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Epidemiology of Carbapenem-Resistant Enterobacteriaceae in Households of UTI Outpatients in Southwestern Uganda: An Urgent Need for One Health Approach

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Abstract

Background: Carbapenem-resistant Enterobacteriaceae (CRE) pose a major public health threat due to limited treatment options. Resistance driven by carbapenemase enzymes (such as *bla*VIM, *bla*KPC, *bla*IMP, *bla*NDM, and *bla*OXA-48), enables CRE to spread beyond healthcare settings into communities. The One Health approach is crucial for understanding the transmission pathways. This study investigated CRE distribution, resistance patterns, and genetic mechanisms among urinary tract infection (UTI) patients, their households, livestock, and environmental sources to inform strategies for controlling its spread. **Methods:** A cross-sectional study was conducted in two health centers in rural southwestern Uganda, involving 104 households (human, livestock and environment) of UTI outpatients who had Enterobacteriaceae harboring carbapenemase genes. The outpatients were traced to their homes. Urine samples were collected from a household member, stool samples from livestock, and boot sock samples from the environment. Enterobacteriaceae were identified, and the carbapenemase resistance genes (*bla*VIM, *bla*OXA-48, *bla*NDM, *bla*KPC, and *bla*IMP) identified using polymerase chain reaction. Data were analyzed using descriptive statistics and presented as frequencies and proportions in tables and charts. **Results:** *Escherichia coli* was the most abundant organism, while livestock demonstrated the most abundant growth of Enterobacteriaceae. Phenotypic carbapenem resistance was highest in the environment isolates (47.73%) whereas the genotypic carbape-

nemase resistance was highest in both human and environment isolates. Nearly a fifth of the households had at least one isolate carrying a carbapenemase gene, and 40% of the households had identical carbapenemase genes with UTI patients. **Conclusions:** The identification of matching carbapenemase genes between UTI patients and household isolates highlights the urgent need for targeted surveillance and infection control strategies to mitigate the spread of resistant pathogens. One Health epidemiological study designs are necessary for explaining the principal routes and dynamics of the spread of AMR bacteria between humans, livestock and the environment.

Keywords

Enterobacteriaceae, Carbapenem Resistance, Urinary Tract Infections (UTI), One Health

1. Introduction

Enterobacteriaceae are a large family of Gram-negative bacteria that are commonly found in the intestines of humans and animals, as well as in the environment. While many members of this family, such as *Escherichia coli* and *Klebsiella* species, are harmless or beneficial, others can cause severe infections, including urinary tract infections (UTIs), bloodstream infections, and pneumonia [1]. Carbapenems are a class of β-lactam antibiotics that serve as last-resort treatments for multidrug-resistant bacterial infections. They are highly effective against a broad spectrum of gram-negative bacteria due to their stability against most β-lactamases [2]. However, the increasing emergence of carbapenem-resistant Enterobacteriaceae (CRE) threatens their clinical efficacy. CRE are Enterobacteriaceae that have acquired resistance to carbapenems through various mechanisms, including the production of carbapenemase enzymes such as *bla*VIM, *bla*KPC, *bla*IMP, *bla*NDM, and *bla*OXA-48, which hydrolyze carbapenems and render them ineffective [3].

The spread of CRE is a growing global health concern, as these bacteria are associated with high morbidity and mortality rates due to limited treatment options [1]. While CRE infections were initially reported in healthcare settings, recent studies indicate their presence in community settings, livestock, and environmental reservoirs, suggesting a complex transmission cycle [4]. Therefore, a One Health approach integrating human, animal, and environmental health, is essential for understanding the epidemiology of CRE and developing effective strategies to mitigate its spread [5]. Myers and colleagues reported antibiotic crossover-use in humans and animals, a practice with potential to contribute to the development and spread of antibiotic resistance between humans and animals [6]. Despite a recent report on carbapenem use in veterinary medicine elsewhere [7] [8], there is no available data on use of carbapenems in livestock in Uganda.

