Association between urinary community-acquired fluoroquinolone-resistant *Escherichia coli* and neighbourhood antibiotic consumption: a population-based case-control study

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Summary

Background **It is unknown whether increased use of antibiotics in a community increases the risk of acquiring antibiotic resistance by individuals living in that community, regardless of prior individual antibiotic consumption and other risk factors for antibiotic resistance.**

Methods **We used a hierarchical multivariate logistic regression approach to evaluate the association between neighbourhood fluoroquinolone consumption and individual risk of colonisation or infection of the urinary tract with fluoroquinolone-resistant *Escherichia coli*. We did a population-based case-control study of adults (aged ≥22 years) living in 1733 predefined geographical statistical areas (neighbourhoods) in Israel. A multilevel study design was used to analyse data derived from electronic medical records of patients enrolled in the Clalit state-mandated health service.**

Findings **300 105 events with *E coli* growth and 1 899 168 cultures with no growth were identified from medical records and included in the analysis. 45 427 (16·8%) of 270 190 women and 8835 (29·5%) of 29 915 men had fluoroquinolone-resistant *E coli* events. We found an independent association between residence in a neighbourhood with higher antibiotic consumption and an increased risk of bacteriuria caused by fluoroquinolone-resistant *E coli*. Odds ratios (ORs) for the quintiles with higher neighbourhood consumption (compared with the lowest quintile) were 1·15 (95% CI 1·06–1·24), 1·31 (1·20–1·43), 1·41 (1·29–1·54), and 1·51 (1·38–1·65) for women, and 1·17 (1·02–1·35), 1·24 (1·06–1·45), 1·35 (1·15–1·59), and 1·50 (1·26–1·77) for men. Results remained significant when the analysis was restricted to patients who had not consumed fluoroquinolones themselves.**

Interpretation **These data suggest that increased use of antibiotics in specific geographical areas is associated with an increased personal risk of acquiring antibiotic-resistant bacteria, independent of personal history of antibiotic consumption and other known risk factors for antimicrobial resistance.**

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Introduction

Urinary tract infections are common, both in the community and among hospitalised patients, and are often caused by antibiotic-resistant bacteria.[1,2] The development and spread of antibiotic resistance is complex and incompletely understood.[3] Although many studies have shown a correlation between the use of antibiotics and the selection for resistant bacteria, it is unknown how much of this selection depends on ecological or individual characteristics.[4–7]

Most of what is known about the transmission of antibiotic-resistant uropathogens derives from hospital, rather than community, settings.[8–10] The association between community consumption of antibiotics and the risk of antibiotic-resistant infection in patients who have not been treated with such antibiotics has not been rigorously assessed. Previous research, analysing both individual-level and practice-level prescribing, found fluoroquinolone resistance among *Escherichia coli* (FQ-R *E coli*) to be strongly associated with recent personal use of antibiotics but not with practice-level antibiotic consumption. This study, however, was limited by its small sample.[11,12]

The availability of comprehensive digital-data infrastructures offers new opportunities to investigate the development of antimicrobial resistance spread.[13–15] We examined how community-level fluoroquinolone consumption affects the likelihood of acquiring FQ-R *E coli*, after controlling for personal antibiotic consumption and other known risk factors for infections caused by drug-resistant bacteria.

Methods

Study design and population

We did a population-based case-control study aimed at assessing the association between neighbourhood fluoroquinolone consumption and the probability of having FQ-R *E coli* in urine cultures. The research was conducted among adult members of Clalit Health Services (CHS), the largest state-mandated health service organisation in Israel, in the years 2010–14. CHS is an integrated payer–provider system with an extensive network of

Research in context

Evidence before this study
The dissemination of antimicrobial resistance in the community is a serious global problem and has both individual and environmental determinants. To understand such resistance and its spread, we must factor into the analysis both accurate measures of individual-level associations and aggregate environmental measures, such as neighbourhood antimicrobial consumption. Past research into antibiotic use in outpatient clinics has proven that patients who are treated with antibiotics are at an increased risk of being colonised or infected with resistant pathogens. We searched PubMed using the search terms "antibiotic resistance" and "multilevel" up until July 25, 2018. We identified one methodological paper followed by a prospective study focusing on both the individual and practice level, which showed that personal fluoroquinolone consumption is strongly associated with individual future risk of harbouring fluoroquinolone-resistant pathogens. However, an association between practice-level prescribing and drug resistance in the community could not be demonstrated, probably owing to a small sample size or unclear definitions of geographical clusters.

Added value of this study
We did a nationwide retrospective cohort study of 2·4 million adult members of a health provider in Israel, living in 1733 geographically delineated statistical areas. We used a hierarchical, multivariate, logistic regression approach to evaluate the association between neighbourhood fluoroquinolone consumption and the individual risk of being colonised or infected with fluoroquinolone-resistant *Escherichia coli*. In this study, we found a significant dose–response relationship between residence in a neighbourhood with higher fluoroquinolone consumption and an increased risk of bacteriuria caused by fluoroquinolone-resistant *E coli*. The odds ratios in the study, although small for the individual, suggest a substantial contribution of community fluoroquinolone consumption to the overall spread of antimicrobial resistance at the population level. Our study is the first such study to demonstrate this important finding.

Implications of all the available evidence
These data suggest that living in specific geographical areas with increased use of fluoroquinolone antibiotics is associated with an increased personal risk of acquiring fluoroquinolone-resistant bacteria, independent of personal history of fluoroquinolone consumption and other known risk factors for antimicrobial resistance. These findings are a strong reminder that antimicrobial resistance is a public health issue that is not limited to antimicrobial use in the individual patient and reinforces the need for effective individual and community antimicrobial stewardship initiatives.

	Value
Total number of GSAs	1733
Total number of towns or villages	216
Total Israeli population living in the GSAs included (% of Israeli population)	6 878 862 (83%)
Median population number, all ages by GSA	4112 (3471)
Population density by GSA (1000 people/1 km²)	8·6 (3·6–13·6)
Proportion of people insured by CHS by GSA	46% (18%)
Fluoroquinolone consumption by GSA (DDD per 1000 people in year before event)	1·51 (0·7)
Escherichia coli fluoroquinolone resistance rate by GSA (men and women)	18% (9%)

Numbers are mean (SD) or median (IQR), unless stated otherwise. GSA=geographical statistical area. DDD=defined daily dose.

