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

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This is to certify that the doctoral dissertation by

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Abstract

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by

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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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I want to thank the Committee Chair of my research project, Professor Raymond Panas, Committee Member Dr. Aaron Mendelsohn for their guidance throughout my dissertation journey. I also thank the Program Director, Dr. Vasileios Margaritis, and the Faculty of Public Health for the valuable help you all provided during my dissertation process. Dr. James Rohrer, University Research Reviewer (URR), whose help and professional attitude during my research helped me work in time whose services turned my research into success. I thank you all for your reviews. Finally, I would like to acknowledge with gratitude, support, and love of my wife, Grace, and the children, Wale, Yemi, Boye, and Lekan, family members and friends, without whom I may not be able to write this dissertation. They are keeping me going through financial assistance, morally and emotionally.

Table of Contents

List of Tables

List of Figures

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 (Piddock, 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 curse 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_0$1: 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_0$2: 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_0$3: 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 susceptive character. The mechanisms susceptive 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, selects, evaluates, and synthesizes 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 unbiases 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-analyses

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-analyses 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 *t*ests. 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 ware not specifically available for ESBL-PE but ware 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 ddeveloped 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?

<center>**Literature Review**</center>

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 inconsistence 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 in 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 (Mangeney 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. (20190). 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 curse 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 (R2) = 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_0$1: 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_0$2: 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_0$3: 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.

<div style="text-align: center">Review Descriptions</div>

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 ware 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 I2 statistic with a *P-value* of <0.05 considered to be statistically significant. The

I2 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 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, 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 (Loannidis, 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_0$1: 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_0$2: 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_0$3: 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
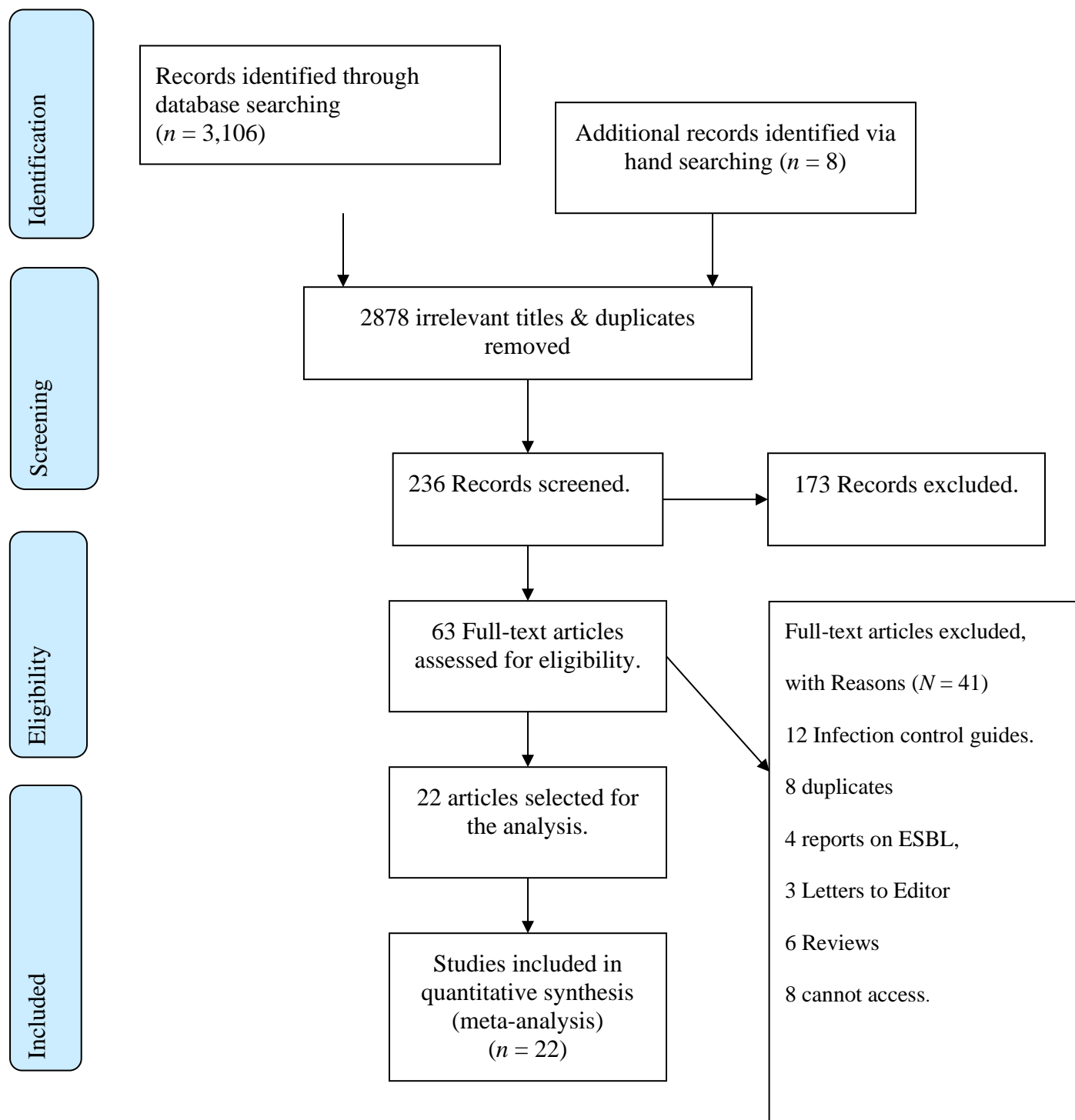
Study Characteristics

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

Study or Subgroup	ESBL PE infections			non-ESBL PE infections			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Duarte, et al. 2017	13.5	13.5	27	21	10.5	21	4.5%	-7.50 [-14.29, -0.71]
Blom, et al. 2016	2	7.4	160	8.1	1.9	81	4.6%	-6.10 [-7.32, -4.88]
Brodrick, at al. 2017	22.5	22.5	45	28	14	28	4.5%	-5.50 [-13.87, 2.87]
Arvand, et al. 2013	21.8	5.4	240	19.7	5.5	217	4.6%	2.10 [1.10, 3.10]
Pobiega, et al. 2013	43.3	6.2	217	40.6	6.4	203	4.6%	2.70 [1.49, 3.91]
Lautenbach, et al. 2012	79.7	7.7	239	77	5.7	231	4.6%	2.70 [1.48, 3.92]
Lim, et al. 2014	28	3.53	112	25	4.1	100	4.6%	3.00 [1.96, 4.04]
van Dulm, et al. 2019	32.1	12.3	385	27.9	12.3	335	4.6%	4.20 [2.40, 6.00]
Naf, et al. 2017	29.6	12.04	680	25.3	13.6	581	4.6%	4.30 [2.87, 5.73]
Arnoldo et al., 2013	9.17	2.8	211	4.2	2.9	97	4.6%	4.97 [4.28, 5.66]
Bastard, et al. 2020	72	28	144	67	33	134	4.5%	5.00 [-2.22, 12.22]
Jans, et al. 2013	63.7	23.7	2610	58.7	23	2405	4.6%	5.00 [3.71, 6.29]
Latour, et al. 2019	49	22.12	1423	43.3	23.3	1255	4.6%	5.70 [3.97, 7.43]
Yokoyama, et al. 2018	11.1	4.4	100	4.8	2	43	4.6%	6.30 [5.25, 7.35]
Rooney, et al. 2009	18.4	10.2	294	10.9	3.8	175	4.6%	7.50 [6.21, 8.79]
McKinnell, et al. 2020	50.7	19.33	1400	42	17.1	1176	4.6%	8.70 [7.29, 10.11]
Willemsen, et al. 2014	71.4	15.7	643	53.7	25.2	573	4.6%	17.70 [15.31, 20.09]
Zhao, et al. 2015	55.7	25.8	390	29.6	9	207	4.6%	26.10 [23.26, 28.94]
Duval, et al. 2019	164.5	164.5	329	137	137	274	4.1%	27.50 [3.44, 51.56]
Overdevest, et al. 2016	98.7	9.74	296	36	15.3	108	4.6%	62.70 [59.61, 65.79]
Jallad, et al. 2015	104	4	208	29.5	0.5	59	4.6%	74.50 [73.94, 75.06]
Luvsansharav, et al. 2012	139	0.816	417	42.7	5.2	128	4.6%	96.30 [95.40, 97.20]
Total (95% CI)			**10570**			**8431**	**100.0%**	**15.78 [0.04, 31.53]**