Livestock, in particular, act as reservoirs for CRE due to the widespread use of antibiotics in animal husbandry, leading to resistance selection and potential

transmission to humans through direct contact, food consumption, or environmental contamination [9]. Similarly, environmental factors such as water sources, soil, and waste disposal sites can harbor CRE and contribute to its dissemination. However, data on the transmission dynamics of CRE among hospital patients, household members, livestock, and the environment remains limited, especially in sub-Saharan Africa [10].

This study investigated the distribution, phenotypic resistance patterns, and genetic mechanisms of carbapenem resistance among household members, livestock, and environmental sources of UTI patients with Enterobacteriaceae uropathogens harboring carbapenemase genes. By applying a One Health approach, this research envisioned to provide insights into the potential cross-transmission of CRE and inform interventions to curb its spread.

2. Materials and Methods

This was a cross-sectional study conducted in rural southwestern Uganda, focusing on the detection of carbapenemase-producing organisms among households of the urinary tract infections (UTIs) outpatients attending Bwizibwera Health Center IV and Rubaya Health Center III.

2.1. Study Population

A total of 104 household members of the UTI patients who harbored Enterobacteriaceae uropathogens harboring carbapenemase genes were traced to their respective homes for sample collection. The 104 participants were traced from an initial total of 111 UTI patients, with seven lost to follow up. The 111 UTI patients were selected from 455 UTI patients who had Enterobacteriaceae pathogens [11].

2.2. Sample Collection

All samples from households (human, livestock and environment) were collected altogether at the same visit, more less at the same time. After collection, the samples were kept on ice and transported to the laboratory for analysis within 4 - 6 hours.

Urine Samples

Urine samples were taken from a midstream clean-catch into sterile urine container. We instructed the participant to pass a small amount of urine before collecting the urine sample into the urine container.

Livestock Fecal samples

Fresh fecal samples passed by the livestock such as pigs, sheep, goats, cows, and chickens were collected using a sterile scoop into a transport media and transported for microbial analysis at the Microbiology Department, Mbarara University of Science and Technology (MUST).

Environmental samples

Environmental samples were collected using boot socks. The boot sock samples were collected from areas such as outside toilets/latrines and around the house.

The samples were later moistened with normal saline and cultured in the laboratory using various preferred media.

2.3. Laboratory Procedures

Urine samples were obtained from the 104 household participants, fecal samples were collected from their livestock, and environmental samples were gathered using boot socks. The samples were analyzed for the presence of Enterobacteriaceae, which were identified through standard biochemical testing methods. To detect carbapenemase resistance genes (blaVIM, blaOXA-48, blaNDM, blaKPC, and *bla*IMP), polymerase chain reaction (PCR) genotyping was employed.

Identification of Enterobacteriaceae

Enterobacteriaceae isolated from urine samples were identified using a series of biochemical tests including oxidase, citrate utilization, indole, urease production, triple-sugar iron, and motility tests [12].

Phenotypic screening for carbapenemases

For susceptibility testing, we used the Kirby-Bauer diffusion method following the Clinical Laboratory Standards Institute (CSLI) guidelines 2019, as described previously in our laboratory [13].

Detection of carbapenemase encoding genes

The presence of carbapenemase resistance genes (blaVIM, blaOXA-48, *bla*NDM, *bla*KPC, and *bla*IMP) was confirmed through polymerase chain reaction (PCR) genotyping as previously described in our laboratory [11].

In brief, for DNA extraction, bacterial colonies were washed with 1X TE buffer twice. Then, 100 µL TE elution buffer was added to the pellet and vortexed for 1 min. The mixture was incubated at 95˚C for 1 hour and 30 min using a heating dry bath and centrifuged at 15,000 rpm for 5 min. The supernatant containing the DNA was transferred to a new ultracentrifuge tube, and the DNA was stored at -20˚C until usage within 4 hours.