***Table 1*: Overview of neighbourhood characteristics, by GSA**

14 hospitals and more than 1400 primary and specialised clinics geographically dispersed across the entire country. In Israel, every citizen is covered by a compulsory health-care system based on four service providers. CHS covers 53% of the total population. CHS members are of all ages, ethnic groups, and socioeconomic backgrounds, and are generally representative of the entire Israeli population.[16] We excluded towns and villages with fewer than 3000 inhabitants, and geographical statistical areas (GSAs). with fewer than 60 CHS members. (The country is divided up into prespecified areas or neighbourhoods [GSAs], by the Central Bureau of Statistics.) We included the proportion of people insured by CHS for each neighbourhood as a potential confounding variable.

We excluded all samples from children younger than 18 years of age and from adults 18–21 years of age; the latter because a large proportion of them are enlisted in compulsory military service and do not receive medical care from CHS.

We excluded patients residing in long-term care facilities (psychiatric and rehabilitation centres) as well as hospital-related samples. The latter were identified by cross-referencing the date of each sample with administrative hospitalisation files, excluding any sample taken during or within 30 days of hospital discharge. We excluded pregnant women and patients undergoing dialysis, patients who had undergone radiotherapy or chemotherapy for cancer, organ transplant recipients, or patients who had taken immunosuppressant or antineoplastic medication during the year preceding an event.

Data were collected from CHS's clinical and administrative data warehouse. Anonymous patient data were compiled from electronic medical records, hospital discharge summaries, pharmacy prescriptions, and laboratory records. Patients' demographic data, including geographically coded data, were collected from the Israeli Central Bureau of Statistics and the Ministry of Internal Affairs. The CHS Helsinki ethical committee approved this retrospective study and waived the requirement for informed consent.

Procedures

We used a three-study framework case–case–control and case–control–control design with a multilevel analysis to compare individual-level and cluster-level patient characteristics. The research hypothesis was assessed by the most widely used case-control approach; and patients with FQ-R *E coli* were compared with controls having a urine culture containing fluoroquinolone-susceptible *E coli* (FQ-S *E coli*; study 1).

We used two additional pairs of comparisons for each sex to assess the magnitude of intrinsic bias related to the detection of resistant versus susceptible bacteria under antibiotic treatment.[17] In study 2, we compared patients with FQ-R *E coli* with controls having a sterile urine culture with no growth of any bacteria. In study 3 we compared patients with FQ-S *E coli* with patients having a sterile urine culture. Study 3 was used to identify determinants associated with FQ-S *E coli* urinary infection that are also expected to be part of the contributing factors to FQ-R *E coli* in study 2.

We searched the database for all urine-culture specimens sent from the community care clinics to CHS laboratories (appendix). We included in the analyses all isolates that had growth of *E coli*[18] and the sterile cultures, those with no pathogen growth. We included only *E coli* and excluded urine cultures with growth of non-*E coli* pathogens or cultures with polymicrobial growth.

See Online for appendix

As this study was aimed to assess the mechanism of drug-resistance spread, we included cultures growing

	Women			Men		
	FQ-R *E coli*	FQ-S *E coli*	Sterile event	FQ-R *E coli*	FQ-S *E coli*	Sterile event
Number of events						
2 199 233	45 427	224 763	1 304 081	8835	21 080	595 047
Age* (years)						
22–40	5477 (12%)	77 131 (34%)	611 863 (47%)	399 (5%)	2603 (12%)	115 879 (19%)
41–65	6772 (15%)	51 811 (23%)	294 716 (23%)	1068 (12%)	5568 (26%)	155 853 (26%)
66–75	12 172 (27%)	48 500 (22%)	236 902 (18%)	2700 (31%)	7021 (33%)	196 859 (33%)
≥76	21 006 (46%)	47 321 (21%)	160 599 (12%)	4668 (53%)	5888 (28%)	126 456 (21%)
Nursing home*						
Yes	4278 (9%)	4165 (2%)	15 621 (1%)	928 (11%)	547 (3%)	8684 (1%)
No	41 149 (91%)	220 598 (98%)	1 288 460 (99%)	7907 (89%)	20 533 (97%)	586 363 (99%)
Ethnicity*						
Orthodox Jewish	1249 (3%)	10 240 (5%)	70 800 (5%)	241 (3%)	771 (4%)	20 617 (3%)
Arab	4267 (9%)	28 728 (13%)	255 986 (20%)	1362 (15%)	3588 (17%)	90 703 (15%)
Non-Orthodox Jewish	39 911 (88%)	185 795 (83%)	977 295 (75%)	7232 (82%)	16 721 (79%)	483 727 (81%)
Body-mass index (kg/m²)*						
Underweight <18·5	984 (2%)	7918 (4%)	45 488 (3%)	224 (3%)	275 (1%)	6395 (1%)
Normal 18·5–24·9	13 524 (30%)	87 293 (39%)	516 648 (40%)	2839 (32%)	5934 (28%)	179 525 (30%)
Overweight 24·9–29·9	15 559 (34%)	70 994 (32%)	405 668 (31%)	3506 (40%)	9142 (43%)	263 719 (44%)
Obese >29·90	15 360 (34%)	58 557 (26%)	336 276 (26%)	2266 (26%)	5730 (27%)	145 408 (24%)
Comorbidity score (JH ACG)*						
1–2 (most healthy)	2933 (6%)	24 216 (11%)	111 804 (9%)	534 (6%)	2267 (11%)	73 759 (12%)
3–4	23 811 (52%)	149 770 (67%)	962 953 (74%)	3687 (42%)	11 958 (57%)	349 798 (59%)
5–6 (least healthy)	18 683 (41%)	50 777 (23%)	229 324 (18%)	4614 (52%)	6855 (33%)	171 490 (29%)
Hospitalisations (n)*						
0	33 067 (73%)	195 565 (87%)	1 154 707 (89%)	4725 (53%)	16 644 (79%)	495 714 (83%)
1	7557 (17%)	21 519 (10%)	114 441 (9%)	2041 (23%)	2799 (13%)	69 265 (12%)
2–3	3917 (9%)	6725 (3%)	31 348 (2%)	1556 (18%)	1377 (7%)	26 448 (4%)
>4	886 (2%)	954 (0%)	3585 (0%)	513 (6%)	260 (1%)	3620 (1%)
Fluoroquinolone personal consumption (DDD year)*						
0	18 945 (42%)	180 643 (80%)	1 096 382 (84%)	3023 (34%)	16 129 (77%)	481 806 (81%)
0·1–5	4266 (9%)	12 256 (5%)	60 394 (5%)	586 (7%)	864 (4%)	26 865 (5%)
5·1–10	10 041 (22%)	20 059 (9%)	92 049 (7%)	1769 (20%)	2308 (11%)	47 627 (8%)
10·1–20	6716 (15%)	8256 (4%)	37 197 (3%)	1516 (17%)	1055 (5%)	23 546 (4%)
>20·1	5459 (12%)	3549 (2%)	18 059 (1%)	1941 (22%)	724 (3%)	15 203 (3%)

