Review Article

Pig Farm Environment as a Potential Reservoir of ESBL-producing *E. coli*: A Systematic Review

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Submission Date: 14-05-2022; Revision Date: 11-06-2022; Accepted Date: 28-07-2022.

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ABSTRACT

Extended-spectrum beta-lactamases (ESBLs) are enzymes that can be observed in some bacterial strains, most commonly in *Escherichia coli,* which are resistant to various antibiotics, specifically beta-lactams. Having the ability to destroy active ingredients of certain antibiotics, the impacts of undesirable utilization of antibiotics increase the development of antibiotic-resistant bacteria, posing additional threats to public health. The purpose of this review is to evaluate the pig farm environments as potential reservoirs of ESBL-producing *E. coli* by its presence in water and soil samples, its gene prevalence, and its negative effects on public health through gathering credible studies from various databases and examining journals that have met the set review standards. Among the isolates from the six included studies, the existence of ESBL-producing *E. coli* was higher in water samples with 13.63% of isolates. From the four studies discussing the prevalence of ESBL-producing *E. coli* genes, the most dominant gene detected in water samples was $bla_{\text{CTX-M}}$ (40%), followed by bla_{TEM} (9%), and bla_{SHV} (0%). In soil samples, the $bla_{\text{CTX-M}}$ gene (36%) still predominates, then the bla_{SHV} gene (27%), and lastly, the bla_{TEM} gene (5%). Without concern for the sample type, the most dominant gene was the $bla_{\text{CTX-M}}$ gene (39%), followed by both bla_{TEM} (8%) and bla_{SHV} genes (8%). The data shows that unsanitary pig farms are potential sources for ESBL-producing *E. coli*. With its ability to resist antibiotics, the increasing distribution of this bacteria to different environmental matrices increases its risk of infections, thereby also affecting the health of the public.

Keywords: ESBL-*E. coli*, $bla_{\text{CTX-M}}$, bla_{SHV}, bla_{TEM}, Pig Farms.

INTRODUCTION

Antibiotic-resistant bacteria are growing in numbers due to inappropriate usage of antibiotics adding risks to public health internationally. Extended-spectrum beta-lactamase (ESBL)-producing bacteria is found to have an increased presence on food-producing animals, continuously affecting food safety and the environment,[1] making the agricultural food industry one of their notable sources.[2] These also cause serious health complications in humans due to their mechanism of resistance to β-lactam antibiotics.[3] Posing a great remark, World Health Organization (WHO) claims that ESBL-producing bacteria contribute to the most crucial problems of the 21st century,[4] and are labeled as the most critical antimicrobial pathogen in humans.[5]

Among the Enterobacteriaceae family, the bacteria that is most often related to ESBL is *E. coli*.[6] ESBL-producing *E. coli* contributes to the increased rates of morbidity and mortality, longer hospital admissions, and financial burden of a country due to its ability to pose community-acquired infections.[7] With this, ESBL-producing *E. coli* were seen in human isolates as well as livestock, pets, and even in the environment, making it the priority pathogen of WHO in discovering new medications.[8]

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DOI: 10.5530/ajbls.2022.11.30

Pig farms may be potential reservoirs of pathogenic microorganisms due to their low hygienic environment.[9] *E. coli* can spread through contaminated water and soil, which can be utilized as a marker of environmental contamination.[10] The detection of ESBL-producing *E. coli* in pigs extends the problems caused by these microorganisms to the environment such as pig farms, where its transmittance can propagate naturally through the soil and water, as well as in the areas near the farms.[11] These transmission routes indicate the possibility of pig farms being situated as probable sources of ESBL-producing *E. coli.*

This review intends to further discuss the presence of ESBL-producing *E. coli*, the prevalence of its genes in the pig farm environment, and its possible threat to public health using published articles from various databases. With this, it will provide knowledge and further information on the threat posed by the existence of ESBL-producing *E. coli* in pig farms, thereby increasing the public's awareness of its occurrence.

