

1 **Cumulative and temporal associations between antimicrobial prescribing and community-**
2 **associated *Clostridium difficile* infection: population-based case control study using administrative**
3 **data**

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14 **Running title: Association between antimicrobials & CDI**

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20 **Abstract**

21 **Background.** Community-associated (CA) *Clostridium difficile* infection (CDI) is a major public health
22 problem. This study estimates the magnitude of the association between temporal and cumulative
23 prescription of antimicrobials in primary care and CA-CDI. CA-CDI is defined as cases without prior
24 hospitalisation in the previous 12 weeks who were either tested outside of hospital or tested within 2
25 days of admission to hospital.

26 **Methods.** Three National patient level datasets –covering CDI cases, community prescriptions and
27 hospitalisations were linked by the NHS Scotland unique patient identifier, the community health
28 index, CHI. All validated cases of CDI from August 2010 to July 2013 were extracted and up to six
29 population-based controls were matched to each case from the CHI register for Scotland. Statistical
30 analysis used conditional logistic regression.

31 **Results.** 1446 unique cases of CA-CDI were linked with 7964 age, sex and location matched controls.
32 Cumulative exposure to any antimicrobial in the previous 6 months has a monotonic dose-response
33 association with CA-CDI. Individuals with excess of 28 defined daily doses (DDD) to any antimicrobial
34 (19.9% of cases) had an odds ratio (OR)=4.4 (95% CI:3.4-5.6) compared to those unexposed.
35 Individuals exposed to 29+ DDD of high risk antimicrobials (cephalosporins, clindamycin co-amoxiclav,
36 or fluoroquinolones) had an OR=17.9 (95% CI:7.6-42.2). Elevated CA-CDI risk following high risk
37 antimicrobial exposure was greatest in the first month (OR=12.5 (8.9-17.4)) but was still present 4-6
38 months later (OR=2.6 (1.7-3.9)). Cases exposed to 29+DDD had prescription patterns more consistent
39 with repeated therapeutic courses, using different antimicrobials, than long term prophylactic use.

40 **Conclusions.** This analysis demonstrated temporal and dose-response associations between CA-CDI
41 risk and antimicrobials with an impact of exposure to high risk antimicrobials remaining 4-6 months
42 later.

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45 **Introduction**

46 *Clostridium difficile* infection (CDI) is a major public health problem and a key focus for antimicrobial
47 stewardship programs. Quantification of the adverse effects of antimicrobial use at population level
48 is essential to support appropriate antimicrobial stewardship policy. Community-associated CDI (CA-
49 CDI) is an increasing public health threat¹ studies indicating 37-79% cases having had antimicrobial
50 exposure in the preceding 90 days.²⁻⁷ A meta-analysis⁸ derived pooled odds ratios from eight studies
51 for the risk of CA-CDI associated with specific antimicrobial groups, but did not consider cumulative or
52 temporal exposure effects. Cumulative and temporal antimicrobial exposure have been examined in
53 healthcare-associated CDI (HA-CDI)⁹⁻¹¹ but for CA-CDI data are limited to considering cumulative effect
54 in an elderly population¹² and considering temporal effects for overall antimicrobial exposure only,¹³
55 with both studies limited to low CA-CDI numbers.

56 The increasing availability of routinely captured electronic administrative health data, readily linkable
57 through use of unique patient identifiers, affords the opportunity to examine complex patterns of
58 drug use over time at population level. This supports the derivation of more accurate estimates of
59 risk informing clinicians and policy-makers to improve patient treatment and minimise harm at
60 individual and population level. The aim of our study was to use nationally collected routine
61 healthcare data to estimate associations between CA-CDI and prior prescription of antimicrobials in
62 primary care, considering exposure to (i) any antimicrobial and (ii) specific broad-spectrum
63 antimicrobials. We examined the effects of any exposure and cumulative exposure, and the temporal
64 relationship between timing of antimicrobial exposure and risk of CA-CDI.

65

66 **Materials and methods**

67 **Data sources**

68 Three National Health Service (NHS) patient level datasets - Electronic Communication of Surveillance
69 in Scotland (ECOSS); Prescribing Information System (PIS) and General / Acute and Inpatient Day Case
70 dataset (SMR01) - all indexed by the NHS Scotland unique patient identifier CHI (Community Health
71 Index) are linked as part of the Infection Intelligence Platform (IIP),¹⁴ allowing generation of the study
72 dataset. The CHI register for Scotland was used for control assignment. The NHS in Scotland has
73 universal coverage so all data, including prescribing,¹⁵ are representative of the whole population.

74 ECOSS records all positive *Clostridium difficile* tests from NHS laboratories in Scotland through
75 mandatory reporting, with standardisation of sampling, testing and reporting across all clinical
76 settings. All diarrhoeal samples are tested in a 2-step algorithm; firstly, identifying the presence of *C.*
77 *difficile* using glutamate dehydrogenase screening and secondly, identifying the presence of toxin using
78 ELISA/PCR. Health Protection Scotland (HPS) then validates with the NHS health boards which positive
79 tests represent individual, clinically symptomatic CDI episodes (toxin positive and experienced
80 diarrhoea not attributable to any other cause). PIS records all prescriptions dispensed and reimbursed
81 within primary care in Scotland. SMR01 contains episode level data on all hospital inpatient and day
82 case discharges from hospitals in Scotland).¹⁶

83 **Data linkage and control assignment**

84 All validated CDI cases with test date from August 2010 to July 2013 were extracted from ECOSS and
85 linked to hospitalisation histories from SMR01. Community-associated cases were defined as those
86 without prior hospitalisation in the previous 12 weeks and were either tested outside of hospital
87 (community-onset (CO)) or tested within 48 hours (2 days) of admission to hospital (healthcare-onset
88 (HO))¹⁷.

