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The Causes and Control Measures of Extended Spectrum Beta-Lactamase Producing Enterobacteriaceae in Long-Term Care Facilities

Ismaila Olatunji Sule
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Walden University

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Ismaila O. Sule

has been found to be complete and satisfactory in all respects,
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Walden University
2021

Abstract

The Causes and Control Measures of Extended Spectrum Beta-Lactamase Producing

Enterobacteriaceae in Long-Term Care Facilities

by

Ismaila O. Sule

MSc., University of Ulster, 2012

Graduate Certificate, University of Ulster, 2008

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health – Epidemiology

Walden University

May 2021

Abstract

Due to extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE), infections among residents are increasing in long-term care facilities (LTCFs), resulting in high rate of morbidity and healthcare costs. ESBL-PE resists empirical antibiotics and reduces treatment options, and a designated infection control team is unavailable to prevent the prevalence of the disease. Ecological theory guided this study. A systematic review and meta-analysis were conducted to characterize the causes of ESBL-PE and evaluate the infection control strategies within LTCFs. Multiple regression analysis (MRA) was included as supplementary statistical analysis to identify relationships between LTCFs, geographical locations, infection control measures (ICMs), and ESBL-PE. A systematic search was conducted for studies from January 2008 to December 2018. Twenty-two from 3,106 met the inclusion criteria. The pooled prevalence for ESBL-PE among LTCFs residents was a mean difference (MD) of 15.78 (95% CI: 0.04, 31.53). Risk factors included the influence of regional areas was standardized mean difference (SMD) of 0.61(95 % CI: 0.32, 0.91) in Europe, SMD was 14.92 (95% CI: 9.17, 20.68) in Asia, and SMD was 0.51(95% CI: 0.35, 0.67) in other regions (North America and Australia). Nine of 22 studies reported ICMs was MD of 13.59 (95% CI: 5.32, 21.86). Meta-analysis and MRA revealed a statistically significant association between LTCF and ESBL-PE among residents ($p= 0.05$). Strict adherence to infection control measures in LTCFs is needed to address this ESBL-PE prevalence among residents. The potential positive social change is promoting knowledge about vulnerable residents in LTCFs and the community factors responsible for ESBL infection.

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Dedication

First and foremost, I dedicate this study to the Almighty God for giving me the strength, wisdom, and knowledge to see me through from the beginning to the end of this project. I also dedicate this project to my beautiful wife, Grace Sule, who has been supportive, encouraged me from the starting of the program, and ensure that I completed what I started a few years ago. To my children (my heroes) -Wale, Yemi, Boye, and Lekan, who have been slightly affected by this financially inclined quest. I thank you, and I cannot quantify my love for you all. God bless you. To my late mummy, Serifat Sule, who shared her words of advice and encouragement to finish this program before she was dead in 2016. I love you, mum.

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Chapter 1: Introduction to the Study

Introduction

Long-term care facilities (LTCFs) serve as a different type of health care setting that provides a certain level of care services for individuals of all ages. The facilities have been increasingly caring for a broader range of residents who need exceptional healthcare services. LTCFs include nursing homes, assisted living facilities, residential care homes, skilled nursing facilities, and domiciliary care homes, etc. The facility homes serve as home and health institutions for approximately 75% of older adults and individuals with intellectual disabilities (Johansson et al., 2017). Despite the caring nature of these facilities, it also, however, provided a unique setting for sharing infections within residents and between health care facilities via workers who work in more than two care homes (Curran, 2017). Essential types of diseases commonly transmitting in LTCFs include urinary tract infection (UTI), respiratory tract infection (RTI), skin and soft tissue infection, and gastrointestinal infection (GI) (Montoya & Mody, 2011). Notably, about 94% of these diseases are found in LTCFs (Cotter et al., 2012; Heudorf et al., 2012). The infections may be caused by pathogens associated with community-acquired infection or hospital-acquired infection; for example, *Enterobacteriaceae* species is an essential cause of several of these diseases (Cassone & Mody, 2015). In a study conducted by Pop-Vicas et al. (2008), the researchers observed a colonization rate of 51%. These isolates included *Escherichia coli*, *Klebsiella pneumonia*, *Morganella morganii*, *Enterobacter species*, *Proteus mirabilis*, and *Providencia stuartii*. The study also indicated that risk factors that caused

pneumonia were due to *Enterobacteriaceae* multidrug-resistance organisms because most of the residents have already exposed to the past six months' uncontrolled use of antibiotics as well as low activities of the daily living score. The rapid dissemination of these infections is severe and can resist multiple drugs, which was considered as one of the main threats to global public health with no sign of abating (Kaarme et al., 2018). The severe modes of these diseases are more evident in elderly residents because of their prolonged exposure to risk factors, already mentioned above, which has been evaluated by most studies as one of the significant risk factors of chronic diseases caused by *Enterobacteriaceae* (Pulcini et al., 2019). For example, older people in LTCFs in France were investigated to have a risk of about 40% higher than their domiciliary elderly clients in the community of having antibiotic resistant *Enterobacteriaceae* cultured from their urine samples (Pulcini et al., 2019). The risen of *Enterobacteriaceae* species occur in a multidrug resistance isolates because of their intent to distribute, acquire additional resistance enzymes, and exhibit complications in the therapeutic management of infected patients, particularly in vulnerable elderly ill patients (Shaikh et al., 2015). More often, these *Enterobacteriaceae* produced extended-spectrum beta-lactamases, beta-lactamase-inhibitor-resistant TEM enzymes, and stably derepressed plasmid-encoded AmpC cephalosporinases (Tsukamoto et al., 2014). The isolates are also characterizing with cross-resistance to aminoglycosides and fluoroquinolone with high mortality and morbidity (Tsukamoto et al., 2014). Even the emergence of *Enterobacteriaceae* species that resist carbapenem types of antibiotics in most communities is sporadically making the treatment of elderly residents so difficult (Gohil et al., 2017). Residents whose care

needs devices like breathing machines, catheters, or intravenous catheters and residents who are taking long courses of certain antibiotics are also most at risk for Extended spectrum beta-lactamase (ESBL) infections and carbapenem-resistant *Enterobacteriaceae* (CRE) infections (Centers for Disease Control and Prevention [CDC], 2015). Because of the sizable number of *Enterobacteriaceae* species involved, this dissertation concentrated on the most common genera and species isolated from clinical settings, include, *Escherichia coli*, *Klebsiella pneumonia*, and *Proteus mirabilis*, *Serratia marcescens*, *Citrobacter species*, and *Enterobacter species* accounted for the majority of *Enterobacteriaceae* isolated from clinical specimens. This study is significant because *Enterobacteriaceae* accounted for a high proportion of infection among residents living in LTCFs in the United Kingdom (UK) and the entire world was a great concern (Public Health Agency, 2019) on how to reduce the spread of the disease. Extended spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL-PE) have limited treatment alternatives and thus endangering a more significant number of patients and residents (Weiner, 2016). The CDC and World Health Organization (WHO) considered ESBL-PE infection as severe threats and recognized the organism as an urgent concern for drug development (Tacconelli et al., 2018; WHO, 2017). The study provided significant insights into *Enterobacteriaceae* resistance patterns and informing public health, infection control, and antimicrobial stewardship approaches to curb the spread of the emerging pathogens. The objective of this systematic review and meta-analysis was to justify the causes of prevalence and control measures of ESBL-PE in LTCFs. The reasons for writing this dissertation were to contribute to knowledge of outbreaks among elderly

residents in LTCFs and be able to find a solution to research questions generated for this dissertation.

Background

Antimicrobials are used to treat infections of various diseases caused by microorganisms, including bacteria, mycobacteria, viruses, parasites, and fungi (WHO, 2016). Since the discovery of the modern era of antibiotics by Sir Alexander Fleming in 1928 (Pidcock, 2012; Sengupta et al., 2013), the transformation of contemporary antibiotic medications that saved millions of lives (CDC, 2013), and the difficulties in the management of antibiotic resistance microorganisms globally, the phenomena are, however, endangering the efficacy of the power of antibiotics (Golkar et al., 2014). In most clinical and public health cases where antibiotics are used, the microbes initiated a means to make antibiotic agents ineffective. Under these circumstances, resistance develops anywhere antibiotics are used, including the community, healthcare, and on the farm (Prestinaci et al., 2015). The microorganisms that caused resistance had always been attributed to the inappropriate prescription or misuse of antibiotic drugs and the inability of the pharmaceutical industry to produce new medication due to the challenging regulatory requirements (Michael, 2014). Based on this characterization, the CDC has classified some multidrug *Enterobacteriaceae* resistance microorganisms responsible for placing a significant clinical and financial burden on the global healthcare system, patients, and their families (CDC, 2018). These *Enterobacteriaceae* species are cross-resistance because they produce ESBL enzyme not only to hydrolyze beta-lactam ring of penicillin and third generation-cephalosporins (TGCs) but also inactivating quinolone

and aminoglycosides. These organisms have caused approximately 26,000 healthcare-associated (HCA) infections per year in the USA (CDC, 2018). Also, it was estimated that 140,000 HCA *Enterobacteriaceae* infections occur in the United States every year, resulting in bloodstream infections that result in more than \$40,000 hospital charges per occurrence (CDC, 2018). However, the threat of this disease is no more limited to the hospitals; it is also a threat to elderly residents in LTCFs (Public Health England, 2016). Pelly et al. (2006) study described nursing homes as a proxy and closed living quarters that could contribute to antibiotic-resistant infections and probably had a relationship with the occurrence of ESBL-PE infection among the residents in the LTCFs (Blom et al., 2016). These ESBL-PE have been consistently inflicted on nursing home residents in the United Kingdom and other parts of the world (Blane et al., 2016). Traditionally, ESBL-PE was associated with hospital settings, but more recent studies have also shown increasing isolation of ESBL strains in the community-based long-term care settings (Flokas et al., 2017; Livermore et al., 2005). Nursing, residential care homes, and other LTCFs have been suggested to be a reservoir for ESBL-PE in the community (Arpin et al., 2003; Rice et al., 1990; Rooney, 2009). Cefotaxime producing (CTX-M) *Escherichia coli* was first reported from Ireland in 2005 (Morris et al., 2005) and was associated with the LTCFs outbreak, soon afterward in 2006 (Pelly et al., 2006). Most of these elderly residents repeatedly at risk of acquiring ESBL-PE because they were often exposed to excess use of antibiotics, previous hospital admission, incontinence, urinary catheters, and decubitus ulcers (Overdevest et al., 2016). Research indicated that there were several approaches to analyzing risk factors and the prevalence of *Enterobacteriaceae* that

produces ESBL enzyme in the community where LTCFs are located. In laboratory surveillance of *Enterobacteriaceae* (Public Health England, 2017), the trends and geographical distribution of *Enterobacteriaceae* species rates were reported. Even cases of these infections were further broken down by bacterial species and by patient age and sex. However, the prevalence of the trends of ESBL-PE colonization differed significantly across the LTCFs (Lautenbach et al., 2012). In one observational study (Sandoval, 2004) of ESBL-PE towards the residence in LTCFs, the research was focused explicitly on resident's early exposure to cephalosporins because of their prior extended stay in the hospital coupled with the increased use of gastrostomy tubes in the care home, of which, resulted in the occurrence of *Enterobacteriaceae* resistance to third-generation cephalosporins. Rooney et al. (2009) also reported that residents were colonized with an extremely high prevalence of multidrug resistance *Enterobacteriaceae* of gut carriage of residents. As noted by each assessment, all the above-mentioned research methods provided credible and logical results. The gaps in the above-highlighted research were unable to give reasons for the significant differences in the prevalence of the trends of ESBL-PE colonization across the sites. The objective of this dissertation was to conduct a systematic review and meta-analysis to identify the causes and risk factors associated with the prevalence of ESBL-PE from the pool evidence and to identify effective control measures for curbing the pathogen. Considering the current knowledge of the epidemiology of ESBL-PE infections in LTCFs, it is, however, poorly understood the incidence of the disease as well as control measures involved. The study is focusing on the assessment of the infection control measures for the prevention of ESBL-PE in

LTCFs, and the data collected from 2008 to 2018 was explored to clarify the measure of the distribution of ESBL-PE and effective infection control in these facilities and informed clinical and public health awareness of this growing problem.

Problem Statement

Enterobacteriaceae that produce extended-spectrum beta-lactamase (ESBL) convey plasmid-encoded enzymes that can effectively dissolve and confer resistance to a variety of beta-lactam antibiotics (Shaikh et al., 2015). Although, in Europe, these enzymes are mostly found in *Escherichia coli* (ECO) and *Klebsiella pneumonia* (KLP), they also present in other members of the *Enterobacteriaceae* (Rawat & Nair, 2010). The rise and transmission of ESBL-PE is a public health threat because they associated with increased morbidity, mortality, and healthcare costs (Rawat & Nair, 2010). Arpin et al. (2003) and Duval et al. (2019) suggested that nursing homes and other LTCFs have been placed as a reservoir for ESBL-PE in the care homes. Most of these residents are repeatedly a risk of acquiring the infection because they were often exposed to unguided use of antimicrobial, previous hospital admission, incontinence, urinary catheters, and decubitus ulcers (Feneley et al., 2015; Nicolle, 2014). Because ESBL-PE is associated with poor patient outcomes, control the transmission of these infections in LTCFs after their acquisition is essential to curb further spread in areas where they have become endemic (Flokas et al., 2017). Effective identifying infection control measures is an essential step to prevent residents from becoming colonized or infected with these infections. Although some LTCFs have addressed the spread of ESBL-PE by creating new strategies to curb the spread, they do not have a designated infection control

practitioner compared with the hospital set-up (Cohen et al., 2015). To control the spread of ESBL-PE in nursing homes, the CDC approved the use of personal protective equipment (PPE) to prevent blood and body fluids split and during high-contact resident care activities (e. g. dressing, bathing/showering, and transferring) that provided opportunities for transfer of ESBL-PE to staff's hands and clothing (CDC, 2019). This systematic review and meta-analysis aim to identify from all available evidence the causes of ESBL-PE prevalence and the efficient use of infection control measures to reduce or stop the spread in LTCFs. The summary of this evidence may be used by LTCFs to develop guidance on this topic and help to control the dissemination of ESBL-PE within residents and between health care facilities via workers who work in more than two care homes.

Purpose of the Study

Long-term care facilities serve a different type of health care settings that cares for individuals of all ages and provides a certain level of care services. The facility homes also serve as home and health institutions for most older adults and individuals with intellectual disabilities (Johansson et al., 2017). Despite the caring nature of these facilities, the facilities also provided a unique setting for sharing multidrug resistance organisms (MDROs), such as ESBL-PE infections within residents and between health care facilities via workers who worked in more than two care homes (Curran, 2017). These organisms can cause urinary tract infections, as well as severe infections in the bloodstream and central nervous system. Numerous journals have conducted research on these MDROs with different methods of controlling the infections without much success.

The purpose of this study is to use systematic review and meta-analysis to identify, evaluate, and compile the findings of all relevant individual studies on the causes of the prevalence and control of ESBL-PE in LTCFs and the evidence for the effectiveness of infection control and prevention strategies. The intervention measures are aimed at preventing and controlling the spread of ESBL-PE in elderly care homes, especially when residents are in a debilitating health condition or transferred from the hospital. The examination of ESBL-PE outbreak within elderly resident homes permitted this research to present the evidence about the role of targeted or non-targeted infection control interventions, which includes screening tests in the etiology of ESBL enzymes in LTCFs. The study identified the effective control measures applied against the prevalence of ESBL-PE in LTCFs of previous research. I developed the search strategy for the publications which are published from 2008 to 2018 from at least two electronic databases like PubMed/Medline, Embase, and Cochrane by using the following terms: extended-spectrum beta-lactamase-producing *Enterobacteriaceae* long term care facilities or ESBL-PE long term care facilities or ESBL-PE long term care facilities and infection control long term care facilities or infection prevention long term care facilities. I screened the search records based on title and abstract through a screen called First Pass Screening (FPS), which was retrieved through databases against the predefined eligibility criteria. Quality assessment based on study design of included studies were evaluated using New Castle Ottawa Scale for observational study. Statistical analyses were performed using the “Cochrane RevMan” statistical software program. The meta-analysis of categorical data was analyzed, and pooled the estimates, and presented as

analysis of continuous data was analyzed, and pooled the estimates, and presented as Mean Difference (MD) along with their 95% confidence intervals (CIs). I also performed a subgroup analysis based on region, ICMs etc., to find the heterogeneity.