MATERIALS AND METHODS

Literature Search

The writing of this review was in parallel with the appropriate reporting items for systematic reviews and PRISMA guidelines. Related literature was gathered from reliable search engines including Science Direct, PubMed, and Research Gate. Additionally, journals from Mary Ann Liebert and documents published by the World Health Organization were used as valid sources. The studies included were published from the year 2015 to the present. The Boolean operators "OR" and "AND" were incorporated into the search terms. Combinations of search keywords including "ESBL," "*Escherichia coli,*" "soil," "water," "$bla_{\text{CTX-M}}$," "bla_{TEM}," and "bla_{SHV}" were utilized to discover studies concentrating on the potentiality of pig farms to be reservoir of ESBL-producing *E. coli*. For reference processing, Zotero, a software program, was used.

Eligibility Criteria

This paper includes experimental studies related to ESBL-producing *E. coli* and its presence in pig farm environments, specifically in water and soil samples, and their gene prevalence particularly $bla_{\text{CTX-M}}$, bla_{SHV}, and bla_{TEM}. Studies selection was not limited to any country where they were conducted. The exclusions in this paper are studies conducted on other types of farms, other agricultural matrices, articles published before the year 2015, and secondary sources such as review and critique papers. Other ESBL genes and the methods used for their detection, and any antimicrobial resistance studies about ESBL-producing *E. coli* were also ruled out.

Data Selection and Extraction

All available data obtained from the selected studies that fall under the eligibility criteria were further analyzed to inspect the amount of ESBL-producing *E. coli* within pig farms. Each data collected from the selected sources were singly assessed for qualification. Only studies published in English were included, wherein each title and abstract were screened, while duplicate studies were removed. The full text of the screened studies that fit the criteria was obtained. Information obtained, including the name of the author(s), publishing year, and data relevant to the review were listed in Microsoft Excel spreadsheets. To generate results out of the selected studies, identification of the journals was done according to the environmental samples they used and the ESBL genes they detected.

During the initial process, 100 studies were gathered upon keying in the combination of search terms in different reliable search engines. To remove duplicated studies, each article was identified manually, where 7 studies were removed and 93 were retained. The remaining articles were screened by the exclusion criteria set by the authors, removing a total of 80 studies. The 13 studies left were assessed in compliance with the eligibility criteria through the samples utilized by the study, as well as the genes it has detected. Following the full-text assessment, a total of 6 studies were included in this review. Figure 1 illustrates the schematic diagram of the study selection process.

RESULTS

Characteristics of Included Studies

The review initially gathered 100 research articles that are either cross-sectional, descriptive-experimental,

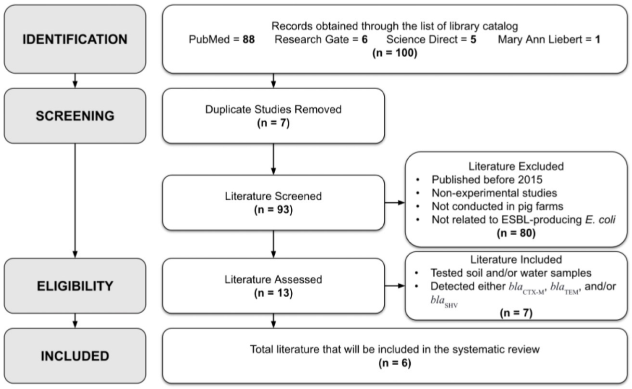

Figure 1: Prisma Diagram for the study selection.

descriptive-observational, experimental, or longitudinal designs. After careful analysis and scrutinization by the set eligibility criteria for literature, out of 100 collections, 6 experimental studies were chosen and all are published in peer-reviewed journals. The publication year of these journals is between 2015-2020. All of the final 6 studies were conducted in different countries, enumerating: 2 studies from China; 2 studies from Brazil; and 1 each from India and Thailand.

