthesis
Aminoglycosides	Gentamicin, streptomycin, spectinomycin	Translation	Phosphorylation, acetylation, nucleotidylation, efflux, altered target.
Tetracyclines	Minocycline, tigecycline	Translation	Mono-oxygenation, efflux, altered target
Macrolides	Erythromycin, azithromycin	Translation	Hydrolysis, glycosylation, phosphorylation, efflux, altered target
Lincosamides	Clindamycin	Translation	Nucleotidylation, efflux, altered target

Streptogramins	Synercid	Translation	C-O lyase (type B streptogramins), acetylation (type A streptogramins), efflux, altered target
Oxazolidinones	Linezolid	Translation	Efflux, altered target
Phenicols	Chloramphenicol	Translation	Acetylation, efflux, altered target
Quinolones	Ciprofloxacin	DNA replication	Acetylation, efflux, altered target
Pyrimidines	Trimethoprim	C_2 Metabolism	Efflux, altered target
Sulfonamides	Sulfamethoxazole	C_2 Metabolism	Efflux, altered target
Cationic peptides	Colistin	Cell Membrane	Efflux, altered target
Lipopeptides	Daptomycin	Cell Membrane	Altered target
Rifamycin	Rifampicin	Transcription	ADP-ribosylation, efflux, altered target

There are several mechanisms through which antibiotic resistance occurs. However, it happens mostly because bacteria display random or spontaneous mutation at a genomic level. As a result, there is an accumulation of non-lethal mutated genes in bacteria bypassing the genes in the next generation and this transfer of resistant genes occurs in one of the two ways- vertical gene transfer or horizontal gene transfer. Vertical gene transfer occurs through replication. Whereas, transduction, conjugation, and transformation help in horizontal gene transfer. After the transfer of resistant genes, the antibiotic resistance occurs in one of the following ways-

- **Drug inactivation or modification-** Here the resistant genes make an antibiotic counteracting substance which is a protein made from resistant genes and is capable of shutting down the antibiotics or evading their mechanism. Also, there is direct

inactivation of antibiotics either by – hydrolysis or transfer of chemical group/ steric hindrance.

