

Trends in Antibiotic Resistance in Uropathogens at Mbarara Regional Referral Hospital (2019–2024): A Retrospective Study

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Background: Urinary tract infections (UTIs) are among the most common bacterial infections globally, with significant morbidity and rising antimicrobial resistance (AMR). This study aimed to investigate the prevalence of uropathogens and their antimicrobial resistance patterns at Mbarara Regional Referral Hospital (MRRH) in Uganda.

Methods: A retrospective analysis of 939 urine culture- positive records from January 2019 to December 2024 was conducted. Isolates were identified, and antimicrobial susceptibility testing was performed using the disc diffusion method. Data on patient demographics, uropathogen distribution, and resistance trends of organisms with greater than or equal to 25 isolates were analyzed using Python-based statistical methods, including Chi-square and Mann–Kendall trend analysis.

Results: *Escherichia coli* was the most isolated pathogen, accounting for 428 isolates (45.6%), followed by *Klebsiella* spp. with 385 isolates (41.0%) while *Citrobacter* spp. and *Enterococcus* spp. contributed 42 (4.5%) and 26 (2.8%) isolates, respectively. The cases were dominated by females (69.0%). There was an extremely high resistance to commonly prescribed antibiotics such as ampicillin (91.3%) and sulfamethoxazole (91.6%). Carbapenem resistance was overall low ($\leq 10.3\%$) but also had a statistically significant rising trend in *Klebsiella* spp. ($p = 0.0415$). Multidrug resistance (MDR) was present in 56.9% of the isolates, predominantly in *Escherichia coli* and *Klebsiella* spp. and 70% of the MDR isolates were ESBL producers.

Conclusion: This study underscores the urgent need for routine culture and sensitivity, and updated treatment guidelines to address the rising AMR among uropathogens in Uganda.

Keywords: antibiotic resistance, multidrug resistance, urinary tract infections, uropathogens

Introduction

Urinary tract infections (UTIs) refer to the infection of the bladder and kidneys having clinical manifestations including cystitis, pyelonephritis, prostatitis, urosepsis, and catheter-associated UTIs.¹ These infections are clinically divided into complicated, uncomplicated, and acute pyelonephritis.² Urinary tract infections are among the most prevalent bacterial infections affecting over 14 million cases reported annually posing significant health and economic burden worldwide.³ Women are disproportionately affected due to their anatomical and physiological features, with 27–48% experiencing recurrent infections.^{4,5}

In Uganda, the national prevalence of UTIs is approximately 24.92%, with higher rates in the Western region including Mbarara District, and the Northern region where the prevalence has reached up to 71.94% and this has been attributed to demographic factors such as age, gender, hygiene practices, and comorbidities, such as diabetes and catheter use.⁶

Gram-negative bacteria, particularly *Escherichia coli*, are the leading uropathogens responsible for UTIs. Other significant pathogens include *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Enterococcus faecalis*.⁶ However, uropathogens have developed resistance to routinely used antibiotics⁷ such as penicillins, cephalosporins and fluoroquinolones, and tetracyclines

from 10% to 20%^{8,9} in 2014 to approximately 44.6–95.7% in 2021^{10,11} posing a challenge for empirical treatment of UTIs. Furthermore, self-treatment and emerging antimicrobial-resistant patterns play an important role in controlling UTIs in Uganda.^{10,12}

Antibiotic resistance is a consequence of inappropriate broad-spectrum antibiotic use, inadequate infection control methods, and environmental contamination by pharmaceutical waste.^{5,10,13}

Regardless of the growing threat of antimicrobial resistance, there is scant local data to guide empiric therapy in Uganda. The specific objectives were to describe the frequency and distribution of isolated uropathogens by specimen type and patient demographic characteristics, and to evaluate temporal trends in antimicrobial resistance, including the prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) phenotypes among these isolates.

Therefore, this study aimed to analyze the prevalence of common uropathogens and their antimicrobial resistance patterns among patients at Mbarara Regional Referral Hospital (MRRH).

Methods and Materials

Study Design and Setting

The retrospective study was conducted at Mbarara Regional Referral Hospital (MRRH) – Microbiology Department, a tertiary-level teaching hospital in south-western Uganda. MRRH has over 600 inpatient beds and is affiliated with Mbarara University of Science and Technology (MUST), the main campus for teaching undergraduate and postgraduate health sciences programs. The clinic has departments for internal medicine, pediatrics, surgery, obstetrics, and diagnostic services. The microbiology lab is staffed with trained microbiologists and can perform routine bacterial culture, biochemical identification, and antimicrobial susceptibility testing (AST). Culture data from 1st January 2019 to 31st March 2024 were retrieved from WHONET, a data platform supported by WHO and used globally for surveillance of antimicrobial resistance (AMR).

Inclusion and Exclusion Criteria

Urine specimens were encompassed if they were culture positive and either obtained via midstream urine (MSU) or catheterization and contained a bacterial load of $\geq 10^5$ colony-forming units per milliliter (CFU/mL). Only information with complete demographic data (age, sex), valid organism identification, and AST profiles were included. To avoid duplication due to repeated infections or prolonged time of stay, only a single patient isolate per patient was used. Excluded were patient records with inadequate demographic data, missing AST values, or uncertain species identification. *Staphylococcus aureus* and other potential skin flora were also excluded when isolated from non-sterile samples due to their established role as contaminants of urine samples without catheters.^{14–16}

Culture Methods and Identification

The cultures for all urine samples were processed within a two-hour period of sample collection. With the assistance of a 0.01 mL calibrated sterile loop, each sample was inoculated on MacConkey agar, blood agar, and chocolate agar (HiMedia, India). Cystine-lactose-electrolyte-deficient (CLED) agar was used occasionally to suppress swarming by *Proteus* species. Plates were incubated aerobically at 37°C for 24 hours. Significant bacteriuria was signaled by growth $\geq 10^5$ CFU/mL, as per WHO GLASS and CLSI recommendations.¹⁷ Identification of the isolate started with Gram staining and colony morphology examination. Gram-negative pathogens were identified further by oxidase, SIM (sulfur, indole, motility), triple sugar iron (TSI), and citrate tests. Gram-positive isolates were identified by catalase and coagulase tests.¹⁴

Antimicrobial Susceptibility Testing

AST was carried out by Kirby–Bauer disc diffusion method on Mueller–Hinton agar (HiMedia, India). Results were interpreted using CLSI M100 (33rd edition, 2023) guidelines.¹⁷ Antibiotics tested reflected empirically prescribed options in Uganda and included beta-lactams (ampicillin, amoxicillin-clavulanate, ceftriaxone), aminoglycosides (gentamicin), fluoroquinolones (ciprofloxacin, ofloxacin), sulfonamides (sulfamethoxazole), nitrofurans (nitrofurantoin), carbapenems (imipenem, meropenem), and erythromycin and chloramphenicol. Conservative

intermediate susceptibility interpretation was considered resistant, as outlined by WHO guidelines. Quality control was ensured by testing for standard reference strains (*Escherichia coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *S. aureus* ATCC 25923) on a weekly basis to ensure disc potency and medium performance.¹⁷

Isolate Selection for Analysis

Isolates were grouped into three categories including true uropathogens, conditional pathogens (often isolated but not necessarily pathogenic), and probable contaminants.^{14,18} Only true uropathogens with ≥ 25 isolates were preserved for future AMR and multi-drug resistance (MDR) testing to ensure statistical power. They included *Escherichia coli*, *Klebsiella* spp., *Klebsiella pneumoniae*, *Citrobacter* spp., and *Enterococcus* spp., microorganisms known to be the most prevalent etiologic urinary tract infection (UTI) pathogens worldwide.^{15–17,19} Although *S. aureus* was repeatedly isolated, it was excluded on microbiological and epidemiological grounds, because its recovery from non-catheterized urine is typically indicative of contamination rather than infection.^{14–17,19}

Classification of Resistance

Resistance was defined as non-susceptibility to one or more agents. Multidrug resistance (MDR) was defined as resistance to greater than one drug in three antimicrobial classes by international consensus.²⁰ A graded classification system was also used: R0 = no resistance, R1 = one class, R2 = two classes, R3 = three classes, and R4 = four or more classes of resistance.²¹ This stratification allowed a gradient interpretation of resistance severity and was used in descriptive tables. Phenotypic resistance mechanisms were inferred where possible: isolates resistant to third-generation cephalosporins were classified as presumptive ESBL producers; carbapenem resistance suggested carbapenemase production; and others were labeled classical MDR in the absence of a known mechanism.