(Table 2 continues on next page)

	Women			Men		
	FQ-R *E coli*	FQ-S *E coli*	Sterile event	FQ-R *E coli*	FQ-S *E coli*	Sterile event
(Continued from previous page)						
Neighbourhood level characteristic (total=1733)						
Socioeconomic status*						
Low	9701 (21%)	57 438 (26%)	428 369 (33%)	2449 (28%)	6077 (29%)	162 253 (27%)
Medium–low	15 722 (35%)	76 229 (34%)	402 889 (31%)	2940 (33%)	7065 (34%)	202 275 (34%)
Medium–high	8955 (20%)	41 541 (18%)	217 858 (17%)	1628 (18%)	3783 (18%)	109 510 (18%)
High	11 049 (24%)	49 555 (22%)	254 965 (20%)	1818 (21%)	4155 (20%)	121 009 (20%)
Population density neighbourhood (1000 people per km²)†						
Mean (SD)	11·5 (8·0)‡	10·5 (7·8)	10·5 (8·2)	11 (8·2)§	9·8 (7·2)‡	10·7 (7·9)‡
Median (IQR)	9·5 (4·5–14·5)	8·5 (3·6–13·4)	8·4 (3·4–13·4)	8·8 (3·85–13·75)	8·1 (3·55–12·65)	8·6 (3·6–13·6)
Proportion covered by CHS (%)‡						
Mean (SD)	0·5 (0·2)	0·5 (0·2)	0·5 (0·2)	0·5 (0·2)	0·5 (0·2)	0·5 (0·2)
Median (IQR)	0·5 (0·4–0·6)	0·5 (0·4–0·6)	0·5 (0·35–0·65)	0·5 (0·4–0·6)	0·5 (0·4–0·6)	0·5 (0·4–0·6)
Study variable, fluoroquinolone consumption§ (DDD/1000 persons per day)						
Mean (SD)	1·7 (0·6)§	1·5 (0·6)	1·4 (0·6)	1·6 (0·6)§	1·5 (0·6)	1·5 (0·6)
Median (IQR)	1·6 (1·15–2·05)	1·4 (0·95–1·85)	1·3 (0·85–1·75)	1·6 (1·15–2·05)	1·4 (1–1·8)	1·4 (0·95–1·85)

Numbers are n (%), mean (SD), or Median (IQR). DDD=defined daily dose. FQ-R=fluoroquinolone resistant. FQ-S=fluoroquinolone susceptible. *E coli=Escherichia coli*. JH ACG=Johns Hopkins adjusted clinical group. *Individual-level variables tested by χ^2 tests: all comparisons were statistically significant p<0·001. †Group variables Kruskal-Wallis test by 3 groups. ‡One-way ANOVA by three groups. §Significant p<0·0001.

Table 2: **Characteristics of the study population**

	Study 1 (FQ-R *E coli*–FQ-S *E coli*) OR (95% CI)	Study 2 (FQ-R *E coli* –SEv) OR (95% CI)	Study 3 (FQ-S *E coli*–SEv) OR (95% CI)
Age (years)			
22–40	1	1	1
41–65	1·51 (1·42–1·60)	1·89 (1·79–1·99)	1·39 (1·36–1·43)
66–75	2·30 (2·17–2·44)	3·38 (3·20–3·56)	1·52 (1·48–1·56)
>75	3·50 (3·31–3·71)	6·91 (6·55–7·30)	2·07 (2·01–2·13)
Nursing home			
Yes	1	1	1
No	0·33 (0·30–0·36)	0·32 (0·29–0·34)	0·97 (0·90–1·05)
Ethnicity group			
Non-Orthodox Jewish	1	1	1
Arab	1·39 (1·25–1·54)	0·90 (0·82–0·99)	0·66 (0·62–0·69)
Orthodox Jewish	0·93 (0·83–1·04)	0·95 (0·85–1·05)	0·95 (0·90–1·01)
Socioeconomic status			
High	1	1	1
Medium–high	1·07 (0·99–1·15)	0·99 (0·92–1·06)	0·99 (0·95–1·04)
Medium–low	1·07 (1·00–1·14)	0·95 (0·89–1·01)	0·95 (0·92–0·99)
Low	1·10 (1·01–1·21)	0·88 (0·81–0·96)	0·82 (0·78–0·86)
Body-mass index (kg/m²)			
Normal 18·5–24·9	1	1	1
Underweight <18·5	1·06 (0·95–1·18)	1·17 (1·06–1·3)	1·14 (1·09–1·20)
Overweight 25–29·9	1·00 (0·96–1·05)	0·98 (0·94–1·01)	0·90 (0·88–0·92)
Obese >29·9	1·13 (1·08–1·18)	1·09 (1·04–1·13)	0·86 (0·84–0·88)
Comorbidity score (JH ACG)			
1–2 (most healthy)	1	1	1
3–4	0·94 (0·88–1·01)	0·73 (0·69–0·78)	0·67 (0·65–0·68)
5–6 (least healthy)	1·06 (0·98–1·13)	0·80 (0·75–0·86)	0·63 (0·61–0·66)

(Table 3 continues on next page)

more than 10^4 colony forming units per mL of *E coli*, regardless of clinical significance. Susceptibility patterns were established by the use of Vitek GN and AST-N098 cards and a Vitek II apparatus (bioMérieux, Marcy l'Étoile, France).

A community-acquired *E coli*-positive event, either fluoroquinolone-resistant or fluoroquinolone-susceptible, was defined when the following conditions were met: there was growth of *E coli*; more than 30 days had elapsed after any hospital admission; and the urine culture was the first recorded sample for that patient, or more than 30 days had elapsed after a prior event, or fewer than 30 days had elapsed after the previous isolation of *E coli* and the isolate had a different resistance profile.[19] A sterile event was defined as the first culture with no growth of any pathogen, and included all consecutive samples, until the end of a 30-day period during which no additional sterile samples were recorded.

