Residual effect of community antimicrobial exposure on risk of hospital onset healthcare associated *Clostridioides difficile* infection: a case-control study using national linked data

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Abstract

Background

Associations between antimicrobial exposure in the community and community-associated *Clostridioides difficile* infection (CA-CDI) are well documented but associations with healthcare-associated CDI (HA-CDI) are less clear. This study estimates the association between antimicrobial prescribing in the community and HA-CDI.

Methods

A matched case-control study was conducted by linking three national patient level datasets covering CDI cases, community prescriptions and hospitalisations. All validated cases of HA-CDI (August 2010 - July 2013) were extracted and up to three hospital-based controls were matched to each case on the basis of gender, age, hospital and date of admission. Conditional logistic regression was applied to estimate the association between antimicrobial prescribing in the community and HA-CDI. We conducted sensitivity analysis to consider the impact of unmeasured hospital antimicrobial prescribing.

Results

930 unique cases of HA-CDI with onset in hospital and no hospital discharge in the 12 weeks prior to index admission were linked with 1810 matched controls. Individuals with prior prescription of any antimicrobial in the community had an odds ratio (OR) = 1.40 (95% CI 1.13-1.73) for HA-CDI compared to those without. Individuals exposed to high risk antimicrobials (cephalosporins, clindamycin, co-amoxiclav, or fluoroquinolones) had an OR=1.83 (95% CI: 1.31-2.56). After accounting for the likely impact of unmeasured hospital prescribing, the community exposure, particular to high risk antimicrobials, was still associated with elevated HA-CDI risk.

Conclusions

Community antimicrobial exposure is an independent risk factor for HA-CDI and should be considered as part of the risk assessment of patients developing diarrhoea in hospital.

Introduction

Clostridioides difficile infection (CDI) is a global challenge[1,2] and a major public health problem in both healthcare and community settings. In Scotland, the annual incidence of healthcare-associated CDI (HA-CDI) in 2016 was 15.4 per 100 000 total bed days compared to 7.5 per 100 000 population for community-associated CDI (CA-CDI)[3]. Although a reduction in HA-CDI in Scotland has been observed over time, 58% of all cases were HA-CDI in 2016.

Antimicrobial exposure is a significant risk factor for CDI that is potentially modifiable. Associations between community antimicrobial exposure and CA-CDI are clearly demonstrated[4-7], but any residual impact on the risk of HA-CDI is challenging to differentiate from the impact of antimicrobial exposure in the healthcare setting. A recent systematic review, found that overall exposure to antimicrobials was associated with a 60% (95% CI 30%-90%) increased risk of HA-CDI however the included studies either only looked at hospital prescribing or did not differentiate between community and hospital prescribing[8]. No studies examined the residual effect of community prescribing on the risk of HA-CDI, and there were limited large studies to enable accurate quantification of the risk of antimicrobial prescribing on HA-CDI[8].

This study included all HA-CDI cases in Scotland (population of ~5.3 million) enabled through our national Infection Intelligence Platform (IIP) which synergizes the wealth of infection-related health data to provide timely and efficient analysis of our antimicrobial stewardship programs[10].

The aims of this study are to estimate the association between antimicrobial prescribing in the community and the development of HA-CDI considering exposure to, (i) any antimicrobial and (ii) specific broad spectrum antimicrobials, whilst accounting for the unmeasured confounder of hospital antimicrobial prescribing. The effect of cumulative antimicrobial exposure on the risk of HA-CDI and the temporal relationship between timing of antimicrobial exposure and risk of HA-CDI are also examined.

Population and methods

Data Linkage & Case-Control Assignment

A matched case control study was conducted by linking three national patient level datasets: ECOSS (Electronic Communication of Surveillance in Scotland – positive microbiology laboratory specimens for key infections); SMR01 (Scottish Morbidity Record– the General / Acute and Inpatient Day Case dataset recording hospital discharges); PIS (Prescribing Information System – prescriptions dispensed in the community)[10]. The completeness for SMR01 extract is around 99%[11] and for PIS extract is over 87%[12]. Due to mandatory surveillance for CDI in Scotland[13], our data should capture all CDI cases. The datasets were linked using the unique patient identifier, the community health index (CHI), used across all health service contacts in Scotland.

All validated CDI cases with a date of testing between August 2010 (to allow 1 year of look back of community prescriptions on PIS) and July 2013 (most recent validated CDI case data available at time of data extraction) were extracted from ECOSS. All diarrhoeal samples are tested using a 2-step diagnostic algorithm: first step, - screen for the presence of *C. difficile* glutamate dehydrogenase antigen; second step, test for the presence of toxin A/B in enzyme immunoassay (only samples positive in both steps are reported as positive). Positive tests were then validated by the NHS board against local laboratory and patient records to confirm all clinically symptomatic CDI episodes and entered into ECOSS.

Cases were linked to hospitalisation history from SMR01 for case classification. Cases were categorised as HA-CDI if the date of positive test was on day three or later of a hospital admission and/or within four weeks of a previous hospital discharge[14]. For this study, only hospital-onset HA-CDI (HO HA-CDI) cases were included, cases with hospital discharge in the 12 weeks prior to index admission were excluded to minimise the impact of unmeasured risk factors in previous admissions. For cases with multiple episodes of HA-CDI, one episode was chosen randomly for inclusion.

Up to three hospital based controls were matched to cases on the basis of age (within 5 years), gender, hospital and admission date (within 7 days, and in hospital on the case's CDI test date). Controls were excluded if they had hospitalisation in the 12 weeks prior to the current admission.

