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Beta-lactamase resistance genes in *Enterobacteriaceae* from Nigeria

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Abstract
This review was carried out to identify different beta-lactamase resistance genes reported in published literature from Nigeria and to determine the proportion estimates of the important beta-lactamase resistance genes in Nigeria. Sixty-three (63) articles were included in this review based on the eligibility criteria. All the beta-lactamases reported were detected from the Gram-negative bacteria, most especially from *Enterobacteriaceae* (n=53). Thirty-six different beta-lactamase genes have been reported from Nigeria. These genes belong to the narrow-spectrum, AmpC, extended-spectrum, and carbapenemase beta-lactamase resistance genes. Eight (8) genes (*bla*$_{\text{DHA}}$, *bla*$_{\text{CTXM-1}}$, *bla*$_{\text{CTXM-14}}$, *bla*$_{\text{GES-1}}$, *bla*$_{\text{VEB-1}}$, *bla*$_{\text{OXA-1}}$, *bla*$_{\text{OXA-2}}$, and *bla*$_{\text{TEM-1}}$) were shared between animals and humans, 5 genes (*bla*$_{\text{SHV-1}}$, *bla*$_{\text{SHV-2}}$, *bla*$_{\text{SHV-11}}$, *bla*$_{\text{SHV-12}}$, and *bla*$_{\text{NDM-1}}$) were common to both humans and environment while none of the genes was unique to both animals and environment. Four genes including *bla*$_{\text{CMY}}$, *bla*$_{\text{TEM-1}}$, *bla*$_{\text{AmpC}}$, and internationally pandemic *bla*$_{\text{CTXM-15}}$ gene were unique to animals, humans, and the environment. No carbapenemase gene was reported from animals yet. The pooled proportion estimate of ESBL genes in Nigeria was 31% (95% CI: 26-36%, P<0.0001), while the estimate of *bla*$_{\text{CTXM-15}}$ gene in Nigeria was 46% (95% CI: 36-57%, P<0.0001). The proportion estimate of AmpC genes was 32% (95% CI: 11-52%, P<0.001), while the estimate for carbapenemases was 8% (95% CI: 5-12%, P<0.001). This study has provided information on the beta-lactamases distribution in Nigeria. This is necessary for a better understanding of molecular epidemiology of clinically important beta-lactamases especially the extended-spectrum beta-lactamases and carbapenemases in Nigeria.

Keywords: Antimicrobial resistance, Beta-lactamase gene, Nigeria, Review

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Introduction

Beta-lactam antimicrobials are one of the most important groups of antimicrobial drugs in both human and animal health. Antimicrobials such as extended-spectrum cephalosporins (ESC) and carbapenems have been categorized by the WorldHealth Organization as a last resort and critically important antimicrobials, with limited alternatives in the cases of resistance development [1]. However, antimicrobial resistance (AMR) to this group of antimicrobials is occurring at a rapid rate on a global scale[2]. Most resistance to beta-lactams in *Enterobacteriaceae* is mainly due to the production of beta-lactamases, which are often encoded either chromosomally or on plasmids [3,4].Production of beta-lactamases such as extended-spectrum beta-lactamases (ESBLs), AmpC beta-lactamases and carbapenemase beta-lactamases have increasingly been detected worldwide to be distributed in food animals, companion animals, wildlife, humans, and environments[4,5]. Also, since AMR is a One Health challenge, several beta-lactamase genes have been disseminated across different resistant bacterial populations from different hosts and environments[6].

Beta-lactamase production in *Enterobacteriaceae* is an emerging public health concern due to therapeutic failure, serious consequences for infection control and increased risk of morbidity and mortality in both animal and human health [7].The predominant ESBL genes encountered are bla_{CTXM}, bla_{TEM}, and bla_{SHV}. The prevalent AmpC beta-lactamase is $bla_{\text{CMY-2}}$, while for carbapenemases; $bla_{\text{NDM-1}}$ and $bla_{\text{OXA-48}}$ have been commonly reported globally[5]. Although several numbers of beta-lactamase genes have been reported worldwide, not all are equally prevalent among human and animal bacteria. Also, the occurrence, as well as the prevalence of these resistance genes, varies across different geographic regions. For instance, while $bla_{\text{CTXM-15}}$ is widely disseminated and have been reported in almost every regions of the

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world, AmpC *bla*$_{CMY-2}$ have been mostly encountered in North America in both animal and human settings[8].

Therefore, there is a need for continuous surveillance of beta-lactamase resistance genes for a better understanding of the epidemiology of these genes locally within a country and to determine the extent of global dissemination. While detailed information on AMR at the national level do exist for the developed countries such as USA, Canada, and other European countries through integrative surveillance, this is often lacking in most developing countries in Africa including Nigeria. Therefore, generation of AMR data through the use of systematic review of published researches is a useful tool that can give a glimpse of state and extent of AMR in developing countries such as Nigeria. In this study, a systematic review was carried out to identify different beta-lactamase resistance genes reported in published literature from Nigeria, to describe the distribution of these genes between animal, human and environmental settings, and to determine the proportion estimates of the different beta-lactamase resistance genes in Nigeria. This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [9].

Methods

Literature search and data sources

The literature search was conducted in PubMed, Google scholars and African Journal Online (AJOL) electronic databases using a combination of Boolean operators (AND/OR) and predefined keywords. We used the following terms for our search: beta-lactamases AND Nigeria OR beta-lactamase resistance genes AND Nigeria, *bla*$_{CTXM}$ AND Nigeria, *bla*$_{TEM}$ AND Nigeria, *bla*$_{SHV}$ AND Nigeria, *bla*$_{OXA}$ AND Nigeria, Carbapenemases AND Nigeria, AmpC beta-lactamase resistance AND Nigeria, extended-spectrum beta-lactamase resistance AND Nigeria.

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The reference lists of all eligible articles were further reviewed and used to carry out a supplementary literature search. The articles were further screened after removal of duplicates based on titles and abstracts for their relevance to the study objectives and purpose. Articles included in this review were limited to the available publications up till December 2019.

Study selection and eligibility

The primary outcome of interest was the distributions and different types of beta-lactamase resistance genes from bacteria from all sources in Nigeria across one health interface. All studies reporting beta-lactamase resistance genes were included in the review. However, for any study to be included in this qualitative review, the studies must have performed molecular detection of beta-lactamase resistance genes. Studies that only reported beta-lactamase production based on phenotypic synergy test without beta-lactamase gene detection were excluded from the review. Studies with extractable data on the proportions of different types of beta-lactamase resistance genes from animals, humans and the environment were further considered.

