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Impact of long-term care facility residence on the antibiotic resistance of urinary tract *Escherichia coli* and *Klebsiella*

Alicia Rosello[1,2]*, Andrew C. Hayward[2], Susan Hopkins[3,4], Carolyne Horner[5], Dean Ironmonger[6], Peter M. Hawkey[7,8] and Sarah R. Deeny[9,10]

[1]Modelling and Economics Unit, National Infection Service, Public Health England, London NW9 5EQ, UK; [2]Institute of Health Informatics, Farr Institute of Health Informatics Research, UCL, London NW1 2DA, UK; [3]Department of Infectious Diseases and Microbiology, Royal Free London NHS Foundation Trust, London NW3 2QG, UK; [4]Healthcare Associated Infections Surveillance, National Infection Service, Public Health England, London NW9 5EQ, UK; [5]Regional Laboratory Leeds, Public Health England, Leeds LS1 3EX, UK; [6]Field Epidemiology Service, Public Health England, Birmingham B3 2PW, UK; [7]Institute of Microbiology & Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK; [8]Public Health England Public Health Laboratory, Heart of England NHS Foundation Trust, Birmingham B9 5SS, UK; [9]Data analytics, The Health Foundation, London WC2E 9RA, UK; [10]Modelling and Economics Unit, National Infection Service, Public Health England and Health Protection Research Unit in Modelling Methodology, London NW9 5EQ, UK

*Corresponding author. Tel: 02083277148; E-mail: alicia.rosello@phe.gov.uk

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Background: Long-term care facilities (LTCFs) are thought to be important reservoirs of antimicrobial-resistant (AMR) bacteria; however, there is no routine surveillance of resistance in LTCF residents, or large population-based studies comparing AMR in LTCFs with the community, so the relative burden of AMR in LTCFs remains unknown.

Objectives: To compare the frequency of antibiotic resistance of urinary tract bacteria from residents of LTCFs for the elderly and adults aged 70 years or older living in the community.

Methods: Positive urine specimens reported to any diagnostic microbiology laboratory in the West Midlands region (England) from 1 April 2010 to 31 March 2014 collected from individuals aged 70 years or older were analysed. The resistance of *Escherichia coli* and *Klebsiella* to trimethoprim, nitrofurantoin, third-generation cephalosporins and ciprofloxacin and the rate of laboratory-confirmed *E. coli* and *Klebsiella* urinary tract infection (UTI) were assessed in LTCF residents and in the community.

Results: LTCF residents had a laboratory-confirmed *E. coli* and *Klebsiella* UTI rate of 21 per 100 person years compared with 8 per 100 person years in the elderly living in the community [rate ratio (RR)=2.66, 95% CI = 2.58–2.73] and a higher rate of developing *E. coli* and *Klebsiella* UTIs caused by bacteria resistant to trimethoprim (RR = 4.41, 95% CI = 4.25–4.57), nitrofurantoin (RR = 4.38, 95% CI = 3.98–4.83), ciprofloxacin (RR = 5.18, 95% CI = 4.82–5.57) and third-generation cephalosporins (RR = 4.49, 95% CI = 4.08–4.94).

Conclusions: Residents of LTCFs for the elderly had more than double the rate of *E. coli* and *Klebsiella* UTI and more than four times the rate of *E. coli* and *Klebsiella* UTI caused by antibiotic-resistant bacteria compared with those living in the community.

Introduction

The spread of antimicrobial resistance (AMR) is a major healthcare concern.[1] Owing to the paucity of new antibiotics being developed, a rise in AMR limits treatment options and increases the risk of treatment failure, leading to increases in morbidity and mortality.[2] Of particular concern are recent increases in hospital infections due to strains of Gram-negative bacteria such as *Klebsiella* and *Escherichia coli* that are resistant to all first-line antibiotics.[1,3] Gram-negative bacteria are now the most common cause of hospital-acquired infection in England, Wales and Northern Ireland, causing 50 000 (63%) bloodstream infections (BSIs) in adults in 2011–12.[1] They were also the most common cause of BSIs in Scotland in 2012.[4] *E. coli* and *Klebsiella* are organisms of particular concern and have been highlighted as bacteria to monitor for resistance in the 5 year AMR strategy for the UK (2013–18).[5] *E. coli* BSIs in England have increased by 15.6% from 2010 to 2014

and *Klebsiella pneumoniae* BSIs in England have increased by 20.8% from 2009 to 2014. BSIs caused by other species have remained constant or declined.[6]

Elderly individuals, particularly long-term care facility (LTCF) residents, are at increased risk of infection-related hospital admissions.[7] Infections and colonization in patients ≥65 years old are more likely to be caused by AMR bacteria, although this varies for different pathogen–antibiotic combinations.[8–11] Urinary tract infections (UTIs), caused primarily by Gram-negative bacteria such as *E. coli*, *Proteus* and *Klebsiella*, are the second most frequent type of infection for elderly women.[12,13] In England, UTIs were found to be the second most common healthcare-associated infection after respiratory tract infections, both in the hospital setting (17.2%) and the LTCF setting (35.7%).[14,15] UTIs were the joint most common healthcare-associated infection with respiratory tract infections (31%), in a point-prevalence survey carried out in LTCFs across Europe.[15]

It is estimated that in England, 4% of those aged >65 years (325 000 people) live in LTCFs.[7] Like hospitals, LTCFs are enclosed environments with high concentrations of frail elderly residents who are more likely to require daily living assistance, antibiotic treatment and invasive devices such as catheters.[16] At any one time in Europe between 4.8% and 15.2% of LTCF residents are being treated with antibiotics and between 47% and 79% of LTCF residents in Canada, the USA and Italy receive at least one course of antibiotics per year.[17] In Hampshire (England), residence in an LTCF has recently been shown to be associated with high antibiotic consumption.[18] Control of infections can be challenging in LTCFs due to frequent opportunities for transmission through group activities, sharing of living space, objects and bathroom facilities, and lack of infection control provision.[16]

AMR is not routinely surveyed in LTCFs, such that the extent of the problem is hidden and there is a lack of co-ordinated action to address the issue. We aimed to compare the frequency of antibiotic resistance of urinary tract bacteria from residents of LTCFs for the elderly and adults aged 70 years or older living in the community. To our knowledge, there are no large population-based studies, which include samples from both general practitioners (GPs) and hospitals that have addressed this question.