89 CA-CDI cases were assigned up to six community-based controls from the CHI register for Scotland,
90 matched on age (within 5 years), gender and location (intermediate zone derived from the patient's
91 postcode). For the healthcare-onset community-associated cases (CA-HO) hospital-based controls
92 were additionally assigned - up to 6 controls were selected from hospitalised individuals without CDI
93 admitted to the same hospital within 7 days of the CDI case's admission date and who were still in
94 hospital on the case's CDI test date.

95 For all cases and controls, prescription records from August 2009 from PIS were linked allowing
96 assignment of antimicrobial, proton pump inhibitor (PPI) and H2 antagonist exposure in the six months

97 prior to CDI test date, and construction of comorbidity measures. Antimicrobial exposure, for this
98 study defined as any systemic antibacterial, was defined as any exposure (present/absent), temporal
99 exposure (how long prior to the test date the antimicrobial was prescribed) and cumulative exposure
100 (in WHO ATC defined daily doses (DDD)),¹⁸ cumulating potentially multiple prescriptions in the
101 previous 6 months.

102 The prescribing measures of comorbidity were counts of the total number of prescriptions and the
103 total number of different prescribed drugs (based on approved name) in the previous year. In addition,
104 five years of hospitalisation records were used to construct a Charlson Index of comorbidity for all
105 cases and controls based on ICD10 diagnosis discharge codes.¹⁹ Individuals with no hospitalisations in
106 the previous 5 years were assigned an “unknown” Charlson index to differentiate from individuals
107 with a hospitalisation and no recorded comorbidities, who were assigned a score of 0. Scottish Index
108 of Multiple Deprivation (SIMD) quintiles – a measure of socioeconomic status which incorporates
109 different aspects of deprivation into a single index, care home residence (yes/no) and NHS health
110 board from the CHI Register was assigned to all records.

111 All linkage was via CHI and case/control assignment was performed by the electronic Data Research
112 and Innovation Service at NSS Information Services Division. No patient identifiers were available to
113 the study team and all data were accessed via the National safe haven.

114 **Ethics**

115 Ethical permission for this study was not required as it used only non-identifiable routine data.
116 Approval for the study was granted by NHS National Services Scotland Privacy Advisory Committee,
117 Study number XRB13122.

118 **Statistical analysis**

119 Associations between antimicrobial exposure and CDI were assessed using conditional logistic
120 regression. The distribution of potential confounding variables – previous hospital admissions,
121 prescription totals, comorbidity score, care home residency status, PPI/H2 exposure and SIMD – was
122 investigated in the cases and controls and adjusted for in the analysis. Four antimicrobial exposure
123 groupings were examined: any antimicrobials, a predefined broad-spectrum, high risk “4C” group [12]
124 - clindamycin, cephalosporins, fluoroquinolones (ciprofloxacin (which accounts for >90% of all
125 fluoroquinolone prescriptions in Scotland), levofloxacin, moxifloxacin, norfloxacin, and ofloxacin) and
126 co-amoxiclav, all “non-4C” antimicrobials, and finally, fluoroquinolones only (FQs). Interaction tests
127 were used to investigate if the effects of antimicrobial prescribing are the same in those prescribed a
128 PPI.

129 Sensitivity analyses examined the effect of restricting the definition of CA-CDI to cases with no
130 hospitalisation in the previous 6 and 12 months. We also provided stratified results for healthcare-
131 onset cases matched to both population and hospital-based controls. All analysis was conducted using
132 R version 3.2.1.

133 **Results**

134 Between 1st Aug 2010 and 31st July 2013 there were 6019 confirmed CDI episodes in Scotland and
135 1612 (26.8%) were CA-CDI. Of these, 1557 were successfully assigned population-based controls
136 (Figure 1). For the patients with more than one CA-CDI episode, a single episode was randomly
137 selected resulting in a sample of 1446 cases with 7964 matched controls.

138 Cases were more likely to have been in hospital in the previous year (43.0% versus 14.0%) and exposed
139 to PPIs (41.8% versus 22.4%), and had more comorbidity by both prescribing measures and Charlson
140 Index (Table 1). Crude odds of CA-CDI were higher with higher comorbidity scores (Charlson Index 4
141 or more *versus* 0 OR=4.2 (95% CI: 2.5-7.0)), with any hospital admission in the previous year (OR=4.9
142 (95% CI: 4.3-5.6)), and with PPI or H2 antagonist exposure (Table 2). After adjustment, the scale of
143 these effects diminished but previous hospital admission (OR=2.15 (95% CI: 1.8-2.6)), higher Charlson
144 Index, and H2 antagonist exposure remained significant but PPI exposure did not (Table 2).

