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Published in:
Journal of Antimicrobial Chemotherapy

DOI:
10.1093/jac/dkw528

Publication date:
2017

Document Version
Peer reviewed version

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

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Running title: Association between antimicrobials & CDI

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Abstract

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

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

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

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

Introduction

Clostridium difficile infection (CDI) is a major public health problem and a key focus for antimicrobial stewardship programs. Quantification of the adverse effects of antimicrobial use at population level is essential to support appropriate antimicrobial stewardship policy. Community-associated CDI (CA-CDI) is an increasing public health threat[1] studies indicating 37-79% cases having had antimicrobial exposure in the preceding 90 days.[2-7] A meta-analysis[8] derived pooled odds ratios from eight studies for the risk of CA-CDI associated with specific antimicrobial groups, but did not consider cumulative or temporal exposure effects. Cumulative and temporal antimicrobial exposure have been examined in healthcare-associated CDI (HA-CDI)[9-11] but for CA-CDI data are limited to considering cumulative effect in an elderly population[12] and considering temporal effects for overall antimicrobial exposure only, [13] with both studies limited to low CA-CDI numbers.

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

Materials and methods

Data sources

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

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

Data linkage and control assignment

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

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

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

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

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

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

Ethics

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

Statistical analysis

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

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

Results

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

Cases were more likely to have been in hospital in the previous year (43.0% versus14.0%) and exposed to PPIs (41.8% versus 22.4%), and had more comorbidity by both prescribing measures and Charlson Index (Table 1). Crude odds of CA-CDI were higher with higher comorbidity scores (Charlson Index 4 or more *versus* 0 OR=4.2 (95% CI: 2,5-7.0)), with any hospital admission in the previous year (OR=4.9 (95% CI: 4.3-5.6)), and with PPI or H2 antagonist exposure (Table 2). After adjustment, the scale of these effects diminished but previous hospital admission (OR=2.15 (95% CI: 1.8-2.6), higher Charlson Index, and H2 antagonist exposure remained significant but PPI exposure did not (Table 2).

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

PPI exposure was common (Table 1) and significantly modified the effect of antimicrobial exposure (interaction test p=0.0001). Of cases, 26.7% were exposed to neither, 31.5% to only antimicrobials (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 (OR=2.7 (95% CI:2.1-3.4)). 231 (16%) CA-CDI cases had no antimicrobial, PPI or H2 antagonist exposure, Charlson Index 0 and no previous hospitalisations.

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

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

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

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

Time since most recent antimicrobial treatment had a significant impact on CDI risk (Table 5). Considering any antimicrobial, the effect was strongest in those exposed in the previous 4 weeks, 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 months the effect of any exposure was lost OR=1.1 (95% CI:0.9-1.4) with a similar pattern observed for non-4C antimicrobials. 4C exposure within the previous month increased the odds of CDI 12.5 (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 effects for both 4C and FQs were still significant 4-6 months post exposure (4C OR=2.6 95% CI:1.7-3.9).

Discussion

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

Our study established that 58.7% of CA-CDI cases had been exposed to an antimicrobial in the preceding 6 months, not dissimilar to other studies.[2-7] A recent meta-analysis, including studies with significant heterogeneity and covering an earlier time frame,[8] reported a higher OR for exposure to any antimicrobial OR=7.3 (95% CI: 4.3-12.6) compared to OR=2.8 in our study. Antimicrobial prescribing has changed over time, particularly in Scotland, in response to high rates and outbreaks of CDI in 2007/8.[20] The antimicrobial with the strongest association with CA-CDI in the meta-analysis, [8] clindamycin, was used very rarely in our study population (2.1% (31/1446) of cases and 0.03% (2/7964) controls have exposure in previous 6 months), and reduced prescribing of the whole 4C group has been successfully targeted in Scotland.[21]

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

Cumulative total exposure to any antimicrobial has been clearly demonstrated to increase HA-CDI risk[9-11] but evidence in CA-CDI is sparse. Marwick *et al.* [12] found a dose-response relationship with OR 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+ days exposure – a higher magnitude than our study. This may partly reflect our inclusion of the entire population rather than only the elderly, known to be at higher risk of CDI. It may also be attributable to our classification of cumulative exposure as DDDs rather than days of therapy derived from prescription directions.

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

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

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

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

The unadjusted effect of PPI prescribing was similar to that reported by previous meta-analysis[22], but the effect diminished with covariate adjustment. The meta-analysis[22] estimated a pooled OR of 1.93 for the association between PPI exposure and CDI, but only three of 29 included studies involved CA-CDI, with effect sizes of OR=0.9,[23] OR=2.9[24] and OR=3.5[2] with each having differing case and exposure definitions. Whilst the effect of PPI exposure was diminished with covariate adjustment, the effect of H2 antagonists remained significant (OR=1.4). This may be due to residual confounding, potentially attributable to prescription of H2 antagonists in preference to PPIs in patients who are deemed to be at a higher risk of CDI.

