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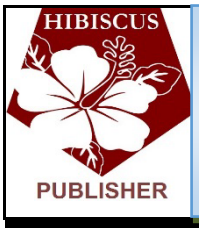


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# Prevalence of Extended-Spectrum Beta-Lactamases (ESBLs)-Producing *Klebsiella pneumoniae* in Malaysian Clinical and Community Infections: A Systematic Review and Meta-Analysis

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**ABSTRACT**

The increasing prevalence of extended-spectrum beta-lactamase-resistant (ESBL) *Klebsiella pneumoniae* in Malaysia is alarming. The lipopolysaccharide (LPS) of *Klebsiella pneumoniae*, particularly its lipid A moiety, plays a central role in the bacterium's toxicological profile by inducing strong pro-inflammatory responses and contributing to septic shock in systemic infections. Morbidity and mortality associated with this condition are alarming. A comprehensive evaluation of the proportion of this phenomenon will aid the Malaysian government and health authorities in their efforts to reduce its burden. Hence, this systematic review and meta-analysis were conducted to evaluate the incidence of ESBL *K. pneumoniae* in Malaysian clinical and community infections. The study was conducted in accordance with the PRISMA guidelines and preceded by the development of an a *priori* protocol. The protocol was then registered in PROSPERO – the public registry for systematic reviews. Six important outcomes, including the assessment of the overall ESBL *K. pneumoniae* prevalence, were designed to be evaluated. A literature search was conducted in four selected electronic databases, and 310 articles were screened. Of these articles, only seven studies that met the eligibility criteria were included in the review. Relevant data were extracted from the included studies. By conducting a meta-analysis of quality effects, the pooled prevalence of ESBL *K. pneumoniae* in Malaysia was estimated at 72% (CI: 39-97). The review also identified ESBL gene types occurring mostly in infections. The high prevalence of ESBL *K. pneumoniae* in this study area is highly significant and of both public health and clinical relevance. Overall, the findings of this review will assist in the effective prevention and control of this threat in the study area.

## INTRODUCTION

Gram-negative bacteria are capable of producing enzymes known as Extended-Spectrum Beta-Lactamases (ESBLs) that can confer resistance to some antibiotics such as cephalosporins (first, second, third, and fourth generation), aminopenicillins, as well as aztreonam, but are inhibited by clavulanic acids [1]. ESBLs are chromosomal or plasmid-mediated enzymes that hydrolyze or inactivate beta-lactam antibiotics, or in other words, are enzymes that hydrolyze a wide variety of beta-lactam antibiotics, including oxymino-cephalosporins and aztreonam, but are inhibited by beta-lactam inhibitors like clavulanic acids, tazobactam, and sulbactam [2]. The emergence of ESBL producers has complicated treatment options, posing a serious

threat in the hospital setting. These enzymes are a significant cause of antibiotic resistance, commonly encountered in clinical settings, which can contribute to resistance or decreased sensitivity toward several antimicrobial classes [3]. The ESBLs are mainly produced by *Klebsiella pneumoniae* and other Enterobacteriaceae. Infections due to β-lactamases producing *Klebsiella* species have been increasingly recognized in recent years, thereby creating clinical concerns because few antibiotics are available as therapeutic options. *Klebsiella pneumoniae* is a significant pathogen, particularly in immunocompromised patients, and is an integral part of the community and nosocomial infection [4].

The major cause of community and health-associated infections has been attributed to *Klebsiella pneumoniae* [5]. *Klebsiella pneumoniae* is often linked to hospital infections. Some underlying diseases, such as biliary diseases, malignancies, diabetes mellitus, cirrhosis, bacteremia, osteomas, urinary infections, and infection of the biliary tract, as well as alcoholism, have been reported to impair the defences of a person and therefore increase the risk of *Klebsiella pneumoniae* infections [6]. The bacterium lipopolysaccharide (LPS), specifically the lipid A moiety, functions as an endotoxin. [7] reported a nosocomial outbreak in Malaysia with an association of the *bla*$_{SHV-5}$ ESBL gene in *Klebsiella pneumoniae*. Restricted data concerning the spread of ESBL genes throughout the Malaysian population, specifically among Malaysian district hospitals, was reported by [3]. The main objective of this review is to determine the pooled prevalence (proportion) of ESBLs *Klebsiella pneumoniae* in both community and clinical infections in Malaysia and to identify a research gap that, when bridged will assist the Malaysian medical teams or the health authority in the treatment and management of infections caused due to ESBLs *Klebsiella pneumoniae* in the study area.

