



Incidence of single-drug resistant, multidrug-resistant and extensively drug-resistant *Escherichia coli* urinary tract infections: An Australian laboratory-based retrospective study



Oyebola Fasugba^{a,*}, Anindita Das^c, George Mnatzaganian^d, Brett G. Mitchell^e, Peter Collignon^{c,f}, Anne Gardner^{a,g}

^a Faculty of Health Sciences, Australian Catholic University, Australian Capital Territory, Australia

^b Lifestyle Research Centre, Avondale College of Higher Education, Cooranbong, NSW, Australia

^c Australian Capital Territory (ACT) Pathology, Canberra Hospital and Health Services, Australian Capital Territory, Australia

^d La Trobe Rural Health School, College of Science, Health and Engineering, Victoria, Australia

^e Faculty of Arts, Nursing and Theology, Avondale College of Higher Education, Wahroonga, NSW, Australia

^f Medical School, Australian National University, Australian Capital Territory, Australia

^g School of Public Health and Social Work, Queensland University of Technology, Queensland, Australia

ARTICLE INFO

Article history:

Received 11 July 2018

Received in revised form 24 September 2018

Accepted 30 October 2018

Available online 6 November 2018

Keywords:

Antimicrobial resistance

Escherichia coli

Urinary tract infection

Incidence

ABSTRACT

Objectives: The aim of this study was to evaluate the incidence of single-drug resistant, multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) *Escherichia coli* urinary tract infections (UTIs) in a sample of Australian Capital Territory (ACT) residents.

Methods: Laboratory-based retrospective data from all ACT residents whose urine samples were processed from January 2009 to December 2013 at ACT Pathology were utilised. Multivariate logistic regression models were constructed to determine the associations of age, sex, urine sample source and socioeconomic status with risk of resistant infections.

Results: A total of 146 915 urine samples from 57 837 ACT residents were identified over 5 years. The mean \pm standard deviation age of residents at first sample submitted was 48 ± 26 years, and 64.4% were female. The 5-year incidence of single-drug resistant *E. coli* UTI was high for ampicillin, trimethoprim and cefazolin (6.8%, 3.5% and 1.9%, respectively). No PDR *E. coli* UTI was detected. Five-year incidences of MDR and XDR *E. coli* UTIs were 1.9% and 0.2%, respectively, which is low in comparison with international rates. Female sex and age ≥ 38 years were significantly associated with single-drug and multidrug resistance. The risk of single-drug resistance was significantly higher in samples from after-hours general practice (GP) clinics compared with hospitals, office-hours GP clinics, and community and specialist health services (adjusted odds ratio = 2.6, 95% confidence interval 2.2–3.1).

Conclusions: These findings have significant implications for antimicrobial prescribing given the identified risk factors for the detection of resistance, especially in patients attending after-hours GP clinics.

© 2018 International Society for Chemotherapy of Infection and Cancer. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Escherichia coli is recognised as the most common cause of urinary tract infection (UTI) [1]. The prevalence of resistance in

urinary *E. coli* is increasing in Australia [2,3] but the resistance incidence is not well described. Whilst prevalence data provide clinicians with information on the burden of disease in the study population, incidence data quantifies the risk of disease [4]. Evaluating not only the prevalence, but also the incidence, of antimicrobial resistance in urinary *E. coli* is important to gain a better understanding of the epidemiology of urinary *E. coli* resistance in order to make meaningful disease management decisions [4]. However, most studies that have investigated urinary *E. coli* resistance did not provide separate data on the incidence of single-drug resistant and multidrug-resistant (MDR) isolates, nor

* Corresponding author at: Australian Catholic University, P.O. Box 256, Dickson, ACT 2602, Australia.

E-mail address: oyebola.fasugba@acu.edu.au (O. Fasugba).

¹ Present address: Nursing Research Institute, Australian Catholic University and St Vincent's Health Australia, Sydney, NSW, Australia.

did they identify patient risk factors for antimicrobial resistance [5,6]. Recent data from the USA showed that the incidence of fluoroquinolone-resistant *E. coli* bacteriuria had significantly increased from 464 to 1116 per 100 000 person-years between 2005 and 2009 in patients aged >80 years [7].

