

## Trends over time in Escherichia coli bloodstream infections, urinary tract infections, and antibiotic susceptibilities in Oxfordshire, UK, 1998–2016: a study of electronic health records

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1 **Trends in *Escherichia coli* bloodstream infection, urinary tract infections and**  
2 **antibiotic susceptibilities in Oxfordshire, 1998-2016: an observational electronic**  
3 **health records study**

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26

## 27 Abstract

28 **Background:** *Escherichia coli* bloodstream infections (EC-BSIs), particularly antibiotic-  
29 resistant EC-BSIs, are increasing in the UK and internationally. The evidence base to guide  
30 interventions against this major public health concern is limited. We aimed to investigate  
31 possible drivers of changes in EC-BSI incidence and antibiotic susceptibilities in Oxfordshire  
32 over the last two decades, while stratifying for hospital-exposure.

33 **Methods:** EC-BSIs and *E. coli* urinary tract infections (EC-UTIs) incidence in one UK region  
34 (Oxfordshire) were estimated from anonymised linked microbiological and hospital electronic  
35 health records, and modelled using negative binomial regression based on microbiological,  
36 clinical and healthcare exposure risk factors. Infection severity, 30-day all-cause mortality,  
37 and community and hospital co-amoxiclav use were also investigated.

38 **Findings:** From 1998-2016, 5706 EC-BSIs occurred in 5215 patients, and 228376 EC-UTIs  
39 in 137075 patients. 1365(24%) EC-BSIs were nosocomial (onset >48h post-admission),  
40 1863(33%) were community (>365 days post-discharge), 1346(24%) quasi-community (31-  
41 365 days post-discharge), and 1132(20%) quasi-nosocomial ( $\leq 30$  days post-discharge).  
42 1413(20%) EC-BSIs and 36270(13%) EC-UTIs were co-amoxiclav-resistant (41% and 30%,  
43 respectively, in 2016). Increases in EC-BSIs were driven by increases in community  
44 (10%/year (95% CI:7%-13%)) and quasi-community (8%/year (95% CI:7%-10%)) cases.  
45 Changes over time in EC-BSI-associated 30-day mortality were at most modest in the  
46 nosocomial (rate ratio=0.98 (95% CI 0.96,1.00),  $p=0.03$ ) and quasi-nosocomial (0.98  
47 (0.95,1.00),  $p=0.06$ ) groups, with no evidence for changes in mortality in the quasi-  
48 community (0.99 (0.96,1.01),  $p=0.32$ ) and community (0.99 (0.96,1.01),  $p=0.21$ ) groups.  
49 Mortality was, however, substantial (14-25% across groups). By contrast, co-amoxiclav-  
50 resistant EC-BSIs increased in all groups (by 11%-19%/year, significantly faster than  
51 susceptible EC-BSIs,  $p_{\text{heterogeneity}} < 0.0001$ ), as did co-amoxiclav-resistant EC-UTIs (by 13%-  
52 29%/year,  $p_{\text{heterogeneity}} < 0.0001$ ). Co-amoxiclav use in primary-care facilities was associated  
53 with subsequent co-amoxiclav-resistant EC-UTIs ( $p=0.03$ ) and all EC-UTIs ( $p=0.002$ ).

54 **Interpretation:** Current increases in EC-BSIs in Oxfordshire are primarily community-  
55 associated, with high rates of co-amoxiclav resistance; nevertheless, there was little or no  
56 change in mortality. Focussing interventions on primary-care facilities, particularly with high  
57 co-amoxiclav usage may be most effective, in this region and more generally.

58 **Funding:** National Institute for Health Research.

