E. coli bacteraemia and antimicrobial resistance following antimicrobial prescribing for urinary tract infection in the community

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Abstract (350 words)

Background: Urinary tract infections are one of the most common infections in primary and secondary care, with the majority of antimicrobial therapy initiated empirically before culture results are available. In some cases, however, over 40% of the bacteria that cause UTIs are resistant to some of the antimicrobials used, yet we do not know how the patient outcome is affected in terms of relapse, treatment failure, progression to more serious illness (bacteraemia) requiring hospitalization, and ultimately death. This study analyzed the current patterns of antimicrobial use for UTI in the community in Scotland, and factors for poor outcomes.

Objectives: To explore antimicrobial use for UTI in the community in Scotland, and the relationship with patient characteristics and antimicrobial resistance in *E. coli* bloodstream infections and subsequent mortality.

Methods: We included all adult patients in Scotland with a positive blood culture with *E. coli* growth, receiving at least one UTI-related antimicrobial (amoxicillin, amoxicillin/clavulanic acid, ciprofloxacin, trimethoprim, and nitrofurantoin) between 1st January 2009 and 31st December 2012. Univariate and multivariate logistic regression analysis was performed to understand the impact of age, gender, socioeconomic status, previous community antimicrobial exposure (including long-term use), prior treatment failure, and multi-morbidity, on the occurrence of *E. coli* bacteraemia, trimethoprim and nitrofurantoin resistance, and mortality.

Results: There were 1,093,227 patients aged 16 to 100 years old identified as receiving at least one prescription for the 5 UTI-related antimicrobials during the study period. Antimicrobial use was particularly prevalent in the female elderly population, and 10% study population was on long-term antimicrobials. The greatest predictor for trimethoprim resistance in *E. coli* bacteraemia was increasing age (OR 7.18, 95% CI 5.70 to 9.04 for the 65 years old and over group), followed by multi-

morbidity (OR 5.42, 95% CI 4.82 to 6.09 for Charlson Index 3+). Prior antimicrobial use, along with prior treatment failure, male gender, and higher deprivation were also associated with a greater likelihood of a resistant *E. coli* bacteraemia. Mortality was significantly associated with both having an *E. coli* bloodstream infection, and those with resistant growth.

Conclusion

Increasing age, increasing co-morbidity, lower socioeconomic status, and prior community antibiotic exposure were significantly associated with a resistant *E. coli* bacteraemia, which leads to increased mortality.

Key words: *Escherichia coli*, Bacteraemia, Bloodstream infection, Antimicrobial resistance, Epidemiology

Introduction

Urinary tract infection (UTI) is the second most common clinical indication for empirical antimicrobial treatment in primary and secondary care, and is the most frequently occurring health care associated infection in the UK National Health System (NHS) (1). Antimicrobial resistance has been recognised as a concern for the future treatment of infections, leading to repeat prescriptions, continued symptoms, complications, increased use of broad spectrum antimicrobials (2), and mortality.

There is a direct relationship between the levels of antimicrobial prescribed and the level of resistance seen in a range of organisms (3). However, the relationship between antimicrobial consumption and development of resistance can be complex (4). At a local level, the correlation between antimicrobial use in the community and resistance is well recognised (5-9), but the correlation between reductions in community prescribing and reductions in resistance are potentially imbalanced. Gram-positive resistance has been reported to decrease in response to primary care stewardship, but the link between reduced antimicrobial use and lower resistance in Gram-negative bacteria is less consistent (10, 11). Prescribing data for UTIs shows that a large reduction of (20%) antimicrobial use in the community correlated to only a small (1%) decrease in resistance to amoxicillin or amoxicillin/clavulanic acid, with similar sized effects seen for trimethoprim usage and resistance (12-14). These small reductions in resistance, despite large reductions in prescribing, are highly dependent on the genetic profile of the organisms, how the resistance determinants are carried and spread due to co-selection by other drugs and the level of bacterial fitness cost (15). The stability of mobile genetic elements (plasmids and integrons) carrying resistance genes is a major factor in the population dynamics of the resistant and sensitive bacterial populations. As a result of the above each drug-bug combination will react very differently to changes/restrictions in the drug use (13, 16).

At the patient level, individuals prescribed an antimicrobial for a UTI are prone to develop resistant infections, with resistance persisting for up to

12 months after the cessation of antimicrobial (6, 17, 18). The time necessary to develop resistance has been shown to be inversely correlated with the amount of antimicrobial given (11). Likewise, multiple prescriptions and longer durations of treatment showed increased rates of resistance (6). The correlation between the number of prescriptions and resistance has been quantified in recent work where multiple prescriptions increased the risk of a resistant *Escherichia coli* (*E. coli)* by two to three fold compared to a single course of treatment (19). Recent work examining *E. coli* urine isolates showed that having a larger number of different antimicrobial prescriptions (more than 4) in the previous six months and also increasing Defined Daily Doses (DDDs) were associated with increased risk of resistance and multiple drug resistance (20).