Data extraction and analysis

The data were abstracted onto Excel (Microsoft Office Excel 2010) spreadsheet. For each eligible study, data extracted included: first author details, year of publication, type of sample collected (animal feces, retail meat products, human clinical samples, environmental samples), sources of the samples (animal, human or environment), bacterial species isolated, study location or geopolitical zone of the study in Nigeria, sample size of bacterial isolated, different types of beta-lactamase resistance genes detected, number of bacterial isolates positive for the beta-lactamase genes phenotypically, number of bacterial isolates positive for the beta-lactamase genes genotypically, antimicrobial susceptibility testing method (disk diffusion, micro-broth

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dilution, agar dilution, E-test, or automated methods), phenotypic and genotypic methods of beta-lactamase detection. The proportion (with respective 95% confidence interval) of each beta-lactamase gene as reported for each study was calculated by dividing the number of bacteria positive for the beta-lactamase gene by the total number of bacteria positive phenotypically or total number of bacteria isolated depending on the data availability.

Random-effects meta-analysis was used to calculate the pooled (weighted) proportions with respective 95% confidence intervals for the different types of the beta-lactamase groups. The analysis was done to allow for any heterogeneity between studies. Studies reporting a low number of bacterial isolates (< 10 isolates) were not included in the meta-analysis. The pooled prevalence and each study estimates were presented using forest plot. The I^2 statistic (a measure of inconsistency) was used to assess the variation between studies due to heterogeneity. A value of 0% shows no observed heterogeneity; increasing values indicate increasing heterogeneity. The I^2 statistic with cutoff values ≤25%, ≥26-≤50%, and >5% were subjectively considered as low, moderate, and substantial heterogeneity. Subgroup analysis was performed to account for potential sources of heterogeneity between studies. A separate meta-analysis was carried out for each of the dominant beta-lactamase group. Statistical significance was set at $P<0.05$ while statistical analysis was carried out using STATA SE/15.0 (College Station, Texas 77845 USA).

Result

Study characteristics

Systematic search from two electronic databases identified 567 articles (197 from PubMed, 30 from AJOL and 340 from Google scholar). The outline of study selection and review process is shown in the PRISMA flowchart (Figure.1). Sixty-three articles (63) were included in the subsequent qualitative review following the assessment of the 128 published

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articles for eligibility. A qualitative review of the 63 studies on beta-lactamase resistance genes in Nigeria was based on studies in animals (n=13), humans (n=41) and environment (n=9). Studies of animal origin were from poultry, pig, cattle, pigeons, and duck. However, all the human studies were hospital-based, with the beta-lactamases reported from clinical samples collected within the hospitals in Nigeria. While for environment-based studies, samples were collected from wastewater, drinking water, beach water, aquatic, and river samples.

Among the 63 studies reviewed, detection of beta-lactamases were all from Gram-negative bacteria most especially from bacterial family *Enterobacteriaceae* (n=60), while others include *Acinetobacter baumannii* (n=2) and *Vibrio* spp. (n=1). Majority of the studies were carried out in the Southwestern Nigeria (n=39), while other regions include South-eastern (n=8), North-central (n=5), North-eastern (n=3), North-western (n=2) and South-southern (n=2) Nigeria. Seventeen (n=17) studies used broth microdilution method to determine the minimum inhibitory concentrations (MIC) for various antimicrobials tested, other methods used for MIC determination include E-test (n=4), and Vitek-2 (n=3). However, disc diffusion method (n=36) was mainly use for the determination of susceptibility of bacteria to various antimicrobials tested. Only 46 of the 63 studies reported the use of phenotypic screening method for beta-lactamase production; this includes modified Hodge test and Carba test (n=6) for carbapenemases production as well as double disk synergy test (n=39) for other beta-lactamase production. Forty-eight studies used polymerase chain reactions (PCR) alone (n=48), PCR with sequencing (n=9), PCR with isoelectric point (n=2), PCR with whole genome sequencing (n=1), PCR with restriction fragment length polymorphism (RFLP, n=1) and whole genome sequencing alone (n=2) for the genotypic detections of various beta-lactamase resistance genes reported in the reviewed studies.

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One health distribution of beta-lactamase resistance genes in Nigeria

Thirty-six (36) different beta-lactamase genes were detected and reported in the 63 studies (Table 1). Seventeen (17) genes were detected from animals, 28 genes from humans and 12 genes from the environment. These genes belongs to the AmpC [10–24], extended-spectrum [10–15,17,19,20,23–56], narrow-spectrum [13–16,19,24,32,35,37,43,57–59], and carbapenemase beta-lactamase resistance genes[19,22,59–66]. One health distribution of beta-lactamase resistance genes between the animal, human and environmental settings was presented in Table 1. Eight (8) genes (*bla*$_{DHA}$, *bla*$_{CTXM-1}$, *bla*$_{CTXM-14}$, *bla*$_{GES-1}$, *bla*$_{VEB-1}$, *bla*$_{OXA-1}$, *bla*$_{OXA-2}$, and *bla*$_{TEM-1}$) were shared between animals and humans, 5 genes (*bla*$_{SHV-1}$, *bla*$_{SHV-2}$, *bla*$_{SHV-11}$, *bla*$_{SHV-12}$, and *bla*$_{NDM-1}$) were common to both humans and environment while none of the genes was unique to both animals and environment. Four genes including *bla*$_{CMY}$, *bla*$_{TEM-1}$, *bla*$_{AmpC}$, and internationally pandemic *bla*$_{CTXM-15}$ gene were unique to animals, humans, and the environment. No carbapenemase gene was reported from animals yet. While 7 genes (*bla*$_{CMY-2}$, *bla*$_{ACT-5}$, *bla*$_{ACC}$, *bla*$_{FOX-1}$, *bla*$_{ECB}$, *bla*$_{CTXM-27}$ and *bla*$_{CTXM-55}$ were unique to animals alone, 12 genes (*bla*$_{TEM-2}$, *bla*$_{CTXM-2}$, *bla*$_{SHV-28}$, *bla*$_{SHV=112}$, *bla*$_{OXA-10}$, *bla*$_{OXA-23}$, *bla*$_{OXA-48}$, *bla*$_{OXA-181}$, *bla*$_{NDM-5}$, *bla*$_{VIM-1}$, *bla*$_{VIM-2}$ and *bla*$_{KPC}$) were unique to humans alone; however, only 2 genes (*bla*$_{VIM-5}$ and *bla*$_{Z}$) were unique to the environment.

