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ORIGINAL ARTICLE

Molecular Pathotyping of *Escherichia Coli* Colonising Urinary Tract and Their Drug Susceptibility Patterns Among Patients at Outpatient Department of Zonal Referral Hospital in Southern Highlands, Tanzania

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ABSTRACT

Background: Uropathogenic E. coli (UPEC) is the most common causative agent of both community-acquired and hospital-acquired urinary tract infections (UTIs). However, ***E. coli*** encompasses several other pathotypes that cause a wide range of intestinal and extraintestinal infections. For intestinal infections, the main pathotypes include Enteropathogenic ***E. coli*** (EPEC), Shiga toxin-producing ***E. coli*** (STEC), Enteroaggregative ***E. coli*** (EAEC), Enterotoxigenic ***E. coli*** (ETEC), Entero-invasive ***E. coli*** (EIEC), and Diffusely Adherent ***E. coli*** (DAEC).

Methods: This was a cross-sectional hospital-based study conducted in the Mbeya Zonal Referral Hospital (MZRH) from December 2022 to March 2023. A total of 315 participants from whom the urine samples were collected conveniently by using a standard formula ($N = (Z^2X\ P\ (1-P)/e^2$. Whereby N = minimum required sample size, Z = corresponding level of confidence (95%), ***P*** = proportion of the characteristics of interest (23%) and e = margin of error (5%). This enabled the calculation of the minimum sample size of 292 plus 10% of non-respondents.

Results: A total of 315 participants were recruited in the study; the median age (IQR) was 37 (25-53), whereby 46.7% were aged between 18 and 34 years, 30.1% were aged between 35 and 54 years, and 23.2% were older than 54 years. Male participants were 44.4%, urban participation made up 52.7% of the participants, and 60.6% of them were unemployed

Conclusions: The findings of this study showed that the predominant pathotype associated with urinary tract infections was UPEC, followed by EAEC and EPEC, with ETEC being the least frequently identified. The study also indicated that all isolated pathotypes were resistant to ampicillin and amoxicillin/clavulanic acid.

BACKGROUND

E. *coli* are facultative anaerobes and gram-negative, and they can be capsulated or non-capsulated. It is normally found in the gut of both man and animals. *E. coli* poses a significant public health burden in Tanzania, particularly concerning antimicrobial resistance (AMR). Studies indicate that *E. coli* is a leading cause of urinary tract infections (UTIs), neonatal meningitis, diarrhoea and bloodstream infections, with resistance rates to commonly used antibiotics such as ampicillin, ciprofloxacin and gentamicin ranging from 28% to over 90% in various settings.[1] In Dar es Salaam, a study found that nearly a quarter of shared and private latrines were contaminated with extended-spectrum beta-lactamase (ESBL)-producing E. coli, highlighting the role of environmental reservoirs in transmission.[2] Furthermore, a study in Zanzibar reported a 13.4% prevalence of ESBL-producing E. coli among UTI patients, with high resistance to multiple antibiotics, including amoxicillin and ceftriaxone. These findings underscore the urgent need for enhanced surveillance, improved sanitation, and judicious antibiotic use to combat the growing threat of AMR in Tanzania.[3] Uropathogenic *E. coli* (UPEC) is the most common causative agent of both community-acquired and hospital-acquired urinary tract infections (UTIs). However, *E. coli* encompasses several other pathotypes that cause a wide range of intestinal and extraintestinal infections. For intestinal infections, the main pathotypes include Enteropathogenic E. coli (EPEC), Shiga toxin-producing *E. coli* (STEC), Enteroaggregative *E. coli* (EAEC), Enterotoxigenic *E. coli* (ETEC), Entero-invasive *E. coli* (EIEC), and Diffusely Adherent *E. coli*(DAEC). For extraintestinal infections, the key pathotypes are neonatal meningitis-causing *E. coli*

(NMEC), sepsis-causing *E. coli* (SEPEC), and Uropathogenic *E. coli* (UPEC).[4]