Statistical Analysis

Data were cleaned and manipulated using Python 3.8 inside Google Colab. Cleaning and transformation were done with the pandas and numpy libraries. Chi-square tests were used to investigate association between categorical variables with the scipy.stats module, and the significance threshold was taken as $p < 0.05$. To evaluate resistance patterns over time, quarterly resistance ratios were calculated for each organism-antibiotic pair. Time trend analysis was performed using the Mann–Kendall non-parametric test of the pymannkendall package, a method used to identify monotonic trends in non-parametric microbiological surveillance data.^{22–25} A 3-quarter rolling average was applied to smooth fluctuations, and a p -value ≤ 0.05 was considered statistically significant.

Results

Patient Demographics and Dataset Overview

The data set comprised 939 unique patient records each representing a culture-positive urine sample. The average age of all patient records is 40 years old, with an 18-year standard deviation. The recorded age ranges from newborns (0 years) to 105 years. The median age is 38 years old, while the 25th percentile of the population is 27 years of age or younger. With an IQR of 25 years, the 75th percentile indicates that 75% of the subjects are 52 years of age or younger. There are 648 (69.0%) females in this dataset, and 291 (31.0%) male, giving a ratio of 1:0.4.

Uropathogen Distribution

Among the 939 isolates, *Escherichia coli* was the most isolated pathogen, accounting for 428 isolates (45.6%), followed by *Klebsiella* spp. with 385 isolates (41.0%). *Klebsiella pneumoniae* was identified in 58 isolates (6.2%) while *Citrobacter* spp. and *Enterococcus* spp. contributed 42 (4.5%) and 26 (2.8%) isolates, respectively.

Distribution of Uropathogens by Gender

Female patients were 648 (69.0%) and 291 (31.0%) to males. *Escherichia coli* was the most frequent isolate, being recovered in 303 out of 428 female-related isolates (70.8%) and 125 out of 428 (29.2%) from males as shown in Figure 1.

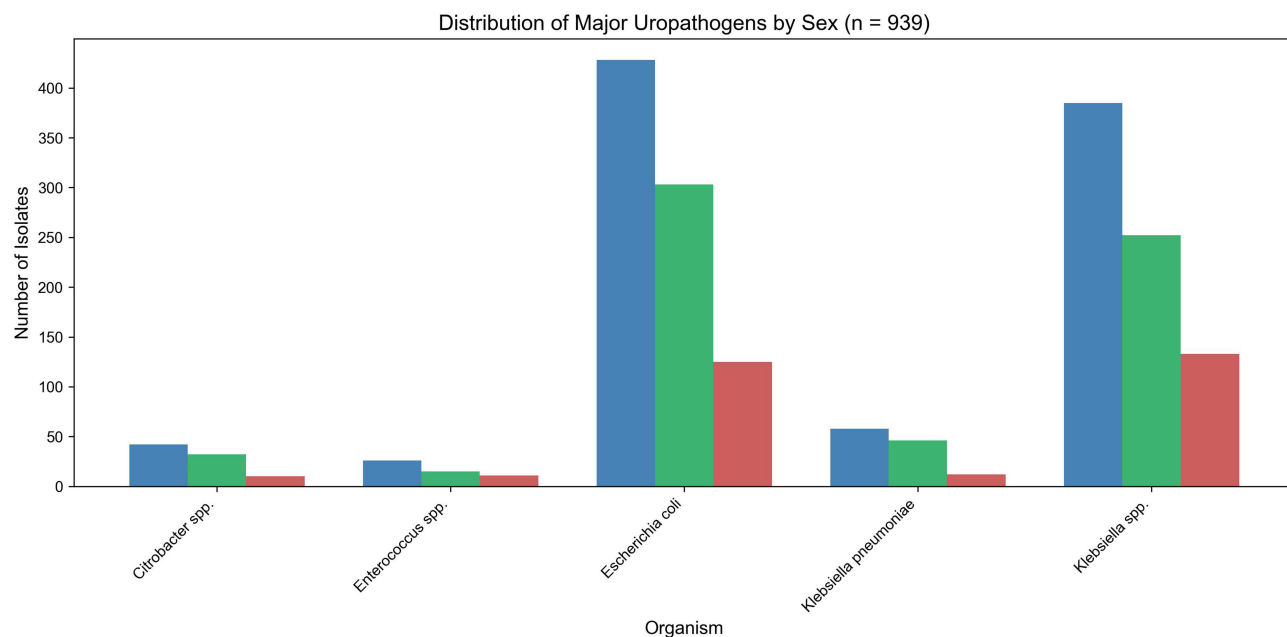


Figure 1 Distribution of the most common uropathogenic isolates (≥ 25 isolates) by sex and organism ($n = 939$). Each organism is represented by three bars: blue for total isolates, green for isolates from female patients, and red for isolates from male patients. Organisms include *Escherichia coli*, *Klebsiella* spp., *Klebsiella pneumoniae*, *Citrobacter* spp., and *Enterococcus* spp.

A predominance of female-related samples was also observed for *Klebsiella* spp. (252/385, 65.5%), with the disparity was most marked for *Klebsiella pneumoniae*, since 46 of 58 isolates (79.3%) were from females. *Citrobacter* spp. showed a similar trend (32/42, 76.2%), while *Enterococcus* spp. had a more equal sex distribution (15/26, 57.7% female). Organism-specific chi-square tests of independence revealed no statistically significant associations between sex and isolate distribution for any of the five organisms: *Citrobacter* spp. ($\chi^2 = 0.373$, $p = 0.5412$), *Enterococcus* spp. ($\chi^2 = 0.469$, $p = 0.4936$), *Escherichia coli* ($\chi^2 = 0.217$, $p = 0.6411$), *Klebsiella pneumoniae* ($\chi^2 = 1.121$, $p = 0.2898$), and *Klebsiella* spp. ($\chi^2 = 0.730$, $p = 0.3930$).

Prevalence of Urine Pathogens and Age

The five most frequently identified uropathogens showed distinct distribution patterns across patient age groups. The uropathogens showed distinct patterns across patient age groups. *Escherichia coli* was most isolated from cultures from individuals from the 46- to 65-year-old age group (99/428, 23.1%) followed by the 36- to 45-year-old (92/428, 21.5%), and 26- to 35-year-old groups (84/428, 19.6%). *Klebsiella* spp. showed a distinct peak in the 26–35 age group (120/385, 31.2%) and remained prevalent in the 46–65 (82/385, 21.3%) and 36–45 (69/385, 17.9%) age groups. *Klebsiella pneumoniae* showed the same trend with the majority being recovered from cultures from individuals between the age group 46–65 years (19/58, 32.8%) and 15–25 years (13/58, 22.4%). *Citrobacter* spp. were found predominantly in adults 36–45 years (12/42, 28.6%) and 46–65 years (10/42, 23.8%), whereas *Enterococcus* spp. reached the 36–45 (9/26, 34.6%) and 26–35 (7/26, 26.9%) age groups. A chi-square test of independence confirmed a statistically significant association between the type of uropathogen recovered and the age group of individuals from whom the culture-positive urine samples were obtained ($\chi^2 = 39.83$, $df = 20$, $p = 0.0052$). The greatest deviations from expected frequencies were noted among *Escherichia coli* and *Klebsiella* spp. within the 26–35 and 46–65-year age group (Figure 2).