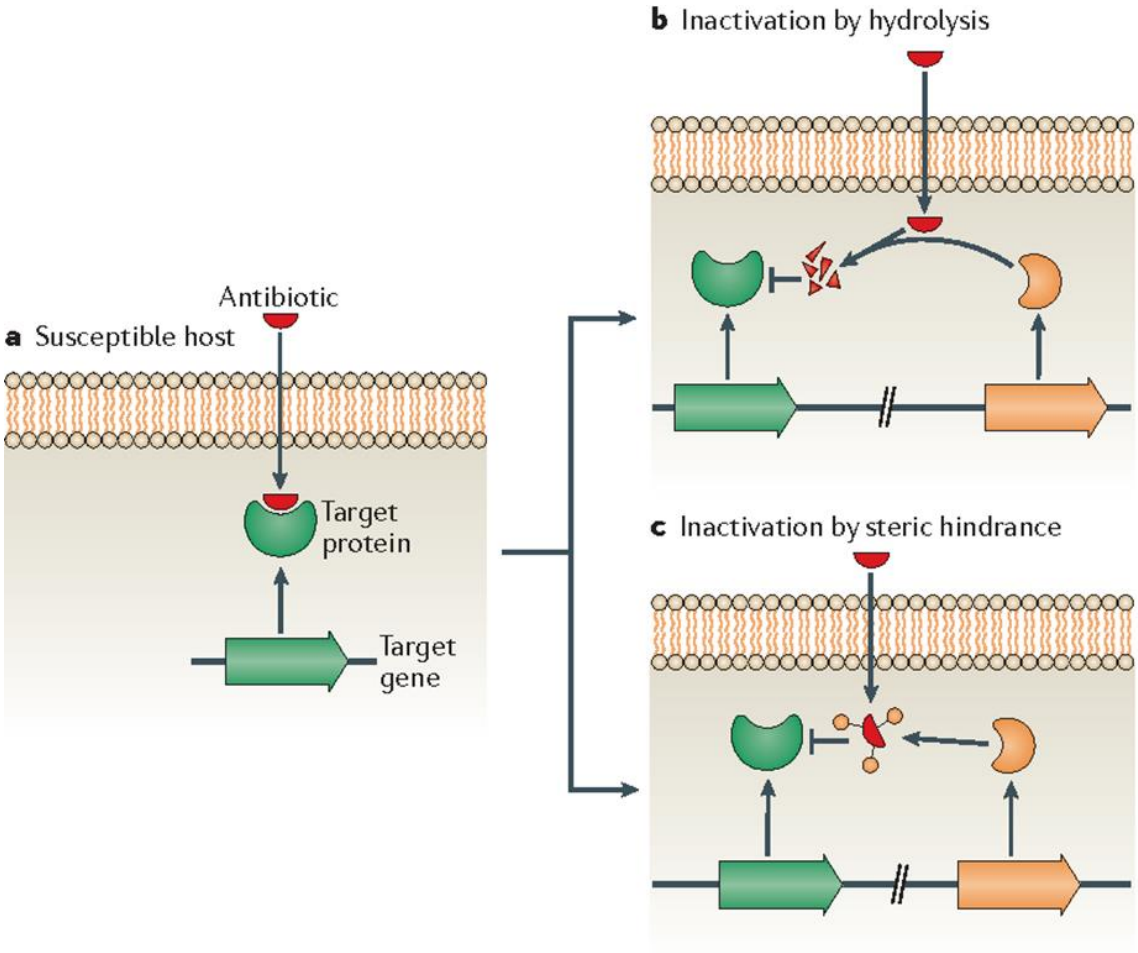


Figure 4: Direct interaction with antibiotics (Adapted from Blair et al., 2015)

- **Alteration of target or binding site of antibiotics-** where the bacteria alter the binding site of antibiotics so that their operation is hindered. This mechanism is more prevalent in Methicillin Resistant *Staphylococcus aureus* (MRSA).

