The Causes and Control Measures of Extended Spectrum Beta-Lactamase Producing Enterobacteriaceae in Long-Term Care Facilities: A Systematic Review and Meta-Analysis

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Abstract

Background: Due to extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-PE), infections among residents are increasing in long-term care facilities (LTCFs), resulting in a high rate of morbidity and healthcare costs. A designated infection control team is unavailable to control the disease.

Methods: 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 of the 3106 studies met the inclusion criteria.

Results: 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 a 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 were MD of 13.59 (95% CI: 5.32, 21.86).

Conclusions: Meta-analysis and MRA revealed a statistically significant association between LTCF and ESBL-PE among residents ($p = .05$). 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.

Keywords

extended-spectrum beta-lactamase-producing enterobacteriaceae (ESBL-PE), long-term care facilities (LTCFs), residents, infection control measures (ICMs), prevention, disease management

Introduction

Antimicrobials are used to treat infections of various diseases caused by microorganisms, including bacteria, mycobacteria, viruses, parasites, and fungi, among residents in long-term care facilities (LTCFs).[1] Since the discovery of antibiotics by Sir Alexander Fleming in 1928[2,3] and the transformation of current antibiotic medications that saved millions of lives[4] the phenomena of antibiotic resistance microorganisms globally, are endangering the efficacy of the power of antibiotics.[5] In most clinical and public health cases where antibiotics are used, microbes initiate a means to make antibiotic agents ineffective.[6] Under these circumstances, resistance develops

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anywhere antibiotics are used, including the farm, community, and healthcare.[6] 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.[7] Based on the reasons mentioned above, the CDC has classified some multidrug Enterobacteriaceae resistance microorganisms as responsible for placing a significant clinical and financial burden on the global healthcare system, patients, and their families.[8] The Enterobacteriaceae species cross-resistance because they produce ESBL enzyme not only to hydrolyze the beta-lactam ring of penicillin and third generations cephalosporins (TGCs) but also to inactivate quinolone and aminoglycosides.[9] These organisms have caused approximately 26,000 healthcare-associated (HCA) infections per year in the USA. 140,000 HCA Enterobacteriaceae infections are estimated to occur in the United States, resulting in bloodstream infections that result in more than $40,000 hospital charges per occurrence.[8] Traditionally, ESBL-PE was associated with hospital settings, but more recent studies have also shown increased detection of ESBL strains in the community-based long-term care settings.[10,11] However, this disease is no longer limited to hospitals; it also threatens elderly residents in LTCFs.[12] Nursing, residential care homes, and other LTCFs have been suggested to be a reservoir for ESBL-PE in the community.[13–15] Pelly et al research study described nursing homes as a proxy. It closed living quarters that could contribute to antibiotic-resistant infections and are probably related to ESBL-PE disease among the residents in the LTCFs.[16] These ESBL-PE have been consistently inflicted on nursing home residents in the United Kingdom and other parts of the world.[17] Cefotaxime beta lactamase producing (CTXM) Escherichia coli was first reported from Ireland in 2005[18] and was associated with the LTCFs outbreak, soon afterward in 2006.[19] Most of these elderly residents are repeatedly at risk of acquiring ESBL-PE because they were often exposed to excessive antibiotics, previous hospital admission, incontinence, urinary catheters, and decubitus ulcers.[20] Research indicated several approaches to analyzing risk factors and the prevalence of Enterobacteriaceae that produces ESBL enzymes in the community where LTCFs are located. In laboratory surveillance of Enterobacteriaceae,[12] these species' trends and geographical distribution were reported. These infections were further broken down by bacterial species, patient age, and sex. However, the prevalence of the tendencies of ESBL-PE colonization differed significantly across the LTCFs.[21] In one observational study[22] of ESBL-PE on the residents 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.[22] Rooney et al research study also reported that residents were colonized with an extremely high prevalence of multidrug resistance Enterobacteriaceae of gut carriage.[15] As noted by each assessment, all the research mentioned above 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 manuscript 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 the control measures involved. The study focused 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 extent of the distribution of ESBL-PE and effective infection control in these facilities and informed clinical and public health awareness of this growing problem.