Proportion estimates of extended-spectrum beta-lactamase genes in Nigeria

Thirty-two studies were included in the meta-analysis for the generation of overall pooled estimate of ESBL. The overall pooled proportion of ESBL was 31% (95% CI: 26-36%, P<0.001). The overall between-study heterogeneity was significant and substantial (I^2 =97.87 %, p < 0.001). Between the studies, the proportions of ESBL genes ranges from 1-95% (Figure 2).

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Subgroup analysis provide some explanation for the between-study heterogeneity and also pooled proportion of ESBL based on one health distribution Subgroup analysis revealed the between study heterogeneity was due to human and animal studies. The overall proportion estimate of ESBL for human was 35% (95% CI: 27-43%, P<0.001), while the estimate for animal was 25% (95% CI: 17-33%, P<0.001) and 22% (95% CI: 0-44%, P=0.06) for the environmental-based studies. A separate meta-analysis was conducted to determine the proportion estimate of *bla*$_{\text{CTXM-15}}$ producing *Enterobacteriaceae* in Nigeria (Figure 3), 17 studies were included in the quantitative analysis. The overall pooled proportion was 46% (95% CI: 36-57%), the unexplained between-study heterogeneity was significant and substantial (I^2 =99.04 %, p < 0.001). The proportion estimate of *bla*$_{\text{CTXM-15}}$ gene from human-based studies was 47% (95% CI: 25-69%), for the animal-based studies, the pooled proportion was 47% (95% CI: 27-67%) and that of the environment was 41% (95% CI: 33-50%). Between subgroups, heterogeneity was non-significant (P=0.812). However, the within-group heterogeneity for both human and animal studies was significant and substantial (I^2 =99%, P<0.001).

Proportion estimates of AmpC and carbapenemase beta-lactamase genes in Nigeria

Based on 13 studies, the overall pooled proportion of AmpC beta-lactamases was 32% (95% CI: 11-52%, P<0.001), with the overall between-study heterogeneity was significant and substantial (I^2 99.15 %, p < 0.001). However, the proportions of AmpC beta-lactamases reported from the studies ranges from 2-88% (Figure 4). Subgroup analysis revealed that between-study heterogeneity was due to studies from human settings. The proportion of AmpC beta-lactamases was higher in human 37% (95% CI: 4-70%, P=0.03) than environment 20% (95% CI: 14-25%, P<0.001) and animals 26% (95% CI: 0-64%, P=0.20).

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Six studies were included in the carbapenemases pooled proportion estimation (Figure 5). The overall pooled proportion of carbapenemases was 8% (95% CI: 5-12%, P<0.001). Between the studies, the proportions of carbapenemase beta-lactamases ranges from 1-48%, while the overall between-study heterogeneity was significant (I^2 =87.6 %, p < 0.001). Subgroup analysis provide some explanation for the between-study heterogeneity and also pooled proportion of carbapenemases based on one health distribution (Figure 4). The proportion of carbapenemases for environment was 15% (95% CI: 8-22%, P<0.001) and was higher than 6% of human (95% CI: 3-10%, P<0.001). Between study heterogeneity was mostly due to studies from human setting.

Discussion

In Africa, data on AMR are often limited due to lack of sustainable integrated surveillance programs at country level. Lack of systematically collected data has contributed largely to the poor understanding of AMR to critically important antimicrobials such as beta-lactam drugs in Africa compared to the developed world. This study was conducted to bridge some of these gaps by identifying different types, distribution and the proportion estimates of beta-lactamase resistance genes reported in published literature in Nigeria. This is for the purpose of generating data and information for the national, continental, and global understanding of molecular epidemiology of beta-lactamases. While this review was based on published articles in Nigeria, it is a step in right direction to provide data that can support the establishment of necessary preventative measures such as integrative surveillance programs and policies for the mitigation of AMR within Nigeria. From this review, beta-lactamases were mainly detected from bacteria of the family *Enterobacteriaceae*. This is unsurprising as the Gram-negative bacteria of the *Enterobacteriaceae* family are ubiquitous in nature, causing different infections (most especially *E.* coli) in both humans and animals and can readily be

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maintained in the environment. Also, the emergence and occurrences of AMR due to beta-lactamases in *Enterobacteriaceae* are driven mainly by MDR characteristics, ease of acquisition of AMR genes, and rapid dissemination of resistance determinants by *Enterobacteriaceae* to other pathogenic and non-pathogenic bacteria [2,67].

Among the 63 studies, 73% reported double-disk synergy test for the phenotypic detection of beta-lactamases prior to the genotypic method. This is in compliance with CLSI guideline for the screening and detection of beta-lactamases in bacteria. However, five different genotypic methods including PCR, DNA sequencing, WGS, isoelectric point, and RFLP were reported by the studies. PCR method was mostly reported from published articles reviewed; this may be due to ease of access and reduced cost associated with PCR compared to other advanced techniques such as DNA sequencing and WGS [68]. While WGS method is commonly used in the developed world both in research and surveillance programs, the use of WGS in beta-lactamase studies in Nigeria is still limited. Only two studies reported the use of WGS for the detection of beta-lactamase genes. This may be due to the lack of accesses to necessary software, technical-know-how, and bioinformatics intricacy as well as other computational difficulties associated with the use of WGS in a developing country as Nigeria.