## 59 **Research in context**

### 60 **Evidence before this study**

61 We searched PubMed for publications from 1999-23 March 2018 , with the terms  
62 (“*Escherichia coli*” OR “*E. coli*”) AND (“bacteraemia” OR “bloodstream infection”), restricting  
63 the search to English language articles, and reviewed titles to identify relevant articles, and  
64 reference lists from relevant articles. *Escherichia coli* (*E. coli*) is one of the most common  
65 causes of bloodstream infection, and the incidence of *E. coli* bloodstream infection, and  
66 particularly antibiotic-resistant infections, is increasing in the UK and Europe. Although a  
67 previous study found increases in *E. coli* bacteraemias in Oxfordshire, this was through 2011  
68 only and did not investigate drivers in detail. The UK government aims to reduce healthcare-  
69 associated *E. coli* bloodstream infection; however, there is only limited evidence to inform  
70 appropriate interventions in the current era. Factors that may have contributed to the  
71 increasing incidence include the aging population and the increase in antibiotic use and  
72 antibiotic-resistant isolates. The percentage of cases that were identified within two days of  
73 admission has increased marginally over time. Voluntarily reported data reveals little change  
74 in terms of the most likely primary focus over time, with urinary tract infection consistently  
75 being the most frequent primary focus for *E. coli* bacteraemia cases. Incidence generally  
76 increases with higher temperatures.

77

### 78 **Added value of this study**

79 We investigated potential drivers for these increases in incidence by exploiting available  
80 linked electronic health records over 19 years for ~5200 patients with *E. coli* bloodstream  
81 infection and ~140000 with *E. coli* urinary tract infection, together with community  
82 antimicrobial prescribing data for the most recent six years. Our study identified several  
83 findings with significant implications for health policy and patient care:

- 84 • Increases in the incidence of *E. coli* bloodstream infections were driven mainly by  
85 non-hospital-associated cases; standardising for age and sex explained only 10-

86 26%, and standardising additionally for blood cultures taken only 9-28%, of the  
87 increase with the smallest percentage explained in non-hospital-associated cases;  
88 increases did not appear to be primarily due to patients with evidence of previous  
89 urinary tract infections

90 • Co-amoxiclav-resistant bloodstream infections rose significantly faster than co-  
91 amoxiclav-susceptible bloodstream infections, with the greatest number of co-  
92 amoxiclav-resistant bloodstream infections in 2016 being in patients discharged more  
93 than a month previously (i.e. community-associated)

94 • Higher co-amoxiclav use in primary care in the previous year was associated with  
95 higher rates of co-amoxiclav-resistant *E. coli* urinary tract infections in the  
96 subsequent year, supporting drives to reduce broad-spectrum and inappropriate  
97 antibiotic use in primary care

- 98       • Despite substantial increases in co-amoxiclav-resistant bloodstream infections there  
99       was no evidence that mortality was increasing in these cases; this does not support  
100       moving to broader empiric antibiotic prescribing in hospitals (i.e. carbapenems,  
101       piperacillin-tazobactam)

102   **Implications of all available advice**

103   This suggests that government strategies to effectively reduce *E. coli* bloodstream infections  
104   should prioritise community settings rather than focus primarily on healthcare-associated  
105   settings. The absence of an increased mortality signal suggests that co-amoxiclav resistant  
106   *E. coli* infections are either being successfully treated by dual empiric therapy in severe  
107   cases (e.g. with concomitant gentamicin), can be “rescued” once isolate susceptibilities  
108   become available, or currently deployed phenotypic susceptibility testing breakpoints do not  
109   adequately correlate with clinical outcome. Crucially, none of these explanations support  
110   broadening empiric antibiotic prescribing from co-amoxiclav.

111

## 112 Introduction

113 *Escherichia coli* is a major cause of bloodstream infection (BSI)<sup>1</sup> and a critical antimicrobial  
114 resistance (AMR) concern;<sup>2</sup> rates are rising across Europe.<sup>3-5</sup> *E. coli* bloodstream infections  
115 (EC-BSIs) reported (voluntarily) to Public Health England rose by 44% between 2003-2011.<sup>6</sup>  
116 After introducing mandatory reporting in July 2011, a further 28% increase occurred by July-  
117 September 2016, to 78.8 cases/100,000 population.<sup>7</sup>