Methods

The Preferred Reporting Items Systematic Reviews and Meta-Analysis (PRISMA) flow chart was used to describe the papers identified from the search strategy. The reasons for exclusion from this systematic review and meta-analysis are shown in Figure 1.

Literature Search Strategy and Selection Criteria

A fundamental approach was used to search the literature outlined[23] by using the horizon-scanning and gathering eligible studies. We ensured that relevant English-language studies published and unpublished were identified by searching electronic databases. The search included observational studies (OS) and random controlled trials (RCT) reporting the causes and control of ESBL-PE in LTCFs. A search strategy was developed for at least two electronic databases from PubMed/Medline, Embase, Google Scholar, and Web of Medicine. We use the following terms individually and in various combinations: extended-spectrum beta-lactamase-producing Enterobacteriaceae or ESBL-PE or ESBLPE and infection control or infection prevention, from January 2008 to December 2018.

Furthermore, the reference lists of published articles retrieved from these electronic databases were hand-searched for additional items. This report's systematic review and meta-analysis adhered to the PRISMA guidelines to prevent the risk of numerous articles addressing the same research questions, reduce noise in accumulated publications and provide transparency in the national institute for health research study. In the First Pass Screening (FPS), we screened the data based on title and abstract retrieved through databases against the predefined eligibility criteria. We screened the full text via Second Pass Screening (SPS) procedures in case the information was unclear at the FPS level. As a result of variation in the terms' infection control' and 'infection prevention'; 'extended-spectrum beta-lactamase-producing Enterobacteriaceae' and 'ESBL-PE,' we 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, we decided to
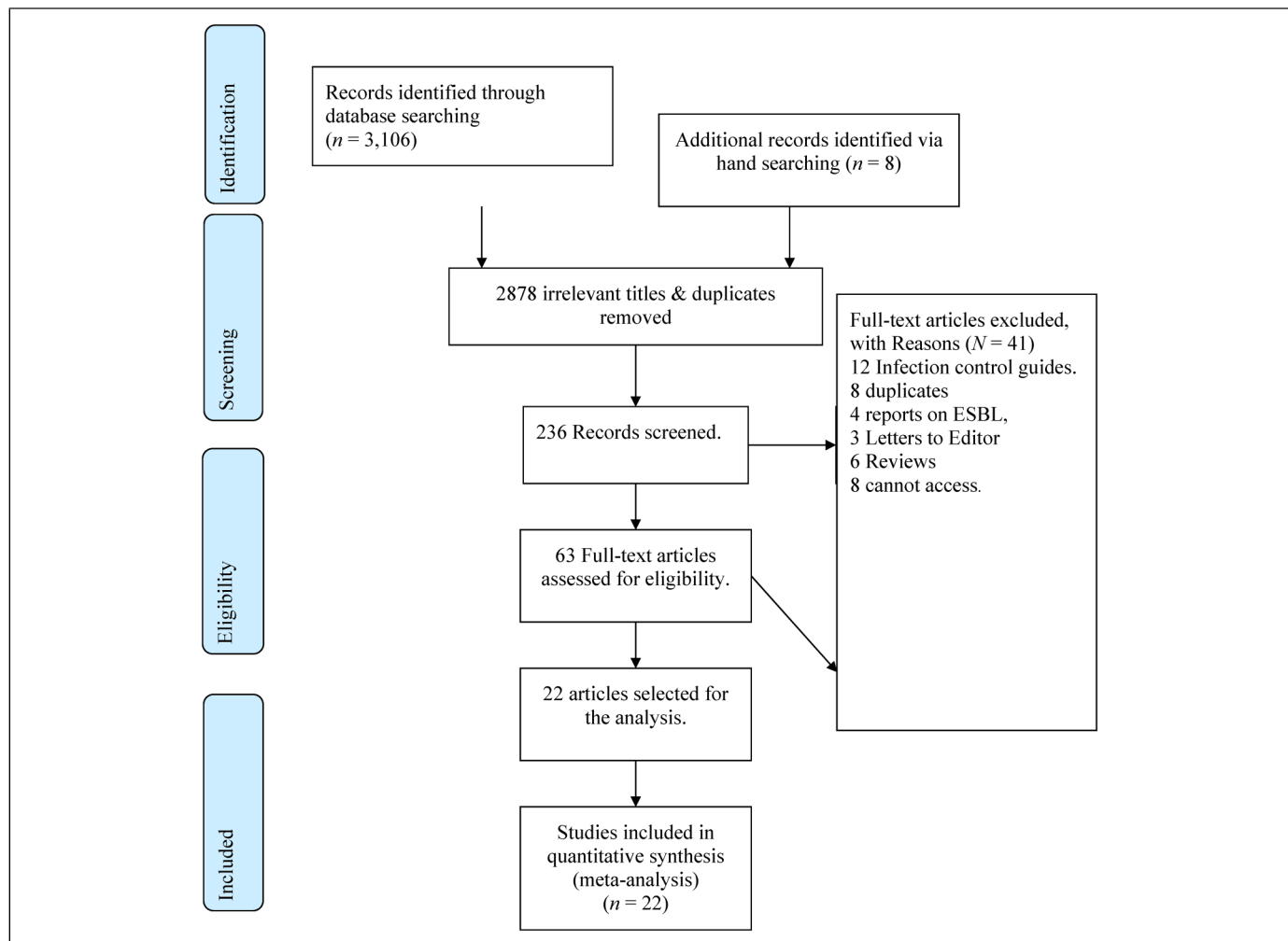
Figure 1. PRISMA flow diagram.