Individual community prescription records from August 2009 onwards and five years of hospitalisation records prior to the CDI date were linked to cases and controls using CHI. Two antimicrobial exposure categories in the six months prior to CDI test date were considered; any antimicrobial (only antibacterials not antivirals or antifungals; Leprosy and TB are very different to most other antibacterials and not implicated in CDI so excluded) and, separately, a higher risk group (clindamycin, cephalosporins, fluoroquinolones and co-amoxiclav – referred to as "4C" antimicrobials). This group of broad-spectrum antibiotics have been shown to have a higher risk of contributing to CDI[4,6,8,9]. Detailed prescribing directions were not available but strength and volume information allowed calculation of each prescription

and cumulative exposure as WHO defined daily doses (DDDs)[15]. DDD is the average maintenance dose per day for a drug used for its main indication in adults[15].

Risk factors considered were: hospital admission (yes/no) in the year prior to CDI; burden of co-morbidities derived from prescribing - number of total prescriptions (all drugs) and number of different prescriptions (based on approved name) dispensed in the year prior to CDI[16] and the Charlson Index - based on International Classification of Diseases 10 (ICD 10) discharge codes from all hospital admissions in the 5 years prior to CDI[17-19]; speciality for the index admission; care home residency (yes/no); Scottish Index of Multiple Deprivation (SIMD) quintile[20] from CHI Registry; length of inpatient stay before infection (days from index admission until CDI test date – each control used the pseudo CDI test date from the matched case); proton pump inhibitor (PPI) and H2 antagonist exposure (present/absent) in the six months prior to CDI.

Analysis

The association between community antimicrobial exposure and HA-CDI was assessed using conditional logistic regression with all other risk factors adjusted for. The residual effect of community antimicrobial exposure might be stronger in those hospitalised for a shorter period of time therefore interaction tests were used to investigate if the effect was the same in those hospitalised for under or over seven days prior to CDI.

For sensitivity analyses, we modelled how the unknown hospital prescribing of antimicrobials during the index CDI admission may influence the estimates[21]. The method specifies the likely proportion of unknown hospital antimicrobial prescribing in those exposed and unexposed to antimicrobials in the community along with the estimate of effect size of hospital prescribing on HA-CDI from the systematic review [8]. We assumed three potential values for the increased odds of HA-CDI associated with hospital antimicrobial prescription, OR=1.6, 1.3 and 1.9 (point estimate and confidence boundaries) and more extreme scenarios of OR= 4 and 6. One third of hospital inpatients are on antimicrobials at any time[22] and we assumed that those with a community antimicrobial prescription were more likely to have a hospital antimicrobial prescription, so we considered imbalances in the proportions with hospital prescribing from 35%/31% to 47%/19% in those with/without community prescribing, respectively. Uncertainty around the antimicrobial prevalence among hospital inpatients and its impact on the results was also investigated – we changed the overall prevalence from assumed 33% to 25%, 50% and 75% and reran the analysis. All analysis was conducted using R version 3.2.1.

Results

In total there were 3727 HA-CDI episodes in the time frame, of which 1235 (33.1%) were hospital onset and had no hospitalisation in the prior 12 weeks (Figure 1). Matched controls (1867) were obtained for 961 cases and after randomly selecting one episode from those with multiple episodes, 930 cases and 1810 matched controls were identified.

The study population was 59% female with median age 79 years (Table I). The average days of current hospitalisation before the matched date of CDI is longer for cases compared to controls (17 vs. 14 days). The cases were more likely than controls to have at least 1 prior hospital admission in previous year (44.4% vs. 39.1 %) but less likely to be resident in a care home (19.1% vs. 23.7%). The adjusted model showed that, there was increased risk of HA-CDI associated with comorbidity (Charlson score 4+ vs. 0 OR=2.72 95% CI: 1.63-4.53), higher numbers of drugs dispensed in the previous year (for unit increase OR=1.01 95% CI: 1.01-1.02 for each additional drug), a longer duration of hospitalisation prior to infection (OR=1.11 95% CI: 1.08-1.15 for each additional day), previous hospital admissions (yes vs. no OR=1.30 95% CI: 1.04-1.63), no care home residency (yes vs.no OR=0.65 95% CI: 0.50-0.83) (Table I).

Compared to the controls, a higher proportion of cases received any antimicrobial (42.6% vs.39.6%) and 4C group (13.0% vs. 9.6%) in the community in the previous 6 months. After adjusting for all other variables, prior antimicrobial exposure vs. no exposure in the community was associated with 40% increased odds of HA-CDI (OR 1.41 95% CI: 1.13 -1.75) (Table 1). The OR was higher for exposure to 4Cs (OR=1.86 95% CI: 1.33-2.59).

The effect of community 4C exposure was stronger in those hospitalised for less than one week prior to CDI diagnosis (Interaction test: p=0.02). For patients hospitalised for less than one week the OR for community 4C exposure vs. no exposure was 2.43 (95% CI: 0.998, 5.94) (Table II).

The scale of the dose response relationship between prior exposure to any antimicrobial in the community and development of HA-CDI was not found to be particularly large (1-7 DDDs exposure adjusted OR=1.31 95% CI: 0.95-1.79; 29+ DDDs OR=1.90 95% CI: 1.31-2.74) although the p value for the linear trend test was significant (p=0.0006). A similar result was found for dose response of prior 4C exposure was - compared to no exposure (Table III).

A slight decreasing trend can be observed in the risk of developing CDI with time since any antimicrobial exposure, adjusted OR for <=30 days post exposure was 2.17 (95% CI: 1.53 - 3.07) and decreasing to 1.75 (95% CI: 1.27-2.41) for 31-90 days post exposure and 0.97 (95% CI: 0.74-1.28) for 91 or more days, but the trend was not statistically significant (linear trend test p=0.5) (Table IV). The effect of 4C exposure was strongest within 90 days with little difference between the first month and those subsequent (OR <=30 days, 2.24 (95% CI: 1.32 -3.78) and OR 31-90 days, 2.47 (95% CI: 1.42-4.32)). The association did not persist after 90 days post exposure (OR 1.27 95% CI: 0.76-2.12).

