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Urinary *Escherichia coli* antimicrobial susceptibility profiles and their relationship with community antibiotic use in Tasmania, Australia

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ABSTRACT

This study assessed urinary *Escherichia coli* antibiotic susceptibility patterns in Tasmania, Australia, and examined their association with community antibiotic use. The susceptibility profiles of all urinary *E. coli* isolates collected in Tasmania between January 2010 and December 2012 were included. The amount of Pharmaceutical Benefits Scheme (PBS)-subsidised use of amoxicillin, amoxicillin/clavulanic acid (AMC), cefalexin, norfloxacin, ciprofloxacin and trimethoprim was retrieved (at the Tasmanian population level) and the number of defined daily doses per 1000 population per day in Tasmania for these antibiotics was calculated for each month during the study period. Antimicrobial susceptibility data were assessed for changes over time in the 3-year study period. Antimicrobial use and susceptibility data were assessed for seasonal differences and lag in resistance following antibiotic use. Excluding duplicates, 28 145 *E. coli* isolates were included. Resistance levels were low; 35% of isolates were non-susceptible to amoxicillin, 14% were non-susceptible to trimethoprim and <5% were non-susceptible to AMC, cefalexin, gentamicin and norfloxacin. Amoxicillin use increased by 35% during winter/spring compared with summer/autumn, and AMC use increased by 21%. No seasonal variation in quinolone use or resistance was detected. The low levels of antimicrobial resistance identified may relate to Tasmania's isolated geographical location. Significant seasonal variation in amoxicillin and AMC use is likely to be due to increased use of these antibiotics for treatment of respiratory tract infections in winter. Quinolone use is restricted by the PBS in Australia, which is the likely explanation for the low levels of quinolone use and resistance identified.

1. Introduction

Bacterial resistance to antibiotics is increasing globally and consumption of antibiotics is the main contributing factor [1,2]. Antimicrobial stewardship programmes aim to prevent unnecessary antibiotic use, decrease the use of broad-spectrum antibiotics, and promote safe and appropriate antibiotic prescribing; they may use a combination of persuasive and restrictive approaches. In Australia, the Pharmaceutical Benefits Scheme (PBS) restricts the prescription of a small number of antibiotics, however there is relatively little control over antimicrobial prescribing in the community. Conversely, antimicrobial stewardship has been included in the Australian Commission on Safety and Quality in Health Service Standards for hospitals since 2011 and is now mandatory for Australian hospital accreditation.

Internationally, surveillance data show that antimicrobial resistance varies greatly in different geographical locations [3–5]. The Australian Group on Antimicrobial Resistance (AGAR) has performed surveillance of antimicrobial resistance since 1985. The AGAR 2010 survey for community-onset infections showed that the prevalence of multiresistant urinary *Escherichia coli* isolates had risen from 4.5% in 2008 to 7.2% in 2010 [6].

The purpose of this study was to investigate antimicrobial resistance trends in *E. coli* isolated from urine specimens in Tasmania between 2010 and 2012, to assess any temporal changes and to explore the relationship between community antibiotic prescribing in Tasmania and *E. coli* antimicrobial resistance.

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Table 1
Antimicrobial use and resistance.

Antibiotic	Proportion (%) non-susceptible, duplicates excluded (n = 28 145)	Proportion (%) non-susceptible, duplicates included (n = 42 691)	Mean (95% CI) subsidised antimicrobial use in DDDs per 1000 population per day	Estimated proportion (%) of total use that is subsidised (95% CI)
Amoxicillin	35	36	2.43 (2.25–2.61)	54 (52–56)
AMC	4	4	1.70 (1.59–1.81)	90 (89–91)
Cefalexin	3	4	1.79 (1.70–1.88)	66 (64–68)
Gentamicin	2	2	N/A	
Norfloxacin	3	4	0.10 (0.09–0.11)	79 (77–82)
Ciprofloxacin	N/T		0.13 (0.13–0.14)	92 (91–93)
Trimethoprim	14	16	0.47 (0.45–0.49)	70 (69–71)

CI, confidence interval; DDD, defined daily dose; AMC, amoxicillin/clavulanic acid; N/A, not applicable; N/T, not tested.