include papers that characterized the etiology of the epidemiology of ESBL-PE and confirmation of Enterobacteriaceae that produced ESBL enzymes. We also decided to review the detection of ESBL-PE in the laboratory, the epidemiology of ESBL-PE, and the evaluation of infection control measures in LTCFs globally, demonstrating the potential link between environmental sources, antibiotic use, and Enterobacteriaceae resistance in LTCFs residents. We discussed the microbiology laboratory's importance 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, and Control for ESBL confirmatory tests. Overall, we developed a well-defined protocol for commencing the search. Firstly, we breakdown the clinical questions into the Population, Intervention, Comparison, Outcome, and Study design (PICOS) format. The research question contains "Infection control of transmitting Beta-Lactamase producing Enterobacteriaceae (ESBL-PE) among residents and between LTCFs. As aptly described above, we developed the search strategy for a minimum of two electronic databases, and

we captured the study details, participants detail, intervention details, and outcome details from the included studies in Table 1.

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 article's relevance, type of publications, study design, and language of the publications. The designating period of the study was used as the first criterion. The keywords reflected the terminology 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 the use of information from annual reports, research reports, or conference reports. All these were also utilized. The study design was divided into reviews versus original works or cross-sectional versus longitudinal. The eligible literature papers were assessed for quality and risk of bias for data relevant to the systematic review and meta-analysis. The languages currently

Table 1. 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

Table I. (continued)

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
									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

predominant in science are English and Spanish,[24] but in this review, only English was used for the study. The differences in either the application of inclusion or exclusion of articles and quality accuracy of data extraction were evaluated to make the final decision.

Data Extraction Process

Data were extracted from the inclusive eligible papers, and reviews 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. We ensured that data were extracted and analyzed twice to remove any lack of consistency.

Review Descriptions

There are three main relationships for this review, to show awareness of ESBL-PE transmitting between hospitals and nursing homes while transferring or moving patients between the two healthcare settings and the effective infection control measures applied. A study was defined based on published papers retrieved from databases, with the only distinction being 'ESBL-PE,' 'LTCFs,' and 'infection control measures.' So, if a single paper meeting the selection criteria reported data on the three subjects, they included three separate studies. Community-acquired infection (CAI) is 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), especially Enterobacteriaceae species.[25] A hospital-acquired infection (HAI) is an infection acquired in a hospital. The infections often contacted after 48 h of hospital admission or within 48 h of hospital discharge.[26] Infection control measures were standard precautions to reduce the risk of transmitting bacteria from recognized and unrecognized sources.[27] Residents in a nursing home are often transferred to an Accident and Emergency Department (AED) when they need urgent and intense medical care. A proportion of these transfers are often performed on an outpatient basis and may be considered inappropriate due to the lack of adequate infection control measures.[28] This review considered the CAI and HAI as a broader definition of healthcare-associated infections (HCAIs). The HCAIs can occur when patients receive health care and probably contract the disease in a hospital or nursing home that first appears after 48 h.[29]