The potential impact of unknown hospital antimicrobial prescribing on the association between community antimicrobial prescription and HA-CDI was examined, with reasonably assumed parameters for unknown hospital prescribing (ORs for hospital prescribing to

develop HA-CDI, prevalence of hospital prescribing in those with community exposure (p1) and without (p0)), Table V. With the increase in odds of HA-CDI associated with hospital antimicrobial exposure set at OR=1.6 the effect of any community antimicrobial exposure lost statistical significance at an imbalance in hospital exposure, between p0 and p1, of 19% versus 47% (OR =1.22 95% CI: 0.98-1.52). However community 4C exposure remained significantly associated with increased odds of HA-CDI at this imbalance (OR =1.61 95% CI: 1.15-2.25). If the OR for hospital prescribing is increased to 6, the effect of any antimicrobial prescribing in the community became insignificant at imbalance of p0 = 29% to p1=37% while the effect of 4C became insignificant at a larger imbalance of p0=25% to p1=41%. The results in Table V assumed that the overall prevalence of hospital prescribing was 33%. The impact of the variation of this overall prevalence to the results was investigated in Table A1. When the OR for hospital prescribing is low (OR=1.3) increasing the overall prevalence of hospital prescribing had little impact (up to 75%) on the measured association between HA-CDI and community prescribing. With a higher association (OR=6) a difference of difference between p0 and p1 of 4%, still showed significant associations even with a prevalence of hospital prescribing at 75%, however if the differential was greater (14%, 28%) then the association became reduced and the estimated odds became insignificant.

Discussion

Summary main findings

This study examined the residual effect of antimicrobial prescribing in the community on the risk of HA-CDI. Prior antimicrobial exposure vs. no exposure in the previous 6 months in community was associated with 40% increased odds of HA-CDI, rising to 80% after exposure to a higher risk antimicrobials group. After accounting for unmeasured hospital antimicrobial exposure, community exposure, particularly to high risk antimicrobials, still appeared to influence the risk of HA-CDI.

Strengths and limitations

The 2014 review paper[8] summarized the results on associations between prior antimicrobial exposure and the risk of HA-CDI. However, no studies examined community prescribing alone - three studies measured exposure during admission only whilst 10 studies measured antimicrobials received prior to and during admission combined. More recent work by Khanafer *et al*[23] also only explored hospital prescribing. This study examined the independent risk of community prescribing on developing HA-CDI, not explored previously to our knowledge. Additionally, most previous studies examined antimicrobial exposure in the prior 4-6 week while our study included exposure up to 6 months before infection.

Furthermore, our study is also at scale, second largest only to the USA Kaiser study[24], the remaining studies in the review comprising mainly of one hospital site with two studies covering 9-12 hospital sites (n=317 and n=237). In contrast, our study covered a national health system with data from 40 hospitals.

A limitation of our study was the unmeasured confounder of hospital prescribing. To minimise this impact, we excluded cases with a hospitalisation in the preceding 12 weeks. Sensitivity analysis, using an approach demonstrated in other clinical studies[25-26], was applied. Our study showed the impact of community prescribing on HA-CDI reduced when the likely impact of hospital prescribing[8] was accounted for but generally remained significant.

All our HA-CDI cases were defined according to the clinical definition[14] however cut-offs in the definition are in fact relatively arbitrary and there is much more of a continuum between the community and hospitals in terms of exposures, i.e. antimicrobials, and risk of infection transmission. Cases are attributed based on symptoms/sampling rather than when/where the bacteria was initially acquired (because it is common to have a period of asymptomatic carriage) so it is possible that some cases are misclassified in terms of acquisition source.

A proportion of PPI/H2 antagonist consumption is likely attributable to over the counter use, which we cannot measure in this study and we are therefore likely to be underestimating exposure to PPI/H2 antagonists which could modify the associations found if there is an imbalance in over the counter use between cases and controls.

Data subsequently recorded since the time of the study (2013-2017), shows a decreasing year on year trend of 6.8% in the incidence rate of CDI in Scotland and a contemporaneous decrease of 10.8% in 4C prescribing in the community[27], in line with antimicrobial stewardship policies. Given that our data predate this period, it is possible that changes in prescribing behaviour may have modified the relationships observed although the ecological pattern of

a decrease in CDI with reductions in community prescribing, is consistent with the associations found in this study and in our previous work on community associated CDI[7]. Future work will seek to use an updated data extract and examine the impact of the change in prescribing on the associations found.

Comparison with other work

The review paper[8] estimated ORs for different classes of antimicrobials (penicillins, clindamycin, trimethoprim, cephalosporins, carbapenems and fluoroquinolones; combined prior hospital and community prescribing) for risk of HA-CDI ranging from 1.45 (95% CI: 1.05-2.02) for penicillin to 3.2 for third-generation cephalosporins (95% CI: 1.8-5.71) which was generally higher than our estimations for community prescribing to any antimicrobial (OR=1.41 95% CI: 1.13-1.75) and 4C (OR = 1.86 95% CI: 1.33-2.59). The differences are expected as our study estimated the residual risk from community prescribing whilst the other studies mainly quantified the risk of mixed hospital and community prescribing. Another potential contributory factor to the difference may be the variation in definition of HA-CDI within the review which led to high heterogeneity in the estimated pooled risk (ranging from >48 hours to >72 hours with one study >5 days and variation in hospitalisation prior to the index admission).

Cumulative total exposure to any antimicrobial has been demonstrated to increase HA-CDI risk[5,25,29] but community prescribing was not investigated alone in these studies. We found a lower effect of cumulative community exposure (OR=1.90 95% CI: 1.31-2.74 for >29 DDDs, 6 months prior to CDI) compared to Hensgens *et al* who reported OR=8.5 95% CI: 4.6-15.9 for >=14 DDDs any antimicrobial use in both community and hospital in the 3 month prior to CDI, the difference most likely attributable to hospital prescribing. Further investigation of the cumulative exposure to the 4C subgroup is required due to small numbers in all studies to date.

