American Journal of BioScience
2025, Vol. 13, No. 6, pp. 210–217
https://doi.org/10.11648/j.ajbio.20251306.13

Research Article

Resistance to Beta-lactams by Klebsiella Co-Producing Resistance Enzymes at the Pietro Annigoni Research Centre (CERBA)

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Abstract

The misuse of antibiotics promotes the development of multi-resistance in bacteria both biochemically and genetically, as well as its ability to transmit to other bacteria. These microorganisms are capable of simultaneously producing resistance enzymes through resistance mechanisms that allow them to resist various classes of antibiotics at the same time and thus become multi-resistant. Our objective was to study resistance to beta-lactams by Klebsiella co-producing resistance enzymes isolated at the Pietro Annigoni Research Center (CERBA). The isolation and purification of bacterial strains isolated from stools, vaginal swabs and urine of internal and external patients of CERBA, were carried out on selective media and Muller Hinton (MH). The antibiogram was carried out according to the disk diffusion method. The API 20E biochemical gallery (Bio Mérieux, France) was used for the identification of enterobacteria and the bla_{NDM}, bla_{SHV} and bla_{TOHO} genes were detected by conventional Polymerase Chain Reaction (PCR). A total of one hundred and twenty-two (122) strains of Gram-negative bacilli were collected and identified. Among them we have 23.77% (29/122) strains of *Klebsiella* including 86.21% isolated from urine, 6.90% isolated from stool and 6.90% isolated from vaginal swab. The antibiogram showed that all 29 *Klebsiella strains* were resistant to at least one of the beta-lactams studied, including 93.10% resistance to amoxicillin plus clavulanic acid, 37.93% resistance to ceftazidime, 27.59% resistance to ceftriaxone, 44.83% to cefotaxime, 20.70% to imipenem and 24.14% to aztreonam. Among the 29 *Klebsiella* strains 24.13% were non-carriers of resistance genes and 76.86% of the strains were carriers of at least one of the resistance genes. However, 62.06% of *Klebsiella* strains harbor the bla $_{SHV}$ gene, 41.38% of strains harbored bla_{NDM} versus 10.34% of strains carrying the *bla* $_{TOHO}$ gene. Among the *Klebsiella* strains, 37.93% of the strains had coexistences of the genes, bla_{SHV} + bla_{NDM}, bla_{SHV} + bla_{TOHO} and bla_{TOHO} + bla_{NDM} respectively. However, the bla_{SHV} gene was most common in Klebsiella (*Klebsiella sp* and *Klebsiella pneumoniae), followed by the bla* $_{NDM}$ gene *and the bla* $_{TOHO}$ gene. This study has highlighted the multi-resistance of *Klebsiella strains* co-producing ESBLs of *the* bla_{NDM}, bla_{SHV} and bla_{TOHO} type. The co-production of genes by certain strains, particularly *Klebsiella* strains, requires the development of new strategies in scientific research in order to find effective therapeutic solutions to destroy multi-resistant bacteria.

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Received: 10 August 2025; **Accepted:** 20 August 2025; **Published:** 9 December 2025

Keywords

Multi-Resistance, Antibiotic, Enterobacteria, *Klebsiella*, *Bla* $_{NDM}$, *Bla* $_{SHV}$, *Bla* $_{TOHO}$, Co-Production

1. Introduction

Klebsiella species are Gram-negative, rod-shaped, non-motile, and usually encapsulated bacteria belonging to the family *Enterobacteriaceae* [1].

Klebsiella that are pathogenic in humans include the following: *K. pneumoniae;* K. *sp; K. oxytoca; K. granulomatis; K. variicola;* and *K. singaporensis. K. planticola, K. terrigena* and *K. orinthinolytica* [1].

Klebsiella species are important common pathogens, causing nosocomial pneumonia (7-14% of all cases), sepsis (4-15%), urinary tract infections (6-17%), wound infections (2-4%), intensive care unit (ICU) infections (4-17%), and neonatal sepsis (3-20%) [1]. *Some* Klebsiella strains, such as those producing carbapenemase (e.g., KPC - *Klebsiella* pneumoniae carbapenemase), can degrade carbapenem antibiotics (considered drugs of last resort). This makes these infections particularly difficult to treat. *Klebsiella* strains exhibit resistance to penicillins, particularly ampicillin and carbenicillin. Given that an increasing number of *Klebsiella strains* appear to produce extended-spectrum cephalosporinases, carbapenemases, and beta-lactamases, *Klebsiella resistance* to current antibiotics appears to be increasing.

antibiotics remain the most widely used class of antibiotics worldwide. This is primarily due to the number of available products covering a relatively broad bacterial spectrum. The mechanism of defense the more widespread And the more developed by bacteria against effects of These beta-lactams are produced by enzymes (beta-lactamases) that chemically modify the beta-lactams to make them inactive [2].

