



## University of Dundee

### Risk factors for resistance and MDR in community urine isolates

Malcolm, William; Fletcher, Eilidh; Kavanagh, Kimberley; Deshpande, Ashutosh; Wiuff, Camilla; Marwick, Charis; Bennie, Marion

*Published in:*

Journal of Antimicrobial Chemotherapy

*DOI:*

[10.1093/jac/dkx363](https://doi.org/10.1093/jac/dkx363)

*Publication date:*

2017

*Document Version*

Peer reviewed version

[Link to publication in Discovery Research Portal](#)

*Citation for published version (APA):*

Malcolm, W., Fletcher, E., Kavanagh, K., Deshpande, A., Wiuff, C., Marwick, C., & Bennie, M. (2017). Risk factors for resistance and MDR in community urine isolates: population-level analysis using the NHS Scotland Infection Intelligence Platform. *Journal of Antimicrobial Chemotherapy*, 73(1), 223-230. <https://doi.org/10.1093/jac/dkx363>

#### General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

#### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

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

3 William MALCOLM<sup>1\*</sup>, Eilidh FLETCHER<sup>2</sup>, Kimberley KAVANAGH<sup>3</sup>, Ashutosh DESHPANDE<sup>4</sup>,  
4 Camilla WIUFF<sup>1</sup>, Charis MARWICK<sup>5</sup>, Marion Bennie<sup>2,6</sup>

5 <sup>1</sup>Health Protection Scotland, NHS National Services Scotland, Glasgow, UK. <sup>2</sup>Information  
6 Services Division, NHS National Services Scotland, Edinburgh, UK. <sup>3</sup>Department of  
7 Mathematics and Statistics, University of Strathclyde, Glasgow, UK. <sup>4</sup>Microbiology  
8 department, Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde,  
9 Glasgow, UK. <sup>5</sup>Population Health Sciences, University of Dundee, UK. <sup>6</sup>Strathclyde Institute  
10 of Pharmacy and Biomedical Science, University of Strathclyde, Glasgow, UK.

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

12 **\*Corresponding author:** Tel +44 (0)141 300 1174; w.malcolm@nhs.net

13

14

15

16

17

18

19

20

21

22

23

## 24 **Synopsis**

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

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

29 *Methods:* Within the National Health Service Scotland Infection Intelligence Platform,  
30 national surveillance patient-level data on community urine isolates (January 2012-June  
31 2015) were linked to hospital activity and community prescribing data. Associations between  
32 age, gender, comorbidity, care home residence, previous hospitalisations, antibiotic  
33 exposure, and resistant (any antibiotic) or MDR ( $\geq 1$  antibiotic from  $\geq 3$  categories) urinary  
34 isolates were quantified using multivariable logistic regression.

35 *Results:* Of 40,984 isolates, 28% were susceptible, 45% resistant, and 27% MDR. Exposure  
36 to  $\geq 4$  different antibiotics in the prior six months increased MDR risk, OR 6.81 (95%CI 5.73-  
37 8.11). MDR was associated with  $\geq 29$  DDD cumulative exposure, in the prior six months, for  
38 any antibiotic (OR 6.54, 95%CI 5.88-7.27), nitrofurantoin (OR 8.56, 95%CI 6.56-11.18) and  
39 trimethoprim (OR 14.61, 95%CI 10.53-20.27). Associations persisted for 10-12 months for  
40 nitrofurantoin (OR 2.31, 95%CI 1.93-2.76) and trimethoprim (OR 1.81, 95%CI 1.57-2.09).  
41 Increasing age, comorbidity, previous hospitalisation and care home residence were  
42 independently associated with MDR. For resistant isolates the factors were the same but  
43 with weaker associations.

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

## 48 **Introduction**

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

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

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

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

## 70 **Methods**

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

74 linked across multiple datasets.<sup>11</sup> Within the IIP, CHI is used to link specific data then patient  
75 identifiers are removed for anonymised analysis.