Majority of the articles published were from southern Nigeria compared to northern Nigeria. Therefore, beta-lactamases reported in this systematic review may not reflect the true picture of the beta-lactamases distributed in Nigeria geographically. However, of all the beta-lactamases detected in Nigeria, the majority of the articles were from human clinical settings compared to the animal and environmental settings which is consistent with what has been reported from a similar study in South Africa [68]. In most cases, human clinical settings routinely carry out antimicrobial susceptibility testing and other AMR phenotypic tests before clinical

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treatment. Also, further genomic laboratory work may routinely be carried out to determine what epidemiological type of beta-lactamases is responsible for the beta-lactam resistance. Therefore, this may explain detection and report of beta-lactam resistance from human clinical settings compared to animal and environmental settings where detections are mostly not routine but research-based

From this review, 36 different types of beta-lactamases have been detected and reported in Nigeria, and these beta-lactamases included the clinically important types such as ESBL, AmpC, and carbapenemases that are commonly responsible for treatment failures in both human and veterinary settings [69,70].While previous reviews within Africa focused mainly on systematic reviews of ESBL in *Enterobacteriaceae* [71–73], this study was conducted to capture as many beta-lactamases detected in Nigeria as possible beyond ESBL. This is because ESBLs, the AmpC-type, and the carbapenemases remain the most clinically challenging beta-lactamase resistance gene families in both human and animal health. Antibiotic resistance is recognized as a one health challenge because of the rapid emergence, molecular relatedness and dissemination of important resistant bacteria and genes among humans, animals, and the environment at a global scale [74].This review showed that of the 36 beta-lactamases reported in Nigeria, some of the genes detected in Nigeria were reported from more than one setting. Between human clinical setting and environment, 5 different beta-lactamases have been reported while between animal and human settings, 8 different genes have been reported. This finding further highlights the importance of one health transmission pathway of AMR between human, animal and environmental settings. Also, it revealed how environmental contamination and food-animal production systems could serve as reservoirs of essential AMR genes, transmission and

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colonization as well as infection with clinically important beta-lactamase producing bacteria in humans [6].

Epidemiologically, all the beta-lactamases detected in Nigeria have been reported from other parts of the world. Five different types of AmpC beta-lactamase group (*bla*$_{CMY-2}$, *bla*$_{ACT}$, *bla*$_{ACC}$, *bla*$_{FOX-1}$, and *bla*$_{DHA}$) were reported in Nigeria to date based on this review. While *bla*$_{CMY-2}$ is the most important AmpC type and with broadest geographic spread, this gene was not common in Nigeria based on this review compared to other countries such as United States of America and Canada where the gene is most common in livestock and retail meat products, as well as in non-typhoidal salmonella infections in humans [8].Within Africa, there are limited reports on AmpC beta-lactamases. However, *bla*$_{CMY-2}$ and *bla*$_{DHA}$ have been reported from Algeria [71], while *bla*$_{ACC}$, *bla*$_{FOX-1}$,and *bla*$_{DHA}$ from Uganda [75].No carbapenemase was reported yet from animals in Nigeria based on this review, however, carbapenemases have been commonly reported from wildlife, food-producing animals, and companion animals from other countries [70,76], the lack of report of carbapenemase from animal setting may be due to lack of research or surveillance in this regard and not necessarily absence of carbapenemase genes in animals from Nigeria. All the epidemiologically important carbapenemases including *bla*$_{OXA-23}$, *bla*$_{OXA-48}$, *bla*$_{OXA=181}$, *bla*$_{NDM-1}$, *bla*$_{VIM-1}$, *bla*$_{VIM-2,}$ *bla*$_{VIM-5,}$ and *bla*$_{KPC}$ reported in Nigeria were mostly from the human clinical setting. These carbapenemases have been described in many African countries including South Africa, Gabon, Angola, Senegal, Kenya, Tanzania, Morocco, Algeria, Tunisia, Libya, and Egypt [77,78]. In most cases, *bla*$_{NDM-1}$and *bla*$_{OXA-48}$ is the commonly reported carbapenemases. While these carbapenemases are known to be prevalent in the South Asian countries most especially from India sub-continent, the trend in Africa may indicate that

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global dissemination of carbapenemase-producing *Enterobacteriaceae* has reached the African continent.

Among the ESBLs, five different groups were reported including *bla*$_{CTXM}$, *bla*$_{SHV}$, *bla*$_{OXA}$, *bla*$_{GES,}$ and *bla*$_{VEB}$, with *bla*$_{CTXM}$ most commonly reported. During the last decade, *bla*$_{CTXM}$–type enzymes have spread globally, is now the most common ESBLs in bacteria of *Enterobacteriaceae* family in both human and animal health[79,80]. Among the different types of *bla*$_{CTXM}$ reported in Nigeria, *bla*$_{CTXM-1}$, *bla*$_{CTXM-2}$, *bla*$_{CTXM-14}$, and *bla*$_{CTXM-55}$ are known to be commonly detected in food animals [4,8]. However, the internationally pandemic *bla*$_{CTXM-15}$ has been reported from every country of the world where it is associated with *E. coli* serotype O25:H4 (ST131) causing both community and hospital acquired human infections[79,81]. The *bla*$_{CTXM-15}$ was also the only ESBL commonly reported from human clinical, animal and environmental settings in this review. This revealed that *bla*$_{CTXM-15}$ is ubiquitous and prevalent in all environments with possible anthropozoonotic and zooanthroponotic transmissions. *bla*$_{CTXM-15}$ has also been commonly reported from other regions of Africa [71], which may suggest *bla*$_{CTXM-15}$ be the predominant ESBL in Africa similar to what's found in USA, Europe, and Asia [82]. *bla*$_{SHV}$ ESBLs, in particular, *bla*$_{SHV-12}$ and *bla*$_{SHV-2}$ reported in Nigeria, have also been frequently detected in Europe and North America [83]. However, the globally disseminated *bla*$_{TEM}$ ESBLs, i.e., *bla*$_{TEM-10}$ and *bla*$_{TEM-52}$ were not detected yet in Nigeria, narrow-spectrum *bla*$_{TEM-1}$ coding for ampicillin resistance was however more common.

The proportion estimate of ESBL in Nigeria was 32% compared to 23% of AmpC and 8% of carbapenemases. This is unsurprising, even though AmpC have been found worldwide and carbapenemases are increasingly being reported, both AmpC and carbapenemases are less prevalent than ESBL on the world stage[5],and this is consistent with the finding of this review.

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The proportion estimate of 29% for AmpC in a human setting in this review was closed to 28.3% estimate from Egypt [84] however, lower than 34% from Canada [85] and 39.6% from Uganda [75]. The proportion estimate of 8% for carbapenemases is comparable to what has been reported from other African countries [77]. However, the lower proportion of carbapenemases for Nigeria is encouraging considering the importance of carbapenems as last resort antimicrobials in the cases of ESBL producing bacterial infections. While carbapenems resistance is emerging globally at a rapid rate, surveillance, and prudent use practices of carbapenems will help to minimize widespread dissemination and prevention of epidemics of MDR bacterial infections at the national level. The proportion estimate of 32% of ESBL in human, animal and environmental settings from this review is higher than 22.6% reported by a similar study from Tanzania [73].The proportion estimate of 35% for ESBL in the human clinical setting is comparable to proportions previously reported for different countries within Africa [72,71]. For *bla*$_{CTXM}$, the proportion estimate of 34% for *bla*$_{CTXM}$ gene in Nigeria was lower compared to 56.7% reported in Iran [86] and 69% from a previous similar systematic review [87].However, the proportion estimate of 45% for *bla*$_{CTXM-15}$ in Nigeria was lower than 78% reported from both Tanzania [73]and Sudan [88].