Extended spectrum beta-lactamases (ESBLs) are mainly produced by Enterobacteriaceae, particularly *Klebsiella pneumoniae* [3].

ESBL-carrying bacteria can also acquire and most often exhibit additional resistance to other classes of antibiotics such as monobactams (aztreonam), quinolones, tetracyclines, aminoglycosides [4].

Our study focused on beta-lactam resistance in *Klebsiella* co-producing resistance enzymes at the Pietro Annigoni Research Centre (CERBA).

2. Materials and Methods

2.1. Framework of the Study

Our isolates were collected at the Pietro Annigoni Biomolecular Research Center (CERBA) in Ouagadougou. CERBA is a biomolecular research center located in Sector 51, District 11, Ouagadougou.

In-depth studies on the various isolates collected; such as identification, antibiotic sensitivity testing, and the search for ESBL genes using conventional PCR techniques were carried out at the Laboratory of Molecular Biology and Genetics (LABIOGENE). LABIOGENE is a research laboratory attached to the Doctoral School of Sciences and Technologies (ED/ST) of Joseph KI-ZERBO University.

2.1.1. Type of Study

This is a cross-sectional study of various ESBL-producing bacterial strains isolated at the Pietro Annigoni Biomolecular Research Center (CERBA) from March 1, 2024 to June 1, 2024.

2.1.2. Sampling

The samples selected were those received at the CERBA laboratory for bacteriological examinations and which, after analysis, detected the presence of enterobacteria. Pus, urine, stool, vaginal and vulvar samples were included in our study. The examination reports that were compliant included, among other things, the identity of the patient, the nature of the sample, the examination requested by the prescriber, the consultation and/or hospitalization service.

Samples collected in non-sterile equipment or suspected of any external soiling were excluded, as were samples collected the day before or days before for stool and urine samples.

2.2. Isolation and Identification of Gram-Negative Bacilli

Bacterial isolation was performed using selective media. Urine and stool samples were inoculated onto standard media (URI select, CLED, BCP, Hektoen, SS) and incubated for 24 h at 37 ℃. Biochemical tests were performed on suspect colonies using Kligler Hajna, mannitol-mobility, Simmons citrate, urea-indole and peptone water media.

The API 20E biochemical gallery (BioMérieux, France) was then used for the identification of Enterobacteriaceae according to the manufacturer's recommendations. The selected colonies were purified by culture at 37 ℃ for 24 h on Muller-Hinton medium and used for antibiogram and DNA extraction.

2.3. Antibiotic Sensitivity Test

The Mueller-Hinton (MH) agar diffusion method was used

for the antibiotic susceptibility test of strains according to the recommendations of the Antibiogram Committee of the French Society of Microbiology [5]. The i noculum Bacterial suspension was prepared by placing a pure colony in 5 ml of physiological saline. The suspension was then homogenized and calibrated to 0.5 McFarlane and then inoculated by tight streaks onto MH agar. The antibiotics were placed at a distance of approximately 20 mm from each other, at a rate of 4 discs per Petri dish. The different diameters of the inhibition zones obtained around the antibiotic discs were measured after 24 h of incubation at 37 ℃ and compared to the CA-SFM standards to determine the sensitive (S), intermediate (I) and resistant (R) phenotypes. The antibiotics Ceftriaxone (CRO), Ceftazidime (CAZ), Cefotaxime (CTX), Imipenem (IMP), Amoxicillin + Clavulanic Acid (AMC) and Aztreonam (AT) were tested.

2.4. Extraction of Bacterial DNA

An isolated colony was picked from MH Petri dishes and suspended in 200 µl of distilled water in Eppendorf tubes. The tubes were then soaked in a 100 ℃ water bath for 15 minutes to release the genetic material from the bacteria. After centrifugation for 10 min at 12000 rpm, the supernatants containing the released DNA were transferred to new Eppendorf tubes. The quantity and purity of the DNA extracts were determined by spectrophotometry using the NanoDrop. The DNA was stored at -80 ℃ until PCR analyses.