#### 76 *Data Sources*

77 The Surveillance of Antimicrobial Resistance in Urinary Isolates in Scotland (SARUIS)  
78 dataset records culture and susceptibility data for a large, representative subset of all  
79 positive urine isolates in Scotland.<sup>12</sup> All NHS Boards are required to submit data on the first  
80 400 consecutive positive urine samples per calendar quarter. Demographic data were  
81 obtained from SARIUS.

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

#### 85 *Cohort identification and variable classification*

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

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

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

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

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

### 121 *Statistical Analysis*

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

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

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

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

#### 140 *Ethical approval*

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

#### 144 **Results**

145 Within the study period 40,984 (62%) of 66,194 urine isolates in SARUIS met the inclusion  
146 criteria. Of these, 11,674 (28%) were susceptible, 18,445 (45%) were resistant, and 10,892  
147 (27%) MDR, and *E. coli* accounted for 73% of all isolates (Table 1). More than half of all  
148 isolates were from people  $\geq 65$  years old, 79% were from female patients and 9% were from  
149 care home residents (Table 1). One third of patients had a Charlson score of  $\geq 1$  but almost  
150 three-quarters had been prescribed drugs from  $\geq 5$  classes in the previous 12 months, and  
151 36% had a hospital stay in the previous 12 months (Table 1). Just over a third of patients

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

156 In univariate analyses, male gender, increasing age, comorbidity, hospitalisation, care home  
157 residence, number of different drug classes and different antibiotics in the previous six  
158 months were all associated with increased risk of having resistant and MDR isolates (Table  
159 2). Associations remained in adjusted analysis, with higher MDR risk associated with being  
160 male (OR 1.17, 95%CI 1.09-1.26), older (OR for  $\geq 85$  versus  $< 25$  years old: 1.81, 95%CI  
161 1.56-2.10), higher Charlson scores (Charlson  $\geq 5$  versus 0 OR 1.31 (95%CI 1.11-1.56)),  
162 numbers of previously prescribed drug classes (OR for  $\geq 20$  versus 0-4: 2.06, 95%CI 1.73-  
163 2.45), numbers of previous admissions (OR for  $\geq 4$  versus 0: 1.82, 95%CI 1.56-2.13), and  
164 care home residence (OR 3.36, 95%CI 2.95-3.83) (Table 2). Having prescriptions for  $\geq 4$   
165 different antibiotics in the previous six months had the highest association with MDR, of any  
166 variable category, in adjusted analysis (OR 6.81, 95%CI 5.73-8.11) (Table 2). Resistance to  
167 one antibiotic had similar associations as MDR but with weaker associations for most  
168 covariates, with care home residence (OR 2.16, 95%CI 1.90-2.45) and an increasing  
169 number of different antibiotics prescribed in the previous six months ( $\geq 4$  versus 0 OR 2.79,  
170 95%CI 2.36-3.31) having the strongest associations with resistance.

171 The sensitivity analysis excluding patients with hospitalisations in the previous 12 months  
172 comprised 26,020 patients (64% of whole cohort). Age was no longer significantly  
173 associated with resistant isolates ( $p=0.961$ ) but remained strongly associated with MDR  
174 ( $p<0.001$ ), and the association between male gender and MDR was not significant ( $p=0.08$ ).  
175 Other associations, particularly higher numbers of different antibiotics, were similar to the  
176 main cohort analysis (Table S1). The sub-group analysis including only isolates not tested  
177 against at least one drug from all seven categories of antibiotics comprised of 6,386 patients  
178 (15.5% of cohort). Most associations with resistance and MDR were similar to the main



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

181 Cumulative exposure in the prior six months had dose-response effects on resistance and  
182 MDR, for total antibiotic, nitrofurantoin, and trimethoprim exposures (Figures 1 & 2). For  
183 MDR,  $\geq 29$  DDD *versus* no antibiotics in the previous six months, had an OR 6.54 (95%CI  
184 5.88-7.27) for total antibiotic exposure, 8.56 (95%CI 6.56-11.18) for nitrofurantoin, and 14.61  
185 (95%CI 10.53-20.27) for trimethoprim (Figure 2).