118

119 As elsewhere, most (>70%) EC-BSIs in England are identified within two days of admission.<sup>7</sup>  
120 However, the impact of previous hospital-exposure on trends in EC-BSI has not been  
121 comprehensively investigated, with only two relevant previous studies, one in the Calgary  
122 Health Region 2000-2006,<sup>8</sup> and another in Oxfordshire in 1999-2011<sup>9</sup>; further, the relevance  
123 of such older studies to current trends is unclear. EC-BSI source may also differ by hospital-  
124 exposure. In a recent study, ~50% of EC-BSIs in England were considered most likely due  
125 to urinary tract infections (UTIs);<sup>10</sup> gastrointestinal foci are more common in inpatients.<sup>7</sup>

126

127 30-day all-cause mortality following EC-BSI is ~16%;<sup>11</sup> and could rise given the impact of  
128 increasing AMR on outcomes.<sup>2</sup> In Oxfordshire, EC-BSI incidence rises through 2011 were  
129 essentially confined to ciprofloxacin-, co-amoxiclav-, cefotaxime- and/or aminoglycoside-  
130 resistant organisms.<sup>9</sup> The reasons for rising resistant EC-BSI, and EC-BSI more generally,  
131 are unclear, with increased antibiotic usage or resistance implicated in some, but not all,  
132 studies;<sup>5,12-18</sup> an aging population is also hypothesised to contribute.<sup>5</sup> Although individual  
133 hospital and primary-care guidelines vary, in England co-amoxiclav is commonly used as  
134 empiric treatment, particularly for community-acquired pneumonia and undifferentiated  
135 sepsis in hospitals,<sup>19</sup> as well as for prophylaxis, making it one of the most commonly used  
136 antibiotics in England.<sup>20</sup> Hence, trends in co-amoxiclav resistance are particularly important.

137 We therefore aimed to investigate possible drivers of changes in EC-BSI incidence and  
138 antibiotic susceptibilities in Oxfordshire over the last two decades, while stratifying for  
139 hospital-exposure. We hypothesized that increases may be due to features of the at-risk

140 population (therefore exploring demographics, recurrent infections, increased  
141 ascertainment), healthcare-history (previous urine cultures, catheter specimens, admission  
142 diagnoses, antibiotic usage), and/or the bacteria (exploring mortality/severity, AMR burden).  
143

## 144 Methods

145 The Infections in Oxfordshire Research Database (IORD)<sup>21</sup> records all admissions to the  
146 Oxford University Hospitals National Health Service Foundation Trust (OUH), Oxfordshire,  
147 UK, from April 1997, linked by patient with microbiology and biochemistry/haematology  
148 results. The four OUH hospitals provide all acute care, microbiology and pathology services  
149 in the region (~680,000 individuals). Out-of-hospital mortality was determined by updates  
150 from a national information system. IORD has Research Ethics Committee and  
151 Confidentiality Advisory Group approvals (14/SC/1069, ECC5-017(A)/2009). Data on  
152 antibiotic prescribing and numbers of registered patients for each primary-care facility were  
153 obtained from the Health and Social Care Information Centre (available January 2011-  
154 December 2016 only).

155

156 The primary study outcome was EC-BSI, defined as *E. coli* isolated from blood cultures  
157 taken 01/Jan/1998-31/Dec/2016 inclusive, including polymicrobial cultures (13%), without  
158 age restriction and de-duplicated within 14-days of each index positive following mandatory  
159 reporting guidelines.<sup>22</sup> For context we also analysed *E. coli* UTIs (EC-UTIs), defined as pure  
160 culture from urine of  $>10^4$  colony-forming-units/ml, de-duplicated within 90-days to avoid  
161 over-counting ongoing infections.<sup>23</sup> We classified EC-BSIs/EC-UTIs as 'nosocomial' if  
162 samples were taken  $>48$ h post-admission until discharge.<sup>24</sup> All other EC-BSIs/EC-UTIs were  
163 classified as 'community', 'quasi-community' or 'quasi-nosocomial' if the last hospital  
164 discharge was  $>1$  year, 31-365 days, or 0-30 days previously.<sup>8,25-27</sup> We also calculated  
165 incidences of first ever and recurrent EC-BSIs. See Supplementary Methods for further  
166 details.