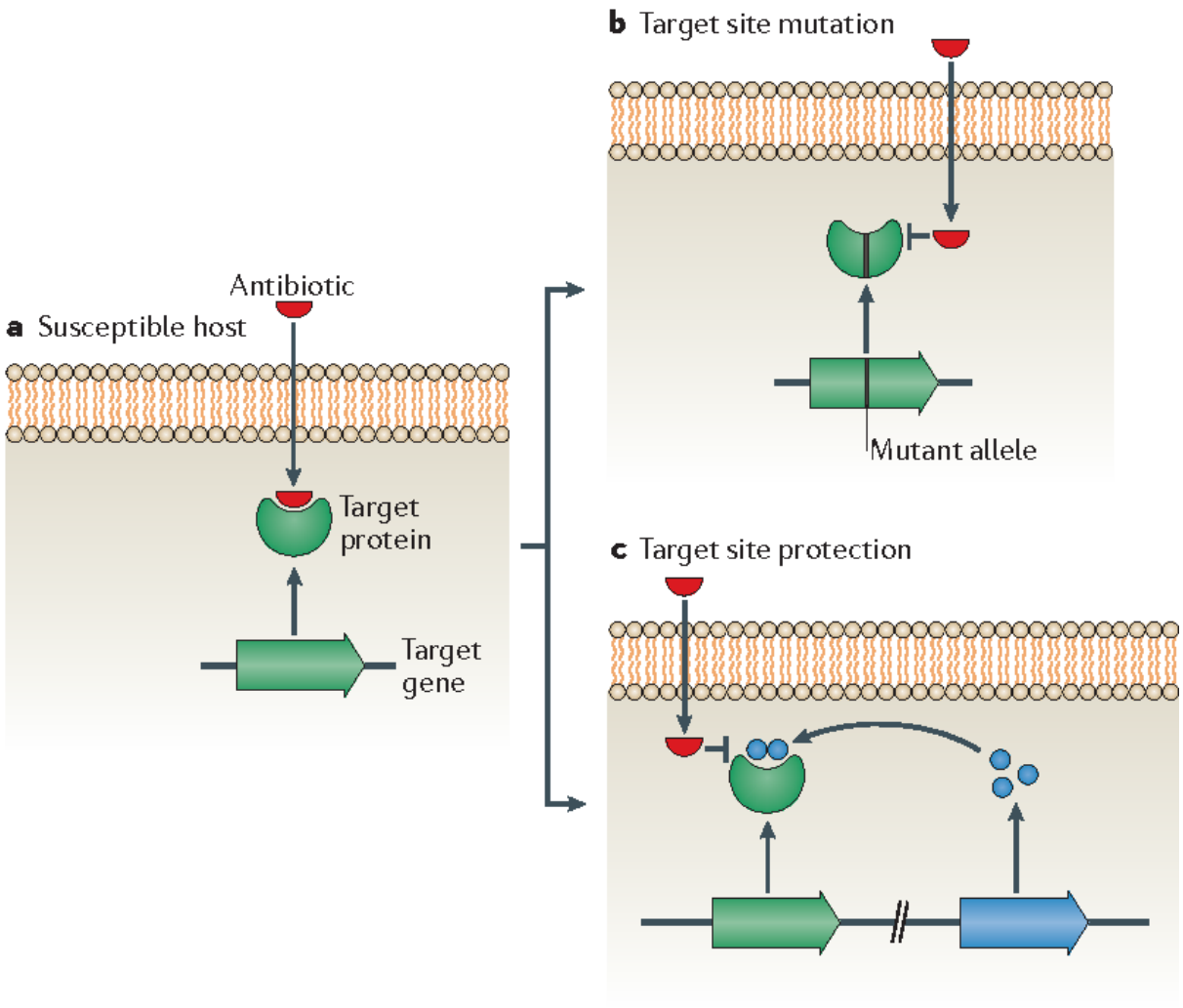


Figure 5: Target site alteration (Adapted from Blair et al., 2015)

- **Active Efflux-** This is the efflux of antibiotics from bacterial cells which causes the genetic elements encoding efflux pumps to be naturally selected that results in overexpression of efflux pump proteins. Therefore, the efflux of antibiotics occurs.

4.2 Mechanism of Action of Multidrug Resistance

Multidrug resistance follows the general mechanisms of antibiotic resistance. Nonetheless, the most customary way is to develop resistance through the membrane efflux pump complex where the antibiotics are effluxed or removed out of the bacterial cell by a tripartite efflux

pump. This pump is capable of extruding multiple types of drug molecules, creating a state of multidrug resistance. Pgp or P-glycoprotein is the most prevalent MDR drug transporter which is an ATP-dependent trans-membrane protein. ATP binds to the interior nucleotide binding domains and pumps the drug out of the cell as drugs enter the drug binding pockets which results in ATP dependent shift in the conformation of the entire pump which causes the drug to be extruded in the extracellular space.

