SECONDARY BACTERIAL INFECTIONS AND ANTIMICROBIAL DRUG RESISTANCE AMONG SARS-COV-2 PATIENTS ADMITTED IN THE INTENSIVE CARE UNITS IN SELECTED HEALTH FACILITIES IN MOMBASA AND NAIROBI COUNTIES, KENYA

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MOUNT KENYA UNIVERSITY

NOVEMBER, 2024

DECLARATION

This thesis is entirely original to me and has not previously been submitted for a degree at any other institution or for any other accolade.

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DEDICATION

This work is dedicated to my wife and children for their unwavering support for most of the time I have been away to undertake my studies.

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ABSTRACT

Antibiotics, particularly broad-spectrum antibiotics, have been overused in the treatment of Severe Acute respiratory Syndrome Corona Virus 2. Evidence suggests that this aids the spread of multidrug resistant bacteria. The number of studies in the country that have examined secondary bacterial infections in SARS-COV-2 patients, the proportion of these infections attributable to antimicrobial resistance (AMR), and the deaths related to this resistance are, however, extremely low. This study, therefore, assessed bacterial infections and AMR among SARS-COV-2 patients in Kenya. Specifically, it sought to determine the proportion of secondary bacterial infections among SARS-COV-2 patients, examine the proportions of these infections caused by antibiotic resistant pathogens and assess the mortality associated with secondary bacterial infections due to antibiotic resistant pathogens among SARS-COV-2 patients. Using a sample size of 385, the retrospective chart review targeted 385 SARS-COV-2 patients admitted with secondary bacterial infections at Kenyatta National Hospital, Mbagathi Hospital, Nairobi Hospital, Aga Khan University Hospital, Avenue Hospital and Coast General Teaching and Referral Hospital. The health facilities were purposively sampled while the number of study participants in each facility were proportionately sampled.Each participatint were randomly recruited from the hospital database. Only patients admitted in the ICU and whose records were complete with measurement of outcomes and availed to the research team were included. In addition, their samples must have been tested for antibiotic susceptibility. During the study period which stretched over 21 months period; from 13th March 2020 to December 2021. The correlation between the indiscriminate use of antibiotics with a broad spectrum and secondary infections caused by bacteria among SARS-COV-2 patients was investigated using a logistic linear regression analysis. Proportion of secondary bacterial infections among the SARS-COV-2 patients admitted in the selected health facilities in Mombasa and Nairobi Counties was higher among smokers ($p \leq .05$). Antibiotics resistance and mortality was also higher among patients who had secondary bacterial infections ($p \leq .05$). Relationship between secondary bacterial infections and antibiotic resistant was also high, a significant majority of patients with secondary bacterial infection developed multi-drug resistance ($\leq .05$) while at the same time mortality incidences attributed to secondary bacterial infections among SARS-COV-2 patients in ICUs in the selected health facilities in Mombasa and Nairobi Counties was high as well ($p \leq .025$). The findings underscore the need for judicious use of antibiotics in treating SARS-CoV-2 patients to mitigate the risk of antibiotic resistance. Healthcare facilities should implement antimicrobial stewardship programs to promote appropriate antibiotic prescribing practices. Further research is warranted to understand the epidemiology of secondary bacterial infections among SARS-CoV-2 patients and their association with antibiotic resistance and mortality in different settings. Public health interventions are necessary to raise awareness among healthcare providers and the general population about the appropriate use of antibiotics and the risks of antibiotic resistance.

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LIST OF ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
COVID-19	Corona Virus Disease of 2019
SARS-COV-2	Severe Acute respiratory Syndrome and Corona Virus 2
HMIC's	High and Middle-Income Countries
LMICs	Low and Low Middle Income Countries
MKUREC	Mount Kenya University Research and Ethics Committee
NACOSTI	National Commission for Science, Technology and Innovation
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
UMICs	Upper and Middle Income Countries
AMR	Anti Microbial Resistance
ICU	Intensive Care Unit
WHO	World Health Organization
UTI	Urinary Tract Infections
HAP/VAP	Hospital/Ventilator-Associated Pneumonia

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CHAPTER ONE

INTRODUCTION

1.0 Introduction

The background of the study, the problem statement, the study's objectives—both general and specific—the research questions, the justification, the scope of the study, its limitations, and its delimitation are all included in this chapter.

1.1 Background of the Study

SARS-COV-2 was responsible for 6,393,496 deaths and 573,833,499 confirmed cases as of July 28, 2022. Kenya reported 337,456 cases and 5,672 fatalities at the time (JU, 2022). The Kenyan government took a number of steps to stop COVID-19 from spreading throughout the nation. In March 2020, the Kenyan government halted all international flights into and out of the nation. Additionally, the government imposed travel restrictions, including curfews and the closing of schools. The government established a system for monitoring and testing contacts with COVID-19 patients in order to find those responsible. Along with building testing facilities across the country, remote areas were provided with mobile testing units. Those who tested positive for COVID-19 were required to be quarantined or isolated in order to prevent the virus from spreading. Facilities for isolation and quarantine were established by the government across the nation. The Kenyan government launched a nationwide vaccination campaign in March 2021, targeting healthcare workers, the elderly, and other vulnerable populations. The government has also been working to increase vaccine uptake among the general population. To increase awareness of COVID-19 and the value of adhering to public health regulations, such as

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donning masks and practicing social seclusion, the government launched public education campaigns. The government rolled out an economic stimulus package to support businesses and individuals affected by the pandemic. The package included tax breaks, loan guarantees, and cash transfers to vulnerable households. In general, the Kenyan the government's action regarding COVID-19 has been defined by an amalgamation of public health initiatives and financial aid for impacted people and businesses. However, issues like resource scarcity and vaccine reluctance among certain groups of people have hindered the effectiveness of these measures.

Weakness, loss of smell, exhaustion, and coughing are among SARS-COV-2's primary symptoms (Çalıca Utku et al., 2020; Cascella et al., 2022). Despite these unpleasant symptoms, most individuals usually have favorable outcomes (Cascella et al., 2022). In some individuals though, they lead to life threatening complications such as organ failure, septic shock, severe pneumonia, among others (Azer, 2020; Desai et al., 2022; Vakili et al., 2020). The case fatality is about 5-10% of the patients who contracts SARS-COV-2 (Çalıca Utku et al., 2020). SARS-COV-2 is associated with several risk factors and age is one of them. Evidence shows that people above the age 50 years have higher odds of dying from SARS-COV-2 (Dessie & Zewotir, 2021; F. K. Ho et al., 2020). The disease is also more pronounced among the males and those with co-morbidity (Li et al., 2020). Notably, individuals whose immune system is compromised or those ailing from tuberculosis, influenza alongside SARS-COV-2 are more likely to develop secondary infections (De Bruyn et al., 2022). Such findings have been reported with diseases like the H1N1. During the H1N1 pandemic in 2009, it is estimated that the disease killed 284,000 people and more

than 30% of these deaths were attributed to secondary bacterial infections (Cr et al., 2018, p. 1).

With this in mind, a surge in SARS-CoV-2 remains a public health concern. First, such an increase may overwhelm a country's health system especially in developing countries such as Kenya. This notwithstanding, studies also shows that most SARS-COV-2 patients especially those admitted in the ICU have a tendency of developing secondary bacterial infections (De Bruyn et al., 2022). (Achoki et al., 2019; Hamid et al., 2020). This problem is made worse by the fact that SARS-COV-2 patients who receive antibiotics without proper guidance run the risk of contracting secondary bacterial infections-related resistance to antibiotics (Zeshan et al., 2021). Despite these risks, indiscriminate administration of antibiotics in and out of ICU is a common practice during the management of SARS-COV-2 patients (Buehrle et al., 2020).

SARS-COV-2 is a self-limiting infection, and treating patients who have unconfirmed secondary infections caused by bacteria shows a clear abuse of antibiotics(Lucien et al., 2021). This practice if left unchecked may become a great threat to antimicrobial resistance and which may lead to poor outcome among the SARS-COV-2 hospitalized patients. Globally, it is estimated that antimicrobial resistance may cause more deaths and millions of dollars in losses than any other condition by 2050. These deaths are estimated at 10 million persons annually and about US$ 100 trillion in losses to the economy. Antimicrobial resistance may result in increased healthcare costs by 2030, with upcoming nations being the worst affected(World Bank, 2017).

However, the impact of SARS-COV-2 was not taken into account in these projections. Antibiotics were given to SARS-COV-2 patients without discrimination, but this did not improve the situation. This practice has the potential of triggering antimicrobial resistance in the world especially in the LMIC's where bacterial multidrug resistance is currently high (Mbelle et al., 2020). And this pegs the question, could SARS-COV-2 be leading to the earlier 2030 AMR estimates than it was predicted?

1.2 Problem Statement

Since the outbreak of SARS-COV-2 in 2019, there has been an increase and indiscriminate use of antibiotics particularly the broad-spectrum regimen in the management of SARS-COV-2 in the intensive care units (ICU) (Lucien et al., 2021). In Kenya, amidst the COVID-19 crisis, the situation remained the same, particularly in ICU settings. This indiscriminate use of antibiotics not only lacks robust clinical evidence but also poses a significant risk of fostering the emergence and spread of multidrug-resistant bacteria (Clancy et al., 2020). Despite these concerns, there is a glaring paucity of empirical studies investigating the prevalence and impact of secondary bacterial infections among COVID-19 patients in Kenyan ICUs, as well as the associated proportions of antimicrobial resistance and related mortality rates.

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1.3 Objectives

1.3.1 Broad Objectives

This study therefore sought to evaluate bacterial infections among SARS-COV-2 patient admitted in ICUs in selected health facilities in Mombasa and Nairobi Counties Kenya and the antimicrobial and deaths associated with these infections.

1.3.2 Specific Objectives

Specifically, it sought to:

1. To determine the proportion of secondary bacterial infections among the SARS-COV-2 patients admitted in ICUs in the selected health facilities in Mombasa and Nairobi Counties.
2. To examine the relationship between secondary bacterial infections and antibiotic resistant among the SARS-COV-2 patients in ICUs in the selected health facilities in Mombasa and Nairobi Counties.
3. To assess the mortality incidences attributed to secondary bacterial infections among SARS-COV-2 patients in ICUs in the selected health facilities in Mombasa and Nairobi Counties.

1.4 Research Questions

1. What is the proportions of SARS-COV-2 patients admitted in ICUs in the selected health facilities in Mombasa and Nairobi Counties with secondary bacterial infections?