167

168 To assess demographic changes such as ageing and population growth, we standardised  
169 incidence against the 1998 Oxfordshire age-sex population (estimates from the UK Office for  
170 National Statistics).<sup>28</sup> To assess ascertainment, we considered the incidence of blood/urine

171 cultures, regardless of result, and also additionally standardised outcome for culture rates.  
172 Both standardisations were done using inverse probability weighting.

173

174 As a proxy for changes in bacterial virulence, we considered separately 30-day mortality  
175 after sample collection, and levels of monocytes, neutrophils, lymphocytes, C-reactive  
176 protein (CRP), creatinine and urea at sample collection (closest value within [-2,+2] days).  
177 To assess the impact of AMR, which might also affect treatment outcomes, we investigated  
178 EC-BSI reported by the diagnostic laboratory as resistant to amoxicillin, co-amoxiclav,  
179 trimethoprim, gentamicin, ciprofloxacin, ceftriaxone, ceftazidime, piperacillin-tazobactam and  
180 meropenem, and EC-UTI reported as resistant to amoxicillin, co-amoxiclav, trimethoprim,  
181 ciprofloxacin, nitrofurantoin and cefalexin (the only drugs consistently tested throughout the  
182 study period). Susceptibility testing was performed using disk-diffusion to 31/Jan/2013, then  
183 by microbroth dilution (BD Phoenix™ Automated Microbiology System, Beckton Dickinson,  
184 Franklin Lakes, NJ, USA) (see Supplementary Methods).

185

186 Guidelines recommend empirical treatment for uncomplicated UTIs and for urine samples to  
187 be sent for microbiological testing only from individuals with clinical treatment failure,  
188 frequent or recurrent UTI or with possibly resistant infections.<sup>20</sup> To investigate this group, we  
189 first classified EC-BSIs by whether the patient had ever had an EC-UTI  $\geq 3$  days previously.  
190 To investigate the contribution of UTI around EC-BSIs, including symptomatic UTIs where *E.*  
191 *coli* was not isolated, we classified EC-BSIs as 'likely urine-associated' (urine sample taken  
192 3-30 days previously; EC-UTI or mixed growth/negative but UTI suspected clinically from  
193 request codes), 'urosepsis' (defined as 'likely urine-associated' but urine samples within (-  
194 3,+2] days of the EC-BSI), 'unlikely urine-associated' (UTI with non-*E. coli* pathogen or no  
195 urine sample), or 'unknown' (other) (details in Supplementary Methods). To investigate the  
196 contribution of catheters, we classified EC-BSIs by whether a catheter urine specimen had  
197 been submitted up to and including the day of blood collection (regardless of result).

198

199 To investigate the contribution of previous admission characteristics, we classified quasi-  
200 nosocomial EC-BSIs by whether the primary diagnostic code of the antecedent admission  
201 was infection-related, or any diagnostic code (primary/secondary) included UTI  
202 (Supplementary Methods and Results).

203

#### 204 *Statistical analysis*

205 Counts of EC-BSI/EC-UTI per month were modelled using negative-binomial regression  
206 (incorporating overdispersion), assuming the same underlying population (no offset). 30-day  
207 mortality following EC-BSI and CRP $\geq$ 156mg/L at EC-BSI (binary) were modelled using  
208 poisson regression (to estimate analogous rate ratios), and absolute values of other test  
209 results were modelled using median quantile regression, both against sample date and  
210 adjusted for age and sex. Changes in trends in all outcomes were estimated using iterative  
211 sequential regression,<sup>29</sup> and compared between outcomes using stacked regression.<sup>30</sup>  
212 Bivariate cross-correlations summarised univariable associations between hospital  
213 antimicrobial usage and nosocomial co-amoxiclav-resistant EC-BSIs. To estimate  
214 associations with primary care co-amoxiclav usage, co-amoxiclav defined-daily-doses  
215 (DDD) per 1000 registered patients in the previous or current year and primary-care facility  
216 were included as explanatory variables with the number of patients per primary-care facility  
217 per year as an offset in negative-binomial regression models for yearly co-amoxiclav  
218 resistant EC-UTIs, EC-UTIs and all urines regardless of result. Full details, including missing  
219 data, are provided in Supplementary Methods.