2.5. PCR Amplification

bla $_{TOHO}$, *bla* $_{SHV}$, *bla* $_{NDM}$ genes were detected by conventional PCR using the specific primer pairs presented in (Table 1). The PCR was carried out in a 20 µL reaction mixture including 4 µL of 5X Firepol Master Mix; 0.5 µL of sense and antisense primer, 14 µL of PCR water and 1 µL of DNA extract from each strain. Amplification was carried out using the GeneAmp PCR System 9700 thermal cycler (Applied Biosystems, California, USA) according to the following program (Table 2): a first denaturation step at 96 ℃ for 5 minutes, followed by 30 cycles for *bla* $_{NDM}$ or 35 cycles for *bla* $_{TOHO}$ and *bla* $_{SHV}$ each including denaturation at 96 ℃ for 30 seconds for *bla* $_{NDM}$ and 1 minute for *bla* $_{TOHO}$ and *bla* $_{SHV}$, hybridization at 62 ℃ for 30 seconds for *bla* $_{NDM}$, 50 ℃ and 60 ℃ for 1 min respectively for *bla* $_{TOHO}$ and *bla* $_{SHV}$ and an elongation at 72 ℃ for 30 seconds for *bla* $_{NDM}$ or 1 mm for *bla* $_{TOHO}$ and *bla* $_{SHV}$. Finally, a final elongation step was carried out at 72 ℃ for 7 minutes for *bla* $_{NDM}$ or 10 minutes for *bla* $_{TOHO}$ and *bla* $_{SHV}$.

Table 1. *Primer sequence for bla* $_{SHV}$, *bla* $_{TOHO}$ *genes and blah*$_{NDM}$.

Genoa	Primers	Sequences (5'- 3')	Sizes	References
Bla $_{SHV}$	Forward	ATG-CGT-TAT-ATT-CGC-CTG-TG	875 bp	(Pagani et al., 2003)
	Reverse	TTA-GCG-TTG-CCA-GTG-CTC		
Bla $_{TOHO}$	Forward	ATGTGCAGTACCAGTAA	876 bp	(Laurent et al., 1999)
	Reverse	TAGGTCACCAGAACCAG		
Bla $_{NDM}$	Forward	CCATGCGGGCCGTATGAGTGATT	500 bp	(Mc Gann et al., 2012)
	Reverse	AAGCTGAGCACGCATTAGCCG		

Table 2. *PCR program.*

Genoa	Condition / duration		
Settings	***Bla*** $_{TOHO}$	***Bla*** $_{SHV}$	**Bla** $_{NDM}$
Initial denaturation	96°C / 5 min	96°C / 5 min	96°C / 5 min
Denaturation	96°C / 1 min	96°C / 1 min	96°C / 30s
Hybridization	50°C / 1 min	60°C / 1 min	62°C / 30s
Elongation	72°C / 1 min	72°C / 1 min	72°C / 30s
Final elongation	72°C / 10 min	72°C /10 min	72°C /7 min
Number of cycles	35	35	30

2.6. Agarose Gel Electrophoresis

PCR-amplified DNA fragments were separated by electrophoresis on a 1% agarose gel prepared in a 1X tris base-borate-EDTA solution containing 0.5 µg/mL ethidium bromide. Migration was performed at 110 mV and 850 mA for 30 minutes. A 100 bp molecular weight marker was used to determine the size of the amplicons visualized under UV light using the GeneFlash device (Syngene, Bio-Imaging, UK).

3. Results

3.1. Distribution of Strains According to Samples

We obtained a total of 23.77% (29/122) of strains *Klebsiella*, of which 86.21% of strains were found in urine, 6.9% of strains were found in feces, and 6.9% of strains were found in vaginal swabs. However, many *Klebsiella strains* were isolated from urine (Figure 1).