Research Questions and Hypotheses

The study was conducted to gain insights into the occurrence and characteristics of ESBL-PE infections among elderly residents in LTCFs reflected in the relationships between variables under study. Because of the type of LTCFs, the geographical location of LTCFs, effective infection control measures, and ESBL-PE infection rates. Based on this information, the research questions mentioned below are relevant to be addressed:

Research Question 1: Is there an association between LTCF and the prevalence of ESBL-PE infection rates among residents in the presence of other predictors?

H_01 : There is no association between LTCF and ESBL-PE infections in the presence of predictors.

H_a1 : There is a significant association between LTCF and ESBL-PE infections in the presence of other predictors.

Research Question 2: Is there an association between geographical locations (environmental sources) and ESBL-PE in LTCFs in the presence of other predictors?

H_02 : There is no association between geographical locations (environmental sources) and ESBL-PE infections in the presence of predictors.

H_a2 : There is a significant association between geographical locations (environmental sources) and ESBL-PE infections in the presence of other predictors.

Research Question 3: Is there an association between Infection Control Measures and ESBL-PE infections?

H_03 : There is no association between infection control measures and ESBL-PE infections in the presence of predictors.

H_a3 : There is a significant association between infection control measure and ESBL-PE infections in the presence of other predictors.

Theoretical Framework

The ecological theory was used as a construct for this research. The theory can detect and improve infection control and public health policy (Smith et al., 2005).

Currently, there were three overlapping conceptual frameworks that have been dominating the study of the emergence and dissemination of infectious disease since decades ago. This overlapping framework only focuses on pathogen infecting a single patient over the population, and researchers thus developed a drug that cures individual patient (Smith et al., 2005). From an ecological context, the risk factors of diseases often emanated from the collection of population and the environment. But the ecological theory used population genetics and dynamics approaches to understand and predict the prevalence of infectious disease that informed patient treatment (Smith et al., 2005). In this concept, the ecological approach was used to provide details on LTCF types, geographical location, demographic of residents in the facilities, and the effective infection control measures and the occurrence of *Enterobacteriaceae* organisms, including *Enterobacteriaceae* that produces ESBL enzymes. The term “LTCF” refers to any different types of care homes which provide broad range of healthcare services to

people with limited ability to respond to action independently (European Centre for Disease Prevention and Control [ECDC], 2016). Each type of LTCFs, or geographical location of LTCFs may have similar risk factors to residents with different outcome variables in the following research questions: (1) Is there an association between LTCF type and the prevalence of ESBL-PE infection rates among residents in the presence of other predictors? (2) Is there an association between environmental sources and ESBL-PE in LTCFs in the presence of other predictors? (3) What are the essential components of effective infection control in preventing LTCFs outbreaks? Under these circumstances, the epidemiological construct was used to detect risk factors for the occurrence of ESBL-PE isolates and preventing residents from these infectious diseases in all types of LTCFs. The ecology theory has achieved various development in the prevention and control of infectious diseases around the world. Because of this theory, public health institutions and Non-governmental organisations (NGOs) were loaded with the design and maintenance of health programs and capitalized on the insights provided by ecological theory to prevent and control infectious diseases (Smith et al., 2005). The theory has used host demography and distribution to predict the emergence of infectious diseases. In this theory, ecological and evolutionary dynamics has been used to predict pathogen–host shifts (Smith et al., 2005), and determining effective and efficient allocation of resources to disease surveillance.

The Nature of the Study

The study was based on a descriptive literature review and meta-analysis of the published and unpublished studies from 2008 to 2018, investigated the prevalence of

ESBL-PE infection in LTCFs, and to identify infection control measures used to reduce the spread. The statistical analysis of combines results of multiple studies on Infection control measures on transmission of ESBL-PE in LTCFs was succinctly examined to answer the research questions. The dissertation was registered with the Preferred Reporting Items Systematic Reviews and Meta-Analysis (PRISMA) guidelines to prevent risk of numerous articles addressing same research questions, reduce bias in accumulated publications, and to provide transparency in the study (National Institute for Health Research [NIHR], 2019). I ensured that all steps of the review process conform to published systematic review designs as recommended in the Cochrane Handbook and Centre for Reviews and Dissemination's (CRD) guidance for conducting systematic reviews. I included all studies involved all designs investigated an infection control intervention for patients admitted in LTCFs who were at risk of becoming infected with ESBL-PE. This study was influenced by the information that I obtained from the databases. I created a list of keywords related to my research topic and research questions to search for published and unpublished literatures. Some useful databases were searched for journals and articles from January 2008 to December 2018, and these included Walden University's library catalogue, Medline, Google Scholar, Ebsco Embase, Cinahl, and bibliographies of identified research and reviewed articles were checked further for more studies. I have been cleared by Walden University IRB to review and synthesize data from unpublished and published studies.

Definitions

The definitions used in this research are intended to help readers understand the clinical and scientific concepts, allowing clarity in the meaning of the terms within the study's context to clarify the purpose and direction of the investigation being conducted.

Cephalosporins refer to a class of antibiotics originally derived from the fungus called Acremonium, which was previously known as "Cephalosporium" Toai Bui; (Charles V. Preuss).

Extended-spectrum beta-lactamases (ESBL) are enzymes that cause resistance to most beta-lactam antibiotics, including penicillin, cephalosporins, and the monobactam aztreonam. These enzymes are found exclusively in gram-negative organisms, such as *Klebsiella pneumonia*, *Klebsiella oxytoca*, and *Escherichia coli*.

Long-term care facilities (LTCFs) represent a different type of health care settings that serve individuals of all ages and provide variable degrees of care. Examples of LTCFs include nursing homes, skilled-nursing facilities providing post-acute care, assisted living facilities, retirement homes, rehabilitation centers,

Drug-resistant gram-negative organisms refer to resistance of microorganisms to three or more different antimicrobial classes.

Enterobacteriaceae refers to a large family of Gram-negative bacteria including *E. coli*, *Klebsiella* species and *Proteus* species.

CTX-M beta-lactamases — These enzymes were named for their greater activity against cefotaxime than other oxyimino-beta-lactam substrates (for example, ceftazidime, ceftriaxone, or cefepime).

Assumptions

The first assumption is that the meta-analyses sum up a few evidence-based articles to examine ESBL-PE prevalence and effective infection prevention measures in LTCFs. The second assumption is that systematic collections of evidence-based journals from the databases like PubMed/Medline, Google Scholar, Embase, and Cochrane for the analysis are reliable and valid. These databases are reliable because it resulted in almost the same search outcomes if it was searched whenever searching the exact keywords. After writing the theoretical foundation of my study, I assumed that my study's foundation is sound. This ecological conceptual framework is a concept that has been tested and proven to prevent or control diseases in the communities in previous research. The theoretical framework that I used is assumed to be an accurate reflection of the systematic review and meta-analysis of prevalence and effective control of ESBL-PE in LTCFs being studied. Therefore, my study results were limited by the theoretical framework's accuracy to reflect the phenomena under study. The fourth assumption is recognizing ESBL enzyme producers among *Enterobacteriaceae* species, confirming ESBL Production through a combination disc method in the laboratory. The ESBL-PE under investigation and finds have been clearly defined, and it is being measured in accredited laboratories. So, I assumed that any documents collected via public databases contained the information necessary to draw valid and reliable conclusions. I conducted a systematic review and meta-analysis; I believed that I was unbiased in reporting what I observed. I also assumed that the variables under investigation are measurable, and the instrument used is valid and reliable instrument to measure those variables. Importantly, I

assumed the methodology used in this research was suitable to the problem being addressed and the purpose of the study. I completed my analysis, and I assumed that the results are generalizable beyond the sample collected for studies. Finally, I assumed that the results of the study were appropriate to stakeholders.

Scope and Delimitations

The study's scope is limited to *Enterobacteriaceae* species microorganisms among residents in LTCFs in a systematic review and meta-analysis approach. One of the aims and objectives of this research is to reduce the spread of microbes among residents in LTCFs. This research has begun with what we are already known about ESBL-PE, what would be added to the topic's synopsis, and the significance for public health practice. I investigated the trends of ESBL-PE and determined their variations according to the types of LTCFs. Residents who were exposed to cases of ESBL-PE introduced by LTCFs. Irrespective of gender, age, and ethnicity. Targeted or non-targeted infection control interventions that included screening tests were employed to determine the infection control level. Standard precautions or placebo screening are used as a comparator. Incidence or frequency of infection was used to assess transmission or spread of ESBL-PE within residents in LTCFs with the outcome of morbidity and mortality rate. Studies that did not report data on acquisition outcomes were excluded from the scope of this research. The research only involved the literature on randomized controlled trials and observational studies. I developed the search strategy for at least two electronic databases like PubMed/Medline, Embase, and Cochrane by using key search terms: The publication period that lasts for ten years, that is, publications published from

2008 to 2018 were investigated. Journals that are published before 2008 and after 2018 were excluded. The variations of the organisms were identified according to the species and their susceptible character. The mechanisms susceptible nature of *Enterobacteriaceae* species in the production of ESBL enzymes that resist third generation-cephalosporins were evaluated. I provided some context to this review, outline the medical significance of ESBL-PE mostly affected LTC residents, highlight the implications of managing the diseases before it confers resistance to universally used empirical beta-lactam antibiotic therapy. A brief description of ESBL-PE distribution was provided, including a discussion on susceptible antibiotic patterns, the development of ESBL among residents, and the mechanisms of ESBL. Notably, a brief detail of the current situation of the medical significance of *Enterobacteriaceae* surveillance in LTCFs was provided, and the key areas for developing effective control and prevention of the disease was highlighted. I discussed the development of ESBL among residents in LTCFs, including the mechanisms of ESBL and the susceptible antibiotic patterns of the pathogens. I investigated the reasons for differences in the trends of ESBL-PE colonization across the different types of LTCFs, understanding if there is an association between the geographical location of LTCFs, targeted infection control, and the occurrence of ESBL-PE infection among the elderly residents. The evidence base for the essentials of ESBL-PE surveillance was discussed with the status of the clinical importance of *Enterobacteriaceae* surveillance in global health. In this analysis, I highlighted the crucial areas for preventing ESBL-PE among the residents in different types of LTCFs. I conducted a high-level systematic review of ESBL-PE scholarly studies to proffer public

health solutions to the research questions mentioned above. I used a systematic review to identify, select, evaluate, and synthesize all high-quality research evidence relevant to the research questions to answer them. Besides, I provided evidence-based insight to describe the potential source of ESBL-PE infection between resident's LTCFs. Also, I used a systematic review to review information from both published and unpublished studies relating to infection control strategies in LTCFs. In a meta-analysis of this review, I used statistical methods, Comprehensive Meta-Analysis (CMA) software to incorporate data from the investigated individual research studies, used the combined information to come to new statistical conclusions by selecting, evaluating, and synthesizing all available evidence.

Limitations

This research seeks to identify and sum up the findings from the eligible available evidence to establish the relationships between ESBL species' trends among residents in LTCFs, their variations according to the types of LTCFs, and to identify effective infection control measures. However, the methodological quality of systematic review and meta-analysis studies often restricts the study's scientific value because of the studies' heterogeneous nature. In this study, I intend to limit my analysis to the included data to represent the best available evidence. The studies examined during an outbreak always take up inadequate methodologies in assessing the efficacy of the infection prevention measures introduced. The methods of pre, during, and post enforcing prevention measures of incidence or prevalence of ESBL-E design, such design is likely to be subjected to some biases, including the risk of confounding. I also intended to examine

groups of targeted and untargeted infection control measures, including screening at a single time point. Only infection prevention measures that changed between the pre- to post-infection prevention measure periods are likely to be considered associated with any change in ESBL-PE prevalence in LTCFs. Under these circumstances, it may be difficult to measure or determine the reasons responsible for the observed effects likely to be poorly reported in many available data. However, the interventions are part of a collection of measures that cannot be examined in isolation. Furthermore, compliance may be poorly reported in some studies implementing infection control. In this study, external circumstances played a role in compliance and enforcing infection prevention measures. For instance, an improvement in compliance can be due to the presence of a known observer, known as the 'observer effect,' a well-documented effect for infection prevention measures, such as hand hygiene. The data intended to be retrieved for this research could be heterogeneous, especially concerning locations, populations, outcomes, outcome evaluation techniques, and infection control measures, precluding quantitative analysis. The low reporting quality may impede the investigation of these studies. However, the reporting guidelines can be readily available to correct the anomaly. For instance, the 'Outbreak Reports and Intervention studies of Nosocomial infection' (ORION) statement are useful reporting guidelines.

Significance

The dissertation is not only significant to the recent release of the UK five-year antimicrobial resistance strategy from January 2014 to December 2018 (Global and Public Health Group, 2017) but also aligning with the public health agency aims and

objectives of establishing Healthcare-Associated Infection and Antimicrobial Stewardship Improvement Board of 2016 in Northern Ireland. The development of this Board is a process of preventing gram-negative *Enterobacteriaceae* infections in public and private care homes through antimicrobial stewardship and infection control initiatives (Global and Public Health Group, 2017). Furthermore, during the global action plans in 2015, the World Health Assembly called all countries to execute national antimicrobial resistance strategies to tackle multidrug-resistant organisms by strengthening surveillance and research. This research aligns with that objective (World Health Organization, 2015). However, the multisectoral collaboration has been emerged to organize its systems to achieve effective action against the spread of MDROs such as ESBL, which can be interpreted into practice (Wesangula & Hickey, 2018). Firstly, the rationale for undertaking this research is to contribute to the evidence base of knowledge on the risks and prevalence of ESBL in LTCFs. The informed knowledge provided data estimates of resistance to commonly used antibiotics (cephalosporins) to treat *Enterobacteriaceae* species and identify the organisms' trends in the LTCFs. The significance of this study may also justify reconsidering use of carbapenem antibiotics for residents in LTCFs, where it is recommended as the last option choice for *Enterobacteriaceae* that resist cephalosporins in the treatment of many diseases (Patterson & Bradley, 2017; Rodríguez-Baño, Gutiérrez-Gutiérrez, Machuca, & Pascual, 2018), and making corrections for antibiotics stewardship strategies to prevent occurring of carbapenems producing *Enterobacteriaceae*. The other significance of this study is the potential outcomes to inform decisions on residents' treatment with diseases caused by ESBL-PE. I

also used the study to identify the reasons for the significant differences in ESBL colonization trends across all the sites and understand relationships between the environmental differences risk factors of LTCFs and ESBL-PE occurrence. Importantly, however, the study helped reveal the underlying presence of ESBL infection in LTCF settings and improve healthcare policymakers to evaluate strategies of reducing the prevalence of this infection. Thirdly, the findings of variables correlated with ESBL infection were identified and contributed to effective infection control knowledge. The study identified the trends of associated risk factors with ESBL infection in these facilities and around the residents, thereby invoking regional or county infection prevention efforts. Although the implications of ESBL are obvious in healthcare facilities, the most significant ESBL-PE are occurring in the community, which directly and indirectly affecting public and private care home residents (Rodríguez-Baño et al., 2018). Comparing ESBL within and between types of LTCFs and community-acquired infection may provide enough data to make infection control policy and antibiotic advice for ESBL infections on-site of acquisition. This research's fourth significance is the potential to offer comprehensive information on residents' environmental risk factors associated with ESBL infection and use this information to determine resistance and susceptibility patterns of *Enterobacteriaceae* species by different geographical locations LTCFs to identify substantial hidden differences from the data collected for the research. The community-related variables such as the geographical location of the LTCFs and types of the facilities may have been unknowingly associated with the community-acquired infection and resulted in the prevalence and severity of diseases caused by

ESBL-PE among the residents living in LTCFs. The fifth essential of this research contributed to improving the quality of surveying on ESBL-PE in LTCFs residents, especially their health status, by re-evaluating and redetermining variables that may result in the introduction of the disease caused by these bacteria. The assessment of these isolates' trends and their antimicrobial susceptibility data would be essential to infection control teams, physicians, and clinical researchers to treat residents in LTCFs with no difficulties. The UK government forced all regions to implement a five-year antimicrobial resistance strategy from 2013 to 2018 (Global and Public Health Group, 2017) to reduce the life-threatening ESBL-PE species in hospitals and long-term care patients. Its significance is that it outlines the UK antimicrobial action plans to slow the growth and spread of these diseases, focusing on ESBL-PE, which was the top three spots of the deadly disease on the World Health Organization (WHO) lists. These studies' outcomes furnished comprehensive information on ESBL-PE trends, their antibiotic susceptibility, and resistance patterns among long-term care residents in the analysis. The knowledge of this analysis would invoke an action towards the development and implementation of ESBL multidrug resistance control policies, identifying areas for interventions, and essential to inform the treatment guidelines for infections caused by these microbes both in the UK and rest of the world. The potential positive social change resulting in this research could promote knowledge about vulnerable residents in public and private LTCFs and community factors responsible for ESBL infection. As we promote awareness for the residents in LTCFs, the care sites at most risk could take further steps to reduce the risks of infecting the subjects.