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2. What is the relationship between secondary bacterial infections and antibiotic resistant among the SARS-COV-2 patients in ICUs in the selected health facilities in Mombasa and Nairobi Counties.
3. How many deaths are attributed to secondary bacterial infections among SARS-COV-2 patients in ICUs in the selected health facilities in Mombasa and Nairobi Counties?

1. 5 Justification of Study

The management of SARS-CoV-2 in intensive care units (ICUs) has raised concerns about antimicrobial resistance (AMR) due to the potential overuse or misuse of antibiotics (Lai et al., 2020). There is evidence suggesting a high incidence of additional bacterial infections among SARS-CoV-2 patients treated in ICUs (Langford et al., 2020). This phenomenon has prompted investigations into the relationship between antibiotic usage and the development of secondary bacterial infections among COVID-19 patients (Rawson, et al. 2020). For instance, a study conducted in a hospital in Wuhan, China, found that secondary infections occurred in 50% of ICU patients with COVID-19 (Zhou et al., 2020). Such findings underscore the importance of monitoring and documenting bacterial infections in COVID-19 patients receiving ICU care.

In Kenya, there is a growing need to investigate the incidence of secondary bacterial infections among COVID-19 patients in ICUs, particularly in medical centers located in the counties of Nairobi and Mombasa. This study aims to fill this gap by documenting the prevalence of bacterial infections among ICU-treated COVID-19 patients in specific

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medical centers in these regions for the first time. Additionally, the study seeks to assess whether the indiscriminate use of antibiotics in the management of COVID-19 patients contributes to the development of antimicrobial resistance and subsequent adverse outcomes, including mortality. By elucidating the relationship between antibiotic usage, bacterial infections, and patient outcomes, this research endeavor aims to inform evidence-based strategies for optimizing antibiotic stewardship and reducing the burden of AMR in Kenya's healthcare system.

1.6 Scope of Study

The study targeted SARS-COV-2 patients admitted in ICUs in selected health facilities namely: Kenyatta National Hospital (KNH), Mbagathi Hospital, Nairobi Hospital, Aga Khan University Hospital (AKUH) and Avenue Hospital in Nairobi County and Coast General Teaching and Referral Hospital (CGTRH) in Mombasa County. However, this was limited to patients whose samples were subjected to antimicrobial resistance sensitivity tests and their results made available to the researchers during the study. The two counties were deliberately chosen due to the substantial number of SARS-COV-2 cases and enrollment in these regions, during the study period which stretched over 21 months period; from 13th March 2020 to December 2021, the selected healthcare facilities served primarily as separation and medical facilities. Data collection was restricted to the first 21 months following the discovery of the nation's first case. No particular age group was excluded from the study. Proportionate sampling was used to obtain the number of participants in each county and participating health facilities. The participants were randomly selected from the hospital database using computer generated simple random sampling.

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1.7 Study Limitations

1. The study's sample size of 385 might not fully represent the diversity of SARS-CoV-2 patients in Kenya. Additionally, the selection of participants from only six health facilities might have introduced selection bias.
2. The study also only included patients with complete and available medical records, potentially excluding cases with incomplete documentation, which could affect the generalizability of the findings.
3. The study duration was 21 months and this might not have captured long-term trends in bacterial infections and AMR among SARS-CoV-2 patients.
4. Lastly, the accuracy of the collected data relied heavily on the completeness and accuracy of medical records, which varied among healthcare facilities.

1.8 Significance of the Study

1. The study highlights the potential consequences of antibiotic overuse in SARS-CoV-2 patients, emphasizing the need for judicious antibiotic prescribing to mitigate the risk of AMR.
2. Findings suggest a correlation between antibiotic resistance and mortality among SARS-CoV-2 patients with secondary bacterial infections, underscoring the importance of appropriate antibiotic therapy.
3. The study addresses a gap in understanding the epidemiology of secondary bacterial infections and their association with antibiotic resistance and mortality in the

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context of SARS-CoV-2, providing a basis for further research and intervention development.

1.9 Assumptions of the Study

The study assumed that findings from selected healthcare facilities in Nairobi and Mombasa Counties are representative of SARS-CoV-2 patients nationwide. It also assumed that the reliability and accuracy of antibiotic susceptibility testing results in identifying antibiotic-resistant pathogens. More so, it assumed a causal relationship between antibiotic overuse, bacterial infections, antibiotic resistance, and mortality among SARS-CoV-2 patients, which may be influenced by confounding factors not accounted for in the analysis.

1.10 Key Definition of Terms

Antibiotics: Drugs used to treat bacterial infections by either killing the bacteria or inhibiting their growth.

Broad-spectrum antibiotics: Antibiotics that are effective against a wide range of bacteria, including both Gram-positive and Gram-negative bacteria.

Multidrug resistant (MDR) bacteria: Bacteria that have developed resistance to multiple antibiotics, making them difficult to treat.

Antimicrobial resistance (AMR): The ability of microbes to resist the effects of medication, specifically antibiotics.

Secondary bacterial infections: Bacterial infections that occur in individuals already suffering from another primary infection, in this case, SARS-CoV-2.

ICU (Intensive Care Unit): Specialized hospital units equipped to provide intensive medical care, particularly for patients with severe illnesses or injuries.

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, the virus responsible for causing the COVID-19 pandemic.

Case Fatality Rate: The proportion of deaths from a certain disease compared to the total number of people diagnosed with the disease over a specific period.

Low- and Middle-Income Countries (LMICs): Countries with relatively low levels of income per capita. These countries often face challenges in healthcare infrastructure, access to medicines, and public health resources.

Public Health Initiatives: Actions taken by governments or organizations to promote and protect the health and well-being of communities. This can include measures such as vaccination campaigns, public education efforts, and the establishment of healthcare infrastructure.

Vaccine Uptake: The proportion of a population that receives a vaccine. High vaccine uptake is crucial for achieving herd immunity and reducing the spread of infectious diseases like COVID-19.

Counties: Administrative divisions in Kenya, of which there are 47. Each county has its own government and administration.

Health Facilities: Locations where medical treatment and care are provided, including hospitals and clinics.

Home-based care: Care provided to patients within their homes instead of in a hospital or medical facility.

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Real-time PCR (Polymerase Chain Reaction): A laboratory technique used to detect the presence of genetic material from the SARS-CoV-2 virus in samples collected from patients.

Confirmed cases: Individuals who have tested positive for SARS-CoV-2 infection.

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CHAPTER TWO

LITERATURE REVIEW

2.0 Introduction

This chapter consists of the introduction to the chapter, literature review and summary of conceptual frame work of the study.

2.1 Antibiotic prescribing patterns among healthcare providers for the treatment of secondary bacterial infections in SARS-CoV-2 patients

It is important to note that antibiotics are not effective against viruses such as COVID-19, as they only work against bacterial infections. However, in some cases, antibiotics may be prescribed alongside antiviral medications to treat secondary bacterial infections among COVID-19 patients. That being said, inappropriate antibiotic prescribing patterns among healthcare providers can have a number of negative consequences. Overuse or misuse of antibiotics can lead to the development of antibiotic-resistant bacteria, which can make it more difficult to treat bacterial infections in the future. Antibiotics can have a range of side effects, including allergic reactions, upset stomach, and diarrhea. Overuse of antibiotics can increase the risk of these side effects (Sharma et al., 2022). Unnecessary antibiotic prescriptions can result in additional healthcare costs, both for patients and healthcare systems. Overreliance on antibiotics can divert attention and resources away from more effective treatments for COVID-19, such as antiviral medications and supportive care measures. It is important for healthcare providers to carefully consider the need for antibiotics in COVID-19 patients and to follow appropriate prescribing guidelines to avoid these negative consequences Chong et al., 2021; Xu et al., 2020).

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The multi-characteristic and multi-step pathogenesis of SARS-CoV-2 suggest that it is ineffective to treat this lethal infection with only one class of medication, such as antibiotics, antivirals, antimalarials, anti-inflammatory medications, or immunomodulatory drugs (Sharma et al., 2022). Broad-spectrum antibiotic use, immunosuppressive/anti-inflammatory treatments, catheterization, and underlying diseases all increase the risk of secondary infections in patients with SARS-CoV-2 infection. Predisposing conditions include mechanical ventilation and ICU admission in critically ill patients (Arastehfar et al., 2020; Chen et al., 2020).

Studies conducted internationally show that SARS-CoV-2 inpatients often and unjustifiably take antibiotics. Empirical reports suggest that 60–100% of inpatients around the world receive broad-spectrum antibiotics (Chong et al., 2021; Xu et al., 2020). Abu-Rub et al. (2021) in a review reported that when considering the intricacy of the unique critical illness and the difficulties in excluding related bacterial co-infections, the reported high rates of antimicrobial medication prescription for SARS-CoV-2 patients admitted to ICUs could be partially understood. Molla et al. (2021) reported that a cross-sectional Point Prevalence Survey (PPS), carried out throughout SARS-CoV-2-specific wards in Dhaka Medical College and Hospital, patients who were in critical condition and those with elevated CRP and d-dimer values had a significant prevalence of numerous antibiotic prescriptions.

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Patients with severe or critical illnesses (75.4%) and those with mild or moderate illnesses (75.1%) experienced similar mean antibiotic prescribing rates over the first six months of the pandemic. In patients with mild or moderate illness and those with severe or critical illness, the proportion of patients who received antibiotic prescriptions without a medical need was 51.5% and 41.9%, respectively (Cong et al., 2021). A review by Rawson et al. 2020) showed that of the 2010 patients included in several studies, 1450 (72%) received antibacterial therapy; where reported, selected agents tended to be broad-spectrum and empiric, being prescribed across critical and noncritical care settings. Despite low rates of bacterial/fungal coinfection in patients with SARS-CoV-2, high rates of antimicrobial prescribing were reported. Other strategies, such as phage therapies, have recently been proposed as potential non-antibiotic therapy options (Manohar et al., 2020).

According to retrospective research, the prevalence of colonization by carbapenem-resistant Enterobacterales rose from 6.7% in 2019 to 50% in March–April 2020 (Tiri et al., 2020). The underlying causes included the high level of care that patients required, the vulnerability of 4-5 healthcare workers (HCWs) who had lengthy interaction with the patient, and the presence of 32 new HCWs who had never worked in an intensive care unit (ICU) environment (Tiri et al., 2020).The first wave of the SARS-CoV-2 pandemic was the subject of numerous research that prospectively examined antibiotic intake. There was a report of the rise in the use of amoxicillin-clavulanate, ceftriaxone, or azithromycin during the early stages of the pandemic, while over the following months, the use of broad-spectrum antibiotics such as carbapenems, daptomycin, linezolid, ceftaroline, and even

novel cephalosporin-lactamase inhibitor combinations rose, particularly in ICU (Abelenda-Alonso et al., 2020; Grau et al., 2021).