## METHODS

### Study design

This study was conducted in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (**S1 File**). A preceding protocol (**S3 File**) was developed for this systematic review and meta-analysis (SR&MA) according to the PRISMA Protocol (PRISMA-P) guidelines (**S2 File**) [8]. The protocol was then registered on the National Institute for Health Research International Prospective Register of Systematic Reviews (PROSPERO, 2022, CRD42022311164). Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022311164

### Eligibility criteria

The eligibility criteria for this SR&MA were defined as follows: Inclusion criteria: any study that satisfies the following criteria was included in this SR&MA:

i. Study type: All observational studies (cross-sectional, cohort, case-control, and prevalence surveys) that investigated cases of ESBLs in *K. pneumoniae* among hospital and community patients will be included.
ii. Studies conducted in humans among hospital and community patients will be included.
iii. Study location: Studies conducted in Malaysia will be included.
iv. Period: There will be no time limitation placed on the period of publication.
v. Age and sex: no restriction
vi. Language of publication: only studies published in the English language will be included.
vii. Publication type: both peer-reviewed and preprint articles will be included.
viii. Studies of community-acquired infections of *Klebsiella pneumoniae* will be included.

Exclusion criteria: studies with any of the following criteria were excluded from this SR&MA:

i. Studies involving healthcare workers' (occupational or work-related) infections will be excluded.
ii. Studies conducted outside clinical/hospital or community settings will be excluded.
iii. Studies of ESBLs in animals will be excluded.
iv. Studies conducted in countries outside Malaysia will be excluded.
v. Studies of ESBLs conducted in other bacteria will be excluded.
vi. *In-silico, In-vitro,* and *In-vivo* (using animal models) studies will be excluded.
vii. Studies with incomplete data will be excluded.
viii. Studies with incorrect content will be excluded
ix. Letters, books, book chapters, dissertations, review articles, opinion papers, reports, and conference papers will all be excluded.

### Outcomes

#### Primary outcome

To determine the overall proportion (prevalence) of ESBLs *Klebsiella pneumoniae* in both hospital and community infections in Malaysia.

#### Secondary outcomes

i. To determine ESBL prevalence in hospital infections
ii. To determine ESBLs *K. pneumoniae* community infections
iii. To assess the predominant ESBL genes occurring in both clinical and community infections.
iv. To examine the differences in the rate of ESBLs *K. pneumoniae* incidence in both community and hospital infections.
v. To determine the rate of ESBL prevalence in different types of hospital samples.
vi. To assess the methods of confirmatory tests used in the determination of ESBL *K. pneumoniae*.

### Search and selection strategy

A pre-specified search approach with precise search terms was developed and used to search four selected electronic bibliographic databases. The approach also comprised a grey literature search by searching references of selected (review) articles and conference proceedings. Furthermore, an internet search was conducted on Google Scholar and Google using specific terms.

### Databases

The selected searched databases include PubMed, CINHAL, Scopus, and MEDLINE. The details of specific database searches are provided in the study protocol (**S3 file**). Nonetheless, the search algorithm used in the Scopus database is given as follows; ("Prevalence" OR "Occurrence" OR "Incidence" OR "Epidemiology" AND "ESBLs" OR "ESBL" OR "Extended Spectrum Beta Lactamases" AND "*Klebsiella pneumoniae*" OR

"*K. pneumoniae*" OR "Klebsiella infection" OR "KP" OR "Kp" AND "Clinical infection" OR "Clinical isolates" OR "Clinical samples" OR "Hospital infection" OR "Hospital-associated infection" OR "Hospital acquired infection" OR "Nosocomial infection" OR "HAI" AND "Community infection" OR "Community isolates" OR "Community samples" OR "Community-associated infection" OR "Community acquired infection" OR "CAI" AND "Malaysia").

**Data management and selection process**
The total citations found from the electronic database search (search results) were exported to the reference manager software Mendeley, where duplicates were removed (**S4 file**). The de-duplicated citations were then exported to the Rayyan Intelligent Systematic Review software[9]. On the Rayyan software, title/abstract and full-text screening were carried out based on the study's inclusion and exclusion criteria. Four (4) independent reviewers did the entire screening process of the review. One other reviewer decided on areas of dispute between the four reviewers.

**Data collection process**
Extraction of data was conducted after the full-text screening. Some of the relevant data extracted include: 1) study characteristics: title, author, year of publication, and study design; 2) baseline characteristics of study population: sample size, sample types; 3) the proportion of ESBLs *K. pneumoniae*, Differences in the rate of ESBL *K. pneumoniae* in both community and hospital infections, predominant ESBL genes, Frequency of ESBLs *K. pneumoniae* in different samples: 4) Common methods of confirmatory tests used. The process of the extraction was carried out by four (4) independent reviewers and cross-checked by a fifth reviewer.