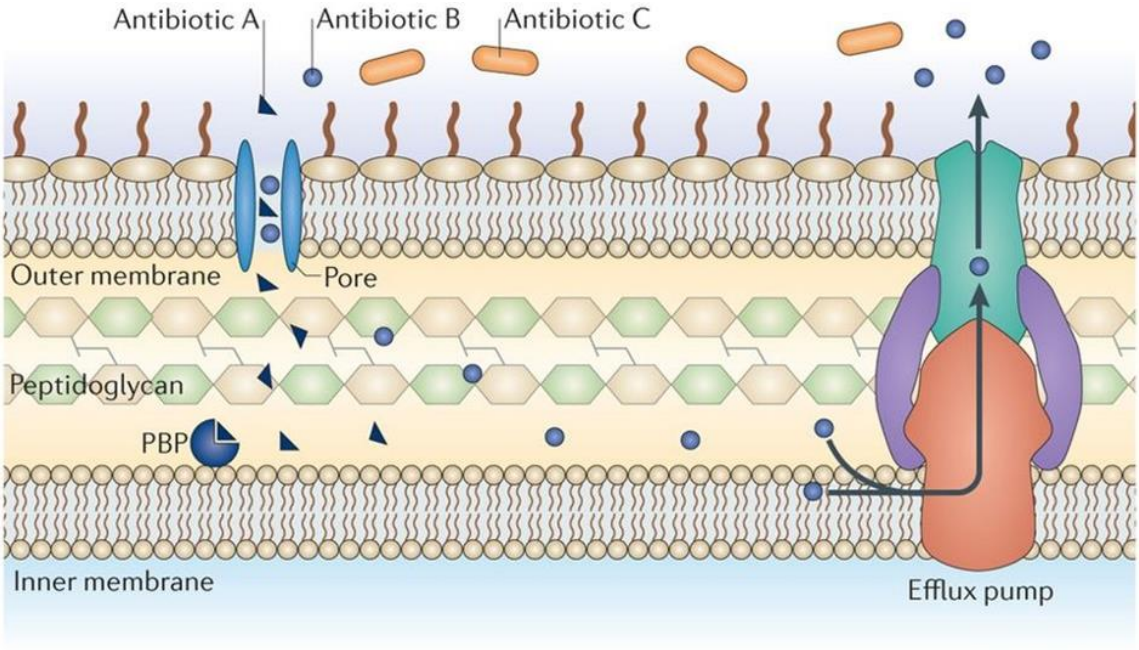


Figure 6: Intrinsic mechanisms of resistance through efflux pump (Adapted from Blair et al., 2015)

Chapter 5

Evaluation on Resistance of the Available Antibiotics for Pneumonia Treatment

5.1 Worldwide perspective

We evaluated the research papers on the available drugs, examined which drugs are susceptible or resistant and found the following pathogens to be multidrug resistant:

Table 6: Multidrug resistant pathogens of pneumonia

Pathogens	Antibiotics used	Resistance	References
Streptococcus pneumonia	Penicillin Penicillin Cotrimoxazole Cephalexin Fluoroquinolone	Resistant Resistant Resistant Resistant Resistant	(Asokan, Ramadhan, Ahmed, & Sanad, 2019),(Adegoke, Faleye, Singh, & Stenström, 2017)
Haemophilus influenza	Ampicillin Penicillin Cephalosporin	Resistant Resistant Resistant	(Asokan et al., 2019)

Staphylococcus aureus	Methicillin	Resistant	(Asokan et al., 2019)
	Penicillin	Resistant	
	Cotrimoxazole	Resistant	
	Cephalexin	Resistant	
	Erythromyxin	Resistant	
	Cephoxitin	Resistant	
	Oxacillin	Resistant	
	Clindamycin	Resistant	
Klebsiella Pneumoniae	Fluoroquinolone	Resistant	(Lautenbach et al., 2001) (Doorduijn, Rooijakkers, van Schaik, & Bardoel, 2016)
	Polymyxin B	Resistant	(Paterson et al., 2004)
	Ciprofloxacin	Resistant	(Paterson et al., 2004)
	Tigecycline	Resistant	(Cartelle et al., 2004)
	Ceftazidime	Resistant	(Cartelle et al., 2004)
	Cephalosporin	Resistant	
	Amoxicillin	Resistant	
E.coli	Fluoroquinolone	Resistant	(Lautenbach et al., 2001)

MDR in the pathogens causing pneumonia is becoming more and more prevalent and microorganisms are fighting back (Table 7). Explicitly, the nosocomial infections caused by multidrug resistant pneumonia pathogens is more alarming apart from community acquired

one. Drug resistant pathogens tend to linger within the hospitals threatening patients who are already ill or in critical condition but some resistant bug has been turning up healthy people as well. Staph infection is one of them which is caused by Methicillin Resistant *Staphylococcus aureus* (MRSA) that has acquired resistance against the major classes of antibiotics including penicillin and penicillin like drugs. As a result, the treatment option for this particular type of pneumonia has been markedly limited. Also, the timing is very critical in patients who acquired this specific type of staph infection. The sooner patients get diagnosed and treated with the right antibiotic the more their chance of survival is. However, the problem is, lab tests can take up to 72 hours to identify drug resistant bacteria including MRSA and only then we can have the opportunity to narrow down, focus and reduce the number of drugs, the spectrum of drugs of the right class based on the information. So, the patient may initially be given an antibiotic which is not effective and that is nothing but a gamble because we need to start the right antibiotic soon and waiting 24-72 hours is too late.

Table 7: Pattern of antimicrobial resistance (Adapted from Ghosh et al., 2016)

Antibiotic Resistance pattern	**Percentage of the isolates involved (%)**
ESBLs	*Klebsiella pneumonia* 100 *Proteus mirabilis* 66.6 *Citrobacter fruendii* 100 *Enterobacter spp.* 100 *Acinetobacter spp*. 60 *Pseudomonas spp*. 57.1

Metallobetalactamases	*Klebsiella pneumonia* 83.3 *Proteus mirabilis* 33.3 *Citrobacter fruendii* 50 *Enterobacter spp.* 100
Amp-C betalactamse	*Klebsiella pneumonia* 60 *Proteus mirabilis* 33.3

Another most significant and notorious nosocomial pneumonia and ventilator associated pneumonia these days is being caused by *Klebsiella pneumoniae* which is a gram negative bacteria of enterobacteriaceae family (Arnold et al., 2011).In hospitals and long term care facilities, this bacteria is causing severe pneumonia, osteomyelitis, uremia, bacteremia, biliary tract infection, multiple organ failure, sepsis, wound infection (Cartelle et al., 2004), liver abscesses (Liao et al., 2011) etc. (Table 8).