Individual level covariates

Age at event was classified into four categories: 22–40 years, 41–65 years, 66–75 years, and more than 75 years, with the youngest age group as the reference category for the multivariate analysis. We classified a patient as living in a nursing home if the patient's treating doctor was registered as holding a nursing-home institutional position related to CHS. Ethnicity was classified into three categories: Arab, Orthodox Jewish, and non-Orthodox Jewish according to the predominant population served by the individual clinics where the patients received medical care. Body-mass index (BMI) was calculated in kg/m² from the last documented weight and height measurements obtained before an event. Where there was no documentation of weight or height, we used multiple imputation to complete BMI values. Morbidity burden was estimated with the Adjusted Clinical Groups case-mix system[20] and distributed into three categories.

Hospital admissions in all non-psychiatric hospitals during the 365 days before the positive event, which are proxy variables for possible unmeasured confounders, were recorded.

Fluoroquinolone purchases were recorded as defined daily dose (DDD) during the year preceding the event, according to the consensus definition of WHO.[21] Using the anatomic therapeutic chemical classification, we searched the CHS database for fluoroquinolones (J01M) dispensed at any pharmacy in Israel. Personal fluoroquinolone consumption was classified into five categories: 0, 0·1–5, 5·1–10, 10·1–20, and greater than or equal to 20·1 DDD.

Over-the-counter purchase of antibiotics is illegal in Israel and, to the best of our knowledge, nearly non-existent. The antibiotics dispensed by all pharmacies (private or CHS) are recorded in the central database. Pharmacy data were validated elsewhere with respect to clinically important outcomes.[22] To validate the purchase data, quantities, and actual clinical indication for prolonged antibiotic use, we asked five district pharmacist supervisors to review the cases of the top 200 antibiotic consumers in each district (roughly 1000 files). They searched the electronic medical records or contacted the patients' primary-care physicians to reveal the cause of the high antibiotic consumption. In 96% of the cases reviewed, there was a clear clinical indication for prolonged or repeated antibiotic administration.

Neighbourhood level covariates

Socioeconomic status (SES) was established on the basis of the SES score of the neighbourhood, as defined by the Israeli Central Bureau of Statistics, and classified into four categories (low, middle-low, middle-high, and high). Population density for each GSA was categorised into quintiles of 1000 people per 1 km², grouped as quintiles: 0–3, 4–7, 8–10, 11–15, and 16–60. To control for potential unmeasured differences in neighbourhoods with low versus high CHS coverage, we calculated the proportion of people insured by CHS in each specific GSA. This variable was classified into quartiles: greater than or equal to 0·62, 0·51–0·61, 0·39–0·50, and less than or equal to 0·38 and included in all analyses.

The exposure variable was defined as neighbourhood consumption of fluoroquinolones by GSA. GSAs were determined by size and number of inhabitants per neighbourhood by the Central Bureau of Statistics[23] (table 1; appendix). Fluoroquinolone consumption was calculated as the total amount of fluoroquinolones purchased by CHS members within 365 days before an event, in DDD per 1000 people living in a neighbourhood (DDD/1000 people per day). Consumption was computed for all 4·3 million people who were registered with CHS between 2010 and 2014. Fluoroquinolonue neighbourhood consumption was classified into quintiles: (0–0·87), (0·88–1·18), (1·19–1·51), (1·52–1·95), and (≥1·96 DDD). The lowest consumption group was used as the reference category for the multivariate analysis.

	Study 1 (FQ-R *E coli*–FQ-S *E coli*) OR (95% CI)	Study 2 (FQ-R *E coli* –SEv) OR (95% CI)	Study 3 (FQ-S *E coli*–SEv) OR (95% CI)
(Continued from previous page)			
Population density (neighbourhood) quintiles (1000 people per km²)			
0–3 low	1	1	1
4–7 medium–low	0·99 (0·91–1·07)	1·00 (0·93–1·08)	0·99 (0·94–1·04)
8–10 medium	1·04 (0·95–1·14)	1·02 (0·94–1·11)	0·94 (0·90–0·99)
11–15 medium–high	1·08 (0·99–1·18)	1·08 (1·00–1·17)	0·94 (0·90–0·99)
16–60 high	1·15 (1·06–1·26)	1·09 (1·00–1·18)	0·90 (0·86–0·95)
Proportion insured by CHS (neighbourhood) quartiles (%)			
≤0·38	1	1	1
0·39–0·50	1·09 (1·02–1·16)	1·05 (0·99–1·12)	0·99 (0·95–1·03)
0·51–0·61	1·10 (1·02–1·18)	1·12 (1·04–1·20)	1·09 (1·04–1·13)
≥0·62	1·10 (1·01–1·20)	1·11 (1·03–1·21)	1·06 (1·01–1·12)
Hospitalisations (n)			
0	1	1	1
1	1·28 (1·22–1·34)	1·29 (1·23–1·34)	0·97 (0·94–1·00)
2–3	1·70 (1·58–1·82)	1·73 (1·62–1·84)	0·99 (0·94–1·05)
≥4	2·34 (2·01–2·72)	2·85 (2·49–3·28)	0·85 (0·72–1·01)
Fluoroquinolone personal consumption (DDD)			
0	1	1	1
0·1–5	3·12 (2·95–3·30)	3·34 (3·17–3·52)	1·12 (1·08–1·17)
5·1–10	4·00 (3·83–4·17)	4·45 (4·27–4·63)	1·13 (1·09–1·16)
10·1–20	6·20 (5·87–6·55)	6·86 (6·53–7·20)	1·10(1·05–1·16)
≥20·1	11·21 (10·5–12·0)	10·2(9·61–10·8)	0·86 (0·80–0·93)
Fluoroquinolone neighbourhood consumption (DDD/1000 people per day) quintiles			
0–0·87	1	1	1
0·88–1·18	1·15 (1·06–1·24)	1·05 (0·98–1·14)	0·98 (0·94–1·01)
1·19–1·51	1·31 (1·20–1·43)	1·13 (1·04–1·23)	0·94 (0·90–0·98)
1·52–1·95	1·41 (1·29–1·54)	1·17 (1·08–1·28)	0·91 (0·87–0·95)
≥1·96	1·51 (1·38–1·65)	1·19 (1·09–1·30)	0·87 (0·83–0·91)
Clustering measures			
Random effect fluoroquinolone neighbourhood consumption	1·08 (1·04–1·14)	1·06 (1·02–1·24)	1·00 (1·00–71·38)
mOR	1·30 (1·02–1·44)	1·23 (1·02–1·33)	1·13 (1·01–1·19)
IOR80	1·00–2·66	0·81–1·74	0·68–1·09