Community use represents the bulk, approximately 80%, of antimicrobial prescriptions within the UK (7), with up to a third considered to be inappropriate (21), mostly consisting of broad-spectrum antimicrobials (22). Many of these antimicrobials are prescribed for the treatment of UTIs (23-29). Five antimicrobials (amoxicillin, ciprofloxacin, amoxicillin/clavulanic acid, nitrofurantoin and trimethoprim) make up approximately 70%-80% of the antimicrobials prescribed for the treatment of UTIs. The majority of cases of antimicrobial therapy for UTI are also initiated empirically before culture results are available (30), as urine cultures are not routinely recommended in certain patient populations (e.g. non-pregnant women) (31). In some cases over 40% of the bacteria that cause UTIs are resistant to some of the antimicrobials used (29) with this increasing risk for relapse and treatment failure (32, 33). *E. coli* is the most common cause of bacteraemia in high-income countries, and the burden of *E. coli* bacteremia is substantial, especially among the elderly (34). To enable the implementation of effective mitigation and prevention strategies, we need to understand better the epidemiology and risk factors of invasive *E. coli* infections. There is growing evidence showing that increases in the rates of *E. coli* bacteraemia are being driven predominantly by community-onset infections (35), particularly infections of the urinary tract (34), yet we do not know how and which specific factors increase the likelihood for

progression to more serious illness requiring hospitalisation, and ultimately death, after treatment for UTI in the community.

This paper describes the epidemiology of the use of trimethoprim, nitrofurantoin, amoxicillin/clavulanic acid, amoxicillin and ciprofloxacin for UTI in the community across Scotland, characterises the population using these antimicrobials and patterns of use, and examines how prior use of antimicrobials is associated with antimicrobial resistance in bloodstream infections and deaths.

Methods

Data linkage

The NHS National Services Scotland (NSS) Prescribing Information System (PIS) (36) holds all community dispensed prescriptions in NHS Scotland at an individual patient level and was examined to identify a cohort of patients who had been dispensed a UTI-related antimicrobial (amoxicillin, ciprofloxacin, amoxicillin/clavulanic acid, nitrofurantoin or trimethoprim) at any point from 1st January 2009 to 31st December 2012. Entry to the cohort was defined as the first prescription in the study period for one of the UTI-related antimicrobials. Gender and age at cohort entry were recorded for all patients. Only adults (age range 16 – 100 years old) were included in the study. Socio-economic status based on home postcode at entry to the cohort was measured by Scottish Index of Multiple Deprivation quintiles (37). The Scottish Index of Multiple Deprivation (SIMD) is a relative measure of deprivation used by the Scottish Government to define socioeconomic deprivation across small geographical areas (also known as datazones), based on income, employment, education, health, access to services, crime and housing. Geographical areas are categorised into five quintiles, with quintile 1 being the most deprived, and quintile 5 the most affluent. Prescribing data for all the UTI-related antimicrobial prescriptions dispensed in the study period was linked to reports of all bacteraemia from the Electronic Communication of Surveillance in Scotland (ECOSS) data, and to patient level data on hospital admission from NSS General/Acute Inpatient and

Day Case (SMR01) data and deaths from National Registrar Scotland (NRS) data. A universal patient registration system in Scotland uses a unique 10-digit identifier called the community health index number (CHI) which allows data linkage of all NHS encounters. The extraction and linkage were performed by the electronic Data Research and Innovation Service (eDRIS) (38) with all identifiers removed and replaced with a project specific pseudonymous identifier and access to the data provided via a Safe Haven secure analytical platform. No identifiable data was accessed by the research team.

In addition to demographic characteristics, potential risk factors associated with the presence of *E. coli* bacteraemia and antimicrobial resistance were examined using patterns of antimicrobial prescribing, prior hospitalisations and co-morbidity.

Patient level antimicrobial use data were used to identify how many prescriptions of each agent they received within each year in the study period. We also calculated total DDDs for each antimicrobial, defined as the assumed average maintenance dose per day for an individual drug's main indication in adults. Patients who had received the same antimicrobial six or more times within any rolling 12-month period were defined as long-term users. Patients who received a different antimicrobial within 60 days were classed as having had a treatment failure as we assumed this was used to treat the same infection.

A Charlson Index of comorbidity (39) was calculated based on diagnostic ICD-10 codes from hospital discharge records. Previous admissions to hospital were also identified from these records including whether a High Dependency Unit (HDU) or Intensive Care Unit (ICU) stay was part of the admission.

Presence of any organism was identified through at least one record of bacteraemia for the patient within the ECOSS dataset. Reporting of urinary isolates for *E. coli* to ECOSS is not mandatory and so whilst these were initially examined they were not included within any analysis as there was only a sample of records available. *E. coli* bacteraemia related

to blood samples, for which mandatory reporting across Scotland exists, was examined and reports on whether the isolate causing bacteraemia was sensitive or resistant to each of the tested antimicrobials was recorded (using Clinical and Laboratory Standard Institute [CLSI] recommended minimum inhibitory concentrations (40)). Each isolate was tested against several different antimicrobials and susceptibility was reported for any, including trimethoprim and nitrofurantoin, which are used primarily for treatment of urinary tract infection (referred to as UTI-specific antimicrobials).