In our study, community exposure to PPI and H2 antagonist was not associated with an increased risk of HA-CDI – similar to[23] where hospital exposure to PPI/H2 was examined with adjustment of prior antimicrobial use. However, the impact of PPI/H2 on CDI remains uncertain with Aseeri *et al*[30] showing a significant increased CDI risk for inpatients with combined community and hospital PPI exposure (OR=3.08 95% CI: 1.61-5.91) when the cases and controls were matched on type, amount and duration of prior antimicrobial exposure.

Finally, previous studies report care home residents as having higher risk of CDI[6-7], due to increasing age, comorbidity, likelihood for infection transmission and antimicrobial exposure[31]. However, care home residents appeared to be at lower risk of HA-CDI in our study (adjusted OR=0.65 95% CI: 0.50-0.83). This is likely due to the selection of controls, matched on age, gender and length of admission before CDI diagnosis date, resulting in a relatively high proportion of care home residents (23.7% vs. 19.1% of cases).

Conclusions

It appears that community prescribing has an impact on risk of hospital onset HA-CDI. Additionally, the study has shown that the impact on risk of HO HA-CDI from antimicrobial exposure in the community can persist for up to 6 months, not reported before[8,23].

This evidence underpins our national strategy to continue to strive for a reduction in broad spectrum antibiotics, now evidenced by a decline in CDI rates and 4C prescribing[31]**.** Our findings also raise the awareness of the persistence of community exposure on risk during hospital stay, noteworthy for the risk assessment and management of patients developing diarrhoea both in Scotland and globally.

Our study has used large scale data analytics to identify and quantify risk association retrospectively. The next phase is to link national data prospectively to inform new clinical decision tools using individual characteristics to derive personalised risk profiles to shape therapeutic management plans in the clinical setting.

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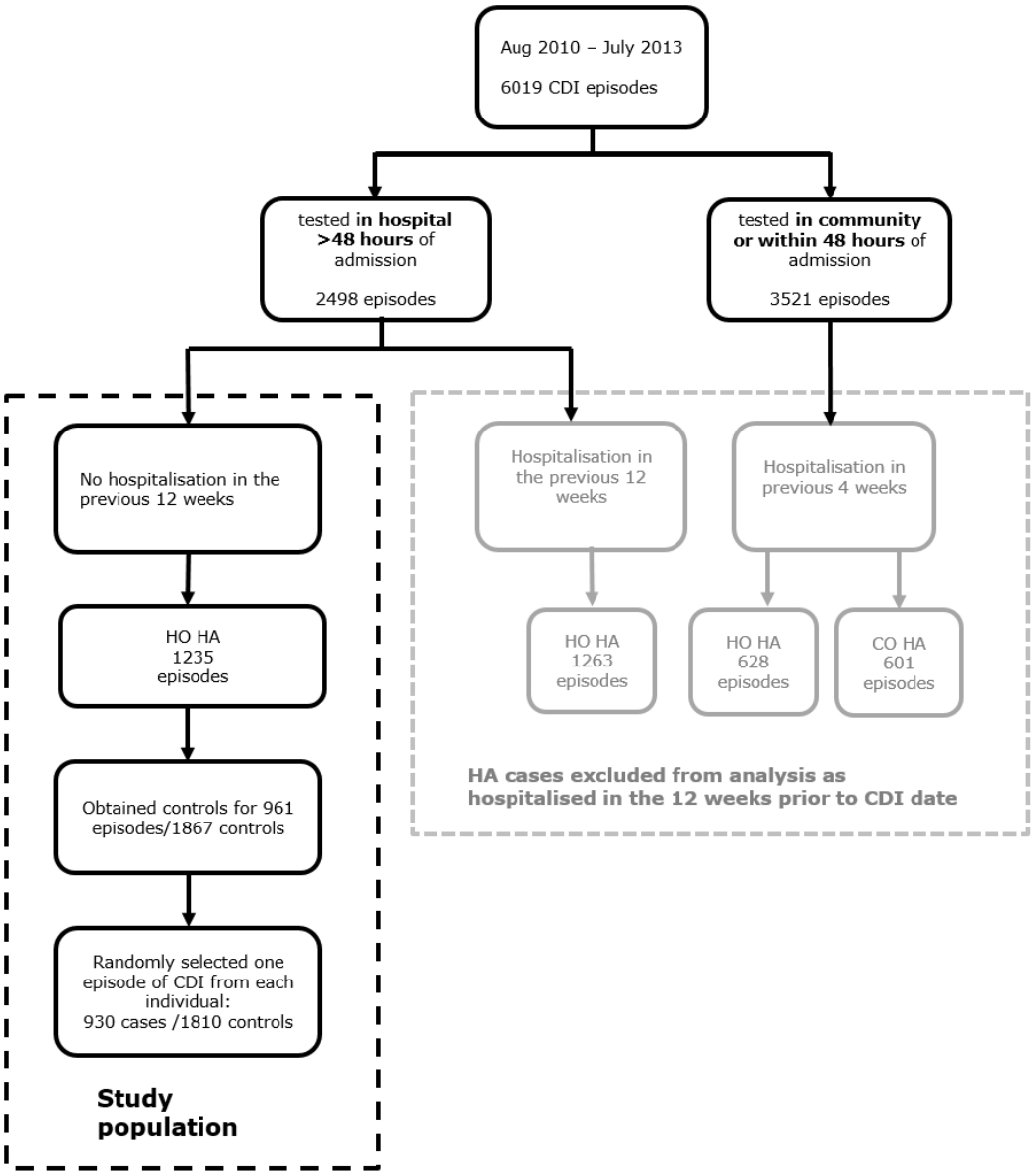
Figure captions

Figure 1: Flow chart of the episode selection and control assignment. HA – Healthcare associated; HO – Hospital Onset; CO – Community Onset.



