# Risk factors for resistance and multidrug resistance in community urine isolates: population level analysis using the NHS Scotland Infection Intelligence Platform

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**Running title:** Resistance risk factors in urines

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**Synopsis**

*Background:* Urinary tract infections (UTI) are common. Antibiotic treatment is usually empirical, with the risk of under-treatment of resistant infections.

Objectives: To characterise risk factors for antibiotic resistant community urine isolates using routine record linked health data.

*Methods*: Within the National Health Service Scotland Infection Intelligence Platform, national surveillance patient-level data on community urine isolates (January 2012-June 2015) were linked to hospital activity and community prescribing data. Associations between age, gender, comorbidity, care home residence, previous hospitalisations, antibiotic exposure, and resistant (any antibiotic) or MDR (≥1 antibiotic from ≥3 categories) urinary isolates were quantified using multivariable logistic regression.

*Results:* Of 40,984 isolates, 28% were susceptible, 45% resistant, and 27% MDR. Exposure to ≥ 4 different antibiotics in the prior six months increased MDR risk, OR 6.81 (95%CI 5.73-8.11). MDR was associated with ≥29 DDD cumulative exposure, in the prior six months, for any antibiotic (OR 6.54, 95%CI 5.88-7.27), nitrofurantoin (OR 8.56, 95%CI 6.56-11.18) and trimethoprim (OR 14.61, 95%CI10.53-20.27). Associations persisted for 10-12 months for nitrofurantoin (OR 2.31, 95%CI 1.93-2.76) and trimethoprim (OR 1.81, 95%CI 1.57-2.09). Increasing age, comorbidity, previous hospitalisation and care home residence were independently associated with MDR. For resistant isolates the factors were the same but with weaker associations.

*Conclusion:* We have demonstrated, using national capability at scale, the risk of MDR in community urine isolates for the first time and quantified the cumulative and sustained impact of antibiotic exposure. These data will inform the development of decision support tools for UTI treatment.

## Introduction

Antimicrobial resistance (AMR) is an increasing global health threat. [1] Resistance among invasive Gram-negative bacterial isolates in Europe and the US is high and increasing,[2,3] including MDR. MDR is associated with increased treatment failures and costs, and increased morbidity and mortality.[4,5]

In Scotland, resistance among Gram-negative bacteremia remains high, particularly to antibiotics commonly prescribed for urinary tract infection (UTI).[6] In 2015, *Escherichia coli (E. coli)* bacteremia in Scotland had an incidence of 85.5 per 100,000 population, 4.9% higher than in 2012. [6]

A key action of the UK Five Year Antimicrobial Resistance Strategy (AMR) (2013-2018) is better access to and use of surveillance data and improved data linkage.[7] National Health Services (NHS) Scotland has developed an Infection Intelligence Platform (IIP) which has increased informatics capability and capacity to link routinely collected national data, with a particular aim of enabling patient-centred treatment through modelling patient-specific risk factors.[8]

UTI is the second most common reason for use of antibiotics in the community.[9] Initial antibiotic treatment is usually empirical, where the prescriber has no information on the causative organism or antibiotic susceptibility. In Scotland national guidance recommends nitrofurantoin or trimethoprim as first line empirical treatment of uncomplicated UTI.[10] However, these empirical options may not be appropriate for patients with high risk of antibiotic resistance. The aim of this study was to quantify risk factors for AMR in urine isolates using individual-level routine national data linked within the IIP.

## Methods

NHS National Services Scotland (NSS) hosts national health and demographic data on behalf of NHS Scotland. In Scotland all individuals have a unique patient identifier, the Community Health Index (CHI) number, which enables records for the same patient to be

linked across multiple datasets.[11] Within the IIP, CHI is used to link specific data then patient identifiers are removed for anonymised analysis.

*Data Sources*

The Surveillance of Antimicrobial Resistance in Urinary Isolates in Scotland (SARUIS) dataset records culture and susceptibility data for a large, representative subset of all positive urine isolates in Scotland.[12] All NHS Boards are required to submit data on the first 400 consecutive positive urine samples per calendar quarter. Demographic data were obtained from SARIUS.

Patient level data on hospitalisations were obtained from the NSS General/Acute Inpatient and Day Case dataset (SMR01)[13] and on all dispensed community NHS prescriptions in the previous 12 months were obtained from the NSS Prescribing Information System (PIS).[13]

*Cohort identification and variable classification*

The study cohort was identified from records with a valid CHI number in the SARUIS dataset as patients ≥16 years old with a clinical urine isolate taken in the community between January 2012 and June 2015. SARUIS records susceptibility data for up to 14 antibiotics for each isolate. European Committee on Antimicrobial Susceptibility Testing (EUCAST)[14] susceptibility testing methodology was gradually introduced in the diagnostic and reference laboratories in Scotland during 2013. This may have resulted in small proportions of isolates that would have been reported as 'susceptible' under Clinical and Laboratory Standards Institute (CSLI)[15] methodology being reported as 'resistant' under the EUCAST methodology later in the study period. Testing and reporting practice varied between laboratories meaning that not all isolates were tested against all antibiotics. From the standard testing panel across NHS Scotland, antibiotics were grouped into seven categories[12]: 1. agents used for the treatment of UTI in Scotland (ciprofloxacin/ co-amoxiclav/ nitrofurantoin /trimethoprim); 2. extended spectrum penicillins (ampicillin/amoxicillin); 3. first and second generation cephalosporins (cefuroxime /

cefalexin); 4. third-generation cephalosporins (cefotaxime/ceftazidime); 5. carbapenems (meropenem/ertapenem); 6. aminoglycosides (gentamicin); and, 7. tetracyclines. Isolates were categorised as susceptible if susceptible to all antibiotics tested, resistant if resistant to one of the antibiotics tested; and MDR if resistant to at least one antibiotic in each of three or more categories. Patients with more than one isolate in the study period had the most resistant isolate selected, or a random isolate selected if they were in the same resistance category.