145 Among cases, 58.7% were exposed to any antimicrobial in the previous 6 months compared to 23.0%
146 of controls. After adjustment, the odds of CA-CDI after any antimicrobial exposure was 2.8 (95%
147 CI:2.4-3.2) compared to no antimicrobial exposure (Figure 2, Table 2). Adjusted odds of CA-CDI were
148 even higher for prior exposure to 4C (OR=6.1 (95% CI:4.8-7.7)) and fluoroquinolone (OR=5.4 (95% CI:
149 3.8-7.8)) antimicrobials.

150 PPI exposure was common (Table 1) and significantly modified the effect of antimicrobial exposure
151 (interaction test $p=0.0001$). Of cases, 26.7% were exposed to neither, 31.5% to only antimicrobials
152 (OR=3.4 (95% CI:2.8-4.1) for CA-CDI), 14.6% to only PPIs (OR=1.38 (95% CI:1.1-1.7)) and 27.3% to both
153 (OR=2.7 (95% CI:2.1-3.4)). 231 (16%) CA-CDI cases had no antimicrobial, PPI or H2 antagonist
154 exposure, Charlson Index 0 and no previous hospitalisations.

155 Sensitivity analysis to extend the exclusion period for prior hospitalisation from 12 weeks to 6 months
156 led to marginally higher associations but little further change when using a 12-month exclusion. All CIs
157 overlapped with the baseline results (4C exclusion 6 months OR=7.4 (95% CI:5.6-9.7); 12-month
158 exclusion OR=7.1 (95% CI:4.9–10.3)). Considering the subset of CA-CDI cases with healthcare-onset,
159 similar effect sizes were found for this group when matched to population-based controls (Table 3).
160 Matching to hospital-based controls reduced the associations found – any antimicrobial exposure had
161 an odds of CDI of 1.5 (95% CI:1.2-2.0) compared to no exposure and 4C exposure gave an increased
162 odds of 2.17 (95% CI:1.5-3.3).

163 Cumulative antimicrobial exposure was high with 19.9% of cases having 29+ DDDs in 6 months.
164 Compared to no exposure, up to 7 DDD of any antimicrobial gives odds of CA-CDI of 2.3 (95% CI:1.9-

165 2.9) compared to 4.4 (95% CI: 3.4-5.6) for 29+ DDDs (Table 4). 4C exposure duration was typically
166 short among controls but more variable among cases. Among cases 3.3% had 29+ DDDs of 4C which
167 has associated odds of CDI of 17.9 (95% CI:7.6-42.2) compared to 4.6 (95% CI:3.4-6.2) for 1-7 DDDs,
168 with similar pattern for cumulative fluoroquinolone exposure (Table 4). Increasing durations of non-
169 4C antimicrobials increased CA-CDI risk, with odds ratio for 29+ DDDs of 3.9 (95% CI:3.0-5.1), which is
170 about half the odds ratio for 29+ DDD of 4C exposure, 6.4 (95% CI:4.6-8.9).

171 Among the 287 cases with 29+DDD exposure the pattern of antimicrobial prescribing is complex and
172 more consistent with repeated short treatment courses prescriptions than long term prophylaxis
173 (Supplementary Figure S1, supplementary Table S1). The most commonly prescribed antimicrobials
174 were amoxicillin, trimethoprim, flucloxacillin, co-amoxiclav, ciprofloxacin and nitrofurantoin, each of
175 which are prescribed to at least 20% of the 287 patients (Supplementary Table S2).

176 Time since most recent antimicrobial treatment had a significant impact on CDI risk (Table 5).
177 Considering any antimicrobial, the effect was strongest in those exposed in the previous 4 weeks,
178 OR=6.3 (95% CI: 5.2-7.7) compared to OR=2.2 (95% CI:1.8-2.7) exposure 2-3 months earlier. By 4-6
179 months the effect of any exposure was lost OR=1.1 (95% CI:0.9-1.4) with a similar pattern observed
180 for non-4C antimicrobials. 4C exposure within the previous month increased the odds of CDI 12.5
181 (95% CI:8.9-17.4) times decreasing to OR=5.1 (95% CI: 3.5-7.5) by 2-3 months post exposure. The
182 effects for both 4C and FQs were still significant 4-6 months post exposure (4C OR=2.6 95% CI:1.7-3.9).

183

184 **Discussion**

185 In this whole population study we linked validated CDI cases to administrative datasets to quantify the
186 risk of CA-CDI associated with community antimicrobial exposure. Any antimicrobial exposure within
187 the previous 6 months increased the risk with elevated risk remaining for up to three months. We
188 found larger associations with high risk antimicrobials and found even higher effects of cumulative
189 exposure among this group and effects persisting up to six months following exposure.

190 Our study established that 58.7% of CA-CDI cases had been exposed to an antimicrobial in the
191 preceding 6 months, not dissimilar to other studies.²⁻⁷ A recent meta-analysis, including studies with
192 significant heterogeneity and covering an earlier time frame,⁸ reported a higher OR for exposure to
193 any antimicrobial OR=7.3 (95% CI: 4.3-12.6) compared to OR=2.8 in our study. Antimicrobial
194 prescribing has changed over time, particularly in Scotland, in response to high rates and outbreaks of
195 CDI in 2007/8.²⁰ The antimicrobial with the strongest association with CA-CDI in the meta-analysis,⁸
196 clindamycin, was used very rarely in our study population (2.1% (31/1446) of cases and 0.03% (2/7964)
197 controls have exposure in previous 6 months), and reduced prescribing of the whole 4C group has
198 been successfully targeted in Scotland.²¹

199 Consistent with this, our estimates are also lower than those reported by Marwick *et al.*¹². This case-
200 control component of this study focused only on elderly individuals in a single region of Scotland (n=62
201 cases, 620 controls). Restricting our analysis to the same age group and geography yields similar
202 estimates, though the confidence intervals become wide due to the small sample size (Supplementary
203 Table S3).