There is a statistically significant association between organism type, age category, and sex ($\chi^2 = 74.886$, $df = 26$, $p < 0.0001$). Frequency pattern trends anticipated that *Escherichia coli* isolates were more frequently isolated from female urine samples in every age group especially among females aged 46–65 years (anticipated: 67.996) compared to males (31.004). Following the same trend, *Klebsiella* spp. showed a more anticipated recovery in females, especially in the 26–35 years age group (82.419 vs 37.581 for males). Although less frequently recovered, *Citrobacter* spp., *Klebsiella pneumoniae*, and *Enterococcus* spp. also exhibited differences in recovery frequencies among age–sex subgroups.

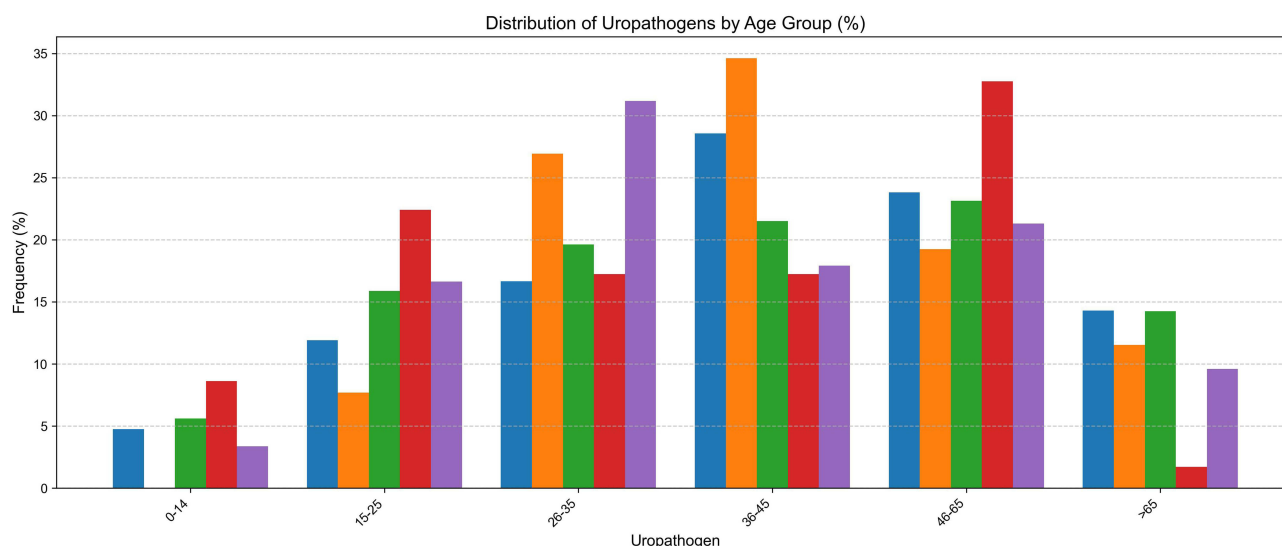


Figure 2 Distribution of the most common uropathogenic isolates (≥ 25 isolates) by age group. Each group of bars represents a single organism. Bars are color-coded by age group: blue for 0–14 years, green for 15–24 years, Orange for 25–44 years, purple for 45–64 years, and red for ≥ 65 years. Bar heights reflect the proportion of isolates from each age group, expressed as percentages.

Overall and Organism-Specific Antibiotic Resistance

A total of 893 (95.1%) were resistant to at least one tested antibiotic. *Klebsiella* spp. was the most resistant with 382 out of 385 isolates (99.2%) being resistant to at least one antibiotic. This was followed by *Escherichia coli* (396/428, 92.5%), *Enterococcus* spp. (25/26, 96.2%), and *Klebsiella pneumoniae* (54/58, 93.1%). *Citrobacter* spp. reported the lowest resistance rate among the top five organisms, having 36 out of 42 isolates (85.7%) resistant.

Trends in Antibiotic Resistance and Statistical Significance 2019–2024

Highest resistance rates were observed sulfamethoxazole showing resistance in 619 of 676 isolates (91.6%), followed closely by ampicillin (274/300, 91.3%). High bacterial resistance to Erythromycin was observed with 16 of 22 isolates (72.7%) demonstrating resistance. Over half of the pathogens were also resistant to clindamycin (306/563, 54.4%), chloramphenicol (326/611, 53.4%), and amoxicillin/clavulanic acid (324/621, 52.2%). Resistance to ceftriaxone and ciprofloxacin was 46.0% and 28.1%, respectively. Lower rates were seen with gentamicin (18.2%) and nitrofurantoin (22.1%).

In contrast, bacteria showed lower resistance rates to carbapenems with 10.3% and 8.7% resistance to Imipenem and Meropenem, respectively, as shown in Table 1.

A detailed summary of the resistance of the uropathogens to different antibiotics is presented in Table 2. Resistance was defined as non-susceptibility to the tested antibiotic (R No [%]), with the total number of isolates tested (T) indicated for each combination. *Escherichia coli* demonstrated significant resistance to several antibiotics, with the highest resistance observed to Ampicillin (174/190, 91.6%), followed by Sulfamethoxazole (240/274, 87.6%) and Clindamycin (148/199, 74.4%). *Escherichia coli* resistance to Chloramphenicol was (214/341, 62.8%) and Clindamycin (122/313, 39.0%). *Klebsiella pneumoniae* displayed significant resistance to Ampicillin (27/28, 96.4%) and Sulfamethoxazole (24/36 isolates, 66.7%), while also showing moderate resistance to Ceftriaxone (15/22 isolates, 68.2%) and Clindamycin (29/32, 90.6%). *Citrobacter* spp. were most resistant to Ampicillin (3/3, 100%), Ciprofloxacin (13/18, 72.2%), and Sulfamethoxazole (16/23, 69.6%). Resistance to Chloramphenicol was also high (4/7, 57.1%). *Enterococcus* spp. were most resistant to Erythromycin (16/22, 72.7%) and Chloramphenicol (7/10, 70.0%). Sulfamethoxazole resistance was found in 13 of 14 isolates (92.9%).

Temporal Mono Resistance Trends

For analysis of trends of mono resistance over time, quarterly data over the period of 2019 to 2024 were analyzed by comparing them using the Mann-Kendall trend test. Rising resistance was observed in *Klebsiella* spp. against Ceftriaxone

Table 1 Resistance Rates to Common Antimicrobial Agents in Urine Cultures at Mbarara Regional Referral Hospital, 2019–2024

Antimicrobial Agents	No. of Cultures Tested	Resistant No (%)
Amoxicillin/Clavulanic Acid	621.0	324 (52.2%)
Ampicillin	300.0	274 (91.3%)
Aztreonam	45.0	29.0 (64.4%)
Cefaclor	25.0	15 (60.0%)
Cefazolin	218.0	80 (36.7%)
Cefotaxime	479.0	126.0 (26.3%)
Cefoxitin 30 Mg	49.0	19 (38.8%)
Ceftazidime	159.0	30.0 (18.9%)
Ceftriaxone	620.0	285.0 (46.0%)
Chloramphenicol	611.0	326 (53.4%)
Ciprofloxacin	626.0	176.0 (28.1%)
Gentamicin	625.0	114 (18.2%)
Imipenem	585.0	60.0 (10.3%)
Meropenem	46.0	4 (8.7%)
Nitrofurantoin	349.0	77.0 (22.1%)
Sulfamethoxazole	676.0	619 (91.6%)
Other agents	81.0	39.0 (48.1%)

Notes: *Other agents* category includes Clindamycin, Erythromycin, Moxifloxacin, and Vancomycin each tested in fewer than 25 urine culture isolates. Resistant No (%) reflects the number and percentage of resistant isolates per agent.