Methods

Ethics

PHE has National Information Governance Board for Health and Social Care approval for the collation and analysis of this surveillance data in accordance with section 251 of the NHS Act 2006. This study was a secondary analysis of routinely collected AmSurv data.

Data sources

Three sources of data were used in this study. First, the antibiotic susceptibility results from all *E. coli* or *Klebsiella* culture-positive urine specimens collected from individuals aged 70 years or older reported from the 15 microbiology laboratories in the West Midlands to AmSurv (an AMR surveillance tool[19]) from 1 April 2010 to 31 March 2014. The West Midlands Region (England) comprises a population of 700 000 aged 70 years or older.[20] Following national guidelines, we assumed that all urine samples were submitted due to clinical need and therefore were indicative of a suspected UTI.[21] The dataset did not contain sufficient clinical information to identify urine samples from catheters or distinguish between UTIs and asymptomatic bacteriuria, common in the elderly population in particular among those residing in LTCFs.[22] Samples from all types of suspected UTIs were considered. All West Midland laboratories undertake UKAS external accreditation to verify competencies and assure of conformity to standard methods.[23] Laboratory information systems are configured to only send significant bacteriuria to PHE and PHE recommends specific cut-offs for clinical laboratory processing.[24] Resistant bacteria were either fully resistant or intermediately resistant to a particular antibiotic. Clinical laboratories in England perform antibiotic susceptibility testing using a variety of methods: EUCAST, BSAC and CLSI (formerly NCCLS); with a mixture of automated (e.g. Vitek and Phoenix) and manual (e.g. disc and Etest) laboratory methods. All laboratories who contribute to this dataset participate in the UK National External Quality Assurance Scheme (NEQAS). Clinical laboratories most commonly use EUCAST breakpoints, and until recently BSAC methodology, but where EUCAST breakpoints are unavailable for key antibiotics, laboratories use alternative published breakpoints such as those of CLSI, and are asked to report their methods to NEQAS when reporting specific organism antibiotic susceptibility results. Specifically in the West Midlands, in 2012, of 15 laboratories, 7 laboratories used BSAC disc diffusion, 4 used Vitek 2, 3 used breakpoint methods and 1 used a combination of Vitek 2 and BSAC disc diffusion (depending on if tests were performed during normal working hours) to test antibiotic susceptibility.[25] The breakpoint method involves seeding agar plates with a concentration of antibiotic equivalent to the breakpoint for each antibiotic.[26] Diluted organisms are spotted on the antibiotic plates and on control plates containing no antibiotics. Seven of the eight laboratories using the BSAC method reported using the latest breakpoints during the study period. The remaining laboratory used an earlier version (version 10). Vitek 2 software uses EUCAST v1.1 (2010) breakpoints. During the study, two laboratories switched from using the BSAC method to a breakpoint technique.

The CLSI breakpoints for ceftazidime [one of the four third-generation cephalosporins (3GCs) tested] changed in 2010 and this change was implemented in automated systems between 2012 and 2013. In 2012, no laboratories in the West Midlands reported using CLSI breakpoints for this antibiotic. However, the methods used may have changed from 2012 to 2014, which is a limitation of the percentage of 3GCs reported. However, in our dataset, ceftazidime resistance constituted a fraction of what we report as 3GC resistance (33% of 3GC tests for *Klebsiella* and 19% for *E. coli*) and there was no stepwise increase or decrease in the percentage of urinary *E. coli* and *Klebsiella* resistant to ceftazidime in any of the West Midlands laboratories. In addition, across all non-specialist microbiology laboratories in the region, 50% of urine samples come from the community with LTCFs sending samples to their closest laboratory rather than having a specific managed contract with one laboratory within the region.

Data cleaning and de-duplication is described in Appendix S1 and Figure S1 (available as Supplementary data at *JAC* Online).

LTCF status (nursing or residential), bed numbers for the entire LTCF and LTCF postcodes (LTCF-pc) were extracted from the publicly available registry of LTCFs by the national regulator of health and social care in England (the Care Quality Commission).[27] LTCFs in the national register were included if they were classified as 'care homes' for elderly residents and recorded as active in the register from 2011 to 2012 (797 LTCFs). Care homes, as defined by the Care Quality Commission, 'offer accommodation and personal care for people who may not be able to live independently'.[28] We subsequently refer to care homes with 24 h medical care from qualified nursing staff as nursing LTCFs and to care homes without this service as residential LTCFs.

Postcodes containing only communal establishments (CE-pc) in the West Midlands and age-stratified population estimates for mid-2014 were taken from open data held by the Office for National Statistics.[20,29]

Data linkage

LTCF residence was determined by matching individuals' full postcodes, based on the request form for microbiological investigation, against the full

Table 1. Characteristics of urine samples positive for *E. coli* and *Klebsiella*