Using SMR01, the number of hospital stays in the previous 12 months, and a Charlson co-morbidity score[16,17] derived from ICD-10[18] discharge codes from the previous five years, were calculated for each patient.

Using PIS, community antibiotic exposure in the previous 12 months was determined and quantified in DDDs.[19] Antibiotic exposure was classified as the number of different antibiotics and, separately, as the cumulative DDD of all antibiotics, nitrofurantoin alone and trimethoprim alone, in the previous six months, and as the time interval between the urine isolate and the last prior antibiotic (in total, nitrofurantoin, trimethoprim) within 12 months.

The number of different drug classes, defined as paragraphs of the legacy British National Formulary (BNF),[20] a patient had dispensed in the previous 12 months was used as a co-morbidity measure, in addition to the Charlson score. Care home (long term care facility in the community providing a supported care environment) residence was assigned if a patient had an admission to hospital from a care home (from SMR01) and/or was registered as a care home resident on a dispensed prescription (from PIS), in the previous 12 months.

*Statistical Analysis*

Associations between gender, age group, comorbidity, previous hospitalisation, care home residence, antibiotic exposure (measured as number of different antibiotics in previous 6 months), and urine isolate susceptibility (susceptible, resistant or MDR) were quantified using multinomial logistic regression, with susceptible the reference category. Associations

significant ($p<0.05$) at univariate level were included in multivariate models. Where the variable was an ordered factor, the p-value for the linear trend was reported. Measurement of the association between both temporal and cumulative antimicrobial exposure were considered in separate models for exposure to each of (i) any antibiotic (ii) nitrofurantoin and (iii) trimethoprim. Again multinomial logistic regression was used adjusted for gender, age group, Charlson score, drug classes prescribed in the previous 12 months, number of hospital stays in previous 12 months and care home residence in the previous 12 months.

A sensitivity analysis was carried out (with number of different antibiotics as the antibiotic exposure variable), excluding patients with hospitalisations in the previous 12 months to negate the potential effect of any hospital prescribing on the associations observed as patient-level hospital prescribing data was not available. A separate sub-group analysis was conducted including isolates that had not been tested against at least one antibiotic from all seven categories.

Data manipulation was carried out in SPSS version 21 and analyses in R version 3.2.0.

*Ethical approval*

All study data were generated during routine care and had all patient identifiers removed prior to analysis. NSS Privacy Advisory Committee approval was granted and all analysis adhered to NSS Information Governance Policy and Procedures.

## Results

Within the study period 40,984 (62%) of 66,194 urine isolates in SARUIS met the inclusion criteria. Of these, 11,674 (28%) were susceptible, 18,445 (45%) were resistant, and 10,892 (27%) MDR, and *E. coli* accounted for 73% of all isolates (Table 1). More than half of all isolates were from people ≥65 years old, 79% were from female patients and 9% were from care home residents (Table 1). One third of patients had a Charlson score of ≥1 but almost three-quarters had been prescribed drugs from ≥5 classes in the previous 12 months, and 36% had a hospital stay in the previous 12 months (Table 1). Just over a third of patients

had no antibiotic prescriptions in the prior six months and 5% had at least four different antibiotics (Table 1). A total of 30% had ≥14 DDD of antibiotic in the preceding six months and the mean time since last antibiotic prescription in the prior 12 months was 75 days (SD=90) the median was 35 days (IQR=104).

In univariate analyses, male gender, increasing age, comorbidity, hospitalisation, care home residence, number of different drug classes and different antibiotics in the previous six months were all associated with increased risk of having resistant and MDR isolates (Table 2). Associations remained in adjusted analysis, with higher MDR risk associated with being male (OR 1.17, 95%CI 1.09-1.26), older (OR for ≥85 *versus* <25 years old: 1.81, 95%CI 1.56-2.10), higher Charlson scores (Charlson ≥5 *versus* 0 OR 1.31 (95%CI 1.11-1.56)), numbers of previously prescribed drug classes (OR for ≥20 *versus* 0-4: 2.06, 95%CI 1.73-2.45), numbers of previous admissions (OR for ≥4 *versus* 0: 1.82, 95%CI 1.56-2.13), and care home residence (OR 3.36, 95%CI 2.95-3.83) (Table 2). Having prescriptions for ≥4 different antibiotics in the previous six months had the highest association with MDR, of any variable category, in adjusted analysis (OR 6.81, 95%CI 5.73-8.11) (Table 2). Resistance to one antibiotic had similar associations as MDR but with weaker associations for most covariates, with care home residence (OR 2.16, 95%CI 1.90-2.45) and an increasing number of different antibiotics prescribed in the previous six months (≥4 *versus* 0 OR 2.79, 95%CI 2.36-3.31) having the strongest associations with resistance.