Table 2 Distribution of the Most Common Uropathogens and Their Resistance to Common Antibiotics at Mbarara Regional Referral Hospital From January 1, 2019, to December 31, 2024

Agent	<i>Citrobacter</i> spp.	<i>Enterococcus</i> spp.	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Klebsiella</i> spp.
Amoxicillin/Clavulanic Acid	11 (78.6%)	2 (13.3%)	136 (55.1%)	30 (81.1%)	145 (47.1%)
Ampicillin	3 (100.0%)	5 (45.5%)	174 (91.6%)	27 (96.4%)	65 (95.6%)
Aztreonam	3 (75.0%)	ND	21 (63.6%)	2 (50.0%)	3 (75.0%)
Cefaclor	ND	ND	7 (70.0%)	0 (0.0%)	8 (57.1%)
Cefazolin	ND	1 (33.3%)	34 (27.0%)	10 (40.0%)	35 (54.7%)
Cefotaxime	3 (100.0%)	ND	42 (29.6%)	5 (50.0%)	76 (23.5%)
Cefoxitin 30 mg	1 (100.0%)	ND	13 (43.3%)	3 (33.3%)	2 (22.2%)
Ceftriaxone	15 (60.0%)	ND	114 (48.3%)	15 (68.2%)	141 (41.8%)
Chloramphenicol	4 (57.1%)	7 (70.0%)	88 (40.6%)	13 (36.1%)	214 (62.8%)
Ciprofloxacin	13 (72.2%)	ND	95 (38.2%)	15 (46.9%)	53 (16.2%)

(Continued)

Table 2 (Continued).

Agent	<i>Citrobacter</i> spp.	<i>Enterococcus</i> spp.	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Klebsiella</i> spp.
Gentamicin	5 (55.6%)	2 (14.3%)	52 (19.8%)	10 (35.7%)	45 (14.4%)
Imipenem	7 (25.9%)	ND	40 (14.3%)	1 (2.9%)	12 (4.9%)
Meropenem	ND	ND	0 (0.0%)	3 (30.0%)	1 (14.3%)
Nitrofurantoin	8 (27.6%)	ND	36 (15.7%)	14 (58.3%)	19 (28.8%)
Sulfamethoxazole	16 (69.6%)	13 (92.9%)	240 (87.6%)	24 (66.7%)	326 (99.1%)
Other agents	ND	23 (50.0%)	2 (100.0%)	1 (50.0%)	1 (25.0%)

Notes: Resistance to commonly tested antibiotics among key uropathogens. R No (%): Number and percentage of resistant isolates among those tested (T). ND: No data available for that antibiotic–organism pair. Other agents include antibiotics tested in fewer than 25 isolates, including Clindamycin, Erythromycin, Moxifloxacin, and Vancomycin.

($\tau = 0.581$, $p = 0.0028$), Cefotaxime ($\tau = 0.5909$, $p = 0.0090$), and Imipenem ($\tau = 0.3099$, $p = 0.0415$). An increasing trend of *Escherichia coli* was observed against Cefotaxime ($\tau = 0.3791$, $p = 0.0291$). As shown in Figure 3a and Table 3, while raw quarterly resistance values (blue line) fluctuate, the 3-quarter rolling average (orange dashed line) reveals

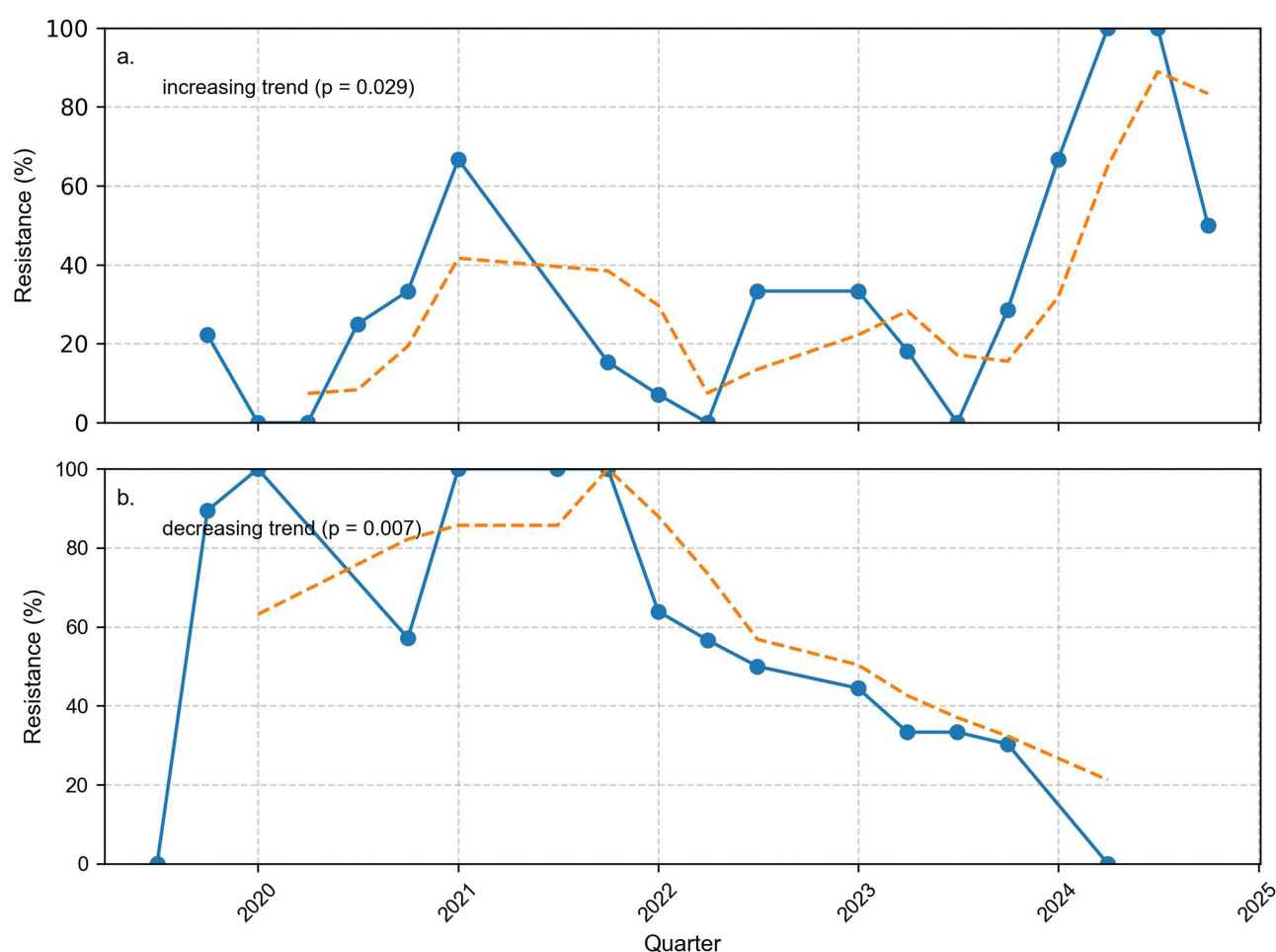


Figure 3 Antimicrobial resistance trends among urinary isolates from Mbarara Regional Referral Hospital (MRRH), 2019–2024. (a) The pattern of resistance to cefotaxime among *Escherichia coli* is increasing ($p = 0.029$); (b) There is declining resistance to amoxicillin/clavulanic acid in *Klebsiella* spp. ($p = 0.007$). Dots: raw percentages of resistance for each quarter. Dashed lines: 3-quarter rolling average, used to reduce short-term fluctuations and expose longer-term trends.