Statistical Analysis

Demographic characteristics, long-term users, treatment failures and number of antimicrobials dispensed were summarised for patients with any prescriptions, in total and by clinically defined group of UTI-related antimicrobials. The proportions of patients with bacteraemia, based on a positive blood culture for *E. coli,* were summarised across the groups for all of these variables and compared between the groups using chi-squared tests. Similarly, the proportions of patients who died within the study period were summarised and compared across demographic and usage groups using a chi-squared test for differences in proportions. Two-sample t-tests were used for comparison of continuous variables.

The main outcome measures were a) first occurrence of positive *E. coli* bacteraemia, and b) first occurrence of resistance to trimethoprim within the study period. Potential predictors of antimicrobial resistance were based on patterns of antimicrobial prescribing (e.g. long-term use, cumulative dose defined as DDDs, treatment failure). For each patient, these predictor variables are time-varying covariates, i.e. they change throughout the follow-up period. The standard analysis approach for incident events is survival analysis (e.g. Cox regression) potentially with time-varying covariates. However, due to the size of the dataset we used a partial logistic regression for survival analysis method (41). We divided the follow-up period into fixed distinct time intervals, to allow for a simplified analysis via logistic regression, with the outcome being the first occurrence of an event during the time interval given that subjects were

event free at the start of the interval, and predictors being based on each patient's status at the start of the interval. We divided the study period into six-month intervals and used information from 2010 – 2012 for the modelling. The initial two intervals for 2009 were used to define patients' status at the beginning of 2010 but no modelling for outcomes was performed over this time period. Hence the modelling was done using six intervals (two intervals per year for three years) with all events each study period modelled as a risk over the next 6-months (180 days).
We developed univariable models associating the two outcomes with each of the predictors and then created a final multivariable model for statistically significant predictors (selected in univariate analysis significant at $p<0.05$) using manual stepwise selection. All analyses were carried out using the Statistical software R version 3.4.0 (42).

Ethics

The project was submitted to and approved by the Privacy Advisory Committee (PAC) of National Services Scotland (Approval Reference: PAC 34/13) and the East of Scotland Research Ethics Committee (Approval Reference: 13/ES/0118).

Results

Demographic characteristics

There were 1,093,227 patients aged 16 to 100 years old identified as receiving at least one prescription for the 5 UTI-related antimicrobials between 1 January 2009 and 31 December 2012 (amoxicillin, ciprofloxacin, amoxicillin/clavulanic acid, nitrofurantoin and trimethoprim - see Table 1). Over two-thirds of the cohort were female, with almost a third of all patients being older than 65 years, and patients tended to be relatively socioeconomically deprived, with almost half of the population (44.2%) belonging to the two most deprived quintiles. Almost half of all patients (44.9%) were prescribed one type of UTI-related antimicrobial during the study period, while just over a third (36.8%) were prescribed two different antimicrobials and 18% had 3 or more different antimicrobials prescribed. When examining the UTI-specific antimicrobials (nitrofurantoin

and trimethoprim) only, there was also a higher proportion of women (615,027 - 81.8%) and patients aged older than 65 years (254,784 - 33.9%) with 14.8% (161,787 patients) receiving both agents within the same year.

Long-term users and treatment failures

Prescribing patterns showed that 85,036 (7.8%) of patients were long-term users of antimicrobials (any antimicrobial); and there were 32,968 long-term users (4.4%) of UTI-specific antimicrobials (defined as patients that had 6 or more prescriptions for the same antimicrobial in any 12-month period).

There were 195,184 (17.9%) patients classed as having a treatment failure (two different antimicrobials prescribed within a 60-day period).

For the UTI-specific antimicrobials, 11.2% of all patients (72,705) prescribed trimethoprim had a treatment failure, while 16.7% (38,625) of those prescribed nitrofurantoin had a treatment failure (Table 1).

E. coli bacteraemia

Of the total sample of 1,093,227 patients, 121,716 (11.1%) patients had a record present in ECOSS and so had an organism isolated, for any infection type. Of these, 36,482 (30.0%) patients had a urinary *E. coli* isolated, of whom 25,715 (70.5%) had an *E. coli* with resistance to any of the 5 UTI-related antimicrobials. There were 7,485 (0.7% of the total sample) patients identified as developing a blood borne *E. coli* bacteraemia following any UTI-related antimicrobial. Patients who were male, older, more deprived, classed as a long-term user or a treatment failure were more likely to have an *E. coli* bacteraemia reported. A slightly higher proportion of patients prescribed the UTI-specific antimicrobial nitrofurantoin, 2,858 (1.2%), reported a subsequent *E. coli* bacteraemia (Table 2).