		LTCF *E. coli* samples ($N = 17\,022$), *n* (%)	Non-LTCF *E. coli* samples ($N = 154\,453$), *n* (%)	LTCF *Klebsiella* samples ($N = 1510$), *n* (%)	Non-LTCF *Klebsiella* samples ($N = 21\,262$), *n* (%)
Age (years)	70–74	807 (4.7)	34 984 (22.7)	91 (6.0)	4621 (21.7)
	75–80	2038 (12.0)	45 300 (29.3)	222 (14.7)	6445 (30.3)
	81–85	3573 (21.0)	35 178 (22.8)	308 (20.4)	5034 (23.7)
	>85	10 604 (62.3)	38 991 (25.2)	889 (58.9)	5162 (24.3)
Gender	female	14 406 (85.0)	124 547 (80.7)	1080 (71.8)	13 150 (61.9)
	male	2545 (15.0)	29 753 (19.3)	425 (28.2)	8094 (38.1)
LTCF type	residential	10 139 (59.6)	NA	823 (54.5)	NA
	nursing	6883 (40.4)	NA	687 (45.5)	NA
Year of study	year 1	2541 (14.9)	25 220 (16.3)	247 (16.4)	3615 (17.0)
	year 2	3958 (23.3)	33 396 (21.6)	337 (22.3)	4926 (23.2)
	year 3	4911 (28.8)	43 784 (28.4)	414 (27.4)	6007 (28.3)
	year 4	5612 (33.0)	52 053 (33.7)	512 (33.9)	6714 (31.6)
Sender	GP	12 571 (74.1)	99 727 (64.9)	1033 (68.5)	11 369 (53.5)
	hospital	4396 (25.9)	54 011 (35.1)	475 (31.5)	9872 (46.5)

NA, not applicable.

postcodes of LTCFs in the West Midlands region registered with the Care Quality Commission as of April 2014. In this study, samples from individuals residing in a postcode that contained an LTCF (LTCF-pc) are referred to as LTCF samples and those with a postcode that did not (non-LTCF-pc) are referred to as non-LTCF samples.

Crude rate comparisons

Positive urinary tract bacterial cultures with *E. coli* and *Klebsiella* reported to AmSurv were used as a surrogate for *E. coli* and *Klebsiella* UTI, as urinary tract specimens should only be sent to the microbiology laboratory when there is a clinical suspicion of a UTI.[21] *E. coli* and *Klebsiella* samples were grouped as these were the most common Gram-negative bacteria with similar antibiotic treatment. *Proteus* isolates were not included as these bacteria are intrinsically resistant to nitrofurantoin.[30] The rates of *E. coli* and *Klebsiella* UTI and *E. coli* and *Klebsiella* UTI caused by resistant bacteria in LTCF-pc and in non-LTCF-pc are calculated as per Appendix S2.

Postcodes may cover several buildings; therefore, LTCF-pc may also include some elderly people who are not LTCF residents. Sensitivity analysis estimated the rates of *E. coli* and *Klebsiella* UTI in LTCFs using only data from LTCF-pc that were classified by the Office for National Statistics as LTCF CE-pc.

Comparison of resistance levels in culture-confirmed samples

Logistic regression models coded in the rms package in R were used to calculate the odds of resistance for bacteria in LTCF samples compared with non-LTCF samples.[31] Further analyses compared nursing and residential LTCFs. Age group (70–74, 75–80, 81–85 and >85 years), sex, year of study (2010–11, 2011–12, 2012–13 and 2013–14) and sender (GP versus hospital) were included in the model as categorical covariates because they are known risk factors of antibiotic resistance for urinary tract bacteria (see Appendix S3). No interactions between the model variables improved model fit; therefore, they were not included in the final model (see Table S1).

Results

A total of 144 738 individuals aged 70 years or older had at least one positive urine specimen reported to the AmSurv database from any of the 15 diagnostic microbiology laboratories in the West Midlands region. The most commonly reported bacterium in the dataset was *E. coli* (57.2%). *Klebsiella* spp. accounted for 6.2% of the samples (of which 65% were *K. pneumoniae*, 19% were *Klebsiella oxytoca* and 15% were other *Klebsiella* of undefined species).

Table 1 describes the key characteristics of *E. coli* and *Klebsiella* in LTCF samples and non-LTCF samples. LTCF samples were more frequently reported from the very elderly age groups (>85) than non-LTCF samples. LTCF samples (and non-LTCF samples) comprised samples sent by both GPs and hospitals (e.g. during an LTCF resident's hospital stay). LTCF samples were more frequently sent by GPs (versus hospitals) than non-LTCF samples. Overall, most samples were taken from females. This difference in gender was greater for LTCF samples than for non-LTCF samples.

The rate of laboratory-confirmed *E. coli* and *Klebsiella* UTI was 20.6 per 100 person years in LTCF residents and 7.8 per 100 person years in community dwelling older adults; giving a rate ratio (RR) of 2.66 (95% CI = 2.58–2.73) (see Table 2). In the sensitivity analysis, the rate of *E. coli* and *Klebsiella* UTI in the LTCFs located in CE-pc was similar (21.5 per 100 person years) giving a similar RR of 2.77 (95% CI = 2.57–2.98) (see Table S2).

The rate of *E. coli* and *Klebsiella* UTI caused by bacteria resistant to trimethoprim per 100 person years was 12.7 in LTCF residents versus 2.9 in community residents (RR = 4.41, 95% CI = 4.25–4.57) (see Table 2). The rate of *E. coli* and *Klebsiella* UTI caused by bacteria resistant to nitrofurantoin per 100 person years was 1.7 in LTCF residents versus 0.4 in community residents (RR = 4.38, 95% CI = 3.98–4.83). The rate of *E. coli* and *Klebsiella* UTI caused by

Table 2. Rate of *E. coli* and *Klebsiella* UTI, and *E. coli* and *Klebsiella* UTI caused by antibiotic-resistant bacteria, for LTCF and non-LTCF residents per 100 person years[a]

	LTCF rate	Non-LTCF rate	RR	95% CI
UTI[b]	20.6	7.8	2.7	2.6–2.7
UTI[b] caused by bacteria resistant to trimethoprim	12.7	2.9	4.4	4.3–4.6
UTI[b] caused by bacteria resistant to nitrofurantoin	1.7	0.4	4.4	4.0–4.8
UTI[b] caused by bacteria resistant to ciprofloxacin	3.3	0.6	5.2	4.8–5.6
UTI[b] caused by bacteria resistant to 3GCs[c]	1.8	0.4	4.5	4.1–4.9

[a]See Table S2 for the sensitivity analysis calculating LTCF rates only for LTCFs in CE-pc.
[b]Urinary tract *E. coli* and *Klebsiella* reported to AmSurv.
[c]3GCs include ceftazidime, cefpodoxime, cefotaxime and ceftriaxone.