Heterogeneity: Tau² = 1411.39; Chi² = 71660.84, df = 21 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.96 (P = 0.05)

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 l^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), l^2 suggested that: $l^2 = 0\%$ is no heterogeneity, $l^2 = 25\%$ and below is low heterogeneity, $l^2 = 50\%$ is moderate heterogeneity, and $l^2 = 75\%$ 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
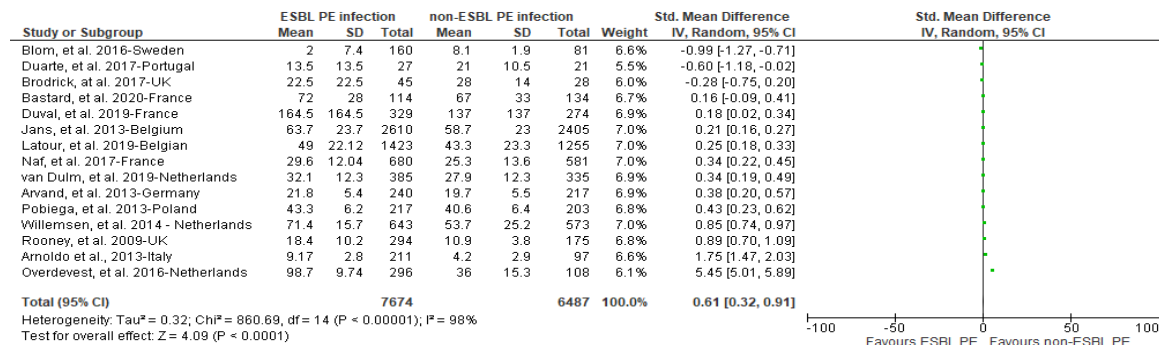
year of study (1998-2012)
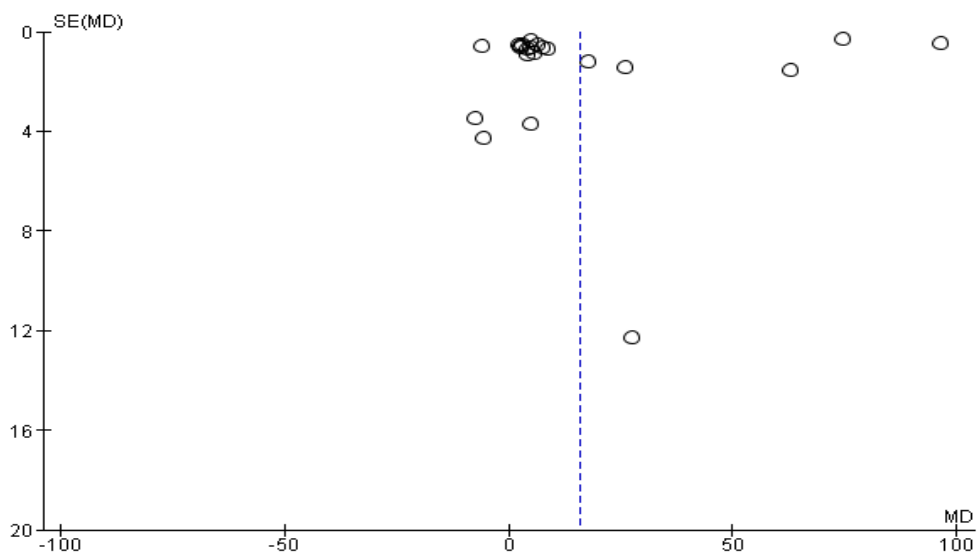
Note. Source: ''Cochrane RevMan'' statistical software program.

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.
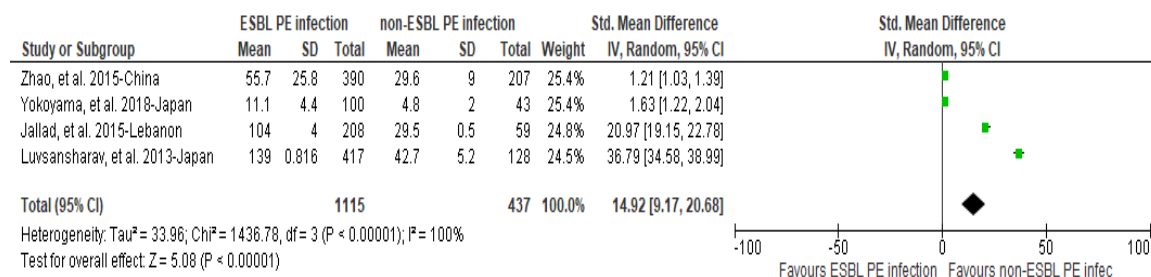
Figure 4

Forest Plot by Europe Region

Study or Subgroup	ESBL PE infection Mean	SD	Total	non-ESBL PE infection Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Blom, et al. 2016-Sweden	2	7.4	160	8.1	1.9	81	6.6%	-0.99 [-1.27, -0.71]
Duarte, et al. 2017-Portugal	13.5	13.5	27	21	10.5	21	5.5%	-0.60 [-1.18, -0.02]
Brodrick, at al. 2017-UK	22.5	22.5	45	28	14	28	6.0%	-0.28 [-0.75, 0.20]
Bastard, et al. 2020-France	72	28	114	67	33	134	6.7%	0.16 [-0.09, 0.41]
Duval, et al. 2019-France	164.5	164.5	329	137	137	274	6.9%	0.18 [0.02, 0.34]
Jans, et al. 2013-Belgium	63.7	23.7	2610	58.7	23	2405	7.0%	0.21 [0.16, 0.27]
Latour, et al. 2019-Belgian	49	22.12	1423	43.3	23.3	1255	7.0%	0.25 [0.18, 0.33]
Naf, et al. 2017-France	29.6	12.04	680	25.3	13.6	581	7.0%	0.34 [0.22, 0.45]
van Dulm, et al. 2019-Netherlands	32.1	12.3	385	27.9	12.3	335	6.9%	0.34 [0.19, 0.49]
Arvand, et al. 2013-Germany	21.8	5.4	240	19.7	5.5	217	6.9%	0.38 [0.20, 0.57]
Pobiega, et al. 2013-Poland	43.3	6.2	217	40.6	6.4	203	6.8%	0.43 [0.23, 0.62]
Willemsen, et al. 2014 - Netherlands	71.4	15.7	643	53.7	25.2	573	7.0%	0.85 [0.74, 0.97]
Rooney, et al. 2009-UK	18.4	10.2	294	10.9	3.8	175	6.8%	0.89 [0.70, 1.09]
Arnoldo et al., 2013-Italy	9.17	2.8	211	4.2	2.9	97	6.6%	1.75 [1.47, 2.03]
Overdevest, et al. 2016-Netherlands	98.7	9.74	296	36	15.3	108	6.1%	5.45 [5.01, 5.89]
Total (95% CI)			**7674**			**6487**	**100.0%**	**0.61 [0.32, 0.91]**