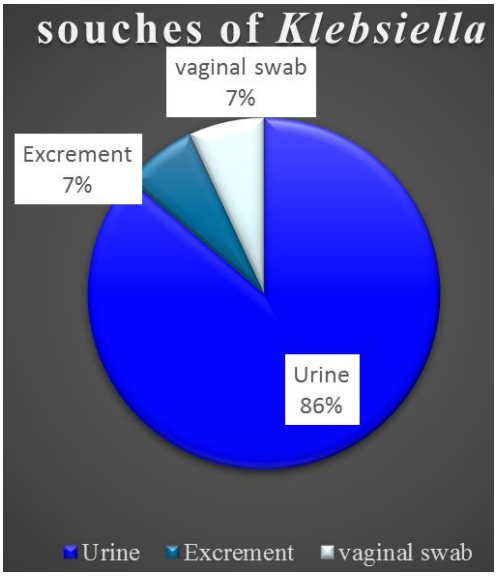
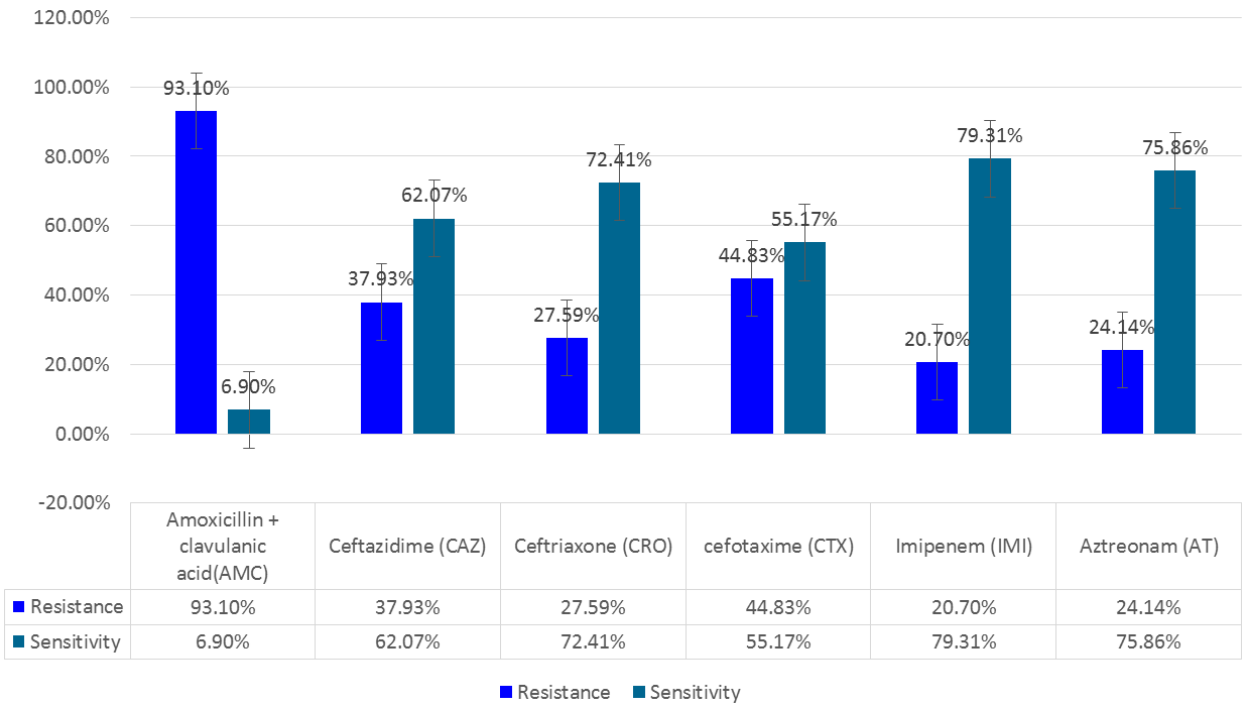


Figure 1. *Distribution of Klebsiella strains according to samples.*

3.2. Resistance of Bacterial Strains to Antibiotics



	Amoxicillin + clavulanic acid(AMC)	Ceftazidime (CAZ)	Ceftriaxone (CRO)	cefotaxime (CTX)	Imipenem (IMI)	Aztreonam (AT)
Resistance	93.10%	37.93%	27.59%	44.83%	20.70%	24.14%
Sensitivity	6.90%	62.07%	72.41%	55.17%	79.31%	75.86%

Figure 2. *Resistance and sensitivity profile of Klebsiella strains.*

The antibiogram performed on each strain of *Klebsiella* allowed to study their resistance profiles with respect to the beta-lactams tested. The results of the study on the resistance of the 29 isolates of *Klebsiella* to different antibiotics show that 93.10% of the strains were resistant to Amoxicillin + clavulanic acid, 37.93% were resistant to Ceftazidime, 27.59% were resistant to Ceftriaxone, 44.83% were resistant to Cefotaxime, 20.70% were resistant to Imipenem, and 24.14% were resistant to Aztreonam (Figure 2).