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.[30,31] The content validity of this tool 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 to be used in a meta-analysis.[31] The NOS is used to assess the quality and risk of bias of the papers included in this review. Using the NOS quality assessment tool to appraise this review critically, the included studies were evaluated based on Cochrane's Risk of bias's assessment of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk of bias according to published criteria.[30]

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, and with patients at risk of ESBL-PE infection were 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.[31] With this approach, we estimated the mean of a distribution of effects in a different population. This approach includes an estimate of within-studies and between-studies variation, which was used when assigning the studies into weights and the standard error of each effect size. The precision of each study's estimated random effect analysis is weighted by the inverse of the results' variance across all the

pooled studies. If the studies' values were within the 95% CI, then the effect size would be statistically significant at the 5% level ($P < .05$). Though the chi-square test provided a significance test for heterogeneity without measuring it, these studies' heterogeneity nature was evaluated using the I^2 statistic with a *p-value* of <.05 considered to be statistically significant. The I^2 values represented the percentage of the total variation due to the variation between studies. According to Higgins and Green research study, 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, we used subgroup analyses to examine different subgroups within our meta-analysis articles to determine the differences of effect in a subset of the subject's risk of bias, study duration, age group, ESBL-PE transmission cause, and Infection control measure. We 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.[32] Also, we did not use meta-regression to examine if covariates explained any of the heterogeneity of infection control effects between studies. In a meta-analysis, we need more studies on covariates.[32] 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.[33] In such a manner, assessing these covariates in each study is impractical.

Moreover, without a doubt, we may not know the association of covariates with the size of the effect. However, Borenstein, Hedges & Rothstein studies, 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 studies, 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. We used a funnel plot to estimate the assessment of publication bias. Furthermore, we analyzed pooled proportions of residents in LTCFs over time using the study year. For studies taking place in 2 years, we used the first year; for studies taking place in 4 years, we used the second year; for those studies in six years, we 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.

Results Study Selection

We searched the electronic database and identified 3106 potential studies, and eight additional records were identified via hand searching. After 2878 irrelevant titles and duplicates were removed, 236 articles remained to be screened for title and abstract. We evaluated 63 as potentially eligible full-text articles to be retrieved. After applying inclusion and exclusion criteria, 22 articles (35%) had information admissible to this systematic review and meta-analysis. These 22 articles include five risk factors associated with fecal 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 the reason for exclusion is shown in Figure 1.

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, two (9.1%) ESBL-PE in LTCFs studies were conducted in developing countries and 20 (91%) studies in developed countries. Most 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 included an observational cohort, nested case-control study, and retrospective were (4.5%; $n = 1$), respectively. The duration of the 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)

