

## Bacterial drug-resistance patterns and genetic diversity of bacteria-associated bacteriuria in diabetic patients in Ghana

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### ABSTRACT

**Objectives:** Our study aimed to determine the etiology of urinary tract infections (UTIs), resistance profiles of isolated bacteria, and virulence factors of *Escherichia coli* associated with bacteriuria in diabetic patients in Ghana. **Methods:** Midstream urine samples from 982 diabetic patients were tested for uropathogens at the National Diabetes Management and Research Centre in Ghana, using standard bacteriological methods, with antibiogram testing of the isolates using the Kirby–Bauer disk diffusion, as per CLSI guidelines. Polymerase chain reaction (PCR) was used to investigate the phylogenetic groupings and virulence factor (VF) genes of isolated *E. coli*. **Results:** The overall prevalence of UTIs was 9.2%, and the main uropathogens were *Klebsiella* spp. (55.6%) and *Escherichia coli* (31.3%). Age, duration of diabetes, and a previous history of UTIs were risk factors associated with UTI ( $p$ -value < 0.05). High levels of antibacterial resistance to cefuroxime (84%), ampicillin (80%), and gentamicin (70.7%) were observed. The distribution of VFs in each phylogenetic group revealed that *sfa-iutA-KpsTMII-KpsTMIII* genes were associated with group B2, and *iutA-ibe* were associated with group D. **Conclusions:** The isolated uropathogens were highly resistant, and the *E. coli* isolates possessed varying VFs. Continuous monitoring of bacteria associated with UTI in diabetics is highly recommended.

### INTRODUCTION

Diabetes mellitus (DM) is a polygenic metabolic disorder characterized by increased blood glucose levels (hyperglycemia) resulting from a defect in insulin secretion or insulin action, or both (Foxman, 2010; Hall et al., 2011). It is a major predisposing factor for urinary tract infections (UTI), with the principal site of infection in diabetics being the urinary tract. UTI are the most common bacterial infection affecting people of all ages, leading to considerable morbidity and costly health problems globally (Foxman, 2010). Diabetic patients have a higher incidence of UTI due to: nerve damage caused by high blood glucose levels, which affects the ability of the bladder to sense the presence of urine; high glucose levels in urine, enabling the growth of the bacteria; or abnormalities of the host defense system (Geerlings et al., 2000; Johnsson et al., 2013; Nitzan et al., 2015; Szucs et al., 1960).

UTI in diabetic patients can cause varying complications, ranging from dysuria to organ damage and complicated UTI (pyelonephritis) (Walsh and Collins, 2017). The common range of aggressive pathogens involved in UTIs in diabetics includes *Escherichia coli*, *Klebsiella* spp., enterococci, group B streptococci, *Pseudomonas* spp., *Proteus mirabilis*,

*Mycoplasma* spp., *Enterobacter* spp., *Staphylococcus aureus*, and *Candida* spp. (Walsh and Collins, 2017).

Several studies have reported the coinfection of DM with UTI. In Ethiopia, a prevalence of 13.6% of bacteriuria among symptomatic diabetic patients has been reported (Yeshitela et al., 2012). In South Africa, a UTI prevalence of 22% was reported in diabetes patients, with women more affected than men (Mgbakogu and Eledo, 2015). A UTI prevalence of 38.3% was reported in diabetic patients in Cameroun (Bissong et al., 2013), while in Kenya and Sudan, varying prevalences of 64% and 35% were reported in males and females, respectively (Mogaka, 2020; Nabaigwa et al., 2017). A slightly lower prevalence (26%) has been reported in Nigeria and Ghana, with *E. coli* being the commonest bacteria isolate (Mgbakogu and Eledo, 2015; Sakyi et al., 2017).

To avoid related UTI complications in diabetic patients, the successful management of UTI depends on accurate identification of pathogens and the selection of effective antibacterial therapy for treatment (Donkor et al., 2017). However, the emergence of multidrug-resistant strains has rendered the treatment of these infections ineffective, posing a major challenge for their treatment. Furthermore, virulence markers carried on a large number of pathogenic-associated islands in bacterial pathogens increase their ability to resist and overcome

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host immune defenses, and subsequently reduce treatment outcomes, leading to severe infections (Malekzadegan et al., 2018). The characterization of virulence factors is critical in improving our understanding of the pathogenicity of the common bacteria associated with UTI (Firoozeh et al., 2014).

Our study investigated the etiology, resistance profiles, and risk factors of bacteria-associated bacteriuria in diabetic patients in Ghana, as well as the types of uropathogen present in the urine of diabetic patients with good and poor glycemic control. Furthermore, the study determined the antibiotic resistance genes, phylogenetic groupings, and virulence factors of *Escherichia coli* isolates associated with UTI in diabetic patients.