None of the articles reviewed reported any risk factors associated with occurrence of beta-lactamase resistance genes in Nigeria, however, the occurrences and proportion estimates of clinically significant beta-lactamases reported maybe due to the uncontrolled and indiscriminate use of antimicrobials as well as the lack of active infection control programs in most animal and human clinical settings. In Nigeria, antimicrobials can readily be purchased from both pharmaceutical and non-pharmaceutical stores in both animal and human clinical settings without prescriptions[89]. This call for concern because indiscriminate use of antimicrobials drives resistance, also, poor hygienic practices in both community and hospital environments facilitates

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the spread and transmission of important MDR bacteria. In addition, extended-spectrum cephalosporins and carbapenems have been designated as critically important antimicrobials by the World Health Organization with limited alternatives in the cases of treatment failure [1]. Lastly, infections with ESBL/AmpC/carbapenemase–producing bacteria may result in prolonged hospitalization, higher treatment costs, delays in the initiation of timely and adequate antimicrobial therapy, increased risk of morbidity and mortality [7]. Therefore, clinically important beta-lactamases represent a significant threat to public health and collaborative efforts at all stakeholders' levels are essential in mitigating the development and dissemination.

While the aim of this review was to provide detailed information on beta-lactamases detected and reported from Nigeria, there are however some limitations of this study. This review was done with the intention of including all available studies that have reported the detection of any beta-lactamase resistance genes in Nigeria. Therefore, there is possibility of selection and information bias introduce due to little emphasis on the quality of the studies reviewed. Also, the literature search for was limited to the PubMed, Google scholar and AJOL electronic databases, therefore, some studies may have been omitted in this review. Also, information on risk factors associated with beta-lactamase resistance was not available. This information is necessary for better explanation for the beta-lactam resistance observed in Nigeria and a better understanding of the epidemiology of beta-lactamase resistance genes in Nigeria. However, this review has provided information on the beta-lactamases distribution in Nigeria. Thirty-six different beta-lactamases have been reported in Nigeria with $bla_{\text{CTXM-15}}$ commonly distributed in the animal, human and environment similar to the reports from other African countries. Carbapenemases are most common in human clinical setting however not reported yet in animals. The information provided on beta-lactamase resistance genes is necessary for better

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understanding of one health and molecular epidemiology of clinically important beta-lactamases especially the AmpC, ESBLs, and carbapenemases both locally in Nigeria and globally.

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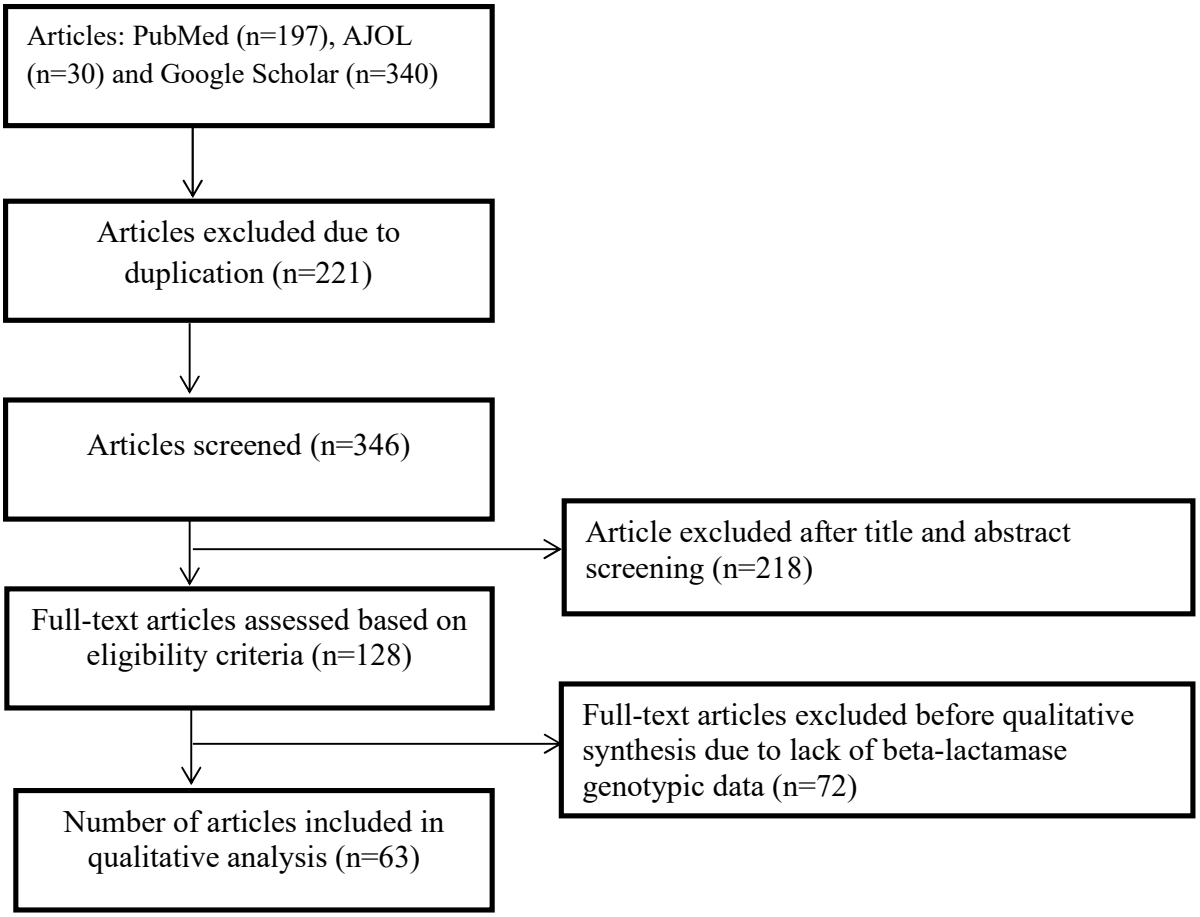
Figure 1. Flow diagram summarizing the process of literature search and selection.