Ethics approval

All data were generated during routine care and linkage, case/control assignment and anonymisation were performed by the electronic Data Research and Innovation Service (eDRIS) at National Services Scotland (NSS) Information Services Division (ISD). No patient identifiers were available to the study team and all data were accessed via the National safe haven. Information governance approval for the study was granted by National Health Service (NHS) NSS Privacy Advisory Committee, Study number XRB13122.

Consent for publication

Not applicable

Availability of data and materials

All data used in this study were held by eDRIS at NSS ISD and not publicly available.

Competing interests

None to declare.

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Contribution

JP performed statistical analysis and prepared manuscript

KK and CR supervised the statistical analysis, contributed to design of the study, obtaining funding as well as drafts and revisions of the manuscript

CM, PD and SB contributed to the design of the study, obtaining funding as well as to drafts and revisions of the manuscript

MB supervised the project, contributed to design of the study, obtaining funding as well as drafts and revisions of the manuscript

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455 **Table I: Demographics, univariate and multivariate odds ratios of prior antimicrobial exposure and potential confounding variables for**
456 **Healthcare associated CDI cases (HA-CDI) vs. hospital based controls.**
457

	Cases (n=930) n(%); median (IQR)[a]	Controls (n=1810) n(%); median (IQR)[a]	Unadjusted OR (95% CI)	Adjusted (Any) OR (95% CI)	Adjusted (4C) OR (95% CI)
No exposure to antibiotics in the previous 6 months	534 (57.4)	1093 (60.4)	1	1	1
Exposed to antibiotics in the previous 6 months	396 (42.6)	717 (39.6)	1.22 (1.02, 1.45)	1.41 (1.13, 1.75)	-
Exposed to non-4C in the previous 6 months	275 (29.6)	544 (30.1)	1.11(0.92, 1.36)	-	1.86 (1.33, 2.59)
Exposed to 4C in the previous 6 months	121 (13.0)	173 (9.6)	1.50 (1.15, 1.97)	-	1.29 (1.02, 1.63)
Age	79 (70-86)	80 (72-86)	-	-	-
Female	536 (57.6)	1086 (60.0)	-	-	-
SIMD 1: most deprived	237 (25.6)	445 (24.7)	1	1	1
SIMD 2	223 (24.1)	386 (21.4)	1.07 (0.82, 1.39)	1.06 (0.79, 1.42)	1.05 (0.78, 1.41)
SIMD 3	159 (17.2)	348 (19.3)	0.82 (0.62, 1.10)	0.81 (0.60, 1.11)	0.81 (0.59, 1.11)
SIMD 4	156 (16.9)	324 (18.0)	0.86 (0.65, 1.15)	0.94 (0.68, 1.29)	0.94 (0.68, 1.29)
SIMD 5: least deprived	150 (16.2)	297 (16.5)	0.97 (0.72, 1.31)	1.08 (0.77, 1.52)	1.07 (0.76, 1.51)
Unknown	5	10	-	-	-
Charlson score 0	375 (40.3)	775 (42.8)	1	1	1
Charlson score 1	156(16.8)	266 (14.7)	1.32 (1.02, 1.72)	1.20 (0.90, 1.61)	1.21 (0.90, 1.62)
Charlson score 2	110 (11.8)	210 (11.6)	1.15 (0.86, 1.54)	1.18 (0.86, 1.63)	1.16 (0.84, 1.6)0
Charlson score 3	52 (5.6)	81 (4.5)	1.46 (0.98, 2.17)	1.28 (0.82, 2.01)	1.28 (0.82, 2.01)
Charlson score 4+	46 (5.0)	50 (2.8)	2.25 (1.42, 3.55)	2.72 (1.63, 4.53)	2.71 (1.62, 4.52)
Charlson score Unknown[b]	191 (20.5)	428 (23.7)	0.93 (0.74, 1.18)	1.06 (0.79, 1.41)	1.05 (0.79, 1.41)
Admission speciality: general medicine	467 (50.2)	921 (50.9)	1	1	1
Admission speciality: geriatric medicine	67 (7.2)	123 (6.8)	1.22 (0.84, 1.77)	1.20 (0.79, 1.82)	1.20 (0.79, 1.83)
Admission speciality: surgery	298 (32.0)	547(30.2)	1.06 (0.87, 1.30)	1.14 (0.90, 1.44)	1.15 (0.91, 1.45)
Admission speciality: other[c]	98 (10.5)	219 (12.1)	0.85 (0.62, 1.15)	0.86 (0.61, 1.2)	0.86 (0.61, 1.21)
Any hospital admission in previous year, No	517 (55.6)	1103 (60.9)	1	1	1
Any hospital admission in previous year, Yes	413 (44.4)	707 (39.1)	1.26 (1.06, 1.49)	1.30 (1.04, 1.62)	1.28 (1.03, 1.60)

Number items dispensed in previous year[d]	65.5 (31-114.8)	51 (27.3-86)	1.01 (1.01, 1.01)	1.01 (1.01, 1.02)	1.01 (1.01, 1.02)
Number different items dispensed in previous year[d]	12 (8-18)	12 (8-17)	1.01 (0.9993, 1.02)	0.92 (0.90, 0.94)	0.91 (0.89, 0.93)
Length of inpatient stay before the date of CDI[d]	17 (8-34)	14 (6-30)	1.11 (1.08, 1.14)	1.11 (1.08, 1.15)	1.12 (1.08, 1.15)
Care home residence, No	752 (80.9)	1381 (76.3)	1	1	1
Care home residence, Yes	178 (19.1)	429 (23.7)	0.75 (0.59, 0.94)	0.65 (0.50, 0.83)	0.65 (0.50, 0.84)
PPI exposure, No	516 (55.5)	1032 (57.0)	1	1	1
PPI exposure, Yes	414 (44.5)	778 (43.0)	1.09 (0.91, 1.29)	0.94 (0.76, 1.16)	0.95 (0.77, 1.18)
H2 exposure, No	871 (93.7)	1707 (94.3)	1	1	1
H2 exposure, Yes	59 (6.3)	103 (5.7)	1.20 (0.85, 1.70)	1.00 (0.67, 1.49)	1.01 (0.68, 1.51)

458 [a]IQR means inter quartile range. [b]Charlson score is unknown means that the patient has not been admitted to hospital in the 5 years before the current admission date. [c]other include: Acute medicine, Cardiology,
459 Infectious disease, Dermatology, Gastroenterology, Renal medicine, Neurology, Respiratory medicine, Rheumatology, Accident and emergency, Ear nose and throat, Ophthalmology, Urology, GP other than
460 obstetrics. [d]Odds ratio for continuous variables are for every unit increase.