## METHODS

This cross-sectional study was carried out with 982 confirmed diabetic patients attending the diabetic clinic in Korle-Bu teaching hospital, from June 2018 to October 2019. The sample size was determined using an assumed UTI prevalence of 50%. The minimum sample size was obtained using the formula  $n = z^2 * p(1-p) / d^2$  (Daniel, 1999). Where  $n$  is the required sample size,  $z$  is the normal deviation (= 1.96) corresponding to the 95% confidence interval,  $p$  is the proportion of the target population with desired characteristics (0.5 = 50%), and  $d$  is degrees of freedom (= 0.05). Confirmed diabetic Ghanaians at the National Diabetes Management and Research Centre (NDMRC) were included in the study, with those on antimicrobial treatments for up to 14 days excluded from this study. After obtaining informed consent from each patient, a self-administered questionnaire was used to obtain information on demographic and socio-economic characteristics. Midstream-clean-catch urine from participants was inoculated onto cysteine lactose electrolyte-deficient (CLED) agar and incubated at 37°C for 16–18 h. UTI was defined as the presence of a positive urine culture ( $\geq 10^5$  colony-forming units [CFU]/ml).

### Bacterial identification

Identification of isolates was performed according to morphological characteristics on the culture media, Gram reaction, and biochemical tests, including triple sugar iron, indole, urease, citrate, catalase, and coagulase tests (KonemannAllen et al., 2006). The API 20E identification system (bioMerieux SA, Marcy l'Etoile, France) was also used to confirm the Gram-negative isolates. Confirmed *E. coli* isolates were kept frozen in tryptic soy broth (Merck Co., Germany), containing 20% glycerol (Merck KGaA, Germany) at  $-70^\circ\text{C}$  until further experiments.

### Antibacterial susceptibility

Antibacterial susceptibility testing of the isolates was performed using the Kirby–Bauer disk diffusion method for sensitivity testing, based on guidelines and breakpoints from the Clinical and Laboratory Standards Institute (CLSI, 2015). The antibiotics tested included ampicillin (10  $\mu\text{g}$ ), amoxicillin/clavulanate acid (10  $\mu\text{g}$ ), cefotaxime (30  $\mu\text{g}$ ), ceftriaxone (30  $\mu\text{g}$ ), nalidixic acid (30  $\mu\text{g}$ ), trimethoprim-sulfamethoxazole (1.25  $\mu\text{g}$ ), gentamicin (10  $\mu\text{g}$ ), and ciprofloxacin (5  $\mu\text{g}$ ). *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, and *Staphylococcus aureus* ATCC 29213 were used as the quality-control strains for antibacterial susceptibility testing.

### Molecular characterization

Genomic DNA was extracted from the *E. coli* isolates by suspending colonies of fresh bacterial culture in 200 ml of sterile water. The suspension was heated at  $98^\circ\text{C}$  for 10 min and centrifuged at 17 900 g for 5 min. The supernatant was recovered and used as a template for polymerase chain reaction (PCR) testing.

Gene amplification was performed for 16 virulence factors relating to adhesions, toxins, iron capture systems, protectins, uropathogenic-specific protein, and the aerobactin system, as previously reported

**Table 1**  
Socio-demographic characteristics of study participants

Characteristics	No.	(%)
Age	20–30	22 (2.2)
	31–40	50 (5.1)
	41–50	202 (20.4)
	51–60	260 (26.3)
	61–70	234 (23.8)
	71–80	170 (17.3)
	81–90	44 (4.5)
Sex	Male	212 (21.6)
	Female	770 (78.4)
Marital status	Divorced	20 (2)
	Married	870 (89)
	Never married	14 (1.4)
	Separated	2 (0.2)
	Widowed	76 (7.7)
Education status	No formal	186 (18.9)
	Basic	220 (22.4)
	Secondary	346 (35.2)
	Tertiary	230 (23.4)
Work status	Gov. employed	182 (18.5)
	Non-employed	72 (7.3)
	Self-employed	56 (5.7)
	Unemployed	524 (53.3)
Type of diabetes	Type1	70 (7.1)
	Type2	912 (92.9)
Duration of diabetes (yrs)	1–5	280 (28.5)
	6–10	298 (30.3)

(Bingen-Bidois et al., 2002; Clermont et al., 2013; Ewers et al., 2005; Huang et al., 1995; 2000; Johnson et al., 2008; Johnson et al., 2003; Yamamoto et al., 1995; Zhao et al., 2009) using the primers listed in Supplementary Table 2. The virulence genes were amplified in five primer pools: 1 (*iron*, *sfa*, *iuc*, *sat*), 2 (*Cnf1*, *iutA*, *papC*, *hlyD*), 3 (*usp*, *ompT*, *KpsMTII*, *papA*), 4 (*KpsMTIII*, *ibeA*), and 5 (*hra*, *ireA*). For the purposes of this study, only *E. coli* isolates were further analyzed for virulence factors and phylogenetic groupings.