The emergence of *E. coli* resistance to multiple antimicrobials poses a significant threat to public health, with limited antimicrobials available for treating MDR infections. These infections may complicate UTI treatment leading to poorer patient outcomes [8]. In Australia, MDR *E. coli* prevalence rates increased from 4.5% in 2008 to 7.6% in 2012 [2]. MDR urinary *E. coli* infections have also been frequently reported in other countries [9–11]. In the USA, the incidence of MDR *E. coli* was 37 per 100 000 person-years in 2009 [7]. Given the high mortality associated with infections caused by these bacteria [9,12], knowledge of the incidence of MDR urinary *E. coli*, including potential risk factors, will contribute to the development of interventions aimed at controlling antimicrobial resistance.

The recently developed Australian antimicrobial resistance strategy lists *E. coli* as a priority organism for resistance surveillance owing to its impact in hospital and community settings [13]. Given the newly established Antimicrobial Use and Resistance in Australia (AURA) surveillance system [13], evaluating antimicrobial resistance incidence at a jurisdictional level will contribute important information to understanding the distribution and impact of resistant *E. coli* UTIs. This study, the first of its kind in Australia, evaluated the incidence and 5-year risk of resistant *E. coli* UTI in a large sample of Australian Capital Territory (ACT) residents. The study also provides novel information on the incidence of MDR, extensively drug-resistant (XDR) and pandrug-resistant (PDR) *E. coli* UTIs, with evidence to inform clinicians, policy-makers and other stakeholders about emerging trends that may impact on public health.

2. Materials and methods

2.1. Study design, setting and population

Laboratory-based retrospective data from all ACT residents who had urine samples processed at ACT Pathology from January 2009 to December 2013 were utilised. Based on available data from Medicare statistics [14] and ACT Pathology (A. Das, personal communication, 11 November 2016), it is estimated that ACT Pathology processes ca. 100% of urine samples from inpatients, emergency department (ED) patients and specialist outpatient clinic patients of public hospitals as well as $\geq 13\%$ of urine samples from patients in the community and private hospitals whose residential status is within ACT. The population of ACT in 2011 was 367 985. The study sample comprised 57 837 unique ACT residents whose urine samples were processed at ACT Pathology during the period 1 January 2009 to 31 December 2013, of whom an estimated 71% were inpatients, ED patients and specialist outpatient clinic patients of public hospitals and the remaining 29% were patients in the community and/or inpatients at private hospitals. Residence in ACT was based on postcode, and those with postcodes from surrounding New South Wales and elsewhere were excluded. Samples collected outside of ACT and from patients without unique identifiers were also excluded.

2.2. Bacterial isolation and identification, and antimicrobial susceptibility testing

Urine samples were processed based on microbiology laboratory standards described previously [3]. Urine cultures with the presence of $\geq 10^7$ CFU/L of urine were considered positive for UTI based on laboratory recommendations. This 10^7 CFU/L cut-off is

commonly used as it increases the sensitivity of the urine culture test making it a practical threshold [15]. The criterion has also been used by several studies reporting on antimicrobial resistance of urinary *E. coli* [16–18].

The Clinical and Laboratory Standards Institute (CLSI) antimicrobial susceptibility testing and interpretive standards (CLSI M100-S19–M100-S23) were used for this study, and there were no changes in breakpoints during the study period.

2.3. Definitions

The incidence of single-drug resistance was assessed separately for ampicillin, trimethoprim, gentamicin, cefazolin, ceftriaxone, trimethoprim/sulfamethoxazole (SXT), meropenem, nitrofurantoin, and fluoroquinolones (nalidixic acid, ciprofloxacin and norfloxacin) and β -lactamase inhibitor combinations [amoxicillin/clavulanic acid (AMC) and piperacillin/tazobactam (TZP)]. Resistance to fluoroquinolones (nalidixic acid, ciprofloxacin and norfloxacin) and β -lactamase inhibitor combinations (AMC and TZP) was considered as one because resistance is strongly linked within these agents. Non-susceptibility to at least one agent in three or more antimicrobial categories was defined as MDR; non-susceptibility to at least one agent in all but two or fewer antimicrobial categories was defined as XDR; and non-susceptibility to all agents in all antimicrobial categories was defined as PDR based on published international standardised definitions [8]. For these definitions to be comparable, isolates must be tested against all antimicrobial agents within the antimicrobial categories. In cases of incomplete testing, it is difficult to distinguish reliably between XDR and PDR isolates. In ACT Pathology, 9 of the 13 potential antimicrobial categories needed to define XDR and PDR were tested by the laboratory. Hence, these isolates were classified as ‘possible PDR’ or ‘possible XDR’ in accordance with the published standard definitions for multi-resistance [8].