Heterogeneity: Tau² = 0.32; Chi² = 860.69, df = 14 (P < 0.00001); I² = 98%
Test for overall effect: Z = 4.09 (P < 0.0001)

Note. Source: Comprehensive meta-analysis software

Figure 5

Forest Plot by Asian Region

Study or Subgroup	ESBL PE infection Mean	SD	Total	non-ESBL PE infection Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Zhao, et al. 2015-China	55.7	25.8	390	29.6	9	207	25.4%	1.21 [1.03, 1.39]
Yokoyama, et al. 2018-Japan	11.1	4.4	100	4.8	2	43	25.4%	1.63 [1.22, 2.04]
Jallad, et al. 2015-Lebanon	104	4	208	29.5	0.5	59	24.8%	20.97 [19.15, 22.78]
Luvsansharav, et al. 2013-Japan	139	0.816	417	42.7	5.2	128	24.5%	36.79 [34.58, 38.99]
Total (95% CI)			**1115**			**437**	**100.0%**	**14.92 [9.17, 20.68]**

Heterogeneity: Tau² = 33.96; Chi² = 1436.78, df = 3 (P < 0.00001); I² = 100%
Test for overall effect: Z = 5.08 (P < 0.00001)

Note. Source: ''Cochrane RevMan'' statistical software program.

Figure 6

Forest Plot by Other Regions (North America and Australia)
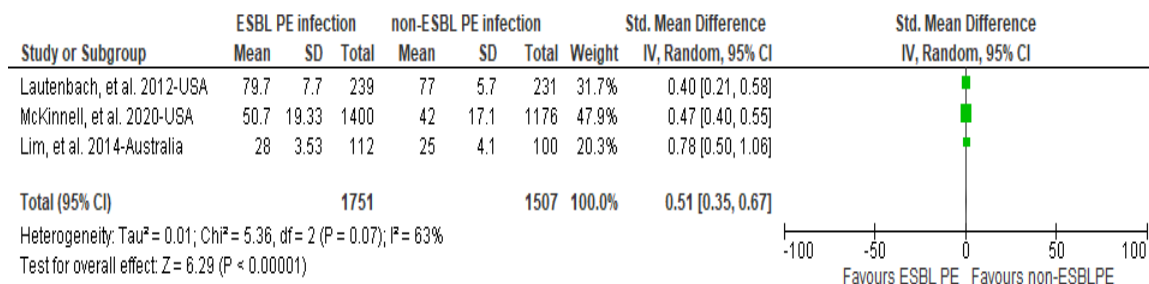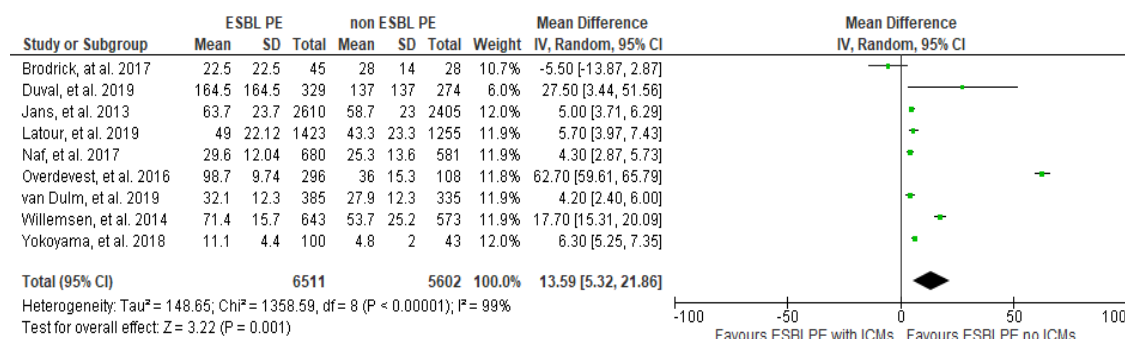

Note. Source: ''Cochrane RevMan'' statistical software program.

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 I2 = 99%.

There was considerable heterogeneity among the LTCFs studies (9 = 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

statistical significance.

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	R	R Square	Adjusted R 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	*df*	Mean Square	*F*	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]

Model		Unstandardized Coefficients B	Std. Error	Standardized Coefficients Beta	t	Sig.	95.0% Confidence Interval for B Lower Bound	Upper Bound	Correlations Zero-order	Partial	Part	Collinearity Statistics 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	-1.544	.140	-8.712	1.332	-.114	-.342	-.266	.845	1.183
	ICMs	23.608	27.776	.161	.850	.407	-34.747	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), Asia18.2% (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 associated 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). Non 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.

References

Abayneh, M., Tesfaw, G., & Abdissa, A. (2018). Isolation of Extended-Spectrum *β*-lactamase- (ESBL-) Producing *Escherichia coli* and *Klebsiella pneumoniae* from Patients with Community-Onset Urinary Tract Infections in Jimma University Specialized Hospital, Southwest Ethiopia. *The Canadian journal of infectious diseases & medical microbiology = Journal canadien des maladies infectieuses et de la microbiologie medicale*, *2018*, 4846159. https://doi.org/10.1155/2018/4846159

Ameringer, S., Serlin, R. C., & Ward, S. (2009). Simpson's paradox and experimental research. *Nursing research*, *58*(2), 123–127. https://doi.org/10.1097/NNR.0b013e318199b517

Arpin, C., Dubois, V., Coulange, L., André, C., Fischer, I., Noury, P., Grobost, F., Brochet, J. P., Jullin, J., Dutilh, B., Larribet, G., Lagrange, I., & Quentin, C. (2003). Extended-spectrum beta-lactamase-producing Enterobacteriaceae in community and private health care centers. *Antimicrobial agents and chemotherapy*, *47*(11), 3506–3514. https://doi.org/10.1128/aac.47.11.3506-3514.2003

Arvand, M., Moser, V., & Pfeifer, Y. (2013). Prevalence of extended-spectrum-β-lactamase-producing *Escherichia coli* and spread of the epidemic clonal lineage ST131 in nursing homes in Hesse, Germany. *Journal of Antimicrobial Chemotherapy*, Volume 68, Issue 11, Pages 2686 2688, https://doi.org/10.1093/jac/dkt226

Bevan, E. R., Jones, A. M., & Hawkey, P. M. (2017). Global epidemiology of CTX-M β-lactamases: Temporal and geographical shifts in genotype. *Journal of Antimicrobial Chemotherapy*, *72*(8), 2145–2155. https://doi.org/10.1093/jac/dkx146