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

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

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

We believe the data in our study to be robust and have high levels of completeness. Reporting of CDI is mandatory and all cases used in our analysis are validated. SMR01 covers all residents in Scotland that receive care in hospital enabling robust classification of community-associated disease. Antimicrobial exposure is assessed via an individual's prescriptions dispensed in the community, which can be robustly measured[15] and during the study period CHI completeness of the prescription data was between 94% and 96%.

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

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

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

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

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

Acknowledgements

We acknowledge the linkage work and support given by the eDRIS team at National Services Scotland, in particular, John Nolan, Lynsey Waugh and Suhail Iqbal. In additional, we thank the members of the NHS Scotland Infection Intelligence Platform team and the Scottish Antimicrobial Prescribing Group for their support.

Funding

This work was funded by the Scottish Infection Research Network (SIRN) and Chief Scientists Office (CSO) grant number SIRN/01.

Transparency declarations

None to declare.

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Table 1. Distribution of matched and potential confounding variables in community-associated CA-CDI CDI cases and population-based controls-presented as median and quartiles for the continuous 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, *n* (%)	942 (65.2)	5186 (65.1)
Male, *n* (%)	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, *n* (%)	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, *n* (%)	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, *n* (%)	622 (43.0)	1118 (14.0)
No hospital admission in previous year	824 (57.0)	6846 (96.0)
Care home residence, *n* (%)	247 (17.1)	723 (9.1)
No care home residence	1199 (82.9)	7241 (90.9)
PPI exposure, *n* (%)	605 (41.8)	1785 (22.4)
No PPI exposure	841 (58.2)	6179 (87.6)
H2 exposure, *n* (%)	93 (6.4)	241 (3.0)
No H2 exposure	1356 (94.6)	7723 (97.0)

[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 to Q3 is known as the interquartile range IQR.

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

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

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

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

[a] SIMD is the Scottish Index of Multiple Deprivation here represented as quintiles 1-5.

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

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

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

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

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

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

Most recent exposure in previous 6 months		% exposed controls *n*=7964	% exposed cases *n*=1446	Adjusted OR (95% CI)	Global *P* 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)	

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404 [a]Linear trend test, evaluating by including temporal exposure as an ordered factor in the conditional logistic regression model

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Figures

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

[a]Numbers of CA-HO cases differ in each analysis as they are matched to different control populations and not all cases are successfully matched.

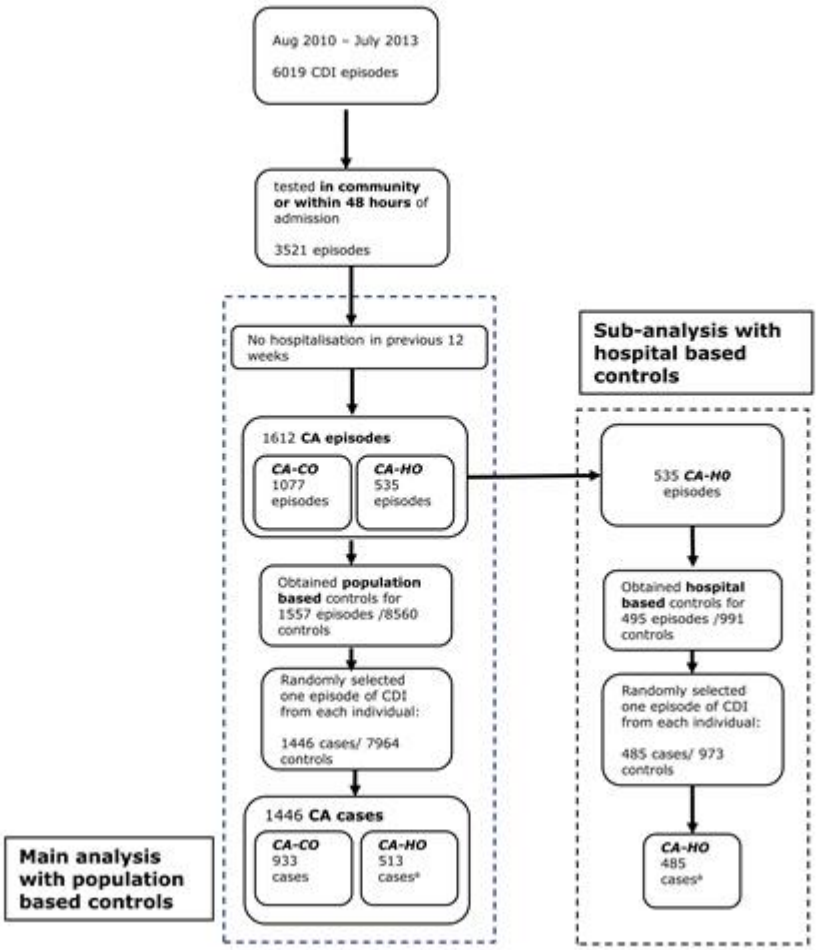

Figure 2: Adjusted odds of CA-CDI, and 95% confidence intervals, following antimicrobial exposure in the previous 6 months compared to no antimicrobial exposure. Vertical dashed line at OR =1