Summary

Enterobacteriaceae are part of healthy bowel flora but can be pathogenic depending on the site of infection. Despite the pathogenic character of the microorganism, the dissemination of multidrug-resistant *Enterobacteriaceae* related to the production of ESBL is also a public health concern throughout the world. In this dissertation, I analyzed data from the public databases to determine the risks and prevalence of ESBL-PE among residents in LTCFs from January 2014 to December 2018. These organisms are thought to be associated with morbidity and mortality and have contributed to the rising burden in public and private healthcare settings across older adults and demographics. Through this research, I identified the relationship of each independent variable to the dependent variable. The study identified risks other than the excessive use of antibiotics and new ways to interpret prior research. From the significant points of this dissertation, I revealed gaps in the literature that need to be investigated and resolved conflicts between transmission of ESBL-PE among residents and infection control measures. Because of the pathogenic nature of *Enterobacteriaceae*, I proposed to analyze the trends of *Enterobacteriaceae* species and to determine their variations according to the geographical location of LTCFs. The dissemination of multidrug-resistance *Enterobacteriaceae* related to the production of ESBL, and their susceptible antibiotic patterns were discussed in detail. The fundamental reasons for the differences in ESBL colonization across LTCFs and their association with community variables were developed and researched among the residents. I exploited a high-level systematic review was conducted on controlling transmission of ESBL-PE between the LTCFs types. The

dissertation investigates the risks causing the prevalence of ESBL-PE in LTCFs, and the effective infection control measures applied.

Chapter 2: Literature Review

Introduction

This chapter provides a detailed discussion of the literature related to the present meta-analytic study's content investigating causes of the prevalence and control measures of Extended Spectrum Beta-Lactamase producing *Enterobacteriaceae* (ESBL-PE) in Long-Term Care Facilities (LTCFs). It explores explicitly research that informs efforts to introduce effective infection control measures against ESBL-PE infection in LTCFs. Several studies have examined the prevalence of ESBL-PE in both hospital and LTCFs and the application of infection control measures since disease discovery. ESBL-PE was identified in the 1960s in Greece as an aggressive hospital and community-acquired infections. The infections have currently spread worldwide (Doi et al., 2017), resulting in increased morbidity and mortality (Huang et al., 2018; Melzera & Petersen, 2017). Transmission of these microorganisms from colonized or infected residents to other residents or other hospital patients does always occur through healthcare personnel's hands and transferring hospitalized patients from their long-stay to community-based nursing homes (Hughes et al., 2013). In a study by Flanagan, Cassone, Montoya, and Mody (2016), the report was that transferring sick residents between hospitals and nursing homes created unnecessary, exposing residents to colonization and infection risk. Because of these risk factors, sometimes, residents always prefer to be treated at the care home to avoid contact with the disease. In a study of Bush (2010), I found that isolates that convey resistance to the cephalosporin indicators in first-line antibiotic panels of testing clinical importance *Enterobacteriaceae* may represent a particular risk to a

resident in nursing homes, and obtainable in the considerable high ESBL-PE colonization rates among elderly patients discharged from hospitals and transferred to the nursing homes (Hughes et al., 2013). Once the residents settled in the nursing home, the possible spread of ESBL-PE within and between residents may occur. This can result in increased colonization of the disease within the nursing home (Rooney et al., 2009) and result in further hospital-onset infection when the residents needed to be hospitalized again (Thaden et al., 2016). Studies have indicated that nursing homes are a suitable and unique environment for residents to receive an extensive range of acute care. These include the provision of medicine, dressing, washing, and taking residents to the toilet, often resulting in the acquisition, and spread of ESBL-PE (Doi et al., 2017; Rooney et al., 2009). The reasons are that the residents have debilitated illness, multiple exposures to antimicrobial agents, and indwelling apparatus. However, many of them are prone to have the risk of ESBL infection (Sandoval et al., 2004). In one study, there was an increase in ESBL-PE colonization in the nursing homes that may increase ESBL colonization in the hospital because of transferring long-stay hospitalized residents to community-based nursing homes (Hagel et al., 2019). Based on currently available evidence provided by Smith et al. (2008) studies, the Association for Practitioners in Infection Control, and the Society for Hospital Epidemiology (APICSHE) guidelines is used as a standard of preventing and controlling infection between nursing homes and hospital. Unfortunately, recruiting personnel and support for infection control in LTCFs are still lagging (Curran, 2017; Mody et al., 2005; Roup et al., 2006) due to the challenges of inadequate implementation of infection control policies to infection control

in these facilities (Smith et al., 2008). There are various types of infection in LTCFs that are frequently affecting residents. These include urinary tract infection (UTI), respiratory tract infection (RTI), skin infection, soft tissue infection, and gastrointestinal infection (Montoya & Mody, 2011). The mechanisms by which these diseases are spreading represented approximately 94% of conditions observed in LTCFs and hospitals (Cotter et al., 2012; Engelhart et al., 2005; Heudorf et al., 2012; Pop-Vicas et al. 2008), which constitute an uncontrollable infection in both hospital and community settings. In this dissertation, I used systematic review and meta-analysis to examine the relationship between ESBL-PE in LTCFs and infection control measures. Infection control measures to prevent transmission of ESBL-PE among residents in LTCFs is essentially needed. All these microbes can present a challenge for healthcare practice if not adequately controlled. However, little is known about these organism's impacts within and between the long-term care facilities. Cochrane Collaboration described the systematic review as a method of collating all evidence-based peer-reviewed related articles that fit eligibility criteria studies to answer research questions (Higgins & Green 2011). I implemented the Cochrane approach with clear-cut objectives, transparency, and unbiased to appraise and synthesize all related literatures specific to the research questions. Moreover, having combined and summarized the results of primary studies, I used the meta-analysis technique using statistics to estimate the outcome of the study population described above by investigating the strengths and weaknesses of the current literature on ESBL-PE infections. I used the systematic review and meta-analysis to appraise the infection

control measures to prevent ESBL-PE transmission in LTCFs by responding to the research questions.

Literature Search Strategy

I used fundamental approaches to search literature outlined by Rothstein (2012) by using the horizon-scanning and gathering eligible studies. I ensured that relevant English-language studies published and unpublished were identified by searching the electronic databases. The search included observational studies and random controlled trials (RCT) reporting the causes and prevalence of ESBL-PE in LTCFs, and the infection control measures. PubMed/Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Google Scholar, and Web of Medicine databases were searched using the keywords relating to the research topic and questions. I developed the search strategy for at least two electronic databases mentioned above using the following terms: *extended-spectrum beta-lactamase-producing Enterobacteriaceae* or *ESBL-PE* or *ESBLPE* and *infection control* or *infection prevention*. Furthermore, the reference lists of published articles retrieved from these electronic databases were hand-searched for additional items. The systematic review and meta-analysis of this report adhered to the Preferred Reporting Items Systematic Reviews and Meta-Analysis (PRISMA) guidelines to prevent the risk of numerous articles addressing the same research questions, reduce noses in accumulated publications, and provide transparency in the study (National Institute for Health Research, 2019). I screened the records based on title and abstract (First Pass Screening), retrieved through databases against the predefined eligibility criteria. After that, I screened the full text via Second Pass Screening (SPS) procedures in

case the information was not clear in the First Pass Screening (FPS) level. As a result of variation in the terms ‘infection control’ and ‘infection prevention’; ‘extended-spectrum beta-lactamase-producing Enterobacteriaceae’ and ‘ESBL-PE,’ I make use of those terms in the search strategies. The reference lists of the journals recovered were also screened to search for additional literature papers. To address and review these studies, I decided to include papers that were delineating the etiology of the epidemiology of ESBL-PE, confirmation of *Enterobacteriaceae* that produced ESBL enzymes, concerned in laboratory detection of ESBL-PE, epidemiology of ESBL-PE, and evaluation of infection control measures in LTCFs globally; demonstration of the potential link between environmental source, antibiotic use and *Enterobacteriaceae* resistance in LTCFs residents; and discussing the importance of the microbiology laboratory in *Enterobacteriaceae* resistance to cephalosporins surveillance. The surveillance included *Enterobacteriaceae*, how to recognize ESBL producers among *Enterobacteriaceae* species, combination disc method, detection of ESBL in Amp C-inducible species, Control for ESBL confirmatory tests. Generally, I developed a well-defined protocol for commencing the search. Firstly, I breakdown the clinical questions into the Population, Intervention, Comparison, Outcome, and Study design (PICOS) format. My research question contains “Infection control of transmitting Beta-Lactamase producing *Enterobacteriaceae* (ESBL-PE) among residents and between LTCFs. As aptly described above, I developed the search strategy for a minimum of two electronic databases, and I captured the study details, participants detail, intervention details, and outcome details from the included studies.

Concern in Laboratory Detection of ESBL-PE

There are β -lactamase family but ESBL consist of large number and most frequent class of enzymes (Gazin et al., 2012). Detecting ESBL-PE can be challenging for some reasons, ranging from other enzymes with different features, clinical and infection control to laboratory concerns. The isolation of ESBL is based upon the resistance they confer to oxyimino-beta-lactam substrates indicators, such as cefpodoxime, ceftazidime, ceftriaxone, cefotaxime, or cefepime and the ability of clavulanate to prevent this resistance. AmpC-type beta-lactamases is a different beta lactam enzyme features that can be misleading in the laboratory detection of ESBL. This enzyme can be determined by plasmid and chromosomal genes because of their ability to provide oxyimino-beta-lactam resistance as well as resisting inhibition by clavulanate. This AmpC enzyme frequently confer resistance to cephamycins, which ESBL do not. Difficulties in the detection of ESBL arise because of their heterogeneous in nature. For example, OXA-type ESBL can be poorly inhibited by clavulanate. Some ESBL are best isolated with ceftazidime and others with cefotaxime, such as CTX-M enzymes. Infection control concerns include lack of nursing home infection control protocols that can recommend active screening. In poor resource settings where infection control measures are difficult to confirm the presence of suspected ESBL. To implement infection control protocols for therapeutic purposes and in a timely manner, it is essential that biomedical scientists in microbiology laboratory can identify ESBL resistance in a timely manner. It is also essential for regional reference laboratories to confirm the presence of ESBL in *Enterobacteriaceae* rapidly (de Kraker et al., 2011). Benchmarks for identifying ESBL

have changed many times from Clinical and Laboratory Standards Institute (CLSI) to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for screening isolates of ESBL producing *Enterobacteriaceae*. CLSI has recommended that *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* should be screened by disk diffusion or broth dilution for resistance, which must undergo confirmatory test in the presence of clavulanate, for increased susceptibility (National Committee for Clinical Laboratory Standards, 1999). The CLSI published new minimum inhibitory concentration (MIC) and disk diffusion breakpoints in 2010 for the *Enterobacteriaceae* testing (National Committee for Clinical Laboratory Standards, 2010). These MIC breakpoints were adjusted to one to three doubling dilutions which is lower than the previous breakpoints, and the new disk diffusion criteria. Similarly, the European Committee on Antimicrobial Susceptibility Testing ([EUCAST], 2010) also adjusted the breakpoint benchmarks in 2010, for susceptibility testing. To certain degree, many *Enterobacteriaceae* that previously would have been classified as susceptible when used the former breakpoints may now be treated resistant or intermediate (Hombach et al., 2012). Under these circumstances, the evidence for the new breakpoints may not be enough (Thomson, 2013) because the test may eliminate the need to perform ESBL screening and confirmatory tests for *Enterobacteriaceae* to make treatment decisions, this treatment could be questionable (Livermore et al., 2012). There are various ways of conducting ESBL tests, tests can be conducted via automated techniques, such as Vitek 2 (bioMérieux, France) and Phoenix (BD Diagnostics, USA). These devices detect ESBL with pure culture double disk-synergy confirmation. Other methods also include

combination disk and double-disk synergy (Moodley et al., 2005). Different antibiotics were used to identify ESBL activity, though, depending on the ESBL variant. For instant, cefpodoxime is a secure substrate for the detection of most SHV and TEM ESBL types, while a combination of cefotaxime and ceftazidime is recommended to detect CTX-M and some TEM ESBL variant. Yet, a high production of AmpC expression and K1 penicillinases can be identified as false ESBL production due to porin or AmpC β -lactamases overexpression (Oliver et al., 2002). For both screening and clinical samples, a drastic reduction in specificity can occur when evaluating isolates with a high production of AmpC β -lactamases overexpression (Gazin et al., 2012). Sequencing data and polymerase chain reaction (PCR)-microarray-based assays can be of essential requirement in the future for a rapid identification of ESBL in hospital and nursing home patients at time of their admission (Livermore et al., 2012).

Epidemiology of ESBL-PE

The extended-spectrum beta-lactamases (ESBL)-producing *Enterobacteriaceae* (*ESBL-PE*) have been reported by Centers for Disease Control and Prevention (CDC) and partners to have increased since 2012 worldwide. The increased of this disease is most often emanated from the hospital specimens but also in samples from the community. Prevalence rates may differ from hospital to hospital, from nursing home to residential care home and from country to country. In the USA, rates of ESBL have reported to be increased as reflected by a study conducted in South-eastern US hospitals. According to Thaden et al., 2016, the incidence of ESBL-producing *Enterobacteriaceae* increased from 11.1 to 22.1 infections per 100,000 patients between 2009 and 2014. The prevalence

of ESBL isolates from Asia, Latin America, and the Middle East have also reported to be higher (Morrissey et al., 2013), extending to a point of 60 percent in *Klebsiella pneumoniae* isolates from Argentina and 48 percent in *Escherichia coli* isolates from Mexico (Sader et al., 2014; Gales et al., 2012). Karanika et al. (2016) reported how increment of community-acquired ESBL pathogens led to the detection of high rate of concomitant and increasing rates of fecal colonization by ESBL-PE worldwide. Risk factors for infection with ESBL include previous stay in healthcare settings, previous use of antibiotics, foreign travel (Karanika et al., 2016), immunocompromised, debilitated and exposure to livestock foods (Liebana et al., 2013). Healthy individuals can also be infected with ESBL-PE. It is of essential to implement effective control measures to prevent spread of ESBL diseases when identifying likely carriers of the disease upon admittance to a healthcare facility. In Lye et al. (2012) study, a prolonged carriage of this disease for over twelve months was identified, which can create a possible dissemination of the ESBL-PE between communities, households and possibly nursing home contacts. The spread of this disease is alarming for public health due to its ability to resist multiple antibiotic agents, spreading within healthcare systems, infect patients, residents and can cause outbreaks when transferred patients between healthcare settings (Khun et al., 2012).

Infection Control

The spread of ESBL-PE between nursing home and hospitals are prevalence, indicating that breaches in infection control were obvious. The transmission of ESBL-PE is a public health threat because the infections are associated with multidrug resistance

organisms (MDROs) and resulted in prolonged hospitalization and high mortality rates (Pineles et al., 2019). Residents have various risk factors for acquiring infections with ESBL-PE, these include frequent hospital visits, increased use of antibiotics, functional impairment, and indwelling devices (Pineles et al., 2019). For the treatment of ESBL-PE or AmpC producers, carbapenems are the antibiotics of choice, however, the rate at which carbapenem resistance emerged has also caused a threat to public health (Rodríguez-Baño et al., 2018). In this situation, the utilization of effective infection control measures is of significance for this disease. But the difficulties in assessing the effectiveness of infection control prevention measures on the transmission of ESBL-PE between nursing home and hospital may force healthcare providers to make use of the ORION statement. The statement was developed as a guideline for the transparent reporting of infection control interventions and outbreaks report of health care associated infection (HCAI) (Stone et al., 2007). Despite guideline that contain infection control measures, the strategies to prevent the spread of infections were not specifically available for ESBL-PE but were available in guidelines for infection control for other MDROs (Tacconelli et al., 2014).

Theoretical Foundation

Ecology became a theory currently used by investigators to control human infectious diseases because the ecologists provided not only datasets for testing mathematical models developed but also to understand the population dynamics of host-pathogen interactions (Smith et al., 2005). The theory was developed by psychologist Urie Bronfenbrenner in 1979, and since that period, ecological theory has been used to

explain how human development is influenced by different types of environmental systems (Bronfenbrenner, 2005). As demonstrated by Smith et al. (2005), prevention and control of the disease have relied upon public health officials who applied knowledge attained from the work of population ecologists and has resulted in an increasing understanding that the dynamics of infectious diseases is as ecological as well as a medical problem. Under those circumstances, the future public policy drives cannot afford to disregard the results of research on disease-related to ecology. Because of the essential varieties present in most ecological system, extensive advantages may be accumulated by identifying and focusing on control and prevention efforts on the individuals or locations playing an unequal role in the transmission of diseases.