Blane, B., Brodrick, H. J., Gouliouris, T., Ambridge, K. E., Kidney, A. D., Ludden, C. M., Limmathurotsakul, D., Török, M. E., & Peacock, S. J. (2016). Comparison of 2 chromogenic media for the detection of extended-spectrum β-lactamase producing Enterobacteriaceae stool carriage in nursing home residents. *Diagnostic Microbiology and Infectious Disease*, *84*(3), 181–183. https://doi.org/10.1016/j.diagmicrobio.2015.11.008

Blom, A., Ahl, J., Månsson, F., Resman, F., & Tham, J. (2016). The prevalence of ESBL-producing Enterobacteriaceae in a nursing home setting compared with elderly living at home: a cross-sectional comparison. *BioMed Central Infectious Diseases*, *16*, 111. https://doi.org/10.1186/s12879-016-1430-5

Bouassida, K., Jaidane, M., Bouallegue, O., Tlili, G., Naija, H., & Mosbah, A. T. (2016). Nosocomial urinary tract infections caused by extended-spectrum beta-lactamase uropathogens: Prevalence, pathogens, risk factors, and strategies for infection control. *Journal de l'Association des urologues du Canada [Canadian Urological Association Journal]*, *10*(3-4), E87–E93. https://doi.org/10.5489/cuaj.3223

Bowers, B. J., Esmond, S., & Jacobson, N. (2000). The relationship between staffing and quality in long-term care facilities: Exploring the views of nurse aides. *Journal of Nursing Care Quality, 14,* 55-64. https://doi.org/10.1097/00001786-200007000-

[00009](#)

Bracken, M. B. (2019). Random-effects assumption in meta-analyses. *JAMA*, *322*(1), 81. https://doi.org/org/10.1001/jama.2019.5443

Bronfenbrenner, U. (2005). *Ecological systems theory (1992).* In U. Bronfenbrenner (Ed.), *Making human beings human: Bioecological perspectives on human development* (p. 106–173). Sage Publications.

Bush K. (2010). Bench-to-bedside review: The role of beta-lactamases in antibiotic-resistant Gram-negative infections. *Critical care (London, England)*, *14*(3), 224. https://doi.org/10.1186/cc8892

Čablová, L, Pates, R, Miovský, M and Noel, J. 2017. How to write a systematic review article and meta-analysis. In Babor, T F, Stenius, K, Pates, R, Miovský, M, O'Reilly, J and Candon, P. (eds.), *Publishing addiction science: A guide for the perplexed* (pp. 173–189). Ubiquity Press. https://doi.org/10.5334/bbd.i

Caljouw, M.A., Cools, H.J. & Gussekloo, J. (2014). Natural course of care dependency in residents of long-term care facilities: Prospective follow-up study. *BMC Geriatr 14*, 67. https://doi.org/10.1186/1471-2318-14-67

Cassone, M., & Mody, L. (2015). Colonization with multi-drug resistant organisms in nursing homes: Scope, importance, and management. *Current Geriatrics Reports*, *4*(1), 87–95. https://doi.org/:10.1007/s13670-015-0120-2

Center for Disease Control and Prevention. (2019). ESBL-producing Enterobacteriaceae in Healthcare Settings. *Healthcare-associated Infections.*

https://www.cdc.gov/hai/organisms/ESBL.html

Cohen, J., Cohen, P., West, S., & Aiken, L. (Eds.). (2013). Applied multiple

regression/correlation analysis for the behavioral sciences. Routledge.

https://doi.org/10.4324/9780203774441

Cotter, M., Donlon, S., Roche, F., Byrne, H., & Fitzpatrick, F. (2012). Healthcare-

associated infection in Irish long-term care facilities: results from the first national

prevalence study. *Journal of Hospital Infection, 80*, 212.

https://doi.org/10.1016/j.jhin.2011.12.010

Crowther, M. A., & Cook, D. J. (2007). Trials and tribulations of systematic reviews and

meta-analyses. *ASH Education Program Book, (1),* 493-497.

Curran, E. T. (2017). Infection outbreaks in care homes: prevention and management.

Nursing Times, *113*(9), 18-21. https://www.nursingtimes.net/clinical-

archive/infection-control/infection-outbreaks-in-care-homes-prevention-and-

management-14-08-2017/

Deen, M., & de Rooij, M. (2019). Cluster Boot strap: An R package for the analysis of

hierarchical data using generalized linear models with the cluster bootstrap.

Behaviour Research Methods. https://doi.org /10.3758/s13428-019-01252-y

Department of Health, Social Service Northern Ireland (2015). Care standards for nursing

homes.

https://www.rqia.org.uk/RQIA/media/RQIA/Resources/Standards/nursing_homes

standards-_april_2015.pdf

Doi, Y., Iovleva, A., & Bonomo, R. A. (2017). The ecology of extended-spectrum β-lactamases (ESBL) in the developed world. *Journal of travel medicine*, *24*(suppl_1), S44–S51. https://doi.org/10.1093/jtm/taw102

Durlak, J. A., & DuPre, E. P. (2008). Implementation matters: A review of research on the influence of implementation on program outcomes and the factors affecting implementation. *American Journal Community Psychology* 41:327. https://doi.org/10.1007/s10464-008-9165-0

Duval, A., Obadia, T., Boëlle, P. Y., Fleury, E., Herrmann, J. L., Guillemot, D., Temime, L., Opatowski, L., & i-Bird Study group (2019). Close proximity interactions support transmission of ESBL-K. pneumoniae but not ESBL-E. coli in healthcare settings. *PLoS computational biology*, *15*(5), e1006496. https://doi.org/10.1371/journal.pcbi.1006496

Engelhart, S. T., Hanses-Derendorf, L., Exner, M., & Kramer, M. H. (2005). Prospective surveillance for healthcare-associated infections in German nursing home residents. *Journal of Hospital Infection 60,* 46. https://doi.org/10.1016/j.jhin.2004.09.037.

Fair, R. J., & Tor, Y. (2014). Antibiotics and bacterial resistance in the 21st century. *Perspectives in medicinal chemistry*, *6*, 25–64. https://doi.org/10.4137/PMC.S14459

Feneley, R. C., Hopley, I. B., & Wells, P. N. (2015). Urinary catheters: history, current status, adverse events and research agenda. *Journal of Medical Engineering & Technology*, *39*(8), 459–470. https://doi.org/10.3109/03091902.2015.1085600

Fennell, J., Vellinga, A., Hanahoe, B., Morris, D., Boyle, F., Higgins, F., O'Connell, L. K., Keady D., & Cormican, M. (2012). Increasing prevalence of ESBL production among Irish clinical Enterobacteriaceae from 2004 to 2008: an observational study. *BioMed Central Infectious Diseases, 12,* 116. https://doi.org/10.1186/1471-2334-12-116

Flanagan, E., Cassone, M., Montoya, A., & Mody, L. (2016). Infection Control in Alternative Health Care Settings: An Update. *Infectious disease clinics of North America*, *30*(3), 785–804. https://doi.org/10.1016/j.idc.2016.05.001

Flokas, M. E., Alevizakos, M., Shehadeh, F., & Mylonakis, E. (2017). ESBL-producing Enterobacteriaceae colonization in long-term care facilities (LTCFs): a systematic review and meta–analysis. *International Journal of Antimicrobial Agents 50* (5). https://doi.org/10.1016/j.ijantimicag.2017.08.003

Freedman, V. A., & Spillman, B. C. (2014). The residential continuum from home to nursing home: Size, characteristics, and unmet needs of older adults. *The Journals of Gerontology, Series B*, *69*(Suppl_1), S42–S50. https://doi.org/10.1093/geronb/gbu120

Frieden, T. (2013). Antibiotic resistance threats in the United States. Centers for Disease Control and Prevention. https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

Global and Public Health Group (2017). UK 5year antimicrobial resistance (AMR) Strategy 2013-2018. - third annual progress report, 2016. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attac

hment_data/file/662189/UK_AMR_3rd_annual_report.pdf

Golkar, Z., Bagazra, O., & Pace, D. G. (2014). Bacteriophage therapy: a potential

solution for the antibiotic resistance crisis. *Journal of Infectious in Developing*

Countries, *8*(2), 129–136. 13. https://doi.org/10.3855/jidc.3573.