461 **Table II: Subset analysis for those hospitalised less than one week - multivariate odds ratios**
462 **of prior 4C exposure and potential confounding variables for HA-CDI vs. controls (221 cases**
463 **and 559 controls).**
464

	Adjusted 4C OR (95% CI)
Exposed to antibiotics in the previous 6 months, No	1
Exposed to 4C in the previous 6 months	2.43 (0.998, 5.94)
Exposed to non-4C in the previous 6 months, Yes	1.11 (0.61, 1.99)
SIMD 1: most deprived	1
SIMD 2	1.28 (0.64, 2.56)
SIMD 3	0.97 (0.47, 2.00)
SIMD 4	1.54 (0.67, 3.52)
SIMD 5: least deprived	0.97 (0.41, 2.31)
Charlson score 0	1
Charlson score 1	1.09 (0.49, 2.45)
Charlson score 2	0.80 (0.35, 1.08)
Charlson score 3	1.88 (0.51, 6.89)
Charlson score 4+	9.47 (1.89, 47.56)
Charlson score Unknown	0.47 (0.23, 0.99)
Admission speciality: general medicine	1
Admission speciality: geriatric medicine	1.56 (0.45, 5.43)
Admission speciality: surgery	0.33 (0.14, 0.80)
Admission speciality: other	0.65 (0.35, 1.21)
Any hospital admission in previous year, No	1
Any hospital admission in previous year, Yes	1.21 (0.72, 2.06)
Number items dispensed in previous year	1.01 (1.01, 1.02)
Number different items dispensed in previous year	0.92 (0.86, 0.98)
Length of inpatient stay before the date of CDI	1.73 (1.49, 2.00)
Care home residence, No	1
Care home residence, Yes	1.11 (0.57, 2.19)
PPI exposure, No	1
PPI exposure, Yes	1.03 (0.62, 1.73)
H2 exposure, No	1
H2 exposure, Yes	0.98 (0.41, 2.33)

465

Table III: The effect of cumulative exposure in a six month period on the adjusted odds of HA-CDI.

Cumulative antimicrobial exposure	Cases (n=930) N (%)	Controls (n=1810) N (%)	Adjusted[a] OR (95% CI)	Global P value
no antimicrobials	534 (57.4)	1093 (60.4)	1	0.0006[b]
1-7 DDDs	96 (10.3)	213 (11.8)	1.31 (0.95, 1.79)	
8-14 DDDs	100 (10.8)	208 (11.5)	1.40 (1.03, 1.92)	
15-28 DDDs	80 (8.6)	163 (9.0)	1.21 (0.85, 1.72)	
29+ DDDs	120 (12.9)	132 (7.3)	1.90 (1.31, 2.74)	
NA[c]	0	1		
Cumulative 4C exposure				
no antimicrobials	534 (57.4)	1093 (60.4)	1	0.006[d]
1-7 DDDs	48 (5.2)	89 (4.9)	1.76 (1.14, 2.73)	
8-14 DDDs	29 (3.1)	41 (2.3)	2.16 (1.19, 3.91)	
15-28 DDDs	21 (2.3)	26 (1.4)	1.94 (0.93, 4.03)	
29+ DDDs	23 (2.5)	16 (0.9)	1.63 (0.69, 3.84)	
Only non-4C	275 (29.6)	545 (30.1)	1.29 (1.02, 1.63)	

[a]Models are adjusted for SIMD, Charlson score, speciality for the index admission, any hospitalisation in the previous year (y/n), total number of prescriptions in the previous year, total number of different prescriptions, days since the index admission until CDI, care home residence, PPI H2 exposure. [b]Linear p value (trend test). [c]To calculate DDD exposure both quantity and a scaling factor representing the recommended daily dose are required. For one observations either or both of these were missing for the antimicrobial exposure variable. The observation are excluded from the analysis. [d]global p value, not trend test p value (trend test was not possible as "Only non-4C" making the levels not ordered).

Table IV: Distribution of temporal antimicrobial exposure and the adjusted odds of HA-CDI.

Most recent exposure in previous 6 months (any antimicrobial)	Cases (n=930) N (%)	Controls (n=1810) N (%)	Adjusted[a] OR (95% CI)	Global P value
no antimicrobials	534 (57.4)	1093 (60.4)	1	0.5[b]
<=30 days	94 (10.1)	120 (6.6)	2.17 (1.53, 3.07)	
31-90 days	126 (13.5)	191 (10.6)	1.75 (1.27, 2.41)	
91+ days	176 (18.9)	406 (22.4)	0.97 (0.74, 1.28)	
Most recent exposure in previous 6 months (4C)				
no antimicrobials	534 (57.4)	1093 (60.4)	1	0.003[c]
<=30 days	45 (4.8)	51 2.8)	2.24 (1.32, 3.78)	
31-90 days	39 (4.2)	44 (2.4)	2.47 (1.42, 4.32)	
91+ days	37 (4.0)	77 (4.3)	1.27 (0.76, 2.12)	
Only non-4C	275 (29.6)	545 (30.1)	1.29 (1.02, 1.63)	

[a]Models are adjusted for SIMD, Charlson score, speciality for the index admission, any hospitalisation in the previous year (y/n), total number of prescriptions in the previous year, total number of different prescriptions, days since the index admission until CDI, care home residence, PPI H2 exposure. [b]Linear p value (trend test). [c]global p value, not trend test p value (trend test was not possible as "Only non-4C" making the levels not ordered).