The Ecological Conceptual Framework

It is always demanding to enforce advancement in healthcare settings, especially residential care homes. However, a growing number of research projects indicated that there are some reasons why health institutions succeed in this while others failed (Nilsen, 2015). But the more common procedure is to identify factors that can promote or delay the successful enforcement of a conceptual framework when using a determinant framework (Nilsen, 2015). One of these concepts, the ecological conceptual framework (Durlak & DuPre, 2008), was purposely developed to advance health advocacy and disease prevention plans' success. This framework's benefit is that it is drawn from an evidence-based and comprehensive review of relevant literature. From the ecological framework point, the success of a preventive health program is mostly influenced by characteristics of the advancement compatibility with existing health quality

needs, attributes of the long-term care facility providers responsible for the advancement of self-efficacy and features of the responsiveness of a broader healthcare system community. The level of support for implementation also influences this preventative healthcare framework success, for instance, training healthcare staff and provision of infection control team and also by natures of the healthcare system within which the concept is implemented, including the general capability of the care homes to integrate the concept framework innovation of ecological theory, specific practices and processes (e.g., formulation of tasks), and staffing considerations relevant to promoting program success (e.g., leadership and supervisory support). This broad, multi-faceted approach of this conceptual framework ensures attention to the various levels at which successful infection prevention program implementation can be compromised or enhanced. Considering the above-mentioned ecological conceptual framework characteristics, it clearly distinguishes the ecological concept from other determinant frameworks because of its sensitivity to influence the socio-political environment in which the ecological theory advancements are implemented. Because LTC is an institution healthcare setting in which the environment is known to impact the adoption of knowledge, best practices, and finally the quality of care (Bowers et al., 2000; Lopez, 2006; Luff et al., 2011; Morgan et al., 2008; Wang et al., 2005). I regard the ecological framework as robust and relevant to identifying essential implementation determinants of preventing ESBL-PE in LTCFs environment. I used the ecological framework to address the following research questions: Is there an association between LTCF types and the prevalence of ESBL-PE infection rates among

residents in the presence of other predictors? Is there an association between environmental sources and the occurrence of ESBL-PE in LTCFs in the presence of other predictors? What are the essential components of effective infection control in preventing LTCFs outbreaks?

Literature Review

During ancient Egyptian, Greek, and Chinese medicine, most deaths were connected to infectious diseases (CDC, 1999), and most of the microbial infections that caused these contagious diseases were managed and well documented (Sengupta et al., 2013). In the shortest time, the discovery of narrow-spectrum penicillin by Sir Alexander Fleming in 1928 changed the face of managing and treatment of infectious diseases that caused deaths to millions of people in the early 1900s (Piddock, 2012; Sengupta, 2013). Penicillin was first prescribed in the 1940s to treat infectious diseases among World War II soldiers, and during this moment, penicillin revolutionized modern medicine that has had an impact on the lives of millions of people (Frieden 2013; Gould & Bal, 2013; Sengupta, 2013). Shortly after the discovery of penicillin, the antibiotic resistance became obvious when Abraham and Chain (1988) reported that *Escherichia coli* isolates inactivated penicillin by producing penicillinase enzymes to hydrolyze the beta-lactam ring of the antibiotic (Spellberg & Gilbert, 2014). In response to this resistance, more antibiotics were produced to cover these gaps. Unfortunately, many of the bacteria emerged resistant. In no time, ESBL-PE were identified in Greece in the early 1960s and further spread to all over the world (Datta & Kontomichalou, 1965). The spread of these organisms related to increased morbidity and mortality. Under these circumstances, most

of the beta-lactam empirical antibiotics used for the treatment of infectious diseases were not effective due to the rise in resistance against antibiotics and resulted in the persistence and spread of multi-resistant species (Tanwar, 2014; van Duin & Paterson 2016) across the globe. The resistance represents a severe worldwide risk to public health (Pana & Zaoutis, 2018). Consequently, despite increased research of these ESBL-PE in hospital settings, there is a lack of practical studies on Long-Term Care Facilities (LTCFs) in correlation with ESBL infection rates (Lautenbach et al., 2012). Additionally, most studies on ESBL infections in both hospital and community settings were often related to the inappropriate use of antibiotics and patient-level factor, and with this use, this factor in determining individual risk factors (Lautenbach et al., 2012; Rodríguez-Baño et al., 2018). In a study conducted by Freedman & Spillman (2014), it was observed that most care homes were proxy and close living settings with shared toilets among elderly residents. This could be the most potent correlated source for the risk and cause of the prevalence of ESBL infection rates. Blom et al. (2016) also pointed out that residential care settings of different geographical areas could be a risk to the residents in the acquisition of these infections because it is an environment that is often regarded as a reservoir for transmitting ESBL organisms between and within residents (High, 2009; Rooney, 2009). Moreover, the research that Thaden et al. (2016) conducted spotted the differences in the incidence of ESBL producers and their implications in the community. For instance, their study indicated that ESBL *Klebsiella pneumonia* infection remained stable, whereas community and nosocomial-associated ESBL *Escherichia coli* infections are driving the upward trend. All the above methods, the research provided credible and

logical results, as noted by each assessment. However, there was an indication in previous studies that the prevalence of ESBL-PE colonization/infection differed significantly across LTCF sites (Lautenbach et al., 2012). Though there were obvious reasons for the increasing rate of community associated ESBL infections in public, private care homes, and tertiary care hospitals (Thaden et al., 2016), the prevalence of ESBL-PE colonization differed significantly across LTCFs. The differences in the isolates may be owing to differences in patient demographic populations, lack of managing antibiotic use, or inconsistency infection control protocols across the health facilities (Lautenbach et al., 2012). For example, dissemination of ESBL within an LTCF may be specifically essential in the epidemiology of ESBL-PE. In Lautenbach et al., 2012 study, the research was apparent that the connection between ESBL-PE infection and fecal incontinence suggested a possible role for person-to-person dissemination of the disease. Despite indifference in the underlying mechanisms of differences in ESBL infection across all the facilities, the implication of this research was an essential public health concern. Because of the rising rate of ESBL-PE, the first national Antimicrobial Resistance Action Plan (AMRAP) Northern Ireland was Launched in 2002 in collaboration with Public Health England (PHE) to curb the threat of ESBL and prioritized organism for targeted action in controlling infection caused by ESBL threat in LTCFs and hospital (Public Health Agency, 2015). In summary, the study aims to assess the prevalence of ESBL-PE among residents in LTCFs and identify effective infection controls against the disease. This evidence can be used by public and private residential care homes to develop guidance to be used by health professionals to

help curb the transmission of ESBL-PE into LTCFs. Through the systematic review and meta-analysis, detailing community acquired ESBL-PE, effect, cause, and prevention were identified. I also briefly discussed surveillance methodologies used in Health and Social Care (HSC) hospital infection control and prevention programs, particularly the use of Northern Ireland Electronic Care Record (NIECR) surveillance systems and infection control teams. The study aims, research questions, and methods were itemized to pursue the objectives of this dissertation. To prevent a further spread of ESBL-PE infections in residents by improving infection control and prevention procedures, I summed up the current knowledge about ESBL-PE in LTCFs. This systematic review and meta-analyses aimed to assess the analytic epidemiology of ESBL-PE by answering the following research questions. Is there an association between LTCF and the prevalence of ESBL-PE infection rates among residents in the presence of other predictors? Is there an association between environmental sources and ESBL-PE in LTCFs in the presence of other predictors? What are the essential components of effective infection control in preventing LTCFs outbreaks?

Summary and Conclusions

Although the study of ESBL-PE prevalence in LTCFs is increased, the higher percentage of healthy elderly residents, in general, were not affected. Through this literature review, the data retrieved from different countries showed a shift in the number of increases in the number of elderly people. With this direction, the elderly residents requiring adequate care in LTCFs. This review reported that in Northern Ireland, the over 65 years old population is increasing and may outnumber younger people in the

nearest future (The Executive Office, 2015). At present, there are about 514 nursing homes and residential care homes in Northern Ireland, approximately two times the number in 2013 (Public Health Agency, 2013). In 2015, the number of older adults was 15.5% and estimated and projected to increase by 74.4% between 2014 and 2039 (The Executive Office, 2015). The likely increase in the elderly population can place significant responsibilities on Northern Ireland's health care and support services. Various studies have shown a higher prevalence of ESBL species in LTCFs, especially in nursing homes. This is due to inefficient infection prevention practices, geographical location differences, proximity among the residents, and excess use of antibiotics (Pelly et al., 2006). Healthcare professionals have an essential role in controlling the spread of ESBL-PE in LTCFs. However, the implementation of targeted infection control protocols based on evidence-based practices must always be carried out. Importantly, adequate knowledge of *Enterobacteriaceae* organism's ability to resist beta-lactam antibiotic in both the hospital and community are fundamental in the provision of efficient healthcare. This review also revealed that appropriate training programs aimed at developing basic skills to provide healthcare staff with the ability to achieve these targets. These training programs should be used to facilitate any potential defects in advanced practice to reduce or control the spread of ESBL-PE. The detection of ESBL organisms could be challenging because of differences among the ESBL-PE and their ability to spread rapidly among the residents. The antibiotics, such as carbapenems agents that are still sensitive to ESBL infections, should only be used in acute health cases to limit or control further spread of ESBL producing species (Rawat & Nair, 2010).

Chapter 3: Research Method

Introduction

Extended-Spectrum Beta-Lactamase (ESBL) associated resistance microorganism is a consistent deep public health concern in both the community and hospital settings. Since the first report of secretion of ESBL by *Enterobacteriaceae* in 1983 (Knothe et al., 1983; Navon-Venezia, Kondratyeva & Carattoli, 2017), ESBL has continued to increase in different level at different healthcare settings and are now a global public health concern that obstructs the treatment of infections in the community and hospital settings. The dissemination of ESBL has adverse effects for health service providers, and a variety of patients have been linked with an unnecessary setback in treatment of these infections (Kang et al., 2004; Pana, & Zaoutis, 2018) poor outcome (Paterson et al., 2001; Paterson et al., 2004; Yadav et al., 2015), increases in the long-term stay in hospital (Mangeny et al., 2000) and high cost of healthcare (Jia et al., 2019; Lautenbach et al., 2001; Lee et al., 2006). Furthermore, ESBLs are also known to be frequently resisted by multiple antibiotic agents, including fluoroquinolones and aminoglycosides, therefore reducing the available antibiotic treatment alternatives. Though ESBLs are traditionally associated with healthcare settings, more recent reports have shown increasing isolation of these organisms in the community setting (Abayneh, Tesfaw & Abdissa, 2018). Nursing homes and other long-term care settings have been suggested as a reservoir for ESBLs in the community (Arpin et al., 2003; Duval et al., 2019). Most vulnerable residents are repeatedly at the risk of acquiring ESBL-PE because they were often exposed to antimicrobials, previous hospital admission, incontinence, urinary catheters, and

decubitus ulcers (Feneley, Hopley, & Wells, 2015; Nicolle, 2014). In Europe, Cefotaxime (CTX)-M phenotypic ESBL producing *Escherichia coli* is the major ESBL strains that emanated from the community patients as a serious health concern (Valenza et al., 2014; Woodford et al., 2004), and have been identified with growing resistance rates to other antibiotic agents (Pana & Zaoutis, 2018). Cefotaxime extended-spectrum beta-lactamase (CTX-M ESBL) producing *Klebsiella pneumonia* occurred in 2001 as the first significant outbreak in the UK. By 2003, exact duplicate and different types of *Escherichia coli* CTX-M-15 were distributed in the UK (Isgren et al., 2019; Livermore & Hawkey, 2005). When Rooney et al., 2009 evaluated ESBL strains in Northern Ireland, it showed a significant level of fecal carriage of *Escherichia coli* in nursing home residents (Blom et al., 2016; Rooney et al., 2009). In a weekly health protection report in England, Wales, and Northern Ireland, the report showed that *Enterobacteriaceae* associated ESBLs strain in these regions were frequently conveyed resistance to multiple antibiotic agents (Public Health England, 2017). The ESBL producing *Escherichia coli* has been thought to convey this multiple resistance to all the antibiotics, especially fluoroquinolones and gentamicin (Fair & Tor, 2014), and were associated with a long-term care facilities outbreak (Pelly et al., 2006). The study is significant and insightful because *Enterobacteriaceae* that convey resistance to third-generation cephalosporin with non-ESBL strains were evaluated and accounted for why the isolates are prevalent among residents in nursing homes in Northern Ireland and are of public health concern (Public Health Agency, 2019). In as much as ESBL-PE has limited treatment options, the disease could endanger a more significant number of patients and residents (Weiner, 2016). The

changing description of the prevalence in ESBLs producing *Enterobacteriaceae* has more tendency to convey resistance to non-beta-lactam antibiotics and vice versa. However, similar observations have been researched in a study conducted by Procop et al. (2003) and Teklu et al. (2019). They need to compare the frequency of resistance of these organisms for five years in Northern Ireland. The outcome of this research could be used to clarify the magnitude of dissemination of these organisms. It should inform healthcare service providers and public health awareness of this growing problem. The research provided the variation of the *Enterobacteriaceae* species with ESBL enzymes among residents of nursing homes in Health and Social Care (HSC) locations in most parts of the world. Notably, the study also provided a significant understanding of ESBL-PE resistance patterns and informing public health, infection control, and antimicrobial stewardship approaches to check the dissemination of the emerging pathogens. This dissertation aimed to provide the first comprehensive systematic review and meta-analysis of ten-year associated risk factors, incidence risks, and the occurrence of ESBL-PE infections among residents in LTCFs. The research was explored better through the research questions.

Purpose of the Study

Long-term care facilities serve a different type of healthcare setting that cares for individuals of all ages and provides a certain level of care services. The facility homes also serve as home and health institutions for most older adults and individuals with intellectual disabilities (Johansson et al., 2017). Despite these facilities' caring nature, the facilities also provided a unique setting for sharing multidrug resistance organisms

(MDROs), such as ESBL-PE infections within residents and between health care facilities via workers who work in more than two care homes (Curran, 2017). These organisms can cause urinary tract infections and severe infections in the bloodstream and central nervous system. Numerous journals have researched these MDROs with different methods of controlling diseases without much success. The purpose of this study was to use systematic review and meta-analysis to identify, evaluate, and compile the findings of all relevant individual studies on the causes of the prevalence and control of ESBL-PE in LTCFs and the evidence for the effectiveness of infection control and prevention strategies. The intervention measures aim to prevent and control the spread of ESBL-PE in elderly care homes, especially when residents are in a debilitating health condition or transferred from the hospital. The examination of ESBL-PE outbreak within elderly resident homes permitted this research to present the evidence about the role of targeted or non-targeted infection control interventions, which includes screening tests in the etiology of ESBL enzymes in LTCFs. The study identified the effective control measures applied against ESBL-PE prevalence in LTCFs of previous research. I developed the search strategy for the publications from 2008 to 2018 from at least two electronic databases like PubMed/Medline, Embase, and Cochrane by using the following terms: extended-spectrum beta-lactamase-producing *Enterobacteriaceae* long term care facilities or ESBL-PE long term care facilities or ESBL-PE long term care facilities and infection control long term care facilities or infection prevention long term care facilities. I screened the search records based on title and abstract through a screen called First Pass Screening (FPS), retrieved through databases against the predefined eligibility

criteria. The quality assessment used on study design included non-Randomized controlled trials; I used the New Castle Ottawa Scale (NCOS) for an observational study. I used statistical software program called RevMan sourced from Cochrane to perform statistical analyses of the research. The meta-analysis of categorical data was analyzed, and pooled the estimates, and presented as Risk Ratio (RRs) and analysis of continuous data was analyzed, and pooled the assessments, and presented as Mean Difference (MD) along with their 95% confidence intervals (CIs). I also performed a subgroup analysis based on gender, region, etc., to find the heterogeneity.

Research Design and Rationale

The study is designed as a systematic review and meta-analysis of published and unpublished articles from January 2008 to December 2018 to investigate the causes of the prevalence and control measures of ESBL-PE in LTCFs. The study will be investigated in Northern Ireland, United Kingdom. In Northern Ireland, there are roughly 1.8 million population with 43,844 nursing homes places available (263 nursing homes) and 19,832 residential care available between January 2014 and December 2018 respectively (251 residential care homes) (Northern Ireland Information Statistics and Research Agency, 2019). I retrieved secondary data for the study population from public databases like PubMed/Medline, Embase, Google scholar, and Walden library. The demographic data regarding LTCFs were obtained from the databases mentioned above. Inclusion and exclusion criteria will be used to determine journal articles to be included in the study.