Grogan, J., Murphy, H., & Butler, K. (1998). Extended-spectrum beta-lactamase

producing Klebsiella pneumoniae in a Dublin pediatric hospital. *British Journal*

of Biomedical Science, 55:111–117. PMID: 10198468

Hagel, S., Makarewicz, O., Hartung, A., Weiß, D., Stein, C., Brandt, C., Schumacher, U.,

Ehricht, R., Patchev, V., & Pletz, M. W. (2019). ESBL colonization and

acquisition in a hospital population: The molecular epidemiology and

transmission of resistance genes. *PloS one*, *14*(1), e0208505.

https://doi.org/10.1371/journal.pone.0208505

Hair, J.F., Ringle, C.M., Gudergan, S.P., Fischer, A., Nitzl, C., & Menictas, C.

(2019). Partial least squares structural equation modeling-based discrete choice

modeling: an illustration in modeling retailer choice. *Bus Res* 12, 115–142.

https://doi.org/10.1007/s40685-018-0072-4.

Health Care Settings: An Update. *Infectious disease clinics of North America*, *30*(3),

785–804. https://doi.org/10.1016/j.idc.2016.05.001

Health Protection Scotland. (2018). Healthcare associated infection annual report 2017.

Annual report. https://www.hps.scot.nhs.uk/web-resources-container/healthcare-

associated-infection-annual-report-2017/

Health Protection Surveillance Centre. (2007). Health protection surveillance centre

annual report. http://www.hpsc. ie/hpsc/AboutHPSC/AnnualReports/File,3377, en.pdf

Heudorf, U., Boehlcke, K., & Schade, M. (2012). Healthcare-associated infections in long-term care facilities (HALT) in Frankfurt am Main, Germany, January to March 2011. *Europe Surveillance, 17(35):*20256. PMID: 22958607.

Higgins, J., & Green, S. (2011). Cochrane handbook for systematic reviews of interventions: Version 5.1.0 [updated March 2011]. http://handbook.cochrane.org/

Hoffman, J. I. E. (2015). Biostatistics for Medical and Biomedical Practitioners. *Science Direct.* https://doi.org/10.1016/C2014-0-02732-3

Huang, Y. Y., Alleyne, A., Leung, V., & Chapman, M. (2018). Urosepsis due to extended-spectrum β-lactamase-producing *Escherichia coli*: a retrospective, single-centre review of risk factors and clinical outcomes. *The Canadian Journal of Hospital Pharmacy*, *71*(2), 119–127.

Hughes, C., Tunney, M., & Bradley, M. C. (2013). Infection control strategies for preventing the transmission of methicillin-resistant Staphylococcus aureus (MRSA) in nursing homes for older people. *Cochrane Database of Systematic Reviews*. *11*. Art. https://doi.org/10.1002/14651858.CD006354.pub4.

Isgren, C. M., Edwards, T., Pinchbeck, G. L., Winward, E., Adams, E. R., Norton, P., Timofte, D., Maddox, T. W., Clegg, P. D., & Williams, N. J. (2019). Emergence of carriage of CTX-M-15 in faecal *Escherichia coli* in horses at an equine hospital in the UK; increasing prevalence over a decade (2008-2017). *Biomed Central*

veterinary research, *15*(1), 268. https://doi.org/10.1186/s12917-019-2011-9

Jia, H., Li, W., Hou, T., Ma, H., Yang, Y., Wu, A., Liu, Y., Wen, J., Yang, H., Luo, X., Xing, Y., Zhang, W., Wu, Y., Ding, L., Liu, W., Lin, L., Li, Y., Chen, M., & Li, L. (2019). The Attributable Direct Medical Cost of Healthcare Associated Infection Caused by Multidrug Resistance Organisms in 68 Hospitals of China. *BioMed research international*, *2019*, 7634528. https://doi.org/10.1155/2019/7634528

Johansson, M., Björne, P., Runesson, I., & Ahlström, G. (2017). Healthy ageing in people with intellectual disabilities from managers' perspective: a qualitative study. *Healthcare (Basel, Switzerland)*, *5*(3), 45. https://doi.org/10.3390/healthcare5030045

Kaarme, J., Riedel, H., Schaal, W., Yin, H., Nevéus, T., & Melhus, Å. (2018). Rapid increase in carriage rates of *Enterobacteriaceae* producing extended-spectrum β-lactamases in healthy preschool children, Sweden. *Emerging Infectious Diseases*, *24*(10), 1874-1881. https://doi.org/10.3201/eid2410.171842.

Kahlert, J., Gribsholt, S. B., Gammelager, H., Dekkers, O. M., & Luta, G. (2017). Control of confounding in the analysis phase – an overview for clinicians. *Clinical Epidemiology*. https://doi.org/10.2147/CLEP.S129886.

Kang, C. I., Kim, S. H., Park, W. B., Lee, K. D., Kim, H. B., Kim, E. C., Oh, M. D., & Choe, K. W. (2004). Bloodstream infections due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial

therapy. *Antimicrobial agents and chemotherapy*, *48*(12), 4574–4581.

https://doi.org/10.1128/AAC.48.12.4574-4581.2004

Khabbaz, R. F., & Tenney, J. H. (1988). Infection control in Maryland nursing homes.

Infection Control Hospital Epidemiology, 9, 159. https://doi.org/10.1086/645821

Knothe, H., Shah, P., Krcmery, V., Antal, M., & Mitsuhashi, S. (1983). Transferable

resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical

isolates of Klebsiella pneumoniae and Serratia marcescens. *Infection*, *11*(6), 315–

317. https://doi.org/10.1007/bf01641355

Laerd Statistics (2015). Hierarchical multiple regression using SPSS Statistics. *Statistical*

tutorials and software guides. https://statistics.laerd.com/

Latifpour, M., Gholipour, A., & Damavandi, M. S. (2016). Prevalence of extended-

spectrum beta-lactamase-producing *Klebsiella pneumoniae* isolates in nosocomial

and community-acquired urinary tract infections. *Jundishapur Journal*

*Microbiol*ogy, *9*(3), e31179. https://doi.org/10.5812/jjm.31179.

Latour, K., Huang, T. D., Jans, B., Berhin, C., Bogaerts, P., Noel, A., Nonhoff, C.,

Dodémont, M., Denis, O., Ieven, M., Loens, K., Schoevaerdts, D., Catry, B., &

Glupczynski, Y. (2019). Prevalence of multidrug-resistant organisms in nursing

homes in Belgium in 2015. *PloS one*, *14*(3), e0 214327.

https://doi.org/10.1371/journal.pone.0214327

Lautenbach, E., Han, J., Santana, E., Tolomeo, P., Bilker, W. B., & Maslow, J. (2012).