The sensitivity analysis excluding patients with hospitalisations in the previous 12 months comprised 26,020 patients (64% of whole cohort). Age was no longer significantly associated with resistant isolates (p=0.961) but remained strongly associated with MDR (p<0.001), and the association between male gender and MDR was not significant (p=0.08). Other associations, particularly higher numbers of different antibiotics, were similar to the main cohort analysis (Table S1). The sub-group analysis including only isolates not tested against at least one drug from all seven categories of antibiotics comprised of 6,386 patients (15.5% of cohort). Most associations with resistance and MDR were similar to the main

analysis with the exception of gender not being significant and previous hospitalisation not being associated with resistant isolates (Table S2).

Cumulative exposure in the prior six months had dose-response effects on resistance and MDR, for total antibiotic, nitrofurantoin, and trimethoprim exposures (Figures 1 & 2). For MDR, ≥29 DDD *versus* no antibiotics in the previous six months, had an OR 6.54 (95%CI 5.88-7.27) for total antibiotic exposure, 8.56 (95%CI 6.56-11.18) for nitrofurantoin, and 14.61 (95%CI 10.53-20.27) for trimethoprim (Figure 2).

There were temporal associations between antibiotic exposure and resistance, particularly MDR (Table 3). Exposure to any antibiotic in the previous one month had an adjusted odds of MDR of 2.89 (95%CI 2.67-3.13) compared to no antibiotics, reducing to an odds of 1.16 (95%CI 1.00-1.34) if the last exposure was 10-12 months previously (Table 3). Exposure to trimethoprim and to nitrofurantoin, compared to no antibiotics, in the previous one month had similar associations with MDR as for any antibiotic exposure, but effects persisted for longer and were still highly significant for exposure 10-12 months previously (nitrofurantoin OR 2.31, 95%CI 1.93-2.76), and trimethoprim OR 1.81 (95%CI 1.57-2.09) (Table 3).

## Discussion

This study is, as far as we know, the first to use national patient-level data linkage to characterise risk factors for AMR in community urine isolates and to examine MDR. We found that antibiotic exposure in the previous six months was strongly associated with MDR, and the effect was stronger with greater cumulative exposure to any antibiotics, to nitrofurantoin and to trimethoprim. The risk of MDR remained elevated following last exposure to any antibiotics for 7-9 months and to nitrofurantoin and trimethoprim for 10-12 months. We also found increasing age, comorbidity (Charlson score and drug classes), hospitalisation in the previous 12 months and care home residence were significantly associated with resistance and MDR after adjustment of other factors.

Previous studies of resistance risk factors in community urine isolates have focussed on exposure to a single or 'any' undefined antibiotic and associations of resistance to one or two antibiotics, without examining MDR. Such studies were small scale (n=398-8833), in single regions rather than at national level and were over 10 years old.[21-23] Our study established that exposure to even one type of antibiotic within the previous six months was associated with resistance (OR=1.19 95%CI, 1.12-1.26) after adjustment for other factors. Steinke *et al* reported isolates with trimethoprim resistance were strongly independently associated with trimethoprim exposure (OR 4.35, 95%CI 3.03-5.73) and to any other antibiotics (OR 1.32, 95%CI1.10-1.60) in the six month prior to the isolate.[21] Donnan *et al* reported trimethoprim resistance was independently associated with ≥1 prescription for trimethoprim (OR 1.22, 95%CI 1.16-1.28) and to ≥1 prescription for other antibiotics (OR 1.18, 95%CI 1.06-1.32) in the six months prior to the isolate.[22] Dromigny *et al* reported prior exposure to any antibiotics was an independent risk factor for trimethoprim/sulfamethoxazole resistance (OR 2.4 (95%CI1.4-4.1)).[23] Our study demonstrated a relationship between prior antibiotic use and resistance to single antibiotics but, more importantly, to MDR. We have established that use of one antibiotic within six months of the isolate to be independently associated with MDR (OR 1.57; 95%CI, 1.46-1.68).

Evidence for a relationship between cumulative antibiotic exposure and resistance is sparse. Hillier *et al* in a study in 10 UK general practices (GP) reported trimethoprim resistance was significantly associated with the number of trimethoprim courses in the previous 12 months with OR 2.08 (95%CI 1.34-3.22) for one prescription rising to OR 7.53 (95%CI 2.71-20.88) for ≥3 prescriptions.[24] Hay *et al* in a study in 12 UK GP practices reported OR 3.14 (95%CI 0.63-15.6) for resistance to amoxicillin and/or trimethoprim associated with ≥4 courses of antibiotics in 12 months in patients with *E. coli* urine isolates.[25] Our study established increasing cumulative exposure to antibiotics was associated with resistance. Moreover it demonstrates a dose response relationship between cumulative total antibiotic, nitrofurantoin or trimethoprim exposure and MDR which has not been reported previously.