Presence of ESBL-producing *E. coli* in Soil and Water Samples

The findings from the six (6) journals involving the presence of ESBL-producing *E. coli* in soil and water samples are graphically illustrated in Figure 2. The data presented confirm the ability of both soil and water to bear ESBL-producing *E. coli*. Between the two samples collected, water harbors more ESBL-producing *E. coli* with 13.63% positive isolates in comparison to the soil with only 13.08% isolates.

Prevalence of ESBL-producing *E. coli* genes in Soil and Water Samples

Results from the included studies about the dominance of three major ESBL-producing *E. coli* genes, namely bla$_{\text{CTX-M}}$, bla$_{\text{SHV}}$, and bla$_{\text{TEM}}$, in water and soil samples are presented in Figure 3. Among the six (6) journals, only four (4) had detected ESBL-producing gene isolates from soil and water specimens. In water samples, the most dominant gene is bla$_{\text{CTX-M}}$ bearing 40% of the isolates. Meanwhile, 9% of the isolates were bla$_{\text{TEM}}$ genes, and no gene isolates of bla$_{\text{SHV}}$ were discovered. In soil samples, the bla$_{\text{CTX-M}}$ gene accounted for 36% of the isolates, the bla$_{\text{SHV}}$ gene recorded 27% of isolates, and the bla$_{\text{TEM}}$ gene was only 5%. By this, it is determined that the soil samples contained lesser gene isolates than the water samples. Concurrently, without concerning the sample type, the most prevalent gene detected is the bla$_{\text{CTX-M}}$ gene with 39% isolates in total, followed by bla$_{\text{SHV}}$ and bla$_{\text{TEM}}$ genes with both 8% isolates.

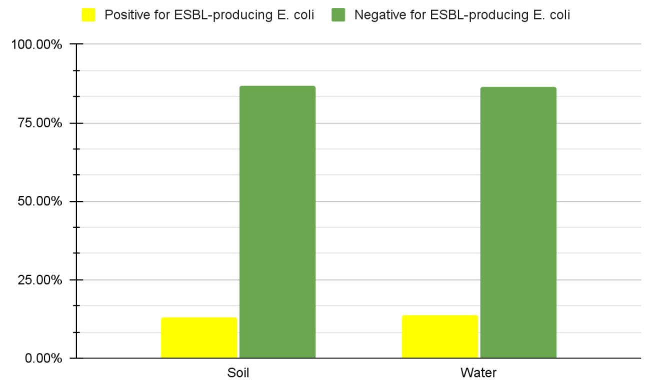

Figure 2: Presence of ESBL-producing *E. coli* from soil and water samples.

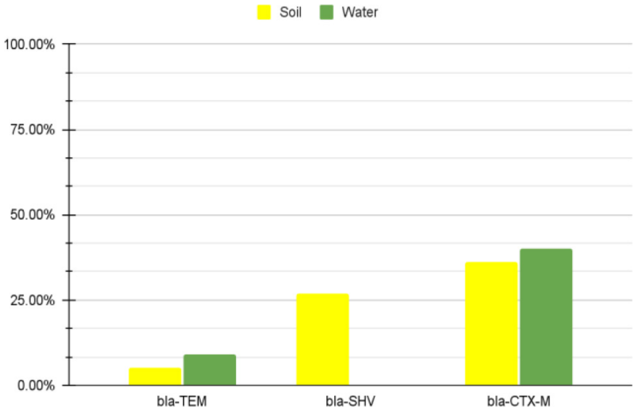

Figure 3: Prevalence of ESBL-producing *E. coli* genes from soil and water samples.