Multivariable analysis showed that the stronger predictor for a positive blood culture for *E. coli* bacteraemia was increasing age, along with male gender (OR 1.26, 95% CI 1.20 to 1.33), greater deprivation, increasing age and co-morbidity, and increasing number of UTI specific

(trimethoprim or nitrofurantoin) prescriptions in the previous 6 months. There was a 15% increase in the risk of *E. coli* bacteraemia for each additional prescription of a UTI specific antimicrobial dispensed over the previous 6-month period. Emergency hospital admission or admission to a high dependency unit in the previous six months was also associated with a greater likelihood of having a *E. coli* bacteraemia (Table 3).

Antimicrobial resistance

There were 7,485 patients who were recorded as having an *E. coli* bacteraemia. Characteristics of patients with *E. coli* bacteraemia are detailed in Supplementary Table 1. Resistance rates were high, with 71.2% patients had an *E. coli* that was resistant to at least one of the antimicrobials examined. Resistance was greater for amoxicillin (68.2% of those tested), followed by trimethoprim (44.9%), amoxicillin/clavulanic acid (34.8%), ciprofloxacin (21.1%) and nitrofurantoin (9.8%).

Patients in the most deprived quintile, who were long-term users or treatment failures had higher proportions of resistant *E. coli* bacteraemia. There were 1,313 (80%) long-term users recorded as having a resistant *E. coli* versus 69% of those who were not long-term users ($p<0.001$); while 1,765 (76%) of patients who reported a treatment failure had a resistant *E. coli* compared to 69% of those with no treatment failures ($p<0.01$). (Supplementary Table 1). Resistance rates were similar across age groups, ranging from 66.2 to 71.6% with no significant difference.

A multivariable model for predictors of resistance in *E. coli* bacteraemia to trimethoprim showed significant predictors were male gender, increasing age, the highest level of deprivation, greater co-morbidity, prior exposure to trimethoprim, a treatment failure with trimethoprim, a sensitive *E. coli* bacteraemia in previous intervals and emergency admission (Table 4). Increasing age and greater co-morbidity were by far the most significant predictor, with a seven-fold likelihood of having a trimethoprim-resistant *E. coli* bacteraemia for those aged 65 years old or older (OR 7.18, 95% CI 5.70 to 9.04), and five-fold for those with a Charlson Index of comorbidity score of 3+ (OR 5.42, 95% CI 4.82 to 6.09).

A similar model for nitrofurantoin showed the number of prescriptions for nitrofurantoin in the previous 6 months (OR=1.31, 95% CI 1.10-1.56), and emergency admission (OR=6.09, 95% CI 2.69-13.79) were also associated with significantly increased risk of resistance to nitrofurantoin in *E. coli* bacteraemia.

Mortality

Amongst the initial population receiving a UTI-related antibiotic male gender, increasing age, higher levels of deprivation, being a long-term user, having a treatment failure and having an *E. coli* bacteraemia all showed significantly higher proportions of mortality (Table 5).

In patients who had an *E. coli* bacteraemia tested against trimethoprim, mortality was higher in those that were female, were long-term users of trimethoprim and who were treatment failures (had a second antibiotic in a 60-day period). Mortality in these patients was increased as age increased and was significantly higher in patients with trimethoprim resistance (39.4% v 31.5%, $p<0.001$, see Table 6).

Discussion

Main findings and comparison with other literature

This is one of the first studies in the UK to use a national linked patient level data set to investigate the population receiving antibiotics for the treatment of UTIs, and has demonstrated an association between primary care prescribing of antimicrobials for UTI and antimicrobial resistance in subsequent *E. coli* bacteraemia.

There were just over 15,000 *E. coli* bacteraemias in Scotland (Health Protection Scotland communication) over the period 2009-12 meaning that almost 50% of all cases came from the initial population within this study. This corresponds to the report by Bhattacharya et al who made similar estimates for the English population (43).

Our study confirms that most treatment for UTI occurs within the elderly female population, a demographic that is set to significantly increase by 2030 with a 50% projected increase in the number of people aged over 75 years (44). In our study, of the overall population receiving antibiotics almost 10% were on long-term antimicrobials, presumably as prophylaxis. 7,485 (0.7%) patients initiated on a UTI-related antibiotic had a positive blood culture for *E. coli*, with 71% of this group reported as being resistant to at least one antibiotic. Prior antimicrobial use, along with prior treatment failure, male gender, higher deprivation and multi-morbidity, were associated with a greater likelihood of an *E. coli* bacteraemia with resistance reported in multivariate logistic regression analysis. Increasing age was associated with both a greater likelihood of being prescribed antibiotics, and higher resistance rates. Prior trimethoprim use within the last 12 months was associated with an increased odds for resistance of 20%, with multiple courses showing increased association, which is in line with previous evidence (6). One-fifth of patients in this national dataset had treatment failures requiring a second different antibiotic to be prescribed within 60 days, with both of the UTI-specific antimicrobials trimethoprim and nitrofurantoin having significant failure rates, of 10% and 16% respectively. Mortality was significantly greater in those with *E. coli* bacteraemia (vs non-bacteraemic [35.3% vs 6.6%, p<0. 001), and those with trimethoprim-resistant *E. coli*. Prior treatment failures were also associated with increased likelihood of mortality, although the

