Multidrug resistance among *Escherichia coli* and *Klebsiella pneumoniae* carried in the gut of out-patients from pastoralist communities of Kasese district, Uganda

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Abstract

Background

Antimicrobial resistance is a worldwide public health emergency that requires urgent attention. Most of the effort to prevent this coming catastrophe is occurring in high income countries and we do not know the extent of the problem in low and middle-income countries, largely because of low laboratory capacity coupled with lack of effective surveillance systems. We aimed at establishing the magnitude of antimicrobial resistance among *Escherichia coli* and *Klebsiella pneumoniae* carried in the gut of out-patients from pastoralist communities of rural Western Uganda.

Methods

A cross-sectional study was carried out among pastoralists living in and around the Queen Elizabeth Protected Area (QEPA). Stool samples were collected from individuals from pastoralist communities who presented to the health facilities with fever and/or diarrhea without malaria and delivered to the microbiology laboratory of College of Health Sciences-Makerere University for processing, culture and drug susceptibility testing.

Results

A total of 300 participants fulfilling the inclusion criteria were recruited into the study. Three hundred stool samples were collected, with 209 yielding organisms of interest. Out of 209 stool samples that were positive, 181 (89%) grew *E. coli*, 23 (11%) grew *K. pneumoniae* and five grew Shigella. Generally, high antibiotic resistance patterns were detected among *E. coli* and *K. pneumoniae* isolated. High resistance against cotrimoxazole 74%, ampicillin

67%, amoxicillin/clavulanate 37%, and ciprofloxacin 31% was observed among the *E. coli*. In *K. pneumoniae*, cotrimoxazole 68% and amoxicillin/clavulanate 46%, were the most resisted antimicrobials. Additionally, 57% and 82% of the *E. coli* and *K. pneumoniae* respectively were resistant to at least three classes of the antimicrobials tested. Resistance to carbapenems was not detected among *K. pneumoniae* and only 0.6% of the *E. coli* were resistant to carbapenems. Isolates producing ESBLs comprised 12% and 23% of *E. coli* and *K. pneumoniae* respectively.

Conclusion

We demonstrated high antimicrobial resistance, including multidrug resistance, among *E. coli* and *K. pneumoniae* isolates from pastoralist out-patients. We recommend a One Health approach to establish the sources and drivers of this problem to inform public health.

Introduction

Antimicrobial resistance is a worldwide public health emergency that requires urgent global attention [1], [2]. Intensive usage of antimicrobials for food animals may cause problems in the treatment of infections by selecting for resistance among bacterial pathogens from animals and humans [3], [4]. Transmission of resistant bacteria from animals to humans may occur via the food chain, environment or by direct interaction with animals and may result in resistant infections. Although *E. coli* and *K. pneumoniae* are commensals, they are also common pathogens in urinary tract infections and sepsis. Exposure of such bacteria to antimicrobials increases the prevalence of carriage of drug resistant bacteria in animals and humans and this can result in longer duration of hospitalization and increased morbidity and mortality in the human population [5]. Multi-drug resistant infections have been reported to account for mortality of at least 23,000 people in the United states annually [6] while the magnitude of the problem in low and middle-income countries(LMIC) is projected to be three times higher [7]. The global emergency and spread of multi-drug resistant Enterobacteriaceae especially CTX-M type ESBLs and strains producing carbapenemases such as KPC and NDM has made bacteria become increasingly untreatable especially in LMIC [8].