Colonization with extended-spectrum β-lactamase-producing Escherichia coli and

Klebsiella species in long-term care facility residents. *Infection Control and*

Hospital Epidemiology, *33*(3), 302–304. https://doi.org/10.1086/664055

Lautenbach, E., Patel, J. B., Bilker, W. B., Edelstein, P. H., & Fishman, N. O. (2001). Extended spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes. *Clinical Infectious Diseases*, *32,* 1162–1171. https://doi.org/10.1086/319757

Lee, S. Y., Kotapati, S., Kuti, J. L., Nightingale, C. H., & Nicolau, D. P. (2006). Impact of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species on clinical outcomes and hospital costs: a matched cohort study. *Infectious Control Hospital Epidemiology*. *27,* 1226–1232. https://doi.org/10.1086/507962

Livermore, D. M. & Hawkey, P. M. (2005). Cefotaxime (CTX-M) changing the face of ESBL in the UK. *Journal Antimicrobial Chemotherapy. 56,* 451–454. https://doi.org/10.1093/jac/dki239

Livermore, D.M., Hope, R., Brick, G., Lillie, M., & Reynolds, R. (2008). Non-susceptibility trends among Enterobacteriaceae from bacteraemia in the UK and Ireland, 2001–06. *Journal of Antimicrobial Chemother*apy, *62*(Suppl 2), ii41–54. ii41-ii54. https://doi.org/10.1093/jac/dkn351

Lloyd, T., Conti, S., Santos, F., & Steventon, A. (2019). Effect on secondary care of providing enhanced support to residential and nursing home residents: a subgroup analysis of a retrospective matched cohort study. *BMJ quality & safety*, *28*(7), 534–546. 10.1136/bmjqs-2018-009130

Lopez, S. H (2006). Culture change management in long-term care: A shop-floor view.

Polit Soc 34:55-80. https://doi.org/10.1177/0032329205284756

Luff, R., Ellmers, T., Eyers, I., Young, E., & Arber, S. (2011). Time spent in bed at night
by care-home residents: Choice or compromise? *Ageing Sociology 31*:1229-50.
https://doi.org/10.1017/S0144686X10001285

Mangeney, N., Niel, P., Paul, G., Faubert, E., Hue, S., Dupeyron, C., Louarn, F., &
https://doi.org/Leluan, G. (2000). A 5-year epidemiological study of extended-
spectrum beta-lactamase producing Klebsiella pneumoniae isolates in a medium-
and long-stay neurological unit. *Journal of Applied Microbiology*, *88,* :504–511.
https://doi.org/10.1046/j.1365-2672.2000.00989.x.

Manson, A. L., Cohen, K. A., Abeel, T., Desjardins, C. A., Armstrong, D. T., Barry, C.
E., 3rd, Brand, J., TBResist Global Genome Consortium, Chapman, S. B., Cho, S.
N., Gabrielian, A., Gomez, J., Jodals, A. M., Joloba, M., Jureen, P., Lee, J. S.,
Malinga, L., Maiga, M., Nordenberg, D., Noroc, E., … Earl, A. M. (2017).
Genomic analysis of globally diverse Mycobacterium tuberculosis strains
provides insights into the emergence and spread of multidrug resistance. *Nature
genetics*, *49*(3), 395–402. https://doi.org/10.1038/ng.3767

Melzera, M. & Petersen, I. (2007). Mortality following bacteraemia infection caused by
extended spectrum beta-lactamase (ESBL) producing *E. coli* compared to non-
ESBL producing *E.* coli. *Journal of Infection, 55*(3), 254-259.
https://doi.org/10.1016/j.jinf.2007.04.007

Michael, C. A., Dominey-Howes. D., & Labbate, M. (2014). The antibiotic resistance
crisis: causes, consequences, and management. *Front Public Health*.

https://doi.org/10.3389/fpubh.2014.00145

Mody, L., Langa, K. M., Saint, S., Bradley, S. F. (2005). Preventing infections in nursing homes: a survey of infection control practices in southeast Michigan. *American Journal Infection Control 33*:489. https://doi.org/10.1016/j.ajic.2005.01.011

Møller, T. S. B., Rau, M. H., Bonde, C. S., Sommer, M. O. A., Guardabassi, L., & Olsen, J. E. (2016). Adaptive responses to cefotaxime treatment in ESBL-producing *Escherichia coli* and the possible use of significantly regulated pathways as novel secondary targets, *Journal of Antimicrobial Chemotherapy*, *71*(9), 2449–2459. https://doi.org/10.1093/jac/dkw198

Montoya, A., & Mody, L. (2011). Common infections in nursing homes: a review of current issues and challenges. *Aging health*, *7*(6), 889–899. https://doi.org/10.2217/AHE.11.80

Morgan, D. G, Crossley, M. F, & Stewart, N. J. (2008). Taking the hit: Focusing on caregiver "error" masks organizational-level risk factors for nursing aide assault. Qual Health Res 18:334-46.

Morris, D., Murphy, A., Pickup, M., Hanahoe, B., Fenelon, L., & Cormican, M. (2005). Recognition of cefotaxime producing E. coli as a urinary tract pathogen in Ireland. *Epidemiology Insight*, *6,* 3–4.

Navon-Venezia, S., Kondratyeva, K., & Carattoli, A. (2017). Klebsiella pneumoniae: a major worldwide source and shuttle for antibiotic resistance, *Federation of European Microbiological Societies Microbiology Reviews*, *41*(3), 252–275. https://doi.org/10.1093/femsre/fux013

NiChulain, M., Murray, A. M., Corbett-Feeney, G., & Cormican, M. (2005).

    Antimicrobial resistance in E. coli associated with urinary tract infection in the

    west of Ireland. *Irish Journal Medical Science,* 174:6–9.

    https://doi.org/10.1007/BF03168974

Nicolle L. E. (2014). Catheter associated urinary tract infections. *Antimicrobial*

    resistance and infection control, *3*, 23. https://doi.org/10.1186/2047-2994-3-23

Nicolle L. E., (2001). SHEA Long-Term-Care-Committee. Urinary tract infections in

    long-term-care facilities. *Infection Control Hospital Epidemiology*. 22:167.

    https://doi.org/10.1086/501886

Nilsen, P (2015). Making sense of implementation theories, models, and frameworks.

    Implement Science10:53. https://doi.org/10.1186/s13012-015-0242-0

Northern Ireland Information Statistics and Research Agency (2019). Health and social

    care statistics. Department of Health.

    https://www.ninis2.nisra.gov.uk/public/PivotGrid.aspx?ds=9496&lh=63&yn=200

    8-2018&sk=134&sn=Health+and+Social+Care&yearfilter=

Overdevest, I., Haverkate, M., Veenemans, J., Hendriks, Y., Verhulst, C., Mulders, A.,

    Couprie, W., Bootsma, M., Johnson, J., & Kluytmans, J. (2016). Prolonged

    colonisation with Escherichia coli O25:ST131 versus other extended-spectrum

    beta-lactamase-producing E. coli in a long-term care facility with high endemic

    level of rectal colonisation, the Netherlands, 2013 to 2014. *Europe Surveillance*,

    20;21(42). https://doi.org/10.2807/1560-7917.ES.2016.21.42.30376

Pana, Z. D., & Zaoutis, T. (2018). Treatment of extended-spectrum β-lactamase-

producing *Enterobacteriaceae* (ESBL) infections: what have we learned until

now? *F1000 Research*, *7*, F1000 Faculty Rev-1347.

https://doi.org/10.12688/f1000research.14822.1

Paterson, D. L., Ko, W. C., von Gottenberg, A., Casellas, J. M., Mulazimoglu, L.,

Klugman, K. P., Bonomo, R. A., Rice, L., McCormack, J. G., & Yu, V. L. (2001).