204 Cumulative total exposure to any antimicrobial has been clearly demonstrated to increase HA-CDI
205 risk⁹⁻¹¹ but evidence in CA-CDI is sparse. Marwick *et al.*¹² found a dose-response relationship with OR
206 of CDI increasing from 2.9 (95% CI: 1.2–6.7) for 1-7 days exposure to 12.7 (95% CI: 5.2-31.3) for 29+
207 days exposure – a higher magnitude than our study. This may partly reflect our inclusion of the entire
208 population rather than only the elderly, known to be at higher risk of CDI. It may also be attributable
209 to our classification of cumulative exposure as DDDs rather than days of therapy derived from
210 prescription directions.

211 There is little published evidence, even for HA-CDI, of the incremental impact of cumulative exposure
212 of different groups of antimicrobials. Marwick *et al.*¹² generated ORs for cumulative 4C antimicrobials
213 but the small sample size prevented meaningful subgroup analysis. Our inclusion of the whole
214 population with confirmed CA-CDI in Scotland over a 3-year period enabled sub-analysis by
215 antimicrobial group. We demonstrate clear increasing odds of CA-CDI with increasing cumulative

216 exposure to antimicrobials and particularly for the 4C antimicrobial subgroup. For fluoroquinolones,
217 the dose-response relationship remained, but there was higher variability surrounding the estimates,
218 due to reducing prescription numbers.

219 We found a high proportion (29.9%) of CA-CDI cases had received 29+ DDDs of antimicrobial in the 6
220 months prior to CDI. This included prescribing consistent with planned long term use for urinary tract
221 infection prophylaxis (nitrofurantion, trimethoprim) and skin conditions (flucloxacillin, doxycycline) as
222 may be expected, but the majority of cases involved various antimicrobials including ciprofloxacin, co-
223 amoxiclav and amoxicillin and the number of prescriptions and DDD per prescription was more
224 consistent with multiple short treatment courses. This prescribing pattern was unexpected and
225 represents potentially avoidable, high risk antimicrobial prescribing and an important message for
226 primary care prescribers.

227 The period of increased risk of CDI following antimicrobial use remains an important clinical question.
228 Previous studies have mainly examined, and found an increased risk associated with CA-CDI, up to 3
229 months after antimicrobial use.^{3,13,22} This has been affirmed in our study and is also similar to the risk
230 observed in HA-CDI studies.^{10,11} One study¹³ examined prior antimicrobial use up to 180 days and found
231 the increased risk remained up to 150 days (OR=2.8 95% CI:1.3-6.0) then returned to baseline. In our
232 study the period of elevated risk for any antimicrobials remained up to 3 months but was lost by 4-6
233 months although was still elevated for 4C and fluoroquinolone antimicrobials. This differential
234 temporal impact of antimicrobial groups up to 6 months is an important finding to support clinical
235 decision support and antimicrobial stewardship initiatives.

236 The unadjusted effect of PPI prescribing was similar to that reported by previous meta-analysis²², but
237 the effect diminished with covariate adjustment. The meta-analysis²² estimated a pooled OR of 1.93
238 for the association between PPI exposure and CDI, but only three of 29 included studies involved CA-
239 CDI, with effect sizes of OR=0.9,²³ OR=2.9²⁴ and OR=3.5² with each having differing case and exposure
240 definitions. Whilst the effect of PPI exposure was diminished with covariate adjustment, the effect of
241 H2 antagonists remained significant (OR=1.4). This may be due to residual confounding, potentially
242 attributable to prescription of H2 antagonists in preference to PPIs in patients who are deemed to be
243 at a higher risk of CDI.

244 After covariate adjustment, in particular adjustment for comorbidities (Charlson score and overall
245 prescription counts), and accounting for antimicrobial prescribing, the effect of care home residence
246 on CA-CDI became insignificant. This effect was lower than the study of Marwick *et al.*¹² which found
247 a significant adjusted association with care home residence (OR=4.1 95% CI: 1.7-9.6), however, this

248 study, did not adjust for Charlson score. Replicating the inclusion criteria and adjusting factors as
249 Marwick *et al.*,¹² analysis of our data gave a non-significant adjusted OR for care home residence of
250 OR=2.2 (95% CI: 0.8-5.7) but similar effect sizes for cumulative antimicrobial prescribing, PPI exposure
251 and total prescriptions in the previous year. The studies took place at different periods, Marwick *et*
252 *al.*¹² from November 2008-October 2009 and our study from 2010-2013 suggesting a reduction in the
253 residual care home effect in the latter period perhaps attributable to improved stewardship over this
254 time period.²⁰

255 This study illustrated that a sizeable proportion (16%) of individuals had exposure to neither PPIs, H2
256 antagonists, nor antimicrobials, had not been an inpatient in the previous year and had no
257 comorbidities recorded, indicating a significant proportion of CA-CDI cases which have not been
258 exposed to the classically understood risk factors. These individuals were a younger subset of the cases
259 (median age 48) but have a considerably higher number of community prescriptions than their
260 matched controls indicating comorbidities not serious enough to require hospitalisation hence not
261 captured reflected in the routinely used Charlson score.