DISCUSSION

By the above statements, pig farm environments as a possible reservoir of ESBL-producing *E. coli* were studied using a systematic review. The authors appraised and analyzed a wide array of published studies that correspondingly review the chosen subject. The study designs utilized were experimental. During the full-text review, multiple studies propound the probability of the pig farm environment as a probable reservoir of ESBL-producing *E. coli* since a significant amount of *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$, and *bla*$_{\text{TEM}}$ genes are identified.[7] Six articles used either soil or water as their samples and four of them depicted evidence that *bla*$_{\text{TEM1}}$, *bla*$_{\text{SHV}}$, or *bla*$_{\text{CTX-M}}$ genes are present.[7,12-14]

Published works that explored ESBL-producing *E. coli* inhabiting samples of either soil or water were evaluated to assess their roles as potential reservoirs in pig farms. From the gathered studies, water samples harbor more isolates (13.63%) compared with soil samples (13.08%). Studies included have also shown the possibility of water and soil samples obtained from pig farms as carriers of ESBL-producing *E. coli*. [7,10,12-15]

As established by several studies, soil samples obtained from pig farms can be a reservoir of ESBL-producing *E. coli*. Gao *et al.,* stated that 12.5% of their collected untreated soil samples were ESBL producers.[13] This incidence of soil harboring soil-dwelling microorganisms contributes to the transmission of ESBL-producing to disseminate to other variables inside pig farms, including humans. The soil was regarded as a reservoir of antibiotic resistance as it serves as a niche for microorganisms, such as ESBL-producing *E. coli*.[13] The mechanism of this contamination is due to the natural occurrence of soil to serve as recipients and absorb other contaminated environmental samples, such as water and manure, within pig farms.[7]

Besides soil samples, water bodies can also be a reservoir for ESBL-producing bacteria, precisely water from pig ranches that carry ESBL-producing *E. coli*.[7] ESBL-producing *E. coli* is reported to be commonly prevalent in water resources including rivers, wastewaters, and groundwater. Environmental factors such as river direction can spread ESBL-producing *E. coli* in soil. Furthermore, it is likely to spread in bodies of water, as it can reach human-inhabited areas and contaminate soil which reaches groundwater which could be utilized as a drinking source. Additionally, discharged materials, such as water from pig farms during rainfall, can be washed directly into nearby water resources, introducing microorganisms into the water.[6] According to Li *et al*., waste from animal farms contributes widely to the contamination of nearby environmental resources such as soils and bodies of water.[14] The ineffective disposal control of both human and animal wastes, improper hygienic practices, and preservation of rodents and animals contribute to the vast factors inducing contamination of water bodies.[10] These two factors are especially common in pig farms which are considered to be unsanitary. In addition, the extensive effects of anthropogenic activity in contributing to water contamination were further confirmed when water samples collected from areas with an altitude of 1000m, which are not usually inhabited nor reached by humans, do not contain any ESBL-producing *Enterobacteriaceae*.[7] This parallels the result observed in this review, as all water samples from the different journals were collected on the ground surfaces of each pig farm.

Due to the observation of ESBL-producing *E. coli* to be present in certain environmental matrices, various articles were evaluated to establish the prevalence of bla_{TEM}, bla_{SHV}, and $bla_{\text{CTX-M}}$ genes in soil and water samples as these are regarded as potential reservoirs of ESBL-producing *E. coli*. Out of all the genes mentioned, $bla_{\text{CTX-M}}$ is a known environmental bacterium that is copiously present in water. Three (3) out of six (6) articles showed that $bla_{\text{CTX-M}}$ is the most dominant gene and is more prevalent in water samples compared with soil samples. The prevalence of $bla_{\text{CTX-M}}$ in water samples is a result of either the excretion of a persistent bacteria from the previous herd or through horizontal gene transfer via a plasmid or vector agent.[7] $bla_{\text{CTX-M}}$ is most commonly detected in water samples worldwide which are linked with extremely self-transferable plasmids.[16] Additionally, the universal rise of ESBL- *E. coli* that produces CTX-M is triggered through the fast spread of the $bla_{\text{CTX-M}}$ gene that is found on every mobile element like plasmids and transposons.[17] By this, numerous factors are considered contributors to the prevalence of $bla_{\text{CTX-M}}$ which is also inlined with ineffective human and animal waste management, and poor hygiene.[10]