186 There were temporal associations between antibiotic exposure and resistance, particularly  
187 MDR (Table 3). Exposure to any antibiotic in the previous one month had an adjusted odds  
188 of MDR of 2.89 (95%CI 2.67-3.13) compared to no antibiotics, reducing to an odds of 1.16  
189 (95%CI 1.00-1.34) if the last exposure was 10-12 months previously (Table 3). Exposure to  
190 trimethoprim and to nitrofurantoin, compared to no antibiotics, in the previous one month had  
191 similar associations with MDR as for any antibiotic exposure, but effects persisted for longer  
192 and were still highly significant for exposure 10-12 months previously (nitrofurantoin OR  
193 2.31, 95%CI 1.93-2.76), and trimethoprim OR 1.81 (95%CI 1.57-2.09) (Table 3).

## 194 **Discussion**

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

204 Previous studies of resistance risk factors in community urine isolates have focussed on  
205 exposure to a single or 'any' undefined antibiotic and associations of resistance to one or  
206 two antibiotics, without examining MDR. Such studies were small scale (n=398-8833), in  
207 single regions rather than at national level and were over 10 years old.<sup>21-23</sup> Our study  
208 established that exposure to even one type of antibiotic within the previous six months was  
209 associated with resistance (OR=1.19 95%CI, 1.12-1.26) after adjustment for other factors.  
210 Steinke *et al* reported isolates with trimethoprim resistance were strongly independently  
211 associated with trimethoprim exposure (OR 4.35, 95%CI 3.03-5.73) and to any other  
212 antibiotics (OR 1.32, 95%CI 1.10-1.60) in the six month prior to the isolate.<sup>21</sup> Donnan *et al*  
213 reported trimethoprim resistance was independently associated with  $\geq 1$  prescription for  
214 trimethoprim (OR 1.22, 95%CI 1.16-1.28) and to  $\geq 1$  prescription for other antibiotics (OR  
215 1.18, 95%CI 1.06-1.32) in the six months prior to the isolate.<sup>22</sup> Dromigny *et al* reported prior  
216 exposure to any antibiotics was an independent risk factor for trimethoprim/sulfamethoxazole  
217 resistance (OR 2.4 (95%CI 1.4-4.1)).<sup>23</sup> Our study demonstrated a relationship between prior  
218 antibiotic use and resistance to single antibiotics but, more importantly, to MDR. We have  
219 established that use of one antibiotic within six months of the isolate to be independently  
220 associated with MDR (OR 1.57; 95%CI, 1.46-1.68).

221 Evidence for a relationship between cumulative antibiotic exposure and resistance is sparse.  
222 Hillier *et al* in a study in 10 UK general practices (GP) reported trimethoprim resistance was  
223 significantly associated with the number of trimethoprim courses in the previous 12 months  
224 with OR 2.08 (95%CI 1.34-3.22) for one prescription rising to OR 7.53 (95%CI 2.71-20.88)  
225 for  $\geq 3$  prescriptions.<sup>24</sup> Hay *et al* in a study in 12 UK GP practices reported OR 3.14 (95%CI  
226 0.63-15.6) for resistance to amoxicillin and/or trimethoprim associated with  $\geq 4$  courses of  
227 antibiotics in 12 months in patients with *E. coli* urine isolates.<sup>25</sup> Our study established  
228 increasing cumulative exposure to antibiotics was associated with resistance. Moreover it  
229 demonstrates a dose response relationship between cumulative total antibiotic, nitrofurantoin  
230 or trimethoprim exposure and MDR which has not been reported previously.

231 The period of increased risk of resistance following antibiotic exposure is important. A meta-  
232 analysis (14,348 participants) by Costelloe *et al* demonstrated a pooled OR of 1.33 (95%CI  
233 1.15-1.53) for associations with resistance in those exposed to trimethoprim, amoxicillin or  
234 any antibiotic in the previous 12 months, but only included resistance to single antibiotics.<sup>26</sup>  
235 In a more recent study, Duffy *et al* found that associations with trimethoprim use and  
236 resistance were not significant beyond 84 days since last exposure in community urinary  
237 isolates from children (n=1373).<sup>27</sup> Importantly our study extends this evidence to the impact  
238 of antibiotic use on MDR. We found the effect on MDR of any antibiotic exposure was still  
239 evident at seven-nine months (OR 1.27, 95%CI 1.12-1.45). For individuals whose most  
240 recent exposure to trimethoprim was up to 10-12 months prior to the positive isolate we  
241 found the effect on MDR was still significant at 10-12 months post-exposure (OR 1.80,  
242 95%CI 1.66-1.95) and the effect was even greater following exposure to nitrofurantoin (OR  
243 2.31, 95%CI 1.93-2.76).