262 We believe the data in our study to be robust and have high levels of completeness. Reporting of CDI
263 is mandatory and all cases used in our analysis are validated. SMR01 covers all residents in Scotland
264 that receive care in hospital enabling robust classification of community-associated disease.
265 Antimicrobial exposure is assessed via an individual's prescriptions dispensed in the community, which
266 can be robustly measured¹⁵ and during the study period CHI completeness of the prescription data
267 was between 94% and 96%.

268 The main data limitation, which impacts on our CA-HO sub-analysis, is the lack of routine patient-level
269 information on hospital prescribing, which is not presently captured electronically in Scotland. The
270 effect of this is mitigated to some extent because the CA-CDI definition excludes those with a
271 hospitalisation in the previous 12 weeks, and our sensitivity analysis showed only marginal impact of
272 extending the period for no prior hospitalisation to 12 months. It does however hinder the
273 generalizability this methodology to examine healthcare associated CDI.

274 A further limitation, common to all observational studies of medication effects, is the inability to
275 measure adherence and it is known that adherence to antimicrobials in the community is variable.
276 Using dispensed prescribing data, as we have, is better in this regard than datasets based on
277 prescriptions generated.

278 Our findings have important implications for antimicrobial prescribing decisions in primary care, and
279 for prescribing guidelines, emphasising that all exposure in the previous six months influences the risk

280 *versus* benefit of prescribing any antimicrobial, and specific antimicrobials. A significant number of
281 patients in our study were at continually high CDI risk. The next phase of research should apply such
282 routine data in cohort studies to derive clinical risk prediction scores and numbers needed to harm,
283 to definitively quantify risk to help frontline clinicians to improve patient centred, safe and effective
284 antimicrobial stewardship.

285 In conclusion, this is the largest study to assess the impact of duration and time since antimicrobial
286 therapy on CA-CDI and demonstrated that antimicrobial exposure had a clear dose response
287 relationship, with the odds of CDI more than doubling when cumulative exposure was increased from
288 one week to over 4 weeks. The temporal effect of exposure is also clear. The risk is highest in the
289 month after exposure but the effect of high risk broad-spectrum antimicrobials remains for up to six
290 months.

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299 **Transparency declarations**

300 None to declare.

301

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363 community-acquired Clostridium difficile-associated disease. *JAMA* 2005; **294**:2989-2995.

364 **Table 1. Distribution of matched and potential confounding variables in community-associated CA-**
 365 **CDI CDI cases and population-based controls-presented as median and quartiles for the continuous**
 366 **variables and number and percentages for the categorical variables**

	Cases (n=1446)	Matched Controls (n=7964)
Age-median (IQR ^a)	71.5 (52-82)	69 (50-81)
Female, <i>n</i> (%)	942 (65.2)	5186 (65.1)
Male, <i>n</i> (%)	504 (34.8)	2778 (34.1)
Number items ^b dispensed in previous year, median (IQR)	59 (20-127.5)	17 (1- 47)
Number different items dispensed in previous year (IQR)	12 (7-18)	5(1-10)
SIMD ^c 1: most deprived, <i>n</i> (%)	320 (22.2)	1580 (19.9)
SIMD 2	323 (22.4)	1763 (22.2)
SIMD 3	285 (19.8)	1641 (20.7)
SIMD 4	261 (18.1)	1564 (19.7)
SIMD 5: least deprived	252 (17.5)	1398 (17.6)
Charlson score ^d 0, <i>n</i> (%)	705 (48.8)	3019 (37.9)
Charlson score 1	167 (11.6)	260 (3.3)
Charlson score 2	120 (8.3)	184 (2.3)
Charlson score 3	41 (2.8)	55 (0.7)
Charlson score 4+	29 (2.0)	38 (0.5)
Charlson score Unknown	384 (26.6)	4408 (55.4)
Any hospital admission in previous year, <i>n</i> (%)	622 (43.0)	1118 (14.0)
No hospital admission in previous year	824 (57.0)	6846 (96.0)
Care home residence, <i>n</i> (%)	247 (17.1)	723 (9.1)
No care home residence	1199 (82.9)	7241 (90.9)
PPI exposure, <i>n</i> (%)	605 (41.8)	1785 (22.4)
No PPI exposure	841 (58.2)	6179 (87.6)
H2 exposure, <i>n</i> (%)	93 (6.4)	241 (3.0)
No H2 exposure	1356 (94.6)	7723 (97.0)

367
 368 ^a Q1 is the lower quartile 1/4 of distribution below this point. Q3 is the upper quartile 3/4 of the data below this point. Q1
 369 to Q3 is known as the interquartile range IQR.

370 ^b An item refers to any prescribed drug (based on approved name). This total count is used as a measure of comorbidity.