Abuse of antibiotics has resulted into the fast-growing problem of antimicrobial resistance on far, in health care settings [9, 10] and the community [11] [12] [13, 14] Previous studies in Uganda report inappropriate usage of antimicrobials in animal husbandry as a major contributor to the emergence of antimicrobial resistance among microbes [15]. Additionally, 40% of the individuals who visit a health- care facility in Uganda are treated with antibiotics [4] [16]. These antibiotics are mostly given over the counter in drug shops and community pharmacies in sub-therapeutic doses. This may result in multi-drug resistance among pathogenic and non-pathogenic bacteria in humans, which may then be transmitted to the environment and animals as the cycle continues. Queen Elizabeth Conservation area in Kasese district, Uganda, has pastoralists communities with domestic animals grazing inside and adjacent to the park [17], creating a porous interface for transmission of infectious agents and antimicrobial resistance. We aimed at establishing the status of antibiotic resistance among indicator bacteria *E. Coli* and *K. pneumoniae* isolated from pastoralist out-patients presenting at Health Centres in and around Queen Elizabeth Conservation Area, rural Western Uganda.

Materials and methods

Study area and setting

A cross-sectional study was carried out among pastoralists living in and around the Queen Elizabeth Protected Area (QEPA). The QEPA lies astride the equator along the latitudes of 0° 39' 36" North, 30° 16' 30" East. QEPA is located in western part of Uganda on the floor of the western arm of the East African Rift Valley. QEPA forms part of an extensive trans boundary ecosystem that includes Kibale National Park to the northeast, Rwenzori Mountains National Park to the northwest and is also contiguous with Virunga National Park in the Democratic Republic of Congo. The northern area has been occupied by pastoralists since the 1920s (Fig 1).
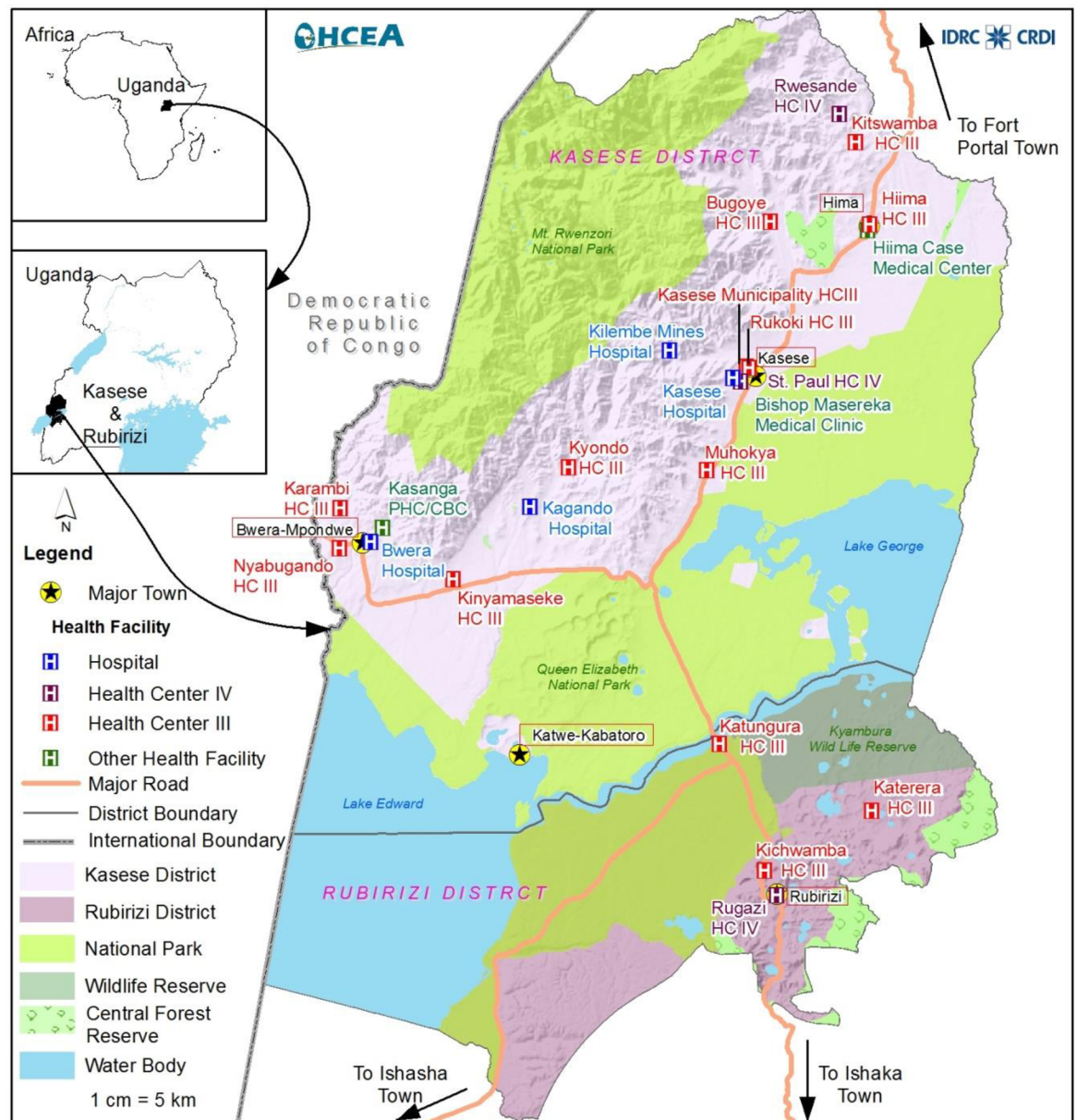