The progression of SARS-CoV-2 cases in hospitals was correlated with the biphasic pattern in antibiotic prescribing. In the absence of accurate information on bacterial co-infection in patients, the early stages of SARS-CoV-2 pneumonia were correlated with a high hospital admission rate and empirical antibiotic coverage of all cases (Ruiz-Garbajosa & Cantón, 2021).Health professionals' fear of contracting SARS-CoV-2 infection and hesitation to enter SARS-CoV-2 ICUs and wards caused the healthcare system to completely collapse and fall into accidental neglect, which ultimately jeopardized the program of antimicrobial stewardship policy. The availability of medications over the counter, the indiscriminate use of steroids, and multiple medical visits made the issue worse to the point where patients with mild symptoms were given many courses of antibiotics (Saini et al., 2021). Azithromycin which was often used alongside hydroxychloroquine during the pandemic, despite the fact that it was not advised outside of SARS-CoV-2 clinical studies, this was according to a survey conducted among Kenyan health workers (n = 379) (Onchonga et al., 2020).

2.2 Proportion of secondary bacterial Infections among people who have contracted SARS-Cov-2

So far, SARS-COV-2 has killed about 5.4 million people worldwide. A total of 240 million people globally have contracted the disease. Clinical symptoms of SARS-CoV-2 vary and may be mild, moderate or severe. In severe cases, the disease may be accompanied with an

acute pneumonia and in some instances, it result to death (Azer, 2020). Co-infection may further complicate the pneumonia (Barnes *et al*., 2021). Hospitalization is usually critical for those with severe cases and mechanical ventilation may be required to aid the patient in breathing (Azer, 2020; De Bruyn et al., 2022).

The variation in SARS-COV-2 may be attributed to several factors and this may include the age, the health condition, sex, medical condition of patient, among many more (Dessie & Zewotir, 2021; Li et al., 2020). Invasion of the lungs by viruses may alter the conditions of the lungs and this may predispose the lungs to secondary bacterial infections (C et al., 2012). In case of co-morbidity with a viral infection, the bacterial infections most often become severe and this has been clearly depicted during influenza outbreak. For instance, during the outbreak of H1NI flu in 2009, close to 30% of case fatality attributed to disease were caused by secondary bacterial infections. A similarly pattern of deaths have also been reported with SARS-COV-2 (Rawson et al., 2020). These deaths varies from 12.4 – 50% (Baghdadi et al., 2021). In China the figure stood at 34.5% (Y et al., 2020). Interestingly, most of the deaths were reported among patients who had been put on antibiotics.

It is not known whether the severity of SARS-COV-2 outcomes is due to secondary infections. But evidence from previous outbreak of influenza may say so (Cui et al., 2010). Data shows that 2 – 65% of severe influenza cases is attributed to secondary bacterial co-infections, and most usually progress to severe illnesses or even deaths (Lee et al., 2021). This situation tends to be complicated in SARS-COV-2 patients whose condition is acute. Severe cases of SARS-COV-2 more often lead to immunosuppression and such conditions

predispose SARS-COV-2 patients to co-infection. About 50% of such conditions will result to the death of the patient (Garcia-Vidal et al., 2020).

Countries which have reported high mortalities attributed to SARS-COV-2 deaths are Italy, China, Spain and the United States. Low mortalities have been reported in Africa and this may be due to underreporting (Africa CDC, (2020). Climatic conditions and variation in genetic composition may also be a factor. Rhinovirus remains the most dominant viral-co-infection among people who have contracted SARS-COV-2 and the least being influenza (Ding *et al*., 2020). Studies from other parts of Africa suggest that *Staphylococcus sp* leads to poor clinical outcomes (Choukrallah *et al*., 2020). Nevertheless, there is still scarcity of evidence on the microbial agents that leads to poor clinical outcome in SARS-COV-2 patients in Kenya.

2.3 Secondary Bacterial Infections Caused by Antibiotic Resistant Pathogens among hospitalized SARS-CoV-2 Patients

There was a drastic shift in managing SARS-COV-2 few months after the outbreak of the disease. One of the areas that were reviewed included administration of broad spectrum of antibiotics. This follows evidence that such practice may encourage development of *C. difficile* infections and this may lead to AMR (O'Neill, 2016). A case in point is Maryland, USA in 2020, which experienced a fast spread of bacterial MDR among SARS-COV-2 patients. Some of the factors associated with the spread of the disease included

overcrowding, excessive administration of antibiotics, severe disease and non-compliance to protocols to curb the spread of the infection (Patel et al., 2021).

Other secondary bacterial infections associated with SARS-COV-2 include *Candida auris* and *P. aeruginosa*. It is believed that these infections are associated with antimicrobial resistance and could be due to indiscriminate use of antibiotics in managing SARS-COV-2. The widespread use of antibiotics may have arisen out of the difficulty in distinguishing between those infections attributed to viral infection alone or pulmonary bacterial co-infections. There are varying experiences and outcomes in managing SARS-COV-2 globally. Some countries have reported that 30 patients out of 1,000 acquire resistant bacterial strains. One study in particular observed that of the 72 patients who were observed, 33% had AMR pathogens during the admission in the intensive care unit (Bogossian et al., 2020). Most likely this could be attributed to the overcrowding of these facilities, low adherence to protocols to control the infection and inadequate personal protective equipment (Magnasco et al., 2021). Long stays in the health facilities as the patient undergoes treatment may have also cause these infections.

Emerging trends from different hospitals also shows an increase in AMR among SARS-COV-2 patients and which may transform into a potentially lethal strain (Townsend et al., 2020). During the peak of the disease in China, about 31% of the patients who were on ventilators were estimated to have contracted pneumonia (Zhou et al., 2020). In India, 2.5% of such patients acquired candidemia (Chowdhary et al., 2020). One particular study

reported a high number of patients on invasive mechanical ventilators who had *A. baumannii* and about10% with *S. aureus* (Sharifipour et al., 2020).

Several bacterial infections occur simultaneously with SARS-COV-2. These include *Escherichia coli, Chlamydia pneumonia*e, *Acinetobacter*, *Mycoplasma pneumonia*e, *Klebsiella pneumoniae, Staphylococcus aureus, Legionella pneumophila, Haemophilus sp., Pseudomonas aeruginosa* and *Enterococcus* (U. Ho, 2021). Of all these pathogens, some like *Mycoplasma pneumonia*e, *Staphylococcus aureus, Chlamydia pneumonia*e, *Klebsiella pneumonia* and *Pseudomonas aeruginosa* occur widely. About 1.3% of the patients admitted in the intensive unit were reported to have developed resistant bacterial strains. This occurs in the backdrop that antibiotics is administered to about 88% of patients with confirmed SARS-COV-2 (L et al., 2020).

There is therefore a need to scale up interventions that can rapidly distinguish between viral and bacterial infections among SARS-COV-2 patients to prevent misuse of antibiotics. Proper guidelines supported with empirical evidence should be enacted. Biomarkers in SARS-COV-2 patients with viral or bacterial infections need to be identified especially those who present with acute symptoms respiratory illness (Pulia et al., 2020). Some evidence suggests that procalcitonin may help in reducing the administration of antibiotics in managing SARS-COV-2 by two days (Heesom et al., 2020).

2.4 Mortality attributed secondary bacterial infections caused by antibiotic resistant pathogens among SARS-CoV-2 patients hospitalized

Africa has a number of challenges which makes it prone to devastating consequences should a serious wave of the disease occurs in the continent. Evidence shows that SARS-COV-2 has severe outcome on the elderly and those whose immune system is compromised. The continent has a high number of people living with HIV/AIDS and prevalence of malnutrition. These two possess a major risk on the outcome of SARS-COV-2 (Yan *et al*., 2020). The situation becomes complex due to the poor health infrastructure which exists in the continent.

In Kenya, bacterial infections usually accompany most of the viral respiratory illnesses like influenza. Most of these co-morbidities more often result into acute diseases and death. In view of this, it usually calls for timely diagnosis and management of the diseases to forestall such poor outcomes (Rice et al., 2012). The percentage of co-infection of influenza and bacterial infection varies widely. However, this proportion is estimated to be between 20 and 30%. Majority of these infections are usually serious, has a great potential to cause death and require extensive amount of resources to treat and manage (Martín-Loeches, 2011).

However, the exact number of SARS-COV-2 patients who die from secondary bacterial infections in Kenya remains unknown. In particular, the deaths attributed to secondary bacterial infections due to antimicrobial resistance among SARS-COV-2 patients are undocumented. This is despite the known fact that widespread use of broad-spectrum antibiotics among SARS-COV-2 may lead to AMR. There is also a likelihood of secondary bacterial infections in managing SARS-COV-2 (Cox et al., 2020). AMR poses a serious

risk to the antibiotics efficacy. By 2050, it is believed that AMR will kill about 10 million people every year (O'Neill et al., 2016).

Knowing the exact the number of SARS-COV-2 patients dying from secondary bacterial infections as a result of antimicrobial resistance in the country is thus critical in formulating guidelines in the use of antibiotics in managing SARS-COV-2. This sentiment has already been advanced in other researchers (Huttner, 2020). There is a general consensus that AMR require an urgent attention both at the local and global level. According the World Health Organization (WHO) there is a need to coordinate these efforts especially in this era of SARS-COV-2 (WHO, 2021). If the observed trend persists, then there is likelihood that the world may brew in future a lethal strain of bacteria in the course treating SARS-COV-2 (Harbarth et al., 2016).

But the challenge is measuring the true scope of AMR especially in a country like Kenya where resources to undertake such an exercise are scarce. In areas of the world like Europe where this is effective, eight bacteria have been noted to have been resistance to antibiotics during the peak of SARS-COV-2 (WHO, 2021). These pathogens were also associated with high mortality. This study therefore will present an estimate of mortalities attributed to secondary bacterial infections among SARS-COV-2 patients.

2.7 Gaps in Literature Review

In Kenya, amidst the COVID-19 crisis, the situation remained the same, particularly in ICU settings. This indiscriminate use of antibiotics not only lacks robust clinical evidence

but also poses a significant risk of fostering the emergence and spread of multidrug-resistant bacteria (Clancy et al., 2020). Despite these concerns, there is a glaring paucity of empirical studies investigating the prevalence and impact of secondary bacterial infections among COVID-19 patients in Kenyan ICUs, as well as the associated proportions of antimicrobial resistance and related mortality rates.

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2.8: The Conceptual framework.