The period of increased risk of resistance following antibiotic exposure is important. A meta-analysis (14,348 participants) by Costelloe *et al* demonstrated a pooled OR of 1.33 (95%CI 1.15-1.53) for associations with resistance in those exposed to trimethoprim, amoxicillin or any antibiotic in the previous 12 months, but only included resistance to single antibiotics.[26] In a more recent study, Duffy *et al* found that associations with trimethoprim use and resistance were not significant beyond 84 days since last exposure in community urinary isolates from children (n=1373).[27] Importantly our study extends this evidence to the impact of antibiotic use on MDR. We found the effect on MDR of any antibiotic exposure was still evident at seven-nine months (OR 1.27, 95%CI 1.12-1.45). For individuals whose most recent exposure to trimethoprim was up to 10-12 months prior to the positive isolate we found the effect on MDR was still significant at 10-12 months post-exposure (OR 1.80, 95%CI 1.66-1.95) and the effect was even greater following exposure to nitrofurantoin (OR 2.31, 95%CI 1.93-2.76).

Previous reports of an association between nitrofurantoin resistance in *E coli* isolates in Finland were at population level rather than individual level.[28] Our study is, as far as we know, the first to establish patient-level associations between nitrofurantoin exposure and resistance and MDR. Here we report that exposure to ≥29 DDDs of nitrofurantoin in the previous six months increased OR of MDR to 8.56 (95%CI 6.56-11.18).

We identified risk factors other than antibiotic exposure to be associated with increased odds of MDR. The adjusted effect of care home residence we report (OR 3.36, 95%CI 2.95-3.83) was similar to that adjusted OR reported by Faine *et al* (4.17, 95% CI 1.13-15.3) for MDR in 360 patients with UTI in an emergency department setting.[29] We found that as number of hospitalisations in the previous 12 months increases so too did the odds of MDR. Our finding is different to a small study (n=828) by Steinke *et al*, in a single region in Scotland, which found that hospitalisation in the previous six months was not independently associated with trimethoprim resistance.[30] Male gender and increasing age have been associated with resistance in other studies and our findings are similar.[21,22,29,31]

Of the risk factors assessed in this study, antibiotic exposure is the most important as it had the strongest association with resistance and is modifiable through antibiotic stewardship interventions. There is evidence that in some uncomplicated UTIs in adult females, symptomatic relief with ibuprofen is non inferior to antibiotics.[32] Our results should support efforts to reduce unnecessary use of any antibiotics to reduce selection pressure for resistance and especially MDR. The recommendation of the European Association of Urology [33] to review and consider discontinuation of antibiotic prophylaxis of UTI is important given the association between cumulative use of antibiotics and MDR demonstrated in our study.

A recent review highlighted the importance of linkage of prescription and outcome data to improve understanding of the risks of and outcomes from AMR in UTI and called for the outputs from such data linkage studies to inform clinical decision making, prescribing practice and guideline development[34]. Our findings demonstrate that the risk of resistance to antibiotics, especially those commonly used for treatment of UTI is influenced by factors such as age, gender, comorbidity, previous hospitalisation, care home residence and antibiotic exposure.

Strengths of our study include that it was conducted at national level using data collected as part of routine clinical practice. As the data source for urine isolates was a national database these data should be representative of all urine isolates collected in the community. The inclusion of MDR as an outcome was a further strength as previous studies have focused on resistance to single antibiotics or a small subgroup of antibiotics, which takes no account of MDR.[21-23] We also examined cumulative and temporal associations between resistance and exposure to all antibiotics, nitrofurantoin and trimethoprim. The sensitivity analysis excluding patients with hospitalisations in the previous 12 months, removes any impact on resistance of antibiotic exposure in hospital, which presently is not captured at individual patient level across all of Scotland, or of recent transmission in hospital.

The work has several limitations that may limit our findings generalizability to all UTIs. Samples collected in the community and submitted for culture and susceptibility to microbiology departments will be biased towards resistance as samples may only be submitted in complicated cases or in cases where patients have failed on initial empirical treatment. This bias while overestimating the true prevalence of resistance in urine isolates should not impact on the association between resistance and other variables. Furthermore, the susceptibility data included in the analysis is dependent on testing carried out in, and national reporting from, individual diagnostic laboratories so we did not have results for all isolates tested against all antibiotics. However, sub-group analysis on those isolates (n = 6386; 16% of total isolates) not tested against all seven categories of antibiotics yielded similar results.

This national level data linkage study has for the first time as far as we know quantified the risk of MDR associated in community urine isolates. We demonstrated a dose-response relationship with MDR increasing with increased cumulative antibiotics exposure. The risk of MDR was highest within one month of antibiotic exposure but an effect for nitrofurantoin and trimethoprim remained for up to 12 months after the last exposure. These data will be used to design and test a clinical decision support tool which could enable clinicians to identify patients, at the point of writing the prescription, who are at high risk of resistance.