**Study quality assessment**
After evaluating the articles for inclusion and exclusion criteria, all included articles were subjected to a quality assessment using the Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data [10]. The appraisal tool has nine questions that were answered either Yes (Y), No (N), Unclear (UC), or Not applicable (NA). Scores were awarded as: Y = 1, N = 0, UC = 0, and NA attracted no score. Based on the scores, the quality of the studies was graded; studies with scores of ≤50% were deemed to be of low quality. Those with a quality rating of 50% to 69% were termed moderate quality studies. At the same time, high-quality studies were those with ≥70% scores. The critical appraisal was conducted by four independent reviewers and cross-checked by two additional reviewers.

**Meta-analysis**

**Statistical Assessment**
MetaXL software (add-in for Microsoft Excel) was used for the quantitative analysis of the extracted data. The meta-analysis and pooling of the prevalence estimate (with the 95% confidence interval) were done using the quality effect (QE) model by employing the transformed) Double arcsine method.

**Assessment of Heterogeneity**
Estimation of statistical heterogeneity amongst the included studies was done using the $X^2$ Test, Cochrane Q, and $I^2$ statistics. An $I^2$ value of 0 to ≤40% was considered low heterogeneity, >40% to 60% was regarded as moderate heterogeneity, >60% to 75% was considered substantial heterogeneity, and >75% to 100% was considered high heterogeneity.

**Sensitivity Analysis**
A sensitivity analysis based on a leave-one-out model was conducted to identify studies that significantly influence the meta-analysis result.

**Subgroup Analysis and Meta-Regression**
Subgroup analysis and meta-regression were not conducted to identify the moderators of heterogeneity in the included studies because the studies included were just seven (7), which is less than ten (10), and therefore, there is no need for subgroup analysis.

**Publication bias**
A funnel plot was constructed to examine for publication bias, and an asymmetry was observed on the funnel plot. Thus, an additional assessment using the Doi plot to estimate the symmetry of the funnel plot was carried out.

## RESULTS

Study selection process and characteristics of included studies. After the completion of database searches, a total of 335 citations were obtained. In addition, four studies were identified from the manual references search and the searches conducted on internet search engines. Of the total citations, 29 duplicates were removed, and 310 articles were screened on title/abstract. After title/abstract screening, 10 articles were subjected to full-text screening (**S1 Table**). Finally, seven articles (**S5 File**) were included in this systematic review and meta-analysis (SR&MA) (**Fig. 1**). The seven (7) included studies were [1,3,4,11–14]. Of the seven included studies, seven reported the prevalence of ESBL in *K. pneumoniae* infections in clinical settings, while only one study reported the prevalence of ESBL in community infections (**Table 1**). The total sample size of all included studies is 477 (ranging from 17 to 141) among varied sampled populations (**Table 1**). Blood samples yield the highest number of ESBL *Klebsiella pneumoniae*-positive cases, at 35% (76) (**Table 2**). The majority of the included studies utilized multiple sample sources, with blood samples being the most frequently used (**Table 2**).

**Table 1**. Characteristics of included studies.

| Author | Sampling period | Year of Publication | Sample size | Study design | ESBLs Prevalence Assessed | |
|---|---|---|---|---|---|---|
| | | | | | Clinical Infection | Community Infection |
| Subramaniam et al. [11] | January 2016-Dec. 2017 | 2021 | 46 | Retrospective study | Yes | Yes |
| Al-Marzooq et al. [12] | 2010-2012 | 2015 | 93 | Investigation | Yes | No |
| Mohd Helmi et al. [3] | 2009 and 2012 | 2016 | 141 | Cross-sectional Descriptive study | Yes | No |
| Lee et al. [13] | 1st June-31st August 2017 | 2021 | 36 | Prospective cohort | Yes | No |
| Low et al. [14] | 2013 | 2017 | 17 | Investigation/Survey | Yes | No |
| Lim et al. [4] | 2004 | 2009 | 51 | - | Yes | No |
| Mobasseri et al. [1] | September-December 2014 | 2020 | 93 | - | Yes | No |