371 ^c SIMD is the Scottish Index of Multiple Deprivation here represented as quintiles 1-5. SIMD was unknown if this could not
 372 be linked from the CHI register-with 5 cases and 18 controls excluded for this reason.

373 ^d High scores represent more comorbidity. Unknown scores are generated if the individual has no previous hospitalisations
 374 in previous 5 years.

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Table 2. Unadjusted and adjusted odds ratios of CA-CDI together with 95% confidence intervals and p values from the fully adjusted model

	Unadjusted	Adjusted	
	OR (95% CI)	OR (95% CI)	p-value
Exposed to antibiotics in the previous 6 months, No	1	1	-
Exposed to antibiotics in the previous 6 months, Yes	4.98 (4.40-5.63)	2.80 (2.41- 3.25)	<0.0001
SIMD ^a 1: most deprived	1	1	-
SIMD 2	0.86(0.71-1.05)	0.85 (0.67-1.08)	0.178
SIMD 3	0.79 (0.64-0.98)	0.88 (0.68-1.14)	0.329
SIMD 4	0.75 (0.60-0.94)	0.95 (0.72-1.24)	0.696
SIMD 5: least deprived	0.83 (0.65-1.06)	0.98 (0.73-1.31)	0.872
Charlson score 0	1	1	-
Charlson score 1	3.59 (2.84- 4.53)	2.42 (1.82-3.21)	<0.0001
Charlson score 2	3.52 (2.71-4.57)	2.60 (1.89-3.57)	<0.0001
Charlson score 3	4.32 (2.81-6.62)	2.23 (1.33-3.74)	0.002
Charlson score 4+	4.19 (2.50-7.03)	2.83 (1.48-5.44)	0.002
Charlson score Unknown	0.32 (0.28-0.37)	0.80 (0.67-0.96)	0.016
Any hospital admission in previous year, No	1	1	-
Any hospital admission in previous year, Yes	4.89 (4.30-5.57)	2.15 (1.80-2.56)	<0.0001
Number items dispensed in previous year	1.019 (1.018-1.021)	1.011 (1.010-1.013)	<0.0001
Number different items dispensed in previous year	1.16 (1.15-1.17)	1.03 (1.01-1.04)	0.002
Care home residence, No	1	1	-
Care home residence, Yes	2.54 (2.09-3.08)	1.15 (0.89-1.48)	0.283
PPI exposure, No	1	1	-
PPI exposure, Yes	2.62 (2.32-2.97)	1.02 (0.86-1.21)	0.819
H2 antagonist exposure, No	1	1	-
H2 antagonist exposure, Yes	2.21 (1.72-2.83)	1.41 (1.02-1.96)	0.036

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^aSIMD is the Scottish Index of Multiple Deprivation here represented as quintiles 1-5.

382

383 **Table 3. Odds of CDI, together with 95% confidence intervals, given antibiotic exposure for**
 384 **community-associated healthcare-onset cases CA-HO matched to both population-based and**
 385 **hospital-based controls**

Exposure	CA-HO $n=476^a$ matched to population- based controls $n=2581$	CA-HO $n=476^a$ matched to hospital-based controls $n=957$
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Any antibiotic exposure: Yes versus No	2.21 (1.67-2.92)	1.52 (1.15-2.01)
4C versus No antibiotic	4.91 (3.18-7.59)	2.17 (1.45-3.26)
any other antibiotic versus No antibiotic	1.66 (1.22-2.26)	1.32 (0.98-1.79)
Fluoroquinolone versus No antibiotic	5.22 (2.76-9.88)	2.14 (1.19-3.83)
any other antibiotic versus No antibiotic	1.96 (1.46-2.63)	1.44 (1.08-1.93)

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387 ^a Number of healthcare-onset cases reduces to $n=476$ when considering the cases which have both population and hospital-
 388 based controls assigned to them.

389

390 **Table 4. The effect of cumulative exposure in a six month period on the adjusted odds of CA-CDI.**
 391 **Models are adjusted for SIMD, Charlson score, any hospitalisation in the previous year y/n, total**
 392 **number of prescriptions in the previous year, total number of different prescriptions, care home**
 393 **residence, PPI and H2 exposure**