2.4. Data analysis

Antimicrobial susceptibility data for all ACT residents who submitted urine samples to ACT Pathology during the 5-year period were assessed from the point of no resistance for each individual until occurrence of the first single-drug resistant, MDR, XDR or PDR *E. coli* UTI during the study period. The first resistant *E. coli*, whether to one agent or two or more agents, was counted and included in the incidence rate. The first resistant *E. coli* to one antimicrobial agent was assessed as single-drug resistance. Subsequent first resistance to more than one antimicrobial agent was assessed as MDR, XDR or PDR.

Five-year cumulative incidence rates of resistance were calculated by dividing the number of incident cases of antimicrobial-resistant *E. coli* UTI by the total number of individuals with urine samples included in the study. Data were also analysed yearly to establish the changing cumulative incidence rates, which were calculated by dividing the yearly number of incident *E. coli* resistant cases by the number of individuals submitting urine samples to ACT Pathology each year. Given that not all ACT residents have their urine samples processed by ACT Pathology, the cumulative incidence rate was expressed per 100 000 people whose urine samples were tested by ACT Pathology over the 5 years, that is the number of people with a resistant *E. coli* UTI among every 100 000 people submitting urine samples to ACT Pathology for testing, rather than using an estimate of the whole ACT population.

Kaplan–Meier curves were plotted to show the effect of age and urine sample origin on the incidence of single-drug resistance. Differences in resistance between age groups and between urine sample origins were evaluated using the log-rank test [19].

Multivariate logistic regression models were constructed for each antimicrobial to determine the effect of age, sex, socioeconomic status (SES) and urine sample origin on the risk of resistance. The Hosmer–Lemeshow test was performed to assess the goodness of fit of logistic regressions, with $P > 0.05$ indicating good fit.

Age was assessed within five categories based on age distribution in the data (≤ 23 , 24–37, 38–56, 57–73 and ≥ 74 years). The Australian Socio-Economic Indexes for Areas (SEIFA) based on residential postcodes derived from 2006 Australian census data was used to determine SES [20]. This validated ecological index score ranks areas in Australia based on relative socioeconomic indicators of advantage and disadvantage, with lower-scored areas being more disadvantaged than higher-scored areas [21]. For this analysis, SES was assessed within three categories (low, middle and high) based on the data set SEIFA score distribution.

The sample origin refers to the health service requesting the urine sample test and was grouped into seven categories, namely: public acute hospitals; private acute hospitals; general practice (GP) clinics; after-hours GP clinics; community health services, including Aboriginal and Torres Strait Islander and youth health services; specialist health services, including minor surgical and procedural outpatient units; and 'others'. This last category included samples sent from non-acute hospitals, correctional services, dialysis clinics, dental clinics, hospice, ambulance services and a life insurance organisation. Further analyses were performed to determine levels of MDR, XDR and PDR isolates. A significance level of 0.05 was used. Data were analysed using STATA Statistical Software: Release 14 (StataCorp LP, College Station, TX).

3. Results

A total of 196 385 urine samples were processed over the 5-year period. When restricted to samples belonging to ACT residents and collected within ACT, there were 163 792 samples, of which unique patient identifiers were missing for 16 877 samples (10.3%), resulting in 146 915 samples belonging to 57 837 ACT residents over 5 years being included in the final analysis. The mean \pm standard deviation age of residents at first sample submitted was 48 ± 26 years and most were female (64.4%; $n = 37\ 234$). Of all included samples, positive cultures accounted for 16.0% ($n = 23\ 486$), of which 56.9% ($n = 13\ 371$) were *E. coli* UTIs.

Overall 5-year and yearly incidences of single-drug resistant *E. coli* UTI per 100 000 people whose urine samples were tested by ACT Pathology are shown in Table 1. The 5-year resistance incidence was highest for ampicillin, trimethoprim and cefazolin (68, 35 and 20 per 1000 people tested, respectively) and was

lowest for meropenem, nitrofurantoin and gentamicin (0.02, 5 and 6 per 1000 people tested, respectively).