Table 3. Prevalence of antibiotic resistance in all samples, in LTCF samples, in non-LTCF samples, in residential LTCF samples and in nursing LTCF samples

		Resistance, *n*/*N* (%)				
Organism	Antibiotic	overall	LTCF samples	residential LTCF samples	nursing LTCF samples	non-LTCF samples
E. coli	trimethoprim	61 879/158 764 (39.0)	9513/15 914 (59.8)	5491/9438 (58.2)	4022/6476 (62.1)	52 366/142 850 (36.7)
	nitrofurantoin	6322/158 501 (4.0)	1059/15 889 (6.7)	571/9425 (6.1)	488/6464 (7.6)	5263/142 612 (3.7)
	ciprofloxacin	16 937/111 220 (15.2)	3075/10 564 (29.1)	1625/6100 (26.6)	1450/4464 (32.5)	13 862/100 656 (13.8)
	3GCs[a]	8581/134 957 (6.4)	1412/13 482 (10.5)	791/8084 (9.8)	621/5398 (11.5)	7169/121 475 (5.9)
Klebsiella	trimethoprim	4759/17 844 (26.7)	513/1257 (40.8)	282/707 (39.9)	231/550 (42.0)	4246/16 587 (25.6)
	nitrofurantoin	4232/12 159 (34.8)	377/916 (41.2)	213/517 (41.2)	164/399 (41.1)	3855/11 243 (34.3)
	ciprofloxacin	1105/13 738 (8.0)	95/918 (10.4)	48/510 (9.4)	47/408 (11.5)	1010/12 820 (7.9)
	3GCs[a]	846/11 593 (7.3)	60/754 (8.0)	29/430 (6.7)	31/324 (9.6)	786/10 839 (7.3)

[a]3GCs include ceftazidime, cefpodoxime, cefotaxime and ceftriaxone.

bacteria resistant to ciprofloxacin per 100 person years in LTCF residents was 3.3 versus 0.6 in community residents (RR = 5.18, 95% CI = 4.82–5.57). The rate of *E. coli* and *Klebsiella* UTI caused by bacteria resistant to 3GCs per 100 person years in LTCF residents was 1.8 versus 0.4 in community residents (RR = 4.49, 95% CI = 4.08–4.94). The sensitivity analysis yielded very similar findings, with LTCF residents having a higher rate of *E. coli* and *Klebsiella* UTI caused by bacteria that were resistant to trimethoprim (RR = 4.44, 95% CI = 4.04–4.89), nitrofurantoin (RR = 4.82, 95% CI = 3.77–6.16), ciprofloxacin (RR = 7.88, 95% CI = 6.76–9.19) and 3GCs (RR = 4.09, 95% CI = 3.14–5.33) (see Table S2).

The prevalence of antibiotic resistance was higher in bacteria from LTCF samples than in non-LTCF samples for all bacterium–antibiotic combinations (Tables 3 and 4). *E. coli* resistance to: trimethoprim was 60% versus 37% [adjusted OR = 2.36, 95% CI = 2.21–2.53]; nitrofurantoin was 7% versus 4% (adjusted OR = 1.74, 95% CI = 1.53–1.97); ciprofloxacin was 29% versus 14% (adjusted OR = 2.42, 95% CI = 2.17–2.69); and 3GCs was 10% versus 6% (adjusted OR = 1.89, 95% CI = 1.64–2.17). *Klebsiella* resistance to: trimethoprim was 41% versus 26% (adjusted OR = 1.89, 95% CI = 1.6–2.24); nitrofurantoin was 41% versus 34% (adjusted OR = 1.31, 95% CI = 1.09–1.59); ciprofloxacin was 10% versus 8% (adjusted OR = 1.54, 95% CI = 1.13–2.1); and 3GCs was 8% versus 7% (adjusted OR = 1.24, 95% CI = 0.85–1.83). Further results of the univariate and multivariate results are shown in Tables S3–S9 and Appendix S4.

LTCFs with nursing support had higher levels of resistance to most antibiotics than residential LTCFs (see Table 3 and Table S10). Levels of antibiotic resistance were also higher in urinary tract bacteria from LTCF residents (obtained both from GPs and hospitals) than from hospitals (including samples from residents of LTCF-pc and non-LTCF-pc) (Table S11). *E. coli* resistance to trimethoprim, nitrofurantoin, ciprofloxacin and 3GCs was higher in LTCF samples than in hospital samples (60% versus 40%, 7% versus 4%, 29% versus 16% and 11% versus 8%). *Klebsiella* resistance to trimethoprim and nitrofurantoin was also higher in LTCFs (41% versus 27% and 41 % versus 32%) but ciprofloxacin resistance was similar (10% versus 10%) and 3GC resistance was higher in hospitals (8% versus 10%).

There were differences in resistance to trimethoprim, nitrofurantoin, ciprofloxacin and 3GCs over the study period for bacteria from LTCF samples and non-LTCF samples. These patterns are plotted in Figure 1. Resistance to other antibiotics is plotted in Figures S2 and S3.