JH ACG=Johns Hopkins adjusted clinical group. DDD=defined daily dose. FQ-R=fluoroquinolone resistant. FQ-S=fluoroquinolone susceptible. SEv=Sterile event. mOR=median odds ratio. IOR80=80% interval odds ratio. *E coli*=*Escherichia coli.*

***Table 3*: Multiple logistic regression analysis: female patients**

Statistical analysis

All analyses were performed separately for women and men. In the demographic comparisons, χ^2 tests were

	Study 1 (FQ-R *E coli*–FQ-S *E. coli*) OR (95% CI)	Study 2 (FQ-R *E coli*–SEv) OR (95% CI)	Study 3 (FQ-S *E coli*–SEv) OR (95% CI)
Age (years)			
22–40	1	1	1
41–65	1·14 (0·98–1·32)	1·69 (1·49–1·91)	1·60 (1·51–1·70)
66–75	2·06 (1·79–2·36)	2·94 (2·62–3·31)	1·64 (1·55–1·75)
≥75	3·52 (3·06–4·06)	6·33 (5·63–7·11)	2·01 (1·88–2·15)
Nursing home address			
Yes	1	1	1
No	0·26 (0·22–0·30)	0·22 (0·20–0·24)	0·80 (0·70–0·92)
Ethnicity group			
Non-Orthodox Jewish	1	1	1
Arab	1·39 (1·16–1·67)	1·35 (1·16–1·56)	0·97 (0·88–1·07)
Orthodox Jewish	0·87 (0·69–1·09)	0·95 (0·80–1·13)	1·16 (1·04–1·30)
Socioeconomic status			
High	1	1	1
Med–high	1·07 (0·93–1·23)	0·97 (0·87–1·10)	0·94 (0·87–1·01)
Med–low	0·99 (0·85–1·16)	0·98 (0·86–1·11)	0·98 (0·91–1·06)
Low	1·22 (1·03–1·45)	1·09 (0·95–1·26)	0·88 (0·81–0·97)
Body-mass index (kg/m²)			
Normal 18·5–24·9	1	1	1
Underweight <18·5	1·73 (1·37–2·18)	2·10 (1·78–2·47)	1·24 (1·05–1·46)
Overweight 25–29·9	0·81 (0·75–0·87)	0·79 (0·74–0·83)	1·00 (0·95–1·04)
Obese >29·9	0·86 (0·79–0·94)	0·94 (0·88–1·00)	1·12 (1·07–1·18)
Comorbidity score (JH ACG)			
1–2 (most healthy)	1	1	1
3–4	0·87 (0·77–0·99)	0·72 (0·65–0·80)	0·87 (0·82–0·92)
5–6 (least healthy)	0·97 (0·84–1·10)	0·77 (0·69–0·85)	0·82 (0·77–0·88)
Population density (neighbourhood) quintiles (1000 people per km²)			
0–3 low	1	1	1
4–7 med–low	1·12 (0·96–1·31)	1·08 (0·94–1·23)	0·93 (0·86–1·00)
8–10 med	1·20 (1·01–1·43)	1·10 (0·95–1·28)	0·94 (0·86–1·02)
11–15 med–high	1·15 (0·97–1·37)	1·07 (0·92–1·24)	0·93 (0·85–1·01)
16–60 high	1·41 (1·19–1·67)	1·15 (1·00–1·33)	0·83 (0·77–0·91)
Proportion insured by CHS (neighbourhood) quartiles (%)			
≤0·38	1	1	1
0·39–0·50	1·12 (0·98–1·28)	1·08 (0·97–1·21)	1·08 (1·01–1·16)
0·51–0·61	1·02 (0·88–1·19)	1·16 (1·02–1·32)	1·31 (1·21–1·41)
≥0·62	0·97 (0·82–1·15)	1·10 (0·95–1·26)	1·32 (1·22–1·44)
Hospitalisations (n)			
0	1	1	1
1	1·52 (1·40–1·65)	1·67 (1·58–1·77)	1·01 (0·96–1·07)
2–3	1·91 (1·73–2·11)	2·42 (2·25–2·59)	1·14 (1·05–1·23)
≥4	2·86 (2·37–3·44)	4·47 (3·95–5·05)	0·93 (0·74–1·17)
Fluoroquinolone personal consumption (DDD)			
0	1	1	1
0·1–5	3·33 (2·94–3·78)	2·83 (2·57–3·11)	0·87 (0·79–0·95)
5·1–10	3·81 (3·51–4·14)	4·45 (4·18–4·75)	1·24 (1·17–1·32)
10·1–20	6·94 (6·28–7·66)	7·25 (6·76–7·78)	1·01 (0·93–1·11)
≥20·1	12·84 (11·5–14·3)	13·48 (12·6–14·4)	0·93 (0·83–1·04)

(Table 4 continues on next page)

used to compare differences in proportions, and *t* tests to compare mean differences by group. Group variables were compared by use of either one-way ANOVAs for normally distributed parameters or Kruskal-Wallis tests for abnormally distributed parameters. All variables found to be significant on univariate analysis were included in the multivariate analysis.

A two-level hierarchical multilevel logistic regression analysis was used, with patients nested within neighbourhoods, to estimate the odds ratios (ORs) of patients having FQ-R *E coli* as a binary variable, adjusting for potential confounders at the individual (eg, personal use of fluoroquinolones) and at the neighbourhood level (eg, neighbourhood population density).[24]

The median odds ratio (mOR) and 80% interval OR (IOR80) are well demonstrated measures to quantifying cluster-level covariates for multilevel logistic regression in a meaningful way.[25] To assess the neighbourhood (GSA) variability related to the dependent variable (incidence of FQ-R *E coli*) between clusters, we calculated the mOR. The low bound of the mOR is equal to one, which indicates no difference between neighbourhoods in the probability of a patient having a urine culture with growth of FQ-R *E coli*. In addition, we used the neighbourhood fluoroquinolone consumption variance as either a fixed or random effect to calculate the IOR80, to check whether it accounted for a significant part of the FQ-R *E coli* variation between clusters. If the interval is narrow and does not contain unity, the residual variation between areas is small and indicates that the effect of the exposure is significant.[25] Cross-level and intra-level interactions were checked for significance.