244 Previous reports of an association between nitrofurantoin resistance in *E coli* isolates in  
245 Finland were at population level rather than individual level.<sup>28</sup> Our study is, as far as we  
246 know, the first to establish patient-level associations between nitrofurantoin exposure and  
247 resistance and MDR. Here we report that exposure to  $\geq 29$  DDDs of nitrofurantoin in the  
248 previous six months increased OR of MDR to 8.56 (95%CI 6.56-11.18).

249 We identified risk factors other than antibiotic exposure to be associated with increased odds  
250 of MDR. The adjusted effect of care home residence we report (OR 3.36, 95%CI 2.95-3.83)  
251 was similar to that adjusted OR reported by Faine *et al* (4.17, 95% CI 1.13-15.3) for MDR in  
252 360 patients with UTI in an emergency department setting.<sup>29</sup> We found that as number of  
253 hospitalisations in the previous 12 months increases so too did the odds of MDR. Our finding  
254 is different to a small study (n=828) by Steinke *et al*, in a single region in Scotland, which  
255 found that hospitalisation in the previous six months was not independently associated with  
256 trimethoprim resistance.<sup>30</sup> Male gender and increasing age have been associated with  
257 resistance in other studies and our findings are similar.<sup>21,22,29,31</sup>

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

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

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

284 The work has several limitations that may limit our findings generalizability to all UTIs.  
285 Samples collected in the community and submitted for culture and susceptibility to  
286 microbiology departments will be biased towards resistance as samples may only be  
287 submitted in complicated cases or in cases where patients have failed on initial empirical  
288 treatment. This bias while overestimating the true prevalence of resistance in urine isolates  
289 should not impact on the association between resistance and other variables. Furthermore,  
290 the susceptibility data included in the analysis is dependent on testing carried out in, and  
291 national reporting from, individual diagnostic laboratories so we did not have results for all  
292 isolates tested against all antibiotics. However, sub-group analysis on those isolates (n =  
293 6386; 16% of total isolates) not tested against all seven categories of antibiotics yielded  
294 similar results.

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

### 302 **Acknowledgements**

303 We acknowledge Jean Sneddon, IIP programme manager

### 304 **Funding**

305 The development of the NHS Scotland Infection Intelligence Platform was funded by the  
306 Scottish Government, Scottish Antimicrobial Resistance and Healthcare Associated Infection  
307 (SARHAI) Commissioning Group. The funder had no role in the decision to submit the article  
308 for publication.