Fig 1. Map of Kasese district showing the distribution of health facilities.

https://doi.org/10.1371/journal.pone.0200093.g001

The pastoralists live adjacent to the park and illegally graze inside the park, creating a very porous wildlife-livestock-human interface and a high disease burden for both humans and livestock [17].

Study population and sampling

Participants were recruited at four health facilities adjacent to the QEPA (Fig 1): Bwera hospital, Kagando hospital, Katwe Health Centre III and Hima Health Centre III. Bwera hospital and Kagando hospital are the major referral centres for patients from the pastoral community health centres whereas Katwe Health Centre III and Hima Health Centre III are health facilities within the pastoralist communities hence their suitability for the study. The inclusion criteria were participants who reared animals, presented with a fever and/or diarrhea but without malaria. Malaria was ruled out by microscopy. The inclusion started in September 2017 and ended in December 2017. A total of 300 stool and 300 blood samples were obtained from 300 participants who presented to the health facilities fulfilling the inclusion criteria.

Sample collection and transportation

Stool samples were collected into sterile leak proof stool containers with screw caps and kept at 4°C for transportation to the laboratory within 24 hours of collection in Carry Blaire transport medium (Fig 2). Sample processing, culture and subsequent tests were performed at the Clinical Microbiology Laboratory of department of medical microbiology of College of Health Sciences-Makerere university.

Culture and isolation

All specimens collected were delivered and processed as per standard operating procedures of the microbiology laboratory of Makerere University College of Health Sciences. This laboratory currently participates in proficiency testing and is under evaluation for College of American Pathologists (CAP) certification. Stool samples were first emulsified in sterile normal saline before inoculation to MacCkonkey agar and then incubated at 37°C for 24 hours. Lactose fermenting bacterial colonies with colonial morphology suggestive of *E. coli* and *K. pneumoniae* were isolated and further identified using the Phoenix automated identification system.