Table 4. Unadjusted and adjusted OR of antibiotic resistance in bacteria from LTCF samples compared with non-LTCF samples

Bacterium	Antibiotic	uOR LTCF[a]	Adjusted 95% CI uOR LTCF	aOR LTCF[b]	Adjusted 95% CI aOR LTCF
E. coli	trimethoprim	2.56	2.4–2.7	2.4	2.2–2.5
	nitrofurantoin	1.86	1.6–2.1	1.7	1.5–2.0
	ciprofloxacin	2.57	2.3–2.9	2.4	2.2–2.7
	3GCs[c]	1.86	1.6–2.1	1.9	1.6–2.2
Klebsiella	trimethoprim	2.01	1.7–2.4	1.9	1.6–2.2
	nitrofurantoin	1.34	1.1–1.6	1.3	1.1–1.6
	ciprofloxacin	1.36	1.0–1.9	1.5	1.1–2.1
	3GCs[c]	1.1	0.8–1.6	1.2	0.9–1.8

[a]uOR LTCF is the unadjusted OR (univariable analysis) of antibiotic resistance in bacteria from LTCF samples compared with non-LTCF samples with 95% CIs adjusted for clustering at the postcode level.
[b]aOR LTCF is the adjusted OR, adjusted for age group, sex, year of study and sender as categorical covariates, of antibiotic resistance in bacteria from LTCF samples compared with non-LTCF samples with 95% CIs adjusted for clustering at the postcode level. Interactions were not included in the model, as they did not improve model fit (see Table S1).
[c]3GCs include ceftazidime, cefpodoxime, cefotaxime and ceftriaxone.

Discussion

Elderly residents of LTCFs are more than twice as likely as community dwelling adults of similar age to present with a laboratory-confirmed *E. coli* or *Klebsiella* UTI. These infections are most commonly caused by *E. coli*. In LTCF residents 60% of samples that yielded *E. coli* were resistant to trimethoprim, 29% to ciprofloxacin, 10% to 3GCs and 7% to nitrofurantoin; 41% of samples that grew *Klebsiella* were resistant to trimethoprim, 41% to nitrofurantoin, 10% to ciprofloxacin and 8% to 3GCs. LTCF residents were over four times more likely than community dwelling older people to develop a laboratory-confirmed *E. coli* or *Klebsiella* UTI caused by resistant bacteria. The increased risk of antibiotic resistance among bacteria causing culture-confirmed *E. coli* and *Klebsiella* UTIs in the elderly residing in LTCFs is seen across antibiotic classes.

Since 2012, all laboratories in the West Midlands report to AmSurv, making data from this region the most complete source of AMR data and providing insight into the burden and temporal changes of AMR within a defined population. Matching patient postcodes to LTCF-pc registered by the national regulator of health and social care in England unearths unprecedented knowledge of AMR in this setting over 4 years. The AmSurv surveillance system collects routine diagnostic samples from both community and hospital settings, permitting a fuller understanding of AMR in the population than other surveillance systems. In the multivariable analyses, statistically significant differences between the odds of antibiotic resistance in LTCF and non-LTCF settings are adjusted for clustering at the postcode level and account for variation in antibiotic resistance due to key risk factors (e.g. samples being sent from hospitals). Differences between residential and nursing LTCFs were also explored.

There were a number of limitations associated with using a large surveillance dataset. The dataset did not contain sufficient clinical information to identify urine samples from catheters or distinguish between UTIs and asymptomatic bacteriuria, common in the elderly population in particular among those residing in LTCFs.[22] However, clinical guidelines emphasize that only urinary samples from patients with a clinically suspected UTI and either a risk factor for resistance or a history of UTIs should be sent for laboratory testing and that catheter samples should not be sent.[21,32] This dataset only included positive samples. The likelihood of an elderly individual with a UTI having a urinary sample submitted might differ in LTCF residents and those living in the community, which could bias results. Separately, there is evidence for variation in the rate of submission of community samples from GPs to laboratories.[33] This is an unquantified potential confounder; however, this variation should be less pronounced in older populations, as English national guidance advocates sampling all patients >65 years old with two or more signs of UTI.[34] Sampling may be biased towards those failing to respond to treatment, which could increase the apparent risk of resistance. However, it is unclear why this bias would be greater in LTCF samples than in samples from the community. Urinary tract samples reported to AmSurv with confirmed culture results for *E. coli* and *Klebsiella* accounted for 63% of urinary tract bacteria samples. Caution must therefore be applied before extrapolating our results to UTIs caused by other bacterial species. Another limitation is that the threshold to diagnose UTI might be lower in LTCFs as staff might notice UTI symptoms earlier than would otherwise be detected in individuals living in their own homes. In addition, cognitive impairment was not recorded. Therefore, the analysis could not take into account differences in this condition in the two populations, which may lower the diagnosis threshold due to the inability of patients to verbalize symptoms. The study also is limited by the *in vitro* measurement of resistance, which does not always equate to clinical failure. It should also be noted that different breakpoints for ceftazidime (one of the four 3GCs tested) may have been used during the time period. However, the majority of laboratories were using BSAC/EUCAST breakpoint standards and this change was not apparent in our data (see the Methods section for details). Finally, as LTCF residence is not routinely recorded, we needed to infer this from patient postcodes. Thus, while those living in non-LTCF-pc are highly unlikely to be LTCF residents, a proportion of those living in LTCF-pc will live in the community in neighbouring households. This will

