

Age-specific trends in antibiotic resistance in *Escherichia coli* infections in Oxford, United Kingdom 2013-2014

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Running title: Antibiotic resistance in *E. coli*

Dear Editor,

We read with interest the article by Martin *et al.* in this journal (1), in which they described the prevalence of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* in France in 2013. We now describe data to complement their study, in which we investigated antibiotic resistance in *E. coli* infections in a large tertiary hospital in the UK, describing prevalence of resistance to commonly-used antibiotics and age-specific trends in antibiotic resistance.

The rapid increase in infections due to antibiotic-resistant bacteria is one of the largest global health threats today. In Europe there are an estimated 25,000 deaths per year from multi-drug resistant organisms (2). In the UK *E. coli* is the commonest cause of bacteraemia (32% of all bacteraemia cases in 2013) (3), and the rate of *E. coli* bacteraemia increased by 16% between 2010 and 2014 (4). Patients with *E. coli* bacteraemia have an extremely high all-cause mortality of 18% (5). The study by Martin *et al.* suggested an increase in the proportion of ESBL-producing isolates with age (1), whereas a previous UK study showed lower proportions of non-susceptible isolates in infants (under 1 year of age) for all antibiotics tested (6).

In this retrospective study, all *E. coli* positive cultures obtained in the Oxford University Hospitals NHS Foundation Trust microbiology laboratory between September 2013 and May 2014 from any sample type were extracted from the microbiology database. The Trust is the sole provider of acute clinical and microbiology services to approximately 600,000 people. Samples obtained from hospitalised patients and the Emergency Department were considered

as ‘hospital’ isolates and samples from general practice, community hospitals and outpatient clinics as ‘community’ isolates. Antibiotic susceptibility testing and detection of ESBL were performed according to EUCAST criteria (<http://www.eucast.org>). Antibiotics for which susceptibility was assessed in at least 90% of isolates were included. Isolates from the same patient and sample type within 7 days of a previous positive culture were considered duplicate and excluded.

Age-specific trends in antibiotic susceptibility were analysed using log binomial regression analyses, adjusting for age and patient location (hospital vs community). Urine isolates from patients <100 years old were included – the small number of non-urine isolates and those from individuals ≥ 100 years of age were removed to avoid skewing the models. Analyses were performed for antibiotics where the overall prevalence of non-susceptibility was $\geq 10\%$. An isolate with “intermediate” susceptibility was classified as non-susceptible. To allow for changes in trend across different age ranges, 101 regression models were generated for each antibiotic by varying the point of change of the regression slope by 1 year intervals from 0 to 100 years. The model with the lowest Akaike information criterion was used as the final model.

There were 13,575 positive cultures for *E. coli*; the majority were urine samples (12,989, 95.7%) and there were 295 (2.2%) blood culture isolates. Highest prevalence of non-susceptibility was observed for amoxicillin (50%), co-amoxiclav (32%) and trimethoprim (31%). Overall, 793/13575 (5.8%) isolates were considered to be ESBL-producing. Prevalence of antibiotic non-susceptibility was significantly higher in hospital patients compared with those in the community for all penicillins and cephalosporins, gentamicin,

ciprofloxacin and fosfomycin (Table 1). The proportion of ESBL-producing *E. coli* was also significantly higher in hospital vs community isolates (9.4% vs 5.2%, $p < 0.0001$), and higher in blood compared with urine isolates (9.5% vs 5.7%, $p = 0.0058$). In multivariable analysis using patient location (hospital vs community) and isolate source (blood vs urine), hospital patients were more likely than community-based patients to have an ESBL-producing organism (adjusted odds ratio [aOR] = 1.94, 95% CI 1.61 to 2.33, $p < 0.0001$), but source of isolate was no longer a significant factor (aOR = 0.89, 95% CI 0.60 to 1.37, $p = 0.574$). For amoxicillin, co-amoxiclav and ciprofloxacin, there was an initial decrease in antibiotic non-susceptibility with age, followed by a later increase (Figure 1). The age at which these trends changed was different for each antibiotic. With trimethoprim and trimethoprim-sulfamethoxazole, there was an increase in antibiotic non-susceptibility throughout the age range, which was more marked in adults over 85 years (Figure 1). For cephalexin, there was no significant change in antibiotic susceptibility until 55 years of age, followed by a subsequent increase with age. ESBL-producing isolates were most common at the extremes of age, with a marked initial decrease up to 3 years of age followed by a steady increase. (Figure 1).