Table 3 Significant Trends in Antimicrobial Resistance Among *Escherichia coli* and *Klebsiella* spp. From 2019 to 2024

Organism	Antibiotic	Trend	p-Value	Tau
<i>Escherichia coli</i>	Amoxicillin/Clavulanic Acid	Decreasing	0.0378	−0.3421
<i>Escherichia coli</i>	Cefotaxime	Increasing	0.0291	0.3791
<i>Klebsiella</i> spp.	Amoxicillin/Clavulanic Acid	Decreasing	0.0068	−0.5238
<i>Klebsiella</i> spp.	Cefotaxime	Increasing	0.009	0.5909
<i>Klebsiella</i> spp.	Ceftriaxone	Increasing	0.0028	0.581
<i>Klebsiella</i> spp.	Imipenem	Increasing	0.0415	0.3099

Notes: Trends were assessed using the Mann–Kendall test. Positive Tau values indicate increasing trends; negative values indicate decreasing trends. Significance was defined as $p < 0.05$.

a sustained upward trajectory, confirming these trends. On the other hand, declining resistance was observed for Amoxicillin/Clavulanic Acid between *Klebsiella* spp. ($\tau = -0.5238$, $p = 0.0068$) and *Escherichia coli* ($\tau = -0.3421$, $p = 0.0378$) as shown in Table 3. This decline is evident in Figure 3b, where both raw values and rolling averages indicate a consistent downward pattern. No statistically significant trends toward antibiotic resistance ($p \geq 0.05$) were detected for the majority of organism–antibiotic pairs under study. These included resistance of *Klebsiella* spp. and *Escherichia coli* to agents in widespread use such as Gentamicin, Ciprofloxacin, Sulfamethoxazole, and Chloramphenicol. Six organism–antibiotic combinations were omitted from the trend analysis due to sparse data (<12 quarters) and primarily affected *Citrobacter* spp., *Klebsiella pneumoniae*, and *Enterococcus* spp.

The observed directional patterns including increasing cefotaxime resistance in *Escherichia coli* and decreasing amoxicillin/clavulanic acid resistance in *Klebsiella* spp. reinforce the value of combining visual smoothing with statistical trend analysis. Through the use of 3-quarter rolling averages coupled with Mann–Kendall trend analysis, we were able to detect persistent, monotonic trends in AMR that would have been obscured by quarterly fluctuation.

Multidrug Resistance Patterns (MDR) Among Uropathogens

The resistance pattern of bacterial isolates by resistance levels (R0 to >R7) shows elevated resistance to multiple antibiotics in major uropathogens, as shown in Table 4. *Escherichia coli* carried a high resistant burden with only 7.5% of the isolates being fully susceptible to all antibiotics tested (R0). The majority were resistant to at least three antibiotics, notably at R2 (32.7%), R3 (22.0%), and R4 (12.1%). *Klebsiella* spp. displayed a similar trend, where 42.3% were resistant to three antibiotics (R3) and 26.3% to four and above (R4–>R7), and only 0.8% of the isolates were fully susceptible as shown in Table 5.

Klebsiella pneumoniae presented with a more ominous resistance profile with 12.1% of the isolates resistant to at least seven antibiotics. *Enterococcus* spp. had elevated levels of resistance with 76.9% isolates in R2–R4 with none of them with greater than four-drug resistance.

Table 4 Distribution of Bacterial Isolates Across Antibiotic Resistance Categories (R0 to R7) From Sensitivity to Increasing Resistance to Multiple Antibiotics Among Patients at Mbarara Regional Referral Hospital From January 1, 2019, to December 31, 2024

Bacterial Isolates	R0 No (%)	R1 No (%)	R2 No (%)	R3 No (%)	R4 No (%)	R5 No (%)	R6 No (%)	>R7 No (%)
<i>Klebsiella</i> spp. (385)	3 (0.8%)	17 (4.4%)	100 (26.0%)	163 (42.3%)	74 (19.2%)	26 (6.8%)	1 (0.3%)	1 (0.3%)
<i>Escherichia coli</i> (428)	32 (7.5%)	69 (16.1%)	140 (32.7%)	94 (22.0%)	52 (12.1%)	18 (4.2%)	7 (1.6%)	16 (3.7%)
<i>Klebsiella pneumoniae</i> (58)	4 (6.9%)	11 (19.0%)	18 (31.0%)	8 (13.8%)	7 (12.1%)	1 (1.7%)	2 (3.4%)	7 (12.1%)
<i>Enterococcus</i> spp. (26)	1 (3.8%)	5 (19.2%)	14 (53.8%)	5 (19.2%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)
<i>Citrobacter</i> spp. (42)	6 (14.3%)	10 (23.8%)	12 (28.6%)	7 (16.7%)	2 (4.8%)	4 (9.5%)	1 (2.4%)	0 (0.0%)

Notes: R0 represents sensitivity to all tested antibiotics, and R1 through R7 reflect increasing levels of resistance.

Table 5 Summary of Organisms, Resistance, and MDR Patterns by Specimen Type

Specimen Type	Organism	Isolate Count	% Within Specimen	Resistance %	MDR %
Catheter	<i>Citrobacter</i> spp.	4	20.0	100.0	100.0
Catheter	<i>Escherichia coli</i>	11	55.0	100.0	72.7
Catheter	<i>Klebsiella pneumoniae</i>	5	25.0	100.0	40.0
Midstream urine	<i>Citrobacter</i> spp.	38	4.1	84.2	44.7
Midstream urine	<i>Enterococcus</i> spp.	26	2.8	96.2	34.6
Midstream urine	<i>Escherichia coli</i>	417	45.4	92.3	44.4
Midstream urine	<i>Klebsiella pneumoniae</i>	53	5.8	92.5	45.3
Midstream urine	<i>Klebsiella</i> spp.	385	41.9	99.2	74.0

Of 939 urine isolates tested, 534 (56.9%) were classified as multidrug-resistant (MDR), 356 (37.9%) were resistant to one or two groups of antimicrobials, and 46 (4.9%) were susceptible. An additional 3 isolates (0.3%) met the criteria for extensively drug-resistant (XDR) phenotype. Of the MDR strains, 374 (70%) were extended-spectrum β -lactamase (ESBL) producers, most commonly in *Escherichia coli* and *Klebsiella* spp. One MDR isolate (0.2%) was classified as carbapenemase-producing *Klebsiella pneumoniae* (KPC), and one (0.2%) produced ESBL and KPC enzymes. The remaining 158 MDR isolates (29.6%) were resistant to more than three antimicrobial classes with no detection of a known resistance mechanism and belonged to the classical MDR category. Among the XDR isolates, one expressed ESBL alone, one KPC alone, and one co-produced ESBL and KPC. None of the strains met the criteria for vancomycin-resistant *Enterococcus* spp. (VRE), or pan-drug-resistant (PDR) phenotypes.

A phenotypic analysis of MDR and XDR phenotypes per organism is demonstrated in Figure 4. Of the 194 MDR *Escherichia coli*, 141 (72.7%) were ESBL producers, and 53 (27.3%) did not have a phenotypic mechanism identified. In