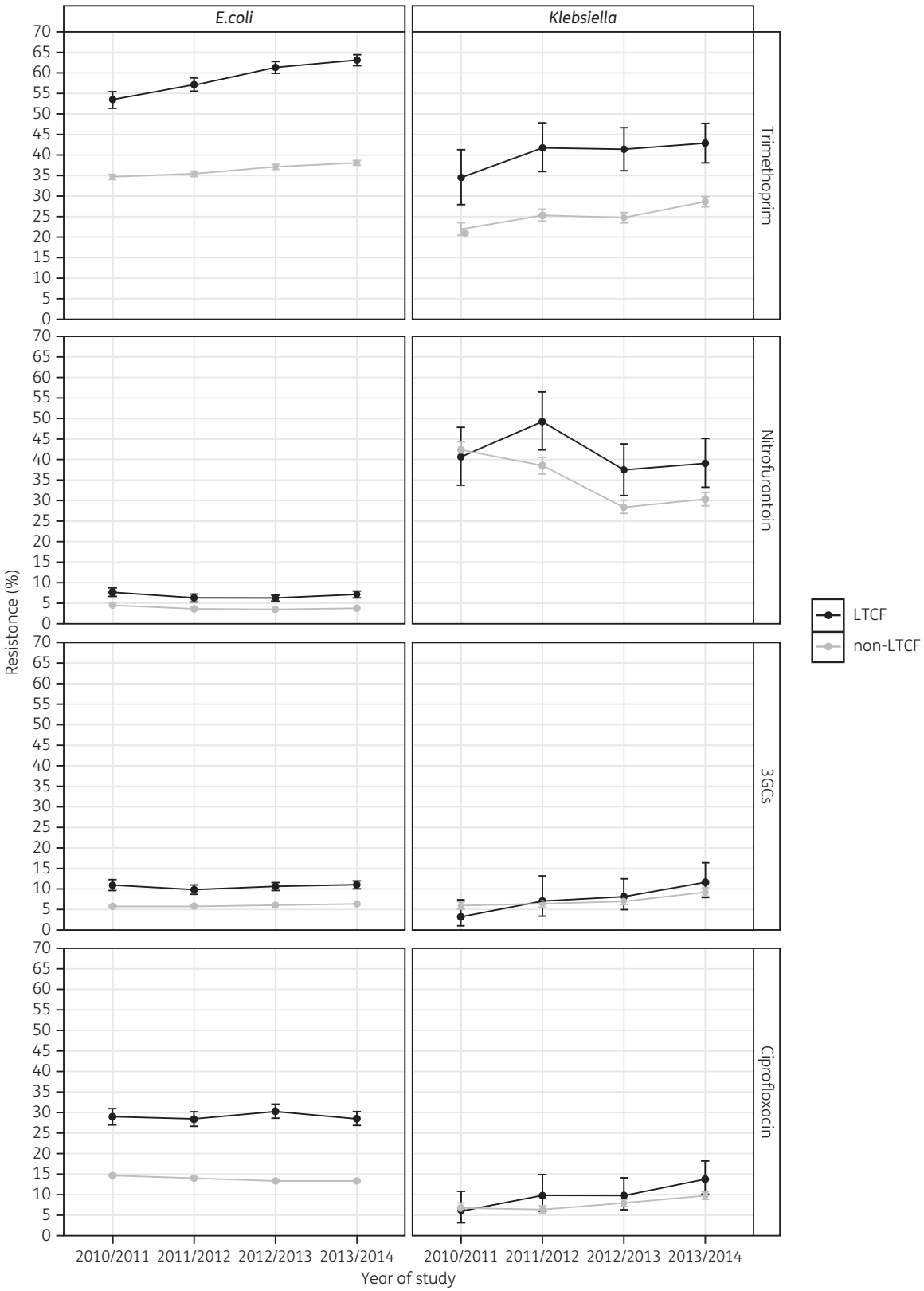

Figure 1. Percentage of *Klebsiella* and *E. coli* samples resistant to trimethoprim, nitrofurantoin, 3GCs and ciprofloxacin. The black line represents LTCF samples and the grey line represents non-LTCF samples. Yearly point estimates are presented with 95% binomial CIs. 3GCs include ceftazidime, cefpodoxime, cefotaxime and ceftriaxone.

tend to bias ORs toward the null hypothesis, potentially leading to underestimates of the impact of LTCF residence on antibiotic resistance. LTCF UTI rates were similar when using the more specific postcodes that contained only communal establishments, suggesting that this bias was minimal. This methodology has previously been employed in other studies.[7,18]

Trimethoprim and nitrofurantoin are recommended as first-line treatments for UTI;[21] therefore, resistance to these agents can result in treatment failure, hospitalization and the subsequent use of antibiotics such as ciprofloxacin or 3GCs that should be reserved for the treatment of more serious infections. Our findings suggest that a large proportion of *E. coli* and *Klebsiella* UTIs in the elderly will not respond to trimethoprim treatment and that this problem is heightened in LTCFs, where the prevalence of resistance is even higher; 39% of UTIs caused by *E. coli* and 27% of UTIs caused by *Klebsiella* (60% and 41%, respectively, in LTCFs) were resistant to trimethoprim, which is the most commonly prescribed antibiotic of those recommended in empirical guidelines for lower UTI (54.2%).[35] One explanation for these high levels of resistance could be the high consumption of this antibiotic in England (6.4% of all antibiotics consumed in the community and 3.9% in hospitals in 2013).[35] Resistance to trimethoprim increased during the study period, faster for LTCF samples (*E. coli* from 53% to 63% and *Klebsiella* from 34% to 43%) than for non-LTCF samples (*E. coli* from 35% to 38% and *Klebsiella* from 22% to 29%). These increases could partly be explained by trimethoprim consumption increasing in England by 4.2% between 2010 and 2013.[35] The prevalence of resistance of *E. coli* and *Klebsiella* to nitrofurantoin was high for *Klebsiella* (35%) but much lower for *E. coli* (4%). This suggests nitrofurantoin might still be very effective in treating UTIs caused by *E. coli* in the elderly, particularly in women, where the adjusted OR of acquiring a UTI caused by nitrofurantoin-resistant *E. coli* is lower. Nitrofurantoin comprised 3.8% of all antibiotics consumed in England in 2013 in the community and was the second most frequently prescribed antibiotic agent of those recommended in empirical guidelines for lower UTI (20.8%).[36] In the West Midlands, the consumption of nitrofurantoin increased by 66% from 2010 to 2014.[6]