Each of the open reading 4 frames of specific targets was amplified separately for each sample using forward and reverse primers each with the following unique sequences:

*bla*KPC forward primer: TCGTCGCGGAACCATTC, reverse primer: ACAGTGGGAAGCGCTCCTC;

*bla*IMP forward primer: CATGGTTTGGTGGTTCTTGT, reverse primer: ATAATTTGGCGGACTTTGGC;

*bla*VIM forward primer: GATGGTGTTTGGTCGCATA, reverse primer: CGAATGCGCAGCACCAG;

*bla*OXA-48 forward primer: GATTTGCTCCGTGGCCGAAA, reverse primer: CCTTGATCGCCCTCGATT;

*bla*NDM forward primer: CCAATATTATGCACCCGGTCG, reverse primer: ATGCGGGCCGTATGAGTGATTG.

We purchased the PCR kit for gene amplification from New England Biolabs Inc. (M0258L Deep Vent DNA Polymerase, ThermoPol reaction buffer, and mag-

nesium sulfate ($MgSO_4$) solution. The initial denaturation was at 95˚C for 30 s, followed by elongation at 72˚C for 1 min, and a final extension at 72˚C for 5 min. DNA amplicon was electrophoresed using 1.5% agarose gel, in 1x Tris-Borate EDTA buffer (TBE), 5 µL DSView Nucleic acid stain (cat. no.: M7011), 6X loading buffer (GDSBio Lot 050), and DNA ladder/marker 100 bp (GDSBio Lot 076). Electrophoresis was run at 200V and 80 mA for 1 hour. Bands were visualized using the gene-flash transilluminator.

2.4. Quality Control

We used KPC-positive control *K. pneumoniae* ATCC BAA-1705, NDM-positive control *K. pneumoniae* ATCC BAA-2146, and a multidrug-resistant strain of *E. coli* harboring multiple carbapenemase genes (blaIMP, blaVIM and blaOXA-48). Distilled water was used as a negative control.

2.5. Data Analysis

Data were entered into Excel, and analyzed using SPSS version 26 to determine the proportions of carbapenem resistance patterns among Enterobacteriaceae in the isolate categories. Frequencies and percentages were calculated for categorical variables. Chi squares to compare proportions of categories were computed, and significance at $p < 0.05$.

2.6. Ethical Considerations

Ethical approval was obtained from the Research Ethics Committee and institutional review board, and written informed consent was obtained from all participants. Confidentiality and anonymity were maintained throughout the study. Consent was obtained or waived by all participants in this study. The Research Ethics Committees of Bishop Stuart University (BSU) #BSU-REC-2023-156 and the Uganda National Council of Science and Technology issued approval #HS3361ES. In addition, permission was sought from the Mbarara district health office and the hospital in charge of Bwizibwera and Rubaya Health Centers to conduct this study.

3. Results

A total of 104 households of UTI outpatients who had organisms harboring a carbapenemase gene were followed and recruited in the study.

Organism distribution

Figure 1 summarizes organisms' distribution in the studied households. *Escherichia coli* was the most abundant organism in humans, livestock and environment sources followed by *Klebsiella* spp., whereas *Proteus* spp. was the least abundant. In addition, livestock demonstrated the most abundant growth of organisms (87/104 or 83.7%) followed by the environment (44/104 or 42.3%). In contrast, humans had the highest proportion of no Enterobacteriaceae organisms isolated on culture (74/104 or 71.2%).

Livestock and organisms. Majority of the livestock kept in households were

goats followed by chickens. In addition, *E. coli* was ubiquitous in all livestock, except in rabbits (Table 1).