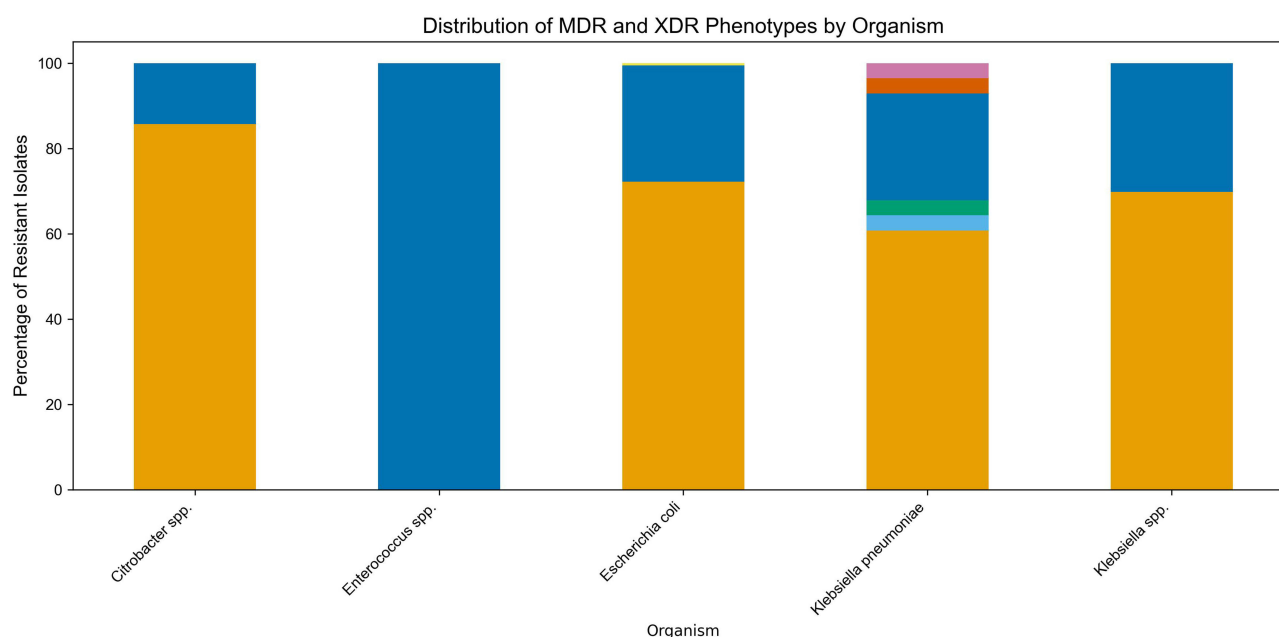


Figure 4 Distribution of MDR and XDR among most common uropathogenic isolates. Each bar represents the relative distribution of phenotypic resistance mechanisms among multidrug-resistant (MDR) and extensively drug-resistant (XDR) isolates for organisms with ≥ 25 resistant isolates. The phenotypes are distinguished by color: Orange (MDR: ESBL), light blue (MDR: ESBL, KPC), green (MDR: KPC), dark blue (MDR: no detected mechanism), yellow (XDR: ESBL), brown (XDR: ESBL, KPC), and pink (XDR: KPC). Organisms included are *Citrobacter* spp., *Enterococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella* spp.

Klebsiella spp. (n = 285), 199 (69.8%) were ESBL producers. Of the 28 MDR *Klebsiella pneumoniae* isolates, 17 (60.7%) were ESBL-positive, 2 (7.1%) expressed KPC, 2 (7.1%) co-produced ESBL and KPC, and 7 (25.0%) showed no phenotypic mechanism. Three additional *Klebsiella pneumoniae* isolates met criteria for XDR, including one ESBL producer, one KPC producer, and one co-producing both. In 21 MDR *Citrobacter* spp. isolates, 18 (85.7%) were ESBL producers, and 3 (14.3%) did not have any detected mechanism. All 9 MDR *Enterococcus* spp. isolates did not have phenotypic evidence of vancomycin resistance.

The prevalence of resistance classes among MDR and XDR uropathogens is depicted in Figures 4 and 5. β -Lactam resistance was the highest among all uropathogens, covering 100.0% of *Enterococcus* spp. (9/9), 96.4% of *Klebsiella pneumoniae* (27/28), 90.7% of *Escherichia coli* (176/194), and 90.5% of *Citrobacter* spp. (19/21). Sulfonamide resistance was also high, and it was highest among *Klebsiella* spp. (92.6%, 264/285) and *Escherichia coli* (68.0%, 132/194). Fluoroquinolone resistance ranged from 17.5% for *Klebsiella* spp. to 39.3% for *Klebsiella pneumoniae*. Resistance to aminoglycosides was found in 22.2% to 28.6% of Gram-negative uropathogens. Macrolide resistance was found only in *Enterococcus* spp. (66.7%, 6/9). Carbapenem resistance was found in 23.8% of *Citrobacter* spp. and 14.3% of *Klebsiella pneumoniae*. Amphenicol resistance was found in 58.2% of *Klebsiella* spp. and 39.3% of *Klebsiella pneumoniae*, while resistance to nitrofurans was highest in *Klebsiella pneumoniae* (39.3%) and *Escherichia coli* (13.9%).

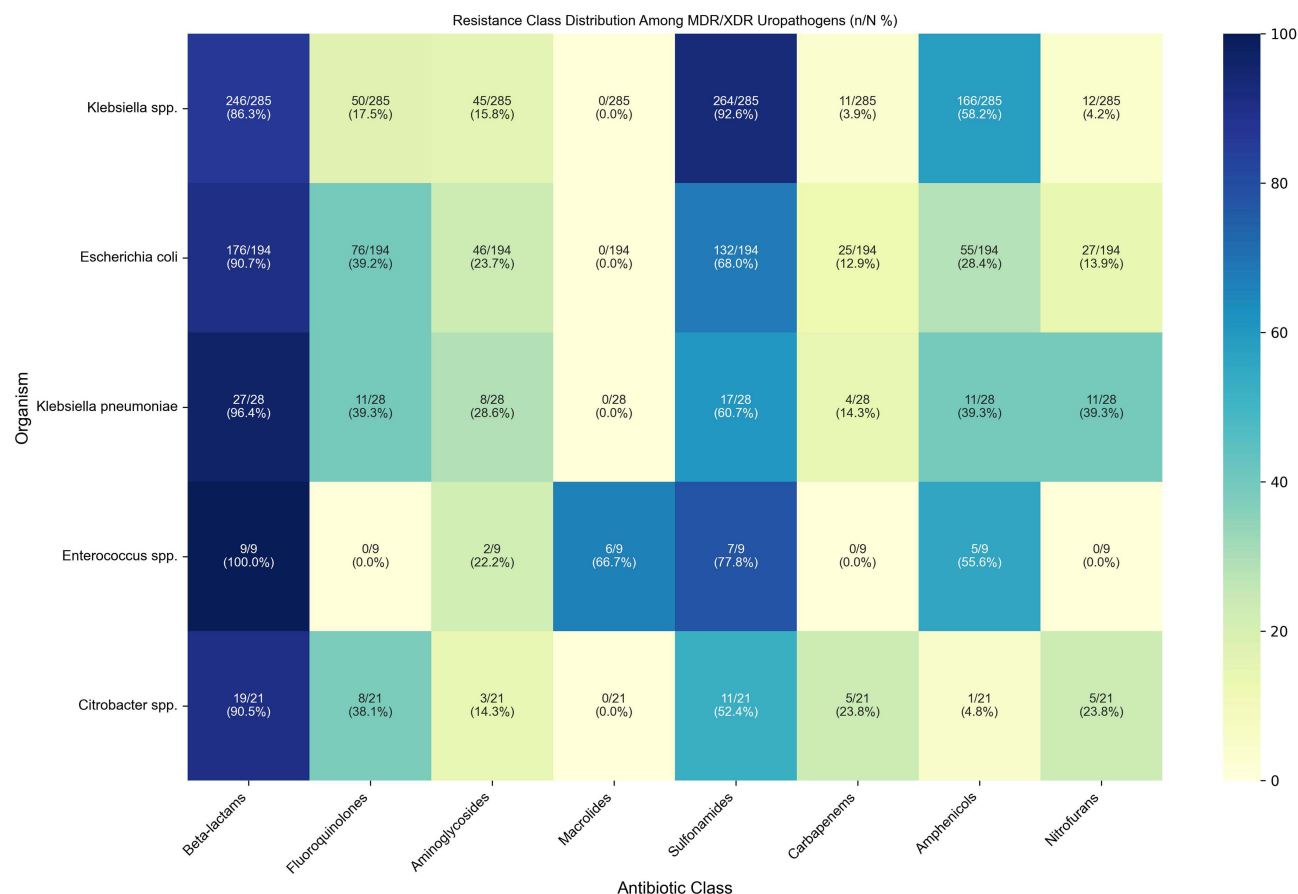


Figure 5 Resistance class profiles of MDR and XDR uropathogens isolated at Mbarara Regional Referral Hospital, 2019–2024. The heat map presents the number and percentage of isolates (n/N, %) resistant to at least one agent within each antibiotic class. Organisms are shown on the y-axis and antibiotic classes along the x-axis. Darker shading reflects higher MDR burden.

Quarterly MDR Trends

Quarterly temporal trends in multidrug resistance (MDR) among uropathogens exhibited organism-specific variability as shown in Figure 6. Trend direction and significance were assessed using the Mann-Kendall non-parametric trend test. *Escherichia coli* demonstrated a statistically significant increasing trend in MDR proportions over time ($p = 0.015$). There was no significant temporal trend in MDR ratios for *Klebsiella* spp. ($p = 0.207$), *Klebsiella pneumoniae* ($p = 1.000$), or *Enterococcus* spp. ($p = 0.333$).