Cumulative antimicrobial exposure	Cases n (%)	Controls n (%)	Adjusted OR (95% CI)
no antimicrobials	597 (41.4)	6133 (77.0)	1
1-7 DDDs	198 (13.7)	659 (8.3)	2.31 (1.88-2.85)
8-14 DDDs	166 (11.5)	584 (7.3)	2.13 (1.69-2.68)
15-28 DDDs	195 (13.5)	334 (4.2)	3.59 (2.81-4.60)
29+ DDDs	287 (19.9)	252 (3.2)	4.36 (3.40-5.61)
NA ^a	3	2	
Cumulative 4C antimicrobial exposure			
no antimicrobials	597 (41.3)	6133 (77.0)	1
1-7 DDDs	114 (7.9)	184 (2.3)	4.60 (3.41-6.21)
8-14 DDDs	85 (5.9)	70 (0.9)	7.58 (5.05-11.37)
15-28 DDDs	66 (4.6)	34 (0.4)	7.23 (4.25-12.28)
29+ DDDs	47 (3.3)	10 (0.1)	17.86 (7.56-42.17)
Any other non 4C antimicrobials	536 (37.1)	1533 (19.2)	2.19 (1.86-2.58)
NA ^a	1	0	
Cumulative fluoroquinolone exposure			
no antimicrobials	597 (41.3)	6133 (77.0)	1
1-7 DDDs	48 (3.3)	72 (0.9)	3.82 (2.41-6.05)
8-14 DDDs	32 (2.2)	19 (0.2)	10.13 (5.03-20.42)
15-28 DDDs	25 (1.7)	5 (0.1)	7.29 (2.29-23.20)
29+ DDDs	15 (1.0)	4 (0.1)	9.17 (2.26-37.14)
Any other non fluoroquinolone antimicrobials	728 (50.4)	1731 (21.7)	2.63 (2.26-3.07)
NA ^a	1	0	
Cumulative non 4C antimicrobial exposure			
no antimicrobials	597 (41.3)	6133 (77.0)	1
1-7 DDDs	194 (13.4)	634 (8.0)	2.33 (1.88-2.88)
8-14 DDDs	159 (11.0)	560 (7.0)	1.98 (1.56-2.51)
15-28 DDDs	167 (11.6)	298 (3.7)	3.03 (2.33-3.95)
29+ DDDs	225 (15.6)	222 (2.8)	3.87 (2.95-5.09)
Only 4C antimicrobials	102 (7.1)	115 (1.4)	6.39 (4.57-8.93)
NA ^a	2	2	

394
 395 ^aTo calculate DDD exposure both quantity and a scaling factor representing the recommended daily dose are required. For
 396 5 observations either or both of these were missing for the antimicrobial exposure variable. 1 was missing for the FQ and
 397 4C exposure. These observations are excluded from the analysis.

398 In the exposure categories for 4C antibiotics individuals may be exposed to non 4C antibiotics as well; in the exposure
 399 categories for non 4C antibiotics individuals may be exposed to 4C antibiotics as well; in the exposure categories for
 400 fluoroquinolone antibiotics individuals may be exposed to non-fluoroquinolone antibiotics as well

401

402 **Table 5. Distribution of temporal exposure and adjusted odds ratios of CA-CDI**

Most recent exposure in previous 6 months		% exposed controls <i>n</i> =7964	% exposed cases <i>n</i> =1446	Adjusted OR (95% CI)	Global <i>P</i> value
Any antimicrobial	no antibiotics	77.0	41.3	1	0.064 ^a
	<= 1 month	6.1	32.0	6.3 (5.16-7.69)	
	2-3 months	8.1	17.8	2.2 (1.78-2.72)	
	4-6 months	8.7	8.9	1.1 (0.86-1.42)	
4C	no antibiotics	77.0	41.3	1	<0.0001
	<= 1 month	1.0	10.9	12.45 (8.89-17.44)	
	2-3 months	1.2	6.4	5.12 (3.5-7.51)	
	4-6 months	1.5	4.4	2.59 (1.74-3.87)	
	other antibiotic	19.2	37.1	2.17 (1.84-2.56)	
Fluoroquinolones	no antibiotics	77.0	41.3	1	<0.0001
	<= 1 month	0.3	3.1	11.06 (5.85-20.9)	
	2-3 months	0.5	3.0	4.96 (2.79-8.82)	
	4-6 months	0.5	2.2	3.13 (1.68-5.83)	
	other antibiotic	21.7	50.3	2.62 (2.25-3.06)	
Non 4C	no antibiotics	77.0	41.3	1	<0.0001
	<= 1 month	5.4	24.9	5.36 (4.34-6.62)	
	2-3 months	7.8	17.2	2.26 (1.82-2.80)	
	4-6 months	8.4	9.5	1.17 (0.91-1.51)	
	Only 4C	1.4	7.1	6.33 (4.50-8.91)	

403

404 ^aLinear trend test, evaluating by including temporal exposure as an ordered factor in the conditional logistic regression model

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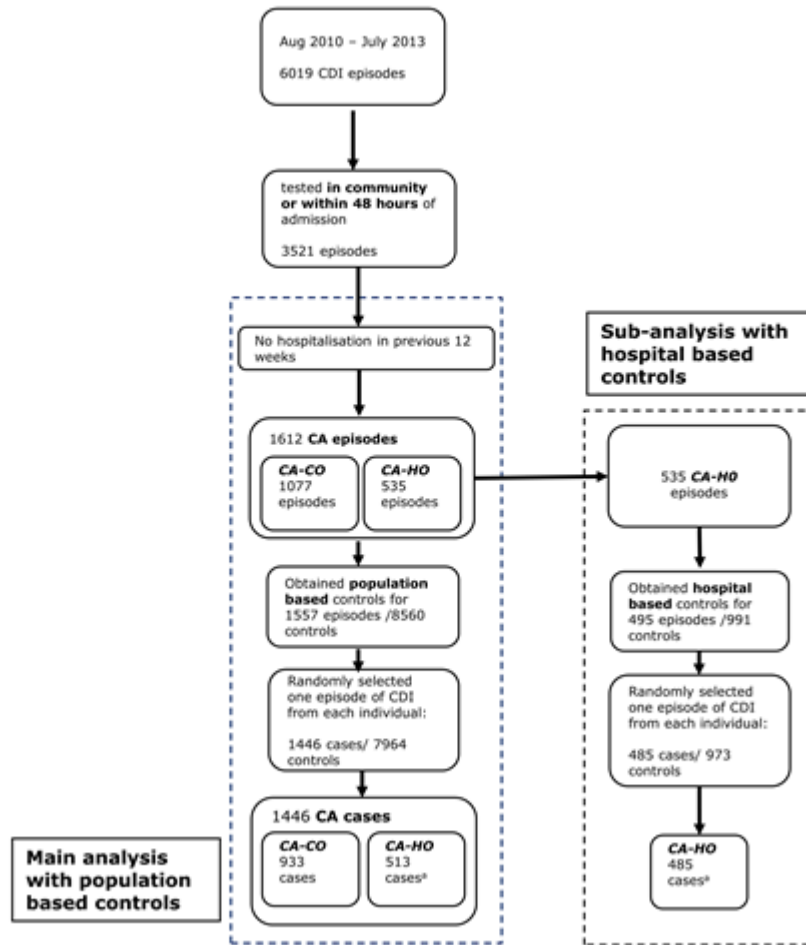
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408 **Figures**