Prevalence of co-amoxiclav and gentamicin resistance in *E. coli* from hospital patients in this study were higher than in a previous study of hospitalised adults in the same hospital, where 23-25% of isolates were resistant to co-amoxiclav and 4-7% resistant to gentamicin during 2007-2010 (7). The prevalence of ESBL-producing *E. coli* has increased dramatically from 1-2% during 2007-2010 to 9% of all hospital isolates in 2013-2014. Prevalence of resistance to amoxicillin, trimethoprim and trimethoprim-sulfamethoxazole were similar to estimates in a recent meta-analysis from Organisation for Economic Co-operation and Development

(OECD) countries (8), however in the same meta-analysis prevalence of co-amoxiclav resistance was only 8% in community-treated urinary tract infections (UTIs) in children. The reason for this discrepancy is unclear, and may represent differences in use of co-amoxiclav or laboratory testing methodologies (9). The rates of resistance in community isolates in our study will be an over-estimate because the majority of UTIs in primary care are treated without a prior urine culture, so positive isolates disproportionately include patients who have failed first line therapy (usually co-amoxiclav, trimethoprim or nitrofurantoin). The dramatic rise in ESBL-producing *E. coli* in this short period is a major concern, and causes difficulty in balancing appropriate empirical antibiotic choice against widespread over-use of broad-spectrum antibiotics.

The age-specific analyses helps to further stratify individual risk based on demographic criteria, allowing potential targeting of broad-spectrum therapy. The high proportion of ESBL-producing *E. coli* in infants (similar to the oldest adults) is of particular concern and warrants further investigation to identify additional clinical risk factors. The reasons for differences in age-specific trends between different antibiotics are unclear. These may represent differences in antibiotic use and therefore selection pressures, differences in age-specific virulence of particular strains or co-location of genes encoding resistance determinants with other virulence factors (including other resistance determinants) which are under selection pressure.

For common pathogens such as *E. coli*, ongoing analysis of susceptibility trends should include use of demographic and other clinical data to identify risk factors, allowing

appropriate stratification of patients to target therapy and preserving broad-spectrum antibiotics for those at highest risk.

Conflict of Interest

The authors have no relevant conflict of interest to disclose.

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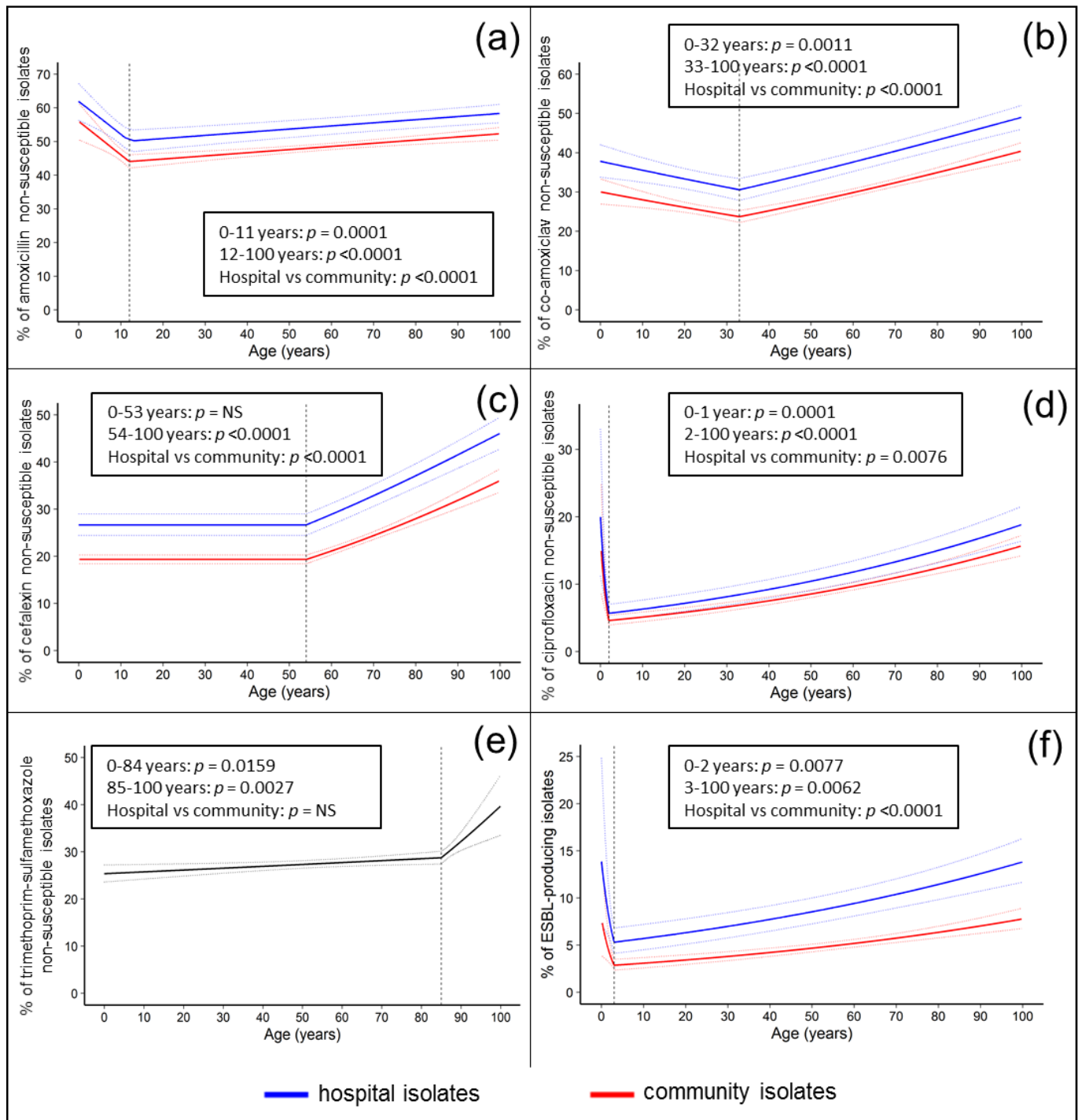
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Table 1. Prevalence rates of antibiotic non-susceptibility of all *E. coli* isolates for 15 antibiotics.