Horizontal gene transfer (HGT) of resistance genes and mutations in *E. coli* enhances the likelihood of antimicrobial resistance and contributes to genetic diversity.[5] Overlapping of genes between different pathotypes can lead to the creation of hybrid strains, enabling a single pathotype to cause infections beyond its original scope.[6-8] As observed in a study conducted in regional referral hospitals of Tanzania, where a single *E. coli* strain was found to possess virulence genes from multiple pathotypes, creating hybrid strains.[9]

Hybrid strain formation accounts for the development of antimicrobial resistance, which is a public health concern.[10] hybrid uropathogens account for increased risk of AMR, as reported in 2019.[11] Antibiotic resistance not only contributes to higher morbidity and mortality rates but also leads to increased healthcare costs.[12] In low-income countries, the situation is exacerbated by limited access to healthcare, which drives patients to self-medicate, increasing the problem of drug resistance.[13]

UTI treatment is often initiated empirically, which is one of the contributing factors to antibiotic resistance and treatment failure.[14] A study conducted in Uganda highlighted that improper use of antibiotics in infection treatment not only has adverse effects but also significantly increases the likelihood of microbes developing resistance.[15] Furthermore, there is limited literature in most low- and middle-income countries like Tanzania regarding the specific *E. coli* pathotypes responsible for UTIs and their resistance patterns. This study aims at molecular pathotyping of *E. coli* colonising urinary tracts and their drug susceptibility patterns among patients attending the medical outpatient department at Mbeya Zonal Referral Hospital.

METHODS

Study Design, Study Participants and Study Sites

This was a cross-sectional hospital-based study conducted in the Mbeya Zonal Referral Hospital (MZRH) from December 2022 to March 2023. A total of 315 participants from whom the urine samples were collected conveniently by using a standard formula ($N = (Z^2X\ P\ (1-P)/e^2$. Whereby N = minimum required sample size, Z = corresponding level of confidence (95%), P = proportion of the characteristics of interest (23%) and e = margin of error (5%). This enabled the calculation of the minimum sample size of 292 plus 10% of non-respondents.

All participants aged 18 years and above who presented with signs and symptoms of UTI were recruited upon their consent. All patients under antibiotics and who were using antibiotics for the past two weeks were excluded.

Sample Collection, Culture, DST, DNA Extraction and PCR

Participants were asked to collect a clear midstream urine sample into a sterile urine container. Mac Conkey (MCA) powder (Oxoid, Hampshire, UK) was used for urine culture. The urine sample was inoculated onto the MCA plate, which was placed in the incubator (ThermoScientific, Massachusetts, USA) under anaerobic conditions at 37 °C for 18 to 24 hours. Colony morphology, lactose fermentation, gram staining, oxidase, triple sugar iron, motility, and indole and citrate utilisation were among the conventional laboratory techniques used for identification and differentiation of *E. coli* from non-*E. coli*. An antibiotic susceptibility test was done by using the Kirby-Bauer disc diffusion method according to the Clinical and Laboratory Standard Institute (CLSI M-100, 2022).

DNA was Extracted through Boiling Method

10 *E. coli* colonies were transferred in 500 µl of sterile distilled water and boiled at 95°C in a water bath for 10 min. Then suspensions were centrifuged at 10000 g for 1 min, and then 200 µl of supernatants obtained from suspensions were suspended into a PCR tube. Multiplex polymerase chain reaction was used for detection of *E. coli* pathotypes. Detection of virulence factor-encoding genes associated with EPEC (*eaeA* and *bfpA*), EAEC (*aatA* and *aaiC*), EHEC (*stx1* and stx2), ETEC (*relt* – heat labile toxin gene and *stla* – heat stable toxin gene), UPEC (*FimH-f*) and EIEC (*ipaH*) (Table 1).