Ciprofloxacin, 3GCs and carbapenems are antibiotics that are almost exclusively administered in hospitals for the treatment of severe infections. Ciprofloxacin treatment is recommended only in UTIs with acute prostatitis or acute pyelonephritis and 3GCs are not recommended in the empirical treatment of UTIs but are needed to treat more severe infections such as bacterial meningitis.[21,35] Given this, the prevalence of resistance to ciprofloxacin in *E. coli* (15%) is concerning, in particular in LTCF samples (29%). The levels of resistance to ciprofloxacin in *Klebsiella* and to 3GCs in *E. coli* and *Klebsiella* were lower (8%, 6% and 7%, respectively). Although low, *Klebsiella* resistance to ciprofloxacin and 3GCs increased steadily during the study period for LTCF samples (from 6% to 14% for ciprofloxacin and 3% to 12% for 3GCs) and also increased, although slower, in non-LTCF samples (7% to 10% for ciprofloxacin and from 6% to 9% for 3GCs). *E. coli* resistance to ciprofloxacin and 3GCs remained stable. During the study period, quinolone consumption in the West Midlands remained fairly stable but the consumption of 3GCs increased by 21%.[6] Importantly, 3GC and ciprofloxacin resistances do not only result in treatment failures but in the prescription of 'last resort' antibiotics such as carbapenems.[1] In our study, the prevalence of resistance in urinary tract bacteria to carbapenems in the over 70s was similarly low in both *Klebsiella* and *E. coli* (0.2% and 0.02%, respectively) compared with what has been reported in the literature between 2010 and 2013 in the overall West Midlands population,[25] which prevented any formal statistical analysis but is reassuring.

This is the first large population study to compare formally the AMR in LTCF residents with that in the elderly living in the community combining hospital and GP surveillance data. It is also the first large-scale study to quantify the burden of AMR in English LTCFs, where resistance levels and the LTCFs themselves could be different to LTCFs in other countries. Other studies were too small to yield statistically robust conclusions for several resistances, did not include GP samples or did not carry out a formal statistical comparison.[36–41] Our findings highlight the very high levels of AMR bacteria in LTCF residents compared with their community counterparts and even to hospital patients, showing the importance of reducing antibiotic usage in LTCFs through antibiotic stewardship programmes and the need for LTCF-specific surveillance that can guide empirical treatment. We found that that a very high proportion of *E. coli* and *Klebsiella* UTIs in the elderly living in LTCFs (and a high proportion of those living in their own homes) will not respond to trimethoprim treatment. However, resistance to nitrofurantoin remains low in UTIs caused by *E. coli* but high in UTIs caused by *Klebsiella*, demonstrating the need to understand further the mechanisms for the selection of resistance. To understand why there are such high levels of resistance in LTCFs, more information about antibiotic prescription, recent hospitalizations and transmission of resistant bacteria is required. It is equally important that interventions are developed to reduce the risk of transmission of AMR bacteria in LTCF residents.

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Transparency declarations

None to declare.

Author contributions

A. R. drafted the original manuscript, which was then amended with suggestions by the other authors. A. R., S. R. D., S. H., A. C. H. and C. H. contributed to the conception and design of the work. A. R. and D. I. contributed to the extraction, management and processing of the data. A. R. and S. R. D.

contributed to the analysis of the data. P. M. H. was involved in the intellectual design, analysis and management of the AmSurv database used for this study. A. R., S. R. D., S. H., A. C. H., C. H. and D. I. contributed to the interpretation of the data. All authors reviewed the manuscript and agreed to be accountable for all aspects of this work. A. R. and S. R. D. are the guarantors for the study. The corresponding author had full access to all the data and was responsible for the final decision to submit for publication.

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, the Department of Health or PHE.

Supplementary data

Appendices S1 to S4, Figures S1 to S3 and Tables S1 to S11 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1 Davies SC. *Annual Report of the Chief Medical Officer, Volume Two, 2011: Infections and the Rise of Antimicrobial Resistance*. London, 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/138331/CMO_Annual_Report_Volume_2_2011.pdf.

2 Review on Antimicrobial Resistance. *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*. 2014. https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.

3 Hawkey PM, Jones AM. The changing epidemiology of resistance. *J Antimicrob Chemother* 2009; **64** Suppl 1: i3–10.

4 Scottish Antimicrobial Prescribing Group. *Report on Antimicrobial Use and Resistance in Humans in 2012*. 2012. https://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Publications/2014-01-28/2014-01-28-SAPG-2012-Report.pdf.

5 Department of Health. *UK Five Year Antimicrobial Resistance Strategy 2013 to 2018*. 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf.

6 PHE. *English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR): Report 2015*. London, 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477962/ESPAUR_Report_2015.pdf.

7 Smith P, Sherlaw-Johnson C, Ariti C *et al*. *Focus on: Hospital Admissions From Care Homes*. 2015. http://www.health.org.uk/sites/health/files/QualityWatch_FocusOnHospitalAdmissionsFromCareHomes.pdf.

8 Adam HJ, Baxter MR, Davidson RJ *et al*. Comparison of pathogens and their antimicrobial resistance patterns in paediatric, adult and elderly patients in Canadian hospitals. *J Antimicrob Chemother* 2013; **68** Suppl 1: i31–7.

9 Denkinger CM, Grant AD, Denkinger M *et al*. Increased multi-drug resistance among the elderly on admission to the hospital—a 12-year surveillance study. *Arch Gerontol Geriatr* 2013; **56**: 227–30.

10 Sanchez GV, Adams SJE, Baird AMG *et al*. *Escherichia coli* antimicrobial resistance increased faster among geriatric outpatients compared with adult outpatients in the USA, 2000-10. *J Antimicrob Chemother* 2013; **68**: 1838–41.

11 Sahuquillo-Arce JM, Selva M, Perpiñán H *et al*. Antimicrobial resistance in more than 100,000 *Escherichia coli* isolates according to culture site and patient age, gender, and location. *Antimicrob Agents Chemother* 2011; **55**: 1222–8.