### 309 **Transparency declaration**

310 None of the authors have any conflict of interest in relation to this work.

311 **References**

- 312 1. World Health Organisation. *Global Action Plan on Antimicrobial Resistance*.  
313 [http://www.who.int/iris/bitstream/10665/193736/1/9789241509763\\_eng.pdf?ua=1](http://www.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1).
- 314 2. European Centre for Disease Prevention and Control. *Antimicrobial resistance*  
315 *surveillance in Europe 2015*.  
316 [http://ecdc.europa.eu/en/publications/\\_layouts/forms/Publication\\_DispForm.aspx?List=](http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1637)  
317 [4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1637](http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1637).
- 318 3. Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the*  
319 *United States, 2013*.  
320 <https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>.
- 321 4. OECD. *Antimicrobial Resistance in G7 Countries and Beyond: Economic Issues,*  
322 *Policies and Options for Action*.  
323 [http://www.oecd.org/els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-](http://www.oecd.org/els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-Beyond.pdf)  
324 [Beyond.pdf](http://www.oecd.org/els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-Beyond.pdf).
- 325 5. The Review on Antimicrobial Resistance. *Antimicrobial Resistance: Tackling a crisis for*  
326 *the health and wealth of nations. 2014*.  
327 [https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-](https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf)  
328 [%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nat](https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf)  
329 [ions\\_1.pdf](https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf)
- 330 6. Health Protection Scotland, Information Services Division. *Report on Antimicrobial Use*  
331 *and Resistance in Humans in 2015*.  
332 [https://www.isdscotland.org/Health-Topics/Prescribing-and-](https://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Publications/2016-08-30/2016-08-30-SAPG-2015-Report.pdf?37868899107)  
333 [Medicines/Publications/2016-08-30/2016-08-30-SAPG-2015-Report.pdf?37868899107](https://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Publications/2016-08-30/2016-08-30-SAPG-2015-Report.pdf?37868899107).
- 334 7. UK Five Year Antimicrobial Resistance Strategy 2013-2018. *Department of Health and*  
335 *Department for Environment, Food and Rural Affairs*.  
336 [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/244058/2](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf)  
337 [0130902\\_UK\\_5\\_year\\_AMR\\_strategy.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf).

- 338 8. Bennie M, Malcolm W, Marwick C *et al.* Building a national Infection Intelligence  
339 Platform to improve antimicrobial stewardship and drive better patient outcomes – the  
340 Scottish Experience. *J Antimicrob Chemother* **10.1093/jac/dkx229**
- 341 9. Morgan MG, McKenzie H. Controversies in the laboratory diagnosis of community-  
342 acquired urinary tract infection. *Eur J Clin Microbiol Infect Dis* 1993; **12**: 491-504.
- 343 10. Scottish Intercollegiate Guidelines Network. *SIGN 88 - Management of suspected*  
344 *bacterial urinary tract infections in adults.*  
345 <http://www.sign.ac.uk/assets/sign88.pdf>.
- 346 11. Information Services Division, NHS National Services Scotland. *ISD Scotland data*  
347 *dictionary.*  
348 [http://www.ndc.scot.nhs.uk/Dictionary-A-](http://www.ndc.scot.nhs.uk/Dictionary-A-Z/Definitions/index.asp?ID=128&Title=CHI%20Number)  
349 [Z/Definitions/index.asp?ID=128&Title=CHI%20Number](http://www.ndc.scot.nhs.uk/Dictionary-A-Z/Definitions/index.asp?ID=128&Title=CHI%20Number).
- 350 12. Health Protection Scotland. *Protocol for Surveillance of Antimicrobial Resistance in*  
351 *Urinary Isolates in Scotland.*  
352 [http://www.documents.hps.scot.nhs.uk/hai/amr/protocol-for-surveillance-of-amr-in-](http://www.documents.hps.scot.nhs.uk/hai/amr/protocol-for-surveillance-of-amr-in-urinary-isolates-in-scotland-v1.0.pdf)  
353 [urinary-isolates-in-scotland-v1.0.pdf](http://www.documents.hps.scot.nhs.uk/hai/amr/protocol-for-surveillance-of-amr-in-urinary-isolates-in-scotland-v1.0.pdf).
- 354 13. Information Services Division, NHS National Services Scotland. *National Data*  
355 *Catalogue.*  
356 <http://www.ndc.scot.nhs.uk/>.
- 357 14. European Society of Clinical Microbiology and Infectious Diseases. *European*  
358 *Committee on Antimicrobial Susceptibility Testing.*  
359 <http://www.eucast.org/>
- 360 15. Clinical and Laboratory Standards Institute.  
361 <https://clsi.org/standards/products/microbiology/>