### Phylogenetic analysis

Phylogenetic groups of the isolates were investigated using the quadruplex PCR method described by Clermont et al. (2013) based on the presence of the genes *chuA*, *yjaA*, *TspE4.C2*, and *arpA*. According to the amplification results, the *E. coli* isolates were classified into one of the major phylogenetic groups: A, B1, B2, C, D, or F.

### Statistical analysis

Data were analyzed using GraphPad Prism software, version 6. Bacteriuria was defined as bacterial growth of  $\geq 10^5$  colony-forming units/ml urine sample on CLED. Associations between socio-demographic characteristics and the development of UTI, phenotypic resistance, and virulence factors were assessed using the chi-square test. A  $p$ -value  $< 0.05$  was considered statistically significant.

## RESULTS

### Socio-demographic characteristics of study participants

The study participants comprised 212 males (21.6%) and 770 females (78.4%) (Table 1). The predominant age group was 51–60 years [260/982 (26.3%)], followed by 61–70 years [234/982 (23.8%)] and 41–50 years [202/982 (20.4%)] (Table 1). Most of the patients were married [870/982 (89%)], unemployed [524/982 (53.3%)], and with type 2 diabetes [912/982 (92.9%)] (Table 1).

**Table 2**  
Risk factors associated with urinary tract infections

Characteristics	Total No. of UTI-positive patients (n = 90) No. (%)	Total No. of UTI-negative patients (n = 892) No. (%)	Odds ratio	p-value
<b>Age in years</b>				
< 60	42 (15.3)	232 (84.7)	0.417	<b>0.003</b>
≥ 60	48 (6.8)	660 (93.2)		
<b>Sex</b>				
Male	12 (5.7)	200 (94.3)	1.89	0.158
Female	78 (10.1)	692 (89.9)		
<b>Previous UTI</b>				
Positive	10 (15.7)	160 (84.2)	0.437	<b>0.013</b>
Negative	30 (7.6)	732 (92.4)		
<b>Hypertension</b>				
Positive	68 (24.3)	212 (75.7)	0.077	<b>0.001</b>
Negative	22 (3.1)	680 (96.9)		
<b>Kidney stone</b>				
Positive	4 (14.3)	24 (85.7)	0.595	0.062
Negative	86 (9.1)	868 (97.3)		
<b>Burning sensation</b>				
Positive	16 (17)	78 (8.7)	0.445	0.062
Negative	74 (8.4)	810 (91.6)		
<b>Frequent urination</b>				
Positive	58 (19.6)	119 (80.4)	0.189	<b>0.001</b>
Negative	32 (4.4)	347 (95.6)		
<b>Rush urine</b>				
Positive	42 (42.9)	28 (57.1)	0.077	<b>0.001</b>
Negative	48 (5.4)	418 (94.6)		
<b>Type of diabetes</b>				
Type1	16 (22.9)	27(77.1)	0.298	<b>0.009</b>
Type2	74 (8.1)	419 (91.9)		
<b>Duration of diabetes</b>				
< 5 yrs	40 (14.3)	120 (85.7)	0.46	<b>0.013</b>
> 5 yrs	50 (7.1)	326 (92.9)		

#### Comparisons between diabetic UTI-positive and UTI-negative patients

Out of a total of 982 diabetic urine samples tested, 9.2% (90/982) had urinary tract infections. Of the 90 positive patients, 86.7% (78/90) were female and 13.3% (12/90) were male (Table 2). The predominant age range among UTI-positive patients was 61–70 years [35.6% (32/90)], followed by 41–50 years [22.2% (20/90)] and 11–20 years [2.2% (2/90)].

There were significant associations between UTI and the following variables: age (OR = 0.417,  $p = 0.003$ ), previous UTI (OR = 0.437,  $p = 0.013$ ), hypertension (OR = 0.077,  $p = 0.001$ ), frequent urination (OR = 0.189,  $p = 0.001$ ), type 2 diabetes mellitus (OR = 0.298,  $p = 0.009$ ), and duration of diabetes > 5 yrs (OR = 0.46,  $p = 0.013$ ) (Table 2). However, gender (OR = 1.89,  $p = 0.158$ ) did not show any significant association with urinary tract infection in this study.