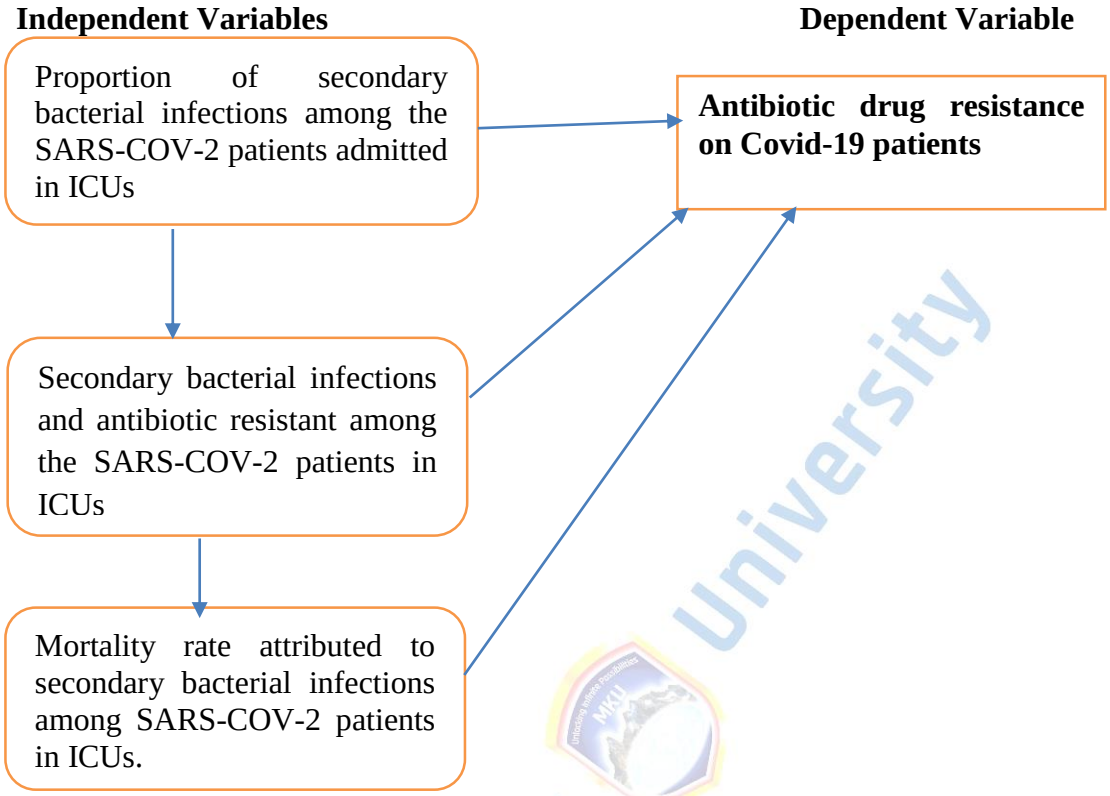

Figure 1 Conceptual framework.Source: Literature review by Researcher.

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CHAPTER THREE

METHODOLOGY

1.10 Introduction

This chapter covers the study's methodology, the population being studied, location, criteria, sampling strategy, sample size calculation, gathering information, management, and analysis, as well as ethical considerations..

3.1 Study Area

Kenya is divided into 47 administrative regions known as counties. During the initial stages of the disease, the Government issued a directive that all confirmed SARS-COV-2 be confined in health facilities. After home-based care guidelines were approved, this regulation was later revised. In Kenya, real-time PCR is the only technique used in government-accredited research facilities for verifying SARS-CoV-2 infection. By the end of 2022, 1,670 people had died from the illness, 662 were being treated in hospitals across the nation, and 3,024 were receiving home-based care (MoH, 2022).

Two counties—Nairobi and Mombasa—have been specifically selected for this study. These were the municipalities with the highest number of SARS-COV-2 cases at the height of the disease. The study concentrated on hospitals in these regions that served as SARS-COV-2 medical hubs. Three of these hospitals were public and three were private. Kenyatta National Referral Hospital (KNH), Mbagathi Hospital in Nairobi, and Coast General Teaching and Referral Hospital (CGTRH) in Mombasa County are the three public medical centers. Nairobi Hospital, Aga Khan University Hospital (AKUH), and Avenue Hospital are the three private hospitals in Nairobi.

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3.2 Research Design

The study was a retrospective cross-sectional study design. It retrieved data over 21 months starting 13th March 2020 and ending 31st December 2021. The information retrieved from the patients' records included admission and autopsy reports in case of deaths. The research design allowed the researcher to estimate the burden of secondary bacterial infection in the ICU and explore the relationship between the secondary bacterial infection and the observed mortalities in the ICU. It was also a cost-effective and robust design compared to other designs in view of the resources at the researchers' disposal.

3.3 Target Population

It targeted SARS-COV-2 confirmed patients admitted and administered antibiotics in health facilities in Nairobi and Mombasa between April 2020 and December 2020. In facilities recognized by the government during that time, Polymerase Chain Reaction (PCR) was used to confirm every SARS-COV-2 case.

3.4 Sample Size and Determination

The sample side was determined using the formula by…….. The sample size was arrived at using proportion an estimate and Standard Error (S.E) below.

$$n = \frac{P(100\% - P)}{(S.E)^2}$$

Where;

n – Desired sample size for each experimental and control group.

P – Proportion of SARS-COV-2 patients admitted and administered antibiotics in the participating health facilities during the study period.

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$$S.E = \frac{\text{Precision}}{\text{Stardard variate}}$$

$$S.E = \frac{5}{1.96} = 2.55$$

$$n = \frac{50\%(100\% - 50\%)}{(2.55\%)^2} = \frac{2500}{6.50} = 384.61 \cong 385$$

3.5 Sampling Criteria

Two counties were purposively sampled out for this study. All the health facilities in the selected counties acted as isolation and treatment centers for SARS-COV-2 patients during the study period. Proportionate sampling was used to obtain the number of participants in each county and participating health facilities. The participants were randomly selected from the hospital database using simple random sampling.

3.5.1 Inclusion criteria

Every individual were included, regardless of their age or co-morbidities. The study only included individuals who were admitted to the ICU and whose records were complete, available, and allowed for the measurement of outcomes. In addition, they were SARS-COV-2 individuals whose samples had been tested for antibiotic susceptibility, with the research team receiving the results.

3.5.2 Exclusion criteria

Prior to the SARS-COV-2 outbreak, any individual with a track record of resistance to antimicrobial drugs was removed from the investigation.

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3.6 Measurement of Outcome

3.6.1 Primary Outcome

Proportion of secondary bacterial infections was determined by the number of patients whose samples i.e. stools, sputum, blood, etc tested positive for bacterial isolate. And the mortality attributed to secondary bacterial diseases due antimicrobial resistance documented in the post-mortem records. Antimicrobial resistance was measured by the prior susceptibility test which was conducted in the sampled health facility during the treatment of the patient.

3.6.2 Secondary Outcomes

Secondary treatment was measured by the type of antibiotics prescribed and the immediate cause of death.

3. 7 Data Collection Procedure

The study sought ethical approval from Mount Kenya University Ethics Committee. Two weeks to data collection, the researcher recruited four research assistants as part of the research team. The researcher trained the four research assistants on the purpose of the study, seeking consent, extraction and summarization of the required data. The team conducted a pilot study a week to the main field work at MTRH in Eldoret. Prior to visiting the health facilities, the team obtained permission from the sampled health facility management to access and use the patients' records. Data from the patient's demographics, medical history, underlying concurrent illnesses, clinical manifestations, laboratory results, treatment and management options, and susceptibility to antimicrobial tests were extracted after reviewing the patients' medical records who tested positive for SARS-CoV2. The

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research team examined autopsy reports for fatalities to determine whether additional infections caused by bacteria were to blame. Data was summarized in a standardized form and then submitted to the principal researcher based at Thika on a daily basis. The principal researcher summarized the data in excel sheet for coding and analysis.

3.8 Data Collection Tools

Data were gathered using a data extraction tool administered by the research assisstants. The socioeconomic background of the patient, how they were treated from being hospitalized to discharge or death, and other information were all systematically gathered from the medical records at the time of admission.

3. 9 Data Management and Analysis

The gathered information was compiled in a Microsoft Excel spreadsheet. Then SPSS version 22 (IBM Corp, 2016) was used to analyze it. The percentages of additional bacterial infections among SARS-COV-2 individuals acknowledged in the chosen medical facilities in the counties of Mombasa and Nairobi were shown. Using chi-square and regression analysis, the connection between antibacterial resistance and additional bacterial infections was examined. It was also used to calculate the connection between attributed deaths and infections caused by secondary bacteria.

3.10 Ethical Consideration

The study sought ethical review and clearance from Mount Kenya University Ethics Committee (MKUEC). It also obtained research permit from the National Commission for

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Science, Technology and Innovation (NACOSTI). The research team obtained permission from all the participating health facilities.

The confidentiality of the individual was protected in accordance with international standards; first, all participants in the study signed consent forms that were informed. Identifiable information, such as names, initials, or hospital numbers, will not be made public in written form or in photographs of the participants unless it is necessary for scientific research and the individual being studied (or a parent or legal guardian) gives informed consent in writing for dissemination.

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CHAPTER FOUR

4.0 RESULTS

4.1 Participants' traits in the Investigation

A half of the patients were aged 41 – 64 (n = 193, 50.1%) and close to a third ≥ 65 years (n = 127, 33.0%). Majority of the parents were not obese (n = 248, 64.4%). However, most were hypertensive and diabetic (n = 259, 67.3%; n = 302, 78.4%). A substantial number did not have coronary heart disease (n = 294, 76.4%), cancer (n = 306, 79.5%) or history of a previous disease (n = 373, 96.9%). The length of stay for most of the individuals in the ICU was 1 – 6 days (n = 301, 78.2%).

The ratio of male to female was almost equal (49.6% vs. 50.4%). Several patients were non-smokers (n = 227, 59.0%). C-reactive protein (CRP) in the majority of the patients was moderate (n = 210, 54.5%) while the number of leukocytes were high among several patients (n = 285, 74.0%). Most of the patients SpO2 were < 90 on admission in the ICU (n = 299, 77.7%). Notably, a huge proportion of patients exhibited a high fever at admission in in the ICU (n = 273, 70.9%). A high number of patients were also administered with iron supplement during their stay in the hospital (n = 242, 62.9%).