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**Transparency declaration**

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**Table 1: Patient and isolate characteristics by resistance classification[a]**

| | Susceptible | Resistant | MDR | Total |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (total %) |
| **Organism Group** | | | | |
| Escherichia coli | 10385 (34.6) | 10966 (36.5) | 8687 (28.9) | 30038 (73.3) |
| *Klebsiella* spp. | 2 (0.1) | 2271 (74.5) | 775 (25.4) | 3048 (7.4) |
| *Enterococci* | 220 (9.2) | 1978 (82.7) | 193 (8.1) | 2391 (5.8) |
| *Proteus* spp. | 70 (4.5) | 1044 (66.8) | 448 (28.7) | 1562 (3.8) |
| Other | 970 (24.6) | 2186 (55.4) | 789 (20.0) | 3945 (9.6) |
| **Gender** | | | | |
| Female | 9704 (29.9) | 14258 (43.9) | 8518 (26.2) | 32480 (79.3) |
| Male | 1943 (22.8) | 4187 (49.2) | 2374 (27.9) | 8504 (20.7) |
| **Age group** | | | | |
| 16-24 | 1112 (39.7) | 1249 (44.6) | 441 (15.7) | 2802 (6.8) |
| 25-34 | 1047 (36.4) | 1342 (46.7) | 487 (16.9) | 2876 (7.0) |
| 35-44 | 1016 (35.2) | 1260 (43.6) | 611 (21.2) | 2887 (7.0) |
| 45-54 | 1334 (32.4) | 1794 (43.6) | 990 (24.0) | 4118 (10) |
| 55-64 | 1648 (30.7) | 2302 (42.9) | 1414 (26.4) | 5364 (13.1) |
| 65-74 | 2272 (27.8) | 3672 (45.0) | 2214 (27.1) | 8158 (19.9) |
| 75-84 | 2174 (23.9) | 4244 (46.6) | 2694 (29.6) | 9112 (22.2) |
| ≥85 | 1044 (18.4) | 2582 (45.6) | 2041 (36.0) | 5667 (13.8) |
| **Charlson score** | | | | |
| 0 | 4110 (29.7) | 6143 (44.4) | 3580 (25.9) | 13833 (33.8) |
| 1-2 | 1880 (21.1) | 4107 (46.1) | 2914 (32.7) | 8901 (21.7) |
| 3-4 | 497 (16.0) | 1453 (46.9) | 1149 (37.1) | 3099 (7.6) |
| ≥5 | 256 (15.1) | 792 (46.8) | 645 (38.1) | 1693 (4.1) |
| Unknown[b] | 4904 (36.4) | 5950 (44.2) | 2604 (19.3) | 13458 (32.8) |
| **Drug classes in previous 12 months[c]** | | | | |
| 0-4 | 4285 (40.2) | 4578 (42.9) | 1801 (16.9) | 10664 (26.0) |
| 5-9 | 3976 (30.8) | 5990 (46.4) | 2951 (22.8) | 12917 (31.5) |
| 10-14 | 2298 (22.6) | 4650 (45.8) | 3204 (31.6) | 10152 (24.8) |
| 15-19 | 838 (16.4) | 2296 (45.0) | 1970 (38.6) | 5104 (12.5) |
| ≥20 | 250 (11.6) | 931 (43.4) | 966 (45.0) | 2147 (5.2) |
| **Hospital stays in previous 12 months** | | | | |
| 0 | 8522 (32.8) | 11627 (44.7) | 5871 (22.6) | 26020 (63.5) |
| 1 | 1892 (24.2) | 3609 (46.1) | 2324 (29.7) | 7825 (19.1) |
| 2 | 673 (19.3) | 1621 (46.6) | 1185 (34.1) | 3479 (8.5) |
| 3 | 266 (16.1) | 718 (43.5) | 668 (40.4) | 1652 (4.0) |
| ≥4 | 294 (14.6) | 870 (43.3) | 844 (42.0) | 2008 (4.9) |
| **Care home residence** | | | | |
| Yes | 350 (10.0) | 1559 (44.4) | 1603 (45.6) | 3512 (8.6) |
| No | 11297 (30.1) | 16886 (45.1) | 9289 (24.8) | 37472 (91.4) |
| **Number of different antibiotics in previous 6 months** | | | | |
| 0 | 5456 (38.0) | 6415 (44.7) | 2493 (17.4) | 14364 (35.0) |
| 1 | 3865 (30.0) | 5818 (45.2) | 3197 (24.8) | 12880 (31.4) |
| 2 | 1652 (20.6) | 3714 (46.3) | 2656 (33.1) | 8022 (19.6) |
| 3 | 490 (13.1) | 1683 (45.0) | 1563 (41.8) | 3736 (9.1) |
| ≥4 | 184 (9.3) | 815 (41.1) | 983 (49.6) | 1982 (4.8) |
| **Total cases** | 11647 (28.4) | 18445 (45.0) | 10892 (26.6) | 40984 |

[a] Isolates were categorised as susceptible if susceptible to all antibiotics tested, resistant if resistant to one of the antibiotics tested; and MDR if resistant to at least one antibiotic in each of three or more categories. [b] An unknown Charlson score suggests the patient had no hospital admissions in the previous 5 years, therefore a Charlson score could not be calculated. [c] Drug classes defined as the number of different British National Formulary paragraphs, for example, ACE-inhibitors (BNF paragraph 2.5.5.1) would be considered a different drug class to angiotensin receptor blockers (BNF paragraph 2.5.5.2).