Bacterial identification and susceptibility testing

Bacterial identification and antibiotic susceptibility testing was done using the BD Phoenix 100 automated identification system (Becton Dickinson, Oxford, UK) [18]. The phoenix system has an advantage of combining identification, antimicrobial susceptibility testing and growth and fluorescent controls. The identification (ID) portion of the phoenix panel exploits a series of conventional, chromogenic and fluorogenic biochemical tests to arrive at the identity of the organism. The phoenix also identified ESBL phenotypes. ESBLs are gram negative bacteria producing beta lactamase enzyme therefore capable of breaking down penicillins and cephalosporins and render them ineffective. Following initial culturing, pure cultures were grown from single colonies [19]. One pure colony from each sample was used for identification and antibiotic susceptibility testing (ID/AST). Conventional identification involved use of biochemical tests like indole, methyl-red, voges-proskaur and Simon's citrate. Only results of automated ID/AST were analyzed for this study. Common drugs used for treatment of suspected Gram negative bacterial infection in Uganda were tested, plus other reserve drugs for Gram negative bacteria commercially available in our setting. A total of 15 drugs used included
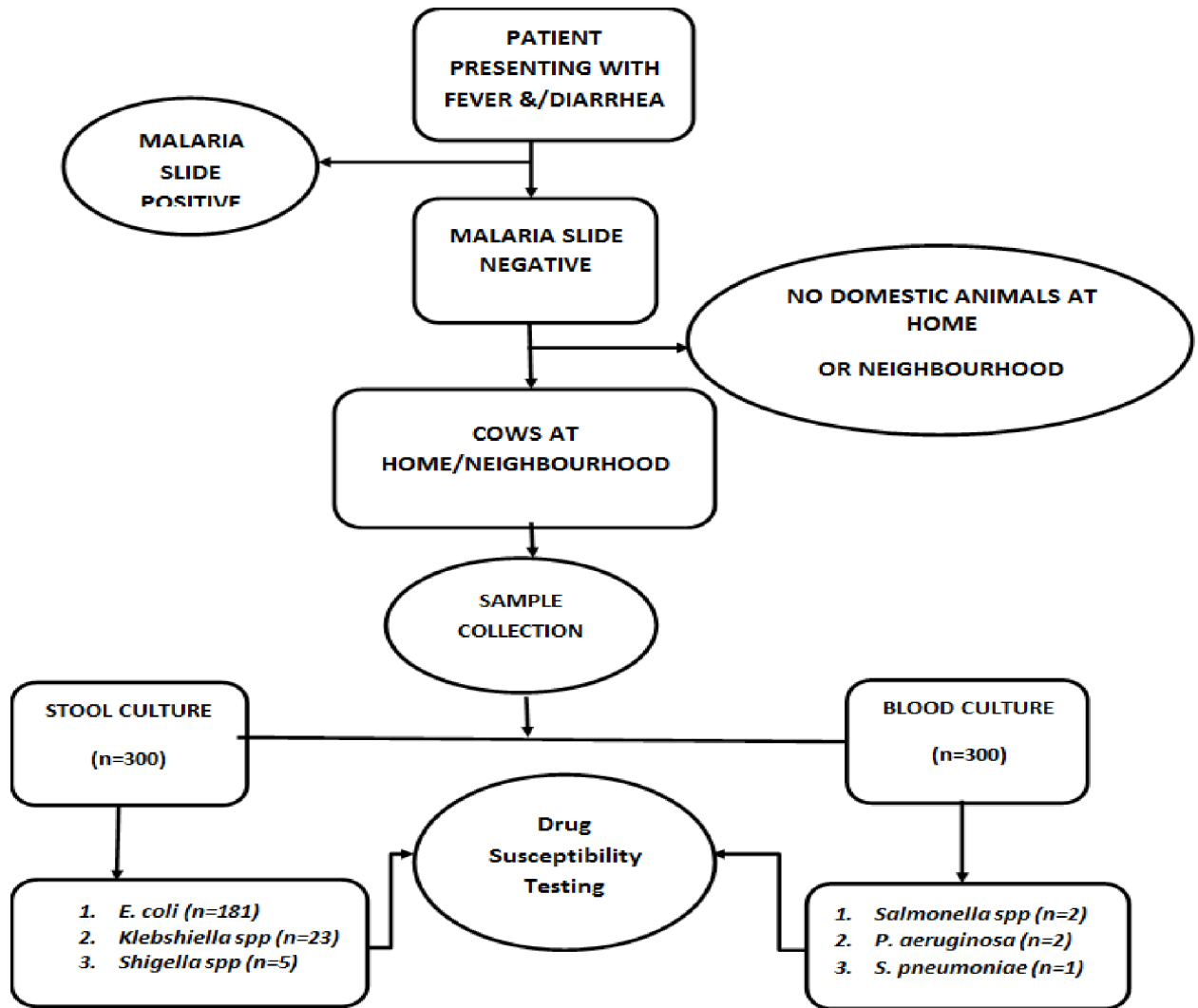
Fig 2. Study profile.