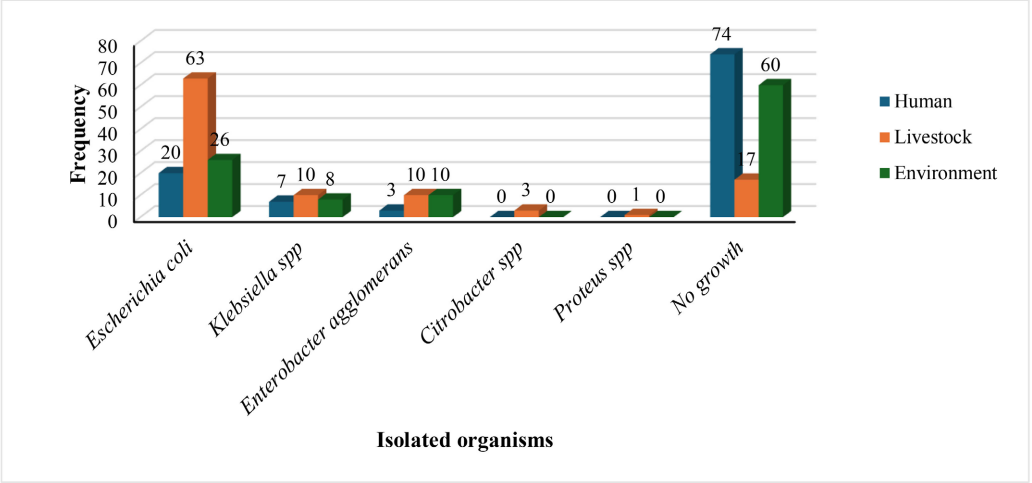

Figure 1. Distribution of organisms isolated from the household member, livestock and environment. Escherichia coli was the most abundant organism, and livestock showed the highest growth of organisms.

Table 1. Distribution of organisms among the livestock in the households.

Organisms	Livestock					
	Goats (n = 44)	Chicken (n = 33)	Duck (n = 1)	Swine (n = 4)	Cattle (n = 21)	Rabbit (n = 1)
Escherichia coli	26	22	1	4	10	0
Klebsiella spp.	6	2	0	0	2	0
Enterobacter agglomerans	4	1	0	0	4	1
Citrobacter spp.	3	0	0	0	0	0
Proteus spp.	0	0	0	0	1	0
No growth	5	7	0	0	4	0

Carbapenem resistance patterns

Organisms showed differential resistance against the studied carbapenems as shown in Table 2. The resistance against ertapenem in humans (p = 0.024) and livestock (p = 0.019) was significantly higher than that of meropenem.

Table 2. Carbapenems resistance in household (humans, livestock and environment).

Drug	Human (n = 30)	Livestock (n = 87)	Environment (n = 44)
Meropenem	5	18	11
Ertapenem	13	32	19
Chi square test	X^2, 5.0794, p = 0.024	X^2, 5.5006, p = 0.019	X^2, 3.2368, p = 0.072

The carbapenem phenotypic resistance patterns and organisms are summarized in Table 3. The proportion of phenotypic resistance was 12/30 (40%) in human isolates, 35/87 (40.2%) in livestock isolates and highest in environment isolates (21/44, 47.73%). The proportion of resistant isolates from females (n = 8) were twice as much as those from males (n = 4), and goats and cattle with the highest proportions in the livestock.

Table 3. Carbapenem phenotypic resistance patterns and organism distribution.

Human (n = 30)	Livestock (n = 87)	Environment (n = 44)
12 isolates	35 isolates, Duck = 1, Goats = 13, Chicken = 8 Cattle = 10, Swine = 2, Rabbit = 1	21 isolates
Organisms		
E. coli = 8 *Klebsiella* spp. = 2 *Enterobacter agglomerans* = 2	*E. coli* = 21 *Klebsiella* spp. = 5 *Enterobacter agglomerans* = 6 *Citrobacter* = 2 *Proteus* spp. = 1	*E. coli* = 12 Klebsiella = 3 *Enterobacter agglomerans* = 2

Overall, *E. coli* demonstrated the highest phenotypic resistance with a proportion of 66.67% (8/12), 60% (21/35) and 57.14% (12/21) in human, livestock and environment isolates.

Table 4 below summarizes the carbapenemase genetic resistance patterns of the studied isolates. The human and environment isolates had the highest and similar proportion of the isolates harboring carbapenemase genes (20% and 20.5% respectively). Overall, *bla*VIM was the most prevalent carbapenemase gene with more than half (13/27) of the isolates harboring the gene. *bla*OXA-48 was found only in environment isolates.

Table 4. Carbapenemase gene distribution among the study isolates.