According to figure 2, The most common isolated bacteria among the studied patients was *A. fumigatus* (n = 195, 50.6%), followed by *Enterobaterales* (n = 89, 23.1%), *K. pneumonia* (n = 68, 17.7%), *P. aeruginosa* (n = 22, 5.7%) and *S. aureus* (n = 11, 2.9%). Eight types of antibiotics were administered to the patients either before or after admission in the ICU. The drugs were administered either solely or in combinations. Those administered before admission in the ICU included *Cefoperazone* and

Ampicillin/Sulbactam while *Fluconazole*, *Meropenem* + *Vancomycin* or *Piperacillin/Tazobactam + Levofloxacin* were administered after admission. *Cefoperazone* was the most common antibiotics administered before ICU admission (n = 274, 71.2%) and combination of *Meropenem + Vancomycin* after admission (n = 164, 42.6%). This was closely followed by a combination of *Piperacillin/Tazobactam + Levofloxacin* (n = 129, 35.5%). A pantry 23.9% (n = 92) had taken Fluconazole as part of their therapy regimen. Table 4.1 below summarizes the characteristics of the patients who were sampled in this study.

Table 4.1: Characteristics of the patients and distribution of secondary bacterial infections

Characteristics of the patient	Secondary bacterial infections		
	Present n=182 (47.3%)	Absent n= 203 (52.7%)	*p*- value at 95 CI
Age			
20-40	29 (15.9)	36 (17.7)	.858
41-64	91 (50.0)	102 (50.2)	
≥ 65	62 (34.1)	65 (32.0)	
Obesity			
Yes	65 (35.7)	72 (35.5)	.960
No	117 (64.3)	131 (64.5)	
Hypertensive patient			
Yes	129 (70.9)	130 (64.0)	.159
No	53 (29.1)	73 (36.0)	
Diabetic patient			
Yes	144 (79.1)	158 (77.8)	.805
No	38 (20.9)	45 (22.2)	
CHD			
Yes	43 (23.6)	48 (23.6)	1.000
No	139 (76.4)	155 (76.4)	
Cancer patient			
Yes	37 (20.3)	42 (20.7)	1.000
No	145 (79.7)	161 (79.3)	
No personal history of disease			
Yes	3 (1.6)	9 (4.4)	.147

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No	179 (98.4)	194 (95.6)	
Duration of ICU Stay (days)			
1-6	148 (81.3)	153 (75.4)	.175
≥ 7	34 (18.7)	50 (24.6)	
Sex			
Male	93 (51.1)	98 (48.3)	.610
Female	89 (48.9)	105 (51.7)	
Smoker			
Yes	158 (86.8)	0 (0.0)	≤ .05*
No	24 (13.2)	203 (100.0)	
CRP on admission to the ICU			
Moderate	100 (54.9)	110 (54.2)	.919
High	82 (45.1)	93 (45.8)	
Leukocytes on admission to the ICU			
Moderate			
High	50 (27.5)	50 (24.6)	.561
	132 (72.5)	153 (75.4)	
SpO2 on admission to the ICU			
<90	137 (75.3)	162 (79.8)	.327
>90	45 (24.7)	41 (20.2)	
Fever at admission in the ICU			
High	43 (23.6)	69 (34.0)	.033*
Very high	139 (76.4)	134 (66.0)	
Type of infecting bacterial organism			
A. fumigatus	94 (51.6)	101 (49.8)	.134
Enterobaterales	45 (24.7)	44 (21.7)	
K. pneumonia	31 (17.0)	37 (18.2)	
P. aeruginosa	11 (6.0)	11 (5.4)	
S. aureus	1 (0.5)	10 (4.9)	
Antibiotic administered before ICU admission			
Ampicillin/Sulbactam	46 (25.3)	65 (32.0)	.176
Cefoperazone	136 (74.7)	138 (68.0)	
Antibiotic administered during ICU admission			
Fluconazole	51 (28.0)	41 (20.2)	.058
Meropenem+Vancomycin	80 (44.0)	84 (41.4)	
Piperacillin/Tazobactam+Levofloxacin	51 (28.0)	78 (38.4)	
Administered iron supplement during the hospital stay			
Yes	125 (68.7)	117 (57.6)	.027*
No	57 (31.3)	86 (42.4)	
Took Fluconazole as part of their therapy regimen			
None	131 (72.0)	162 (79.8)	.074

Took fluconazole	51 (28.0)	41 (20.2)	

Even more dangerous to public health than SARS and MERS is the unknown SARS-CoV-2, which had its first noteworthy outbreak in China in 2019. By June 15, 2020, it had infected nearly eight million people worldwide and killed 434,000 people (Guarner, 2020; Kannan et al., 2020). From being undetected to having serious viral pneumonia and breathing problems, which frequently result in mortality, there are various degrees of illness severity (Li et al., 2020). There are many different clinical COVID-19 symptoms and signs. Antiviral treatments that can lower fatalities and morbidity during an epidemic or pandemic must be developed and implemented right away. A condition that is or asymptomatic illness as well as serious breathing problems and death are all on the COVID-19 clinical manifestation spectrum, which is highly variable. Some people who contract the virus might not exhibit any symptoms at all, while others might experience a wide range of symptoms, including a high temperature, coughing, shortness of breath, exhaustion, discomfort in their bodies, loss of smell or taste, a sore throat, and migraines. According to a number of variables, including age, underlying medical conditions, immune status, and other factors, the illness's severity can also differ significantly from person to person. While the majority of COVID-19 infected individuals encounter mild to intermediate symptoms and recuperate without hospitalization, a small number may experience severe illness and necessitate hospitalization and even intensive care. The risk of contracting the virus and passing it on to others can be decreased by taking the necessary precautions, such as donning masks, engaging in physical distancing, and frequently washing your hands. It's critical to seek healthcare right away and heed the advice of

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medical professionals if you experience COVID-19 symptom (Guarner, 2020; Kannan et al., 2020).

Additional bacterial infections are an important factor to the progression of illness among individuals with advanced infection, despite a variety of possible new and reinvented anti-viral drug candidates that are able to avert virus replication as well as attachment. Although antibacterial agents have no effect on the virus its own identity, almost all critically ill individuals receive antibiotic treatment in an effort to stop the development of secondary bacteria-related infections. Any increase in the dosage of antibiotics given to SARS-Cov-2 patients will have a negative impact on the prevalence of nosocomial infections caused by bacteria that are resistant to antibiotics, which will lead to an increase in antibiotic-resistant bacterial pathogenic microbes globally (Reardon, 2020).

According to studies by Morris et al. (2017) and Wang et al. (2018), subsequent bacterial infections frequently cause a sizable amount of illness and death in individuals during or after their first encounter with a transmitted pathogen, which frequently results from a viral infection. While secondary infections frequently occur after the primary infection has spread, concurrent infections are brought on by several pathogens of a viral, bacteria, or fungal infections nature and show up at the same time. In particular for the viral-bacterial conditions that individuals experience the greatest number of times, there is often an intense commitment to an individual pathogen as opposed to a wide range of pathogens (Jamieson et al., 2010). Some of the most frequently isolated microbes during subsequent infections include Staphylococcus aureus among other genera (Handel et al., 2009).

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According to different studies (Hu et al., 2020; Wu et al., 2020; Zhu et al., 2020), the COVID-19 virus, also known as SARS-CoV-2, spreads and impacts a population at different rates. Among them are the distribution of ages, underlying health conditions, socioeconomic status, the density of the population, and ease of access to medical care. The severe condition and adverse effects of COVID-19 are more likely to cause older adults' deaths. Both COVID-19 infection and mortality have been found to be higher in Italy and Japan than in other countries because of their higher proportions of elderly people. People who have underlying medical conditions such as type 2 diabetes, cardiovascular disease, and being obese are more likely to suffer a serious injury or pass away from COVID-19. Countries with a high prevalence of these diseases, like the United States, have seen higher COVID-19 deaths and incidence rates.Individuals with lower socioeconomic status might be more likely to have jobs that require travel and may have fewer access to healthcare opportunities, both of which increase their likelihood of contracting certain diseases. COVID-19. For instance, compared to White Americans, Black and Hispanic Americans are more likely to contract COVID-19 and die from it. The COVID-19 virus may spread more readily in areas of dense population and crowded living. Cities with a dense population, such as New York City and Mumbai, have higher COVID-19 infection and mortality rates. For the purpose of diagnosing and treating COVID-19 infections, access to healthcare is crucial. In general, better healthcare systems and higher medical costs have produced better outcomes in terms of limiting COVID-19's spread and consequences. Population traits have a significant impact on the prevalence and consequences of COVID-19. The development of public health strategies to halt the

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pandemic must take into account these factors (Azuma et al., 2020; Hu et al., 2020; Sit et al., 2020; Zhang et al., 2020).

This study found that the majority of the patients with additional bacterial infections were between the ages of 41 and 61. Individuals in this age group may have had underlying illnesses like diabetes, heart disease, or pulmonary disease that raised their risk for subsequent infections caused by bacteria. This is a plausible explanation. These ailments can impair immunity and make it more difficult for the immune system to fight off diseases. The results conflict with the majority of studies, which show that people over the age of 61 were the group most affected by SARS-Cov-2(Ahamad et al., 2020; Collier et al., 2021). However, it agrees with a study that found that people under 61 are the most affected (Eva et al 2022). The age range of the SARS-Cov-2 patients admitted to the ICU ranged from 20 to 64 years old for 67% of them. The findings of Eva et al. (2020), who discovered that 52% of the individuals admitted to Spanish medical institutions were young adults between the ages of 18 and 65, are more in line with this outcome. In contrast to the Spanish study, neither patients under the age of 20 nor those over the age of 64 were included in this study (Eva et al., 2020).

4.2 Proportion of secondary bacterial infections among the SARS-COV-2 individuals admitted in the selected health facilities in Mombasa and Nairobi Counties

As provided in figure 3, of the 385 patients studied, 182 (47.3%) had developed secondary bacterial infections. This number was about half of the cases. This figure is higher than

what Mylene & Peter (2020) reported. However, it was lower than the rate of infection reported in earlier studies (Huang et al., 2020; Martinez-Guerra et al., 2021; Cheng et al., 2020), which ranged from 6% to 14%. The study also observed that, COVID-19 individuals experienced more secondary respiratory infections brought on by bacteria than individuals who had previously been afflicted by the H1N1 and Spanish flu pandemics (Morris et al., 2017, Morens et al., 2008, Louria et al., 1959). The KNH and Mbagathi hospital had almost equal number of patients with secondary bacterial infections (n = 54, 29.7% vs. n = 52, 28.6%). This was followed by those admitted at Avenue hospital (n = 32, 17.6%), CGTRH (n = 20, 11.0%), AKUH (n = 13, 7.1%) and then Nairobi hospital (n = 11, 6.0%). A half of the patients with secondary bacterial infections were 41 – 64 years (n = 91, 50.0%). Most of the patients who were not obese had a high number of secondary infections compared to their counterparts who were obese (n = 117, 64.3% vs. n = 65, 35.7%). There were also a remarkably high number of secondary infections among the hypertensive patients (n = 259, 67.3%) and diabetic patients (n = 144, 79.1%).