ampicillin 10μg, amoxicillin/clavunate 20/10μg, cefazolin 30μg, cefuroxime 30μg, ceftazidime 30μg, Ceftriaxone 30μg, Cefepime 30μg, Erteapenem 10μg, Imipenem 10μg, Gentamycin10μg, Ciprofloxacin 5μg, Levofloxacin 5μg, Tetracycline 30μg, Nitrofurantoin 10μg and Cotrimoxazole 1.25/ 23.75μg. Multidrug resistance was defined as one isolate being resistant to three or more classes of antibiotics tested [20–22]. For the case of *K. pneumoniae*, this definition applies with exception of ampicillin since Klebsiella is known to be intrinsically resistant to ampicillin. For the case of ESBLs-MDR, the above definition was used with exception of penicillins and cephalosporins. The AST results obtained were interpreted using the CLSI break points. The *E. coli* isolate was also subcultured on sorbitol MacConkey to screen for possible zoonotic origin.

Data management

Data collected from the study was entered, cleaned using Microsoft excel and imported to Stata version 14 for analysis. The primary outcome was multi-drug resistance and the

secondary outcome was ESBL. Data was analyzed using descriptive statistics, frequencies and bivariate analyses (cross-tabulations). Associations were tested using Pearson's Chi square. A significant level was set at p = 0.05.

Data quality control

Laboratory procedures were performed by laboratory scientists under close supervision of a clinical microbiologist to ensure quality results are obtained. Data was double entered into Microsoft excel for accuracy and reliability. ATCC 259922 *E. coli* was used as a control strain for quality assurance during isolation and drug susceptibility testing.

Ethics approval and consent to participate

The study was approved by the Makerere University School of Biomedical Sciences Higher Degrees Research and Ethics Committee (SBS-HDREC) and written informed consent was obtained from participants.

Results and discussions

Results

Socio-demographic characteristics of the study participants. Three hundred (300) participants presenting with fever and/or diarrhea took part in this study. The mean age of the respondents was 21.7 -/+ 14.5 years. The youngest participant was 1 year and the oldest 70 years. Participants below 20 years constituted the majority, (n = 174; 58%) while those above 60 years constituted the minority, (n = 7; 2.3%). Of the 300 participants recruited, 241 presented with fever while 59 reported with diarrhea. Demographic characteristics such as age group, health facility or sex were not associated with MDR or ESBL production "Table 1". There was no significant difference in ESBL prevalence between the patient group that presented with fever, and the group that presented with diarrhea.

Antimicrobial resistance. Out of the 209 stool samples that were positive on culture, 87% (n = 181) grew *E. coli*, 23 (11%) were *K. pneumoniae* and five were Shigella. Shigella species

Table 1. Socio demographic characteristics and distribution of drug resistance.

	MDR n (%)	OR(95% CI)	P-value	ESBL n (%)	OR (95% CI)	P-value
Sex						
Male	48 (42)	1		11 (39)	1	
Female	67 (58)	1.13(0.652–1.992)	0.3	17 (61)	1.2(0.532–2.715)	0.658
Age group (years)						
1–10	30 (26)	1		5 (18)	1	
11–20	31 (27)	0.56(0.263–1.209)	0.141	6 (21)	0.89(0.255–3.107)	0.855
21–30	21 (18)	1.05(0.419–2.632)	0.917	7 (25)	2.32(0.666–8.055)	0.187
31–40	16 (14)	0.87(0.333–2.290)	0.782	6 (21)	2.46(0.672–8.984)	0.174
Above 40	17 (15)	0.68(0.274–1.685)	0.405	4 (14)	1.23(0.304–0.497)	0.773
Health facility						
Bwera	36 (31)	1		7 (25)	1	
Kagando	14 (12)	0.58(0.224–1.518)	0.3	5 (18)	1.6(0.455–5.623)	0.465
Katwe	22 (19)	0.44(0.197–0.984)	0.18	4 (14)	0.62(0.171–2.283)	0.477
Hima	43 (37)	0.63(0.307–1.303)	0.23	12 (43)	1.24(0.454–3.386)	0.675