Multiplex PCR was used to detect *E. coli* pathotypes. Detection of virulence factor-encoding genes associated with EPEC (eae), EAEC (aatA), STEC (eae, stx1 and stx2), ETEC (elt and est), and EIEC (ipaH). Pathotyping was performed by employing specific primers for each of the genes investigated. Each pair of primers (0.15 µl of forward and reverse primers) was used for amplifications, with 25 µl of PCR mix containing 12.5 µl of PCR master mix (Qiagen Inc., Valencia, CA, USA), 7.2 µl of nuclease-free water, and 5 µl of DNA template. The reference used strains that were *E. coli* ATCC 43887 positive for *eaeA* and *bfpA* genes of EPEC, *E. coli* ATCC 35401 positive for r*elt* and *stla* genes of ETEC, and *E. coli* 43893 positive for the ial gene of EIEC. Negative control was ATCC E. coli 25922, which was used for standardisation of the multiplex PCR. PCR setup was: an initial denaturation step at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 10 s, annealing at 55°C for 30 s, and extension at 72°C for 10 s, followed by a final extension step at 72°C for 2 min.

Data Analysis

Data were coded, entered and analysed by using Statistical Package for Social Sciences (SPSS) version 20 (IBM SPSS Statistics V.20). Categorical variables were presented using frequencies and proportions, and numerical variables were presented using medians along with respective measures of dispersion (IQR).

Ethics Approval and Consent to Participate

This study received ethical approval from the KCMUCo Research Ethics Committee under approval number PG-175/2022. Informed consent was obtained from all participants before using their sample for research purposes.

RESULTS

Study Participants Characteristics

A total of 315 participants were recruited in the study; the median age (IQR) was 37 (25-53), whereby 46.7% were aged between 18 and 34 years, 30.1% were aged between 35 and 54 years, and 23.2% were older than 54 years. Male participants were 44.4%, urban participation made up 52.7% of the participants, and 60.6% of them were unemployed (Table 2).

TABLE 1: Primer Sequences for E. Coli Pathotyping

SN	Organism	Amplicon size (bp)	Oligonucleotide sequence (5' to 3')
1	ETEC (lt)		
	ETEC	508	5′-CACACGGAGCTCCTCAGTC-3′
	ETECR		5′-CCCCCAGCCTAGCTTAGTTT-3′
	ETEC (st)		
	ETECF	147	5′-GCTAAACCAGTA$^{G}_{A}$GGTCTTCAAAA-3′
	ETECR		5′-CCCGGTACA$^{G}_{A}$GCAGGATTACAACA-3′
2	EHEC (Stx1)		
	EHECF	180	5′-ATAAATCGCCATTCGTTGACTAC-3′
	EHECR		5′-AGAACGCCCACTGAGATCATC -3′
	EHEC (Stx2)		
	EHECF	255	5′-GGCACTGTCTGAAACTGCTCC-3′
	EHECR		5′-TCGCCAGTTATCTGACATTCTG-3′
3	EPEC (eae)		
	EPECF	367	5′-TTCTTGGTGCTTGCGTGTCTTTT-3′
	EPECR		5′-TTTTGTTTGTTGTATCTTTGTAA-3′
4	EIEC (ipaH)		
	EIECF	320	5′-CTGGTAGGTATGGTGAGG-3′
	EIECR		5′-CCAGGCCAACAATTATTTCC-3′
5	EAEC (aatA)		
	EAECF	650	5′-CTGGCGAAAGACTGTATCAT-3′
	EAECR		5′-CAATGTATAGAAATCCGCTGTT-3′
	EAEC (aaiC)		
	EAECF	215	5′-ATTGTCCTCAGGCATTTCAC-3′
	EAECR		5′-ACGACACCCCTGATAAACAA-3′

TABLE 2: Social Demographic Characteristics of Study Participants (N = 315)

Variable	Frequency (n)	n%	
Age			
18-34	147	46.7%	
35-54	95	30.1%	
> 54	73	23.2%	315
Median Age (IQR[a])	37.0 (25.0, 53.0)		
Sex			
Female	175	55.6%	
Male	140	44.4%	315
Occupations			
Not Employed	191	60.6 %	
Employed	124	39.4 %	315
Residence			
Urban	166	52.7 %	
Rural	149	47.3 %	315

IQRa – Interquartile range

Proportion *E. coli* Isolates among Study Participants

Out of 315 participants, those between the ages of 35- 54 had the highest prevalence of *E. coli* at 38.5%, followed by those between the ages of 18- 34 with a prevalence of 37.5%. *E. coli* was more common in females than in males, at 66.3%. Among all participants, unemployed had 63.5% proportion of *E. coli* higher than employed. Rural individuals also had 51.9% proportion of *E. coli* (Table 3).