12 Flores-Mireles AL, Walker JN, Caparon M *et al*. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol* 2015; **13**: 269–84.

13 Matthews SJ, Lancaster JW. Urinary tract infections in the elderly population. *Am J Geriatr Pharmacother* 2011; **9**: 286–309.

14 HPA. *English National Point Prevalence Survey on Healthcare Associated Infections and Antimicrobial Use, 2011: Preliminary Data*. 2012. http://webarchive.nationalarchives.gov.uk/20140714084352/http:/www.hpa.org.uk/Publications/InfectiousDiseases/AntimicrobialAndHealthcareAssociatedInfections/1205HCAIEnglishPPSforhcaiandamu2011prelim/.

15 ECDC. *Point Prevalence Survey of Healthcare-associated Infections and Antimicrobial Use in European Long-term Care Facilities*. Stockholm, 2014. http://ecdc.europa.eu/en/publications/publications/healthcare-associated-infections-point-prevalence-survey-long-term-care-facilities-2013.pdf.

16 Horner C, Wilcox M, Barr B *et al*. The longitudinal prevalence of MRSA in care home residents and the effectiveness of improving infection prevention knowledge and practice on colonisation using a stepped wedge study design. *BMJ Open* 2012; **2**: e000423.

17 van Buul LW, van der Steen JT, Veenhuizen RB *et al*. Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc* 2012; **13**: 568.e1–13.

18 Sundvall P-D, Stuart B, Davis M *et al*. Antibiotic use in the care home setting: a retrospective cohort study analysing routine data. *BMC Geriatr* 2015; **15**: 71.

19 Ironmonger D, Edeghere O, Gossain S *et al*. AmWeb: a novel interactive web tool for antimicrobial resistance surveillance, applicable to both community and hospital patients. *J Antimicrob Chemother* 2013; **68**: 2406–13.

20 Office for National Statistics. *Population Estimates for UK, England and Wales, Scotland and Northern Ireland*. 2014. http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk-england-and-wales-scotland-and-northern-ireland/mid-2014/index.html.

21 PHE. *Management of Infection Guidance for Primary Care for Consultation and Local Adaptation*. London, 2015.

22 Nicolle LE. Urinary tract infections in long-term-care facilities. *Infect Control Hosp Epidemiol* 2001; **22**: 167–75.

23 United Kingdom Accreditation Service. *UKAS Website*. https://www.ukas.com/.

24 PHE. *UK Standards for Microbiology Investigations*. 2014. https://www.gov.uk/government/collections/standards-for-microbiology-investigations-smi.

25 Ironmonger D, Edeghere O, Bains A *et al*. Surveillance of antibiotic susceptibility of urinary tract pathogens for a population of 5.6 million over 4 years. *J Antimicrob Chemother* 2015; **70**: 1744–50.

26 Waterworth PM. Sensitivity testing by the break-point method. *J Antimicrob Chemother* 1981; **7**: 117–26.

27 Care Quality Commission. *Active Locations for Providers Registered Under the Health and Social Care Act*. CQC database at 1 April 2014. http://www.cqc.org.uk/.

28 Care Quality Commission. *Care Homes*. 2015. http://www.cqc.org.uk/content/care-homes.

29 Office for National Statistics. *Postcode Headcounts and Household Estimates—2011 Census—Nomis—Official Labour Market Statistics*. 2011. https://www.nomisweb.co.uk/census/2011/postcode_headcounts_and_household_estimates.

30 Brumfitt W, Hamilton-Miller JM. Efficacy and safety profile of long-term nitrofurantoin in urinary infections: 18 years' experience. *J Antimicrob Chemother* 1998; **42**: 363–71.

31 Harrell FE, *rms: Regression Modeling Strategies*. R Package version 4.3-1. 2015. http://cran.r-project.org/package=rms.

32 McNulty CA, Thomas M, Bowen J *et al*. Improving the appropriateness of laboratory submissions for urinalysis from general practice. *Fam Pract* 2008; **25**: 272–8.

33 McNulty CAM, Bowen J, Clark G *et al*. How should general practitioners investigate suspected urinary tract infection? Variations in laboratory-

confirmed bacteriuria in South West England. *Commun Dis Public Health* 2004; **7**: 220–6.

34 PHE. *Urinary Tract Infection: Diagnosis Guide for Primary Care*. 2014. https://www.gov.uk/government/publications/urinary-tract-infection-diagnosis.

35 PHE. *English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR): Report 2014*. London, 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/362374/ESPAUR_Report_2014__3_.pdf.

36 Fagan M, Lindbæk M, Grude N *et al*. Antibiotic resistance patterns of bacteria causing urinary tract infections in the elderly living in nursing homes versus the elderly living at home: an observational study. *BMC Geriatr* 2015; **15**: 98.

37 Xie C, Taylor DM, Howden BP *et al*. Comparison of the bacterial isolates and antibiotic resistance patterns of elderly nursing home and general community patients. *Intern Med J* 2012; **42**: e157–64.

38 Sundvall P-D, Elm M, Gunnarsson R *et al*. Antimicrobial resistance in urinary pathogens among Swedish nursing home residents remains low: a cross-sectional study comparing antimicrobial resistance from 2003 to 2012. *BMC Geriatr* 2014; **14**: 30.

39 Laupland KB, Ross T, Pitout JDD *et al*. Community-onset urinary tract infections: a population-based assessment. *Infection* 2007; **35**: 150–3.

40 Marwick C, Santiago VH, McCowan C *et al*. Community acquired infections in older patients admitted to hospital from care homes versus the community: cohort study of microbiology and outcomes. *BMC Geriatr* 2013; **13**: 12.

41 Brabazon E, Carton M, Dornikova G *et al*. Epidemiology and resistance patterns in urinary pathogens from long-term care facilities and GP populations. *Ir Med J* 2012; **105**: 177–80.