Methodology

Target Population

The target populations that I intend to investigate are the resident's data living in different types of LTCFs. The data were retrieved from the public databases mentioned under the research design and rationale. These target populations were investigated based on their different level of environmental independent variables that could cause risk to the occurrence of Enterobacteriaceae that produce ESBL enzymes. The relationship between these risk factors and the occurrence of ESBL infections within and between the LTCFs were examined to determine variables that are correlate with these organisms. The difference occurrence of these organisms between residents living in the LTCFs was analyzed.

Estimated Size of Target Population and Sample

LTCFs are a different type of healthcare settings that serve residents of all ages and provide variable degrees of care. These facilities serve as a home as well as a place of caring for residents (Department of Health, Social Service Northern Ireland, 2015). The facilities are also a special environment for transmitting infections between and within residents (High, 2009; Rooney, 2009). In the past 40 years, the Northern Ireland population of over 65 years old is increasing and may outnumber younger people in nearest future (The Executive Office, 2015). At present, there are about 514 nursing homes and residential care homes in Northern Ireland (Northern Ireland regulation and quality improvement authority,2019), approximately two times the number in 2013 (Public Health Agency, 2013). In 2015, the older adults were 15.5% and had been

estimated and projected to increase by 74.4% between 2014 and 2039 (The Executive Office, 2015). The likely increase in the elderly population can place significant responsibilities on Northern Ireland health care and support services. One of the objectives of this study is to attain a statistical power of at least 0.95 of detecting the relationship between LTCFs and ESBL infection rates, and in detecting the relationship between geographical locations (environmental sources) and ESBL infection rates. A commonly used interpretation based on benchmarks suggested by Cohen (1988) was used as power analysis for meta-analytical procedures of this research where ($d = 0.2$) represents the small size, ($d = 0.5$) medium, and ($d = 0.8$) large. Sample sizes in this research are small. I expected the average group size to be 20. I expected to find ten studies to be frequent in this research. And my anticipation was to achieve moderate heterogeneity as $= .50$. In the end, the sample size that I included for meta-analytical research was $N = 22$. In the supplementary statistics, the G*Power 3.1.9.4 was used to conduct the power analysis. The G*Power calculation for a multiple linear regression with three predictors and an effect size of R-square (f^2) = 0.467. In the context of multiple regression power analysis, two layers of tests needed to consider—the R-square value test already tested to be a value of $= 0.467$ (Table 4). By using G*Power, we needed to include. the projected - alpha level for the test = 0.05, The Number of predictors in the regression model was 3, the desired level of power for the test was 0.95. Estimated population effect size (R^2) = 0.467 (Table 4). Under this condition, the expected sample size was 36 after the G*Power calculation with all the requirements mentioned above. Already, the included sample size for this research was $N = 22$. All data analyses were

listed with hypotheses. Table 1 contained a list of the variables and the statistical tests were used in each hypothesis.

Table 1

Variables for the LTCFs Study and Elderly Residents' Study

Types of variable	Variables	Measurement
Dependent variables	ESBL producing Enterobacteriaceae Infections	Interval
Independent variables	Types of LTCFs	Categorical
Independent variables	Geographical location of LTCFs	Interval
Independent variables	infection control measures	interval

Hypothesis 1

H_01 : There is no association between LTCF and ESBL-PE infections in the presence of predictors.

H_a1 : There is a significant association between LTCF and ESBL-PE infections in the presence of other predictors.

According to Northern Ireland Regulation and Quality Improvement Authority (NIRQIA) (2019), there is a collection of LTCF types. The regulation recognized nursing homes, residential care homes, domiciliary care, mental health, and learning disability service. In this study, LTCFs were considered for systematic review and meta-analysis study. I used the hypothesis to conduct effect of LTCF on ESBL-PE infection rates in the presence of other predictors. LTCF is a categorical variable. Meta-analysis and

multivariate linear regression (MLR) were conducted to determine if LTCF was associated with ESBL infection.

Hypothesis 2

H_02 : There is no association between geographical locations (environmental sources) and ESBL-PE infections in the presence of predictors.

H_{a2} : There is a significant association between geographical locations (environmental sources) and ESBL-PE infections in the presence of other predictors.

Included data retrieved from different countries via databases provided statistical information relating to the geographical location of LTCFs. The geographical location of Long-term care facilities is an interval measurement. The LTCFs environment were evaluated in the presence of other environmental factors to determine if there was significant association to ESBL-PE infection rates. Meta-analysis and MLR were used to conduct relationship between the geographical location of LTCFs and ESBL-PE infection in the presence of the other environmental variables.

Hypothesis 3

H_03 : There is no association between infection control measures and ESBL-PE infections in the presence of predictors.

H_{a3} : There is a significant association between infection control measures and ESBL-PE infections in the presence of other predictors.

Sampling and Sampling Procedures

According to National Health Service (NHS), samples collection criteria, clinical samples must be collected in line with the appropriate microbiology departmental

procedure, laboratory handbook information, ward protocol or LTCFs procedure for the test required. The prompt and accurate isolation of infecting bacteria is directly influenced by the quality of the specimen. Consequently, more clinical details of each patient aid laboratory testing. The NHS laboratory handbook information states that except for suspected meningitis it is recommended that appropriate specimens should be collected before commencing antibiotic therapy; specimen should be transported to the laboratory as soon as possible; ensure that the specimen container is clearly labelled with the patient's details, and we should remember that we may be dealing with pathogenic microorganisms and care should be taken while obtaining and handling the specimen.

Inclusion and Exclusion Criteria

Papers were included if they reported residents, irrespective of gender, age, ethnicity, and were exposed to cases of ESBL-PE introduced by LTCFs transfer. Papers excluded if they reported residents were not exposed to cases of ESBL-PE introduced by LTCFs. Data that contain targeted or non-targeted infection control interventions included screening tests as well as standard precautions or placebo screening. All the information were included in this study. Studies that reported transmission or spread of ESBL-PE within residents in LTCFs causing incidence or frequency of infection, mortality rate, including length of residents in care homes and resources used were included. Studies which did not report data on acquisition outcomes were excluded. The study design was not limited regarding study type, that is, randomized controlled trials (RCTs) and observational studies. Publications which are published from 2008 to 2018 were included. Publications which are published before 2008 and after 2018 were

excluded. Research studies related to nonhuman infections, nonhealthcare-related studies, conference abstracts, letters to the editor, commentaries, weekly reports, and editorials were excluded also. Only articles written in English included.

Review Descriptions

There are three main relationships for this review, to show awareness of ESBL-PE transmitting between hospitals and nursing homes while transferring or moving patients between the two healthcare settings, and the effective infection control measures applied. A study was defined based on published papers retrieved from databases with the only distinction being 'ESBL-PE', 'LTCFs', and 'infection control measures.' So, if a single paper meeting the selection criteria reported data on the three subjects, they included three separate studies. Community-acquired infection (CAI) was defined as infections contracted outside of a hospital. These infections can be obtained from nursing homes, elderly residential care facilities, or outpatient clinics that require hospitalization. A number of these infections are caused by gram-negative bacteria (GNB), most especially *Enterobacteriaceae* species (Grosso et al., 2015). A hospital-acquired infection (HAI) was defined as infections acquired in a hospital. The infections often contacted after 48 hours of hospital admission or within 48 hours of hospital discharge (Peleg & Hooper, 2010). Infection control measures were defined as standard precautions to reduce the risk of transmitting bacteria diseases from both recognized and unrecognized sources (World Health Organization, 2006). Residents in a nursing home are often transferred to an Accident and Emergency Department (AED) when they need urgent, intense medical care. A proportion of these transfers often performed on an outpatient basis and may be

considered inappropriate due to the lack of effective infection control measures (Lemoyne et al., 2019). This review is considered the CAI and HAI as a wider definition of healthcare-associated infections (HCAIs). The HCAIs can occur when patients are receiving health care and probably contracted the disease in a hospital or nursing home that first appears after 48 hours (Haque et al., 2018).

Determination of Study Selection

The relevant published and unpublished articles and the processed results were selected based on the following analysis criteria: year of publication, keywords, the relevance of the article, type of publications, study design, and language of the publications. The designating period of the study was used as the first criterion. The key words reflected the terminology were employed in the selected articles and helped in identifying the most relevant studies. Each abstract publication was thoroughly checked and rejected any irrelevant studies. Original and reviewed studies was selected, but some papers required the use of information from annual reports, research reports, or conference reports, all these were also be utilized. The study design was divided into reviews versus original works or, with cross-sectional versus longitudinal. The eligible literature papers were assessed for quality and risk of bias for data that were relevant to the systematic review and meta-analysis. The languages that currently predominate in science are English and Spanish (Čablová et al., 2017), but in this review, only the English language was used for the study. The differences in either the application of inclusion or exclusion of articles, quality accuracy on data extraction were evaluated to make the final decision.

Data Extraction Process

Data were extracted from the inclusive eligible papers and reviewed were carried out on the studies. Papers extracted have been scrutinized, double-checked for eligible criteria, and variables were assessed and evaluated for processing. The data extracted from acceptable studies consist of; Author and year of publication, study aim, the country where the study was conducted, study design, infection control measures, strains of ESBL-PE detected, number of Patients, Interventions, age, and sex distribution. I ensured that data were extracted and analyzed twice to remove any lack of consistency.

Risk of Bias in each of Studies

Modified version of the Newcastle-Ottawa Scale (NOS) is a risk of bias appraisal tool for studies supported by the Cochrane Collaboration (Higgins & Green, 2011; Wells et al. 2014). The content validity of this tool has been established based on a critical review studies across different researchers in the field who evaluated its clarity for critical review of appraising the quality of studies to be used in a meta-analysis (Wells et al., 2014). The NOS is used to assess the quality and risk of bias of the papers included in this review. Using NOS quality assessment tool to appraise this review critically, the included studies were evaluated based on Cochrane 'Risk of bias's assessment of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias according to published criteria (Higgins & Green, 2011).

Data Analysis

The combined proportions of patients admitted into the LTCFs or moved to the nursing home (with 95% confidence intervals), with or without pre-arranged infection

control measures, with patients at risk of ESBL-PE infection was calculated separately and compared between possible transmission of ESBL-PE among residents in LTCFs, and infection control applied using a random-effects meta-analysis model based on DerSimonian-Laird approach (Cooper et al., 2009; DerSimonian & Laird, 1986). With this approach, I estimated the mean of a distribution of effects in a different population. This approach includes an estimate within-studies and between-studies variation, which was used when assigned the studies into weights and the standard error of each effect size. The precision of an estimated random effect's analysis from each study is weighted by the inverse of the results' variance across all the pooled studies. If the studies' value were within the 95% CI, then the effect size would be statistically significant at the 5% level ($P < 0.05$). Though the chi-square test provided a test of significance for heterogeneity without measured it, these studies' heterogeneity nature was evaluated by using the I^2 statistic with a P -value of < 0.05 considered to be statistically significant. The I^2 values represented the percentage of the total variation which was due to the variation between studies. According to Higgins et al. (2003), I^2 suggested that: $I^2 = 0\%$ is no heterogeneity, $I^2 = 25\%$ and below is low heterogeneity, $I^2 = 50\%$ is moderate heterogeneity, and $I^2 = 75\%$ is high heterogeneity. This measurement is used to define the level and presence of the index of heterogeneity in a meta-analysis. Study between-study heterogeneity make the effect size estimate less accurate because of slight differences in the study design or intervention components between the studies. Many other differences in the study population are possible and may also be associated with differences in the overall effect. In this case, I used subgroup analyses to examine different subgroups

within our meta-analysis articles to determine the differences of effect in a subset of subject's risk of bias, study duration, age group, ESBL-PE transmission cause, and Infection control measure. I calculated the Standard Error of the differences between subgroup effect sizes to calculate confidence intervals and compared the size of each subgroup's effects to know if this difference is significant (Borenstein et al., 2011). Also, I did not use meta-regression to examine if covariates explained any of the heterogeneity of infection control effects between studies because in meta-analysis, I need an appropriate larger number of studies to covariates (Borenstein et al., 2011). However, it is not reasonable to deduce that all the heterogeneity should be elucidated because the residual heterogeneity is expected to be recognized in the statistical analysis (Ioannidis, 2008). In such a manner, it is impractical to assess these covariates in each study. And without doubt, I may not know the association of covariates with the size of the effect. However, Borenstein, Hedges & Rothstein, 2007, admitted that the association of the effect's size with covariates did exist but may lead to variations in a high degree of effect. According to Rothstein, Sutton, & Borenstein, 2006, the publication bias problem is a study with high effect sizes that are more likely to be published than a study with a small effect size. I used a funnel plot to estimate the assessment of publication bias. Furthermore, I analysed pooled proportions of residents in LTCFs over time using the study year. For studies taking place in 2 years, I used the first year; for studies taking place in 4 years, I used the second year; for those studies in six years, I used the third year. The non-parametric Spearman's rho correlation coefficient was calculated to determine significance in ESBL-PE transmission among residents and between LTCFs

trend over time. Statistical analyses were undertaken using Cochrane RevMan statistical software.

Summary of Design and Data Analysis Plan

Generally, I developed a well-defined protocol before commencing the systematic review and meta-analysis.

Step 1: Firstly, I breakdown the clinical question into PICOS (Population, Intervention, Comparison, Outcome, and Study design) format. My research question contains “Infection control of transmitting or prevalence of ESBL-PE among residents in LTCFs”.

- *P (Population)* included residents who were exposed to cases of ESBL-PE introduced by LTCFs environment. Residents Irrespective of gender, age, and ethnicity were included. Residents who were not exposed to cases of ESBL-PE introduced by LTCFs environment were excluded.
- *I (Intervention)* included targeted or non-targeted infection control interventions which includes screening tests.
- *C (Comparator)* included standard precautions or placebo screening.
- *O (Outcome)* included transmission or spread of ESBL-PE within residents in LTCFs and between facilities: incidence or frequency of infection, Mortality rate, and resources used. Studies with no report data on acquisition outcomes were excluded.
- *S (Study design)* I included data with limit to study type (Randomized controlled trials (RCTs) and observational studies).

- *T (Time period)* I included publications published from 2008 to 2018 and publications before 2008 and after 2018 were excluded.

Step 2: I developed the search strategy for at least two electronic databases like PubMed/Medline, Embase, Google Scholar and Cochrane by using following terms: extended spectrum beta lactamase producing Enterobacteriaceae or ESBL-PE or ESBLPE and infection control or infection prevention.

Step 3: Screening the records based on title and abstract via First Pass Screening (FPS) which are retrieved through databases against the predefined eligibility criteria. After that I did the full-text screening via Second Pass Screening (SPS) if the information is not clear in the FPS level.

Step 4: I captured study details, participants detail, intervention details, and outcome details from the included studies.

Step 5: Quality assessment based on study design of included studies were examined. I used the Risk of Bias tool for RCTs and the New Castle Ottawa scale for observational study.

Step 6: Statistical analyses were performed using 'Cochrane RevMan statistical software'. A The meta- analysis of categorical data was analyzed, and pooled the estimates, and presented as Risk Ratio (RRs). Also, the analysis of continuous data was analyzed, and pooled the estimates, and presented as Mean Difference (MD) along with their 95% confidence intervals (CIs).

Step 7: Subgroup analysis was performed to find the heterogeneity.

Step 8: Publication bias was performed if 10 studies are there for at least one outcome.

The purpose of the design and data analysis summary was to create a plan for the meta-analysis study in next chapter. The concepts in this section were used to summarize study data and to process the relevant statistical tests.

Threats to Validity

Bias in each of the Studies and random error could threaten this research's validity if I did not put adequate strategies to limit them. These strategies include a complete search for relevant articles and explicit, reproducible criteria in the selection of articles included in the review. The study is a systematic quantitative review that summarized the results of the published and unpublished studies and used statistical methods to sum up the results of the different tasks into a single pooled estimate of effect. I have appraised the research designs and study characteristics, synthesized the data, and interpreted the results using a predefined systematic approach to conform to evidence-based methodological principles. The guidance below is organized and employed to limit the threats of the validity of this research. Data were extracted from the inclusive eligible papers and reviewed were carried out on the studies. Papers selected have been scrutinized, double-checked for eligible criteria, and variables were assessed and evaluated for processing. The data extracted from acceptable studies consist of; Author and year of publication, study aim, the country where the research was conducted, study design, infection control measures, strains of ESBL-PE detected, number of Patients,

Interventions, age, and sex distribution. I ensured that data were extracted and analysed twice to remove any lack of consistency.