Table 8: Hospital acquired bacterial infections caused by Klebsiella spp (Adapted from Ullmann, 1998)

Infection	%
Urinary tract infections	6-17
Pneumonia	7-14
Septicemia	4-15
Wound Infections	2-4
Nosocomial infections in ICU	4-17
Neonatal septicemia	3-20

Resistance of this species to third generation cephalosporins were first coming into surface in 1980 (Asensio et al., 2000) and now, with the emergence of hypervirulent, multidrug-resistant gene which is capable of causing infection even in the healthy, ambulatory or outpatients, it is considered as one of the most fatal microorganism (Shon & Russo, 2012). Countless outbreaks have occurred in the western countries along with Greece, Israel, Asia, and most of the developing countries (Tumbarello et al., 2012).

All these conditions are making pneumonia, especially hospital borne pneumonia more deadly over time.

5.2 Bangladesh Perspective

Like other developing South-Asian countries, the occurrence of antibacterial or antibiotic resistance is surging menacingly (Sarkar et al.2016, and Ahmed et al., 2019). Recently, a study was done on several pathogens including Escherichia coli, *Klebsiella pneumoniae, Pseudomonas spp, Staphylococcus aureus, Salmonella spp, Acinetobacter, Enterococcus, Streptococcus pneumoniae,* etc. so as to find the percentage of antimicrobial resistance and among that both *Klebsiella and Staphylococcus* were found to be the most fatal and multidrug resistant. Especially, in Chittagong and Dhaka region it was found to be more vulnerable (Sarkar et al. 2016).

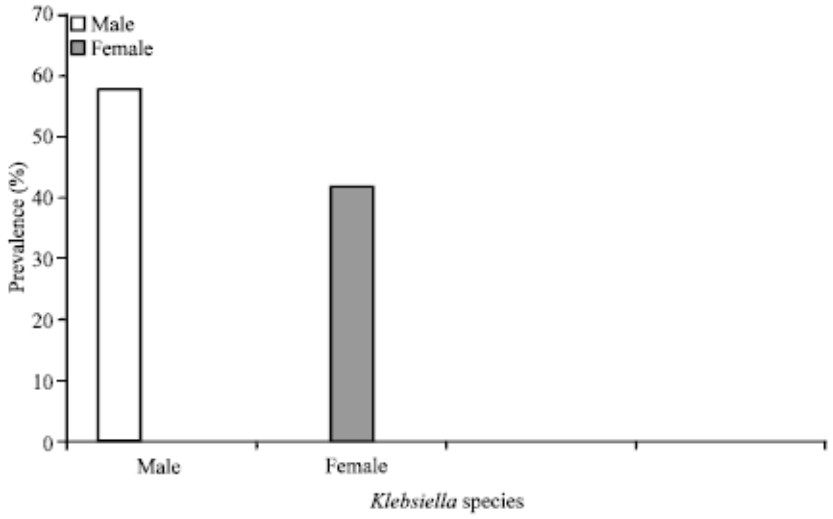


Figure 7: Prevalence of Klebsiella according to gender classification (Adapted from Akter et al. 2014)