relationship was weaker in the case of trimethoprim. Our population with an *E. coli* bacteraemia had just over 35% all-cause mortality during the three-year follow-up and whilst this cannot be directly compared to the 30-day figure in the Bhattacharya paper it is also high. We were unable to examine attributable mortality to *E. coli* or to estimate the excess mortality in this patient group, as we looked into all-cause mortality within the study period modelled at risk over the next 6-months, as opposed to 30-day mortality.

Our findings are consistent with those seen elsewhere. Lishman et al examined the relationship between primary care prescribing for urinary tract infections and resistance in *E. coli* bacteraemia in adult women in England. Similar to our study, they demonstrated that primary care antibiotic use for UTIs was linked to the development of an UTI-related bacteraemia, with higher rates of resistance associated with prior antimicrobial use (45). Bou-Anton S et al examined the incidence, risk factors and antimicrobial susceptibility profile on *E. coli* bacteraemia in England over a two-year period. Increasing age and female gender were both associated with an increased likelihood of *E. coli* bacteraemia, with a large proportion of cases (over 40%) found to be originating from urinary tract infections (34), supporting our findings. Results from Costelloe et al suggest that primary care prescription of antibiotics was associated with trimethoprim resistance up to 12 months after exposure in patients admitted to hospital with urinary tract infections (unadjusted OR 3.58) (18), and another French study also found that resistance to amoxicillin/clavulanic acid was four times higher with exposure to it in the month before, in patients hospitalised with urinary tract infection (46). However, the majority of these studies are relatively small, and Lishman included only women, through an ecological, population, approach. We included nationwide Scottish data for all adults from 16 years old and both genders, showing that male gender was a significant factor for resistance. Also, the availability of patient-level data makes it possible to draw patient-level conclusions, avoiding ecological bias. O Blandy et al also demonstrated that presence of antimicrobial resistance, increasing age and comorbidities as main contributing factors for increased mortality

(35), similar to our results, with the majority of cases being of community-onset, highlighting the need for improving antimicrobial use and reduce the burden of *E. coli* infections in the community. Similarly, increasing co-morbidity and an adverse antimicrobial resistance profile have been described as risk factors for poorer outcomes in studies looking more widely at Gram-negative bacteraemias (47).

Implications for policy and practice

There were over 1 million adult patients receiving at least one prescription for the 5 UTI-related antimicrobials within the study period, which means that 24.9% of the Scottish population (based on mid-2011 estimates of numbers aged 16-95+) (48) were exposed to these antimicrobials in this time frame. Primary care antimicrobial exposure was associated with increased occurrence of resistance in *E. coli* bloodstream infections (particularly for trimethoprim or nitrofurantoin), which in turn was associated with increased mortality. Our findings reinforce national policy efforts trying to reduce total antimicrobial use in the community in Scotland (49), and particularly antibiotic use in urinary tract infections, similar to the English Quality Premium initiative to reduce Gram-negative bloodstream infections (50). Improving surveillance of resistance has also been described as a key action point for both UK Government (51), and internationally (52). This study has helped demonstrate the value of enhanced surveillance systems, such as ECOSS, and routine data linkage for monitoring resistance trends nationally, understanding precipitating factors (including primary care antibiotic use), and examining adverse outcomes, such as mortality.

Both UTI-related antimicrobials had significant failure rates. This will have considerable resource and patient outcome implications, including longer hospital stays, increased mortality, and increased cost related to suboptimal antimicrobial use (53-55). Furthermore, this has implications for the recommendations for empiric therapy of UTIs. The majority of prescribing is done without knowledge of the infecting organism or its sensitivities as, although laboratory reporting can influence GPs' prescribing of antibiotics for UTIs and other infections (56), current

guidelines recommend against routine sampling for uncomplicated urinary tract infections in the community (30).

Conclusion

Increasing age, increasing co-morbidity, lower socioeconomic status, and prior community antibiotic exposure were significantly associated with a resistant *E. coli* bacteraemia, which leads to increased mortality, with older age being the strongest predictor. This highlights the need for prudent primary care antibiotic use, particularly in the frail, multi-morbid population.

Strengths & Limitations

The major strength of this study is that we report data on the burden of antimicrobial resistance in *E. coli* bacteraemia in Scotland at national level, and the association with prior antimicrobial use for UTI in the community among other factors, and mortality at the patient-level, which is unique. Completeness is a common concern with using routinely collected data. However, the data presented in this study derived from the ECOSS data set, which entails a surveillance and reporting system across Scotland. Reporting of *E. coli* bacteraemia to ECOSS remains mandatory, so missing data is unlikely.