3.3. Molecular Characterization of Resistance Genes

Classical PCR detection of *bla* SHV, *bla* NDM and *bla* TOHO genes showed that 62.06% of strains harbored the *bla* SHV gene, 41.38% of strains harbored the *bla* NDM gene against 10.34% of strains carrying the *bla* TOHO gene. The *bla* SHV gene was the most frequent in *Klebsiella* (*Klebsiella sp* and *Klebsiella pneumoniae)* (Figure 3).

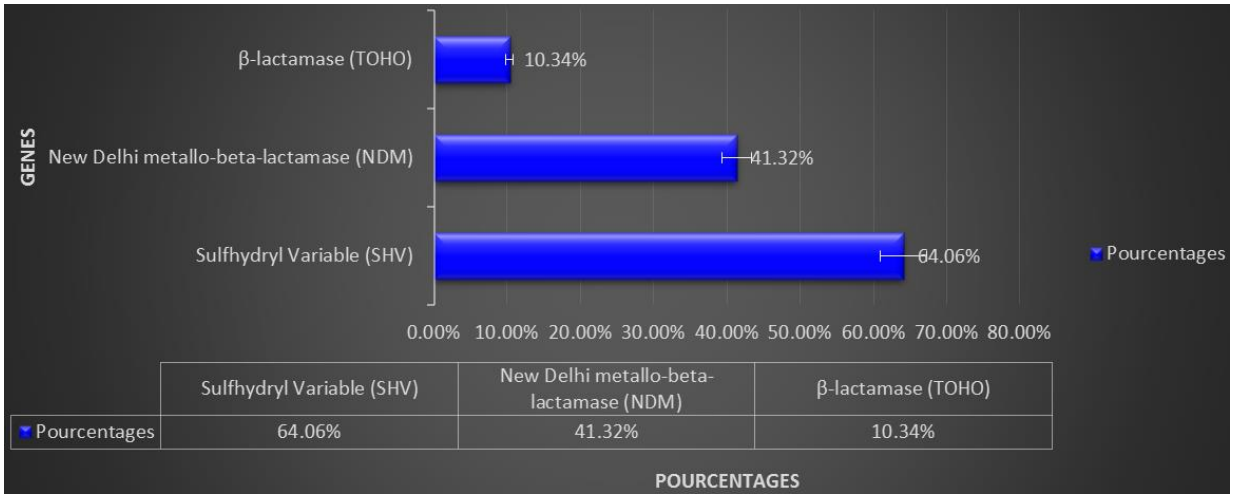


Figure 3. *Distribution of genes in Klebsiella strains (Here, the shv gene was found much more frequently in Klebsiella strains, at 64.06%).*

3.4. Distribution of Genes According to Samples

Strains carrying resistance genes were found much more frequently in urine, with 64% of strains carrying the SHV gene, 40% of strains carrying the NDM gene and 12% of strains carrying the TOHO gene (Figure 4).