The 22 studies from 2008 to 2018 were published in the English language. Fifteen studies were conducted in Europe, four studies were conducted in Asia, two studies were performed in North America, and one study was performed in Australia. The pooled prevalence of ESBL-PE infections among LTCF residents was 15.78 (95% CI 0.04-31.53). Heterogeneity is confirmed by a high I^2 value of = 100% and a significantly associated *p-value* (<.00001). In 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 due to variation between studies. According to Higgins et al studies, 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. We 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 is interpreted as no difference in Enterobacteriaceae infection scores in ESBL-PE and non-ESBL-PE infection. In observation of the pooled effect estimate, the black diamond almost crossed the vertical line (mean difference: 15.78, 95% CI: 0.04, 31.53), thus showing a statistically significant effect favoring ESBL-PE infection. The overall effect test corroborates the results by presenting a p- equal to .05 ($p = .05$).
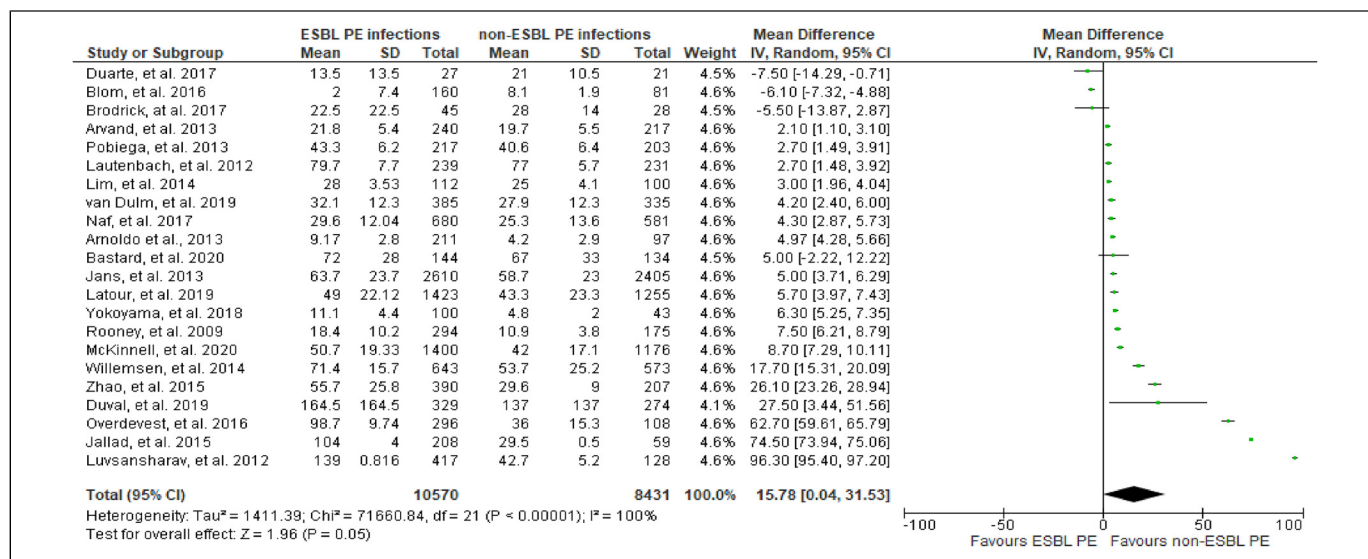
Figure 2. Forest plot of included studies.
Note. Observed infection rates between ESBL-PE and non-ESBL-PE in all studies, effect size (ES) and confidence interval (CI). 'Cochrane RevMan' statistical software program.

Forest Plots by Regional Locations. 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. (Figures 3 to 5)

The above regional forest plot studies have been conducted in different countries and other contexts (for instance, in nursing or residential homes managed by government and non-governmental organizations) with residents of 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 showed no difference in *Enterobacteriaceae* infection scores between ESBL-PE and non-ESBL-PE infections in each region. Comparison observation of the pooled effect estimate between the areas, the black diamond 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 the prevalence of ESBL-PE infection in each of the regions (<.0001), and the test for the overall effect of these regions corroborated the results by presenting a *p-value* <.05 (p = <.0001). These show a significant association between each environmental/regional source and the prevalence of ESBL-PE in LTCFs. (Figure 6)

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 < .0001), which

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. 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 .05 (p = .001).

Multiple Regression Statistics

Supplementary multiple regression analyses have been conducted to analyze the included meta-analytic studies' correlation matrices and standardized regression models. 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 2)