220

221 Analyses were conducted using R 3.2.2,<sup>31</sup> and STATA 14.1 for stacked regression and  
222 probability weighted analyses.

223

#### 224 *Role of the funding source*

225 The study sponsor had no role in design, data collection, analysis, interpretation, or writing of  
226 the report. The corresponding author had full access to all the data and had final  
227 responsibility for the decision to submit for publication.  
228

## 229 Results

230 After 14-day de-duplication, from 1998-2016 5706 EC-BSIs occurred in 5215 patients (i.e.  
231 9% recurrences (relapse and/or reinfection)). Recurrences occurred a median(IQR) 144(39-  
232 577) days apart: of 391 patients with recurrences, 324(83%) had one and 52(13%) had two  
233 (range 1-8). Overall incidence increased year-on-year (annual incidence rate ratio  
234 (IRR)=1.06 (95% CI 1.05-1.06)). Most (5393(95%)) EC-BSI cases were admitted to OUH  
235 before or within 24h following blood culture (remainder mostly sampled in emergency  
236 departments/community hospitals). Only 1365(24%) EC-BSIs were 'nosocomial' ( $\geq 48$ h post-  
237 admission). A further 1132(20%) were 'quasi-nosocomial' (discharged up to 30 days  
238 previously), 1346(24%) were 'quasi-community' (discharged 31-365 days previously) and  
239 1863(33%) were 'community' cases (discharged  $>1$  year previously or never previously  
240 admitted to OUH). The 1132 quasi-nosocomial EC-BSI were most commonly previously  
241 admitted for malignancy (395,35%), gastrointestinal disorders (177,16%), and  
242 renal/urological disorders (164,14%) (**Supplementary Table 1**), with no major temporal  
243 variability (**Supplementary Figure 1A**).

244

245 Incidence trends for EC-BSIs varied substantially with hospital-exposure (**Figures 1A&2A**,  
246 **Supplementary Table 2**), with overall increases clearly driven by community and quasi-  
247 community hospital-exposure groups, and no evidence of different incidence trends between  
248 these two groups in 2016 ( $p_{\text{heterogeneity}}=0.27$ ). By contrast, quasi-nosocomial and nosocomial  
249 EC-BSIs increased more slowly. Considering only the first EC-BSI per patient or subsequent  
250 EC-BSIs (**Figure 2A**, **Supplementary Figure 2**) gave broadly similar results. Year-on-year  
251 increases in the incidence of first EC-BSI became smaller (but still significant) the more  
252 recent the hospital exposure. Quasi-community recurrent EC-BSI increased faster than first  
253 EC-BSIs ( $p_{\text{heterogeneity}}<0.0001$ ) and the stable current trend in the incidence of all quasi-  
254 nosocomial EC-BSIs was driven by reduced recurrences in this group.

255

256 After 90-day de-duplication, 228376 EC-UTIs occurred in 137075 patients (i.e. 40%  
257 recurrences (relapse/re-infection)). Recurrences occurred a median(IQR) 457(200-1119)  
258 days apart: of the 41371(30%) patients with recurrences, 22011(53%) had one and  
259 8742(21%) had two (range 1-33). 12898(9%) patients had two EC-UTI within six months.  
260 EC-UTIs were predominantly community (160359,70%), and less commonly quasi-  
261 community (44283,19%), quasi-nosocomial (12764,6%) or nosocomial (10970,5%).  
262 Incidence of EC-UTI increased over 1998-2016 in community, quasi-community and quasi-  
263 nosocomial groups, although current trends were fairly stable, but declined significantly in  
264 the nosocomial group (**Figure 1B&2B**). Furthermore, increases were accounted for entirely  
265 by substantial increases in recurrent EC-UTI episodes, with decreasing overall trends in first  
266 EC-UTI per patient (**Supplementary Figure 3**).