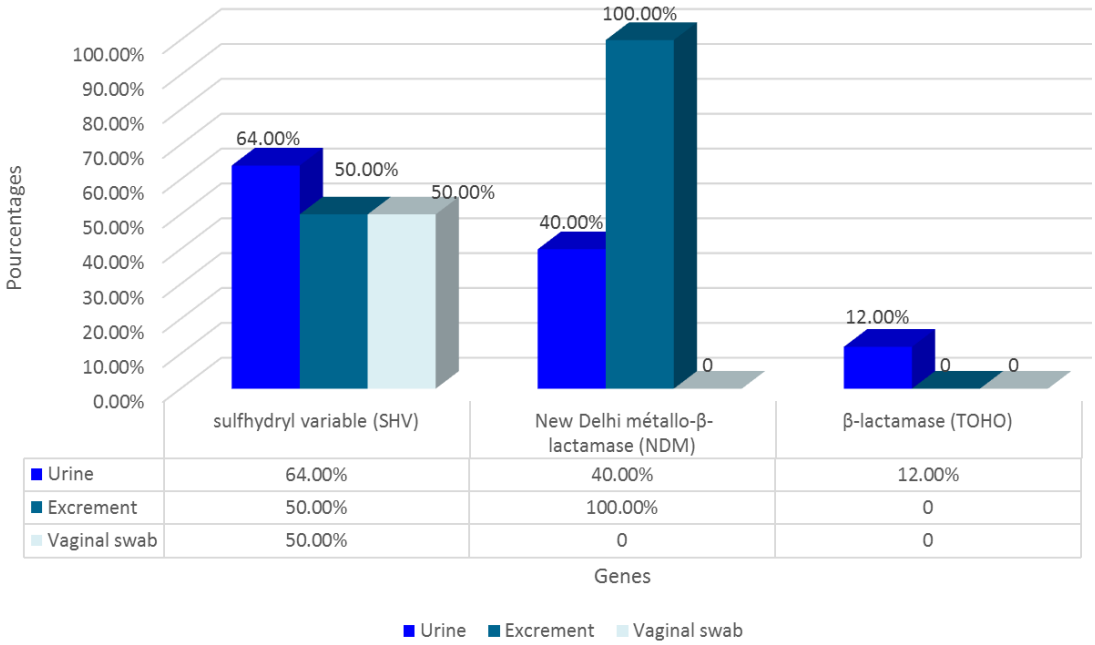


Figure 4. *Distribution of genes according to samples (Strains carrying resistance genes were found much more frequently in urine, with 64% of strains carrying the SHV gene, 40% of strains carrying the NDM gene and 12% of strains carrying the TOHO gene, the differences are statistically significant in these three groups).*

3.5. Coexistence of Resistance Genes

PCR analysis also showed the *bla* $_{SHV}$ genes and *bla* $_{NDM}$ which were simultaneously found in 72.72% of the isolates. As for the double carriage of *bla* $_{TOHO}$ genes and *bla* $_{SHV}$, it was observed in 18.18% of isolates against 9.09% with double carriage of *bla* $_{TOHO}$ genes and *bla* $_{NDM}$ observed in strains (Figure 5).

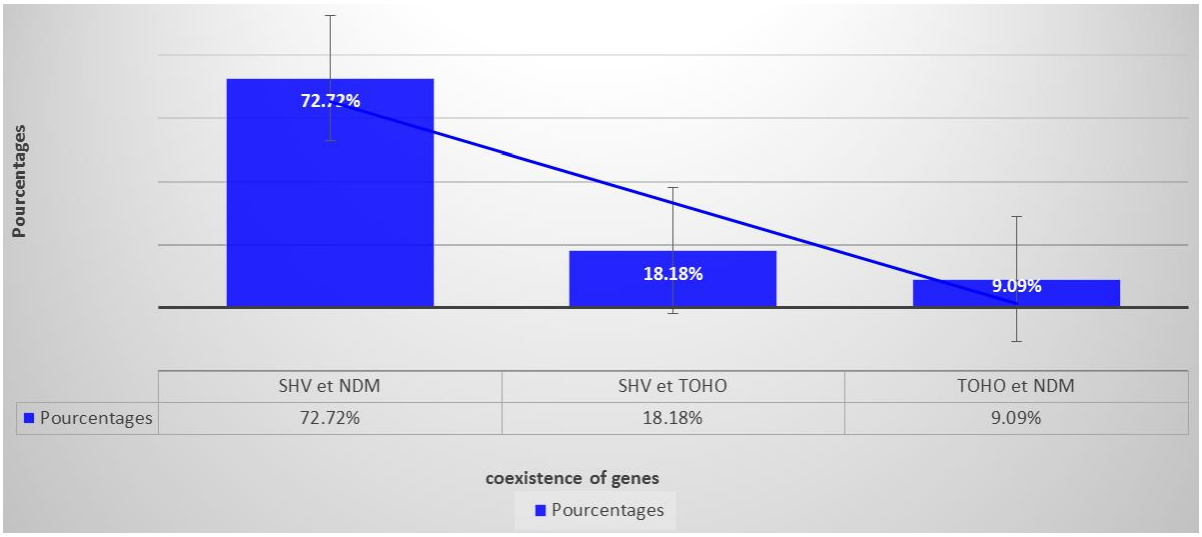


Figure 5. *Coexistence of genes depending on bacterial strains.*

4. Discussion

Klebsiella bacteria are equipped with plasmids, a fragment of DNA located outside the bacteria's chromosomes, which produce enzymes that attack antibiotics. These enzymes, beta-lactamases, have the ability to inactivate or destroy molecules that normally attack the bacterial cell wall, beta-lactams.