Patients were identified as having an antimicrobial prescription of any of the five specified antimicrobials at any point during the study period. Patients having other or no antimicrobials but still an *E. coli* bacteraemia could have been missed. The five antimicrobials examined however represent up to 80% antimicrobial use for UTI in the community, and are all relevant for the treatment of Gram-negative bacteraemia (23). However, we did not have the indication for the prescription as this is not available within the PIS database, which may introduce selection bias, and so assumed that UTI was the reason for the prescription. This is more valid for trimethoprim and nitrofurantoin but less so for the other antimicrobials especially amoxicillin and so we presented data grouped in different ways.

We defined treatment failure as needing a different, second, antimicrobial within 60 days (which is longer than some other studies (23)), as we assumed this was used to treat the same infection. We acknowledge this is a strong assumption, however we decided to use a 60-day window to identify treatment failure as not all PIS data has the correct dispensed date attached as it may default to the date the pharmacist was paid which is commonly the end of the month. We therefore chose a 60-day window to allow for this limitation with the data. There is also the issue that treatment failure is actually empirical treatment of an existing undiagnosed resistant *E. coli* which is only detected at a later stage, but we were unable to explore the data to examine this further and it also reflects clinical practice.

532 **Table 1: Characteristics of patients with at least one UTI-related antimicrobial prescribed**

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Antimicrobial Group	Amoxicillin, ciprofloxacin, amoxicillin/clavulanic acid, nitrofurantoin or trimethoprim	Nitrofurantoin or trimethoprim
Any	**1093227 (100.0%)**	**752225 (68.8%)**
Gender		
Male	310974 (28.4%)	137198 (18.2%)
Female	782253 (71.6%)	615027 (81.8%)
Age group		
16-34	268896 (24.6%)	184476 (24.5%)
35-49	242173 (22.2%)	152857 (20.3%)
50-64	247287 (22.6%)	160108 (21.3%)
>65	334871 (30.6%)	254784 (33.9%)
SIMD quintile (Q1= Most Deprived, Q5=Least Deprived)		
Q1	247671 (22.8%)	169301 (22.7%)
Q2	232451 (21.4%)	159286 (21.4%)
Q3	215015 (19.8%)	147401 (19.8%)
Q4	198832 (18.3%)	138783 (18.6%)
Q5	190210 (17.5%)	131272 (17.6%)
Long-term users of any antimicrobials		
Yes	85036 (7.8%)	32968 (4.4%)
No	1008191 (92.2%)	719257 (95.6%)
Treatment failures		
	195184 (17.9%)	Trimethoprim: 72,705 (11.2%) Nitrofurantoin: 38,625 (16.7%)
Number of antimicrobials received per patient		
1	491315 (44.9%)	590438 (54.0%)
2	402731 (36.8%)	161787 (14.8%)
3	144671 (13.2%)	
4	44179 (4.0%)	
5	10331 (0.9%)	

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535 **Table 2: Characteristics of UTI-related antimicrobial users who did / did not have an *E. coli* positive blood**
536 **culture during study period 2009-2012**
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		All	Blood culture positive for *E. coli*	
			No	Yes
	N	1093227	1085742	7485 (0.7%)
Gender				
	Female	782253 (71.6%)	777775 (99.4%)	4478 (0.6%)
	Male	310974 (28.4%)	307967 (99.0%)	3007 (1.0%)
Age category at sample				
	16-34	268896 (24.6%)	268610 (99.9%)	286 (0.1%)
	35-49	242173 (22.2%)	241693 (99.8%)	480 (0.2%)
	50-64	247287 (22.6%)	246045 (99.5%)	1242 (0.5%)
	>65	334871 (30.6%)	329394 (98.4%)	5477 (1.6%)
Mean age at sample				
	Mean(SD)	51.8 (20.6)	51.6 (20.5)	70.9 (15.6)
SIMD quintile (Q1= Most Deprived, Q5=Least Deprived)				
	Q1	247671 (22.8%)	245735 (99.2%)	1936 (0.8%)
	Q2	232451 (21.4%)	230731 (99.3%)	1720 (0.7%)
	Q3	215015 (19.8%)	213604 (99.3%)	1411 (0.7%)
	Q4	198832 (18.3%)	197581 (99.4%)	1251 (0.6%)
	Q5	190210 (17.5%)	189084 (99.4%)	1126 (0.6%)
Long-term users of any antimicrobials				
	No	1008191 (92.2%)	1002338 (99.4%)	5853 (0.6%)
	Yes	85036 (7.8%)	83404 (98.1%)	1632 (1.9%)
Treatment failures				
	No	898043 (82.1%)	892839 (99.4%)	5204 (0.6%)
	Yes	195184 (17.9%)	192903 (98.8%)	2281 (1.2%)
Patients receiving sentinel antimicrobials				
	Amoxicillin	449099 (41.1%)	445529 (99.2%)	3570 (0.8%)
	Ciprofloxacin	260266 (23.8%)	257583 (99.0%)	2683 (1.0%)
	Amoxicillin/clavulanic acid	335784 (30.7%)	333095 (99.2%)	2689 (0.8%)
	Nitrofurantoin	244612 (22.4%)	241754 (98.8%)	2858 (1.2%)
	Trimethoprim	669400 (61.2%)	664343 (99.2%)	5057 (0.8%)
	Excl.Amoxicillin[a]	1092151 (99.9%)	1084667 (99.3%)	7484 (0.7%)
	UTI-Specific[b]	752225 (68.8%)	746421 (99.2%)	5804 (0.8%)