The multivariate logistic regression model for single-drug resistance (resistance to any of the antimicrobial agents tested) found higher odds of resistance in females and older people (Table 2). Samples from after-hours GP clinics had the highest odds of being resistant [odds ratio (OR) = 2.6, 95% confidence interval (CI) 2.2–3.1; Kaplan–Meier analysis, log-rank test, $P < 0.001$] (Fig. 1).

A separate multivariate logistic regression model was constructed for each antimicrobial (excluding meropenem, which had only one resistant isolate identified) adjusting for age, sex, SES and sample origin. Although the results varied for each antimicrobial, consistent findings included significantly higher odds of resistance in females and older people (Supplementary Table S1). The risk of ampicillin, cefazolin, trimethoprim and SXT resistance was significantly higher in people aged ≤ 23 years. There was no significant association between antimicrobial resistance and SES.

Further analyses showed no possible PDR *E. coli*, but the 5-year incidence of MDR and possible XDR *E. coli* was found to be 19 and 2 per 1000 people tested, respectively. Female sex and age ≥ 38 years were significantly associated with MDR isolates (Table 2). After adjusting for age, sex and SES, urine samples from after-hours GP clinics, specialist health services and the 'other' category were associated with significantly higher odds of MDR isolates [OR = 1.6 (95% CI 1.1–2.3), OR = 1.8 (95% CI 1.1–2.9) and OR = 2.3 (95% CI 1.3–4.0), respectively]. Given the low incidence of possible XDR *E. coli* UTI, and because this group was a subset of MDR, logistic regression analysis was not performed. The Hosmer–Lemeshow tests showed good fit for all regression models ($P > 0.05$).

4. Discussion

To our knowledge, this is the first study examining the incidence of resistant *E. coli* UTIs in Australia. Notably, this study is the first in Australia to assess the associations of age, sex and urine sample source with risk of *E. coli* UTI. This study has identified: (i) a high incidence of resistance to ampicillin, trimethoprim and cefazolin; (ii) the presence of MDR and possible XDR *E. coli* UTIs; (iii) a significantly higher risk of resistance in females and people aged ≥ 38 years; (iv) a significantly higher risk of resistance to some antimicrobials in the high SES group; and (v) that the risk of resistance varied by health service requesting the urine sample.

The UTI resistance incidence was highest for ampicillin, trimethoprim and cefazolin, consistent with national and territory

Table 1
Overall 5-year and yearly cumulative incidence rates of antimicrobial-resistant *Escherichia coli* urinary tract infections per 100 000 people whose urine samples were tested by ACT Pathology.

Antibiotic	Rate (n) ^a					5-year total
	2009	2010	2011	2012	2013	
Ampicillin	4697.8 (722)	5181.6 (863)	5814.6 (1015)	5247.3 (956)	5469.0 (835)	6760.4 (3910)
Trimethoprim	2322.9 (357)	2635.8 (439)	3001.8 (524)	2629.1 (479)	2908.0 (444)	3483.9 (2015)
Cefazolin	1067.1 (164)	1495.0 (249)	1638.4 (286)	1432.6 (261)	1644.0 (251)	1974.5 (1142)
SXT	943.5 (145)	1296.9 (216)	1598.3 (279)	1427.1 (260)	1441.0 (220)	1751.5 (1031)
FQs	1034.6 (159)	1140.8 (190)	1432.2 (250)	1284.4 (234)	1401.6 (214)	1673.7 (968)
BLIs	481.5 (74)	912.6 (152)	1077.0 (188)	1235.0 (225)	1310.0 (200)	1390.1 (804)
Ceftriaxone	214.7 (33)	366.3 (61)	618.7 (108)	735.5 (134)	792.5 (121)	741.7 (429)
Gentamicin	292.8 (45)	420.3 (70)	532.8 (93)	526.9 (96)	635.3 (97)	629.4 (364)
Nitrofurantoin	240.7 (37)	276.2 (46)	297.9 (52)	384.2 (70)	648.4 (99)	506.6 (293)
Meropenem	0.0 (0)	6.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	1.7 (1)
Any antibiotic ^b	5446.0 (837)	5619.9 (936)	6261.5 (1093)	5554.6 (1012)	5901.2 (901)	7311.9 (4229)

SXT, trimethoprim/sulfamethoxazole; FQs, fluoroquinolones (nalidixic acid, ciprofloxacin and norfloxacin); BLIs, β -lactamase inhibitor combinations (amoxicillin/clavulanic acid and piperacillin/tazobactam).