This war is not turning in favor of antibiotics since Klebsiella have been developing enzymes resistant to different types of beta-lactams for 30 years. The majority of strains were resistant to amoxicillin, a semi-synthetic penicillin, in combination with clavulanic acid which is a β-lactamase inhibitor [6]. The behavior of Klebsiella towards beta-lactamase inhibitors reports: 93.10% for amoxicillin-clavulanic acid (AMC) in our study, these results are respectively comparable to those of 98.7% at BATJECK in Rabat.

Resistance is certainly very high but not far from that obtained against this same antibiotic by Monzer Hamze in France, including 100% for AMC. Klebsiellae exhibit natural resistance to aminopenicillins by production of "a low-level penicillinase", corresponding to the wild-type phenotype [7]. This tendency towards resistance to aminopenicillins could be explained by the fact that the strains secrete broad-spectrum β-lactamases and high-level penicillinases.

Furthermore, the production of chromosomal penicillinase of type SHV1 means that these strains are naturally resistant to aminopenicillins.

The frequencies of resistance of *Klebsiella* to 3rd cephalosporins reported by our study were: 37.93% for Ceftazidime, 27.59% for Ceftriaxone, 44.83% for Cefotaxime. Our results are lower than those of BATJECK, with a resistance of 99.3% for cefotaxime (CTX); 93.3% for ceftriaxone (CRO); 94.9% for ceftazidime (CAZ). BATJECK's results in Rabat are practically similar to those obtained by Monzer Hamze in France.

On the other hand, Nawal found a resistance rate equal to 33.87% [7], which is lower than the rate found in our results.

Imipenem has a strong activity against isolated Klebsiella strains with a resistance rate of 20.69%. Furthermore, Nawal found a resistance rate (8.06%) which is lower than that found in our study, Nawal's result is equivalent to that reported by [8] where no resistance to imipenem was observed.

Drug pressure in hospitals, poor treatment control, and the overuse of antibiotics, sometimes without medical prescription, are the main causes of the emergence and spread of multidrug-resistant pathogenic Enterobacteriaceae. In addition, acquired resistance has a high dissemination power due to its plasmid determinism. The resistance rate of *Klebsiella* to Aztreonam (monobactams) was 24.14%. Aztreonam resistance could be better explained by the presence of other resistance mechanisms, including AmpC β-lactamase or a combination of permeability defects and efflux mechanisms.

In the 1980s–1990s, the main resistance genes encoding extended-spectrum ß-lactamase enzymes associated with *K. pneumoniae* were derived from TEM and SHV ß-lactamases. A change in this global distribution is observed. ESBLs of the CTX-M type, and in particular CTX-M-15, initially associ-

ated with community-acquired *Escherichia coli* infections, are now increasingly isolated from *K. pneumoniae* [9].

Bacteria use various resistance mechanisms such as inactivation of antibiotics by enzymes. The *bla* $_{SHV}$ gene 62.06% was the most common in *Klebsiella* (*Klebsiella sp* and *Klebsiella pneumoniae), followed by the bla*$_{NDM}$ gene *41.38% and the bla* $_{TOHO}$ gene 10.34%.

SHV-type beta-lactamases, including SHV-1 and at least twenty-three variants, generally exhibit extended-spectrum activity against newer broad-spectrum cephalosporins. Their likely ancestor is a chromosomal penicillinase from *Klebsiella pneumoniae*. SHV enzymes belong to the molecular class A of serine β-lactamases and share high functional and structural similarity with TEM β-lactamases [10].

Bla $_{SHV}$ -1 has spread, via plasmids, to virtually all species of enterobacteria but is most commonly found in *Klebsiella pneumoniae*.