Outcome of cephalosporin treatment for serious infections due to apparently

susceptible organisms producing extended-spectrum beta-lactamases:

implications for the clinical microbiology laboratory. *Journal Clinical

Microbiology*, *39*:2206–2212. https://doi.org/10.1128/JCM.39.6.2206-2212.2001

Paterson, D. L., Ko, W. C., von Gottenberg, A., Mohapatra, S., Casellas, J. M., Goossens,

H., Mulazimoglu, L., Trenholme, G., Klugman, K. P., Bonomo, R. A., Rice, L.

B., Wagener, M. M., McCormack, J. G., Yu, V. L. (2004). Antibiotic therapy for

Klebsiella pneumoniae bacteraemia: implications of production of extended

spectrum beta lactamases. *Clinical Infectious Diseases*, *39*:31–37.

https://doi.org/10.1086/420816

Patterson, L., & Bradley, D. (2017). Surveillance of antimicrobial use and resistance in

Northern Ireland, Annual Report, 2017. Public Health Agency. Retrieved from

https://www.publichealth.hscni.net/sites/default/files/AMR_annual_report_final_

0.pdf.

Pelly H, Morris D, O'Connell E, Hanahoe B, Chambers C, Biernacka K, Gray S, &

Cormican, M. (2006). Outbreak of extended spectrum beta-lactamase producing

Escherichia coli in a nursing home in Ireland, May. *Europe Surveillance*, *11*:

E060831. https://doi.org/10.2807/esw.11.35.03036-en

Piddock, L. J. (2012). The Crisis of no new antibiotics—What is the way forward? *Lancet Infectious Diseases, 12*(3), 249–253. https://doi.org/10.1016/S1473-3099(11)70316-4

Pop-Vicas, A., Mitchell, S. L., Kandel, R., Schreiber, R., & D'Agata, E. M. (2008). Multidrug-resistant Gram-negative bacteria in a long-term care facility: prevalence and risk factors. *Journal American Geriatrics Society, 56*, 1276. https://doi.org/10.1111/j.1532-5415.2008.01787.x.

Pourhoseingholi, M. A., Baghestani, A. R., & Vahedi, M. (2012). How to control confounding effects by statistical analysis. *Gastroenterology and hepatology from bed to bench*, *5*(2), 79–83.

Prestinaci, F., Pezzotti, P., & Pantosti, A. (2015). Antimicrobial resistance: a global multifaceted phenomenon. *Pathogens and global health*, *109*(7), 309–318. https://doi.org/10.1179/2047773215Y.0000000030

Procop, G. W., Marion J., Tuohy, M. T., Wilson D. A., Williams, D., Hadziyannis, E., & Hall, G. S. (2003). Cross-class resistance to non–β β-lactam antimicrobials in extended-spectrum β-lactamase–producing Klebsiella pneumoniae. *American Journal Clinical Pathology, 120*:265-267. https://doi.org/10.1309/BWQKWB2WN6W5X1CC

Public Health Agency. (2019). Northern Ireland points prevalence survey of hospital associated infections and antimicrobial Use 2017. *Health Protection.* https://www.publichealth.hscni.net/publications/northern-ireland-point-

prevalence-survey-hospital-associated-infections-and.

Public Health England (2017). Health Protection Report. *Weekly Infection Report, 11*(18). https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attac hment_data/file/618299/hpr1817_ecoli_crrctd.pdf

Public Health England. (2015). Identification of Enterobacteriaceae. *UK Standards for Microbiology Investigations. ID 16*(4). https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories.

Public Health England. (2016). Detection of Enterobacteriaceae producing extended spectrum β-lactamases. *United Kingdom Standards for Microbiology Investigations. B 59*(4.1). https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories.

Public Health England. (2017). Laboratory surveillance of Escherichia coli bacteraemia in England, Wales, and Northern Ireland: 2017. *Health Protection Report, 12*(22). https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attac hment_data/file/718820/hpr2218_ecoli.pdf.

Rawat, D., & Nair, D. (2010). Extended-spectrum β-lactamases in Gram Negative Bacteria. *Journal of global infectious diseases*, *2*(3), 263–274. https://doi.org/10.4103/0974-777X.68531

Rice, L. B., Willey, S. H., Papanicolaou, G. A., Medeiros, A. A., Eliopoulos, G. M., Moellering, R. C., & Jr. Jacoby, G. A. (1990). Outbreak of ceftazidime resistance caused by extended-spectrum beta-lactamases at a Massachusetts chronic-care

facility. *Antimicrobial Agents Chemotherapy*. 34:2193–2199.

https://doi.org/10.1128/AAC.34.11.2193

Rodríguez-Baño, J., Gutiérrez-Gutiérrez, B., Machuca, I., & Pacscual, A. (2018).

Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-,

and carbapenemase-producing Enterobacteriaceae. *Clinical Microbiology*

Reviews, 31(2), e00079-17. https://doi.org/10.1128/CMR.00079-17

Rooney, P. J., O'Leary, M. C., Loughrey, A. C, McCalmont, M., Smyth, B., Donaghy, P.,

Badri, M., Woodford, N., Karisik, E., & Livermore, D. M. (2009). Nursing homes

as a reservoir of extended-spectrum beta-lactamase (ESBL)-producing

ciprofloxacin-resistant Escherichia coli. *Journal of Antimicrobial Chemotherapy*;

64:635–41. https://doi.org/10.1093/jac/dkp220

Roup, B. J., Roche, J. C., & Pass, M. (2006). Infection control program disparities

between acute and long-term care facilities in Maryland. *American Journal*

Infection 34:122. https://doi.org/10.1016/j.ajic.2005.12.010

Russo M. W. (2007). How to Review a Meta-analysis. *Gastroenterology &*

hepatology, *3*(8), 637–642.

Sandoval, C., Walter, S. D., McGeer, A., Simor, A. E., Bradley, S. F., Moss, L. M., &

Loeb, M. B. (2004). Nursing home residents and Enterobacteriaceae resistant to

third generation cephalosporins. *Emerging infectious diseases*, *10*(6), 1050–1055.

https://doi.org/10.3201/eid1006.030662

Sengupta, S., Chattopadhyay, M. K., & Grossart, H. P. (2013). The multifaceted roles of

antibiotics and antibiotic resistance in nature. *Front Microbiology,* 47(*4*),

https://doi.org/10.3389/fmicb.2013.00047

Shaikh, S., Fatima, J., Shakil, S., Rizvi, S. M., & Kamal, M. A. (2014). Antibiotic

resistance and extended spectrum beta-lactamases: types, epidemiology, and

treatment. *Saudi Journal Biological Science*. *22* (1):90-101.

https://doi.org/10.1016/j.sjbs.2014.08.002.