^a The number of residents was as follows: 2009, 15 369; 2010, 16 655; 2011, 17 456; 2012, 18 219; 2013, 15 268; and 5-year period, 57 837.

^b Resistance to at least one of the antibiotics.

Table 2

Multivariate logistic regression model for the effects of age, sex, socioeconomic status (SES) and urine source on the risk of developing urinary *Escherichia coli* resistance to any of the 13 antimicrobial agents tested or a multidrug-resistant infection.

Variable	Categories	N ^a	Any resistance ^b		Multidrug-resistance	
			Odds ratio	95% CI	Odds ratio	95% CI
Age (years)	≤23	11 570	1.3	1.2–1.5	1.0	0.8–1.3
	38–56	11 566	1.3	1.1–1.4	1.6	1.3–2.0
	57–73	11 567	1.9	1.7–2.1	2.5	2.1–3.1
	≥74	11 567	2.9	2.6–3.2	3.3	2.7–4.0
	24–37 (reference)	11 567	1.0	–	1.0	–
Sex	Female	37 234	3.3	3.0–3.5	2.6	2.2–3.0
	Male (reference)	20 593	1.0	–	1.0	–
SES	Middle	20 450	1.0	1.0–1.1	1.0	0.9–1.1
	High	16 168	1.0	0.9–1.1	1.0	0.9–1.2
	Low (reference)	21 051	1.0	–	1.0	–
Sample origin	Private acute hospitals	1313	0.7	0.6–0.9	1.0	0.7–1.5
	GP clinics	12 446	1.1	1.0–1.2	1.0	0.9–1.2
	After-hours GP clinics	1024	2.6	2.2–3.1	1.6	1.1–2.3
	Community health services	1284	1.4	1.1–1.7	1.5	1.0–2.1
	Specialist health services	533	1.1	0.8–1.4	1.8	1.1–2.9
	Others ^c	363	1.3	0.9–1.9	2.3	1.3–4.0
	Public acute hospitals (reference)	40 874	1.0	–	1.0	–

CI, confidence interval; GP, general practice.

Hosmer–Lemeshow test for resistance to any of the 13 antimicrobials model: χ^2 statistic = 8.13; $P = 0.42$.

Hosmer–Lemeshow test for multidrug-resistance model: χ^2 statistic = 7.65; $P = 0.47$.

^a N = number of residents [some data were missing for sex ($n = 10$) and SES ($n = 168$)].

^b Antimicrobials included ampicillin, amoxicillin/clavulanic acid, cefazolin, ceftriaxone, trimethoprim, trimethoprim/sulfamethoxazole, nalidixic acid, ciprofloxacin, norfloxacin, gentamicin, meropenem, nitrofurantoin and piperacillin/tazobactam.

^c Non-acute hospitals, correctional services, dialysis clinics, dental clinics, hospice, ambulance services and a life insurance organisation.