267

268 In 2016, therefore, recurrences accounted for at least half of community, quasi-community  
269 and quasi-nosocomial EC-UTIs, and around a fifth of quasi-community and quasi-  
270 nosocomial EC-BSIs (**Supplementary Table 3**).

271

#### 272 *Impact of population and sampling on EC-BSI*

273 Blood culture submission rates increased substantially from 1998-2016 for community/quasi-  
274 community/quasi-nosocomial groups (**Figure 2A, Supplementary Figure 4**), raising the  
275 possibility that observed increases in EC-BSIs were driven by increases in the use of blood  
276 cultures as a diagnostic test. However, there was no suggestion that the indications for blood  
277 culture changed with time: changes in neutrophils and CRP when cultures were taken were  
278 small and not clinically meaningful and 30-day mortality post blood culture sampling was  
279 stable (**Supplementary Figure 5**). Further, increases in community blood culture  
280 submission rates were significantly smaller than increases in community EC-BSIs  
281 ( $p=0.0006$ , **Figure 2A**). Standardising for age and sex explained only 10-26%, and  
282 standardising additionally for blood cultures taken only 9-28%, of the increase in overall or  
283 first-per-patient EC-BSIs, with the greatest percentage explained in nosocomial EC-BSIs and

284 the least in community EC-BSIs (**Supplementary Tables 4,5**). In contrast, urine sample  
285 submission was more stable over time (**Supplementary Figure 6**).

286

### 287 *Disease severity of EC-BSIs*

288 30-day mortality following EC-BSI declined slightly in the nosocomial (IRR=0.98 (95% CI  
289 0.96,1.00), p=0.03) and quasi-nosocomial (IRR=0.98 (0.95,1.00), p=0.06) groups, but there  
290 was no evidence for changes in quasi-community (IRR=0.99 (0.96,1.01), p=0.32) and  
291 community (IRR=0.99 (0.96,1.01), p=0.21) groups (**Supplementary Figure 7**, adjusting for  
292 age and sex). Mortality was substantial at 25% (340/1363), 19% (217/1128), 16%  
293 (219/1344) and 14% (254/1784) across the groups, respectively (**Supplementary Table 6**).

294 Changes in haematology/biochemistry test results over time were small and/or non-  
295 significant (**Supplementary Figure 7**), and did not indicate that less severe infections were  
296 being identified, or that there were changes in pathogen virulence.

297

### 298 *Impact of previous illness on EC-BSI*

299 1755(31%) EC-BSI occurred in patients with an EC-UTI  $\geq 3$  days previously (median(IQR)  
300 213(43-918) days previously). However, incidence trends were broadly similar for EC-BSIs  
301 with or without EC-UTIs  $\geq 3$  days previously, although quasi-community EC-BSIs were rising  
302 particularly fast in those with previous EC-UTIs ( $p_{\text{heterogeneity}} < 0.0001$ , **Figure 2A**,  
303 **Supplementary Figure 8**). We next explored whether EC-BSI increases were associated  
304 with past symptomatic UTIs, including those without positive urine cultures. Considering  
305 urine samples/results taken within 30 days before the EC-BSI, and incorporating information  
306 on mixed growth and request codes, only 760(13%) EC-BSIs were 'likely urine-associated',  
307 with 1613(28%) 'urosepsis', 1613(28%) 'unlikely urine-associated' (of which 181[11%] had a  
308 contemporaneous urine specimen positive for another pathogen), and 1720(30%) unknown.  
309 However, the relative proportions of these did not vary substantially over time (**Figure 3**),  
310 suggesting no specific subgroup was associated with incidence increases. Percentages of  
311 EC-BSIs with a previous catheter urine specimen (CSU) increased across hospital-exposure

312 groups, being present in 365(20%) community, 364(32%) quasi-community, 541(40%),  
313 quasi-nosocomial, 584(43%) nosocomial cases. However, incidence trends were broadly  
314 similar for EC-BSIs with or without a previous CSU (**Figure 2A, Supplementary Figure 9**),  
315 although quasi-nosocomial EC-BSIs were rising particularly fast in those with previous CSUs  
316 ( $p_{\text{heterogeneity}}=0.0002$ ), while increases in nosocomial EC-BSIs were restricted to those without  
317 previous CSUs ( $p_{\text{heterogeneity}}=0.03$ ).