Table V: Adjusted odds of HA-CDI associated with community prescribing of antimicrobials (Baseline) and assessment of the potential unmeasured confounder.

hospital prescribing ratio: P0/P1[b]	Any antimicrobial Adjusted[a] OR of community prescribing (95% CI)				
	OR[c]=1.3	OR[c]=1.6	OR[c]=1.9	OR[c]=4	OR[c]=6
33/33 (baseline)	1.41 (1.13, 1.75)	1.41 (1.13, 1.75)	1.41 (1.13, 1.75)	1.41 (1.13, 1.75)	1.41 (1.13, 1.75)
31/35	1.39 (1.12, 1.73)	1.38 (1.11, 1.71)	1.37 (1.10, 1.70)	1.32 (1.07, 1.64)	1.30 (1.05, 1.62)
29/37	1.38 (1.11, 1.71)	1.35 (1.09, 1.68)	1.33 (1.07, 1.65)	1.25 (1.00, 1.55)	1.21 (0.97, 1.50)
27/39	1.36 (1.10, 1.69)	1.32 (1.07, 1.64)	1.29 (1.04, 1.61)	1.17 (0.95, 1.46)	1.12 (0.90, 1.39)
25/41	1.35 (1.08, 1.67)	1.30 (1.05, 1.61)	1.26 (1.01, 1.56)	1.10 (0.89, 1.37)	1.04 (0.84, 1.29)
23/43	1.33 (1.07, 1.65)	1.27 (1.02, 1.58)	1.22 (0.99, 1.52)	1.04 (0.84, 1.29)	0.96 (0.77, 1.19)
21/45	1.32 (1.06, 1.64)	1.25 (1.00, 1.55)	1.19 (0.96, 1.48)	0.98 (0.79, 1.21)	0.89 (0.71, 1.10)
19/47	1.30 (1.05, 1.62)	1.22 (0.98, 1.52)	1.16 (0.93, 1.44)	0.92 (0.74, 1.14)	0.82 (0.66, 1.02)
	4C Adjusted[a] OR of community prescribing (95% CI)				
	OR[c]=1.3	OR[c]=1.6	OR[c]=1.9	OR[c]=4	OR[c]=6
33/33 (baseline)	1.86 (1.33, 2.59)	1.86 (1.33, 2.59)	1.86 (1.33, 2.59)	1.86 (1.33, 2.59)	1.86 (1.33, 2.59)
31/35	1.83 (1.31, 2.57)	1.82 (1.30, 2.54)	1.80 (1.29, 2.52)	1.75 (1.25, 2.44)	1.72 (1.23, 2.41)
29/37	1.82 (1.30, 2.54)	1.78 (1.27, 2.49)	1.75 (1.25, 2.45)	1.64 (1.18, 2.30)	1.59 (1.14, 2.23)
27/39	1.80 (1.28, 2.51)	1.75 (1.25, 2.44)	1.71 (1.22, 2.39)	1.55 (1.11, 2.16)	1.48 (1.06, 2.07)
25/41	1.78 (1.27, 2.48)	1.71 (1.22, 2.39)	1.66 (1.19, 2.32)	1.46 (1.04, 2.04)	1.37 (0.98, 1.91)
23/43	1.76 (1.26, 2.46)	1.68 (1.20, 2.35)	1.61 (1.15, 2.26)	1.37 (0.98, 1.91)	1.27 (0.91, 1.77)
21/45	1.74 (1.24, 2.43)	1.64 (1.18, 2.30)	1.57 (1.12, 2.20)	1.29 (0.92, 1.80)	1.17 (0.84, 1.64)
19/47	1.72 (1.23, 2.40)	1.61 (1.15, 2.25)	1.53 (1.09, 2.13)	1.21 (0.86, 1.69)	1.08 (0.77, 1.51)

[a]Models are adjusted for SIMD, Charlson score, speciality for the index admission, any hospitalisation in the previous year (y/n), number of prescriptions in the previous year, number of different prescriptions in the previous year, days since the index admission until CDI, care home residence (y/n), PPI exposure (y/n) and H2 exposure (y/n) in the previous 6 months and unmeasured hospital prescribing. [b]P0: the prevalence of hospital antimicrobial prescribing in those who had not been given antimicrobials in the community; P1: the prevalence of hospital antimicrobial prescribing in those who have been prescribed antimicrobials in the community. [c]OR: assumed OR of hospital prescribing.

Table A1: Sensitivity analysis - adjusted odds of HA-CDI associated with community prescribing of antimicrobials (Baseline) and assessment of the potential unmeasured confounder with different assumption of hospital antimicrobial prescribing rate (25%, 50%, 75%).