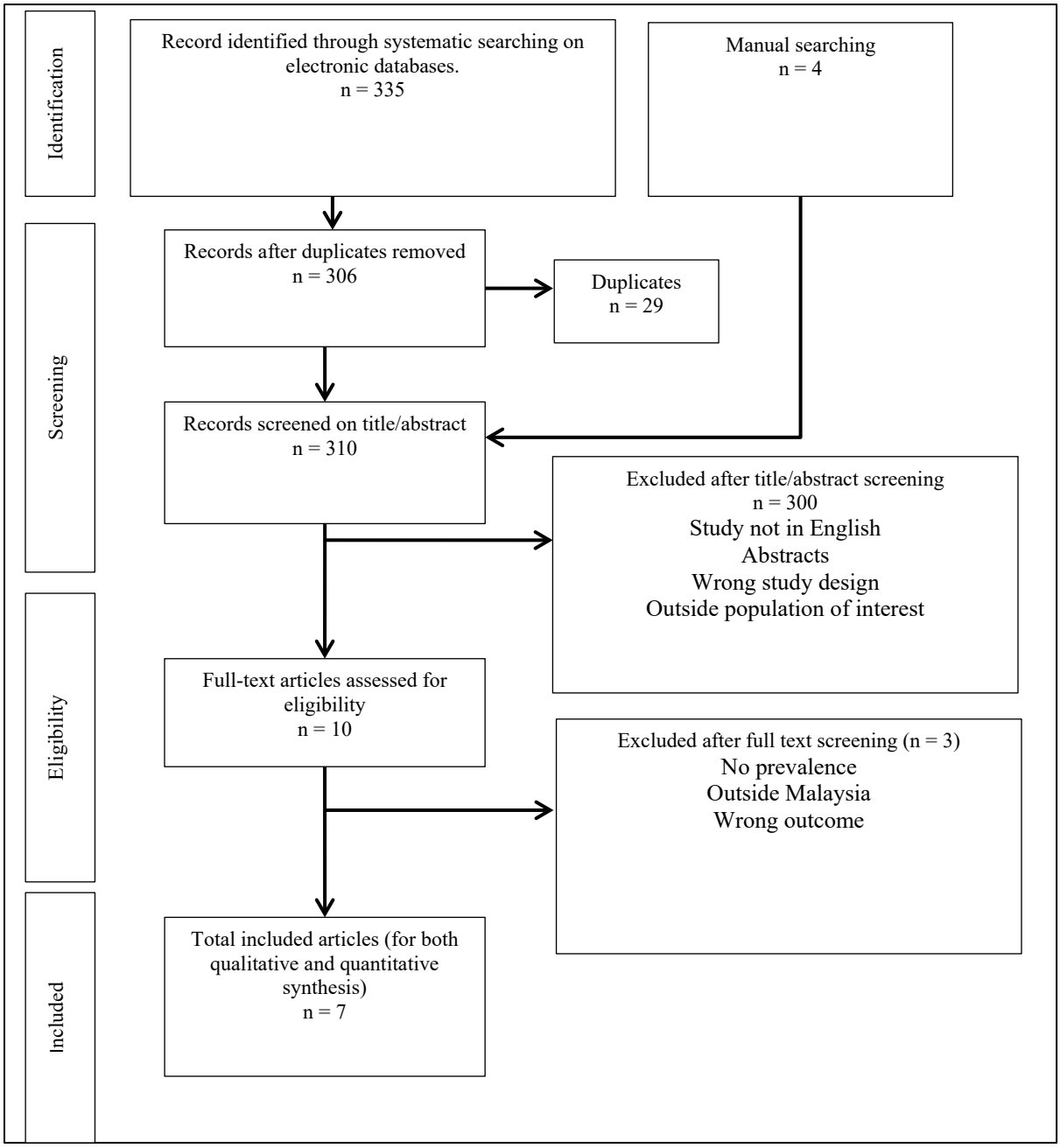


**Fig. 1**. PRISMA Flow diagram.

**Table 2**. Sampling characteristics of the included studies.

| Study | Study Population | Sample types | | | | | |
|---|---|---|---|---|---|---|---|
| | | Blood | Urine | Sputum | Aspirate | Pus | Others (Specify) |
| Subramaniam et al. [11] | Children admitted to paediatric and neonatal wards | Y (46) | - | - | - | - | - |
| Al-Marzooq et al. [12] | Patients attending the University of Malaya medical centre | - | - | - | - | - | - |
| Mohd Helmi et al. [3] | Inpatients attending Hospital Parkar Sultannah Fatimah | - | - | - | - | - | - |
| Lee et al. [13] | Preterm infants | - | - | - | - | - | Stool (31), Tracheal secretion (5) |
| Low et al. [14] | - | Y (4) | Y (4) | Y (1) | Y (1) | - | Swab (3), PTBD (2), Tissue (1) |
| Lim et al. [4] | Patients attending five different hospitals located in peninsula Malaysia | Y (1) | Y (2) | Y (1) | Y (21) | Y (1) | Catheter tips (2), Swabs (3) |
| Mobasseri et al. [1] | - | Y (25) | Y (8) | Y (8) | Y (24) | Y (6) | Wound tissue (9), Swab (10), Poc (3), Slough (1), and Bone (1) |

## Risk of bias (quality) assessment

The quality of the included studies was assessed using the JBI appraisal tool for prevalence studies. Only one of the seven included studies is of low quality, four are of moderate quality, and the remaining two are of high quality (**S2 Table**).