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1 Table 1. Distribution of beta-lactamase resistance genes between animals, humans and environmental settings in Nigeria

Beta-lactamase types	Genes	Animals	Humans	Environment	Reference
AmpC beta-lactamases	*bla*$_{ampC}$	1[a]	5	1	10–24
	bla$_{CMY-2}$	1			
	bla$_{CMY}$ like	1	1	1	
	bla$_{ACT-5}$	1			
	bla$_{ACC}$	1			
	bla$_{FOX-1}$	2			
	bla$_{DHA-1}$	1	1		
	bla$_{ECB}$	1			
Extended-spectrum beta-lactamases	*bla*$_{CTX-M}$ like	3	12	1	10–15,17,19,20,23–56
	bla$_{CTX-M-1}$	2	2		
	bla$_{CTX-M-2}$		1		
	bla$_{CTX-M-14}$	1	1		
	bla$_{CTX-M-15}$	6	14	2	
	bla$_{CTX-M-27}$	1			
	bla$_{CTX-M-55}$	1			
	bla$_{SHV-2}$		1	1	
	bla$_{SHV-12}$		2	1	
	bla$_{SHV-28}$		1		
	bla$_{SHV-112}$		1		
	bla$_{OXA-10}$		1		
	bla$_{VEB-1}$	1	1		
	bla$_{GES}$	1	1		
Narrow-spectrum beta-lactamases	*bla*$_{OXA-1}$	2	4		13–16,19,24,32,35,37,43,57–59
	bla$_{OXA-2}$	1	1		
	bla$_{SHV-1}$		2	1	
	bla$_{SHV-11}$		2	1	
	bla$_{TEM-1}$	3	6	1	
	bla$_{TEM-2}$		1		
	bla$_{Z}$			1	

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Carbapenemases	*bla*$_{KPC}$		1		19,22,59–66
	bla$_{OXA-23}$		1		
	bla$_{OXA-48}$		1		
	bla$_{OXA-181}$		3		
	bla$_{NDM-1}$		5	1	
	bla$_{NDM-5}$		1		
	bla$_{VIM-1}$		5		
	bla$_{VIM-2}$		1		
	bla$_{VIM-5}$			1	

[a] Value in each cell represents the number of articles reporting the beta-lactamase genes

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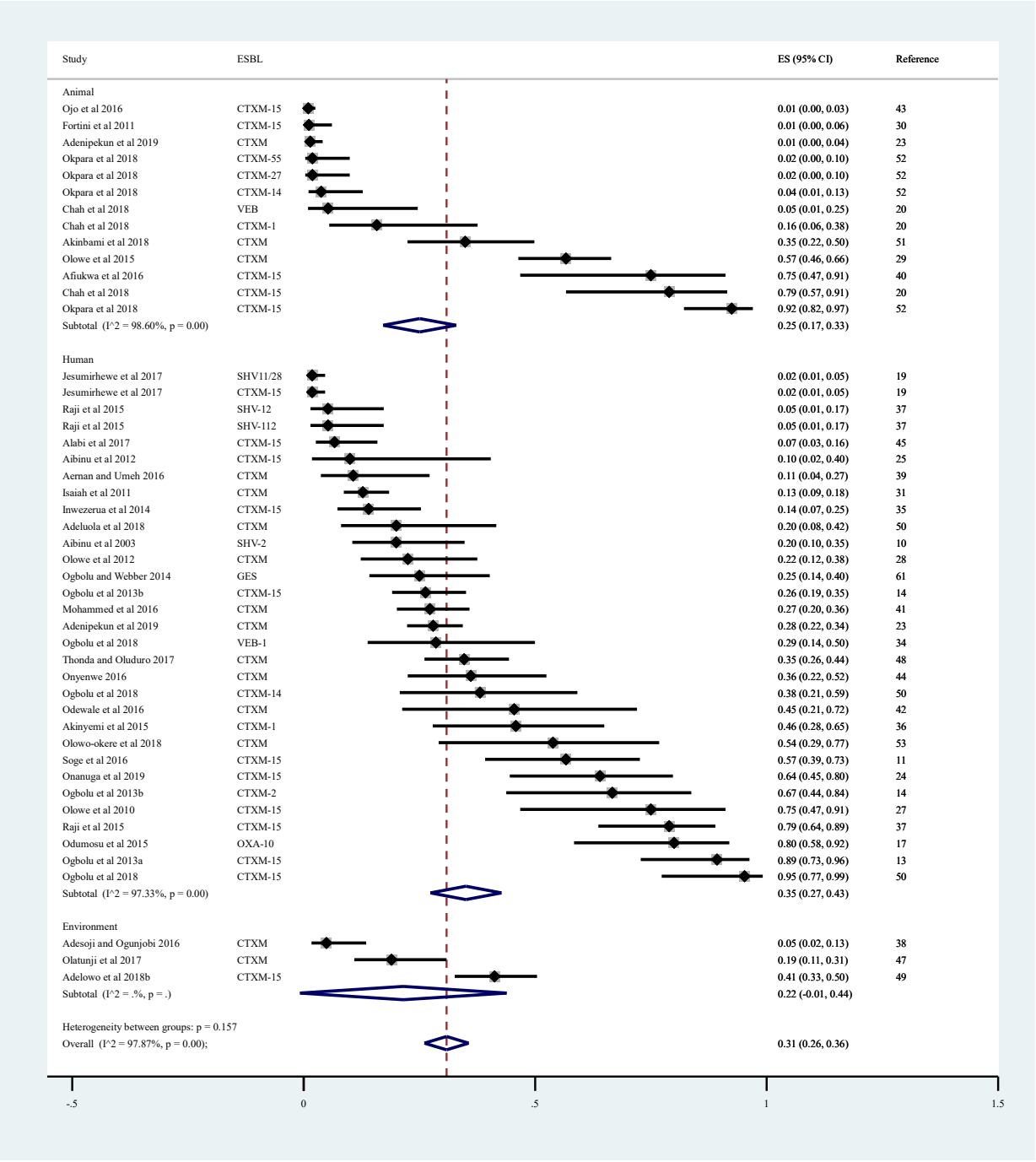

Figure 2: Subgroup analysis and forest plot of proportion estimates of extended-spectrum beta-lactamases (ESBL) for human, animal, and environmental settings in Nigeria. Midpoint of each horizontal line segment shows the proportion estimate of ESBL resistance genes in each study. Diamond sign represents the pooled proportion from all studies included in the random-effect meta-analysis. CI: Confidence interval.