Proportion of Isolated Bacteria

Of 315 study participants, only 138 (43.8%) had culture-positive results. Among all positive cultures eight bacterial species were isolated. Of all isolated bacteria, *E. coli* was the most common bacteria with proportion of 75.4%. And other bacteria isolated (non-E. *E. coli*) like *Proteus*, *Klebsiella spp* and the others accounted for 24.6% (Figure 1).

Proportion of *E. coli* Pathotypes

Out of the individuals who participated in the study, 104 cases of *E. coli* were identified. Out of these, 100 *E. coli* were successfully pathotyped, while four isolates turned out to be negative for neither of the target pathotypes. Among all the isolated *E. coli* pathotypes, the most common was UPEC (47.0%), followed by EAEC (13.0%), EPEC (13.0%), EHEC (12.0%), EIEC (10%), and finally ETEC (5.0%) (Table 4).

Drug susceptibility of the *E. coli* pathotypes

Of the 13 EAEC isolated among study participants, the majority were 92.3% resistant to both amoxicillin/clavulanic acid and ampicillin, followed by trimethoprim-sulfamethoxazole 69.2%, ciprofloxacin 53.8%, ceftriaxone 22.1%, nitrofurantoin 7.7% and meropenem 7.7%.

Of the 12 EHEC isolated, 83.3% were resistant to both amoxicillin/clavulanic acid and ampicillin, followed by trimethoprim/sulfamethoxazole 83.3%, ciprofloxacin 50.0% and ceftriaxone 33.3%. Of 10 EIEC, 100% were resistant to ampicillin, amoxicillin/clavulanic acid 90%, trimethoprim-sulfamethoxazole 80%, ceftriaxone 60.0%, ciprofloxacin 50.0%, nitrofurantoin 50% and meropenem 10%. Of the 13 EPEC, the majority were resistant to 100% ampicillin, 84.6% trimethoprim-sulfamethoxazole, 61.5% ciprofloxacin, 53.8% ceftriaxone and 30.8% nitrofurantoin. Moreover, out of 5 ETEC, 100% were resistant to amoxicillin/clavulanic acid and ampicillin, followed by 80% for ciprofloxacin, ceftriaxone and trimethoprim-sulfamethoxazole, and 20.0% for nitrofurantoin and meropenem. From 47 UPEC, 93.6% were resistant to ampicillin, 89.4% to amoxicillin/clavulanic acid, 78.7% to trimethoprim-sulfamethoxazole, 61.7% to ciprofloxacin, 51.1% to ceftriaxone, 19.1% to nitrofurantoin, and 8.5% to meropenem. EPEC and EHEC were not resistant to meropenem (Table 5).

TABLE 3: Proportion of E. Coli Isolated Among Study Participants (N=104)

Variable	Frequency (n)	n%
Age		
18-34	39	37.5%
35-54	40	38.5%
> 54	25	24.0%
Sex		
Male	35	33.7%
Female	69	66.3%
Occupations		
Employed	38	36.5%
Not Employed	66	63.5%
Residence		
Urban	50	48.1%
Rural	54	51.9%

TABLE 4: Proportion of Pathotypes of the Isolated E. Coli (N=100)

Pathotype	Frequency (n)	n%
UPEC	47	47.0%
EAEC	13	13.0%
EPEC	13	13.0%
EHEC	12	12.0%
EIEC	10	10.0%
ETEC	5	5.0 %
Total	100	100%