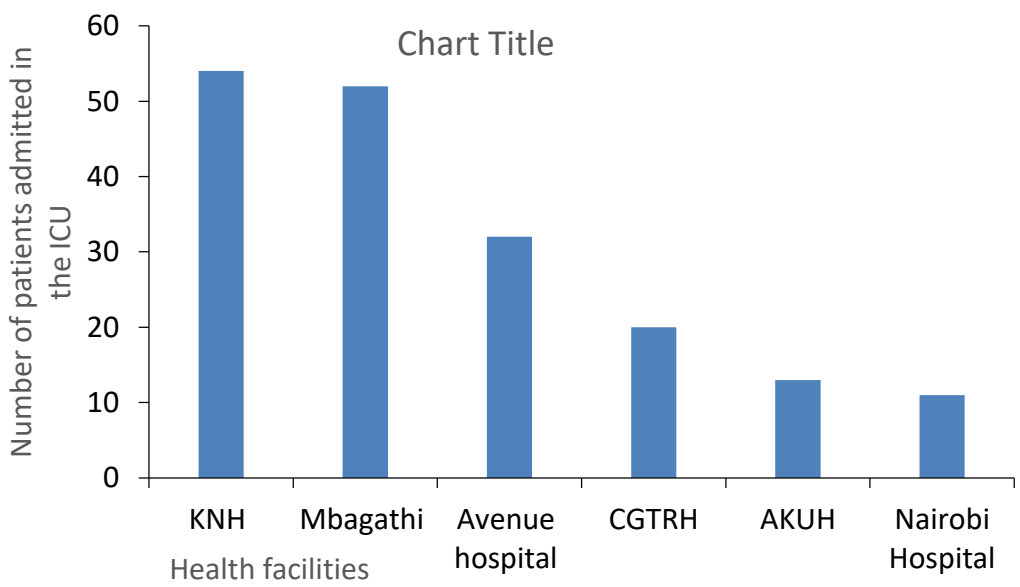

Figure 2: Number of patients that developed secondary bacterial infections from different hospitals

As indicated in figure 3, the high number of individuals with secondary infections was also reported among patients with no CHD (n = 294, 76.4%), non-cancer patients (n = 145, 79.7%), no personal history of disease (n = 179, 98.4%) and among those who had stayed in the ICU for 1 – 6 days (n = 148, 81.3%). The proportion of secondary bacterial infections was slightly more than half in male patients. (n = 93, 51.1%). It was also higher among patients who reported that they were smokers (n = 158, 86.8%). Those who had moderate CPR at admission in the ICU (n = 100, 54.9%), had a Sp02 < 90 at admission (n = 137, 75.3%) and high leukocytes levels (n = 132, 72.5%).

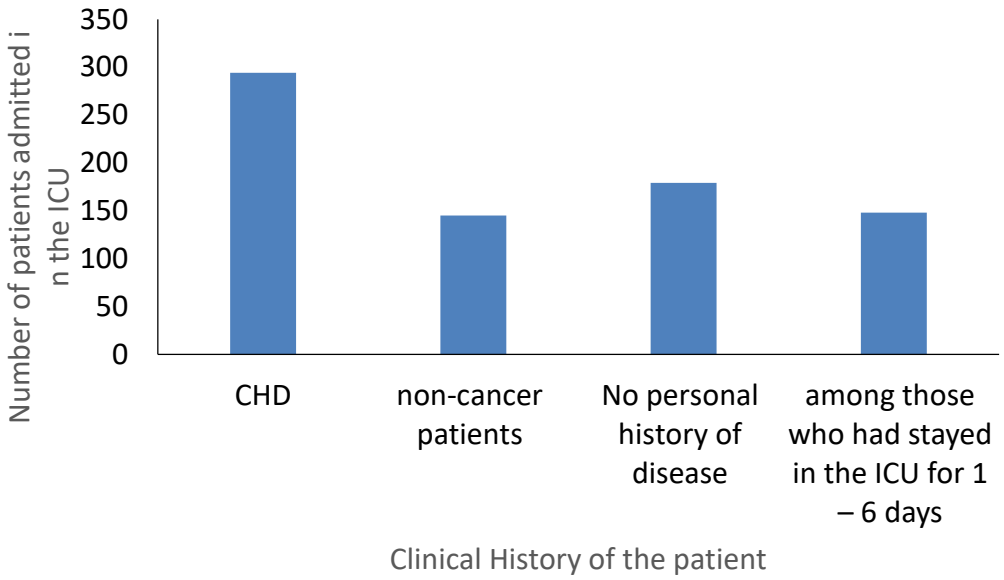

Figure 3: Number of patients with secondary infections among different patients

There was no significant difference in the proportion of secondary bacterial infections among patients who had the infections and those without with regards to age (p = .858),

obesity status (p = .960), hypertension (p = .159), diabetic status (p = .805), CHD (p = 1.000), cancer status (p = 1.000), no personal history of disease (p = .147), length of stay in the ICU (p = .175), sex of the patient (p = .610), leukocytes levels (p = .561), Sp02 (p = .327), antibiotics administered before admission in the ICU (p = .176), during admission in the ICU (p = .058), type of infecting bacteria (p = .134) and level of CRP at the time of admission in the ICU (p = .919). However, the proportions differed significantly with smoking ($p \leq .05$), fever (p = .033) and administration of iron supplement during admission in the ICU (p = .027).

Multiple regression analysis was used to analyze the three variables (smoking, fever at admission in the ICU and took fluconazole as part of their therapy regimen) further. Only the difference in proportion of secondary bacterial infections among the smokers and non-smokers remained significant ($p = \leq .05$). The difference in the proportions in the other two variables was insignificant. The model accounted for 78% of the observed difference in the proportions in the three variables (R^2 = .78). See Table 4.2 below.

Table 4.2: Regression coefficients for the analysis of the relationship between patient characteristics and secondary bacterial infections

	Coefficients that is Unstandardized		Coefficients that is Standardized			95% CI for B	
	B	Std. Error	Beta	*t*	Sig.	Lower Bound	Upper Bound
(Constant)	.05	.07	.00	0.75	.452	-.09	.20
Smoking	.89	.02	.88	35.95	.000	.84	.94
Iron	.04	.03	.04	1.67	.096	-.01	.09
Fever	.00	.03	.00	-.02	.986	-.05	.05

R = .88, Adjusted R^2 = .78

As shown above, patients who smoked most frequently had additional infections caused by bacteria. It is well known that tobacco smoke raises the risk of contracting a variety of bacterial infections (Juhi et al. 2008). Thus, it might have made the patients' conditions worse.

4.3 Relationship between secondary bacterial infections and antibiotic resistant among the SARS-COV-2 patients in the selected health facilities in Mombasa and Nairobi Counties

Of the 385 patients who were studied, antibiotics resistance was reported among 150 (39.0) patients. Of these patients, a significant number of those who had acquired secondary bacterial infections had developed antibiotics resistance (n = 149, 38.7%; $p = \leq .05$). See Table 3 below. Gram negative was the most common type of bacteria (133, 73.1%). The bacterial pathogens were isolated from cerebrospinal fluid, sputum, blood, urine and pus. As provided in figure 5. the main medium was the sputum (n = 107, 58.8%), then blood (n = 41, 22.5%), pus (28, 15.4%) and cerebrospinal fluid (n = 6, 3.3%).

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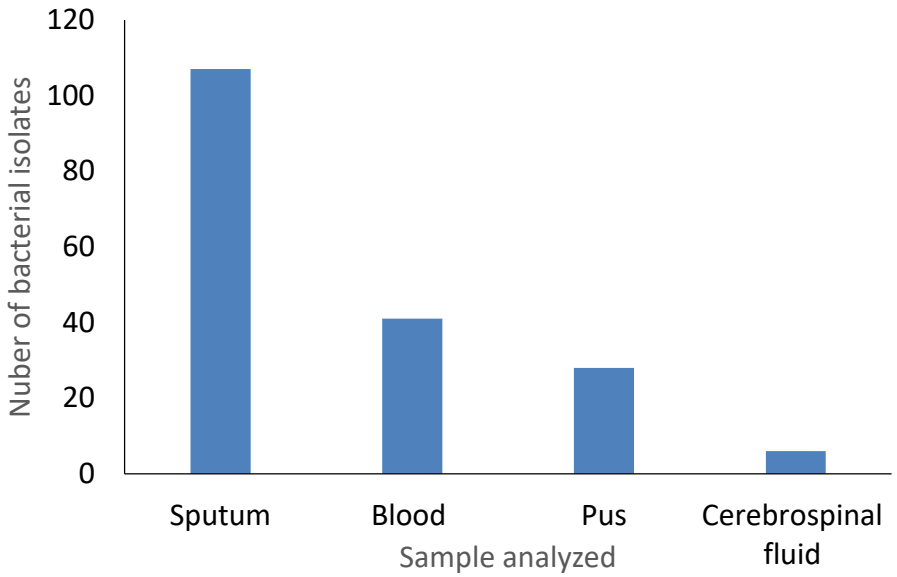

Figure 4: Quantity of bacterial pathogens isolated from different specimens

Table 4.2: Chi-square cross-tabulation of secondary bacterial infection and antibiotics resistance

	Secondary bacterial infections		
	Present n (%)	Absent n (%)	*p*- value at 95 CI
Multidrug resistance			
Yes	149 (99.3)	1 (0.7)	≤ .05
No	33 (14.0)	202 (86.0)	

The above relationship remained significant in multivariate analysis (p = .021). The model explained 69% of the relationship between secondary bacterial infections and antibiotics resistance (R^2 = .69). These findings are summarized in Table 4.4 below.