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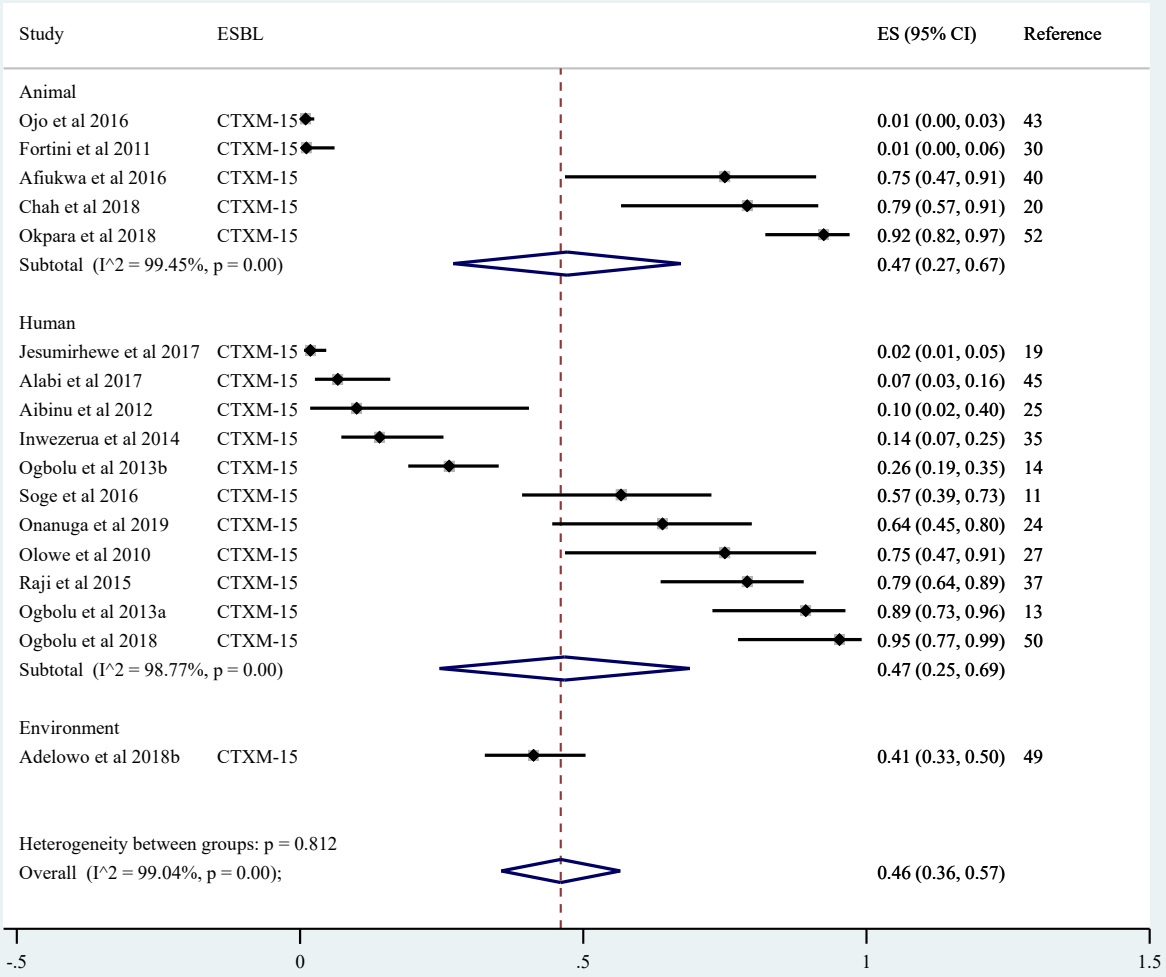

Figure 3: Subgroup analysis and forest plot of proportion estimates of *bla*$_{\text{CTXM-15}}$ extended-spectrum beta-lactamase (ESBL) in Nigeria. Midpoint of each horizontal line segment shows the proportion estimate of *bla*$_{\text{CTXM-15}}$ resistance gene in each study. Diamond sign represents the pooled proportion from all studies included in the random-effect meta-analysis. CI: Confidence interval.

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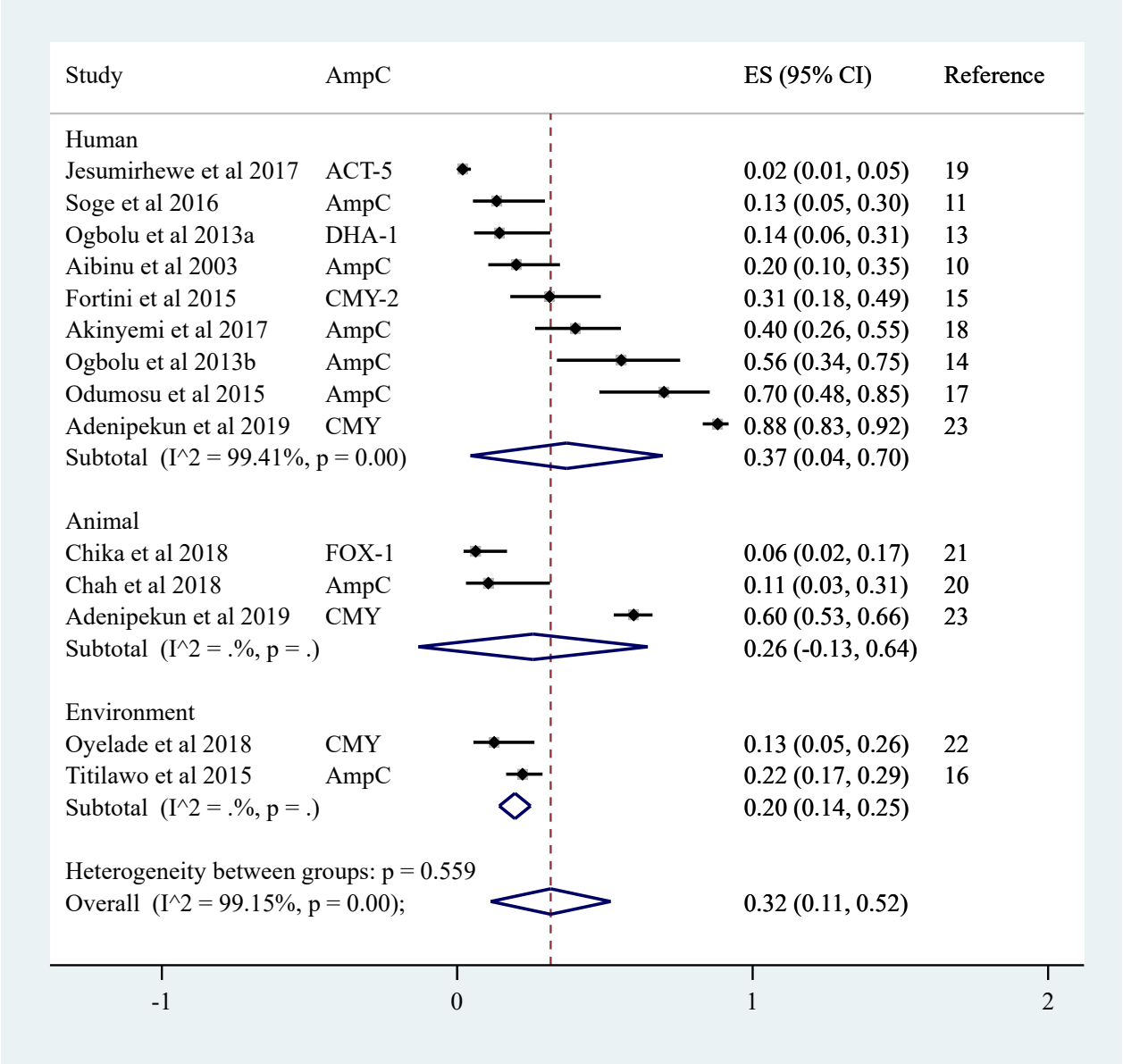