Despite the absence of monotonic trends in a few of the species, MDR levels were consistently high throughout the entire duration of the study. *Klebsiella pneumoniae* tended to have MDR percentages of or near 100% in many quarters but with huge variations. *Enterococcus* spp. experienced an elevation in short-term MDR from 2021 to 2022 but dropped. *Klebsiella* spp. experienced MDR rates far beyond the 50% mark for the majority of portions but with huge quarter-to-quarter variability.

Specimen-Type Distribution of Resistance and MDR Patterns

Organism-specific resistance and MDR pattern analysis stratified by specimen type revealed considerable differences. The vast majority of isolates were from midstream urine (97.9%, $n=919$), while catheter-derived samples comprised a minority proportion (2.1%, $n=20$). Of the catheter samples, the predominant organism was *Escherichia coli* (55.0%), followed by *Klebsiella pneumoniae* (25.0%) and *Citrobacter* spp. (20.0%). All catheter specimen isolates were 100% resistant, with MDR in 70.0% overall. Significantly, 100% of the catheter *Citrobacter* spp. were MDR, followed by 72.7% *Escherichia coli* and 40.0% *Klebsiella pneumoniae*.

Escherichia coli was the predominant organism in midstream urine cultures (45.4%), followed by *Klebsiella* spp. (41.9%), but less often were *Klebsiella pneumoniae*, *Citrobacter* spp., and *Enterococcus* spp. The resistance rates for

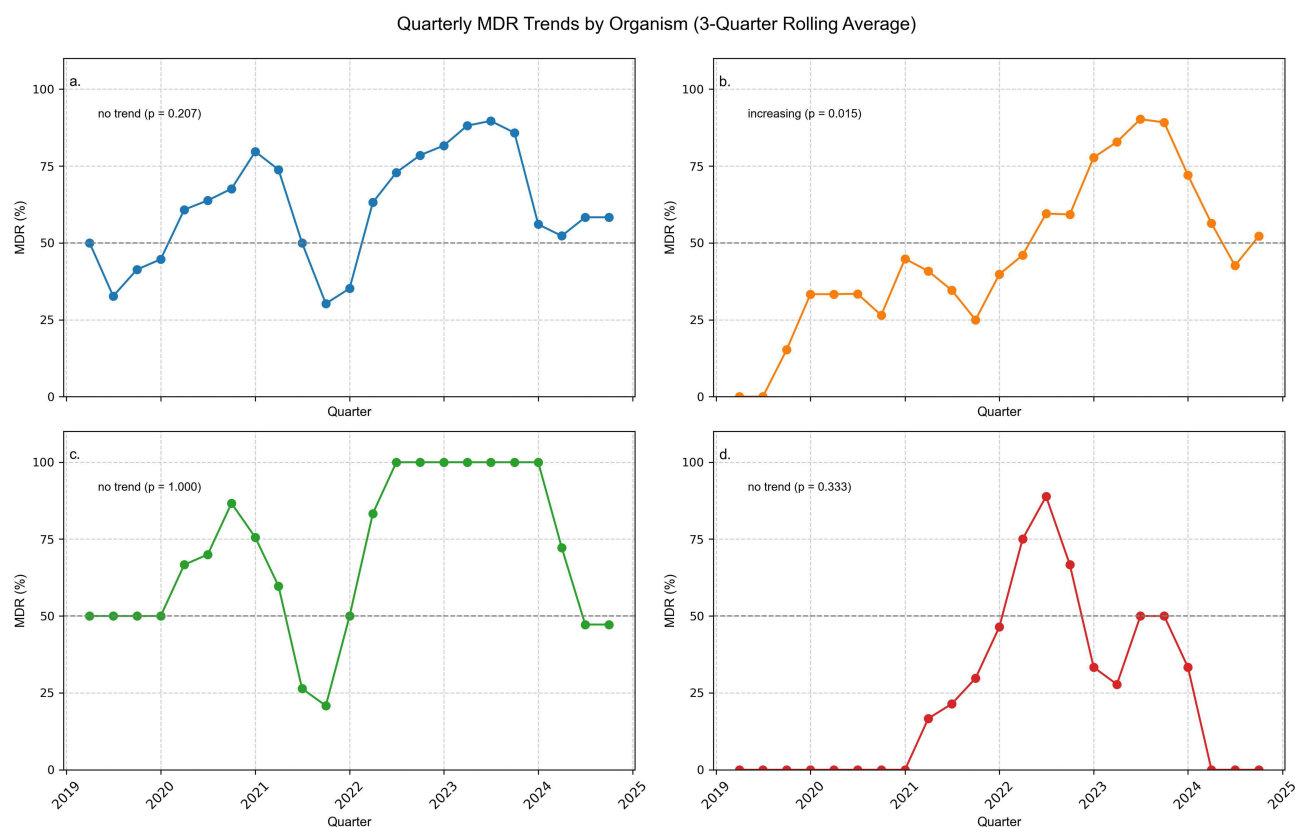


Figure 6 Quarterly trends in multidrug resistance (MDR) among predominant uropathogens isolated at Mbarara Regional Referral Hospital between 2019 and 2024. Panels depict 3-quarter rolling average MDR proportions for (a) *Klebsiella* spp., (b) *Escherichia coli*, (c) *Klebsiella pneumoniae*, and (d) *Enterococcus* spp. Trends were assessed using the Mann-Kendall test; corresponding p-values are displayed within each plot. A horizontal reference line at 50% indicates the mid-threshold for MDR burden.

these organisms were all high and ranged from 84.2% among *Citrobacter* spp. to 99.2% among *Klebsiella* spp. Prevalence of MDR among midstream isolates was also high, with the highest recorded in *Klebsiella* spp. (74.0%), followed by *Klebsiella pneumoniae* (45.3%), *Escherichia coli* (44.4%), *Citrobacter* spp. (44.7%), and *Enterococcus* spp. (34.6%). These findings highlight specimen type-specific variation in resistance and MDR prevalence among leading uropathogens.

Discussion

The study is in agreement with the global observation that females are disproportionately affected by urinary tract infections (UTIs). The higher prevalence of UTIs in females may be attributed to anatomical differences, such as the shorter urethra, which facilitates bacterial entry into the urinary tract, and hormonal changes which may alter vaginal and urinary flora, and anterior vaginal prolapse.^{26–28}

Furthermore, *Escherichia coli* was the most frequently isolated organism in this study, particularly among females (70.8%), aligning with global findings that identify *Escherichia coli* as the leading cause of community-acquired and healthcare-associated urinary tract infections (UTIs).^{27,29,30} Comparable studies from Uganda,^{9,31,32} Sub-Saharan Africa^{29,33,34} Asia,^{35,36} and America³⁷ revealed *Escherichia coli* prevalence rates of 30–70% that is consistent with our findings, highlighting its global clinical importance. This may be attributed to the virulence factors of *Escherichia coli*, like as adhesins, hemolysins, and biofilm-formation, which enhance its ability to colonize the urinary tract.³⁸ While *Klebsiella* spp., *Klebsiella pneumoniae*, and *Citrobacter* spp. also showed a female predominance, *Enterococcus* spp. were more evenly distributed by sex.

The difference in aetiological agents among males and females underscores the importance of gender considerations in diagnosing and treating urinary tract infections, as the prevalence of specific organisms may significantly vary between male and female patients.

Age distribution highlighted two high-risk populations; young adults (26–45 years) and the elderly (>65 years). In young adults, social factors such as increased sexual activity and contraceptive use may contribute to the high incidence of urinary tract infections while in the elderly, comorbid conditions such as diabetes, weakened immunity, and frequent catheterization may contribute to a higher prevalence of UTIs.^{39,40} These trends are in line with recent reports demonstrating age-specific colonization by dominant uropathogens.^{41,42} This distinct distribution of urinary tract infections among the age groups highlights the need for age-appropriate diagnostic and treatment choices.