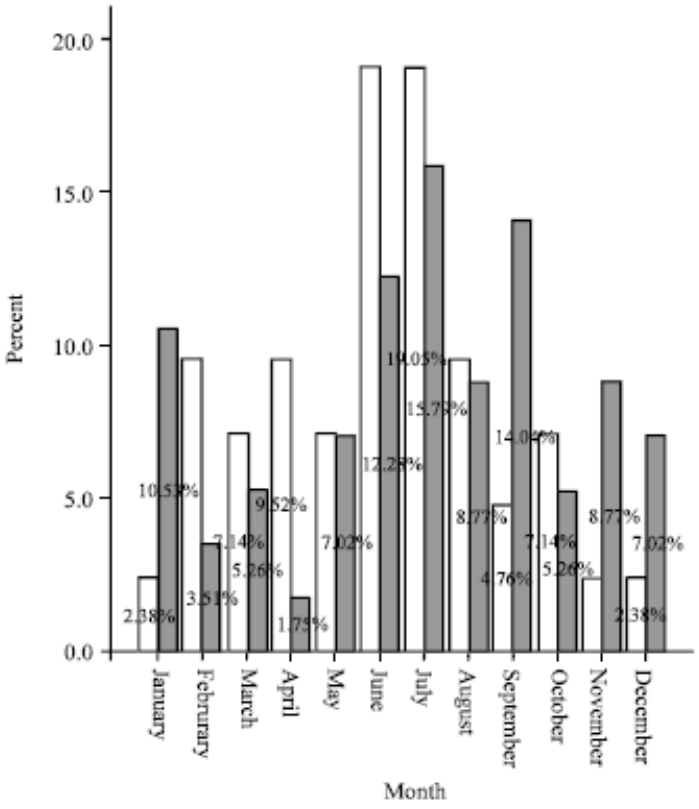


Figure 8: Month wise observation of patients by Klebsiella infection (Adapted from Akter et al. 2014)

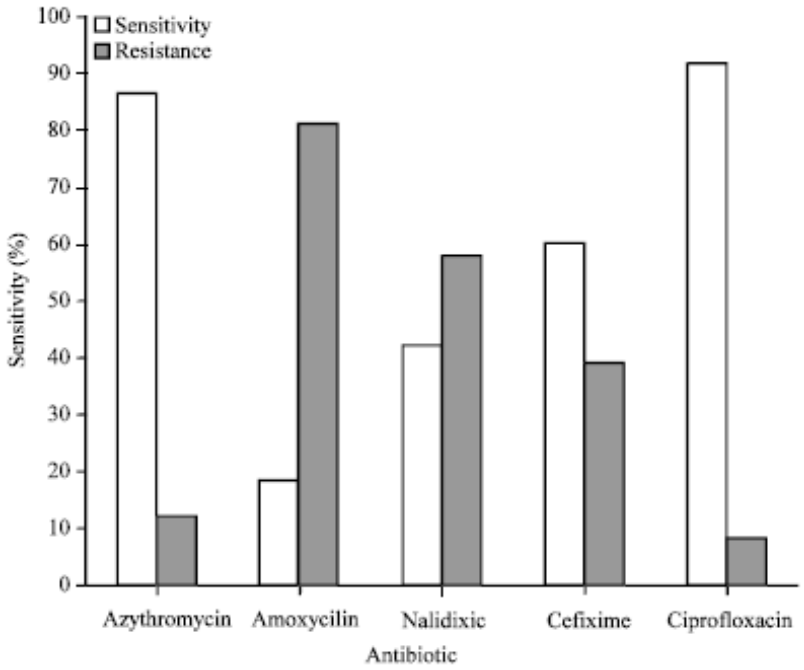


Figure 9: Antibiotic sensitivity/resistance pattern of Klebsiella spp isolates recovered from patients (Adapted from Akter et al.2014)