**Table 2: Multivariable analysis of risk factors – resistant cases and MDR compared to susceptible cases**

| | Resistant isolate compared to susceptible isolate[a] | | | MDR isolate compared to susceptible isolate[a] | | |
|---|---|---|---|---|---|---|
| | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | p-value[b] | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | p-value[b] |
| **Gender** | | | | | | |
| Female | 1 | 1 | <0.001 | 1 | 1 | <0.001 |
| Male | 1.47 (1.38-1.56) | 1.36 (1.27-1.44) | | 1.39 (1.3-1.49) | 1.17 (1.09-1.26) | |
| **Age group** | | | | | | |
| 16-24 | 1 | 1 | 0.031 | 1 | 1 | <0.001 |
| 25-34 | 1.14 (1.02-1.28) | 1.11 (0.99-1.25) | | 1.17 (1.01-1.37) | 1.11 (0.95-1.30) | |
| 35-44 | 1.10 (0.98-1.24) | 1.00 (0.89-1.12) | | 1.52 (1.31-1.76) | 1.29 (1.10-1.50) | |
| 45-54 | 1.20 (1.08-1.33) | 1.00 (0.90-1.12) | | 1.87 (1.63-2.15) | 1.40 (1.21-1.61) | |
| 55-64 | 1.24 (1.12-1.38) | 0.96 (0.86-1.06) | | 2.16 (1.90-2.47) | 1.41 (1.23-1.62) | |
| 65-74 | 1.44 (1.31-1.58) | 1.00 (0.91-1.11) | | 2.46 (2.17-2.78) | 1.37 (1.20-1.57) | |
| 75-84 | 1.74 (1.58-1.91) | 1.09 (0.98-1.21) | | 3.12 (2.76-3.54) | 1.47 (1.28-1.68) | |
| ≥85 | 2.20 (1.98-2.45) | 1.21 (1.07-1.37) | | 4.93 (4.31-5.63) | 1.81 (1.56-2.10) | |
| **Charlson score** | | | | | | |
| 0 | 1 | 1 | | 1 | 1 | |
| 1-2 | 1.46 (1.37-1.56) | 1.13 (1.05-1.22) | 0.001 | 1.78 (1.65-1.91) | 1.11 (1.02-1.21) | 0.011 |
| 3-4 | 1.96 (1.75-2.18) | 1.30 (1.15-1.46) | <0.001 | 2.65 (2.37-2.98) | 1.27 (1.12-1.44) | <0.001 |
| ≥5 | 2.07 (1.79-2.40) | 1.36 (1.16-1.59) | <0.001 | 2.89 (2.49-3.37) | 1.31 (1.11-1.56) | 0.002 |
| Unknown[c] | 0.81 (0.77-0.86) | 0.98 (0.92-1.04) | 0.471 | 0.61 (0.57-0.65) | 0.89 (0.82-0.95) | 0.002 |
| **Drug classes prescribed in previous 12 months[d]** | | | | | | |
| 0-4 | 1 | 1 | <0.001 | 1 | 1 | <0.001 |
| 5-9 | 1.41 (1.33-1.49) | 1.13 (1.06-1.20) | | 1.77 (1.64-1.90) | 1.07 (0.99-1.16) | |
| 10-14 | 1.89 (1.77-2.02) | 1.22 (1.13-1.32) | | 3.32 (3.07-3.58) | 1.35 (1.23-1.48) | |
| 15-19 | 2.56 (2.35-2.80) | 1.42 (1.27-1.57) | | 5.59 (5.07-6.17) | 1.71 (1.51-1.92) | |
| ≥20 | 3.49 (3.01-4.03) | 1.61 (1.37-1.90) | | 9.19 (7.92-10.68) | 2.06 (1.73-2.45) | |
| **Number of hospital stays in previous 12 months** | | | | | | |
| 0 | 1 | 1 | 0.002 | 1 | 1 | <0.001 |
| 1 | 1.40 (1.31-1.49) | 1.09 (1.01-1.17) | | 1.78 (1.66-1.91) | 1.16 (1.07-1.26) | |
| 2 | 1.77 (1.61-1.94) | 1.19 (1.07-1.31) | | 2.56 (2.31-2.83) | 1.36 (1.21-1.52) | |
| 3 | 1.98 (1.71-2.28) | 1.21 (1.04-1.41) | | 3.65 (3.15-4.22) | 1.70 (1.45-2.00) | |
| ≥4 | 2.17 (1.89-2.48) | 1.25 (1.08-1.45) | | 4.17 (3.63-4.78) | 1.82 (1.56-2.13) | |
| **Care home residence** | | | | | | |
| No | 1 | 1 | <0.001 | 1 | 1 | <0.001 |
| Yes | 2.98 (2.65-3.35) | 2.16 (1.90-2.45) | | 5.57 (4.95-6.27) | 3.36 (2.95-3.83) | |
| **Number of different antibiotics prescribed in previous 6 months** | | | | | | |
| 0 | 1 | 1 | <0.001 | 1 | 1 | <0.001 |
| 1 | 1.28 (1.21-1.35) | 1.19 (1.12-1.26) | | 1.81 (1.69-1.94) | 1.57 (1.46-1.68) | |
| 2 | 1.91 (1.79-2.05) | 1.64 (1.53-1.77) | | 3.52 (3.26-3.80) | 2.65 (2.44-2.88) | |
| 3 | 2.92 (2.63-3.25) | 2.34 (2.09-2.62) | | 6.98 (6.24-7.81) | 4.63 (4.11-5.22) | |
| ≥4 | 3.77 (3.20-4.44) | 2.79 (2.36-3.31) | | 11.69 (9.92-13.78) | 6.81 (5.73-8.11) | |