According to Hair et al research study, the VIF statistic is an alternative to Tolerance (that is, one divided by Tolerance resulted in VIF value),[34] but I only need to consult one of these measures. In this data analysis, all the Tolerance values exceeded 0.1, and the lowest was 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.[34] The coefficient for LTCFs was 4.233. The slope coefficient value was positive and showed that more LTCFs could be associated with the prevalence of ESBL-PE. The multiple regression equation predicts that the more we have residents in the LTCFs, the more likely that they would be
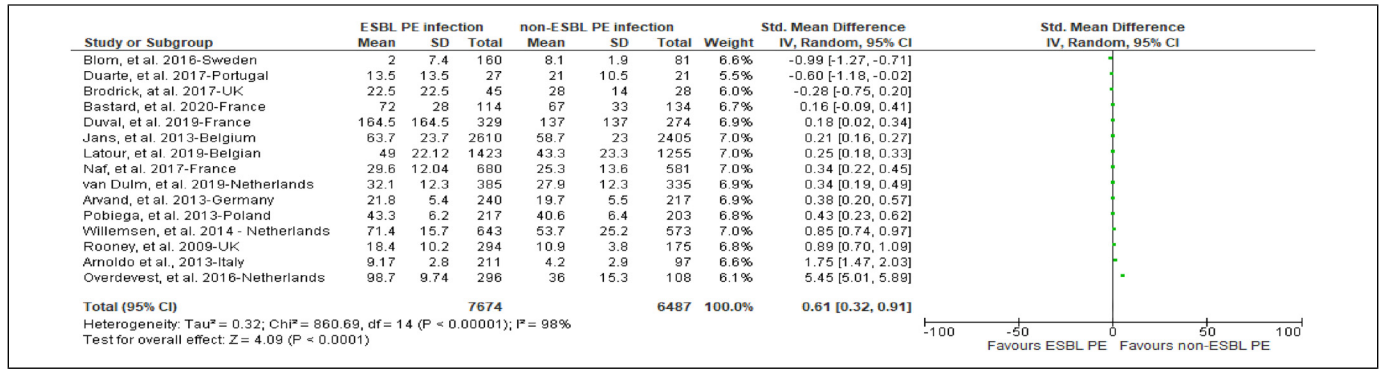
Figure 3. Forest plot by Europe Region.
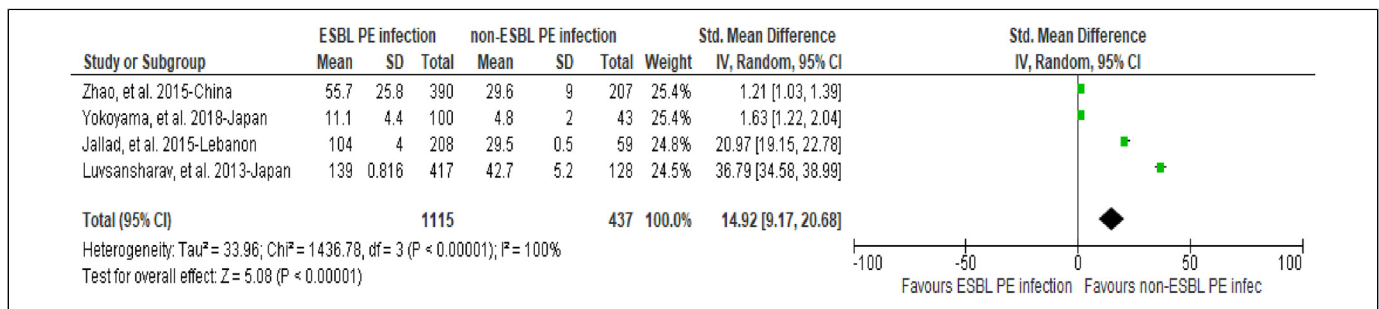Note. Source: Comprehensive meta-analysis software.

Figure 4. Forest plot by Asian Region.
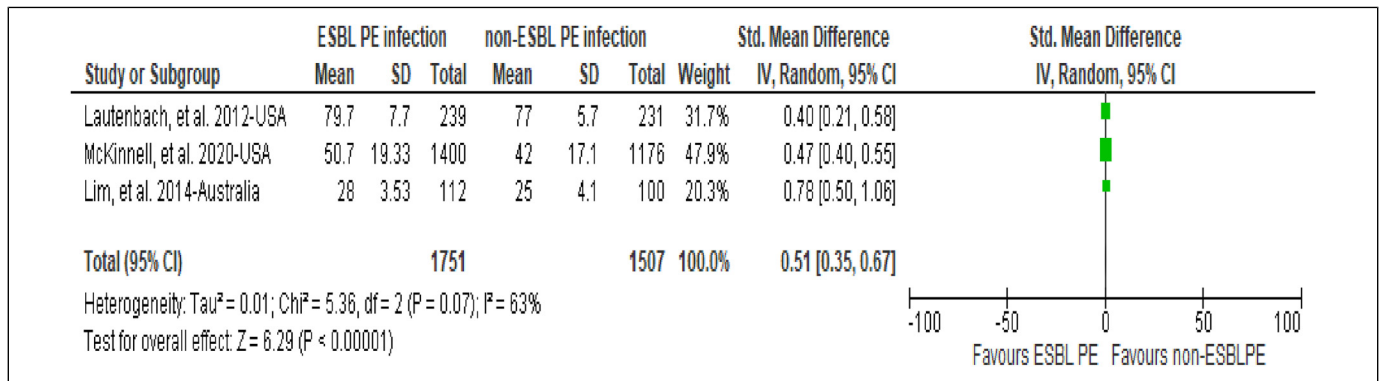Note. Source: 'Cochrane RevMan' statistical software program.