Human (n = 30)	Livestock (n = 87)	Environment (n = 44)
6 isolates	12 isolates	9 isolates
Gene distribution		
*bla*VIM = 3, *bla*IMP = 1, *bla*NDM = 1 *bla*VIM + *bla*KPC = 1	*bla*VIM = 3, *bla*KPC = 2, *bla*IMP = 3, *bla*NDM = 1, *bla*VIM + *bla*KPC = 1 *bla*VIM+ *bla*IMP = 2	*bla*VIM = 2, *bla*KPC = 2, *bla*IMP = 1, *bla*NDM = 1, *bla*OXA-48 = 1, *bla*VIM + NDM = 1 *bla*VIM + *bla*IMP + *bla*NDM = 1

In addition, a number of isolates showed phenotypic resistance but no presence of studied carbapenemase genes, and as well a number of isolates harbored carbapenemase genes without exhibiting phenotypic resistance as summarized in Figure 2, Figure 3 respectively. It was observed that majority of the human isolates (9/12 or 75%), livestock (29/35 or 82.86%) and environment (14/21, 66.67%) that exhibited phenotypic resistance did not harbor the studied carbapenemase

genes (Figure 2). In contrast, half of both human and livestock isolates that harbored gene never showed phenotypic resistance Figure 3.

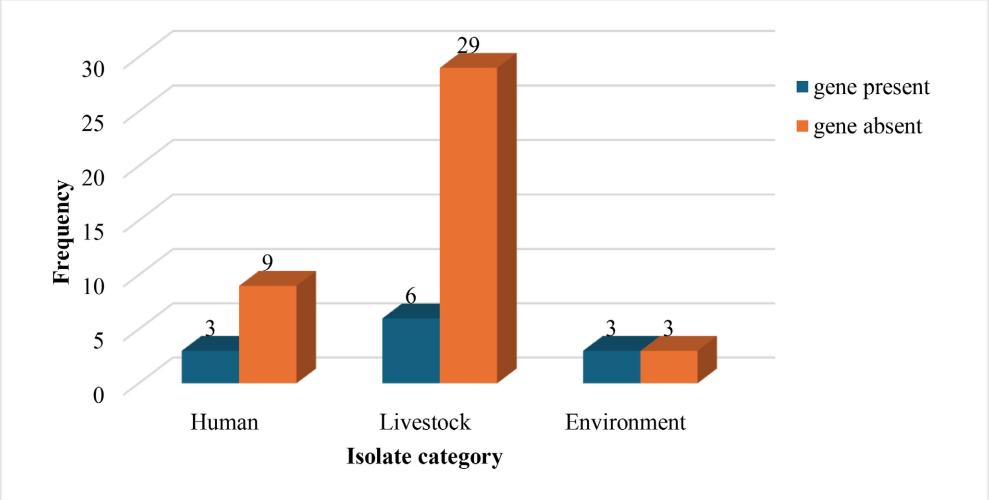

Figure 2. The figures illustrate carbapenemase gene distribution amongst organisms that exhibited phenotypic resistance. 9, 29 and 3 of human, livestock and environment isolates respectively, did not harbor any of the carbapenemase genes studied.