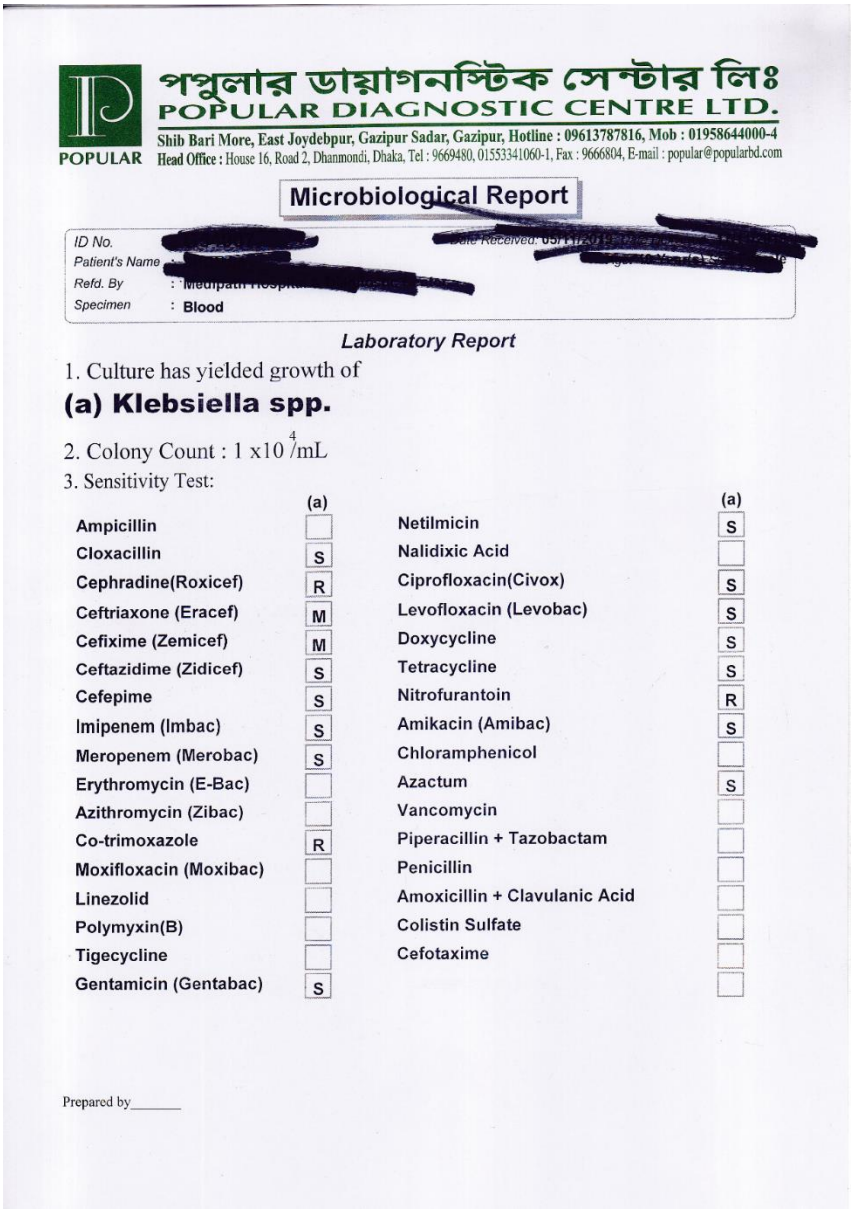
5.3. Research Data Evaluation

Quantitative blood culture reports (Figure 10) of 30 patients collected from different diagnostic centers of Gazipur city of Bangladesh on the antibiotic resistance pattern of pneumonia pathogen *Klebsiella pneumoniae* showed the following results:

In case of patient 1, the involved *Klebsiella spp* was found to be resistant toward Amoxycillin, Cephradine, Azithromycin and Polymyxin B. whereas in case of the pathogen found in patient 2, it was resistant to Azithromycin, Co-trimoxazole, Tigecyclin and Ciprofloxacin,. On the other hand the *Klebsiella pneumoniae* found in patient 3, 4 and 5 was noticed to be resistant to Ciprofloxacin, Levofloxacin and Nalidixic acid simultaneously.

The pathogen that caused pneumonia in patient 6 was resistant to polymyxin B, Cefetaxime and Penicillin whereas pathogen derived from patient 7 was resistant to Cephradine and Ciprofloxacin only. Again, the *Klebsiella spp.* isolated from patient 8, 9, 10, and 11 showed the similar pattern and were resistant to Amoxicillin, Levofloxacin, Cephradine and Nalidixic

acid. Moreover, pathogens derived from almost 4 out of 30 patients did not show multi- drug resistance and were resistant toward one specific class of antibiotics only. However, all the pathogens found from the rest of the blood culture reports showed multidrug resistance and were resistant to Ciprofloxacin, Cephradine, and Azithromycin which observed approximately 44-45% isolates.