362



- 363 16. Charlson, M.E, Pompei, P, Ales *et al.* A new method of classifying prognostic  
364 comorbidity in longitudinal studies: development and validation. *Journal of Chronic*  
365 *Diseases* 1987; **40**: 373-383.
- 366 17. Quan, H, Sundararajan, V, Halfon, P *et al.* Coding Algorithms for Defining  
367 Comorbidities in ICD-9-CM and ICD-10 Administrative Data. *Medical Care* 2005; **43**:  
368 1130-1139.
- 369 18. World Health Organisation. *ICD-10 Classifications of Mental and Behavioural Disorder:*  
370 *Clinical Descriptions and Diagnostic Guidelines.*  
371 <http://apps.who.int/classifications/icd10/browse/2016/en>.
- 372 19. World Health Organisation. *ATC/DDD methodology.*  
373 [https://www.whocc.no/atc\\_ddd\\_methodology/purpose\\_of\\_the\\_atc\\_ddd\\_system/](https://www.whocc.no/atc_ddd_methodology/purpose_of_the_atc_ddd_system/).
- 374 20. BMJ Group and Pharmaceutical press. *BNF Legacy March 2017.*  
375 <https://www.medicinescomplete.com/mc/bnflegacy/64/>.
- 376 21. Steinke DT, Seaton RA, Phillips G *et al.* Prior trimethoprim use and trimethoprim-  
377 resistant urinary tract infection: a nested case-control study with multivariate analysis  
378 for other risk factors. *J Antimicrob Chemother.* 2001; **47**: 781-7.
- 379 22. Donnan P.T. Wei, L. Steinke *et al.* Presence of Bacteriuria Caused by Trimethoprim  
380 Resistant Bacteria in Patients Prescribed Antibiotics: Multilevel Model With Practice  
381 and Individual Patient Data. *BMJ* 2004; **328**: 1297-1300
- 382 23. Dromigny JA, Nabeth P, Juergens-Behr A *et al.* Risk factors for antibiotic-resistant  
383 *Escherichia coli* isolated from community-acquired urinary tract infections in Dakar,  
384 Senegal. *J Antimicrob Chemother* 2005; **56**: 236-239
- 385 24. Hillier S, Roberts Z, Dunstan F *et al.* Prior antibiotics and risk of antibiotic-resistant  
386 community-acquired urinary tract infection: a case-control study. *J Antimicrob*  
387 *Chemother* 2007; **60**: 92-9
- 388 25. Hay AD, Thomas M, Montgomery A *et al.* The relationship between primary care  
389 antibiotic prescribing and bacterial resistance in adults in the community: a controlled

- 390 observational study using individual patient data. *J Antimicrob Chemother* 2005;  
391 **56**:146-53.
- 392 26. Costelloe C, Metcalfe C, Lovering A *et al.* Effect of antibiotic prescribing in primary  
393 care on antimicrobial resistance in individual patients: systematic review and meta-  
394 analysis. *BMJ* 2010; 340:c2096
- 395 27. Duffy MA, Hernandez-Santiago V, Orange G *et al.* Trimethoprim prescription and  
396 subsequent resistance in childhood urinary infection: multilevel modelling analysis. *Br J*  
397 *Gen Pract* 2013; **63**:e238-43
- 398 28. Bergman M, Nyberg ST, Huovinen P *et al.* Association between antimicrobial  
399 consumption and resistance in *Escherichia coli*. *Antimicrob Agents Chemother* 2009;  
400 **53**: 912-7
- 401 29. Faine BA, Harland KK, Porter B *et al.* A clinical decision rule identifies risk factors associated  
402 with antimicrobial-resistant urinary pathogens in the emergency department: a retrospective  
403 validation study. *Ann Pharmacother* 2015; **49**: 649-55.
- 404 30. Steinke DT, Seaton RA *et al.* Factors associated with trimethoprim-resistant bacteria isolated  
405 from urine samples. *J Antimicrob Chemother* 1999; **43**: 841-843.
- 406 31. Sotto A, De Boever CM, Fabbro-Peray P *et al.* Risk Factors for Antibiotic-Resistant  
407 *Escherichia coli* Isolated from Hospitalized Patients with Urinary Tract Infections: a  
408 Prospective Study. *J Clin Microbiol* 2001; **39**: 438–444.
- 409 32. Bleidorn J, Gogyor I, Kochem MM *et al.* Symptomatic treatment (ibuprofen) or antibiotics  
410 (ciprofloxacin) for uncomplicated urinary tract infection? - Results of a randomized controlled  
411 pilot trial. *BMC Medicine* 2010; **8**:30
- 412 33. European Association of Urology. *Guidelines on urological infections*.  
413 [http://uroweb.org/wp-content/uploads/19-Urological-infections\\_LR2.pdf](http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf).
- 414 34. Chin TL, McNulty C, Beck C *et al.* Antimicrobial resistance surveillance on urinary tract  
415 infections in primary care. *J Antimicrob Chemother* 2016; **10**: 2723-2728