MDR = Multi-drug resistant, ESBL = Extended Spectrum Beta lactamase, OR = Odds ratio

https://doi.org/10.1371/journal.pone.0200093.t001

were not analyzed because we only had few isolates (Fig 2). We screened for zoonotic *E. coli* using sorbitol MacConkey and we found that 16% of the *E. coli* were categorized as zoonotic using this method. Resistance against cotrimoxazole was 74%, ampicillin 67%, amoxicillin/clavulanate 37%, and ciprofloxacin 31% was noted among the *E. coli* whereas among *K. pneumoniae*; cotrimoxazole 68%, amoxicillin/clavulanate 46%, were the most resisted. MDR was reported among 122 (59.8%) of the total Isolates whereas ESBL was reported in 28 (13.7%). Additionally, 57% and 82% of the *E. coli* and *K. pneumoniae* respectively were resistant to at least three classes of antibiotics. None of the *K. pneumoniae* was resistant to carbapenems and only 0.6% of the *E. coli* was resistant to carbapenems "Table 2".

Resistance to different antibiotic classes. The prevalence of resistance of the isolates to Penicillins like ampicillin among the *E. coli* was 66.8% and 51.6% resistance to β-lactamase inhibitors such as amoxicillin-clavulanic acid. Also 11.8% of *E. coli* and 24.6% of *K. pnuemoniae* were resistant to the 3rd and 4th generation cephalosporins "Table 2". All non-ESBL isolates were sensitive to Carbapenems while 3.6% of the ESBL were resistant to carbapenems. The 28 ESBL isolates were significantly more resistant to Quinolones/Fluoroquinolones, Aminoglycosides, Tetracyclines, Nitrofurantoins and Folate pathway inhibitors than the non ESBL producers, $p < 0.05$ "Table 3".

Discussion

Prevalence and antibiotic resistance. Out of 300 stool samples cultured, 209(69.7%) grew Gram negative bacteria of interest. A related study showed a higher recovery rate (87%) for *E. coli* and *K. pnuemoniae* combined in Kampala and rural districts of Uganda [23]. The same study revealed 97% prevalence *E. coli* and 16 3% of *K. pneumonia*e. This discrepancy with other studies may be due to different identification systems employed. *E. coli* was the most

Table 2. Proportion of *E. coli* and *K. pneumoniae* isolates resistant to drugs classes and individual drugs.

Antimicrobial categories	Drugs	*E. coli* (n = 181)		*K. pneumoniae* (n = 22)		Total
		N (%) by drug	N (%) by category	N (%) by drug	% by category	
Penicillins	Ampicillin	121(66.8)	121(66.8)	IR	IR	121 (66.8)
β-lactamase inhibitors	Amoxicillin-clavulanic acid	66 (36.5)	66(36.5)	11 (47.8)	11(47.8)	77 (37.7)
1st generation cephalosporins	Cefazolin	75 (41.4)	75(41.4)	11 (47.8)	11(47.8)	86(42.2)
2nd generation cephalosporins	Cefuroxime	38 (21)	38(21.0)	8 (34.8)	8(34.8)	46(22.5)
Extended Spectrum cephalosporins; 3rd and 4th generation cephalosporins	Ceftazidime	22 (12.2)	21(11.8)	5 (21.7)	6(24.6)	27(13.2)
	Ceftriaxone	21 (11.6)		6 (26.1)		27(13.2)
	Cefepime	21 (11.6)		6 (26.1)		27(13.2)
Quinolones/ Fluoroquinolones	Ciprofloxacin	27 (14.9)	25(13.8)	3 (13.0)	3(10.9)	30(14.7)
	Levofloxacin	23 (12.7)		2 (8.7)		25(12.3)
Aminoglycosides	Gentamycin	11 (6.1)	11(6.1)	3 (13.0)	3(13.0)	14 (6.9)
Tetracyclines	Tetracycline	64 (35.4)	64(35.4)	12 (52.2)	12(52.2)	76(37.3)
Nitrofurantoins	Nitrofurantoin	33 (18.2)	33(18.2)	15 (65.2)	15(65.2)	48(23.5)
Carbapenems	Imipenem	1 (0.6)	1 (0.6)	1 (4.3)	1(4.3)	2 (1.0)
	Erteapenem	1 (0.6)		0 (0)		1 (0.5)
Folate pathway inhibitors	Cotrimoxazole	133(73.5)	133(73.5)	15 (65.2)	15(65.2)	148 (72.5)