Simpson, E. H. (1951). The interpretation of interaction in contingency tables. *Journal of*

the Royal Statistical Society. Series B (Methodological), Vol. 13, No. 2 (1951),

pp. 238-241. http://www.jstor.org/stable/2984065

Smith, K., Dobson, A., McKenzie, E., Real, L., Smith, D., & Wilson, M. (2005).

Ecological theory to enhance infectious disease control and public health policy.

*Frontiers in Ecology and the Environment, 1*3(1), 29–37.

https://doi.org/10.1890/1540-9295(2005)003

Smith, P. W., Bennett, G., Bradley, S., Drinka P., Lautenbach, E., Marx, J., Mody, L.,

Nicolle, L., & Stevenson, K. (2008). SHEA/APIC guideline: infection prevention

and control in the long-term care facility, *Infection Control Hospital*

Epidemiology 29(9):785-814. https://doi.org/10.1086/592416

Smith, P. W., Helget, V., & Sonksen, D. (2002). Survey of infection control training

program graduates: long-term care facility and small hospital practitioners.

American Journal Infection Control 30:311.

https://doi.org/10.1067/mic.2002.122437

Stat Trek, (2019). Residual Analysis in Regression. Teach yourself statistics.

https://stattrek.com/regression/residual-analysis.aspx

Tacconelli, E., Carrara, E., Savoldi, A., Harbarth, S., Mendelson, M., Monnet, D. L, & Magrini, N. (2018). Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infectious Disease, 18*, 318–327. https://doi.org/10.1016/S1473-3099(17)30753-3

Tang, W., Hu, J., Zhang, H., Wu, P., & He, H. (2015). Kappa coefficient: a popular measure of rater agreement. *Shanghai archives of psychiatry*, *27*(1), 62–67. https://doi.org/10.11919/j.issn.1002-0829.215010

Teklu, D. S., Negeri, A. A., Legese, M. H., Bedada, T. L., Woldemariam, H. K., & Tullu, K. D. (2019). Extended-spectrum beta-lactamase production and multi-drug resistance among *Enterobacteriaceae* isolated in Addis Ababa, Ethiopia. *Antimicrobial resistance and infection control*, *8*, 39. https://doi.org/10.1186/s13756-019-0488-4

Thaden, J. T., Fowler, V. G., Sexton, D. J., & Anderson, D. J. (2016). Increasing incidence of extended-spectrum β-lactamase-producing Escherichia coli in community hospitals throughout the South-eastern United States. *Infection control and hospital epidemiology*, *37*(1), 49–54. https://doi.org/10.1017/ice.2015.239.

Tsukamoto, N., Ohkoshi, Y., Okubo, T., Sato, T., Kuwahara, O., Fujii, N., Tamura, Y., & Yokota, S. (2014). High prevalence of cross-resistance to aminoglycosides in fluoroquinolone-resistant *Escherichia coli* clinical isolates. *Chemotherapy, 59*(5), 379-384. https://doi.org/10.1159/000361011.

Tumbarello, M., Trecarichi, E. M., Bassetti, M., De Rosa, F. G., Spanu, T., Di Meco, E.,

& Cauda, R. (2011). Identifying patients harboring extended-spectrum-beta-lactamase-producing Enterobacteriaceae on hospital admission: derivation and validation of a scoring system. *Antimicrobial agents and chemotherapy*, *55*(7), 3485–3490. https://doi.org/10.1128/AAC.00009-11

University of Virginia Library (2016). Hierarchical Linear Regression. Research Data Services and Sciences. https://data.library.virginia.edu/hierarchical-linear-regression/

Valenza, G., Nickel, S., Pfeifer, Y., Eller, C., Krupa, E., Lehner-Reindl, V., & Höller, C. (2014). Extended-spectrum-β-lactamase-producing Escherichia coli as intestinal colonizers in the German community. *Antimicrobial agents and chemotherapy*, *58*(2), 1228–1230. https://doi.org/10.1128/AAC.01993-13

van den Dool, C., Haenen, A., Leenstra, T., & Wallinga, J. (2016). The Role of Nursing Homes in the Spread of Antimicrobial Resistance Over the Healthcare Network. *Infection control and hospital epidemiology*, *37*(7), 761–767. https://doi.org/10.1017/ice.2016.59

Wang, P. S., Schneeweiss, S., & Avorn, J (2005). Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *New England Journal of Medicine 353:2335-41*. https://doi.org/10.1056/NEJMoa052827

Weiner, L. M., Webb, A. K., Limbago, B., Dudeck, M. A., Patel, J., Kallen, A. J., Edwards, J. R., & Sievert, D. M. (2016). Antimicrobial-resistant pathogens Associated with healthcare-associated infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and

Prevention, 2011-2014. *Infection control and hospital epidemiology*, *37*(11), 1288–1301. https://doi.org/10.1017/ice.2016.174

Wells, G., Shea, B., O'connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2014). The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Wesangula, E. & Hickey, B. (2018). Tackling antimicrobial resistance (AMR) together working Paper 1.0: multisectoral coordination. *World Health Organization*. https://www.who.int/antimicrobial-resistance/publications/tackling-AMR-multisectoral-coordination-june2018.pdf?ua=1

Wiener, J., Quinn, J. P., Bradford, P. A., Goering, R. V., Nathan, C., Bush, K., Weinstein, R. A. (1999). Multiple antibiotic resistant Klebsiella and Escherichia coli in nursing homes *Journal of the American Medical Association*. *281:*517–523. https://doi.org/10.1001/jama.281.6.517

Woodford, N., Ward, M. E., Kaufmann, M. E., Turton, J., Fagan, E. J., James, D., Johnson, A. P., Pike, R., Warner, M., Cheasty, T., Pearson, A., Harry, S., Leach, J. B., Loughrey, A., Lowes, J. A., Warren, R. E., & Livermore, D. M. (2004). Community and hospital spread of Escherichia coli producing CTX-M extended-spectrum beta-lactamases in the UK. *Journal of Antimicrobial Chemotherapy* *54*:735–743. https://doi.org/10.1093/jac/dkh424

World Health Organization (2015). World Health Assembly addresses antimicrobial resistance, immunization gaps and malnutrition.

https://www.who.int/mediacentre/news/releases/2015/wha-25-may-2015/en/

World Health Organization (2016). Critically important antimicrobials for human

medicine (5th Rev.). Ranking of medically important antimicrobials for risk

management of antimicrobial resistance due to non-human use.

https://apps.who.int/iris/bitstream/handle/10665/255027/9789241512220-eng.pdf

World Health Organization (2017). Global priority list of antibiotic-resistant bacteria to

guide research, discover, and development of new antibiotics.

http://apps.who.int/medicinedocs/documents/s23171en/s23171en.pdf

World health organization (2020). long term care in developing countries: ten case-

studies; 2002. https://www.who.int/chp/knowledge/publications/Case_studies/en/

Yadav, K. K., Adhikari, N., Khadka, R., Pant, A. D., & Shah, B. (2015). Multidrug

resistant Enterobacteriaceae and extended spectrum β-lactamase producing

Escherichia coli: a cross-sectional study in National Kidney Center, Nepal.

Antimicrobial resistance and infection control, *4*, 42.

https://doi.org/10.1186/s13756-015-0085-0

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 at 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
Overdevest 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.