**Table 1: Patient and isolate characteristics by resistance classification<sup>a</sup>**

	Susceptible n (%)	Resistant n (%)	MDR n (%)	Total n (total %)
<b>Organism Group</b>				
Escherichia coli	10385 (34.6)	10966 (36.5)	8687 (28.9)	30038 (73.3)
<i>Klebsiella</i> spp.	2 (0.1)	2271 (74.5)	775 (25.4)	3048 (7.4)
<i>Enterococci</i>	220 (9.2)	1978 (82.7)	193 (8.1)	2391 (5.8)
<i>Proteus</i> 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)
<b>Gender</b>				
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)
<b>Age group</b>				
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)
<b>Charlson score</b>				
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 <sup>b</sup>	4904 (36.4)	5950 (44.2)	2604 (19.3)	13458 (32.8)
<b>Drug classes in previous 12 months<sup>c</sup></b>				
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)
<b>Hospital stays in previous 12 months</b>				
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)
<b>Care home residence</b>				
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)
<b>Number of different antibiotics in previous 6 months</b>				
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)
<b>Total cases</b>	<b>11647 (28.4)</b>	<b>18445 (45.0)</b>	<b>10892 (26.6)</b>	<b>40984</b>

<sup>a</sup> 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. <sup>b</sup> An unknown Charlson score suggests the patient had no hospital admissions in the previous 5 years, therefore a Charlson score could not be calculated. <sup>c</sup> 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 <sup>a</sup>			MDR isolate compared to susceptible isolate <sup>a</sup>		
	Unadjusted	Adjusted	p-value <sup>b</sup>	Unadjusted	Adjusted	p-value <sup>b</sup>
	OR (95% CI)	OR (95% CI)		OR (95% CI)	OR (95% CI)	
<b>Gender</b>						
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)	
<b>Age group</b>						
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)	
<b>Charlson score</b>						
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 <sup>c</sup>	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
<b>Drug classes prescribed in previous 12 months<sup>d</sup></b>						
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)	
<b>Number of hospital stays in previous 12 months</b>						
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)	
<b>Care home residence</b>						
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)	
<b>Number of different antibiotics prescribed in previous 6 months</b>						
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)	

<sup>a</sup> 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. <sup>b</sup> 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). <sup>c</sup> An unknown Charlson score suggests the patient had no hospital admissions in the previous 5 years, therefore a Charlson score could not be calculated. <sup>d</sup> 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).

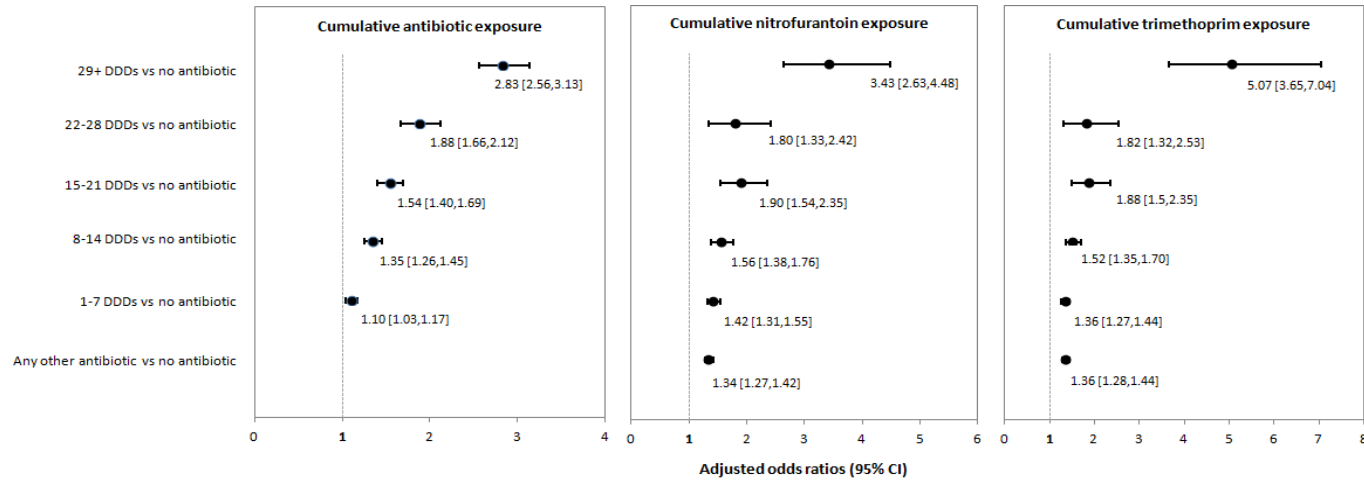
**Table 3: Temporal antibiotic exposure – time since last antibiotic in previous 12 months**