## Outcomes

Primary outcome: All seven studies were included in the meta-analysis to obtain the overall prevalence estimate of ESBL *Klebsiella pneumoniae* in Malaysian clinical infections. The pooled prevalence of ESBL in *Klebsiella pneumoniae* in Malaysia, obtained from the seven studies, is 72% (95% confidence interval [CI]: 39–97). Cochrane Q value (Q; 242.18), $I^2$; 98%, and $p < 0.0001$ (**Fig. 2**). The overall prevalence estimate of ESBL *Klebsiella pneumoniae* in the Malaysian community infection could not be determined because only one study within our reach reported ESBL *Klebsiella pneumoniae* in community infections.

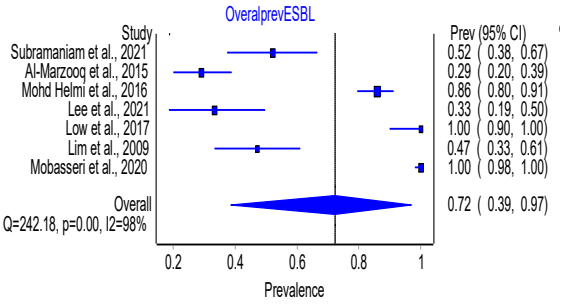


**Fig. 2**. Forest plot of overall meta-analysis ESBL *Klebsiella pneumoniae* in Malaysia.

## Secondary outcomes

ESBL *Klebsiella pneumoniae* was detected in various types of samples, with blood samples recording the highest number of 76 (35%), followed by aspirate, which had 46 (21.2%). These results are presented in detail in **Fig. 3**, which provides a graphical representation (Simple scatter plot) of the results.

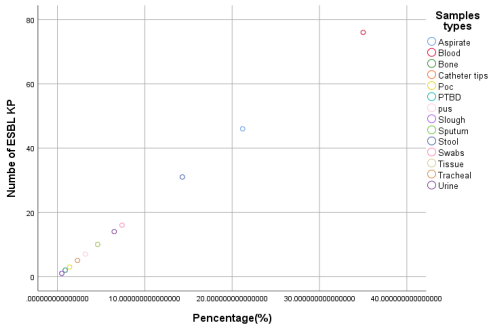


**Fig. 3**. Simple scatter plot of the percentage occurrence of ESBL *K. pneumoniae* prevalence in Malaysia clinical and community infections.

## Sensitivity analysis

The study [3] with the highest weight (and largest sample size) was removed for the sensitivity analysis. The excluded study had a significant impact on the overall estimate giving a prevalence of 67% (**Fig. 4**).

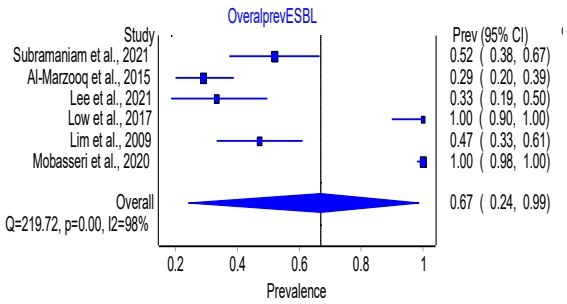


**Fig. 4**. Forest plot of sensitivity analysis of *K. pneumoniae* ESBL prevalence in Malaysian clinical infections.

## Subgroup analysis and meta-regression

To explore the factors responsible for the observed heterogeneity, a subgroup analysis was conducted. Five (5) pre-specified factors were used for the subgroup analysis (**Table 5**). Graphical presentations of the different subgroups analyses are presented in the **SI figures**.

**Table** 5. Summary of the subgroup analysis results.

| Subgroups | Number of studies | Pooled prevalence | | *Heterogeneity* | |
|---|---|---|---|---|---|
| | | % | 95% CI | $I^2$ | P |
| Year of Publication | | | | | |
| 2009 to 2017 | 4 | 65 | 20-100 | 97 | <0.0001 |
| 2018 to 2021 | 3 | 77 | 12-100 | 98 | <0.0001 |
| Weight-Based | | | | | |
| Less than 10 | 2 | 68 | 0-100 | 96 | <0.0001 |
| 10-15 | 2 | 44 | 26-63 | 65 | <0.0001 |
| More than 15 | 3 | 80 | 27-100 | 99 | <0.0001 |
| Sample-Size-Based | | | | | |
| Less than 50 | 3 | 54 | 8-98 | 94 | <0.0001 |
| More than 50 | 4 | 76 | 32-100 | 98 | <0.0001 |
| Study-Quality-Based | | | | | |
| Low | 1 | 47 | 33-61 | 98 | <0.0001 |
| Moderate | 4 | 82 | 34-100 | 98 | <0.0001 |
| High | 2 | 44 | 26-63 | 65 | <0.0001 |
| ESBL Determination | | | | | |
| Methods | 2 | 86 | 0-100 | 99 | <0.0001 |
| Disk diffusion | 1 | 86 | 0-91 | - | |
| Disk combination | 1 | 29 | 20-39 | - | |
| E-test | 1 | 47 | 33-61 | - | |
| DDST | 1 | 100 | 90-100 | - | |
| PCR Not specific | 1 | 52 | 38-67 | - | |