Other ESBL-producing genes were also found in the drinking water and soil swabs around the pig farm environment.[7] Although the $bla_{\text{CTX-M}}$ gene is the predominant gene and is known to cause a global threat, the bla_{TEM} gene was still observed in the samples. Ejaz *et al*., discussed the origins of these genes stating that bla_{TEM} and bla_{SHV} were mutant forms of beta-lactamases, whereas $bla_{\text{CTX-M}}$ came from environmental bacteria.[18] From the six (6) journals included, only two (2) articles have shown significant results for the bla_{TEM} gene. The bla_{TEM} isolates from water samples were 9%, while soil samples have 5% of the isolates, fewer compared with water. With the bla_{TEM} gene being more prevalent in water samples, it was found to be mostly associated with ponds and receiving rivers.[7,14] In support, Membreve and Rivera stated that bodies of water are crucial in the transmission of antibiotic resistance as it is known to be a reservoir for antibiotic-resistant bacteria and genes.[19] In the study of González *et al.,* high production of β-lactamase by certain bacteria as well as waterfowl migration causes the dissemination of the bla_{TEM} gene, resulting in it being the most detected in water samples.[20] This has only shown that ESBL-producing bacteria were found to harbor bodies of water resulting in water bodies being their reservoir preceding its contamination. Lastly, the bla_{SHV} gene, which encodes drug resistance genes, is found in many *Enterobacteriaceae* and is one of the major β-lactamase genes. The bla_{SHV} gene was detected in one (1) of the six (6) publications, with the gene being found in 27% of soil samples and 0% of water samples. From the publications, bla_{SHV} is more prevalent in soil than in water, but its threats do not go away in the water. As studies effectively identified the bla_{SHV} gene in soil but not in the water, poor living circumstances and anthropogenic activities may have led to the disparity. Placing manure on the soil surface, for example as a source of infection, aids in the proliferation of the ESBL-producers.[7] The majority of bla_{SHV} genes, according to Liakopoulos *et al*., owe their effective relationship with the food-producing animals to conjugative plasmids,[21] a momentary interaction between cytoplasms of each bacteria, allowing horizontal gene transfer.[22] Therefore, the presence of the three genes, $bla_{\text{CTX-M}}$, bla_{SHV}, and bla_{TEM} genes, in soil and water samples only shows that ESBL-producing *E. coli* can proliferate in environmental matrices that pose risks of transmission to living beings.

In general, water samples harbor more ESBL-producing bacteria compared with the soil samples. Vital *et al.,* stated that agricultural settings highly depend on the surface and irrigation waters for their crop irrigation, harvest, and production.[23] In the study, it was found that these waters possess high resistance to antibiotics, such as tetracycline, causing the production of ESBL which are present in the detected samples. This is attributable to the fact of pollutants being present in the water such as feces, agricultural runoff, wastewater discharge, septic leakage, and other microbial pathogens. As these waterways are utilized for irrigation, harmful contaminants can be transferred to agricultural goods. With these circumstances, widespread ESBL-producing bacteria and other multidrug-resistant organisms can be seen in different products of agriculture, where Vital *et al.,* also suggested that the transfer of pathogens may be due to horizontal transmission of *E. coli*.[23] Hence, the study has shown that irrigation and surface waters are places for antibiotic-resistant bacteria and affect the agricultural environment and production due to their usage in these settings.

The strengths of this paper involve the identification of specific genes isolated in two different samples that negatively impact public health. The limitations of this review must be considered about results interpretation. Given the restricted time, limited resources, and bounded access to various databases, documenting the findings in a more exact and detailed way will strengthen the reliability of evidence. Assessing the mechanisms that led to the presence of ESBL-producing *E. coli* as an alarming concern in public health can further aid in maximizing and strengthening strict regulations that everyone must adhere to. Therefore, through careful evaluations, this systematic review suggests that the pig farm environment threatens public health as it leads to the establishment and dissemination of antibiotic-resistant *E. coli*. The existence of ESBL-producing *E. coli* isolates in numerous pig farms suggests that this type of setting might be a reservoir, a long-lasting cause of infection that aids in their propagation. As a result, concerns about public health rise. Correspondingly, the spread of such bacteria in a community is also affected by the environment, with animal farms playing an important effect.[7]