2. Materials and methods

This was a population-based, retrospective, observational study based in the Australian island-state of Tasmania between January 2010 and December 2012.

2.1. Antimicrobial susceptibility data

Antimicrobial susceptibility profiles of all *E. coli* isolates from urinary specimens collected between January 2010 and December 2012 in Tasmania were retrieved from the laboratory information systems of the three microbiology laboratories servicing communities and hospitals within Tasmania. It was not possible to differentiate with certainty between community and hospital isolates, however the vast majority were community-onset isolates. Demographic and clinical data linked to the isolates were not available.

Susceptibility testing had been performed for amoxicillin/ampicillin, amoxicillin/clavulanic acid (AMC), cefalexin, gentamicin, norfloxacin and trimethoprim using the disc diffusion technique with Calibrated Dichotomous Sensitivity (CDS) methodology [7], with the exception of 2011 and 2012 isolates from one laboratory that were tested with European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology [8]. Isolates were classified as either susceptible or non-susceptible (intermediate or resistant) to each antibiotic tested. Data were assessed for duplicate isolates from the same patient; only the first isolate from each patient was used in the analyses.

2.2. Antimicrobial use data

The number of PBS-subsidised prescriptions each month in Tasmania for amoxicillin, AMC, cefalexin, norfloxacin, ciprofloxacin and trimethoprim was retrieved from the PBS website [9]. These data were at the state population-level, not linked to region or individual patients/isolates. For the purpose of epidemiological studies on drug consumption, the World Health Organization (WHO) suggests a defined daily dose (DDD) for each medication to be used as the unit of measurement [10]. The DDD is the assumed average maintenance dose per day of a drug used for its main indication in adults. The prescription data were converted to DDDs per 1000 population per day using the WHO definitions of DDDs and the Tasmanian population estimates from the Australian Bureau of Statistics [11].

The PBS provides government-subsidised access to medicines in Australia; the price of the medicine up to a certain amount is paid by the consumer and the remaining cost is covered by the PBS. All antibiotics assessed in this study cost less than the general co-payment amount but greater than the co-payment amount for concession card-holders; the PBS antibiotic subsidisation data used in this analysis therefore represent prescriptions filled by concession card-holders only. Concession card-holders include war veterans, people who receive the aged-care pension and low income-earners.

Unsubsidised (under co-payment) use of antibiotics was monitored by the Department of Human Services from June 2012 until December 2012. The proportion of total community antibiotic use represented by PBS-subsidised use was estimated using these data.

2.3. Outcome measures

Antimicrobial susceptibility data were assessed for changes over time over the 3-year study period. Antimicrobial use and susceptibility data were assessed for seasonal differences and lag in resistance following antibiotic use. For this analysis, the seasons were defined as follows: summer, December–February; autumn, March–May; winter, June–August; and spring, September–November.

2.4. Statistical methods

Statistical analyses were performed using IBM SPSS Statistics for Windows v.21 (IBM Corp., Armonk, NY) and Stata 10 (StataCorp LP, College Station, TX). Comparisons of proportions were made using the χ^2 test. Comparisons of continuous variables were assessed for normality and were then analysed using the unpaired t-test for equal or unequal variance. Linear regression was used to assess whether the proportion of resistant isolates had increased over time. Univariate and multivariate logistic regression was done to further evaluate the effects of time, season, antimicrobial use and lag following antimicrobial use on resistance. In these models, the outcome variable was the proportion of non-susceptible isolates each month; the number of non-susceptible isolates was assumed to have a binomial distribution determined by the proportion not susceptible and the number of isolates collected for the month. Season was transformed from month of year into a sine wave taking on values between −1 and +1, with the peak in July and the nadir in January. Where X month is the value of the month variable (January to December, 1–12), the season variable was given by

$$X_{season} = \sin\left(\frac{X_{month} - 4}{12} 2\pi\right).$$

2.5. Ethics

The study was approved by the Tasmanian Human Research Ethics Committee.

3. Results

Excluding duplicates, there were 28 145 urinary *E. coli* isolates included in the study. A summary of susceptibility profiles and antimicrobial use is presented in Table 1. Less than 5% of isolates were non-susceptible to AMC, cefalexin, gentamicin and/or