318

### 319 *Antimicrobial susceptibility*

320 Exploring the possibility that EC-BSI increases were associated with AMR, the only EC-BSI  
321 antibiotic-resistant phenotype that consistently increased across all hospital-exposure  
322 groups was co-amoxiclav ( $p<0.0001$ ; **Figures 2A&4**), with 212(41%) of 515 EC-BSIs in  
323 2016 being co-amoxiclav resistant (**Supplementary Tables 6,7**). Co-amoxiclav-resistant  
324 EC-BSIs increased significantly faster than co-amoxiclav-susceptible EC-BSIs  
325 ( $p_{\text{heterogeneity}}<0.0001$ ), but community and quasi-community co-amoxiclav-susceptible EC-  
326 BSIs were still increasing significantly in 2016 ( $p<0.0001$ ) (**Figure 4**). Most (942/1412, 67%)  
327 co-amoxiclav-resistant EC-BSIs remained susceptible to gentamicin and ciprofloxacin  
328 (**Figure 4**).

329

330 Increases in other antibiotic-resistant EC-BSIs were most notable in the community and  
331 quasi-community groups, with significant year-on-year increments in all but trimethoprim-  
332 resistant EC-BSIs, which remained stable in these groups (**Supplementary Figure 10**). Co-  
333 amoxiclav-resistant EC-UTIs also rose consistently and significantly regardless of  
334 healthcare-exposure, but trends were more variable for other antibiotics (**Supplementary**  
335 **Figure 11**). In 2016, 3921/13792(28%) EC-UTIs were co-amoxiclav-resistant.

336

337 Given the substantial increase in co-amoxiclav resistant EC-BSIs, we investigated whether  
338 severity differed in susceptible versus resistant cases. There was no strong evidence that  
339 co-amoxiclav-resistant EC-BSIs were associated with higher neutrophil counts in any

340 hospital-exposure group ( $p > 0.04$ , adjusting for age and sex), or that neutrophil counts were  
341 changing differently over time in co-amoxiclav-resistant versus co-amoxiclav-susceptible EC-  
342 BSI ( $p_{\text{heterogeneity}} > 0.67$ ; **Supplementary Figure 12**). Mortality was higher for co-amoxiclav-  
343 resistant vs co-amoxiclav-susceptible nosocomial EC-BSIs (unadjusted 30% (117/395) vs  
344 23% (222/967) respectively; rate ratio adjusting for age and sex = 1.32 (1.13-1.46)  $p = 0.002$ ).  
345 However, there was no evidence of higher mortality in co-amoxiclav-resistant  
346 community/quasi-community/quasi-nosocomial EC-BSIs ( $p > 0.48$ ), and mortality did not  
347 change differently over time in any group ( $p_{\text{heterogeneity}} > 0.35$ ; **Supplementary Figure 12**,  
348 **Figure 2C**) (**Supplementary Table 6**).

349

350 The strongest associations with nosocomial co-amoxiclav-resistant EC-BSIs were with  
351 hospital co-amoxiclav (cross-correlation 0.75) and third-generation cephalosporin (0.80) use  
352 (**Supplementary Table 8**; available only financial years 2003-2014). Community prescribing  
353 data was only available from 2011, and co-amoxiclav-resistant EC-BSIs were too few to  
354 consider relationships with co-amoxiclav use. However, from 2012-2016, primary care  
355 facilities prescribing more co-amoxiclav in the previous year had higher rates of subsequent  
356 co-amoxiclav-resistant-community-EC-UTIs (IRR (per 100DDD higher) = 1.05 (95% CI 1.02-  
357 1.08)  $p = 0.003$ , **Figure 5**), co-amoxiclav use in the current year did not add any predictive  
358 value ( $p = 0.12$  adjusted for previous year vs  $p = 0.64$  alone). In contrast, facilities prescribing  
359 more co-amoxiclav in the current year had higher rates of community-EC-UTIs and urine  
360 specimen submission (IRR = 1.02 (1.00-1.04)  $p = 0.01$  and 1.02 (1.01-1.03)  $p = 0.0001$   
361 respectively); co-amoxiclav use in the previous year did not add any predictive value ( $p = 0.58$   
362 adjusted for current year vs  $p = 0.11$  alone, respectively  $p = 0.21$  adjusted for current year vs  
363  $p = 0.006$  alone).. Results were seen across all samples regardless of hospital-exposure  
364 group (**Supplementary Figure 13**), and also when adjusting instead for the proportion aged  
365 over 65 and male in 2017 per practice. There was no association between current/prior  
366 quinolone use and any of these outcomes ( $p > 0.9$ ).