#### Distribution of uropathogens and the renal threshold levels

The following isolates were identified in the tested urine samples: *Klebsiella* spp. [55.6% (50/90)], *Escherichia coli* [31.1% (28/90)], *Citrobacter* spp. (6.7%), *Proteus* spp. (4.4%), and *Pseudomonas* spp. (2.2%). Patients with urine cultures positive for uropathogens had the following fasting blood sugar levels: 60% (30/50) of patients with *Klebsiella* spp. had a fasting plasma glucose (FPG) level lower than the threshold of 10 mmol/l, while 40% (20/50) of patients with *Klebsiella* spp. had an FPG greater than the threshold of 10 mmol/l (Figure 1). Of the patients with *Escherichia coli* isolates, 71.4% (20/28) had an FPG below the threshold, compared with 28.6% (8/28) of patients whose FPG values were above the threshold. However, patients with *Pseudomonas* spp., *Proteus* spp., and *Citrobacter* spp. isolates in their urine samples had FPG levels below the renal threshold of 10 mmol/l.

#### Antibiotic susceptibility patterns of uropathogens

According to sensitivity testing of uropathogens, *Klebsiella* spp. exhibited a relatively high level of resistance to ampicillin (88.8%),

moderate resistance to trimethoprim-sulfamethoxazole (48%), nalidixic acid (48%), and ceftriaxone (40%), and low resistance to cefotaxime (28%), amoxicillin-clavulanate (24%), ciprofloxacin (24%), and gentamicin (12%) (Table 3). *Escherichia coli* showed similar patterns of resistance to ampicillin (85.7%), trimethoprim (42.8%), nalidixic acid (50%), cefuroxime (35.7%), cefotaxime (28.6%), amoxicillin-clavulanate (21.4%), ciprofloxacin (21.4%), and gentamicin (14.3%) (Table 3).

#### Multidrug-resistant prevalence profiles of uropathogens

Most of the *Klebsiella* spp. and *E. coli* isolates were resistant to amoxicillin-clavulanate, cefotaxime, ceftriaxone, ciprofloxacin, and gentamicin. *Klebsiella* spp. exhibited a multidrug-resistant prevalence of 52% (26/50), compared with *E. coli* [50% (14/28)] and *Citrobacter* spp. [33.3% (2/6)]. The multidrug-resistant profiles of multidrug-resistant isolates were highly variable among *Klebsiella* spp. and *E. coli* (Table 4).

#### Phylogenetic groups, distributions of VFs, and antibiotic resistance patterns of isolates

In total, 22 *E. coli* isolates were characterized for phylogenetic grouping and virulence factors. The phylogenetic distribution analyses revealed higher numbers of the *E. coli* isolates were group D [41% (9/22)] and group B2 [32% (7/22)] (Table 5). The distribution of VFs in each phylogenetic group was compared with those of the other phylogenetic groups combined. The results indicated that *sfa-iutA-KpsTMII-KpsTMIII* genes were commonly associated with group B2, while *iutA-ibe* were also associated with group D. The *hrA* gene was associated with only two group C isolates. Although group B2 accounted for most of the virulence genes, group C was more resistant to most of the tested antibiotics (Table 5).

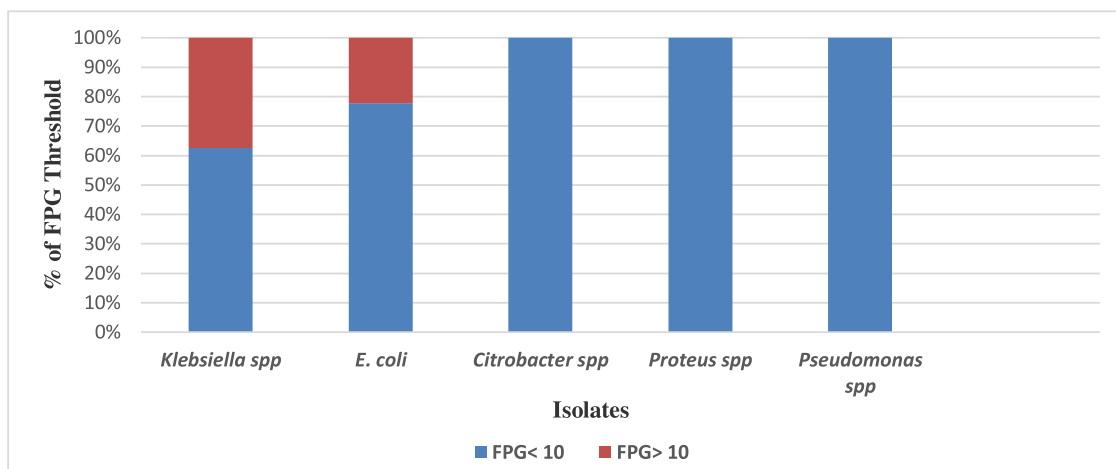


Figure 1. Distribution of uropathogens and fasting plasma glucose (FPG) measurements in patients.