Included and excluded Studies: I selected the relevant published and unpublished articles and the processed results based on the following analysis criteria: year of publication, keywords, the relevance of the article, type of publications, study design, and publications' language. The designating period of the study was used as the first criterion. The keywords reflected the terminology was employed in the selected articles and helped identify the most relevant studies. Each abstract publication was thoroughly checked and rejected any irrelevant studies. Original and reviewed studies were selected, but some papers required information from annual reports, research reports, or conference reports; all these were also be utilized. The study design was divided into reviews versus original works or, with cross-sectional versus longitudinal. **Assessment of Risk of Bias in each of Studies:** A modified version of the Newcastle-Ottawa Scale (NOS) is a risk of bias appraisal tool for studies supported by the Cochrane Collaboration (Higgins & Green, 2011; Wells et al., 2014). This tool's content validity has been established based on critical review studies across different researchers in the field who evaluated its clarity for critical review of appraising the quality of studies used in a meta-analysis (Wells et al., 2014). The eligible literature papers were assessed for quality and risk of bias for data relevant to the systematic review and meta-analysis. The NOS is used to evaluate the quality and risk of bias of the papers included in this review. Using NOS quality assessment tool to appraise this review critically, the included studies were evaluated based on Cochrane' Risk of bias's assessment of 'Low risk' of bias, 'High risk' of bias, or

'Unclear risk' of bias according to published criteria (Higgins & Green, 2011). The languages currently predominate in science are English and Spanish (Čablová et al., 2017), but I only used the English language for the study in this review. I evaluated the differences between the inclusion or exclusion of articles and quality accuracy on data extraction to make the final decision. To further minimize the potential for bias in each publication, I conducted a complete literature search to include the strategies discussed in Question 3. I used a graphical funnel plot of studies in a meta-analysis for identifying bias in each study.

Chapter 4: Results

Introduction

The purpose of this quantitative systematic review and meta-analysis was to gather all available empirical research about the causes of prevalence and control measures of ESBL-PE among residents in LTCFs by using clearly defined, systematic approaches to achieve answers to the following research questions.

Research Question 1: Is there an association between LTCF and the prevalence of ESBL-PE infection rates among residents in the presence of other predictors?

H_01 : There is no association between LTCF and ESBL-PE infections in the presence of predictors.

H_a1 : There is a significant association between LTCF and ESBL-PE infections in the presence of other predictors.

Research Question 2: Is there an association between geographical (environmental sources) and ESBL-PE in LTCFs in the presence of other predictors?

H_02 : There is no association between environmental sources and ESBL-PE infections in the presence of predictors.

H_a2 : There is a significant association between environmental sources and ESBL-PE infections in the presence of other predictors.

Research Question 3: Is there an association between Infection Control Measures and ESBL-PE infections?

H_03 : There is no association between infection control measures and ESBL-PE infections in the presence of predictors.

H_{a3} : There is a significant association between infection control measure and ESBL-PE infections in the presence of other predictors.

These hypotheses have been tested through the meta-analysis of continuous data, pooled the estimates, and presented as mean difference (MD) along with their 95% confidence intervals (CIs). The analysis process was based upon the data analysis plan as stated in Chapter 3.

Data Collection

Data collection is one of the essential stages in conducting a meta-analysis. The data collection method was the evidence used to describe in detail the analysis of prevalence and control measures of ESBL-PE in LTCFs. The data provided in this project served as information to determine if the studies that were included were suitable for a combined analysis. I developed the search strategy using electronic databases PubMed/Medline, Embase, Cochrane and Google Scholar by using following terms: extended spectrum beta lactamase producing *Enterobacteriaceae* OR ESBL-PE or ESBLPE AND infection control OR infection prevention. I collected data such as information on transmission or spread of ESBL-PE within residents (participants) in LTCFs: incidence or frequency of infection, mortality rate, length of care homes stays, and resources used. Where applicable, information on control measures were also collected, these includes general control measures, standard precautions, active surveillance, environmental control, prophylaxis based on the World Health Organization (WHO), hand hygiene, training and educating HCWs employee, and containment measures. After the collection of all information, through the First Pass Screening (FPS),

I screened the records based on title and abstract which are retrieved through databases against the predefined eligibility criteria. In case the information was not clear in the FPS level, I conducted the full-text screening called Second Pass Screening (SPS). At this stage, the study details, participants detail, intervention details, and outcome details from the included studies were captured. Quality assessment based on study design of included studies was evaluated using New Castle Ottawa scale (NOS), a risk of bias assessment tool for observational study. Statistical analyses were performed using the “Cochrane RevMan” statistical software program. The meta-analysis of categorical data was analyzed, and pooled the estimates, using inverse variance statistical method with random effects (RE) analysis model and analysis of continuous data, and presented as mean difference (MD) along with their 95% confidence intervals (CIs). I also performed a subgroup analysis based on ESBL prevalence on geographical (regions), targeted and untargeted infection control measures, to find the heterogeneity.

Data Analysis

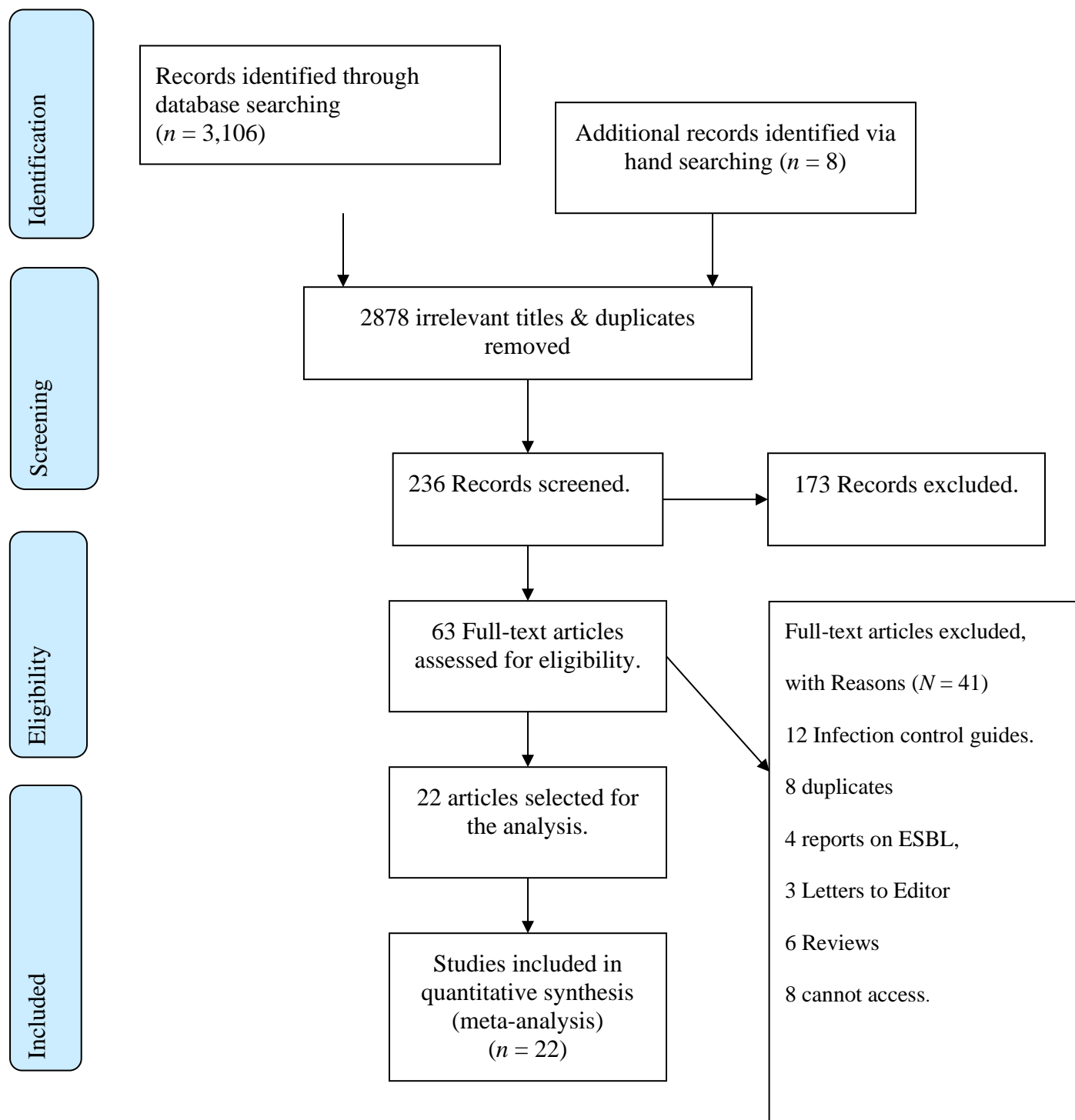
The combined proportions of residents in LTCFs (with 95% confidence intervals), with or without ESBL-PE infection were calculated and compared, using a random-effects meta-analysis model based on DerSimonian-Laird approach (Cooper et al., 2009; DerSimonian & Laird, 1986). With this approach, I estimated the mean of a distribution of effects in a different population. This approach includes an estimate within-studies and between-studies variation, which were used when assigned the studies into weights and the standard error of each effect size. The precision of an estimate random effect's analysis from each study was weighted by the inverse of the variance of the results across

all the pooled studies. The studies' value was within the 95% CI, then the effect size would be statistically significant at the 5% level ($P < 0.05$). Though the chi-square test provided a test of significance for heterogeneity without measured it, the heterogeneity nature of these studies was evaluated by using the I^2 statistic with a P value of <0.05 considered to be statistically significant. The I^2 values represented the percentage of the total variation which was due to variation between studies. According to Higgins et al. (2003), I^2 suggested that: $I^2 = 0\%$ is no heterogeneity, $I^2 = 25\%$ and below is low heterogeneity, $I^2 = 50\%$ is moderate heterogeneity, and $I^2 = 75\%$ and above is high heterogeneity. This measurement was used to define the level and presence of index of heterogeneity in meta-analysis. However, if the study between study heterogeneity turned the effect size estimate to be less accurate, this could be as a result of slight differences in the study design or intervention components between the studies. Many other differences in the study population are possible and may also be associated with differences in the overall effect. In this case, I used subgroup analyses to examine different subgroups within the articles of our meta-analysis to determine the differences of effect in subset of subject's risk of bias, study duration, regional areas of ESBLs PE transmission cause, and Infection control measure. I calculated the Standard error of the differences between subgroup effect sizes, to calculate confidence intervals and compared the size of the effects of each subgroup to know if this difference is significant (Borenstein et al. 2011). Also, I did not used meta-regression to examine if covariates explained any of the heterogeneity of infection control effects between studies because in meta-analysis, I need an appropriate larger number of studies to covariates (Borenstein et

al., 2011). However, this was not reasonable to deduce that all the heterogeneity should be elucidated because the residual heterogeneity is expected to be recognized in the statistical analysis (Loannidis, 2008). In such manner, it was impractical to assess these covariates in each study, and I did not know the association of covariates with the size of the effect. However, Borenstein et al. (2007) admitted that the association of the size of the effect with covariates did exist but may lead to variations in a high degree of effect. Publication bias problem, according to Rothstein et al. (2006), was a study with high effect sizes that more likely to be published than a study with a low effect size. I used a funnel plot to estimate the assessment of publication bias. Statistical analyses were undertaken using “Cochrane RevMan” statistical software program.

Results Study Selection

I searched electronic database and able to identify 3,106 potential studies and 8 additional records were identified via hand searching. After 2878 irrelevant titles and duplicates removed, 236 articles remained to be screened for title and abstract. I evaluated 63 as potentially eligible full-text articles to be retrieved. After the application of inclusion and exclusion criteria, 22 articles (35%) considered to have information admissible to this systematic review and meta-analysis. These 22 articles include five risk factors associated with faecal carriage of ESBL-PE studies and seventeen prevalence of ESBL-PE in LTCFs studies. The PRISMA flow chart describing the papers identified from the search strategy and reasons for exclusion is shown in Figure 1.

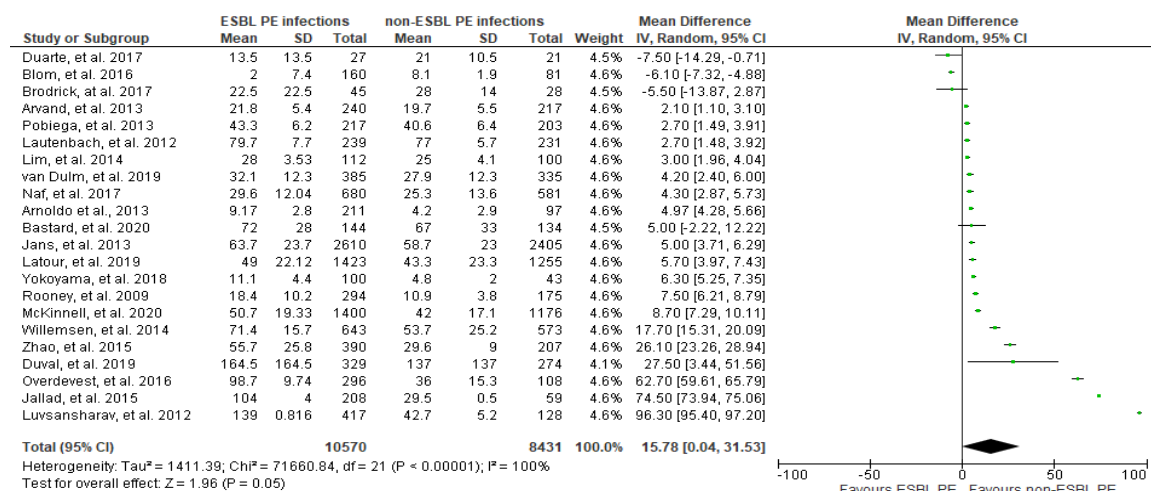
Figure 1*PRISMA Flow Diagram*

Study Characteristics

Geographically, 15 of the 22 studies were carried out in Europe (68.1%; $n=15$), Asia (18.2%; $n=4$), North America (9.1%; $n=2$) and Australia (4.5%; $n=1$). In this analysis, there were two (9.1%) ESBL-PE in LTCFs studies conducted in developing countries and 20 (91%) studies conducted in developed countries. Most of the studies (40.9%; $n=9$) followed a cross sectional design. Other studies followed point prevalence study (27.2%; $n=6$) and screening (18.2%; $n=4$) respectively, while each study including observational cohort, nested case-control study and retrospective were (4.5%; $n=1$) respectively. The duration of studies ranged from 0 to 107 months. The study populations of the studies included residents of both sexes. Appendix A provides further details on the characteristics of the included studies.

Figure 2

Forest Plot of Included Studies

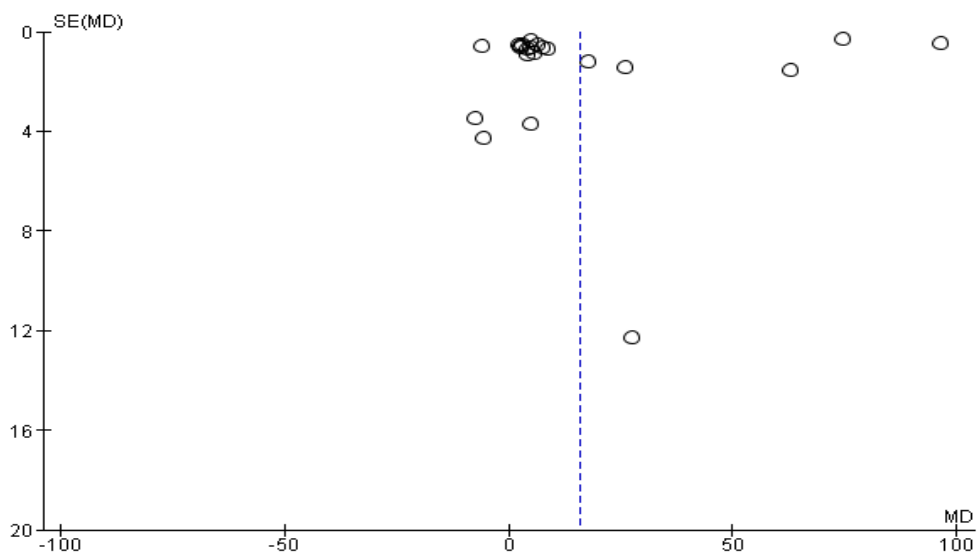


Note. Observed infection rates between ESBL-PE and non-ESBL-PE in all studies, effect size (ES) and confidence interval (CI). “Cochrane RevMan” statistical software

program. Figure 2 shows the forest plots of included studies reporting on ESBL-PE and non-ESBL-PE infections. The 22 studies from 2008 to 2018 were published in the English language. Fifteen studies were conducted in Europe, four studies were conducted in Asia, two studies were performed in North America, and one study was performed in Australia. The pooled prevalence of ESBL-PE infections among LTCF residents was 15.78 (95% CI 0.04 – 31.53). Heterogeneity is confirmed by a high I^2 value of = 100% and a significantly associated p-value (<0.00001). In the light of such a large significant heterogeneity, caution is justified in explaining the summary estimate (diamond shape). The I^2 values represented the percentage of the total variation, which was due to variation between studies. According to Higgins et al. (2003), I^2 suggested that: $I^2 = 0\%$ is no heterogeneity, $I^2 = 25\%$ and below is low heterogeneity, $I^2 = 50\%$ is moderate heterogeneity, and $I^2 = 75\%$ and above is high heterogeneity. I used heterogeneity measurement to define the level and presence of the index of heterogeneity in this study. The outcome effect measure for *Enterobacteriaceae* infection is expressed as a mean difference. The vertical line at 0 interpreted to be no difference in *Enterobacteriaceae* infection scores in ESBL-PE infection and non-ESBL-PE infection. Observation at the pooled effect estimate, the black diamond was almost crossed the vertical line (mean difference: 15.78, 95% CI: 0.04, 31.53), and thus showing a statistically significant effect favoring ESBL-PE infection. The overall effect test corroborates the results by presenting a p- equal 0.05 ($p = 0.05$).