Figure 5. Forest plot by North America and Australia.
Note. Source: 'Cochrane RevMan' statistical software program.

infected with the ESBL-PE. The 95% confidence interval (CI) is between 1.752 and 6.714. That is, we can be 95% confident that the true value of the slope coefficient is between 1.752 and 6.714. We can observe that the *p-value* was.002 (ie, *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. I can observe that the *p-value*

was.140 (ie, *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, it 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
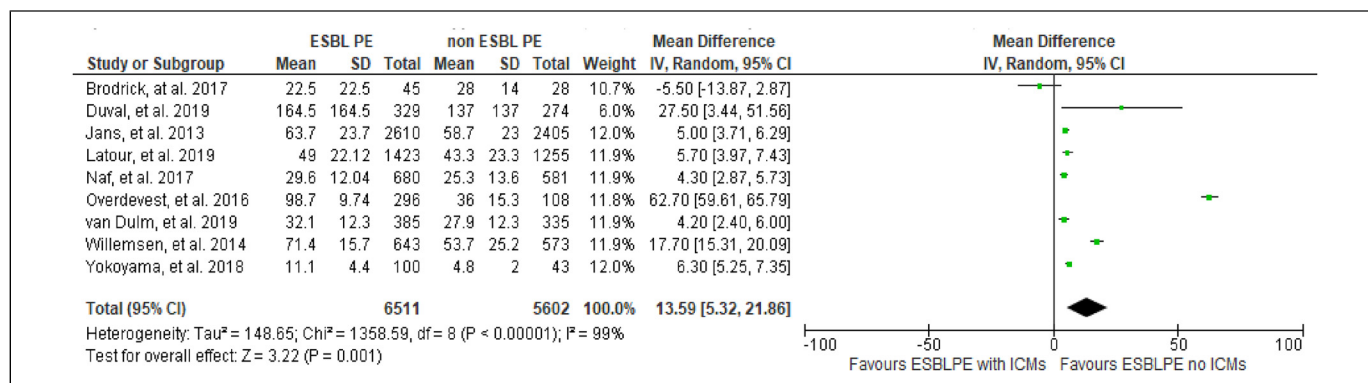
Figure 6. Forest plot of included studies reporting on Enterobacteriaceae infection in the LTCFs by infection control measures, effect size (ES) and confidence interval (CI).
Note. Source: 'Cochrane RevMan' statistical software program.

Table 2. Coefficients.

						95.0% Confidence						
	Unstandardized		Standardized									
Model	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound	Zero-order	Partial	Part	Tolerance	VIF
1 (Constant)	68.031	28.771		2.365	.029	7.585	128.476					
LTCFs	4.233	1.181	.639	3.585	.002	**1.752**	**6.714**	.627	.645	.617	.933	1.072
Regions	−3.690	2.390	−.289	—	.140	−8.712	1.332	−.114	−.342	−.266	.845	1.183
ICMs	23.608	27.776	.161	1.544 .850	.407	−34.747	81.964	.206	.196	.146	.821	1.218

a. Dependent Variable: ESBL

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), which showed that there was no statistically significant slope coefficient ($p > .05$) between ICMs and ESBL-PE. We can observe that the *p-value* was .407 (ie, $p = .407$). 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. Likewise, the coefficient for ICMs was 23.608. The 95% confidence interval (CI) was between −34.747 and 81.964. That is, we 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. We can observe that the p-value was .407 (ie, $P = .407$). 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.

Results

The 22 studies included in the analysis of a total of 10 570 participants from studies between 2008 and 2018. Fifteen studies were conducted in Europe (three in France and Netherlands, two in Belgium and the UK, and one in Sweden, Portugal, Germany, Poland, and Italy). Four studies were conducted in Asia (two in Japan, one in China, and one in Lebanon), while two were completed in the USA and one in Australia. Non-studies included from the African 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 the USA and Australia (95% CI: 0.35-0.67). Nine (9) of the 22 studies implemented targeted and untargeted ICMs, including screening, and a 13.5% colonization rate was revealed (95% CI: 5.32-21.86). In a meta-analysis, LTCFs were statistically significant in association with an increased prevalence of ESBL-PE among residents ($p = .05$). In the statistical supplement technique, the multiple regression analysis, the regional differences ($p = .140$), and the implementation of ICMs ($p = .407$) were not statistically significant. However, multiple