Table 3  
Susceptibilities and resistance profiles of uropathogens

Antibiotic	Pattern	<i>Klebsiella spp.</i> (50)	<i>E. coli</i> (28)	<i>Citrobacter spp.</i> (6)	<i>Proteus spp.</i> (4)	<i>Pseudomonas spp.</i> (2)	Total No. (90)
AMP	S (%)	6 (12)	4(14.3)	0(0)	0(0)	0(0)	10 (11.1)
	R (%)	44(88)	24(85.7)	6(100)	4(100)	2(100)	80(88.9)
AMC	S (%)	38(76)	22(78.6)	4(66.7)	4(100)	2(100)	70(77.8)
	R (%)	12(24)	6 (21.4)	2(33.3)	0(0)	0(0)	20(22.2)
CTX	S (%)	36(72)	20(71.4)	4(66.7)	4(100)	2(100)	66(73.3)
	R (%)	14(28)	8(28.6)	2(33.3)	0(0)	0(0)	24(26.7)
CTR	S (%)	30(60)	18(64.3)	4(66.7)	4(100)	2(100)	38(42.2)
	R (%)	20(40)	10(35.7)	2(33.3)	0(0)	0(0)	32(35.6)
CIP	S (%)	38(76)	22(78.6)	6(100)	4(100)	2(100)	72(80)
	R (%)	12(24)	6(21.4)	0(0)	0(0)	0(0)	18(20)
GEN	S (%)	44(88)	24(85.7)	6(100)	4(100)	2(100)	80(88.9)
	R (%)	6(12)	4(14.3)	0(0)	0(0)	0(0)	10(11.1)
NAL	S (%)	26(52)	14(50)	4(66.7)	0(0)	0(0)	44(48.9)
	R (%)	24(48)	14(50)	2(33.3)	4(100)	2(100)	46(51.1)
TRIM	S (%)	26(52)	16(57.1)	4(66.7)	4(100)	2(100)	52(57.8)
	R (%)	24(48)	12(42.8)	2(33.3)	0(0)	0(0)	38(42.2)

Key: AMP: ampicillin, AMC: amoxicillin-clavulanate, CTX: cefotaxime, CTR: ceftriazone, CIP: ciprofloxacin, GEN: gentamicin, NAL: nalidixic acid, TRIM: trimethoprim-sulfamethoxazole

Table 4  
Resistance profiles of multidrug-resistant uropathogens

Isolates	No. of isolates	Resistant patterns
<i>Klebsiella spp.</i>	6	AMP+AMC+CTX+CTR+CIP+GEN+NAL+TRIM
	6	AMP+AMC+CTX+CTR+CIP+NAL+TRIM
	2	AMP+CTX+CTR+CIP+NAL+TRIM
	4	AMP+CTR+NAL+TRIM
<i>Escherichia coli</i>	8	AMP+CIP+NAL+TRIM
	6	AMP+AMC+CTX+CTR+CIP+GEN+NAL+TRIM
	4	AMP+AMC+CTX+CTR+CIP+NAL+TRIM
	2	AMP+CTR+NAL+TRIM
<i>Citrobacter spp.</i>	2	AMP+NAL+TRIM
	2	AMP+AMC+CTX+CTR+NAL+TRIM

Key: AMP: ampicillin, AMC: amoxicillin-clavulanate, CTX: cefotaxime, CTR: ceftriazone, CIP: ciprofloxacin, GEN: gentamicin, NAL: nalidixic acid, TRIM: trimethoprim-sulfamethoxazole

## DISCUSSION

Urinary tract infection is a common disease associated with diabetic patients, and its diagnosis and treatment have important implications for patients' health and healthcare costs (Alimohammadi, 2007; Orenstein and Wong, 1999; Yadav and Prakash, 2016). An overall UTI prevalence of 9.2% was found among diabetic patients in this study. This is in line with studies carried out in the USA, Romania, Ethiopia, and

Canada, which reported prevalences of 8.2%, 8.4%, 10.9%, and 7.9%, respectively (Chiță et al., 2013; Yu et al., 2014; Zhanel et al., 1995). However, in contrast to our findings, higher prevalences of 35%, 26.4%, 21%, 17.5%, 22.5%, and 22% have been reported in previous studies carried out in Kuwait, Ghana, Nepal, Ethiopia, Germany, and Uganda, respectively (Alimohammadi, 2007; Johnson and Stell, 2002; Kabiswa et al., 2018; Rabindra et al., 2013; Sakyi et al., 2013; Sewify et al., 2016; Storme et al., 2019; Yadav and Prakash 2016). The variation in prevalence across these countries may be due to varying socio-demographic and cultural differences (Kebamo et al., 2017).