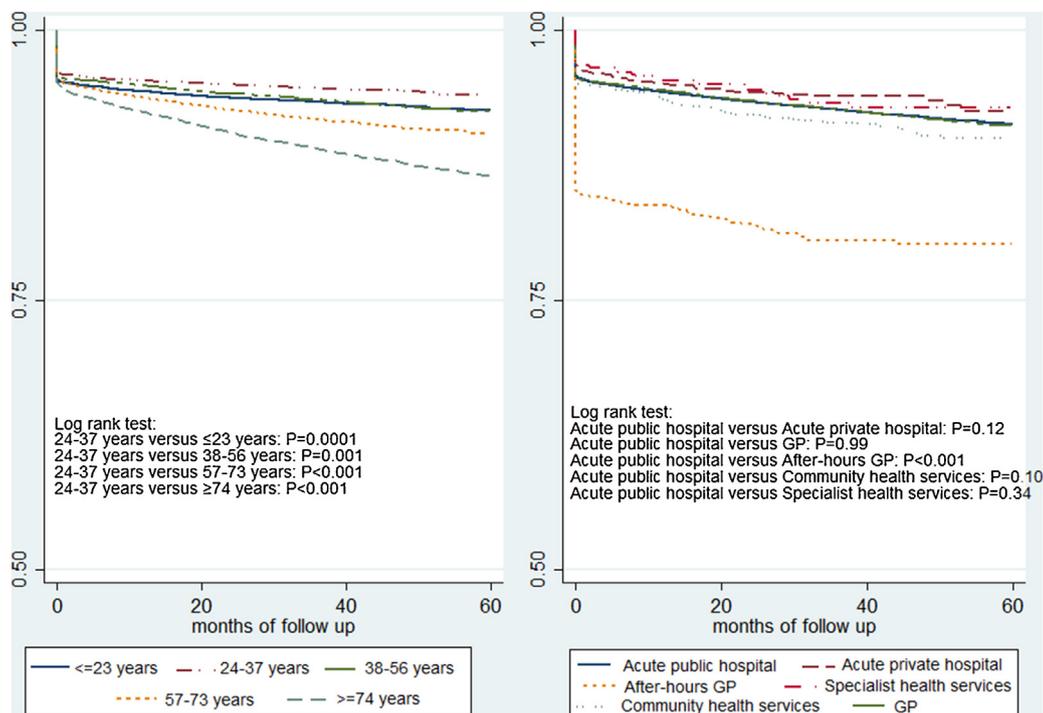


Fig. 1. Kaplan–Meier curves of the incidence of single-drug antimicrobial resistance by age group and urine sample origin. GP, general practice.

blood culture prevalence [13]. The high resistance for these three antimicrobials recommended for first-line UTI therapy raises concern about the selection of an appropriate empirical treatment for UTI. The low resistance for last-line antimicrobials such as meropenem, ceftriaxone and gentamicin in comparison with published European data is notable [22,23]. The current study also reports MDR and possible XDR *E. coli* UTIs, although in relatively low numbers compared with countries such as the Netherlands [23]. Globally, Australia is considered one of the countries with

high antimicrobial use [13]. Despite this, the incidence of single-drug resistant, MDR and XDR *E. coli* is relatively low. Likely reasons may be that many people acquire resistant bacteria through food, water, travel and the environment rather than through antimicrobial use [24]. Although no PDR *E. coli* UTI was identified in this study, the presence of MDR and possible XDR isolates raises concern because these pathogens are associated with poorer patient outcomes owing to limited availability of drugs for treatment.

Resistance risk was higher in females and people aged ≥ 38 years in this study. There are inconsistent findings for the effect of sex on resistance [18,25,26]. Possible explanations include higher predisposition to UTI in females resulting in more antimicrobial prescriptions [27]. The current finding of higher resistance risk in older age groups has been previously described and may be due to increasing cumulative exposure to antimicrobials and healthcare settings with age [25]. A significantly higher risk of ampicillin, ceftazidime and SXT resistance was also found in people ≤ 23 years, supported by a recent systematic review [28]. Interventions aimed at reducing further development and spread of resistance should take account of patient age and sex.

The highest resistance risk was noted in samples from after-hours GP clinics. Patients receiving treatment from these clinics typically require medical services outside regular office hours, usually between 18:00 h and 08:30 h weekdays and during weekends. Evidence shows higher resistance in hospitals compared with community settings [29], hence the higher resistance risk in samples from after-hours GP clinics is surprising. The reason for this finding is unknown but it could be postulated that patients attending after-hours GP clinics are similar to patients presenting at EDs. These patients are likely to be too unwell to wait for appointments during regular office hours and more likely to require antimicrobials. In the UK, compared with regular office-hours GPs and hospitals, after-hours GPs and other community health services also had higher antimicrobial prescribing rates [30]. As antimicrobial use is a major factor contributing to resistance [13], this finding highlights the importance of judicious antimicrobial prescribing by clinicians. Education campaigns should be tailored towards clinicians consulting in after-hours clinics, and health services should develop systems that continuously monitor antimicrobial prescriptions to ensure their rational use.

This study has limitations. This study comprised patients whose samples were processed by ACT Pathology, which captures all inpatient public hospital samples, samples from outpatients attending public hospital EDs and specialist clinics as well as ca. 13% of private hospital and community samples. Hence, the calculated resistance incidence rates are based on sample data and may not be directly generalised to the total ACT population. As a result of the data not being a complete enumeration of ACT residents, the incidence rate was expressed per 100 000 people whose urine samples were tested as opposed to using an estimate of the ACT population. These findings are, however, the most reliable estimates to date of ACT *E. coli* UTI resistance incidence. Whilst clinicians are likely to refer to prevalence than incidence, these two measures of disease frequency provide separate information. Prevalence quantifies the proportion of people with a disease and is generally used to evaluate the occurrence or burden of a specific disease, whilst incidence quantifies the number of new cases of a disease in people at risk of developing the condition during a specified time period [4].