regression analysis also reported LTCF to be linearly 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. Three studies said ESBL general screening was performed, and two investigated Infection risk scan (IRIS) control measures. In contrast, four studies performed control measures in each method: 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 the potential for transmitting bacteria with enzyme-mediated antibiotic resistance across and within residential homes.[35] In most ESBL-PE studies, the colonization rate has spread globally, and almost one in five LTCF residents was colonized with the ESBL infection.[10] Urinary tract infection (UTI) is the most common infection site among residents in LTCFs and is the most common reason for prescribing antibiotics in LTCFs.[36] UTIs' risk factors include residents with an indwelling catheter, benign prostatic hypertrophy and prostatitis in men, and estrogen deficiency in women.[36] Attention to the fact that residents are residing and extensively used healthcare facilities as their day-to-day caring[37] can disseminate resistant enzymes to other residents' populations.[38] Significantly, this could further cause negative implications for public health because most care homes' proxy nature, which may further spread the disease. Concerning the geographical variability of the studies we included in this analysis; most studies were performed in Europe.

In contrast, fewer studies were conducted in North America and Australia. This study's 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 African continent. The relative lack of data from the developing country may result from the fact that LTCFs in many developing countries provide home care services for their elderly parents at home instead of at formal institutions.[39] However, retrieval of ESBL data is also underrepresented in specific regions, for instance, Oceania and North America. 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. However, unguided antibiotic use, history of recent hospitalization, and urinary catheter use are risks 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.[38] Unfortunately, antibiotics are commonly prescribed unguided in this setting.[10]

Concerning the limitation of the study, all estimates' outcomes were only based on a limited number of studies provided for this analysis. The selection bias in the included studies could cause a limit to the study since both high risk of bias (n = 5) and unclear risk of bias (n = 4) was reported to be 41%. The included studies were written only in English for this analysis, so we likely 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 studies, based on the available quality evaluation tool. The danger of combining results from cohort studies is that the study population among cohort studies is more likely to be heterogeneous.[40] Data from the African continent were unavailable in this study, limiting our findings' generalization. A limited number of studies with targeted infection control measures were included in this study, limiting the generalization of the infection control's impacts on this patient population.

Conclusion

In conclusion, the overall research findings have contributed insight and new knowledge to understanding the current epidemiology of ESBL among residents in LTCFs of a few regions of the world. It provides information on how *Enterobacteriaceae* produced beta-lactam enzymes to cross-resist empirical antibiotics for patient treatment. The research has been especially timely because it coincided with the UK's five-year antimicrobial resistance strategy from 2014 to 2018.[41] 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 informs the multisectoral collaboration to organize its systems to achieve effective action against the spread of ESBL-PE, which can be interpreted into practice. Based on the research, we hope that the recommendations suggested in this research can be instituted to maintain strict adherence to effective infection control measures.

Infection Control

The spread of ESBL PE between nursing homes and hospitals is prevalent, indicating that breaches in infection control were apparent. The transmission of ESBL PE is a public health threat because the infections are associated with multidrug resistance organisms (MDROs), resulting in prolonged hospitalization and high mortality rates.[42] Residents have various risk factors for acquiring infections with ESBL PE, including frequent hospital visits, increased use of antibiotics, functional impairment, and indwelling devices.[42] For treating 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.[43] In this situation, the utilization of adequate infection control measures is of significance for this disease. However, the difficulties in assessing the effectiveness of infection control prevention measures on

transmitting ESBL-PE between a nursing home and hospital may force healthcare providers to use the ORION statement. The statement was developed as a guideline for the transparent reporting of infection control interventions and outbreaks report of healthcare-associated infection.[44][46] Despite guidelines containing infection control measures, the strategies to prevent the spread of infections were not specifically available for ESBL-PE but in guidelines for infection control for other MDROs.[45]

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Declaration of Conflicting Interests

Ethical Committee Approval

Ethical Committee approval was sought and approved by Institutional Review Board (IRB), Walden University Minneapolis, MN, 55401, USA.

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