Of those diabetic patients who were positive for urinary tract infections in our study, 86.7% were female. This finding was similar to the 88.5% figure reported in Kuwait (Johnson et al., 2013). Several other studies — in Germany, Nepal, Ethiopia, and the USA — have reported higher UTI rates in females than in male counterparts (Iranpour et al., 2013; Johnson et al., 2003; Johnson et al., 2002; Kabiswa et al., 2018). Anatomical variations in the urethra between males and females, which is shorter in females than in males, and the proximity of the urethral meatus to the anus may be responsible for an elevated UTI prevalence among females (Kebamo et al., 2017).

Our study found a higher occurrence of urinary tract infections [32 (35.6%)] in the 61–70 years age group. This finding was in agreement with studies carried out in Romania, Saudi Arabia, the UK, Netherlands, and Washington State, USA (Al-Rubeaan et al., 2013; Boyko and Lipsky, 1995; Chiță et al., 2017; Hirji et al., 2012; Venmans et al., 2009).



**Table 5**  
Distribution of virulence factor genes and resistant patterns among different phylogenetic groups of *E. coli* isolates

Virulence genes	Phylo-groups B2 (n = 11) (%)	D (n = 11) (%)	C (n = 6) (%)	Total (%) 28 (100%)
<i>sfa</i> (n = 2)	1 (9.1)	0	1 (16.7)	2 (7.1%)
<i>iutA</i> (n = 5)	2 (18.2)	2 (18.2)	1 (16.7)	5 (17.9%)
<i>cnf1</i> (n = 1)	1 (9.1)	0	0	1 (3.6%)
<i>papA</i> (n = 1)	1 (9.1)	0	0	1 (3.6%)
<i>hrA</i> (n = 1)	0	0	1 (16.7)	1 (3.6%)
<i>ibe</i> (n = 2)	0	2 (18.2)	0	2 (7.1%)
<i>KpsTMII</i> (n = 2)	2 (18.2)	0	0	2 (7.1%)
<i>KpsMTIII</i> (n = 4)	3 (27.3)	0	1 (16.7)	4 (14.3%)
<b>Resistant patterns</b>				
CTX (n = 6)	2 (18.2)	4 (36.4)	0	6 (21.4%)
AMP+CTR+NAL+TRIM (n = 2)	1 (9.1)	1 (9.1)	0	2 (7.1%)
AMP+AMC+CTX+CTR+CIP+GEN+NAL+TRIM (n = 5)	1 (9.1)	0	4 (66.7)	5 (17.9%)

**Key:** AMP: ampicillin, AMC: amoxicillin-clavulanate, CTX: cefotaxime, CTR: ceftriazone, CIP: ciprofloxacin, GEN: gentamicin, NAL: nalidixic acid, TRIM: trimethoprim-sulfamethoxazole

This supports the suggestion that, as society advances in age, the burden of urinary tract infections might be expected to escalate (Rowe and Juthani-Mehta, 2013). Moreover, the older participants were found to have other forms of comorbidity, which increased with the duration of diabetes. This finding was in line with a review report from the USA, which highlighted the impact of chronic comorbid conditions on diabetes care (Piette and Kerr, 2006).

The associated risk factors for UTI — age, duration of diabetes, previous urinary tract infection, and hypertension — were found to be statistically significant. This finding was in agreement with studies carried out in India, the Netherlands, Canada, and the USA (Boyko and Lipsky, 1995; Geerlingset et al., 2000; Janifer et al., 2009; Zhanel et al., 1995). A study by Yu et al. (2014) reported an association between advanced age, duration of diabetes, and previous UTIs with a high risk of contracting UTI (Yu et al., 2014). However, in contrast to our findings, an Ethiopian study found diabetic patients with no previous history of UTI to have higher odds of contracting a UTI (Gutema et al., 2019). It is noteworthy that the female gender did not show a significant association with urinary tract infections. However, a study carried out in Spain reported male gender as a risk factor for contracting urinary tract infection (Briongos-Figuero et al., 2012). Another study in Ethiopia found that sex was not significantly associated with bacteriuria (Nigussie and Amsalu, 2017). Furthermore, a study in Sudan found no significant association between age, duration of diabetes, or type of diabetes and the prevalence of UTI (Hamdan et al., 2015).