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539 [a] This includes patients receiving any of ciprofloxacin, amoxicillin/clavulanic acid,
540 nitrofurantoin, trimethoprim.
541 [b] UTI-specific includes either trimethoprim or nitrofurantoin.
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543 **Table 3: Multivariable logistic model for predictors for testing positive for an *E. coli* bacteraemia in relation to**
544 **UTI-specific drug**

	OR	95% CI
Gender (Male)	1.26	(1.20, 1.33)
SIMD2	0.87	(0.81, 0.93)
SIMD3	0.82	(0.76, 0.88)
SIMD4	0.77	(0.71, 0.83)
SIMD5	0.78	(0.72, 0.85)
Age (35-49)	1.61	(1.35, 1.91)
Age (50-64)	3.41	(2.93, 3.97)
Age (> 65)	7.67	(6.64, 8.85)
Charl. Index: 1	2.49	(2.27, 2.73)
Charl. Index: 2	3.64	(3.32, 3.99)
Charl. Index: 3+	5.74	(5.30, 6.21)
Number of UTI spec. prescriptions in past 6 months	1.15	(1.13, 1.18)
Emergency admissions in prior interval (Yes)	1.24	(1.16, 1.32)
Routine admissions in prior interval (Yes)	0.93	(0.87, 0.99)
High dependency admissions in prior interval (Yes)	1.14	(1.01, 1.27)

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547 **Table 4: Multivariable logistic model for predictors of trimethoprim resistance in *E. coli* bacteraemia isolates**

	OR	95% CI
Gender (Male)	1.29	(1.19, 1.40)
SIMD2	0.83	(0.74, 0.94)
SIMD3	0.77	(0.68, 0.87)
SIMD4	0.74	(0.65, 0.84)
SIMD5	0.86	(0.75, 0.97)
Age (35-49)	1.58	(1.20, 2.09)
Age (50-64)	3.21	(2.52, 4.10)
Age (> 65)	7.18	(5.70, 9.04)
Charl. Index: 1	2.65	(2.31, 3.03)
Charl. Index: 2	3.46	(3.01, 3.97)
Charl. Index: 3+	5.42	(4.82, 6.09)
Number of trimethoprim prescriptions in last 6 months (per increase of one)	1.14	(1.04, 1.24)
Prescribed trimethoprim in previous intervals (Yes)	1.24	(1.20, 1.28)
Treatment failure of trimethoprim (Yes)	2.03	(1.81, 2.28)
Had sensitive blood test in previous intervals (Yes)	3.21	(2.44, 4.22)
Emergency admissions in prior interval (Yes)	1.45	(1.31, 1.60)

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549 **Table 5: Characteristics of all patients prescribed any UTI-related antimicrobial who did/did not die**
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	All	Died		P-value
		No	Yes	
N	1093227	1018822	74405 (6.8%)	
Gender				
Female	782253 (71.6%)	736686 (94.2%)	45567 (5.8%)	p<0.001
Male	310974 (28.4%)	282136 (90.7%)	28838 (9.3%)	
Age category at first antimicrobial use				
16-34	268896 (24.6%)	268286 (99.8%)	610 (0.2%)	p<0.001
35-49	242173 (22.2%)	239897 (99.1%)	2276 (0.9%)	
50-64	247287 (22.6%)	238739 (96.5%)	8548 (3.5%)	
>65	334871 (30.6%)	271900 (81.2%)	62971 (18.8%)	
Age at first antimicrobial use				
Mean (SD)	51.8 (20.6)	49.9 (19.8)	77.0 (12.8)	p<0.001
SIMD quintile (Q1= Most Deprived, Q5=Least Deprived)				
Q1	247671 (22.8%)	230413 (93.0%)	17258 (7.0%)	p<0.001
Q2	232451 (21.4%)	215630 (92.8%)	16821 (7.2%)	
Q3	215015 (19.8%)	200047 (93.0%)	14968 (7.0%)	
Q4	198832 (18.3%)	185222 (93.2%)	13610 (6.8%)	
Q5	190210 (17.5%)	178846 (94.0%)	11364 (6.0%)	
Long-term users of any antimicrobials				
No	1008191 (92.2%)	945356 (93.8%)	62835 (6.2%)	p<0.001
Yes	85036 (7.8%)	73466 (86.4%)	11570 (13.6%)	
At least one treatment failure of any antimicrobials (different antimicrobial within 60 days)				
No	898043 (82.1%)	841648 (93.7%)	56395 (6.3%)	p<0.001
Yes	195184 (17.9%)	177174 (90.8%)	18010 (9.2%)	
***E. coli* bacteraemia**				
No	1085742 (99.3%)	1013978 (93.4%)	71764 (6.6%)	p<0.001
Yes	7485 (0.7%)	4844 (64.7%)	2641 (35.3%)	