Figure 4: Subgroup analysis and forest plot of proportion estimates of AmpC beta-lactamases for human, animal, and environmental settings in Nigeria. Midpoint of each horizontal line segment shows the proportion estimate of AmpC resistance genes in each study. Diamond sign represents the pooled proportion from all studies included in the random-effect meta-analysis.
CI: Confidence interval.

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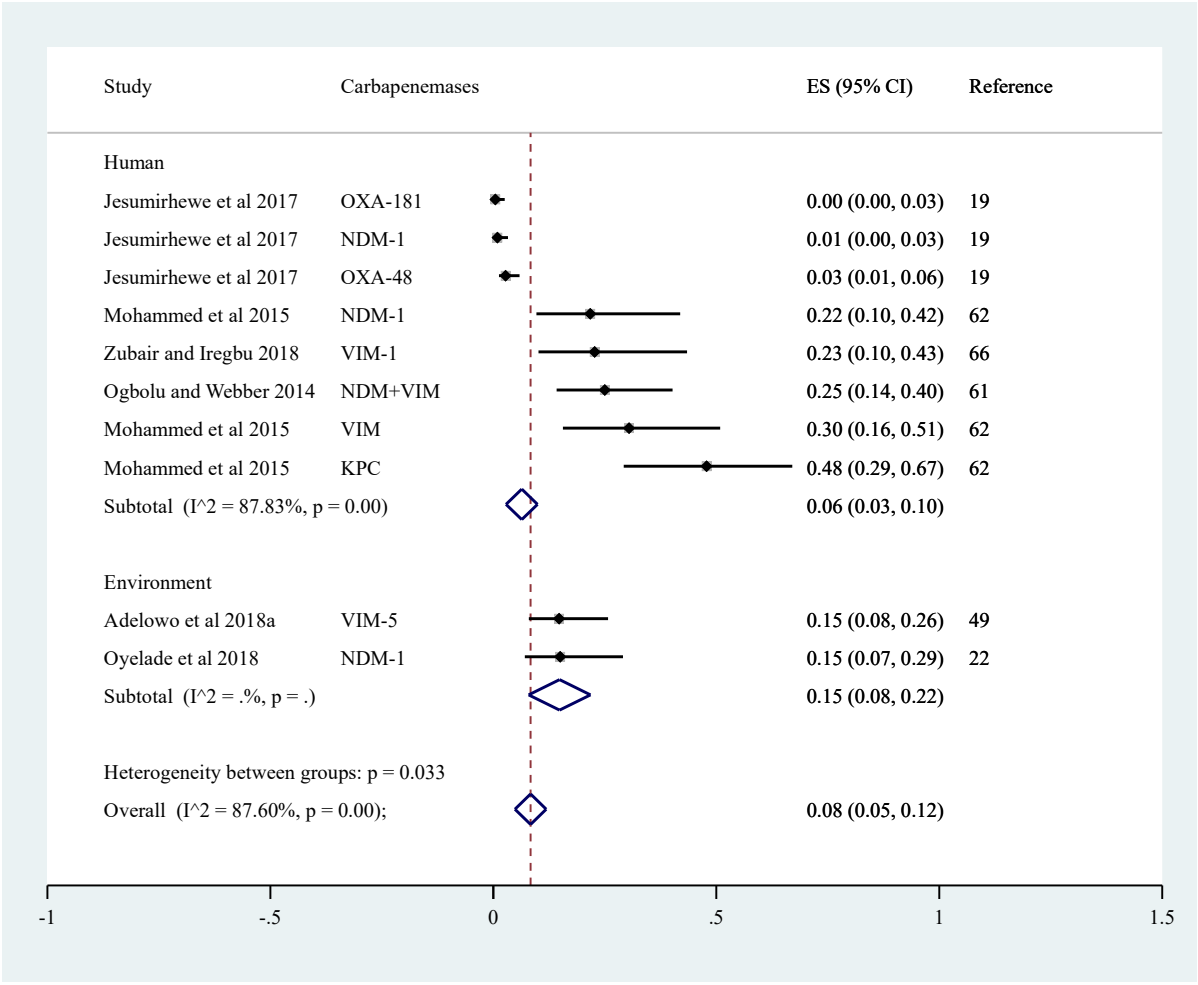

Figure 5: Subgroup analysis and forest plot of proportion estimates of carbapenemase beta-lactamases for human and environmental settings in Nigeria. Midpoint of each horizontal line segment shows the proportion estimate of carbapenemase resistance genes in each study. Diamond sign represents the pooled proportion from all studies included in the random-effect meta-analysis. CI: Confidence interval.