The predominant uropathogens identified in this study were *Klebsiella* spp. (55.6%), followed by *Escherichia coli* (31.1%) and *Citrobacter* spp. (6.7%). However, in contrast to our findings, most studies have reported a higher prevalence of *Escherichia coli* as compared with *Klebsiella* spp., for example in Egypt (38.6% vs 21.5%), Uganda (8.6% vs 2.85%), Ethiopia (25.6% vs 20.5%), India (41.5% vs 14.4%), Nepal (58.1 vs 21.8%), and Nigeria (42.9% vs 28.6%) (Antwi et al., 2008; Desouky et al., 2020; Ifediora et al., 2016; Sakyiet et al., 2013; Sharma et al., 2012; Yadav and Prakash, 2016). Members of the Enterobacteriaceae family of Gram-negative bacilli have been implicated as etiological agents of UTIs, and is estimated that more than 85% of the Enterobacteriaceae family are responsible for UTIs (Antwi et al., 2008). Another Ethiopian study on diabetic patients with UTI reported *Escherichia coli* and *Klebsiella* spp. to have an equal prevalence of 12.1% each (Kebamo et al., 2017). The variations in prevalence among uropathogens may be due to differences in study design and sample size. It is noteworthy that members of the Enterobacteriaceae have many factors accountable for their uro-epithelial attachment, including the colonization of phenotype receptors in the urogenital mucosa with adhesives, pili, fimbriae, and P-1 (Das et al., 2006).

A high level of resistance to various classes of antibiotic was found among uropathogenic isolates. Forty-six per cent of the isolates isolated

were multidrug-resistant (MDR), as defined by resistance to at least three or more antimicrobial agents (Magiorakos et al., 2012). Higher prevalences of MDR isolates have been reported in Nepal (67.2%), Turkey (68.7%), and Ethiopia (93.9%) (Alimohammadi, 2007; Gulay et al., 2019; Nigussie and Amsalu, 2017). The emergence of multidrug-resistant bacterial strains may be due to the indiscriminate administration of multiple courses of antibiotic therapy for asymptomatic or mild symptomatic UTI. Patients with chronic diseases such as diabetes are most likely to harbor multidrug-resistant bacteria during UTI, including extended-spectrum  $\beta$ -lactamase Enterobacteriaceae and fluoroquinolone-resistant uropathogens (Desouky et al., 2020). *Klebsiella* spp. and *Escherichia coli* exhibited resistance rates to ampicillin of 88% and 85.7% respectively. This was comparable with studies in Ethiopia (100% and 100%), Nigeria (100% and 100%), and India (88.9% and 86.3%) (Aswani et al., 2014; Ifediora et al., 2016; Kebamo et al., 2017). However, in contrast to our findings, lower levels of resistance to ampicillin (53.5% and 72.13%) in *Klebsiella* spp. and *Escherichia coli* have been reported in Egypt (Desouky et al., 2020). The very high level of resistance to ampicillin may be due to the fact that ampicillin is an old  $\beta$ -lactam antibiotic with minimal side-effects has been abused through incessant misuse. With regard to the  $\beta$ -lactam inhibitors, *Klebsiella* spp. and *Escherichia coli* showed resistances of 24% and 21.4% to amoxicillin-clavulanate. This findings is consistent with studies in Kuwait (24% and 20%), Turkey (12%), Ethiopia (12.5% and 30%), and Egypt (43.2% and 9.9%) (Desouky et al., 2020; Gutema et al., 2019; Gulay et al., 2019; Sewify et al., 2016). In contrast to our findings, higher levels of resistance to amoxicillin-clavulanate have been reported for *Klebsiella* spp. and *Escherichia coli* in Nepal (89.7% and 90.1%) and India (82%) (Nigussie and Amsalu, 2017; Sewify et al., 2016). These differences in resistance levels may be due to varying dependency on antibiotic usage among diabetic patients in various countries.

*Klebsiella* spp. and *Escherichia coli* uropathogens demonstrated resistance levels of 28% and 28.6% to cefotaxime, which is in the third-generation cephalosporin class of antibiotics. This was consistent with studies in Egypt (19.7% and 28.7%) and Kuwait (25% and 28%) (Desouky et al., 2020; Sewify et al., 2016). In contrast, a higher levels of *Klebsiella* spp. and *Escherichia coli* resistance to cefotaxime have been reported in India (61.1% and 55.6%) (Aswani et al., 2014). This was comparable to a study from India (51.7% and 50%, respectively) (Aswani et al., 2014). However, in contrast to our findings, a study in Nigeria reported no resistance to ceftriaxone for both pathogens (Ifediora et al., 2016). The high levels of resistance observed among uropathogens in some regions could be the result of high levels of extended-spectrum  $\beta$ -lactamases (ESBLs) induced by selective pressure from broad-spectrum antimicrobial therapy (We et al., 2014).

Our study found high levels of resistance to ciprofloxacin by *Klebsiella* spp. and *Escherichia coli* (24% and 11.4%, respectively). This is

comparable to levels reported in studies in Kuwait (34% and 34%), Nepal (32.7%), and Ethiopia (37.5% and 30%) (Desouky et al., 2020; Sewify et al., 2016; Yadav and Prakash, 2016). In contrast to our study findings, resistance levels for *Klebsiella* spp. and *Escherichia coli* to ciprofloxacin of 0% and 0% were reported in a study in Nigeria (Ifediora et al., 2016). Opintan et al. (2015) study on antimicrobial resistance, reported a resistance prevalence of > 50% to third-generation cephalosporins and fluoroquinolones throughout Ghana. In Ghana, the standard treatment guidelines recommend the use of ciprofloxacin for treating urinary tract and bloodstream infections (MOH, 2010) and this may be one of the reasons for the relatively low resistance to ciprofloxacin detected in this study.