	Resistant isolate compared to susceptible isolate <sup>a</sup>			MDR isolate compared to susceptible isolate <sup>a</sup>		
	Unadjusted	Adjusted		Unadjusted	Adjusted	
	OR (95% CI)	OR (95% CI)	p-value <sup>b</sup>	OR (95% CI)	OR (95% CI)	p-value <sup>b</sup>
<b>All antibiotics</b>						
<i>No antibiotics</i>	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)	
<b>Nitrofurantoin</b>						
<i>No antibiotics</i>	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
<b>Trimethoprim</b>						
<i>No antibiotics</i>	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

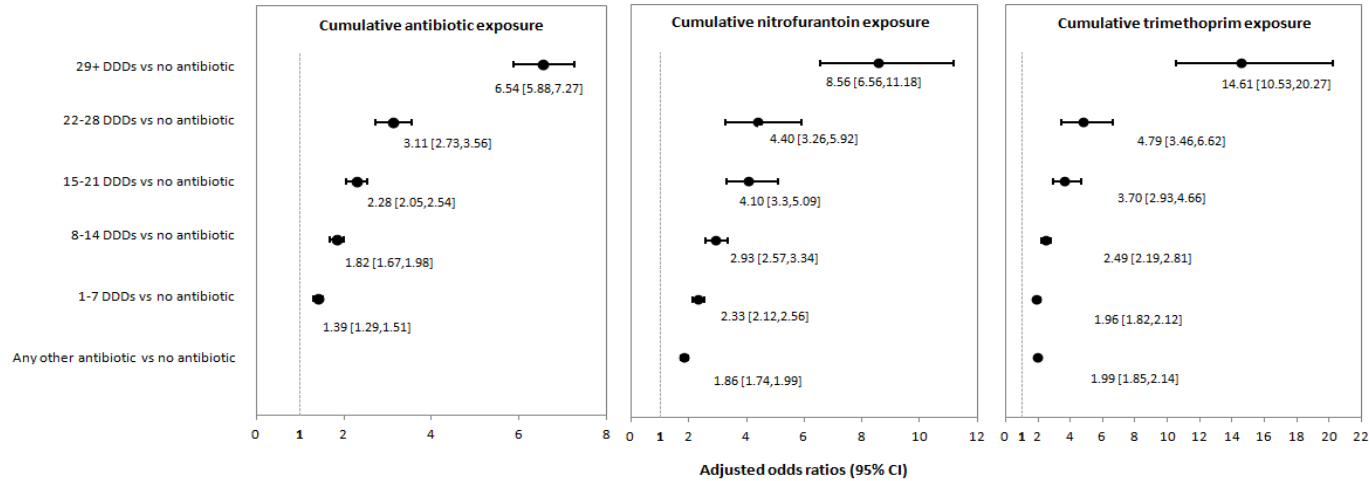
*Data adjusted for: gender, age group, Charlson score, drug classes in previous 12 months, hospital stays in previous 12 months and care home residence in previous 12 months.*

<sup>a</sup> 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. <sup>b</sup> 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.