**Publication bias**

A funnel plot was constructed to examine for publication bias (**Fig. 5**).

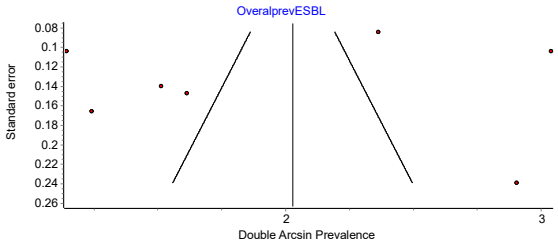


**Fig. 5**. Funnel plot of meta-analysis of *K. pneumoniae* ESBL prevalence in Malaysian clinical infections.

An observed asymmetry was noted in the funnel plot, and therefore, a further assessment using the Doi plot was carried out to evaluate the symmetry of the funnel plot (**Fig. 6**). The Doi plot showed a major asymmetry with an LFK index of 1.13 which shows a minor asymmetry.

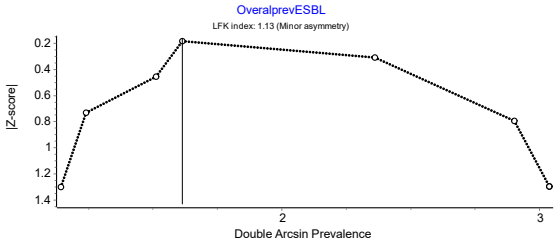


**Fig. 6**. Doi plot of meta-analysis of *K. pneumoniae* ESBL prevalence in Malaysian clinical infections.

Predominant ESBL-occurring genes: ESBL genes were not identified in one of the included studies [11]. The remaining six studies identified 134 different ESBL genes, with BlaSHV being the most frequently identified in 71 (53%) of these studies across three studies (**Table 3**). *Bla*$_{CTX}$ occurred 36 (26.9%) times in two studies out of the 134 identified genes. Another identified ESBL gene is *Bla*$_{TEM,}$ which occurred 27 (20.1%) times in only one study.

**Table 3**. Characteristics of determined genes and confirmatory methods.

| | Predominant ESBL genes | | | |
|---|---|---|---|---|
| | Name genes | of Frequency (n) | Number | Confirmatory Methods |
| Subramaniam et al. [11] | - | - | - | - |
| Al-Marzooq et al. [12] | *Bla*$_{CTX-M}$ | 85(93) | 20 | E- test |
| Mohd Helmi et al. [3] | *Bla*$_{SHV}$ | 106(121) | 35 | Disk combination |
| Lee et al. [13] | *Bla*$_{SHV}$ | 33(36) | 32 | Disk diffusion |
| Low et al. [14] | *Bla*$_{CTX-M}$ | 17(17) | 16 | PCR |
| Lim et al. [4] | *Bla*$_{SHV}$ | 46(51) | 4 | DDST |
| Mobasseri et al. [1] | *Bla*$_{TEM}$ | 26 (27) | 27 | Disk diffusion |

ESBL confirmatory methods used: The review revealed several methods used for the isolation of ESBL *Klebsiella pneumoniae*, including E-test, Disk combination, Disk diffusion, PCR, and DDST (**Table 3**). The most common confirmatory method was disk diffusion, which was reported in two included studies [1]..

The differences in the rates of ESBL *K. pneumoniae* in both clinical and community infections: The differences in the rates of ESBL *Klebsiella pneumoniae* occurrence in both clinical and community infections were examined in this systematic review and meta-analysis and were revealed in the study that 317 (67%) of ESBL *Klebsiella pneumoniae* occurred in clinical infections while only 1 (2%) of it occurred in community infections (**Table 4**).