Knowledge both of the prevalence and incidence of antimicrobial resistance in *E. coli* UTIs is necessary to appropriately address the issue of antimicrobial resistance. Population-level analysis based on setting of infection onset, that is community versus inpatients, was considered. This analysis was not possible because data from the Medicare statistics website used to estimate the proportion of community samples processed by ACT Pathology do not separate community from private hospital inpatient samples. In defining incident UTI, there was a possibility that pre-existing infections (not verified) were carried over from the year before study commencement. Exclusion of samples from patients treated empirically without laboratory culture as well as likely inclusion of multiple samples from people with recurrent UTI and asymptomatic bacteriuria potentially overestimated the resistance incidence. Patient risk factors including co-morbidities and urinary tract

instrumentation that could influence resistance incidence could not be accounted for in the analysis because retrospective data were used. Given the composition of de-identified data, 10% of samples were excluded due to lack of unique patient identifiers, thereby underestimating the resistance incidence.

5. Conclusions

Detection of single-drug resistant, MDR and possible XDR *E. coli* UTIs emphasises the need for continued monitoring of antimicrobial resistance to ensure suitable empirical therapeutic agents remain available. This study highlights the importance of the development of interventions aimed at reducing resistance based on patient risk factors. A higher risk of resistance in patients attending after-hours GP clinics necessitates further research to investigate antimicrobial prescribing practices within these health services.

Acknowledgments

The authors thank Ms Angelique Clyde-Smith and ACT Pathology staff for assisting with data retrieval.

Funding

OF was supported by an Australian Catholic University Postgraduate Award.

Competing interests

None declared.

Ethical approval

Ethics approval was granted by ACT Health Human Research Ethics Committee's Low Risk Sub-Committee [ETHLR.14.223] and Australian Catholic University Human Research Ethics Committee [2014276N].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jgar.2018.10.026>.

References

- [1] Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *Urol Clin North Am* 2008;35:1–12 v.
- [2] Australian Group on Antimicrobial Resistance (AGAR). Gram-negative survey: 2012 antimicrobial susceptibility report. AGAR; 2013 <http://agargroup.org.au/wp-content/uploads/2017/08/AGAR-GNB12-Report-FINAL.pdf>. [Accessed 19 February 2019].
- [3] Fasugba O, Mitchell BG, Mnatzaganian G, Das A, Collignon P, Gardner A. Five-year antimicrobial resistance patterns of urinary *Escherichia coli* at an Australian tertiary hospital: time series analyses of prevalence data. *PLoS One* 2016;11:e0164306.
- [4] Buttner P, Muller R. *Epidemiology*. Docklands: VIC Australia Oxford University Press ANZ; 2011.
- [5] Kennedy KJ, Roberts JL, Collignon PJ. *Escherichia coli* bacteraemia in Canberra: incidence and clinical features. *Med J Aust* 2008;188:209–13.
- [6] Meumann EM, Mitchell BG, McGregor A, McBryde E, Cooley L. Urinary *Escherichia coli* antimicrobial susceptibility profiles and their relationship with community antibiotic use in Tasmania, Australia. *Int J Antimicrob Agents* 2015;46:389–93.
- [7] Swami SK, Liesinger JT, Shah N, Baddour LM, Banerjee R. Incidence of antibiotic-resistant *Escherichia coli* bacteriuria according to age and location of onset: a population-based study from Olmsted County, Minnesota. *Mayo Clin Proc* 2012;87:753–9.
- [8] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;18:268–81.