CONCLUSION

Pig farms that have low hygienic environments contribute to the contamination of surrounding environmental resources. The identification of ESBL-producing *E. coli* in certain pig farm environmental extracts contributes to the public health threat as its predominance in the said setting can greatly play a part in the increasing risks of antibiotic resistance. Furthermore, ESBL-producing *E. coli* genes are widely disseminated in an unsanitary pig farm environment. The review's findings support the possibility that the pig farm environment harbors *E. coli* that produces ESBL. The analyses of the literature found that the percentages of the major ESBL genes in *E. coli* were notably high. Among the most common genes across both samples, the most frequent isolate was led by $bla_{\text{CTX-M}}$, followed by bla_{SHV}, then bla_{TEM} in soil samples. Meanwhile, in water sources, $bla_{\text{CTX-M}}$ genes are followed by bla_{TEM}, and bla_{SHV} with no isolates observed. The epidemiology of *E. coli* as an ESBL producer was also investigated, and it was discovered that this bacterium is increasingly widespread and raises the risk of infections, consequently endangering the health of the public.

RECOMMENDATIONS

With the review only focusing on pig farms, the authors would like to advise future researchers to center on other types of farms, specifically broiler farms, as wide literature is also available for this setting. It would also be beneficial if future researchers would utilize other environmental matrices, such as boot swabs, and even air, as there are data that discuss the ability of these samples to also harbor ESBL-producing *E. coli.*

ACKNOWLEDGEMENT

The authors would like to extend their gratitude to Ms. Charlene Princess Tolenada, for her effort in thoroughly providing constructive feedback and willingness to share her academic expertise on the topic to write this paper suitably. To their Research 2 intructors, for imparting their knowledge to improve the quality of this paper. Lastly, the authors wish to encompass their appreciation to their families, for their financial and moral support. Also, to Almighty God, whose grace and blessings made this study possible.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ESBL: Extended-spectrum beta-lactamases. ***E. coli:*** *Escherichia coli.*

SUMMARY

The potentiality of pig farms to harbor pathogenic microorganisms due to unsanitary practices predisposes its environment to contamination. With the alarming cases of ESBL-producing bacteria, such as *E. coli*, this review article focuses on the ability of the pig farm environment, specifically in soil and water samples, to be a reservoir of this microorganism. Journals that were collated from different databases were thoroughly screened and assessed to satisfy the criteria set by the authors. The chosen studies center on the presence of ESBL-producing *E. coli* in pig farm environments, as well as the genes they carry. The results generated establishes the presence of ESBL-producing *E. coli* in pig farm environments, with water samples harboring more isolates in comparison with soil samples. Also, the predominance of ESBL genes was reviewed, and $bla_{\text{CTX-M}}$ was conferred as the most widely occurring gene in both samples. For the dominant genes in soil samples, $bla_{\text{CTX-M}}$ was followed by bla_{SHV} and then bla_{TEM}, and for water samples, bla_{TEM} preceded $bla_{\text{CTX-M}}$, as no bla_{SHV} was reported in any of the isolates.

AUTHORS' CONTRIBUTION

The contributions of the study were divided among the authors. Each author individually contributed to the completion of the review paper. Authors A, B, C, D, E, and F contributed to the accomplishment of the paper's introduction, methodology, results, and conclusion. The abstract was constructed by Authors B, C, and D, while Authors E and F formed the Prisma Diagram. Author I supervised and assisted the authors with the writing of the review article. Lastly, Authors G and H were responsible for the citation and referencing of the entire paper.

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Cite this article: Burahim FZJ, Sapiandante DJA, Ramos KLB, Garbino JAMP, Lacambra FNB, Edem KII, Espiritu MFV, Rillera DKC, Tolenada CPS. Pig Farm Environment as a Potential Reservoir of ESBL-producing *E. coli*: A Systematic Review. Asian J Biol Life Sci. 2022;11(2):218-24.