Table 3.4: Regression coefficients for regression analysis between secondary bacterial infection and mortalities attributed to SARS-COV-2

	Coefficients that is Unstandardized		Coefficients that is Standardized			95% CI for B	
	B	Std. Error	Beta	*t*	Sig.	Lower Bound	Upper Bound
(Constant)	.15	.05	.00	3.16	.002	.06	.25
Antibiotics resistance	.85	.03	.83	29.48	.021	.80	.91

R = .82, Adjusted R^2 = .69

The infectious diseases known as "invasive illnesses" brought on by infectious agents frequently occur in healthcare settings, where antimicrobial medications are frequently used. As a result, many of these diseases have developed resistance to a variety of antibiotics. The deliberate choice of pathogens that exhibit MDR is the result of decades of misuse of antibiotics and over prescription. MDR poses a threat to global health because, in many instances, there currently are no (chemical) antibiotics readily accessible to treat these types of infections, including follow-up infections. Recurrent bacterial infections are caused by exposure to infectious pathogens as well as by immune system dysfunction brought on by the initial infection caused by viruses.

International media attention has been focused on antibiotic resistance because it frequently results in fatal therapeutic failure, especially in patients with critical illnesses. When antibiotics are used as a "last resort" or in extremely high amounts, they frequently have negative side effects. Antibiotic resistance has developed in many major human infections (Kumar and Chordia, 2017).

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Gram-negative bacteria predominated in the current investigation's pathogen growth, with A. fumigatus, Enterobaterales, K. pneumonia, and P. aeruginosa being the most prevalent species. These pathogens and nosocomial infection are closely related. As opposed to some studies' findings (Li et al., 2020; Vijay et al., 2021; De Santis et al., 2022) that A. baumannii and K. pneumoniae had been the most prevalent infectious agents among the gram-negative bacteria, these findings are different. The most common pathogenic organisms, according to a study, are Mycoplasma species, Haemophilus influenzae, and Pseudomonas aeruginosa (Langford et al., 2020). The variations in the colonization of bacteria across each medical center and the variations in patient initial characteristics may be one of the causes of the variations in the bacterial structures in these studies.

Individuals with respiratory infections caused by viruses, such as COVID-19, are frequently given prophylactic antimicrobial drugs to reduce the risk of additional ailments (Holshue et al., 2020; Wang et al., 2020). These treatments are frequently used as an alternative to a distinct prescription antibiotic once the virus responsible for the disease has been identified. The prevalence of bacteria that are resistant to antibiotics is increasing, making super-infection more likely in patients with serious illnesses, especially in critical care facilities (ICUs).

Most patients with other infections may have developed MDR as a consequence, which is likely the root of the problem. Numerous clinical studies of COVID-19 individuals have been released throughout the country during the COVID-19 outbreak, but they primarily focus on the virus that causes the infection itself. Few studies have been done regarding AMR, and even fewer have covered additional bacterial infections. This study was unique

in that it brought attention to COVID-19 patients' subsequent bacterial infections and AMR. The rising number of measures needed for COVID-19 patients, the excessive administration of antibiotics, and the deterioration of hospital proper sanitation protocols are all likely contributing factors to the spreading of MDR strains of nosocomial pathogenic bacteria (Costa et al., 2022; Garcia-Vidal et al., 2021).

4.4 Mortality rate attributed to secondary bacterial infections among SARS-COV-2 individuals in the selected health facilities in Mombasa and Nairobi Counties.

Eighty-two patients died during the study period. This constituted 21.3% of the total participants. Significant number of these deaths were among patients who had secondary bacterial infections (n = 48, 58.5%; p = 0.025). See Table 4.5 From figure 5, the main bacterial pathogens isolated from the 48 patients was *A. fumigatus* (n = 23, 47.9%), followed by *Enterobaterales* (n = 10, 20.8%), *K. pneumonia* (n = 8, 16.7%), *P. aeruginosa* (n = 4, 8.3%) and then *S. aureus* (n = 3, 6.3%). Majority of the deceased patients had taken *Cefoperazone* before being admitted in the ICU (n = 36, 75.0%). The rest were on Ampicillin/Sulbactam (n = 12, 25.0%). A high proportion was also given a combination of *Meropenem + Vancomycin* while in the ICU (n = 32, 66.7%) with the remaining patients given *Fluconazole* or *Piperacillin/Tazobactam + Levofloxacin* in a ratio of 1:1 (n = 8, 16.7% vs. n = 8, 16.7%).

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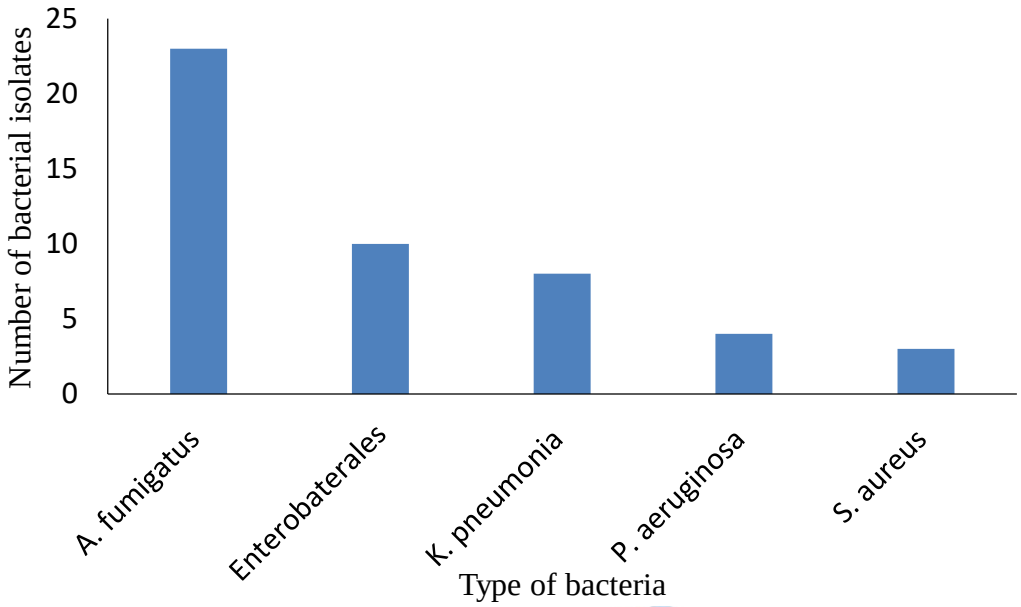

Figure 5: Proportion of bacterial pathogens isolated from SARS-COV-2 patients

Table 4.4: Chi-square cross-tabulation of secondary bacterial infection and mortalities attributed to SARS-COV-2

	Secondary bacterial infections		
	Present n (%)	Absent n (%)	*p*- value at 95 CI
Mortalities			
Yes	48 (58.5)	34 (41.5)	.025*
No	134 (44.2)	169 (55.8)	

*Significant at 95 % CI.

The association between mortalities and secondary infection bacterial infection were analyzed further with multivariate analysis. The analysis affirmed the earlier finding which associated secondary bacterial infections with SARS-COV-2 deaths in the ICU (p = .021). The model did a good fit in explaining 1% of this association (R^2 =.01). Refer to Table

4.6. This implies that there were other factors other than secondary bacterial infections which were causing mortalities in the selected hospitals in Nairobi and Mombasa.

Table 4.5: Regression analysis of secondary bacterial infection and mortalities attributed to SARS-COV-2

	Coefficients that is Unstandardized		Coefficients that is Standardized			95% CI for B	
	B	Std. Error	Beta	*t*	Sig.	Lower Bound	Upper Bound
(Constant)	1.27	.11	.00	11.21	.000	1.05	1.49
Mortality	.14	.06	.12	2.31	.021	.02	.26

R = .12, Adjusted R^2 = .01

As opposed to other investigations done in India and China (Zhou et al., 2020; Li et al., 2020; Huang et al., 2020), the findings of the current research revealed that the general mortality rate of COVID-19 patients who had additional respiratory infections was as high as 48.4%. Because COVID-19 was more well-known at the start of the global epidemic, patient care might have been administered differently, raising death rates. Kenya is also a low resourced country as compared to India and China who are advanced in the medical field and this could have led to high mortality observed in this investigation. According to (Khurana et al., 2021b), the high antibiotic demand in ICUs for managing COVID-19 individuals with contextual antimicrobials exacerbated the issue of AMR. This is particularly true for COVID-19 centers that lacked adequate microbiological support for culturing as well as lack the methods of culturing due to a lack of regulations, resources, or a fear of collecting samples.

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In the early stages of the COVID-19 outbreak, next bacterial infections caused 15% of cases seen in medical facilities, and 50% of those admitted passed away (Zhou et al., 2020). These outcomes corroborated the investigation's findings. In clinical COVID-19 cases, bacterial secondary pneumonia has been caused by additional bacterial infections in up to 50% of cases. 50 percent of COVID-19 fatalities had one or more secondary infections, whether they were pulmonary or not, which may have contributed to their demise. The air sacs in the lungs swell throughout severe COVID-19 ailments with pneumonia, providing a nutrient-rich environment for infectious agents like P. aeruginosa and S. aureus.

The virus's cytolytic enzymes rip through tissues, allowing bacteria to move forward and release toxins that further harm neighboring cells as they advance deeper into the tissue. When compared to COVID-19 survivors, patients who died from the disease experienced adverse effects related to bacterial involvement more frequently (30–40%) (Zhou et al., 2020). Breathing difficulties brought on by severe pneumonia, which may have been brought on by SARS-CoV-2 or may have developed as a result of a subsequent bacterial infection, are the most common cause of death in devastating COVID-19 cases (Tetro, 2020).

This research has some restrictions. Due to the retrospective aspect of the investigation and the fact that PCT testing was not consistently and uniformly done at the same time, it is likely that the true rate of additional pulmonary bacterial infection is higher than that identified in the present investigation. Clinical symptoms play a significant role in decisions about the likelihood of infection, the start of an infection, and the selection of an antibiotic. As a result, it's probable that PCT and bacterial microbiological assessments

were skipped for individuals with relatively mild symptoms, particularly in those who had received empiric antibiotics, which could lead to inaccurate results.

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CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusion

Secondary infections brought on by bacteria have a significant impact on the mortality and morbidity rates among people who are initially diagnosed with breathing problems viral illnesses. The findings of this study lend credence to the idea that infections brought on by bacteria resistant to antibiotics pose a significant risk to COVID-19 patients obtaining care in the ICU.