IR = inherently resistant; % = percentage.

Table 3. Resistance pattern of ESBL and Non-ESBL isolates to different drug categories.

Antibiotic category	NON ESBL (n = 176)	ESBL (n = 28)	Total (n = 204)	*P-value*
Quinolones/Fluoroquinolones	13 (7.4%)	17 (60.7%)	30 (14.7%)	P<0.05
Aminoglycosides	2 (1.1%)	12 (42.9%)	14 (6.9%)	P<0.05
Tetracyclines	49 (27.8%)	27 (96.4%)	76 (37.3%)	P<0.05
Nitrofurantoins	34 (19.3%)	14 (50%)	48 (23.5%)	P<0.05
Carbapenems	0 (0%)	1 (3.6%)	1 (0.5%)	P<0.05
Folate pathway inhibitors	122 (69.3%)	26 (92.9%)	148 (72.5%)	P<0.05

frequently isolated bacterium in this study (60.3%) and this makes its role as a conduit of drug resistance to pathogenic organism important to study. Another organism with the potential of transmission from animals to humans isolated was *K. pnuemoniae* (7.7%). Bacteria isolated from blood and Shigella from stool were not included for analysis in this study due to their small proportions, but the results were given to the clinicians for patient management (Fig 2). This study categorized 16% of *E. coli* as zoonotic using sorbitol MacConkey. Whereas growth on sorbital MacConkey is not confirmatory of zoonotic *E. coli*, our inclusion criteria involving participants with animals or having animals at the neighborhood may indicate a high likelihood of transmission of antimicrobial resistance from animals to humans. However, our results only remain speculative.

Overall, high resistance patterns were detected among our isolates. Our study demonstrates a high prevalence of resistance to cotrimoxazole (74%, 65%) among *E. coli* and *K. pneumoniae* respectively. The high prevalence to cotrimoxazole is probably due to the wide use of the drug for prophylaxis in HIV care especially that the pastoralists lived close to the fishing villages where the HIV prevalence is usually high. Studies in Uganda and the rest of East African region have reported similar findings [24, 25], [26]. Like in related studies [23], [27], [28], resistance to ampicillin in this study was high (67%) and similarly cefazolin (41%), amoxicillin/clavulanate (37%), tetracycline (35%) and ciprofloxacin (31%) among the *E. coli*. Among *K. pneumoniae*; cotrimoxazole (68%), nitrofurantoin (64%), tetracycline (50%), amoxicillin/clavulanate (46%) and cefazolin (46%) were the most resisted. Similar trends were reported by other studies [27], [28] indicating that the burden of antimicrobial resistance may be uniformly distributed across East Africa.