Variables known to affect the risk of bacterial acquisition or of being infected with resistant bacteria were included as potential confounders in all comparisons. To estimate the chance of overfitting, we split our initial dataset of samples taken from female patients into separate training (50%) and test (50%) subsets. When we ran the final analysis in the test sample, the estimates remained similar to those for the training set; the final analyses contain all the data. Since there was a relatively small number of men we analysed the entire male sample.

To further separate the possible effects of personal-level versus neighbourhood-level consumption of fluoroquinolones, we did a post-hoc subgroup analysis of patients who had not used fluoroquinolone within 1 year of the index culture. Analyses were done using SPSS version 23. Results were considered significant when the p value was less than 0·05 in a two-sided test.

Role of the funding source

This study had no external funding. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

The research included data from 1733 GSAs (table 1). In these neighbourhoods live 6 878 862 inhabitants, 83% of the total Israeli population, 3 164 276 (46%) of whom are CHS members. Between January, 2010 and December, 2014, almost 5 million urine samples were collected in CHS laboratories (appendix). Of the 2 572 007 eligible adult events for analysis, 340 783 (13%) were positive for *E coli*, 2 133 283 (83%) had no bacterial growth (sterile), and 97 941 (4%) were positive for other bacteria. Of the 340 783 events with *E coli*, 300 105 (88%) were included in the final analysis; 40 678 (12%) were excluded because the patients were living in the excluded small towns or neighbourhoods. Of the 300 105 *E coli* bacteriuria events, 270 190 (90%) occurred in women. The number of FQ-R *E coli* events was 45 427 (16·8%) of 270 190 for female patients, and 8835 (29·5%) of 29 915 for male patients (table 2).

A large proportion of female patients with FQ-R *E coli* were in the oldest age group (>75 years) compared with patients with FQ-S *E coli* or with sterile urine cultures (table 2). Patients with FQ-R *E coli* events had a higher comorbidity score, a higher prevalence of nursing home residence, and a higher number of hospitalisations in the year before an index event.

Personal fluoroquinolone consumption was associated with resistance: among women with FQ-R *E coli* events, 58% had received fluoroquinolones in the year before the event; only 20% in the FQ-S *E coli* group and 16% in the sterile urine culture group had received fluoroquinolones in the year preceding the event. Prevalence of previous fluoroquinolone use among women and men was similar. Women with FQ-R *E coli* lived in neighbourhoods with higher (p<0·0001) population density, compared with the two other study groups. Findings for men were similar (table 2).

The mean fluoroquinolone consumption in the whole population was 1·51 DDD/1000 per day (SD 0·7; table 1). In the female FQ-R *E coli* group, the mean fluoroquinolone consumption by GSA was 1·7 DDD/1000 per day (SD 0·6), and the means for the other two groups were significantly lower (p<0·001 for each comparison). Among men, the mean fluoroquinolone consumption was 1·6 DDD/1000 per day (SD 0·6) in the FQ-R *E coli* and similarly higher (p<0·0001) compared with the other groups (table 2).

The personal-level variables entered in the final studies were age, nursing home residence, ethnicity, BMI, comorbidity score, number of hospitalisations in the previous year, and personal consumption of fluoroquinolones. The cluster-level variables included were SES, population density, proportion of people insured by CHS, and neighbourhood fluoroquinolone consumption in the previous year (tables 3, 4).

Personal consumption of fluoroquinolones was strongly associated in a dose–response manner with subsequent isolation of FQ-R *E coli* compared with FQ-S *E coli* for women and men (tables 3, 4). ORs were similar when we compared people with FQ-R *E coli* with those with a sterile urine culture (tables 3, 4).

	Study 1 (FQ-R *E coli*–FQ-S *E coli*) OR (95% CI)	Study 2 (FQ-R *E coli*–SEv) OR (95% CI)	Study 3 (FQ-S *E coli*–SEv) OR (95% CI)
(Continued from previous page)			
Fluoroquinolone neighbourhood consumption (DDD/1000 people per day) quintiles			
0–0·87	1	1	1
0·88–1·18	1·17 (1·02–1·35)	1·06 (0·94–1·18)	0·95 (0·88–1·02)
1·19–1·51	1·24 (1·06–1·45)	1·01 (0·89–1·15)	0·91 (0·84–0·98)
1·52–1·95	1·35 (1·15–1·59)	1·04 (0·92–1·19)	0·85 (0·78–0·92)
≥1·96	1·50 (1·26–1·77)	1·07 (0·94–1·23)	0·80 (0·74–0·87)
Clustering measures			
Random effect fluoroquinolone neighbourhood consumption	1·10 (1·03–1·36)	1·05 (1·02–1·09)	1·02 (1·01–1·03)
mOR	1·35 (1·02–1·53)	1·23 (1·02–1·33)	1·13 (1·01–1·19)
IOR80	0·85–2·64	0·73–1·57	0·68–1·1

DDD=defined daily dose. FQ-R=fluoroquinolone resistant. FQ-S=fluoroquinolone susceptible. *JH ACG=Johns Hopkins adjusted clinical group. SEv*=sterile event. mOR=median odds ratio. IOR80=80% interval odds ratio. *E coli=Escherichia coli.*

***Table 4*: Multiple logistic regression analysis: male patients**

At the cluster level, increasing neighbourhood fluoroquinolone consumption was associated with an increased risk of FQ-R versus FQ-S *E coli*, with similar associations among women and men (table 3). ORs for men were similar, with a dose–response relationship among women and men (figure A). Among women, ORs for growth of FQ-R *E coli* in a urine culture, as opposed to no growth at all, increased steadily with increasing neighbourhood consumption of fluoroquinolone (tables 3, 4; figure C). Finally, in study 3 comparing the risk of FQ-S *E coli* growth with a sterile urine culture, increasing neighbourhood fluoroquinolone consumption was associated with a decreased risk of growth (figure E).

There was a moderate cluster heterogeneity between neighbourhoods in the propensity for acquiring FQ-R *E coli* (study 1); mOR 1·30 (95% CI 1·02–1·44) among women and 1·35 (1·02–1·53) among men. The neighbourhood fluoroquinolone consumption accounted for a significant part of this variation between clusters among women: (IOR80 1·00–2·66), and less so among men (IOR80 0·85–2·64; tables 3, 4).

The cluster heterogeneity for acquiring FQ-S *E coli* (study 3) was weaker among women and men, mOR 1·13 (CI 1·01–1·19). In this comparison, fluoroquinolone consumption did not account for a significant part of the variation in IOR80 (0·68–1·09).