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Microbiological Report

ID No.
Patient's Name
Refd. By : Medipath Hospital
Specimen : Blood

Laboratory Report

1. Culture has yielded growth of
(a) Klebsiella spp.
2. Colony Count : 1×10^{4} /mL
3. Sensitivity Test:

	(a)		(a)
Ampicillin		Netilmicin	S
Cloxacillin	S	Nalidixic Acid	
Cephradine(Roxicef)	R	Ciprofloxacin(Civox)	S
Ceftriaxone (Eracef)	M	Levofloxacin (Levobac)	S
Cefixime (Zemicef)	M	Doxycycline	S
Ceftazidime (Zidicef)	S	Tetracycline	S
Cefepime	S	Nitrofurantoin	R
Imipenem (Imbac)	S	Amikacin (Amibac)	S
Meropenem (Merobac)	S	Chloramphenicol	
Erythromycin (E-Bac)		Azactum	S
Azithromycin (Zibac)		Vancomycin	
Co-trimoxazole	R	Piperacillin + Tazobactam	
Moxifloxacin (Moxibac)		Penicillin	
Linezolid		Amoxicillin + Clavulanic Acid	
Polymyxin(B)		Colistin Sulfate	
Tigecycline		Cefotaxime	
Gentamicin (Gentabac)	S		

Prepared by_____

Figure 10: A sample of the data collected

Depending on the research done on the patients of Gazipur, the effectiveness of first line antibiotic treatment was not satisfactory, as study showed evidence of multi-drug resistance, specially, significant resistance in case of macrolides, beta-lactam antibiotics and also the cephalosporins that too just for a specific pathogen. However, this particular study does not represent the scenario of the whole country as –

- This study was only clustered on to Gazipur region
- The sample size was smaller
- Reports on only *Klebsiella spp* were collected
- Only the blood culture reports were collected

All the numerical and review data suggest that pneumonia is a serious condition and to be taken seriously because of the constant evolvement of the pathogens and this era of multidrug resistant bacteria. Every year a million hospitalization occurs due to pneumonia and it is still one of the preeminent cause of death worldwide. What is more concerning is, you do not have to be elderly or be in hospital setup to acquire pneumonia these days. You can get pneumonia anywhere, anytime, at any age. Therefore, it is high time we find out a proper solution to this startling condition.

Chapter 6

Opportunities and Challenges

The focal challenge in dealing AMR and MDR is the impact that it has on people's lives. If we do not dig up the solution now, significant numbers of deaths will happen as a result of drug resistance.

6.1 Solution

To come up with a solution, it is fundamental to dig up the underlying problem. Antimicrobial resistance did not develop in a day. The fact is, it would not have been this difficult to be dealt with if we were focusing on the development of more novel antibiotics with a more robust mechanism of action which ultimately could have revolutionized our healthcare sector instead of heading back to the pre-antibiotic era. However, there are still plenty of ways to slow down this most urgent health threat of our time. Tons of researches has already been done to figure out how to deal with resistance, multidrug resistance, and evolution of superbugs. Based on those, our solutions are following:

- **Drug repurposing**- trying to find out and navigate the triumvirate between drug, target, and disease, testing a therapy approved for one disease for it's effect to another.
- **Use of Metallopolymers**- for complex formation which has high resistance toward beta-lactamase induced hydrolysis (Ganewatta et al., 2013).
- **Iron Chelation-** to reduce microbial growth and debilitate the deescalated immune function during infection (Islam et al., 2019).

6.2 New Discovery

Recent research done in 2015 has shown significant progress in the discovery of novel antibiotics. The researchers even claimed that they invented a new antibiotic which invades and destroys pathogens without detectable resistance. The antibiotic was termed as 'Teixobactin' which inhibits bacterial cell wall synthesis by binding to a highly conserved motif of both lipid II and lipid III that are precursors of peptidoglycan and teichoic acid respectively. They also challenged that this particular antimicrobial works against a broad range of pathogens including *Staphylococcus aureus* and *Klebsiella pneumonia* (Ling et al., 2015).

Chapter 7

Conclusion and Future Directions

To conclude, our position in dealing with multidrug resistant pneumonia pathogens is not satisfactory at all. The pace at which antimicrobial resistance is spreading is a thousand fold faster than the introduction of new compounds, ultimately resulting into a grave health crisis. Unless we consider directing our future concern and research work on this field more on how to ameliorate the efficacy of the existing drugs and exploring novel approaches to meet the current unmet treatment options for the resistant pathogens, there is hardly any hope. One of the biggest guidance for future evolvement is not only to come up with an action plan but most importantly to implement the solution. Also, apart from introducing new antibiotics, preventing the spread of these resistant bacteria could be the key–whether by reducing the selective pressure that is to use fewer antibiotics or by preventing transmission through better infection control.

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