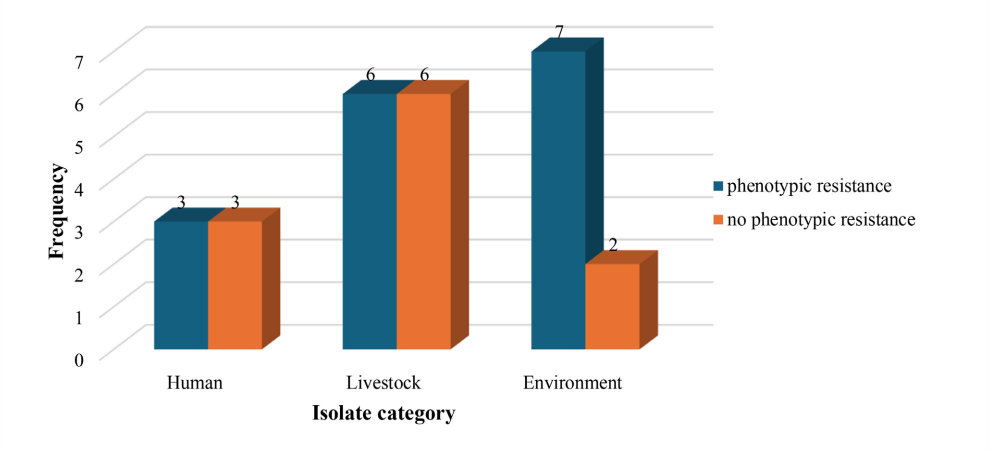

Figure 3. The figures illustrate phenotypic resistance amongst organisms that harbored carbapenemase genes. 3, 6 and 2 human, livestock and environment isolates respectively did not show phenotypic resistance to the studied carbapenems.

Comparison of gene distribution between UTI patients and household members, livestock and environment

The proportion of carbapenemase gene resistance in households (from either human, livestock or environment) was 19.23% (20/104). Eight out of the 20 households representing 40% shared matching carbapenemase genes with a UTI patient from the health centers. The shared genes were *bla*VIM (n = 3), *bla*KPC (n = 2), *bla*IMP (n = 2) and *bla*NDM (n = 1). Multiple carbapenemase genes were observed in four out of the eight households who had matching single carbapenemase genes with UTI patients.

4. Discussion

Our study aimed at investigating the distribution, phenotypic resistance patterns, and genetic mechanisms of carbapenem resistance among household members, livestock, and environmental sources of UTI patients with Enterobacteriaceae uropathogens harboring carbapenemase genes. *Escherichia coli* was the most prevalent organism detected across all sampled sources, including humans, livestock, and the environment. Livestock exhibited the highest bacterial growth of Enterobacteriaceae uropathogens (83.7%). Resistance to ertapenem was higher than that of meropenem. Phenotypic carbapenem resistance was found to be highest in environmental isolates (47.73%), whereas the prevalence of carbapenemase genes was highest and comparable in human and environmental isolates. The study also found that nearly a fifth of the households had at least one isolate carrying a carbapenemase gene, and 40% of the households had identical carbapenemase genes with UTI patients from healthcare centers.

Escherichia coli was the most prevalent organism detected across all sampled sources, including humans, livestock, and the environment. This dominance of *E. coli* in antimicrobial resistance (AMR) studies has been widely reported due to its high adaptability and capacity for horizontal gene transfer [14]. Livestock exhibited the highest Enterobacteriaceae growth (83.7%). Livestock are known to carry Enterobacteriaceae which are important zoonotic foodborne bacteria capable of causing danger to human health with a high increasing prevalence [15]. This trend indicates that livestock serves as potential reservoirs for Enterobacteriaceae, with a potential risk of transmission to humans via direct contact, contaminated food, or shared environments [16].

In our study, goats and chickens were the most common livestock in the households. Enterobacteriaceae have been reported earlier in livestock harboring antimicrobial resistance genes [17] [18]. The widespread presence of *E. coli* and other Enterobacteriaceae harboring resistance genes to carbapenems in livestock [19] [20] is concerning, as it suggests the potential for zoonotic transmission of AMR pathogens. *Klebsiell*a spp. was also present, though at lower frequencies, highlighting its role as an emerging AMR pathogen in both human and animal populations as reported earlier [21].

Carbapenem resistance was observed at varying levels across humans, livestock, and environmental isolates. Resistance to ertapenem was significantly higher than meropenem in both human ($p = 0.024$) and livestock isolates ($p = 0.019$), suggesting differences in the selective pressure exerted by these antibiotics. Meropenem and ertapenem are often used in clinical settings to treat multidrug resistant infections. However, the higher resistance to ertapenem than meropenem observed in our study has been previously reported in Uganda [22]. This differential resistance exhibited toward ertapenem by Enterobacteriaceae, has been reported elsewhere [23]. Essentially, in addition to carbapenemase enzymes, ertapenem has been reported to be the most affected by other resistance mechanisms such as efflux pumps and alteration of porins in particular the loss of *OprD* porin [23] [24].