We did a post hoc subgroup analysis restricted to patients who were not treated with fluoroquinolone during the year preceding the taking of the index culture. ORs for the association between neighbourhood fluoroquinolone consumption and growth of FQ-R versus FQ-S *E coli* among women were 1·10 (95% CI 0·99–1·21), 1·31 (1·19–1·46), 1·38 (1·24–1·53), and 1·47 (1·33–1·65)

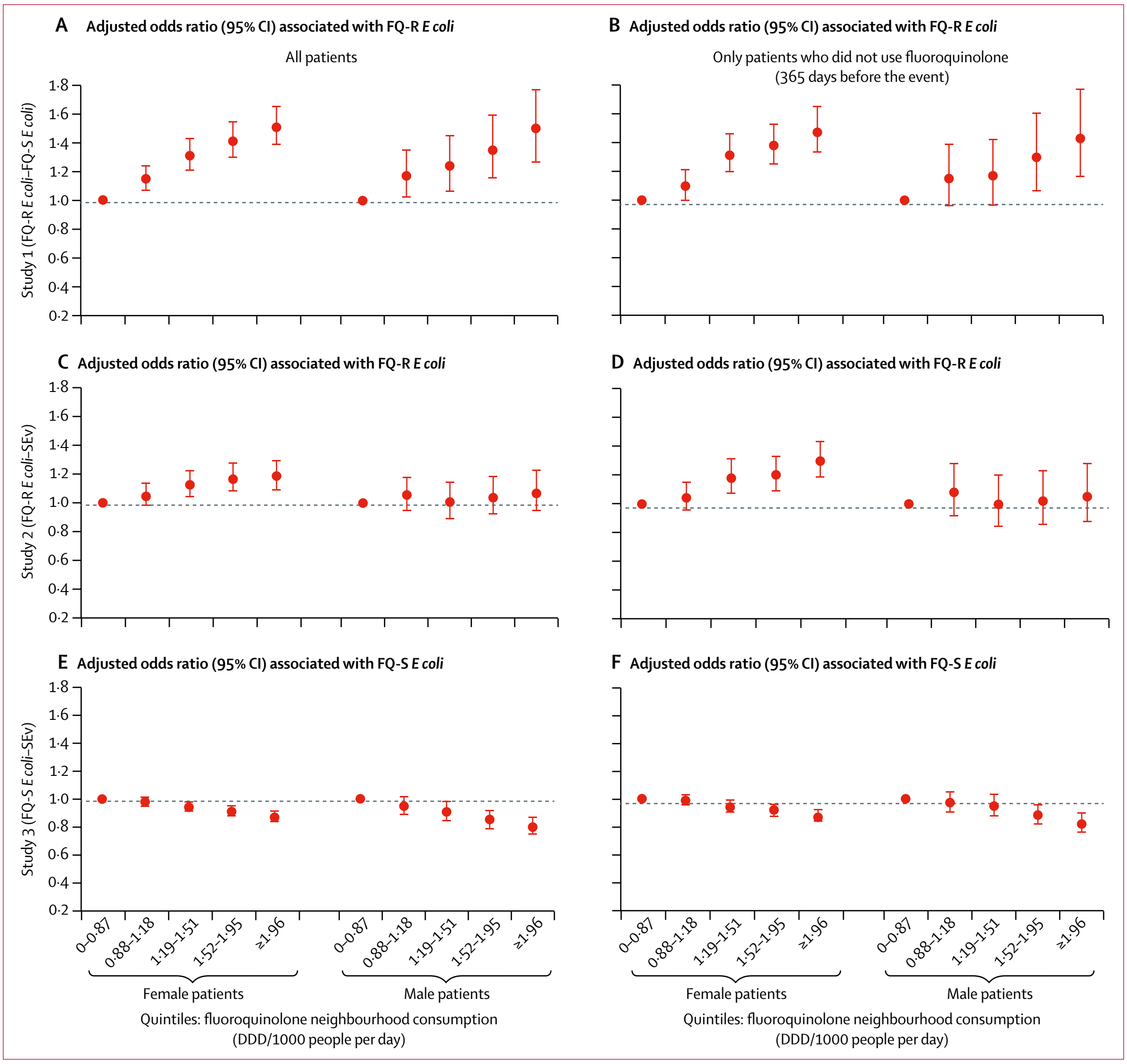

Figure 1: **Multiple logistic regression adjusted* odds ratios for *Escherichia coli* resistant and susceptible bacteria growth associated with neighbourhood fluoroquinolone consumption**

FQ-R=fluoroquinolone resistant. FQ-S=fluoroquinolone susceptible. SEv=sterile event. *Adjusted for: age, nursing home residence, ethnicity, BMI, comorbidity score, number of hospitalisations in the previous year, and personal consumption of fluoroquinolones, socioeconomic status, population density, proportion of people insured by CHS, and neighbourhood fluoroquinolone consumption in the previous year.

for the four quintiles of increasing neighbourhood fluoroquinolone consumption, compared with the first quintile of the lowest quinolone consumption. Among men, the respective ORs were similar (table 5; figure B).

Discussion

Our findings show an increased risk of acquiring fluoroquinolone-resistant *E coli* in neighbourhoods with higher fluoroquinolone consumption, independent of previous personal use of antibiotics and other known risk factors for antibiotic resistance.

An association between environmental antibiotic consumption and bacterial resistance is consistent with the results of previous ecological studies.[5,26] A multilevel approach incorporating individual-level and group-level factors associated with antibiotic-resistant bacterial infection has been used in another study, but the association between clustered antibiotic consumption and the individual-level risk of acquiring resistant bacteria was not observed.[12] The authors attributed this finding to the relatively low number of clusters and small cluster size. The large sample size, clear definitions of geographical clusters, and individual patient data included in our research enabled us to further clarify the complex picture of interacting factors linked to antibiotic resistance. Our results suggest that increased GSA-level use of antibiotics might pose a small, but real, risk for other individuals in the community in terms of acquiring resistant bacteria.

This effect might be quantitatively small for an individual, but its overall contribution to the spread of antibiotic resistance in the population is important. According to our multilevel study, the population fraction of urinary FQ-R *E coli* attributed to personal fluoroquinolone consumption among women is 46%, whereas the neighbourhood fluoroquinolone consumption above 0·87 DDD/1000 people per day accounted for 25% of the cases[27] (appendix).