[a] Isolates were categorised as susceptible if susceptible to all antibiotics tested, resistant if resistant to one of the antibiotics tested; and MDR if resistant to at least one antibiotic in each of three or more categories. [b] Linear trend test, evaluated by including variable as an ordered factor in the multinomial logistic regression model (excluding gender, care home and Charlson score as not ordered factors). [c] An unknown Charlson score suggests the patient had no hospital admissions in the previous 5 years, therefore a Charlson score could not be calculated. [d] Drug classes defined as the number of different British National Formulary paragraphs, for example, ACE-inhibitors (BNF paragraph 2.5.5.1) would be considered a different drug class to angiotensin receptor blockers (BNF paragraph 2.5.5.2).

**Table 3: Temporal antibiotic exposure – time since last antibiotic in previous 12 months**

| | Resistant isolate compared to susceptible isolate[a] | | | MDR isolate compared to susceptible isolate[a] | | |
|---|---|---|---|---|---|---|
| | Unadjusted | Adjusted | | Unadjusted | Adjusted | |
| | OR (95% CI) | OR (95% CI) | p-value [b] | OR (95% CI) | OR (95% CI) | p-value [b] |
| **All antibiotics** | | | | | | |
| *No antibiotics* | 1 | 1 | 0.001 | 1 | 1 | <0.001 |
| <=1 month | 1.96 (1.85-2.09) | 1.62 (1.52-1.73) | | 4.21 (3.91-4.53) | 2.89 (2.67-3.13) | |
| 2-3 months | 1.75 (1.63-1.89) | 1.38 (1.28-1.49) | | 3.31 (3.04-3.61) | 2.08 (1.90-2.28) | |
| 4-6 months | 1.35 (1.24-1.46) | 1.12 (1.03-1.22) | | 2.01 (1.82-2.22) | 1.39 (1.25-1.54) | |
| 7-9 months | 1.29 (1.17-1.42) | 1.11 (1.00-1.23) | | 1.72 (1.52-1.94) | 1.27 (1.12-1.45) | |
| 10-12 months | 1.18 (1.06-1.32) | 1.06 (0.94-1.19) | | 1.44 (1.25-1.66) | 1.16 (1.00-1.34) | |
| **Nitrofurantoin** | | | | | | |
| *No antibiotics* | 1 | 1 | | 1 | 1 | |
| <= 1 month | 1.94 (1.77-2.12) | 1.58 (1.43-1.74) | <0.001 | 4.61 (4.16-5.11) | 3.06 (2.74-3.41) | <0.001 |
| 2-3 months | 2.07 (1.86-2.31) | 1.60 (1.43-1.80) | <0.001 | 5.42 (4.82-6.08) | 3.28 (2.90-3.71) | <0.001 |
| 4-6 months | 2.21 (1.96-2.50) | 1.71 (1.50-1.94) | <0.001 | 5.23 (4.59-5.97) | 3.13 (2.73-3.60) | <0.001 |
| 7-9 months | 1.94 (1.68-2.24) | 1.52 (1.31-1.76) | <0.001 | 4.19 (3.59-4.89) | 2.55 (2.17-3.00) | <0.001 |
| 10-12 months | 1.90 (1.62-2.22) | 1.51 (1.29-1.78) | <0.001 | 3.64 (3.07-4.33) | 2.31 (1.93-2.76) | <0.001 |
| Other antibiotic in previous 12 months | 1.51 (1.43-1.59) | 1.28 (1.21-1.36) | <0.001 | 2.36 (2.20-2.53) | 1.74 (1.61-1.88) | <0.001 |
| **Trimethoprim** | | | | | | |
| *No antibiotics* | 1 | 1 | | 1 | 1 | |
| <= 1 month | 1.79 (1.66-1.93) | 1.55 (1.43-1.68) | <0.001 | 3.69 (3.38-4.02) | 2.72 (2.48-2.98) | <0.001 |
| 2-3 months | 1.91 (1.75-2.09) | 1.49 (1.35-1.63) | <0.001 | 4.01 (3.62-4.44) | 2.44 (2.19-2.72) | <0.001 |
| 4-6 months | 1.70 (1.54-1.87) | 1.32 (1.20-1.46) | <0.001 | 3.32 (2.98-3.70) | 2.00 (1.78-2.24) | <0.001 |
| 7-9 months | 1.65 (1.47-1.84) | 1.29 (1.15-1.45) | <0.001 | 2.95 (2.60-3.35) | 1.80 (1.57-2.06) | <0.001 |
| 10-12 months | 1.53 (1.35-1.73) | 1.21 (1.07-1.37) | 0.003 | 2.89 (2.52-3.31) | 1.81 (1.57-2.09) | <0.001 |
| Other antibiotic in previous 12 months | 1.55 (1.46-1.64) | 1.29 (1.21-1.37) | <0.001 | 2.58 (2.39-2.78) | 1.80 (1.66-1.95) | <0.001 |

*Data adjusted for: gender, age group, Charlson score, drug classes in previous 12 months, hospital stays in previous 12 months and care home residence in previous 12 months.*

[a] Isolates were categorised as susceptible if susceptible to all antibiotics tested, resistant if resistant to one of the antibiotics tested; and MDR if resistant to at least one antibiotic in each of three or more categories. [b] Linear trend test, evaluated by including variable as an ordered factor in the multinomial logistic regression model (all antibiotics only).