Phenotypic carbapenem resistance was highest in environmental isolates (47.73%) in our current study. The environment likely plays a crucial role in the persistence and spread of resistant bacteria, acting as a reservoir for AMR genes [25]. Among livestock, goats and cattle exhibited the highest resistance levels, further implicating these livestock as key reservoirs of AMR pathogens. In our study, majority of isolates (from human, livestock and environment) exhibited phenotypic resistance against carbapenems, but no genetic resistance. This could be attributed to the fact that a few carbapenemase resistance genes were studied in our study. In addition to the unstudied carbapenemase gene subtypes such as *bla*OXA-24, other mechanisms including altered porins and efflux pumps, could have played a role in resistance against the carbapenems [23]. The higher phenotypic resistance compared to the genotypic resistance means that where carbapenem resistance is suspected, other mechanisms of resistance in addition to carbapenemases and in the study setting should always be considered.

The overall prevalence of carbapenemase genes was highest in human and environmental isolates. The most frequently detected gene was *blaVIM* (48.15% of all carbapenemase-producing isolates), consistent with findings that *blaVIM* is a dominant carbapenemase in both clinical and environmental settings [2] [26]. *blaOXA-48*, a gene commonly associated with hospital outbreaks, was exclusively found in environmental isolates, suggesting potential environmental contamination from healthcare settings [27]. Conversely, some isolates harbored carbapenemase genes without exhibiting phenotypic resistance, highlighting potential gene silencing, lack of gene expression, or suboptimal testing conditions for resistance [28].

The study found that 19.23% of households had at least one isolate carrying a carbapenemase gene. Notably, 40% of these households shared identical carbapenemase genes with UTI patients from healthcare centers. The presence of identical genes between clinical and household isolates reinforces the hypothesis of AMR transmission between humans, animals, and the environment [29]. Conversely, the presence of dissimilar genes among households and UTI outpatients might be explained by the fact that the UTI patients might have acquired uropathogens from other places other than their homes. In addition, the detection of multiple carbapenemase genes in some households further suggests the acquisition of these genes from other organisms through horizontal gene transfer within microbial communities [30].

Altogether, our results suggest that the environment might be an important component of transmission dynamics, especially considering it as an interface between humans and animals. This emphasizes the need for the One Health approach to allow a better understanding of influencing factors and their interplay as supported by some previous studies [29] [31] [32]. In the study setting, policies aimed at curbing further spread of carbapenem resistance in households of patients who are found to have CRE are emphasized. Patients with CRE and their respective households should be thoroughly investigated to delineate the mechanisms of

resistance of carbapenems, and not only carbapenemases, but also all other mechanisms, including efflux pumps and porins.

5. Study Limitation

The study did not study all genetic variants of the carbapenemase genes but studied the most prevalent genes associated with carbapenem resistance. Randomized selection of humans, livestock and environment might have reduced the chances of obtaining CRE, but reduced selection bias.

6. Conclusion

The high prevalence of carbapenem resistance in livestock and environmental samples suggests that efforts to curb AMR must extend beyond clinical settings to encompass agricultural and environmental interventions. The identification of matching carbapenemase genes between UTI patients and household isolates highlights the urgent need for targeted surveillance and infection control strategies to mitigate the spread of resistant pathogens. These findings underscore the complexity of AMR transmission in household settings, particularly in the context of One Health interactions between humans, animals, and the environment.

7. Recommendation

One Health epidemiological study designs is necessary for explaining the principal routes and dynamics of the spread of AMR bacteria between humans, animals and the environment, for example, whole genome studies to investigate transmission dynamics at the hospital-community interface, identifying genetic links between clinical and environmental isolates. This knowledge is an important prerequisite to developing effective public health measures to tackle the disturbing AMR situation. Furthermore, strengthening policies on antimicrobial use in livestock and humans, improving sanitation, and raising public awareness about AMR risks will further help mitigate the spread of resistance.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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