New Delhi metallo-β-lactamase-1 (NDM-1) is an enzyme capable of hydrolyzing most β-lactam antibiotics. The *bla* $_{NDM1}$ gene is located on plasmids harboring multiple resistance determinants, thus conferring widespread drug resistance, leaving little to no therapeutic options [11]. Molecular characterization of NDM-type metallo-β-lactamases by PCR revealed that 41.38% carried the *bla* $_{NDM}$ gene, this result is higher than that of Ouattara AK et *al.* With 10.00% (1/10) of the strains that carried the *bla* $_{NDM}$ gene [12].

K. pneumoniae strains has been reported in several countries [12]. The emergence of clinical strains of *Klebsiella pneumoniae* Co-producing KPC-2 and NDM-1 and resistant to carbapenems has also been reported in the literature [13] suggesting continued surveillance efforts and the imperative need for new therapeutic solutions to combat the expansion of multidrug resistance [12]. However, the utility of carbapenems is seriously threatened by the emergence of cabapenemases, including the newly characterized NDM1.

In a previous study in Burkina Faso, molecular characterization of 39 bacterial strains by PCR showed TOHO-type ESBLs in 25 isolates, 13 of which were *Klebsiella pneumoniae* [14]. On the other hand, our study found 3 *Klebsiella strains that harbored the bla* $_{TOHO}$ gene. TOHO1 was an ESBL that achieved effective activity not only against penicillins but also against third-generation cephalosporins [1].

The coexistence of *bla* $_{TOHO}$ and *bla* $_{SHV}$ genes was found in 18.18% of *Klebsiella strains.* M ètuor-Dabir é et *al.* reported the coexistence of *bla* $_{TOHO}$ and *bla* $_{BES}$ genes in *Klebsiella pneumoniae* (21.9%) at Saint Camille Hospital in Ouagadougou in 2019 [15]. The coexistence of *bla* $_{SHV}$ and *bla* $_{NDM}$ genes as well as *bla* $_{TOHO}$ and *bla* $_{NDM}$ was found in 72.72% and 9.09% of the isolates in our study. A recent study in Egypt reported a high incidence of multidrug resistance with the emergence of the coexistence of *bla* $_{NDM-1}$ (70.0%) and *bla* $_{OXA-48}$ (52.0%) genes in carbapenem-resistant *K. pneumoniae* isolates [16]. This suggests that these genes are carried by the bacterial chromosome and/or plasmids promoting rapid spread both vertically and horizontally to bacteria of other species.

5. Conclusion

Multi-resistance of *Klebsiella strains* through co-production of resistance enzymes represents an enormous danger to public health, leading to therapeutic failures and the death of millions of people worldwide. This study identified *bla*$_{NDM}$, *bla*$_{SHV}$ and *bla*$_{TOHO}$ genes in ESBL co-producing *Klebsiella* strains isolated mainly from urine. The co-production of genes in the *Klebsiella* strain suggests a rapid spread of multi-resistance. This requires rapid development of new effective therapeutic combinations or solutions at the local level to prevent and combat bacterial multi-resistance in Burkina Faso.

Abbreviations

CERBA	Pietro Annigoni Research Center
MH	Muller Hinton
PCR	Polymerase Chain Reaction
SHV	Sulfhydryl Variable
NDM	New Delhi m étallo-b êta-lactamase
KPC	*Klebsiella pneumoniae* Co-Producing KPC
ESBLs	Extended Spectrum Beta-Lactamases
CLED	Cystine Lactose Electrolyte Deficient
BCP	BromoCr ésol Pourpre
SS	Salmonella-Shigella
DNA	Deoxyribonucleic Acid
CRO	Ceftriaxone
CAZ	Ceftazidime
CTX	Cefotaxime
IMP	Imipenem
AMC	Amoxicillin + Clavulanic Acid
AT	Aztreonam (AT)
TEM	Temoneira
EUCAST/ CASFM	European Committee on Antimicrobial Susceptibility Testing / Antibiogram Committee of the French Society of Microbiology

Author Contributions

Rhaina Olivia Badini: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – original draft

Amana M ètuor Dabir é: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Validation, Visualization

Rabi étou Niki éma: Formal Analysis, Investigation, Methodology

Bambara Eliada Lionel: Formal Analysis, Investigation, Methodology

Abdoul Karim Ouattara: Formal Analysis, Investigation, Methodology, Supervision, Visualization

Th éodora Mahouk ènd è Zohoncon: Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Validation

Jacques Simporé: Conceptualization, Investigation, Supervision

Conflicts of Interest

The authors declare no conflicts of interest.

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