5.2 Recommendations

The elevated incidences of additional bacterial infections and antimicrobial drug resistance among SARS-CoV-2 infected individuals admitted to intensive care departments (ICUs) in facilities can be addressed by a combination of various strategies.

i. Facilities should put a high priority on implementing stringent infection-prevention and management procedures, including washing hands frequently, wearing personal protective gear, isolating infected patients, and disinfecting surfaces and equipment. These steps can lessen the risk of antibiotic resistance while preventing the spread of bacterial and viral infections..

ii. Health care providers should use antibiotics judiciously and only when necessary. Antibiotic overuse can result in antimicrobial resistance and raise the danger of additional bacterial infections. When prescribing antibiotics, clinicians should take into account variables like the individual's clinical circumstance, microbiological findings, and local resistance patterns.

iii. Facilities should monitor and track antibiotic use to identify patterns of overuse and misuse. This can help guide the development of antimicrobial stewardship programs and inform clinicians of local resistance patterns. Monitoring can also help identify patients who may be at risk of developing secondary bacterial infections and facilitate early interventions.

iv. To enhance the diagnosis and treatment of infections caused by bacteria, facilities should make laboratory capacity investments. Clinicians can choose the best antimicrobial therapy and lower the risk of resistant bacteria with the aid of rapid and precise identification of bacteria-related infections.

v. Research can aid in determining the best approaches to treating COVID-19 patients' secondary bacterial infections. Facilities should conduct research on the epidemiological investigations, diagnosis, and treatment of infections brought about by microorganisms in COVID-19 patients. This can enhance patient outcomes and provide data for the development of evidence-based recommendations..

vi. By following these suggestions, facilities can lower the number of SARS-CoV-2 patients admitted to ICUs who develop additional bacterial infections and resistance to antibiotics.

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Annexes

A. Data Collection Tool

Patient Research No:				
Patient county of origin				
Date of birth?	DD	MM	YY	

Tick the most appropriate response

What is the age of the patient?	20-40	
	41-64	
	≥ 65	
Patients gender	Male	
	Female	
Was the patient obese?	Yes	
	No	
Was the patient hypertensive?	Yes	
	No	
Was the patient diabetic?	Yes	
	No	
The patient had coronary heart disease?	Yes	
	No	
Was the patient having cancer?	Yes	
	No	

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No personal history of disease	Yes	
	No	
Duration of ICU Stay (days)	1 - 6	
	≥ 7	
Was the patient smoking?	Yes	
	No	
CRP on admission to the ICU	Moderate	
	High	
Leukocytes on admission to the ICU	Moderate	
	High	
SpO2 on admission to the ICU	<90	
	>90	
Fever at admission in the ICU	High	
	Very High	
Type of infecting bacterial organism	*A. fumigatus*	
	Enterobaterales	
	K. pneumonia	
	P. aeruginosa	
	S. aureus	
Antibiotic administered before ICU admission	Ampicillin/Sulbactam	
	Cefoperazone	

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Antibiotic administered during ICU admission	*Fluconazole*	☐
	Meropenem+Vancomycin	☐
	Piperacillin/Tazobactam+Levofloxacin	☐
Administered iron supplement during the hospital stay	Yes	☐
	No	☐
Took Fluconazole as part of their therapy regimen	Yes	☐
	No	☐

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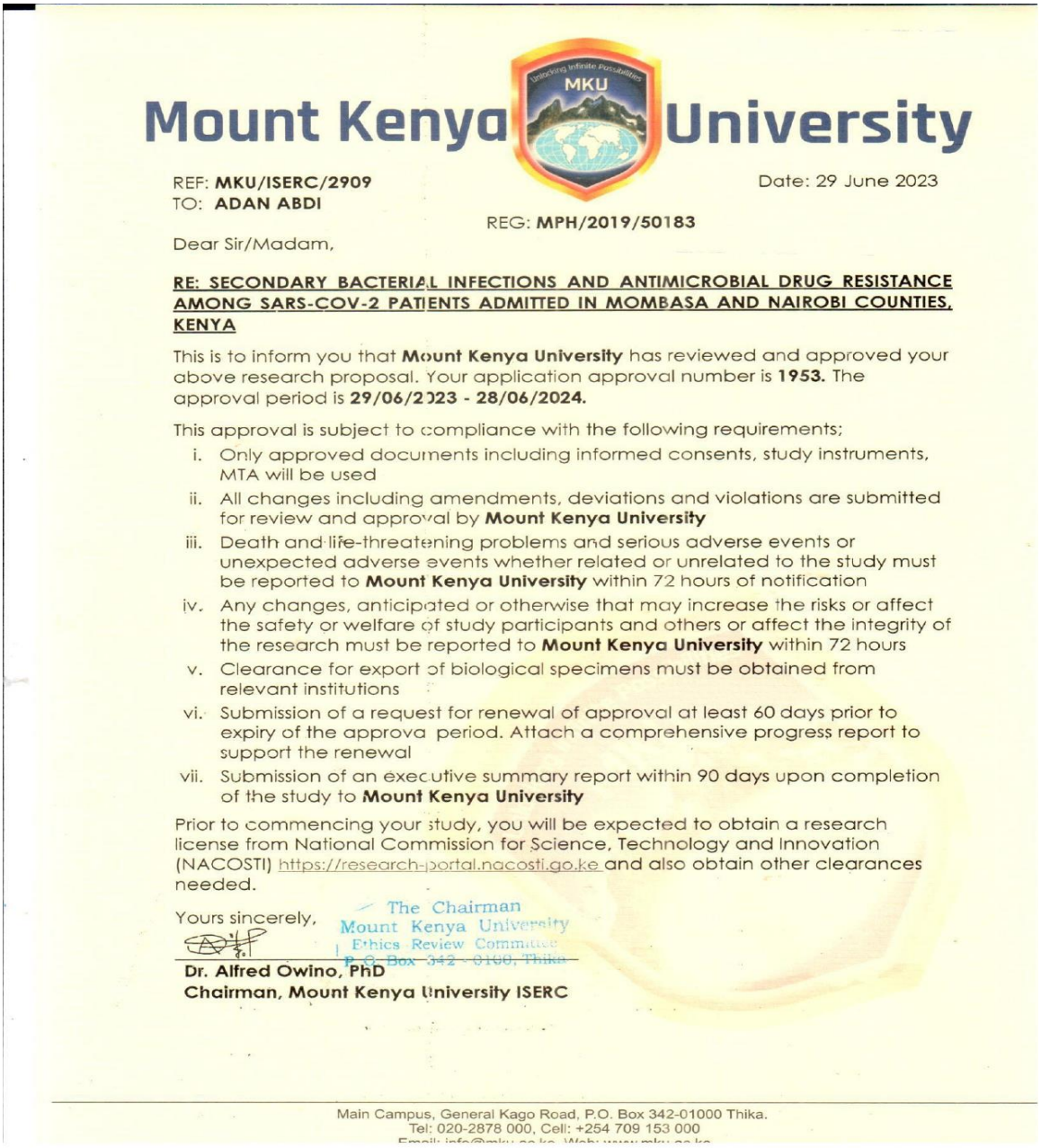
B: ERC Certificate



Mount Kenya University

REF: **MKU/ISERC/2909**
TO: **ADAN ABDI**

Date: 29 June 2023

REG: **MPH/2019/50183**

Dear Sir/Madam,

RE: SECONDARY BACTERIAL INFECTIONS AND ANTIMICROBIAL DRUG RESISTANCE AMONG SARS-COV-2 PATIENTS ADMITTED IN MOMBASA AND NAIROBI COUNTIES, KENYA

This is to inform you that **Mount Kenya University** has reviewed and approved your above research proposal. Your application approval number is **1953.** The approval period is **29/06/2023 - 28/06/2024.**

This approval is subject to compliance with the following requirements;

i. Only approved documents including informed consents, study instruments, MTA will be used
ii. All changes including amendments, deviations and violations are submitted for review and approval by **Mount Kenya University**
iii. Death and life-threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to **Mount Kenya University** within 72 hours of notification
iv. Any changes, anticipated or otherwise that may increase the risks or affect the safety or welfare of study participants and others or affect the integrity of the research must be reported to **Mount Kenya University** within 72 hours
v. Clearance for export of biological specimens must be obtained from relevant institutions
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal
vii. Submission of an executive summary report within 90 days upon completion of the study to **Mount Kenya University**

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

The Chairman
Mount Kenya University
Ethics Review Committee
P. O. Box 342 - 0100, Thika

Dr. Alfred Owino, PhD
Chairman, Mount Kenya University ISERC

Main Campus, General Kago Road, P.O. Box 342-01000 Thika.
Tel: 020-2878 000, Cell: +254 709 153 000

C.Introductiory letter

Mount Kenya University

DIRECTORATE OF GRADUATE STUDIES

MPH/2019/50183

30th June, 2023

National Commission for Science Technology & Innovation (NACOSTI)
Off Waiyaki Way, Upper Kabete,
P.O Box 30623- 00100
NAIROBI, KENYA

Dear Sir/Madam,

RE: ADAN ABDI - REGISTRATION NO. MPH/2019/50183

The purpose of this letter is to introduce the above named student who is pursuing **Master of Public Health** in the department of **Epidemiology and Biostatistics** in the school of **Public Health.**

The title of the research is **"Secondary Bacterial Infections and Antimicrobial Drug Resistance among SARS-COV-2 Patients Admitted in Mombasa and Nairobi Counties, Kenya."** It has been cleared by the University's Ethics Review Committee (Certificate attached) and now has to proceed to the field to collect data between **July, 2023 and September, 2023.**

Any assistance accorded to the student will be highly appreciated.

Thank you.

Mount Kenya University
P.O. Box 342-01000, THIKA
Office of the Director
Graduate Studies

Dr. Samuel M. Karenga, Ph.D
Director, Graduate Studies
Enc.

Main Campus, General Kago Road, P.O. Box 342-01000 Thika.
Tel: 020 2878 000, Cell: +254 709 153 000

D. NACOSTI License

REPUBLIC OF KENYA

NATIONAL COMMISSION FOR SCIENCE, TECHNOLOGY & INNOVATION

Ref No: **260276**

Date of Issue: **20/July/2023**

RESEARCH LICENSE

This is to Certify that Mr.. ADAN ABDI ALI of Mount Kenya University, has been licensed to conduct research as per the provision of the Science, Technology and Innovation Act, 2013 (Rev.2014) in Mombasa, Nairobi on the topic: SECONDARY BACTERIAL INFECTIONS AND ANTIMICROBIAL DRUG RESISTANCE AMONG SARS-COV-2 PATIENTS ADMITTED IN THE INTENSIVE CARE UNITS IN SELECTED HEALTH FACILITIES IN MOMBASA AND NAIROBI COUNTIES, KENYA for the period ending : 20/July/2024.

License No: **NACOSTI/P/23/27668**

260276

Applicant Identification Number

Director General
NATIONAL COMMISSION FOR SCIENCE, TECHNOLOGY & INNOVATION

Verification QR Code

NOTE: This is a computer generated License. To verify the authenticity of this document, Scan the QR Code using QR scanner application.

See overleaf for conditions

E: Map of the Study Area