FIGURE 1: Proportion of *E. coli* vs. non-*E. coli* (N=138)

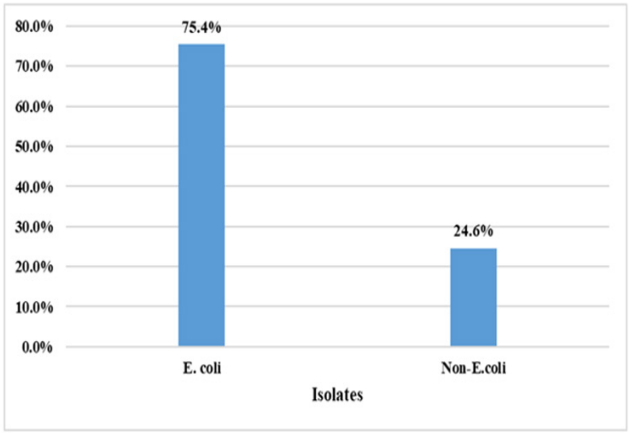

TABLE 5: Drug Resistance Profile of the Isolated *E. Coli* Pathotype (N = 100)

Antibiotic	EAEC(n=13)	EHEC(n=12)	Pathotypes EIEC(n=10)	EPEC(n=13)	ETEC(n=5)	UPEC(n=47)
AMC	12 (92.3%)	10 (83.3%)	9 (90.0%)	10 (76.9%)	5 (100.0%)	42 (89.4%)
AMP	12 (92.3%)	10 (83.3%)	10 (100.0%)	13 (100.0%)	5 (100.0%)	44 (93.6%)
CRO	3 (22.1%)	4 (33.3%)	6 (60.0%)	7 (53.8%)	4 (80.0%)	24 (51.1%)
CIP	7 (53.8%)	6 (50.0%)	5 (50.0%)	8 (61.5%)	4 (80.0%)	29 (61.7%)
SXT	9 (69.2%)	10 (83.3%)	8 (80.0%)	11 (84.6%)	4 (80.0%)	37 (78.7%)
NIT	1 (7.7%)	0 (0.0%)	5 (50.0%)	4 (30.8%)	1 (20.0%)	9 (19.1%)
MEM	1 (7.7%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	1 (20.0%)	4 (8.5%)

AMC: Amoxicillin/Clavulanic Acid, AMP: Ampicillin, CRO: Ceftriaxone, CIP: Ciprofloxacin, MEM: Meropenem, NIT: Nitrofurantoin, SXT: trimethoprim/sulfamethoxazole

DISCUSSION

E. coli was the leading bacterium isolated in this study with a proportion of 75.4%. Similar results were reported in Bangladesh, Northern Ethiopia and Dar es Salaam, Tanzania.[10-12] Also, current study results showed some similarity with the study done in Norway whereby *E. coli* was the most common isolate associated with UTI.[19] These results highlight the fact that *E. coli* is the commensal of most animals and humans and is readily available in the environment. In contrast, the studies conducted in Ghana, Bosnia and Herzegovina and Cape Verde report a lower proportion of *E. coli* infections.[9,14,15] These differences might be attributed to differences in locality, study design and sometimes ethnicity. The findings of the current study also differ from a study conducted in Kilimanjaro, which reported an *E. coli* prevalence of 46.2%.[23] The participants' ages, geographical regions and the study design may explain these disparities in findings. Different studies have used participants with different age and gender limits but also with varying sample types with different disease conditions, e.g., swab or blood samples with different disease manifestations, thus accounting for discrepancies in sample size. Ethnic differences account for different attitudes, which can be attributed to social and cultural issues and the way they practice disease prevention strategies. Other studies have deployed the more sophisticated technique such as whole genome sequencing (WGS), which gives more explanatory results.[9] These results have varied effects on healthcare and medical research, including the necessity for specialised therapies, preventive measures, and additional research into the elements that contribute to *E. coli*'s predominance in causing UTIs.