**Figure 1: Effect of cumulative antibiotic exposure in the 6 months prior to infection – resistant isolates [OR (95% CI)]**

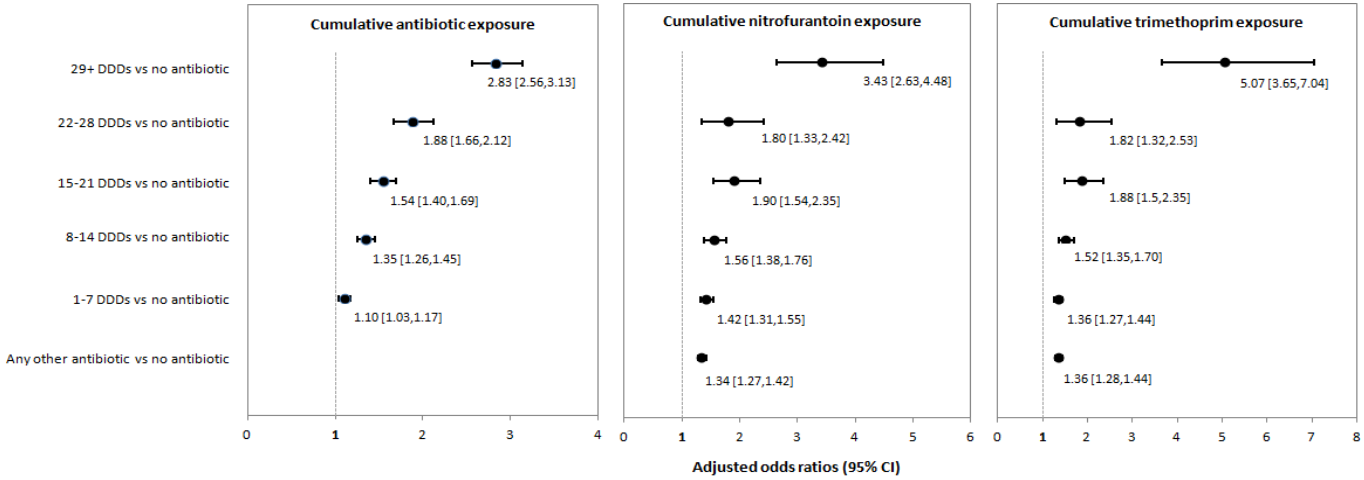
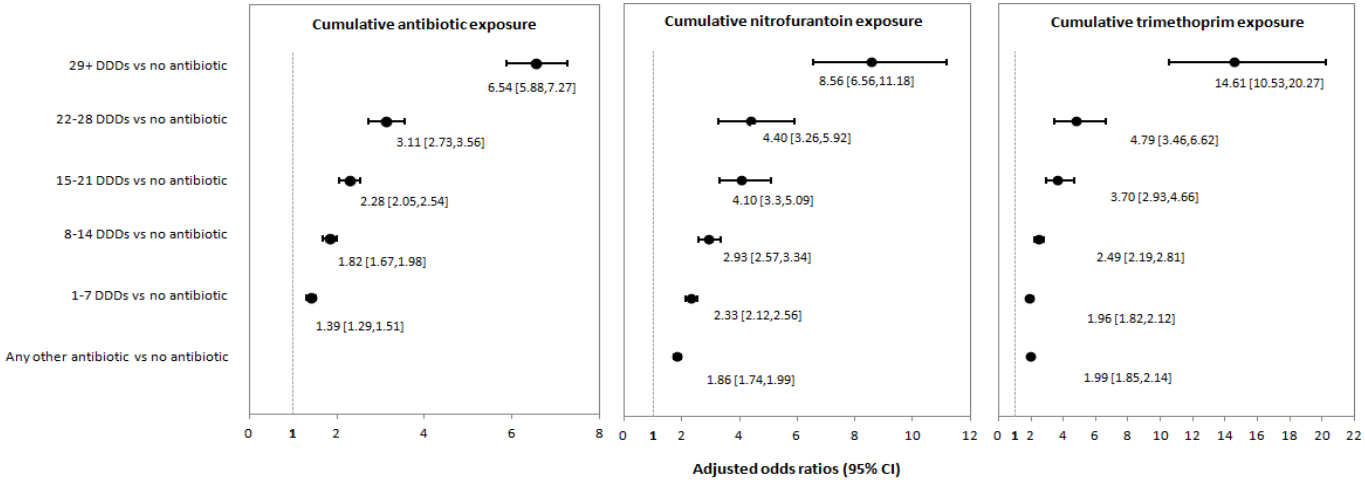



**Figure 2: Effect of cumulative antibiotic exposure in the 6 months prior to infection – MDR isolates [OR (95% CI)]**




*Figures 1 and 2: Data adjusted for: gender, age group, Charlson score, drug classes in previous 12 months, hospital stays in previous 12 months and care home residence.*