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Table 6: Characteristics of patients with *E. coli* bacteraemia tested for trimethoprim resistance who did/did not die

	***E. coli* blood test for trimethoprim resistance**	**Died**		**P-value**
		No	Yes	
N	6401	4157 (64.9%)	2244 (35.1%)	
Ever received trimethoprim				
No	2071 (32.4%)	1261 (60.9%)	810 (39.1%)	p<0.001
Yes	4330 (67.6%)	2896 (66.9%)	1434 (33.1%)	
Gender				
Female	3807 (59.5%)	2603 (68.4%)	1204 (31.6%)	p<0.001
Male	2594 (40.5%)	1554 (59.9%)	1040 (40.1%)	
Age category at first trimethoprim use				
16-34	233 (3.6%)	217 (93.1%)	16 (6.9%)	
35-49	416 (6.5%)	332 (79.8%)	84 (20.2%)	p<0.001
50-64	1052 (16.4%)	765 (72.7%)	287 (27.3%)	
>65	4700 (73.4%)	2843 (60.5%)	1857 (39.5%)	
Age at first trimethoprim use				
Mean (SD)	70.9 (15.6)	71.0 (16.1)	72.8 (14.2)]	p=0.332
SIMD quintile (Q1= Most Deprived, Q5=Least Deprived)				
Q1	1625 (25.5%)	1084 (66.7%)	541 (33.3%)	
Q2	1483 (23.3%)	963 (64.9%)	520 (35.1%)	
Q3	1215 (19.1%)	796 (65.5%)	419 (34.5%)	p=0.071
Q4	1052 (16.5%)	678 (64.4%)	374 (35.6%)	
Q5	989 (15.5%)	605 (61.2%)	384 (38.8%)	
Long-term users of trimethoprim				
No	6136 (95.9%)	3968 (64.7%)	2168 (35.3%)	p=0.030
Yes	265 (4.1%)	189 (71.3%)	76 (28.7%)	
At least one treatment failure of trimethoprim (different antimicrobial within 60 days); includes prescriptions dispensed before 01/11/2012				
No	5698 (89.0%)	3678 (64.5%)	2020 (35.5%)	p=0.065
Yes	703 (11.0%)	479 (68.1%)	224 (31.9%)	
Resistant				
No	3523 (55.0%)	2412 (68.5%)	1111 (31.5%)	p<0.001
Yes	2878 (45.0%)	1745 (60.6%)	1133 (39.4%)	

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List of abbreviations

AMR	Antimicrobial resistance
CHI	community health index number
CI	Confidence interval
CLSI	Clinical and Laboratory Standard Institute
DDDs	Defined Daily Doses
E. coli	*Escherichia coli*
ECOSS	Electronic Communication of Surveillance in Scotland (microbiology dataset)
eDRIS	electronic Data Research and Innovation Service
ICD-10	International Classification of Diseases
NHS	National Health System
NRS	National Registrar Scotland (mortality dataset)
NSS	NHS National Services Scotland
OR	Odds ratio
PAC	Privacy Advisory Committee
PIS	Prescribing Information System (prescribing dataset)
SMR01	NSS General/Acute Inpatient and Day Case (hospital admission dataset)
UTI	Urinary tract infection(s)

Declarations

Ethics approval and consent to participate

The project was submitted to and approved by the Privacy Advisory Committee (PAC) of National Services Scotland (Approval Reference: PAC 34/13) and the East of Scotland Research Ethics Committee (Approval Reference: 13/ES/0118).
The study was an observational study performing secondary data analysis of routinely collected health data. No experiments or interventions on humans were performed as part of the study. The research team did not collect any human samples. The study analyses anonymised information from blood cultures collected as part of routine healthcare practice. Analysis of anonymised information was done as per UK Good Clinical Practice guidelines, in a secure, password-protected Safe Haven part of Information Services Division (eDRIS) at Public Health Scotland, under NHS Scotland Research Ethics approval as detailed above.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available to named researchers from the Electronic Data Research and Innovation Service (eDRIS) at Public Health Scotland, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Competing interests

The authors declare they have no conflicts of interest.

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Authors' contributions

CMC, AL and WM conceived this study. AB, SJEB and AMcC cleaned, analysed, and verified the underlying data. All authors contributed to the study design. CMC and VHS led the writing of the paper. All authors contributed to drafting the paper and revised the manuscript for important intellectual content. AB, SJEB and AMcC had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

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