In the current study, UPEC was found to have a 42.0% prevalence as the leading cause of UTI. Similar to a previous study that was conducted in Bangladesh.[24] In contrast with the study done in Germany, it was observed that the proportion of UPEC was 89.3%, which is two times higher compared to the current study.[25] According to the current study's findings, the proportions of EAEC, EPEC, and EIEC were 13%, 13%, and 10%, respectively. This study was consistent with earlier studies conducted in Cape Town, South Africa.[26] EAEC, EPEC, and ETEC proportions in this study were 13%, 13%, and 5%, respectively, which contrasted with studies conducted in Egypt and Dar es Salaam.[19, 20] The disparities in findings are accounted for by factors like detection technology, like WGS, as well as study sites, as it has been explained elsewhere.[9] In the current study, we discovered that ETEC and EPEC were 5% and 13% the same in the proportion of ETEC to studies conducted in India but differed in the EPEC strain.[29] Also, in this study we discovered that the proportion of ETEC, EHEC, EAEC and EPEC differs significantly from the study done in Iran.[30]

In addition, the proportion of UPEC strains was 42.0% in the current study, contrary to the German study.[25] Also, EHEC was 13%, similar to the study conducted in Iran with a prevalence of 10%.[31] These differences are attributed to several factors, like geographic location, sample type, age, laboratory technique used, study population and ethnicity. This implies that there is a need for medical professionals to pay special attention to cases of UTIs caused by intestinal *E. coli*, as these infections might have distinctive characteristics, clinical presentations, or treatment responses compared to UTIs caused by UPEC.

In the current study all *E. coli* pathotypes were resistant to ampicillin, which was comparable with studies done in Haydom, Tanzania, Iran and Bosnia and Herzegovina.[15, 24, 25] Similarly, in the current study, all *E. coli* pathotypes were more sensitive to meropenem, which was comparable to a study done in Iran.[30] Also, this study found that *E. coli* pathotypes isolated have a high resistance rate to ampicillin, which is in line with the previous studies conducted in South Africa.[26] In this study, *E. coli* pathotypes isolated were more resistant to ampicillin as well as amoxicillin/clavulanic acid, but they were more sensitive to meropenem, similar to a previous study conducted in India.[33] According to a current study, *E. coli* pathotypes isolated were more resistant to ampicillin and amoxicillin/clavulanic acid, which was similar to a study conducted in Dar es Salaam and KCMC-Moshi.[18, 35] The present study discovered that nearly all *E. coli* pathotypes isolated were resistant to nitrofurantoin, which is similar to research done in Dar es Salaam.[18]

Drug susceptibility patterns among *E. coli* pathotypes were almost similar across a range of *E. coli* pathotypes. These similarities might be accounted for by the fact that all the samples were collected from people living in the same geographical location with minimal variations in terms of geographic factors like humidity and temperature. In addition, the Southern Highland regions exhibit and share the same weather conditions, which can account for a constant horizontal gene transfer among the *E. coli* strains within the environment.[35]

Furthermore, this study observed multidrug resistance among nearly all *E. coli* pathotypes, which was consistent with previous studies in Iran, which reported numerous multidrug resistance DEC pathotypes.[30] Also similar to a study done in Palestine which showed MDR for isolated *E. coli*.[34] The findings from this study showed that ampicillin and amoxicillin/clavulanic acid exhibited levels of resistance. These results are likely to be attributed to their widespread distribution, low cost and accessibility that may encourage drug abuse and misuse. Meropenem was reported to show no resistance; this is because this drug has been used as the last resort in the study area. Its low frequency in use has demonstrated its ability to confer its effectiveness to date. This phenomenon has also been reported previously.[3,9,11]

CONCLUSION

The findings of this study showed that the predominant pathotype associated with urinary tract infections was UPEC, followed by EAEC and EPEC, with ETEC being the least frequently identified. The study also indicated that all isolated pathotypes were resistant to ampicillin and amoxicillin/clavulanic acid. Additionally, the investigation discovered all *E. coli* pathotypes isolated were susceptible to meropenem and nitrofurantoin.

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