Figure 3

Scatter funnel plot of Enterobacteriaceae among residents in LTCFs included studies year of study (1998-2012)



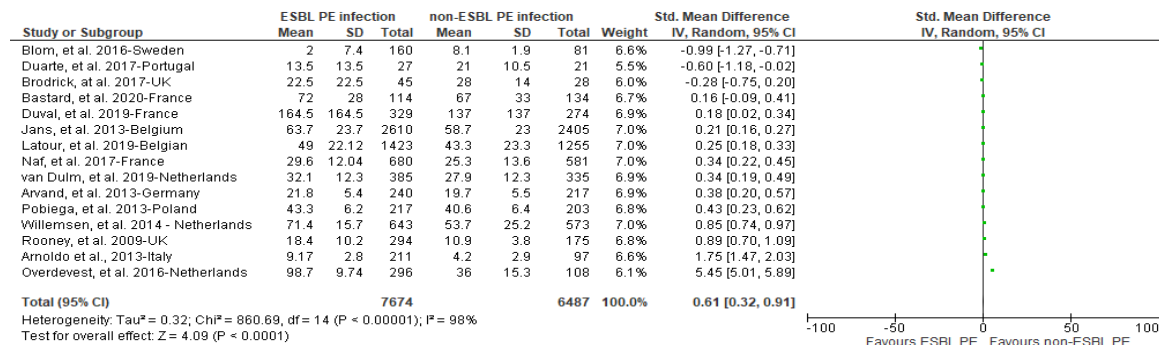
Note. Source: “Cochrane RevMan” statistical software program.

Regional Forest Plots

Forest plot of studies reporting on ESBL and non-ESBL-PE infection in the LTCFs by geographical locations (continents): Europe (68.1%; n=15), Asia (18.2%; n=4), others North America (9.1%; n=2) and Australia (4.5%; n=1), respectively.

Figure 4

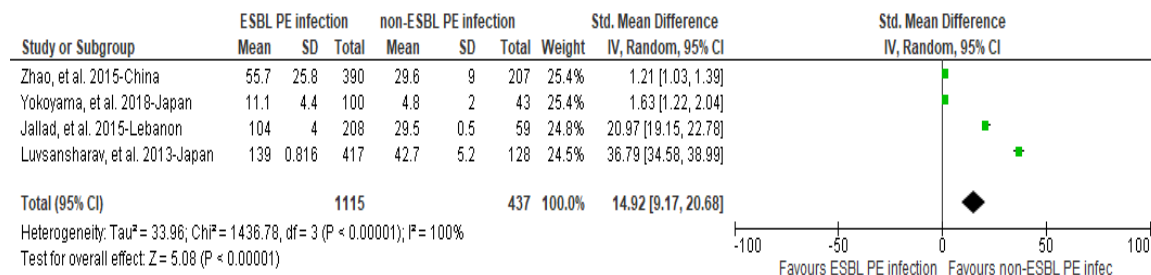
Forest Plot by Europe Region



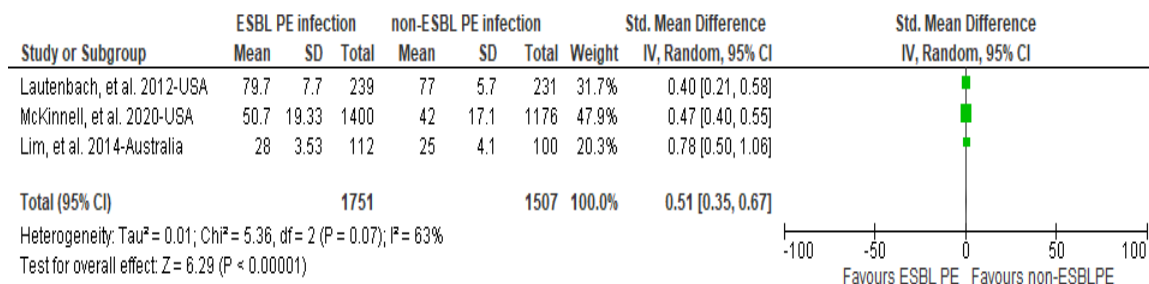
Note. Source: Comprehensive meta-analysis software

Figure 5

Forest Plot by Asian Region



Note. Source: “Cochrane RevMan” statistical software program.

Figure 6*Forest Plot by Other Regions (North America and Australia)*

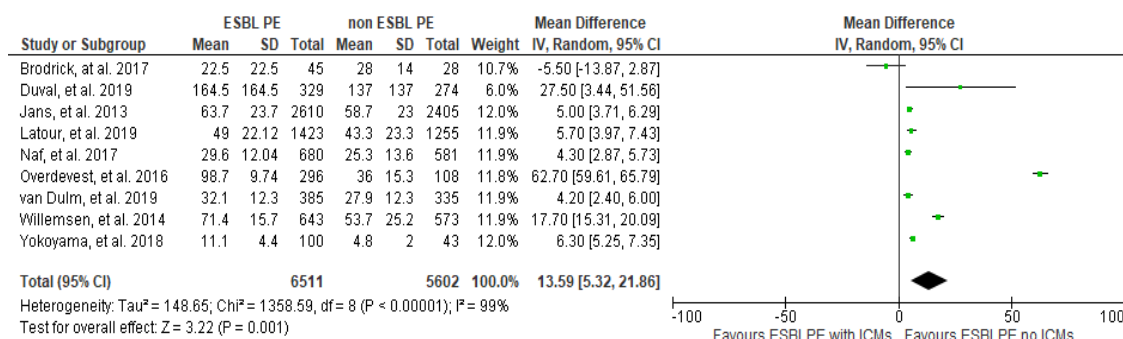
Note. Source: “Cochrane RevMan” statistical software program.

The above regional forest plot studies have been conducted in different countries, in other contexts (for instance, in nursing or residential homes managed by government and non-governmental organizations) with residents from different genders, ages, and various social backgrounds. The outcome effect measure for *Enterobacteriaceae* infection in each regional forest plot is expressed as a standard mean difference. The vertical line at 0 was interpreted to be no difference in *Enterobacteriaceae* infection scores between ESBL-PE and non-ESBL-PE infections in each region. Comparison observation at the pooled effect estimate between the areas, the black diamond was barely crossed the vertical line 0.61 (95% CI: 0.32, 0.91) in the Europe region but crossed the vertical line 14.92 (95% CI: 9.17, 20.58) in Asia region, and the diamond was at the center, that is, there is no apparent difference 0.51(95% CI: 0.36, 0.67) between the intervention group and the control group in other regions (North America and Australia). The standard mean difference of the regional infection was thus showing a statistically significant effect favoring prevalence of ESBL-PE infection in

each of the regions (<0.0001), and the test for the overall effect of these regions have corroborated the results by presenting a p-value <0.05 ($p = <0.0001$). These show a significant association between each environmental/regional source and prevalence of ESBL-PE in LTCFs.

Figure 7

Forest plot of included studies reporting on Enterobacteriaceae infection in the LTCFs by infection control measures, effect size (ES) and confidence interval (CI)



Note. Source: “Cochrane RevMan” statistical software program.

In the analysis of pooled ESBL and non-ESBL-PE prevalence, infection control measures were reported and implemented in nine of twenty-two studies with 13.59 (95% CI: 5.32 – 21.86). The level and presence of the index of heterogeneity in this study is $I^2 = 99\%$. There was considerable heterogeneity among the LTCFs studies ($I^2 = 99\%$, $P < 0.0001$), this means that the meta-analytic effect is statistically significant. The meta-analysis aims to test the hypothesis that there is a significant association between targeted infection control measures and ESBL-PE infections, then the null hypothesis can be rejected, and the alternative hypothesis (that there is an effect) is deemed more likely in this study. The observed pooled effect estimate showed the black diamond that crossed the vertical line

(mean difference: 13.59 (95% CI: 5.32 – 21.86), showing a statistically significant effect favoring infection control measures against ESBL-PE infection. The overall effect test corroborates the results by presenting a p-value less than 0.05 ($p = 0.001$).

The Relationship between Regions (environmental sources) and ESBL-PE

These meta-analyses included 22 studies that investigated the relationship between regional sources and ESBL-PE included 15 studies were from the Europe, 4 studies from the Asia and 4 studies from other regions (two from the USA and one from Australia). The characteristics of studies that participated included in these meta-analyses are summarized in figure 4,5 and 6, respectively. The random-effect model was chosen for computing a weighted mean of the effect sizes to determine the effect variation of the included studies. The combined mean effect sizes for the regional sources of infection and each ESBL-PE were computed separately. The analyses revealed that the Europe region and ESBL-PE ($r = 0.61$, 95% CI [0.32 – 0.91], $p = <.0001$) were statistically significant. The combined standard mean effect size for Asia region and ESBL-PE ($r = 14.92$, 95% CI [9.17 – 20.68], $p = <.00001$) were statistically significant. Similarly, the combined standard mean effect size for other regions and ESBL-PE ($r = 0.51$, 95% CI [0.36 – 0.67], $p = <.00001$) were statistically significant too. The tests of homogeneity effects for the Europe and Asia regional sources of ESBL-PE infection demonstrated that the studies included in the analyses share a common homogeneity effect size with $I^2 = 98\%$ (Europe), and $I^2 = 100\%$ (Asia). While other regions (USA and Australia) with $I^2 = 63\%$ did not share a common effect size with them.

The Relationship between types of LTCFs and ESBL-PE

These meta-analyses included 22 studies that investigated the relationship between LTCFs and ESBL-PE and non-ESBL microorganisms. The characteristics of studies that participated included in these meta-analyses are summarized in figure 2. The random-effect model was chosen for computing a weighted mean of the effect sizes to determine the effect variation of the included studies. The combined mean effect sizes for the LTCFS sources of infection and each ESBL-PE and non-ESBL were computed separately. The analyses revealed that the LTCFs, ESBL-PE and non-ESBL ($r = 15.78$, 95% CI [0.04 – 31.53], $p = 0.05$) were slightly statistically significant. The tests of homogeneity effects for the LTCFs sources of ESBL-PE infection demonstrated that the studies included in the analysis's homogeneity effect size with $I^2 = 100\%$.

The Relationship between Infection Control Measures (ICMs) and ESBL-PE

These meta-analyses included 9 studies that investigated the relationship between infection control measures (ICMs) and ESBL-PE and non-ESBL microorganisms. The characteristics of studies that participated included in these meta-analyses are summarized in figure 7. The random-effect model was chosen for computing a weighted mean of the effect sizes to determine the effect variation of the included studies. The combined mean effect sizes for the ICMs against ESBL-PE and non-ESBL were computed separately. The analyses revealed that the ICMs against ESBL-PE and non-ESBL ($r = 13.59$, 95% CI [5.32 – 21.86], $p = 0.001$) were statistically significant. The tests of homogeneity effects for the impact of ICMs on ESBL-PE infection demonstrated that the studies included in the analysis's homogeneity effect size with $I^2 = 99\%$.

Risk of Bias

When studies were assessed for risk of bias, I used Newcastle-Ottawa scale, 45% (n=10) were assessed as having a low risk of bias; 14% (n=3) unclear risk of bias and 41% (n=9) were deemed to have a high risk of bias. An increasing prevalence of ESBL-PE trend in all regions of LTCFs over time was also observed, however this increase was not statistically significant.

Multiple Regression Statistics

A supplementary multiple regression analyses have been conducted to analyze the correlation matrices and standardized regression models of the included meta-analytic studies. Based on the data provided in included studies for meta-analyses, the relationships between types of LTCFs, regional (environmental source), infection control measures and ESBL-PE were analyzed through the SPSS statistical software.

Table 3

Descriptive Statistics

	Mean	Std. Deviation	N
ESBL	83.18	73.591	22
LTCFs	11.05	11.108	22
Regions	11.18	5.762	22
ICMs	.41	.503	22

Table 4*Model Summary*

Model	<i>R</i>	<i>R</i> Square	Adjusted <i>R</i> Square	Std. Error of the Estimate	Durbin-Watson
1	.683 ^a	.467	.378	58.037	2.152

Note. a. Predictors: (Constant), ICMs, LTCFs, Regions

b. Dependent Variable: ESBL

The Durbin-Watson statistic for this analysis was 2.152. According to Laerd Statistics (2015), the Durbin-Watson statistic range from 0 to 4. Based on this value, there was independence of (errors) residuals, as determined by a Durbin-Watson statistic of 2.152. The *R* is used to measure the strength of the linear relationship between these two variables and can signify the goodness of the model fit with a value that can range from 0 to 1. A multiple correlation coefficient of 0 (zero) signifies not linear association between the dependent variable and the predictor variables and a value of 1 a perfect linear association. A value of 0.683, indicated a moderate level of relationship between variables. Though, multiple correlation coefficient, *R*, is not a commonly used measure to assess goodness of fit. I observed that R^2 was equal to 0.467. This indicated that the addition of all independent variables into a regression model explained 46.7% of the variability of dependent variable, (ESBL-PE). The adjusted R^2 was 0.378. Adjusted R^2 was used to report value proportion of variance explained (that is, report 37.8% rather than 46.7%) although researcher might be able to report both. Adjusted R^2 is also an estimate of effect size, which at 0.378 (37.8%) is an indication of a medium effect size according to Cohen's (1988) classification. R^2 for the overall model

was 46.7% with an adjusted R^2 of 37.8%, a medium size effect according to Cohen (1988).

Table 5

ANOVA

	Model	Sum of Squares	<i>df</i>	Mean Square	<i>F</i>	Sig.
1	Regression	53097.313	3	17699.104	5.255	.009 ^b
	Residual	60629.959	18	3368.331		
	Total	113727.273	21			

Note. a. Dependent Variable: ESBL

b. Predictors: (Constant), ICMs, LTCFs, Regions

The *F*-ratio in the ANOVA table above tests whether the overall regression model is a good fit for the data. "Sig." was observed as the *p*-value = .009 (i.e., $p = .009$). the *p* value was < .05. This result shows that the independent variables were statistically significantly predict the dependent variable, $F(3, 18) = 3368.33, p < .05$; rather than just a *p*-value.

The breakdown of the last part is as follows, $F(3, 18) = 3368.33, p < .05$, as shown above in the ANOVA table. ICMs, LFCFs, and Regions statistically significantly predicted ESBL-PE, $F(3, 15) = 3368.33, p < .05$.