- [9] Eshetie S, Unakal C, Gelaw A, Ayelign B, Endris M, Moges F. Multidrug resistant and carbapenemase producing Enterobacteriaceae among patients with urinary tract infection at referral hospital, Northwest Ethiopia. *Antimicrob Resist Infect Control* 2015;4:12.
- [10] Khawcharoenporn T, Vasoo S, Singh K. Urinary tract infections due to multidrug-resistant Enterobacteriaceae: prevalence and risk factors in a Chicago emergency department. *Emerg Med Int* 2013;2013:258517, doi:<http://dx.doi.org/10.1155/2013/258517>.
- [11] Yadav KK, Adhikari N, Khadka R, Pant AD, Shah B. Multidrug resistant Enterobacteriaceae and extended spectrum β -lactamase producing *Escherichia coli*: a cross-sectional study in National Kidney Center. *Nepal Antimicrob Resist Infect Control* 2015;4:42.
- [12] Nikaido H. Multidrug resistance in bacteria. *Annu Rev Biochem* 2009;78:119–46.
- [13] Australian Commission on Safety and Quality in Health Care (ACSQHC). AURA 2016: first Australian report on antimicrobial use and resistance in human health. Sydney, NSW: Australia ACSQHC; 2016.
- [14] Medicare Australia. Medicare Australia statistics—medicare item report. http://medicarestatistics.humanservices.gov.au/statistic/do.jsp?_PROGRAM=%2Fstatistics%2Fmbs_item_standard_report&DRILL=ag&group=69333&VAR=services&STAT=count&RPT_FMT=by+time+period+and+state&PTYPE=ca-lyear&START_DT=200901&END_DT=201312 [Accessed 13 November 2016].
- [15] Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. *Clin Infect Dis* 2004;38:1150–8.
- [16] Laupland KB, Ross T, Pitout J, Church D, Gregson D. Community-onset urinary tract infections: a population-based assessment. *Infection* 2007;35:150–3.
- [17] Linhares I, Raposo T, Rodrigues A, Almeida A. Frequency and antimicrobial resistance patterns of bacteria implicated in community urinary tract infections: a ten-year surveillance study (2000–2009). *BMC Infect Dis* 2013;13:19.
- [18] McGregor JC, Elman MR, Bearden DT, Smith DH. Sex- and age-specific trends in antibiotic resistance patterns of *Escherichia coli* urinary isolates from outpatients. *BMC Fam Pract* 2013;14:25.
- [19] Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol* 1972;34: 187–120.
- [20] Australian Bureau of Statistics. Census of population and housing: socio-economic indexes for Areas (SEIFA), Australia –data only. 2006 <http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/2033.0.55.0012006?OpenDocument> [Accessed 18 August 2016].
- [21] Walker R, Hiller J. The index of relative socio-economic disadvantage: general population views on indicators used to determine area-based disadvantage. *Aust N Z J Public Health* 2005;29:442–7.
- [22] Allocati N, Masulli M, Alexeyev MF, Di Ilio C. *Escherichia coli* in Europe: an overview. *Int J Environ Res Public Health* 2013;10:6235–54.
- [23] van der Donk CF, van de Bovenkamp JH, De Brauwier EI, De Mol P, Feldhoff K, Kalka-Möll WM, et al. Antimicrobial resistance and spread of multi drug resistant *Escherichia coli* isolates collected from nine urology services in the Euregion Meuse-Rhine. *PLoS One* 2012;7:e47707.
- [24] Collignon P. Antibiotic resistance: are we all doomed? *Intern Med J* 2015;45:1109–15.
- [25] Lagacé-Wiens PR, Simner PJ, Forward KR, Taylor F, Adam HJ, DeCorby M, et al. Analysis of 3789 in- and outpatient *Escherichia coli* isolates from across Canada—results of the CANWARD 2007–2009 study. *Diagn Microbiol Infect Dis* 2011;69:314–9.
- [26] Sahn DF, Thornsberry C, Mayfield DC, Jones ME, Karlowsky JA. Multidrug-resistant urinary tract isolates of *Escherichia coli*: prevalence and patient demographics in the United States in 2000. *Antimicrob Agents Chemother* 2001;45:1402–6.
- [27] Al-Badr A, Al-Shaikh G. Recurrent urinary tract infections management in women: a review. *Sultan Qaboos Univ Med J* 2013;13:359–67.
- [28] Bryce A, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association with routine use of antibiotics in primary care: systematic review and meta-analysis. *BMJ* 2016;352:i939.
- [29] Fasugba O, Gardner A, Mitchell BG, Mnatzaganian G. Ciprofloxacin resistance in community- and hospital-acquired *Escherichia coli* urinary tract infections: a systematic review and meta-analysis of observational studies. *BMC Infect Dis* 2015;15:545.
- [30] Public Health England (PHE). English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) 2010 to 2014. PHE; 2015 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477962/ESPAUR_Report_2015.pdf [Accessed 30 July 2016].