Overall hospital prescribing rate	hospital prescribing ratio: P0/P1[b]	Difference between P0 and P1	Any antimicrobial Adjusted[a] OR of community prescribing (95% CI)				
			OR[c]=1.3	OR[c]=1.6	OR[c]=1.9	OR[c]=4	OR[c]=6
	baseline[d]	0	1.41 (1.13, 1.75)	1.41 (1.13, 1.75)	1.41 (1.13, 1.75)	1.41 (1.13, 1.75)	1.41 (1.13, 1.75)
33%	31/35	4	1.39 (1.12, 1.73)	1.38 (1.11, 1.71)	1.37 (1.10, 1.70)	1.32 (1.07, 1.64)	1.30 (1.05, 1.62)
25%	23/27	4	1.39 (1.12, 1.73)	1.38 (1.11, 1.71)	1.37 (1.10, 1.70)	1.31 (1.06, 1.63)	1.29 (1.04, 1.60)
50%	48/52	4	1.39 (1.12, 1.73)	1.38 (1.11, 1.71)	1.37 (1.11, 1.70)	1.34 (1.08, 1.66)	1.33 (1.07, 1.65)
75%	73/77	4	1.39 (1.12, 1.73)	1.38 (1.11, 1.72)	1.38 (1.11, 1.71)	1.36 (1.09, 1.68)	1.35 (1.09, 1.67)
33%	25/41	14	1.35 (1.08, 1.67)	1.30 (1.05, 1.61)	1.26 (1.01, 1.56)	1.10 (0.89, 1.37)	1.04 (0.84, 1.29)
25%	17/33	14	1.35 (1.08, 1.67)	1.29 (1.04, 1.61)	1.25 (1.01, 1.55)	1.07 (0.86, 1.32)	0.98 (0.79, 1.22)
50%	42/58	14	1.35 (1.09, 1.67)	1.31 (1.05, 1.62)	1.27 (1.03, 1.58)	1.16 (0.93, 1.44)	1.12 (0.90, 1.39)
75%	67/83	14	1.35 (1.09, 1.68)	1.32 (1.06, 1.63)	1.29 (1.04, 1.60)	1.21 (0.98, 1.51)	1.19 (0.96, 1.47)
33%	19/47	28	1.30 (1.05, 1.62)	1.22 (0.98, 1.52)	1.16 (0.93, 1.44)	0.92 (0.74, 1.14)	0.82 (0.66, 1.02)
25%	11/39	28	1.30 (1.05, 1.61)	1.22 (0.98, 1.51)	1.14 (0.92, 1.42)	0.86 (0.69, 1.07)	0.74 (0.60, 0.92)
50%	36/64	28	1.31 (1.05, 1.62)	1.24 (1.00, 1.53)	1.18 (0.95, 1.47)	1.00 (0.81, 1.24)	0.94 (0.76, 1.16)
75%	61/89	28	1.31 (1.06, 1.63)	1.25 (1.01, 1.55)	1.21 (0.97, 1.50)	1.08 (0.87, 1.35)	1.05 (0.84, 1.30)
Overall hospital prescribing rate	hospital prescribing ratio: P0/P1[b]	Difference between P0 and P1	4C antimicrobial Adjusted[a] OR of community prescribing (95% CI)				
			OR[c]=1.3	OR[c]=1.6	OR[c]=1.9	OR[c]=4	OR[c]=6
	baseline[d]	0	1.86 (1.33, 2.59)	1.86 (1.33, 2.59)	1.86 (1.33, 2.59)	1.86 (1.33, 2.59)	1.86 (1.33, 2.59)
33%	31/35	4	1.83 (1.31, 2.57)	1.82 (1.30, 2.54)	1.80 (1.29, 2.52)	1.75 (1.25, 2.44)	1.72 (1.23, 2.41)
25%	23/27	4	1.83 (1.31, 2.57)	1.82 (1.30, 2.54)	1.80 (1.29, 2.52)	1.73 (1.24, 2.42)	1.70 (1.21, 2.37)
50%	48/52	4	1.84 (1.31, 2.57)	1.82 (1.30, 2.55)	1.81 (1.29, 2.53)	1.77 (1.26, 2.47)	1.75 (1.25, 2.45)
75%	73/77	4	1.84 (1.31, 2.57)	1.82 (1.30, 2.55)	1.82 (1.30, 2.54)	1.79 (1.28, 2.50)	1.78 (1.27, 2.49)
33%	25/41	14	1.78 (1.27, 2.48)	1.71 (1.22, 2.39)	1.66 (1.19, 2.32)	1.46 (1.04, 2.04)	1.37 (0.98, 1.91)
25%	17/33	14	1.77 (1.27, 2.48)	1.71 (1.22, 2.39)	1.65 (1.18, 2.31)	1.41 (1.01, 1.97)	1.30 (0.93, 1.81)
50%	42/58	14	1.78 (1.27, 2.49)	1.72 (1.23, 2.41)	1.68 (1.20, 2.35)	1.53 (1.09, 2.14)	1.47 (1.05, 2.06)
75%	67/83	14	1.78 (1.28, 2.49)	1.74 (1.24, 2.43)	1.70 (1.22, 2.38)	1.60 (1.14, 2.24)	1.57 (1.12, 2.19)
33%	19/47	28	1.72 (1.23, 2.40)	1.61 (1.15, 2.25)	1.53 (1.09, 2.13)	1.21 (0.86, 1.69)	1.08 (0.77, 1.51)
25%	11/39	28	1.72 (1.23, 2.40)	1.60 (1.15, 2.24)	1.51 (1.08, 2.11)	1.14 (0.81, 1.59)	0.97 (0.70, 1.36)
50%	36/64	28	1.72 (1.23, 2.41)	1.63 (1.17, 2.28)	1.56 (1.11, 2.18)	1.32 (0.95, 1.85)	1.24 (0.88, 1.73)
75%	61/89	28	1.73 (1.24, 2.42)	1.65 (1.18, 2.31)	1.60 (1.14, 2.23)	1.43 (1.02, 2.00)	1.38 (0.99, 1.93)

[a]Models are adjusted for SIMD, Charlson score, speciality for the index admission, any hospitalisation in the previous year (y/n), number of prescriptions in the previous year, number of different prescriptions in the previous year, days since the index admission until CDI, care home residence (y/n), PPI exposure (y/n) and H2 exposure (y/n) in the previous 6 months and unmeasured hospital prescribing. [b]P0: the prevalence of hospital antimicrobial prescribing in those who had not been given antimicrobials in the community; P1: the prevalence of hospital antimicrobial prescribing in those who have been prescribed antimicrobials in the community. [c]OR: assumed OR of hospital prescribing. [d]baseline OR are the same for different overall hospital antimicrobial prescribing rate (33%, 25%, 50%, 75%) as long as P0=P1.