**Table 4**. Rates of ESBLs occurrence in both clinical and community infections.

| Study | ESBL in clinical infection | | ESBL in community infection | |
|---|---|---|---|---|
| | Frequency (n) | Number | Frequency (n) | Number |
| Subramaniam et al. [11] | 23/46 | 23 | 1/46 | 1 |
| Al-Marzooq et al. [12] | 27/93 | 27 | - | - |
| Mohd Helmi et al. [3] | 121/141 | 121 | - | - |
| Lee et al. [13] | 12/36 | 12 | - | - |
| Low et al. [14] | 17/17 | 17 | - | - |
| Lim et al. [4] | 24/51 | 24 | - | - |
| Mobasseri et al. [1] | 93/93 | 93 | - | - |

## DISCUSSION

Our primary outcome, which is the overall prevalence of ESBL *Klebsiella pneumoniae* in Malaysian clinical and community infections, was achieved using all seven included studies [1,3,4,11–14] that reported the prevalence of ESBL Klebsiella pneumoniae. The meta-analysis of these seven studies demonstrated an overall prevalence of ESBL Klebsiella pneumoniae of 72% (CI: 39–97). The pooled prevalence of ESBL *Klebsiella pneumoniae* obtained in this study is similar to the 72.4%, 39.6%, and 35.4% prevalence reported for South America, Asia, and the Middle East regions, respectively, in a subgroup analysis study [15]. A prevalence of 43.5% was reported for ESBL KP in Iran [16]. Many other developing countries have also reported high ESBL KP prevalence, ranging from 38% to 55% [16,17]. Although slightly higher than the global average of 32.8% reported in a systematic review that evaluated the global prevalence of nosocomial MDR KP [15]. An equally high prevalence of ESBL (Enterobacteriaceae) was reported in a similar review in the East African subregion at 42% [18]. In another study, the global prevalence of ESBL Enterobacteriaceae was reported to be 25% [19]. Similarly, another systematic review reported ESBL KP prevalence in Africa ranging from 0.7% to as high as 75.8% [20]. However, the ESBL prevalence found in our analysis is higher than that obtained in Europe (5%), South America (4%), and North America (3%) [19].

Our study has further confirmed that the prevalence of ESBL Klebsiella pneumoniae is high in the study area compared to the global average. It might also not be out of place to assume that the developing regions contribute more to the global prevalence of ESBL *Klebsiella pneumoniae*. All seven studies included in this meta-analysis are from Malaysia, a developing country, which may be responsible for the high prevalence rate recorded. Other possible reasons for the high prevalence include the high transmission rate of nosocomial ESBL *Klebsiella pneumoniae* in the study area, severely ill patients, prolonged hospitalization, and antibiotic policy among others [21]. To ensure reliability, a quality effect model was used for the meta-analysis. Expectedly, however, there was high heterogeneity among the included studies for the prevalence of ESBL Klebsiella pneumoniae. However, predesigned subgroup and meta-regression analyses with factors anticipated to moderate the heterogeneity were conducted (Subgroup analyses) despite the fact that the included studies are fewer than ten. The effect of the

factors on the ESBL *Klebsiella pneumoniae* prevalence was evaluated individually. In the year of publication, subgroup analysis showed an increasing pattern. The result revealed that the prevalence of ESBL Klebsiella pneumoniae increased from 65% in the period of 2009-2017 to 77% between 2018 and 2021. The progressively increasing prevalence of ESBL *Klebsiella pneumoniae, as revealed in this review, implies that inhabitants of the study region are at a high* risk of infections due to ESBL *Klebsiella pneumoniae.* The reasons for the liberal increase of ESBL *Klebsiella pneumoniae* prevalence in the study region might be a result of records of prolonged illnesses and hospitalization, being a developing country, and irrational use of antibiotics. Therefore, frequent research on the subject matter needs to be undertaken to closely monitor the outrageous increase in ESBL *Klebsiella pneumoniae* prevalence subsequently in the region. In addition, regular surveillance would help further prevent the prevalence of ESBL Klebsiella pneumoniae in the study region.

To further explore the factors contributing to heterogeneity in our meta-analysis, we did subgroup analyses for sample size, study quality, and study weight. The sample size of the included studies was grouped into two categories (less than 50 and more than 50). The results showed an increase in ESBL *Klebsiella pneumoniae* prevalence from 54% for samples with fewer than 50 to 76% for samples with more than 50. This suggests that studies with smaller sample sizes have lower prevalence rates compared to those with larger sample sizes, which tend to have higher prevalence rates of ESBL *Klebsiella pneumoniae.* In the same vein, it was observed that larger weighted studies showed a higher prevalence (80%) of ESBL *Klebsiella pneumoniae* than moderate and small weighted studies (44% and 68% respectively). Equally, subgroup analysis based on study quality revealed that high-quality studies had a lower prevalence of ESBL *Klebsiella pneumoniae* (44%), while moderate-quality studies showed a higher prevalence of ESBL *Klebsiella pneumoniae* (82%).