409 **Figure 1:** Flow chart of the episode selection and control assignment. CA – Community-associated;
410 CO – Community-onset; HO – Healthcare-onset.

411 ^aNumbers of CA-HO cases differ in each analysis as they are matched to different control populations and not all cases are
412 successfully matched.

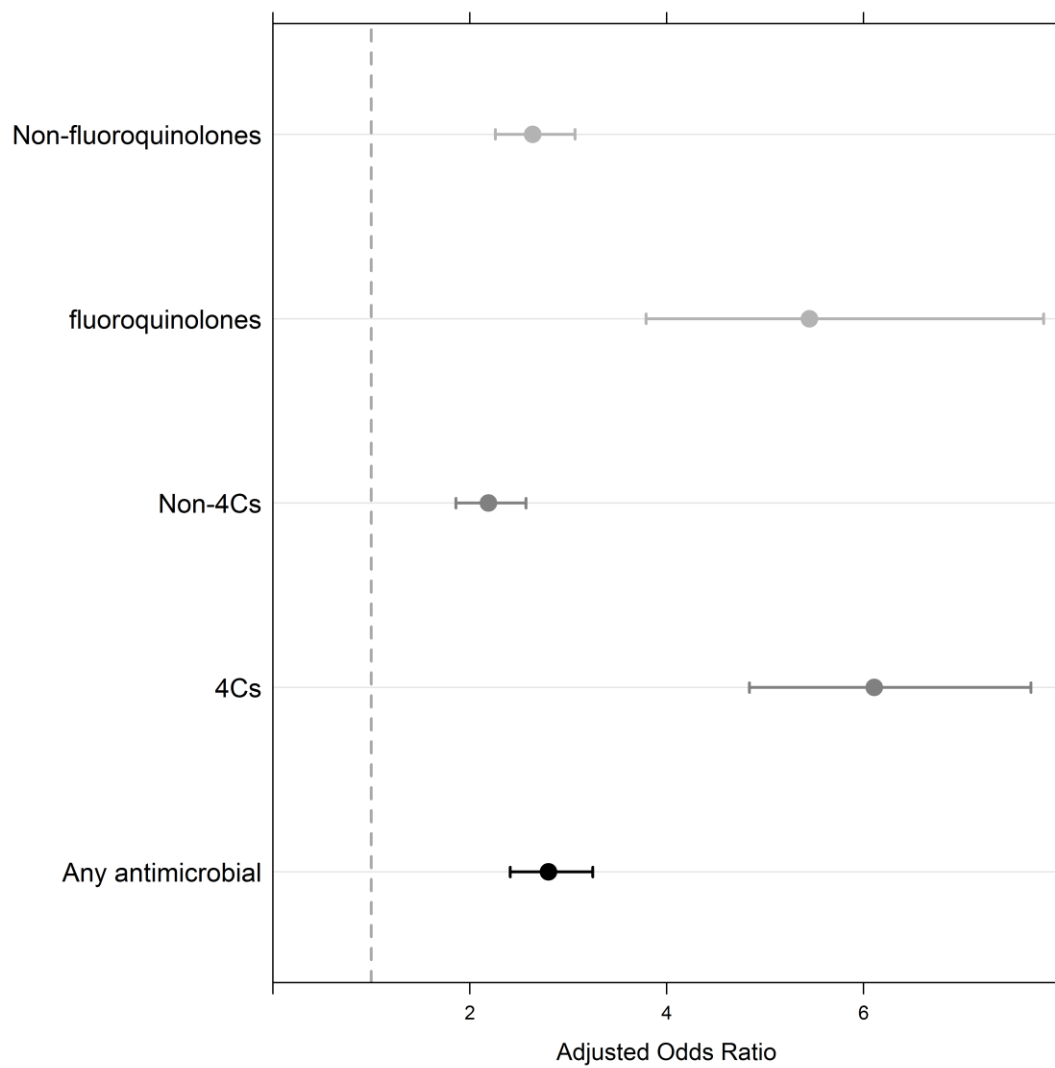
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416 **Figure 2:** Adjusted odds of CA-CDI, and 95% confidence intervals, following antimicrobial exposure in
417 the previous 6 months compared to no antimicrobial exposure. Vertical dashed line at OR =1



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