Resistance levels to gentamicin — an aminoglycoside class of antibiotic — in *Klebsiella* spp. and *Escherichia coli* were found to be 12% and 14.3%, respectively. This findings is in agreement with levels of 20% and 12.5% reported in Ethiopia (Gutema et al., 2019). In contrast to our findings, levels of 0% and 0% have been reported in Nigeria (Ifediora et al., 2016). However, higher levels of resistance to gentamicin have been reported in India (31.8% and 31.5%), Nepal (40.9%), and Ethiopia (72.1%) (Aswani et al., 2014; Nigussie and Amsalu, 2017; Yadav and Prakash, 2016). Aminoglycosides, such as gentamicin, are often used as a combination therapy, and the low usage of this antibiotic may have contributed to the low resistance levels observed in our findings.

With regard to trimethoprim-sulfamethoxazole antibiotic, our study found resistance levels of 48% and 42.8% for *Klebsiella* spp. and *Escherichia coli*. This finding was consistent with levels of 47% and 48% reported in Kuwait (Sewify et al., 2016). An even higher level of resistance of 81.8% was reported in a study in Turkey (Gulay et al., 2019). The levels of resistance observed for trimethoprim-sulfamethoxazole in our study are quite concerning, and may be due to the inappropriate use of these antibiotic.

Our study also reports for the first time the prevalences of phylogenetic groups and their virulence factors in 22 *E. coli* isolates from diabetic patients in Ghana. The majority of the virulence genes were found to be more diverse in phylogenetic group B2 isolates, and the detection of toxin gene *cnf1* may participate in the dissemination of *E. coli* strains (Wiles et al., 2008). Furthermore, the association of toxin gene *cnf1* with group B2 supports the identity of this group as a more virulent strain. The rapid surge in the population of resistant *E. coli* among hospitalized patients is of public health concern (Lee et al., 2015). Therefore, the timely detection of antibacterial-resistant *E. coli* strains, phylogenetic groupings, and virulence factor genes is of utmost priority in order to monitor resistance phenotypes as well as to provide physicians with appropriate treatment guidelines (Aghemwenhio et al., 2017). It has been reported that *E. coli* of the phylogenetic groups A and B1 are commensals, while groups B2 and D are more pathogenic and have been associated with extra-intestinal infections (Clermont et al., 2000). The majority of *E. coli* in this study belonged to phylogenetic group B2, and these contained most of the virulence genes. This finding was consistent with studies from different geographical regions that have documented higher prevalences of group B2 (Bashir et al., 2012; Iranpour et al., 2015; Miranda-Estrada et al., 2017). However, in contrast to our findings, a previous study has reported a higher prevalence of group A (Kabiswa et al., 2018). The prevalences and distributions of *E. coli* phylogenetic groups have been recorded to be largely associated with the health status of the patients, patients' genetic factors, dietary factors, antibiotic stewardship, and geographical conditions (Derakhshandeh et al., 2013).

## CONCLUSION

Our study revealed a UTI prevalence of 9.2% among diabetic patients, with *Klebsiella* spp. and *Escherichia coli* being the predominant uropathogens identified. Female patients within the age range 61–70 years were the most infected. The associated risk factors for urinary tract infections in this study were age, duration of diabetes, and previous history of UTI. The uropathogens exhibited a high level of resistance to

ampicillin, ceftriaxone, trimethoprim-sulfamethoxazole, nalidixic acid, and amoxicillin-clavulanate. Most of the *E. coli* isolates identified in this study belonged to the phylogenetic groups B2 and D, and they contained a range of virulence factor genes.

## Declaration of Competing Interests

The authors declare that they have no competing interests.

## Ethical approval and consent to participate

This study was approved by the Ethics Committee of the College of Health Sciences, the University of Ghana (Ethics Identification Number: CHS-ET/M.2-PS.9/2018-2019). Participation was voluntary, and written consent was obtained from each participant, following the Ethics Committee's guidelines.

## Consent to publish

Not applicable

## Availability of data and materials

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

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## Authors' contributions

FOA and FSC conceived, designed, and performed the study, and drafted the manuscript. DAM and MNQ performed the experiments and drafted some sections of the manuscript. SBD and OTM assisted with experimental analysis, and interpreted the data. All authors were involved in the drafting of the manuscript. All authors read and approved the final manuscript.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2021.10.007.

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