Moreover, *Escherichia coli* was disproportionately recovered from cultures taken from females in all age groups, most notably those between 46 and 65 years old, a finding substantiated by the existence a significant organism–age–sex interaction ($\chi^2 = 74.886$, $df = 26$, $p < 0.0001$). This age group-specific prevalence testifies to the multivariate etiology of UTIs and yet again emphasizes the importance of considering host biology as well as habits in epidemiologic risk stratification. These findings are consistent with other research noting female gender and reproductive-age exposures as essential determinants of pathogen recovery profiles.^{43,44} Incorporating sex-specific empiric therapies and targeted surveillance for high-risk patients may improve clinical outcomes and antimicrobial stewardship.

According to these patterns of populations, a comprehensive analysis of susceptibility to antimicrobials revealed staggering baseline resistance among uropathogens to several commonly prescribed antibiotics. The study highlights the rising antimicrobial resistance among Uropathogens to commonly used antibiotics such as ampicillin (91.3%) and sulfamethoxazole (91.6%) reflecting inadequate treatment options. Unfortunately, such findings are very similar to previous studies done in other regions of Uganda^{11,45} as well as in the world, particularly in low- and middle-income countries (LMICs) such as Ethiopia⁴⁶ and the Democratic Republic of Congo.⁴⁷ In contrast, high-income countries report lower resistance rates to first-line antibiotics due to improved regulated antibiotic use^{39,48} emphasizing the need for policy interventions in Uganda.

In *Klebsiella* spp., rising mono resistance to Imipenem ($\tau = 0.3099$, $p = 0.0415$) is of particular concern because carbapenems are drugs of last resort for complicated infections. The 3-quarter moving average also confirmed long-term increasing trends in these patterns of resistance, establishing the clinical importance of these findings. This trend is worrisome because cephalosporins, a subgroup of beta-lactams are commonly used for both community-acquired and healthcare-associated infections in Uganda.^{49,50} This puts their continued effectiveness as keystone drugs at risk.

Similarly, increasing gentamicin resistance, a primary aminoglycoside used on more than one level of care contributes to empiric treatment limitations, particularly to *Escherichia coli*.

Conversely, there was a statistically significant decline in resistance to Amoxicillin/Clavulanic Acid for *Klebsiella* spp. and *Escherichia coli*. This shift can be interpreted as evidence of reduced prescribing pressure or improved stewardship and laboratory accuracy. Evidence elsewhere testifies to this possibility. For example, 2010 study demonstrated that restriction of AMC use in hospital settings was associated with a precipitous drop in *Escherichia coli* resistance, from 37% to 11% within one year ($p < 0.0001$), illustrating the capacity for fast action on targeted antibiotic policy on resistance trends.⁵¹

On the other hand, resistance to Gentamicin and Ciprofloxacin did not statistically vary over time. The two medications, however, recorded relatively high frequencies of resistance in our study limiting their applicability as empirical drugs irrespective of stability. This corresponds with observations made from Uganda and other regions,^{32,52} where resistance to aminoglycoside and fluoroquinolone is not insignificant among isolates of *Escherichia coli* and *Staphylococcus aureus*. Most concerning is the uniformly high frequency of the resistance to Sulfamethoxazole, which was greater than 90% for the entire study period. Even in the absence of an upward trend, resistance of this magnitude renders the drug clinically irrelevant for empiric use in this context. This result is consistent with previous reports in Southeast Asia and East Africa,^{30,33,53} reinforcing the importance of not only tracking resistance trends, but recognizing when frequency alone is sufficient to disqualify an agent from therapeutic consideration. These results highlight the limitations of static antibiograms in settings with high burdens. It is only through longitudinal surveillance and statistical modeling, such as Mann-Kendall trend analysis, which early trends in resistance can be detected and acted upon. This underlines the need not only to monitor resistance frequencies, but also to monitor their directionality over time, guiding enhanced antimicrobial stewardship and treatment planning.

Furthermore, MDR patterns in the present study are alarming and widespread. Over half (56.9%) of all isolates were found to be multidrug-resistant (MDR), with an additional subgroup possessing criteria for extensive drug resistance (XDR). The most alarming species was *Klebsiella pneumoniae* with more than two-thirds (69%) of its isolates being resistant to three or more agents, and more than 12% showing resistance to seven or more agents. Of MDR *Klebsiella pneumoniae*, 60.7% were ESBL producers and others had carbapenemase phenotypes such as KPC alone or in combination. The high rates of MDR reported in this work are fueled by intrinsic as well as acquired mechanisms. Gram-negative bacteria like *Escherichia coli* and *Klebsiella pneumoniae* carry extended-spectrum β -lactamases (ESBLs) that break down penicillins and cephalosporins, making these widely used drugs ineffective. In addition, efflux pumps, reduced outer membrane permeability, and plasmid-borne resistance genes are also responsible for MDR phenotypes. These mechanisms represent global reports of MDR in Africa, Asia, Europe, and the Americas and not only restricted in Uganda.

Although carbapenemase-producing isolates were rare in this study, their presence in *Klebsiella pneumoniae* alongside high levels of classical multidrug resistance remains a cause for concern. Carbapenem resistance, often facilitated by carbapenemase-producing Enterobacterales (CPE), is an international public health threat. Examples of such genes as KPC, NDM, and OXA-48, usually harbored on mobile genetic elements, facilitate horizontal gene transfer and spread of resistance.⁴⁰ While carbapenem resistance remains uncommon in Uganda,⁴¹ its increasing frequency in India⁵⁴ and other low- and middle-income nations (LMICs) calls for enhanced monitoring and the preservation of carbapenems as drugs of last resort.

Temporal trends using Mann-Kendall trend testing showed an increasing trend over time in MDR *Escherichia coli* isolates that was statistically significant ($p = 0.015$), aligning with other regional and international reports of rising multidrug resistance.^{55,56} The consistently high MDR rates particularly for *K. pneumonia* indicate a continued resistance burden that remains to be tackled.

The integration of longitudinal statistical modeling, such as Mann-Kendall trend analysis, allows early warning about resistance increase and informs adaptive antimicrobial stewardship policy. Infection control needs to be directed by more than frequency, but by direction of resistance, allowing timely intervention and preserving effective antimicrobial therapy.

This study relied only on secondary data and this may introduce biases and limit generalizability. Additionally, small sample sizes for less common pathogens and catheter-derived specimens reduce statistical power, and therefore larger prospective studies to confirm these findings. Future research should also explore the molecular mechanisms underlying resistance in these pathogens, which could inform the development of targeted therapies and diagnostics.

Conclusion

This study highlights the significant burden of AMR among uropathogens at Mbarara Regional Referral Hospital, with *Escherichia coli* as the most prevalent pathogen. High resistance rates were observed for commonly used antibiotics, and rising trends in cefotaxime, ceftriaxone, and imipenem resistance were detected, particularly among *Escherichia coli* and *Klebsiella* spp. Multidrug resistance was widespread, with a significant upward trend in *Escherichia coli*, emphasizing the need for urgent interventions, including updated treatment guidelines and functional surveillance systems. The Mann–Kendall trend test proved useful for identifying sustained changes in resistance over time. This analysis provides a solid basis for further study with more elaborate time-series models, such as SARIMA and Bayesian models, to refine trend estimation and resistance prediction. The findings support the imperative of refreshing empirical treatment guidelines, enhancing regular diagnostic capacity, and expanding antimicrobial stewardship efforts.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request. Additionally, the Python code utilized for data analysis has been cleaned and uploaded to GitHub to facilitate replication and future collaborations. You can access the repository at https://github.com/nakatoconstance/MDR2020_2021.git.

Ethics Statement

The study is under a big project “AMR Surveillance, Modelling Antimicrobial Pharmaceutical Needs and PCR/Herbal/Biotechnological Products Development” in Uganda. Approval was obtained from Busitema University Faculty of Health Sciences REC with REC number BUFHS-2022-15. This study did not interface with patients as the clinical isolates were obtained from patients under routine hospital procedures.

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Disclosure

The authors confirm that they had no conflicts of interest.

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