Table 6

		Coefficients ^a											
		Unstandardized Coefficients		Standardized Coefficients		95.0% Confidence Interval for B		Correlations			Collinearity Statistics		
Model		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	68.031	28.771		2.365	.029	7.585	128.476					
	LTCFs	4.233	1.181	.639	3.585	.002	1.752	6.714	.627	.645	.617	.933	1.072
	Regions	-3.690	2.390	-.289	-	.140	-8.712	1.332	-.114	-.342	-.266	.845	1.183
	ICMs	23.608	27.776	.161	1.544	.850	-.34747	81.964	.206	.196	.146	.821	1.218

a. Dependent Variable: ESBL

According to Hair et al. 2019, the VIF statistic is an alternate to Tolerance (that is, 1 divided by Tolerance resulted in VIF value) but I only need to consult one of these measures. In this data analysis, all the Tolerance values exceeded 0.1, and the lowest is 0.821. So, with this value, I have no problem with collinearity in this data set. If the Tolerance value is less than 0.1, I might have a collinearity problem (Hair et al., 2019). The coefficient for LTCFs was 4.233. The slope coefficient value was positive and showed that the more of the LTCFs could be associated with prevalence of ESBL-PE. The multiple regression equation predicts that the more we have residents in the LTCFs the likely that they would be infected with the ESBL-PE. The 95% confidence interval (CI) is between 1.752 and 6.714. That is, I can be 95% confident that the true value of the slope coefficient is between 1.752 and 6.714. I can observe that the p -value was .002 (i.e., $p = .002$). The p was less than .05. the slope coefficient is statistically significant. This means that there is a linear relationship between LTCFs and ESBL-PE. Similarly, the coefficient for regions was -3.690. The 95% confidence interval (CI) was between -8.712 and 1.332. That is, I can observe that the p -value was .140 (i.e., $p = .140$). The p was greater than .05. the slope coefficient is not statistically significant. This means that there was no linear relationship between regions and ESBL-PE. Likewise, the coefficient for ICMs was 23.608. The 95% confidence interval (CI) was between -34.747 and 81.964. That is, I can be 95% confident that the true value of the slope coefficient is between -34.747 and 81.964. A link between the 95% confidence interval (CI) of the slope coefficient and the statistical significance of the slope coefficient can be used to determine a statistically significant slope coefficient in this case. The confidence intervals

under this circumstance do cross the zero (0) (-34.747 and 81.964), it showed that there was no statistically significant slope coefficient ($p > .05$) between ICMs and ESBL-PE. I can observe that the p -value was .407 (i.e., $p = .407$). The p was greater than .05. the slope coefficient is not statistically significant. This means that there was no linear relationship between ICMs and ESBL-PE.

Summary

I performed a quantitative meta-analysis on eligible 22 researched studies to describe the relationship between the variables of interest. A meta-analytical analysis was performed to summarize large amounts of information about the prevalence and infection control measures against ESBL-PE among residents in LTCFs, identified gaps in those studies, and identified interventions useful for the public health community and policymakers. The studies characteristics were examined, and I found studies from Europe to be 68.1% (n=15), Asia 18.2% (n=4), North America 9.1% (n=2), and Australia 4.5% (n=1). In most of the studies, 40.9% (n=9) followed a cross-sectional design, 27.2% (n=6) followed point prevalence study, and 18.2% (n=4) followed screening respectively, while each study including observational cohort, nested case-control study, and retrospective were (4.5%; n=1) respectively. The duration of included studies ranged from 0 to 107 months. The populations of the included studies were residents of both sexes who resided in LTCFs. Heterogeneity confirmed by a high I^2 value of = 100% and a significantly associated p -value (< 0.00001). The I^2 values represented the percentage of the total variation, which was due to variation between studies. These regional forest plot studies in Figures 4, 5, and 6 were conducted to determine the relationship between the

environmental (regions) source of the LTCFs and ESBL-PE. Multiple regression analysis also reported LTCF to be linear associated with ESBL-PE ($p = .002$), regions and ICMs were not associated with ESBL-PE ($p = .140$), ($p = .407$) respectively. Adjusted R^2 estimated the effect size at 0.378 (37.8%) proved to be an indication of a medium effect size of this regression study according to Cohen's (1988) classification. The results obtained in this chapter provided discussions, conclusion, and recommendations in chapter 5.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this study was to gather all available empirical research about the relationship between the LTCFs, the geographical location of LTCFs, ICMs, and ESBL-PE. The geographical location of LTCFs was regarded as the regions in which the studies were conducted. The LTCFs were regarded as the facility in which residents were residing. The infection control measures were targeted, or untargeted infection control measures implemented during the studies. Quantitative meta-analyses were conducted to analyze data for the presence of these relationships. The supplementary statistic technique, multiple regression statistics were used to find relationships between independent variables and dependent variable. The meta-analysis results demonstrated that all regional sources' combined standard mean effect size was statistically significantly associated with ESBL-PE. The analyses for the Europe region and ESBL-PE ($r = 0.61$, 95% CI [0.32 – 0.91], $p = <.0001$) revealed to be statistically significant related. The combined standard mean effect size for Asia region and ESBL-PE ($r = 14.92$, 95% CI [9.17 – 20.68], $p = <.00001$) were also statistically significant related. Equally, the combined standard mean effect size for other regions and ESBL-PE ($r = 0.51$, 95% CI [0.36 – 0.67], $p = <.00001$) were statistically significant related too. The analyses of relationship between LTCFs and ESBL-PE and non-ESBL ($r = 15.78$, 95% CI [0.04 – 31.53], $p = 0.05$) were slightly statistically significant related. In like manner, the analyses of ICMs and ESBL-PE and non-ESBL also revealed ($r = 13.59$, 95% CI [5.32 – 21.86], $p = 0.001$) to be statistically significant related. The results obtained after

performing multiple regression analyses were demonstrated to be different from the previous reports. The analysis reported for LTCFs showed a linear association with ESBL-PE ($p = .002$), whereas regions (environmental sources) and ICMs were not statistically significant ($p = .140$), ($p = .407$) respectively.

Interpretation of Findings

The 22 studies included in the analysis of a total of 10570 participants from studies between 2008 and 2018. Fifteen studies were conducted in Europe (three each in France and Netherlands, two each in Belgium and the UK, one each Sweden, Portugal, Germany, Poland, and Italy), four studies were conducted in Asia (two in Japan, one in China and one in Lebanon), while three studies were performed in other regions, these include (two in USA and one in Australia). No studies included from Africa continent. The pooled prevalence of ESBL-PE colonization among LTCF residents in this meta-analytic study was 15.78% (95% CI 0.04 – 31.53). The ESBL-PE colonization rate in Europe was 61% (95% CI: 0.32 – 0.91), in Asia was 14.92% (95% CI: 9.17 – 20.68) and was 51% in other regions, these include the USA and Australia (95% CI: 0.35 – 0.67). Nine (9) of the 22 studies implemented targeted and untargeted ICMs, including screening and 13.5% colonization rate was revealed with (95% CI: 5.32 – 21.86). In meta-analysis, LTCFs was the only statistically significant association with an increase prevalence of ESBL-PE among residents ($p = 0.05$). In the supplement statistical technique, the multiple regression analysis, the regional differences ($p = 0.140$) and implementation of ICMs ($p = .407$) were not statistically significant. However, multiple regression analysis also reported LTCF to be linear associated with ESBL-PE ($p = .002$),

whereas regions (environmental sources) and ICMs were not significantly associated with ESBL-PE ($p = .140$), ($p = .407$) respectively. Methods including screening to control the prevalence of ESBL-PE were reported in 9 of the 22 reviewed papers, as plotted in figure 7. Three studies reported that ESBL general screening were performed, 2 studies conducted Infection risk scan (IRIS) control measures, whereas four different studies performed control measure in each of these methods genomic surveillance, hand hygiene, national guidelines for empirical therapy, and Close Proximity Interactions (CPIs) network.

Discussion

LTCFs with the colonization of ESBL-PE among residents have raised concern due to their impact on morbidity and mortality and the potential for transmitting resistant enzymes across and within the residential homes (Doi et al., 2017). In most ESBL-PE studies, the colonization rate has spread globally, and almost one in five LTCF residents was colonized with the ESBL infection (Flokas et al., 2017). Urinary tract infection (UTI) has been attributed to the most common infection site among residents in LTCFs and is the most common reason for prescribing antibiotics in LTCFs (Nicolle, 2001). UTIs' risk factors include residents with an indwelling catheter, benign prostatic hypertrophy and prostatitis in men, and estrogen deficiency in women (Nicolle, 2001). With attention to the fact that residents residing and extensively used healthcare facilities as their day-to-day caring (Caljouw et al., 2014) can disseminate resistant enzymes to other residents' populations (van den Dool et al., 2016). Significantly, this could further cause negative implications for public health because of the proxy nature of most care homes that may

further spread the disease. Concerning the geographical variability of the studies that I included in this analysis, most studies were performed in Europe. In contrast, a smaller number of studies were conducted in North America and Australia. In this study, the finding signified that ESBL-PE prevalence rates in developed nations are alarming. Comparatively, there was not enough data to be retrieved from developing countries, especially the Africa continent. The relative lack of data from the developing country may result from the fact that LTCFs in many developing countries provided home care service for their elderly parents at home instead of at formal institutions (World health organization, 2020). However, retrieval of ESBL data is also underrepresented in specific regions, for instance, Oceania and North America. The underrepresentation of different geographical areas may likely lead to an inaccurate worldwide ESBL-PE colonization rate. In this analysis, ESBL-PE colonization was associated with the LTCFs. Though, unguided use of the antibiotic, history of recent hospitalization, and urinary catheter use are risk to ESBL-PE, the gastrointestinal tract also serves as the main reservoir for ESBL-PE, and infection with this type of organism is a vital risk factor for consequent disease in patients. As can be seen, the risk factors mentioned above for ESBL-PE conditions are repeatedly detected among residents in the LTCFs (Caljouw et al., 2014). Unfortunately, antibiotics are commonly prescribed unguided in this setting (Flokas et al., 2017).

Limitations of the Study

Although meta-analyses were essential in all estimates on the overall effect, the results were only based on a limited number of studies provided for this analysis. I

acknowledged the selection bias in the included studies, this could cause a limit to the study since both high risk of bias (n =5) and unclear risk of bias (n=4) were reported to be 41% and only included studies written in the English language for this analysis. So, it is likely that my review missed data of interest written in other languages. The study quality evaluation was performed on different research designs, including cross-sectional, point prevalence surveys, case-control, and cohort study based on applying the quality evaluation tool available. The dangers of combining results from cohort studies is that the study population among cohort studies are more likely to be heterogeneous (Russo 2007). Data from the Africa continent were not available in this study and limiting the generalizability of our findings. A limited number of studies with targeted infection control measures were included in this study, limiting the generalizability of the infection control's impacts on this patient population.

Recommendations

There are several gaps in the knowledge around this meta-analysis study on prevalence of ESBL-PE in LTCFs research. The study aimed was to identify relationship between LTCFs, geographical location and impact of infection control measures and ESBL-PE. Though limited data were retrieved for the meta-analysis, the prevalence of ESBL-PE is linked with all the independent variables with infected residents. The supplement statistical analysis, multiple regression, used in this study only showed a strong linked between LTCFs and ESBL-PE. Hence, I recommended that more methodological work is needed to be employed to cover data from all regions to increase confidence in the generalizability of the study. Although meta-analytical method is

challenging, it would be especially useful to conduct data that involved targeted infection control measures to quantify the impact of these measures on residents who are at risk of acquiring ESBL-PE colonization. It would also be helpful to capture residents who have had previous hospitalization to determine the rate at which ESBL-PE transmit from hospital to residential care homes and vice-versa. Future research should also be developed to carry out a full comparative analysis between hospital patients and residents acquired ESBL-PE colonization.

Implications

Various studies have shown a higher prevalence of ESBL species in LTCFs, especially in nursing homes. This is due to inefficient infection prevention practices, geographical location differences, proximity among the residential homes, and excess use of antibiotics (Pelly et al., 2006). Healthcare professionals have an essential role in controlling the spread of ESBL-PE in LTCFs. However, the implementation of targeted infection control protocols based on evidence-based practices must always be carried out. Importantly, adequate knowledge of *the Enterobacteriaceae* organism's ability to resist beta-lactam antibiotics in the hospital, community, and LTCFs are fundamental in the provision of efficient healthcare. This dissertation also revealed that appropriate training programs aimed at developing necessary skills to provide healthcare staff with the ability to achieve these targets. The training programs should facilitate any potential defects in advanced practice to reduce or control the spread of ESBL-PE. The detection of ESBL organisms could be challenging because of differences among the ESBL species and their ability to spread rapidly among the residents. The antibiotics, such as carbapenems agents

that are still sensitive to ESBL infections, should only be used in acute health cases to limit or control further spread of ESBL producing species (Rawat & Nair, 2010). The positive social change is to promoting awareness for the residents in long-term care facilities so that the care sites at most risk could take further steps to reduce the risks of infecting the residents.

Conclusion

In this dissertation, I have reviewed, collated, examined, and assessed ESBL-PE prevalence among residents in LTCFs. The overall research findings have contributed insight and new knowledge to understand the current epidemiology of ESBL among residents in LTCFs of each region. The research provides evidence of the current state of ESBL-PE globally. It makes available information on how *Enterobacteriaceae* produced beta-lactam enzymes to cross-resist empirical antibiotics for patient's treatment. For that reason, the findings apply to the United Kingdom (UK) and all over the world. The research undertaken has been especially timely because it coincided with the UK five-year antimicrobial resistance strategy from 2014 to 2018 (Global and Public Health Group, 2017). It was also aligned with the UK public health agency's aims and objectives of establishing the Healthcare-Associated Infection and Antimicrobial Stewardship Improvement Board of 2016 in Northern Ireland. This development will inform the multisectoral collaboration to organize its systems to achieve effective action against the spread of ESBL-PE, which can be interpreted into practice. I hoped that the recommendations I suggested in this research, based on the research undertaken, can be instituted to maintain strict adherence to effective infection control measures.

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Appendix A: Characteristics of Included Studies

Author & Year	Country	Design	LTCF Settings	Risk of bias	Number of Residents assessed	Assessment period (month/s)	Number of ESBL-PE isolated	ESBL-PE prevalence (P%)	Infection control measure
Arnoldo et al., 2013	Italy	Point prevalence. surveys (PPS)	23 LTCFs	Low	211	107	114	54.0	Control not reported (CNR)
Arvand et al., 2013	Germany	Screening	11 NHs	Low	240	13	23	9.58	CNR
Bastard et al., 2020	France	PPS	2 NHs	High	144	NR	10	6.9	CNR
Blom et al., 2016	Sweden	Cross-sectional comparison	10 NHs	Unclear	91	3	10	10.99	CNR
Brodrick et al., 2017	UK	Cohort	1 LTCFs	Low	45	6	17	38.0	genomic surveillance
Duarte et al., 2017	Portugal	Screening	1LTCF	Low	27	4	6	22.2	CNR
Duval et al., 2019	France	PPS	1LTFs	High	329	4	55	16.7	Close Proximity Interactions (CPIs) network
Jallad et al., 2015	Lebanon	Cross-sectional	2 NHs	Unclear	208	4	149	71.6	CNR
Jans et al., 2013	Belgium	Cross-sectional prevalence	41 NHs	High	2610	5	205	8.0	National guidelines for empirical therapy
Latour et al., 2019	Belgian	Cross-sectional	29 NHs	High	1423	5	168	11.8	Screening
Lautenbach et al., 2012	USA	Cross-sectional study	3 LTCFs	Unclear	239	31	8	3.34	CNR
Lim et al., 2014	Australia	Nested case-control study	4 LTCFs	High	112	NR	12	10.71	CNR

Luvsansharav et al., 2013	Japan	Screening	3 NHs	High	225	7	49	21.78	CNR
McKinnell et al., 2020	USA	PPS	28 NHs	Low	1400	12	244	16.0	CNR
Naf et al., 2017	France	PPS	23 NHs	Low	680	1	99	14.5	Rectal swabbing screening
Overdeest et al., 2016	Netherlands	Cross-sectional surveys	3 LTCFs	High	296	14	188	17.9	Hand hygiene, and improved cleaning strategies
Pobiega et al., 2013	Poland	PPS & prospective infection control	3 RCHs & 2 NHs	Low	217	12	14	13.9	CNR
Rooney et al., 2009	UK	Retrospective	16 NHs	Low	294	12	119	40.48	CNR
van Dulm et al., 2019	Netherlands	Cross-sectional	12 LTCFs	High	385	10	50	12.98	Infection risk scan (IRIS)
Willemsen et al., 2014.	Netherlands	Cross-sectional survey	9 NHs	High	643	2	70	10.88	Infection prevention Risk Scan (IRIS)
Yokoyama et al., 2018	Japan	Screening	9 SNHs	Low	100	5	57	57.0	Screening of ESBL-E
Zhao et al., 2015	China	Cross-sectional	7 NHs	Low	390	3	183	46.92	CNR

CNR- Control not Reported; ESBL-PE- Extended-spectrum β -lactamase-Producing Enterobacteriaceae; RCHs- Residential Care Homes; IRIS - Infection control Risk Infection Scan; NHs – Nursing Homes; SNHs - Specialist Nursing Homes.