Antibiotic	Overall		Community		Hospital		<i>p</i> -value (hospital vs community)
	Number of isolates	Non-susceptible, n (%)	Number of isolates	Non-susceptible, n (%)	Number of isolates	Non-susceptible, n (%)	
Amoxicillin	13564	6736 (49.7)	11519	5615 (48.7)	2045	1121 (54.8)	<0.0001
Co-amoxiclav	13571	4332 (31.9)	11520	3537 (30.7)	2051	795 (38.8)	<0.0001
Piperacillin-tazobactam	13548	495 (3.7)	11507	374 (3.2)	2041	121 (5.9)	<0.0001
Cefalexin	13544	3328 (24.6)	11505	2689 (23.3)	2039	639 (31.3)	<0.0001
Ceftriaxone	13568	710 (5.2)	11517	538 (4.7)	2051	172 (8.4)	<0.0001
Ceftazidime	13344	405 (3.0)	11337	291 (2.6)	2007	114 (5.7)	<0.0001
Ertapenem	13550	29 (0.2)	11511	25 (0.2)	2039	4 (0.2)	0.8499
Meropenem	13558	0 (0)	11510	0 (0)	2048	0 (0)	n/a
Aztreonam	13423	545 (4.1)	11409	413 (3.6)	2014	132 (6.6)	<0.0001
Gentamicin	13561	779 (5.7)	11513	595 (5.2)	2048	184 (9.0)	<0.0001
Ciprofloxacin	13560	1360 (10.0)	11509	1108 (9.6)	2051	252 (12.3)	0.0002
Trimethoprim	13540	4210 (31.1)	11498	3573 (31.1)	2042	637 (31.2)	0.9141
Trimethoprim-sulfamethoxazole	13514	3768 (27.9)	11480	3204 (27.9)	2034	564 (27.7)	0.8669
Nitrofurantoin	12805	306 (2.4)	11219	262 (2.3)	1586	44 (2.8)	0.2840
Fosfomycin	12861	175 (1.4)	11260	152 (1.3)	1586	44 (2.8)	<0.0001

Overall rates and rates for hospital and community isolates shown separately. *p*-values indicate comparison of rates of non-susceptibility for hospital vs community isolates; significant *p*-values (*p* <0.05) indicated in bold.

Figure 1. Prevalence rates of antibiotic non-susceptibility by age.



Graphs represent 5 antibiotics with high rates of non-susceptibility (a-e) and ESBL-producing isolates (f). Solid lines represent best-fit log binomial regression models demonstrating change in rates of antibiotic susceptibility by age and dotted lines show 95% confidence intervals. For analyses where there was a significant difference ($p < 0.05$) between hospital and community isolates, separate regression lines are shown (hospital isolates in blue, community isolates in red). Adjusted p -values for each variable in the model are indicated. Vertical dashed lines represent the age cut-off where there was a change in the slope of the regression line. NS indicates not significant ($p \geq 0.05$). Note that model for trimethoprim is not shown because it was almost identical to the model with trimethoprim-sulfamethoxazole, although the age at which the regression line slope changed was 84 years.