It has been previously shown that exposure to fluoroquinolones results in a significant increase in gut colonisation with fluoroquinolone-resistant Enterobacteriaceae,[28] and that maternal colonisation with fluoroquinolone-resistant bacteria is also associated with such colonisation among healthy children in the same household.[29] These data, which support transmission through close contact, could explain how an increase in neighbourhood antibiotic-consumption rate might lead not only to the appearance of resistant bacteria but also to the transmission of such bacteria to people who have never used antibiotics. We hypothesised that crowded living conditions might be associated with increased physical contact between people and with less hygienic conditions that further increase this transmission. This hypothesis is supported by the fact that patients with FQ-R *E coli* lived in more-crowded neighbourhoods, whereas patients with FQ-S *E coli* and patients with sterile cultures lived in neighbourhoods with similar population density. It seems that more crowded conditions did not confer increased risk for urinary tract infections in general but facilitated the transmission of resistant bacteria or resistance genes within the population.

We used a three-study case–control–control approach,[17] with the inclusion of a third study comparing FQ-S *E coli* events with sterile events, to evaluate for a misclassification effect of exposure to antibiotics regarding FQ-S *E coli* growth in urine cultures. Patients with fluoroquinolone-susceptible bacteria who were exposed to antibiotics before urine culture was taken might have had a greater probability of being excluded from the control (fluoroquinolone-susceptible) group and of being misclassified as a sterile event. Study 3 showed opposite dose–response ORs compared with studies 1 and 2; people living in the highest quintile of neighbourhood fluoroquinolone consumption were less likely to have samples with FQ-S *E coli*, an observation which supported our approach.

This research has several limitations. Patient characteristics, accessibility to medical services, and cultural health habits in areas with higher antibiotic consumption might be inherently different from those in areas with low antibiotic consumption.

We controlled for part of the potential confounders that were available in the electronic records but a residual confounding is still possible. Detection of FQ-R *E coli* in the urine depends on the physicians' and patients' decision to send the urine culture. Therefore, the cases probably do not include all incident cases in the population. We expect that the incident groups assumed to be missed are equally distributed across both the FQ-R and the FQ-S groups.

Our analyses were based on recorded home addresses. This approach could be inaccurate and does not account for time spent outside the home (eg, in a workplace). Such bias is likely to be similar across the three groups, but we cannot exclude some inaccuracies in our spatial data. Finally, as we did not do genotype analyses, we cannot ascertain the biological basis of the observed associations. We presume that close contact leads to the transfer of bacteria or of antibiotic-resistance genes within a given population.[30]

The association between neighbourhood fluoroquinolone consumption and FQ-R *E coli*, but not FQ-S *E coli*, further supports a true effect. Unmeasured variables, such as recent urinary-instrumentation, urinary-catheterisation, or genitourinary surgery, can potentially

	Study 1 FQ-R *E coli*–FQ-S *E coli*) OR (95% CI)	Study 2 (FQ-R *E coli*–SEv) OR (95% CI)	Study 3 (FQ-S *E coli*–SEv) OR (95% CI)
Female patients			
Fluoroquinolone neighbourhood consumption (DDD/1000 people per day)			
0–0·87	1	1	1
0·88–1·18	1·10 (0·99–1·21)	1·04 (0·95–1·15)	0·99 (0·95–1·03)
1·19–1·51	1·31 (1·19–1·46)	1·18 (1·07–1·31)	0·94 (0·90–0·99)
1·52–1·95	1·38 (1·24–1·53)	1·20 (1·08–1·33)	0·92 (0·87–0·96)
≥1·96	1·47 (1·33–1·65)	1·30 (1·18–1·43)	0·87 (0·83–0·92)
Random effect fluoroquinolone neighbourhood consumption	1·10 (1·02–1·14)	1·04 (1·02–1·12)	1·02 (1·01–1·03)
mOR	1·23 (1·02–1·34)	1·22 (1·01–1·32)	1·13 (1·01–1·19)
IOR80	1·00–2·2	0·82–1·75	0·69–1·1
Male patients			
Fluoroquinolone neighbourhood consumption (DDD/1000 people per day)			
0–0·87	1	1	1
0·88–1·18	1·15 (0·96–1·39)	1·08 (0·91–1·28)	0·97 (0·90–1·05)
1·19–1·51	1·17 (0·96–1·42)	1·00 (0·84–1·20)	0·95 (0·87–1·03)
1·52–1·95	1·30 (1·06–1·60)	1·02 (0·85–1·23)	0·88 (0·81–0·96)
≥1·96	1·43 (1·16–1·77)	1·05 (0·87–1·28)	0·82 (0·75–0·90)
Random effect fluoroquinolone neighbourhood consumption	1·19 (1·06–1·66)	1·20 (1·08–1·53)	1·01 (1–1·24)
mOR	1·49 (1·03–1·75)	1·51 (1·03–1·78)	1·08 (1·01–1·11)
IOR80	0·68–3·04	0·48–2·30	0·72–0·95

DDD=defined daily dose. FQ-R=Fluoroquinolone resistant. FQ-S=Fluoroquinolone susceptible. SEv=sterile event. mOR=median odds ratio. IOR80=interval odds ratio. *Adjusted for age, nursing home residence, ethnicity, body-mass index, comorbidity score, number of hospitalisations in the previous year, and personal consumption of fluoroquinolones, socioeconomic status, population density, proportion of people ensured by CHS, and neighbourhood fluoroquinolone consumption in the previous year.

Table 5: **Multiple logistic regression adjusted ORs* including only patients who were not consuming fluoroquinolones 1 year before the index event**

confound the observed association. We tried to control for such confounders by including the number of hospital admissions in the year preceding the recorded event.

To summarise, in this study we observed and quantified the associations between antibiotic consumption in a given geographical area and an increased risk for the entire community of acquiring antibiotic resistance. These data should serve as yet another driving force in the effort to avoid unnecessary antibiotic use. Further studies should quantify the effect of interventions that encourage prudent antibiotic use in hospitals, outpatient clinics, veterinary medicine, and agriculture on antibiotic-resistance prevalence in the community.

Contributors

ML chaired the group, devised the project, had full access to all study data, and takes responsibility for the integrity of the data and the accuracy of the data analysis. AN helped with interpreting the data and drafting and revising the manuscript. TMH contributed critical revision of the manuscript. MSG helped develop the methodology and revise the manuscript. RDB helped with critical revision of the manuscript. RR co-supervised the project. RA helped develop the methodology, did the analyses, and contributed to drafting and revision of the manuscript.

Declaration of interests

We declare no competing interests.

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