Our review also did a subgroup analysis on the ESBL determination methods used in the detection of ESBL. To determine how the methods mediate ESBL prevalence, five methods were used for the detection of ESBL in the studies included (disk diffusion, disk combination, E–test, DDST, and PCR). However, one of the studies did not specify the test methods used. The result revealed high heterogeneity. Nevertheless, it is also a known fact that the use of different detection methods produces high heterogeneity in prevalence study meta-analysis [22]. The most commonly used detection method is the disk diffusion, which was observed in two studies [1,13] with a pooled prevalence of 86%. The E-test method had the least prevalence of 29%, possibly due to its high sensitivity. This finding suggests that recommending the adoption of this method for ESBL detection may be justified.

In summary, among all the five factors considered in the subgroup analyses, high heterogeneity was observed in year of publication, sample size and ESBL determination methods however, substantial heterogeneity was observed in weight-based (10-15) and study-quality (high), hence, it can be suggested that factors such as sample size, year of publication and ESBL determination are responsible for the study high heterogeneity although meta-regression analysis was not conducted to ascertain the responsible factors due to the number of the included studies which are less than ten (10). Rate of ESBL *Klebsiella pneumoniae* in different types of hospital samples: There are several hospital samples (blood, urine, sputum, aspirates, stool, tracheal, swabs, tissues, catheter tips, poc, pus, bone, slough, and percutaneous transphetic biliary drainage (PTBD) from which ESBL *Klebsiella pneumoniae* were isolated in the hospital setting amongst the included studies. However, ESBL *Klebsiella pneumoniae* occurred most in a blood sample with a frequency of 76 (35%), followed by aspirates samples with an occurring frequency of 46 (21.1%), then stool samples came third of the hospital samples with the highest occurring frequency of ESBL *Klebsiella pneumoniae* with 31 (14.3%) while the least occurring frequency was observed in bone and slough samples with an occurring frequency of 1(0.5) each. This was demonstrated in **Fig. 3**.

Internationally, concerns are growing about the consequences of ESBL-producing bacteria on the development of treatments for bacterial infections. Therefore, our study evaluated the major ESBL genes from *Klebsiella pneumoniae* isolates in Malaysian clinical and community infections. The identified ESBL genes in this study were consistent with the three known major types: TEM, SHV, and CTX-M [23]. However, in this review, SHV was the predominantly identified ESBL gene type. This result, however, is in agreement with the rising prevalence of ESBL-producing bacteria in Asia [23]. The result revealed by our review is also in line with the report of[3], who also observed the SHV gene to be dominant in one of the Malaysian districts.

Meanwhile, only one study included in the community infection does not specify the predominant gene in the community infection. Given the increased resistance, it warrants continued robust surveillance of antimicrobial resistance. This situation, therefore, will require an environmental control rather than the classical approach [24]. The differences in the rate of ESBL *Klebsiella pneumoniae* incidence in both clinical and community infections: A High rate of ESBL *Klebsiella pneumoniae* prevalence (72%) was revealed by our review in clinical infections, but the rate of ESBL *Klebsiella pneumoniae* prevalence could not be determined in Malaysian community infections due to the lack of included studies that reported ESBL *Klebsiella pneumoniae* prevalence in Malaysian community infections at our disposal.

The outcome of ESBL Klebsiella pneumoniae prevalence in community infections, however, was not assessed because only one of the included studies reported the outcome, making it difficult to determine the prevalence. Thereby providing a very vital research gap that needs to be explored. It is worth noting that, to the best of our knowledge, this is the first systematic review and meta-analysis that broadly evaluates the prevalence of ESBL *K. pneumoniae* (KP) in the study area. This review, we believe, is comprehensive because we robustly evaluated five important outcomes associated with the prevalence of KP in clinical and community infections: overall ESBL KP prevalence, ESBL KP prevalence in clinical infections, predominant ESBL genes in KP isolates, rate of ESBL KP prevalence in different types of hospital samples, and commonly used confirmatory test methods for ESBL detection. However, the study has limitations, as it only included English language publications in the review. This may have implications for the generalization of the findings. Therefore, the interpretation of the review findings should be made in the context of the limitations.

Conclusively, our review has revealed that ESBL KP is highly prevalent in Malaysian clinical infections. The ESBL KP prevalence is, however, highly variable, and the factors responsible for the variation may be sample size, study quality, and methods of detection. The study also reveals that EBL KP prevalence is endemic in the study area, necessitating urgent

attention to develop lasting solutions for controlling the ESBL KP threat in the antimicrobial resistance domain.

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