Resistance to different drug categories. The resistance rates of the isolates to Penicillins and β-lactamase inhibitors tested in this study, i.e ampicillin and amoxicillin-clavulanic acid were 66.8% and 51.6% among *E. coli*. Resistance to amoxicillin-clavulanic acid, a beta lactam inhibitor among *K. pneumoniae* was 47.8%. In a study in Tanzania, at least 43.5% of isolates were reported as resistant to 3rd generation cephalosporins [27]. This is similar to the trends observed in this study with 11.8% of *E. coli* and 24% of K. pneumoniae showing resistance to 3rd and 4th generation cephalosporins. All non-ESBL producing isolates were susceptible to Carbapenems while ESBL resistance to carbapenems was 3.6%. In neighboring Kenya, none of the 912 gram negative bacteria tested was resistant to carbapenems implying that carbapenems were still effective for the treatment of illnesses caused by these organisms [29]. The 28 ESBL isolates were significantly more resistant to Quinolones/Fluoroquinolones, Aminoglycosides, Tetracyclines, Nitrofurantoins and Folate pathway inhibitors than the non-ESBL isolates (*P<0.05*). Comparable results were reported in Tanzania [14] where ESBL isolates were significantly more resistant to trimethoprim/sulphamethoxazole, tetracycline, ciprofloxacin and gentamicin than the ones that are non ESBL producing (P<0.001).

Multi drug resistance. Multi-drug resistance was noted among 57% of *E. coli* and 82% of *K. pnuemoniae*. This is probably attributed to inappropriate use of these antibiotics in Uganda

without guidance of culture results coupled with unavailability of functional microbiology laboratories in the country and unregulated over-the counter purchase of suboptimal doses. In Uganda, at least 40% of the patients who visit a health facility are treated with an antibiotic [4]. Nonexistence of policy on over-the-counter access to antibiotics is a big problem in Uganda. Due to unrestricted use of antimicrobials, participants could have taken antibiotics before coming to hospital and this has a direct influence on the above results since participants were recruited only basing on whether they had fever or diarrhea. While restricted access to antibiotics is important, the dilemma also comes in the need to balance it against the need to maintain access for the sizable proportion of the population that lacks access to doctors since lack of access to effective and affordable antibiotics still can lead to worse consequences.

Prevalence of ESBLs.   ESBL production is a very vital mechanism of resistance among Enterobacteriaceae. In our study, ESBL production among *Escherichia coli* was 12%; lower than a similar study in Kampala-Uganda that reported 23% [23]. This is probably because more antibiotic use and abuse is likely to happen in the City than in the rural setting of Kasese where our study participants came from. The ESBLs prevalence among *E. coli* reported in our study is similar to that described in Tanzania of 15.5% [14]. There was higher isolation of ESBL among *K. pneumoniae* (23%) than that reported by other authors [14] [29] in Neighboring Tanzania and Kenya. Studies from other African countries show high ESBL rates of 33% (133/408) in Guinea Bissau [30] 34% (37/110) in Gabon [31] and 22% (54/244) in Madagascar [32]. A significant proportion of neonates in neighboring Tanzania, 25%(32/126) have been reported to carry ESBL with K. pneumoniae being the most predominant carrier [33]. In Niger [34], ESBL carriage among admitted children was 31% (17/55) and by the time of discharge, a further 15/16 had gained the carriage status. Whereas different studies employed different methods of detection of ESBLs, the results show a rising trend of ESBLs across the African continent.

Different ESBL prevalence rates have been recorded across Africa as generally high. Since there are few functional microbiology laboratories in most of the developing countries and medicines are dispensed without culture and resistance testing data, β-lactam antibiotics are likely to be glossily misused. Rising numbers of ESBLs in Uganda may have far reaching consequences and may mean that Uganda's expenditure on effective antibiotics will rise if no effective mitigation interventions are put in place. Similar studies across the world have documented the predominance of ESBL producing *E. coli* and *K. pneumoniae* in the gastrointestinal tract and their potential to evolve into multiple drug resistant strains [32].

Conclusion

We demonstrated high antimicrobial resistance, including multidrug resistance, among *E. coli* and *K. pneumoniae* isolates in pastoralist out-patients of rural Western Uganda (S1 Table).

Recommendations

We recommend a study to link the high rates of drug resistance in humans to drug resistance in animals and environment in a One Health approach to establish the sources and drivers of this problem to inform public health. We also recommend molecular studies like whole genome sequencing to further characterize the resistance genes in these bacteria.

Supporting information

S1 Table.
(DTA)

Acknowledgments

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