## 367 Discussion

368 We have explored potential explanations for continuing increases in EC-BSI in Oxfordshire  
369 over 19 years using extensive, routinely-collected data, including laboratory/microbiology  
370 results. Incidence varied dramatically by hospital-exposure, with increases being driven by  
371 community/quasi-community cases. This is important given the National Health Service  
372 ambition to reduce Gram-negative BSIs by targeting 'healthcare-associated' cases (although  
373 this definition incorporates recent community antibiotic use). Previous successful campaigns  
374 to reduce methicillin-resistant *Staphylococcus aureus* (MRSA) BSI and *Clostridium difficile*  
375 infections also focussed on nosocomial risk factors. Our data suggest that defining  
376 appropriate strategies aiming to reduce community/quasi-community associated EC-BSIs,  
377 such as improved catheter care and improved quality of antibiotic use for UTI management  
378 in the community, might have a greater impact. Given that recent antibiotic use is the  
379 greatest risk factor for subsequent resistant UTIs,<sup>32</sup> many people prescribed antibiotics may  
380 not have bacterial UTIs,<sup>33</sup> and many bacterial UTIs may resolve in a similar timeframe  
381 without antibiotics,<sup>34</sup> better point-of-care tests that predict benefit from antibiotics are  
382 urgently needed to guide prescribing decisions. Co-amoxiclav-resistant EC-BSIs rose  
383 significantly faster than co-amoxiclav-susceptible EC-BSIs, regardless of hospital-exposure,  
384 with the greatest number of co-amoxiclav-resistant EC-BSIs in 2016 being community/quasi-  
385 community EC-BSIs. Primary-care facilities with higher co-amoxiclav prescribing rates in the  
386 previous year had more co-amoxiclav resistant EC-UTIs in the subsequent year. Co-  
387 amoxiclav is one of the most commonly prescribed antibiotics nationally in both the  
388 community and hospitals in England,<sup>20,35</sup> and our findings are consistent with this exerting  
389 selection pressure for co-amoxiclav resistant EC-UTI and EC-BSI. Despite co-amoxiclav  
390 being used for empiric BSI treatment, there were no clinically important changes in mortality.  
391  
392 EC-BSI is generally considered 'community-acquired' although there are differing definitions  
393 of healthcare-associated BSI.<sup>7,26</sup> By linking to previous hospital admissions, one major study  
394 strength is that we could identify that incidence trends for non-nosocomial EC-BSIs varied

395 significantly by time since discharge. Blood sample submission also increased significantly  
396 over time, potentially increasing ascertainment of 'mild' cases. However, blood cultures are  
397 key to the assessment of unwell patients whenever infection is suspected, and there were no  
398 clinically important changes in EC-BSI-associated severity at presentation or mortality,  
399 despite substantially increasing incidence, suggesting major ascertainment bias is unlikely.  
400 As standardising for age/sex using crude data available had at most modest effects, main  
401 analyses did not use this.

402

403 The increasing trend in nosocomial EC-BSI was significantly smaller than for  
404 community/quasi-community EC-BSI in Oxfordshire, as observed nationally.<sup>10</sup> Multiple  
405 infection control interventions were rolled out in UK hospitals from 2005-2010<sup>36,37</sup> in  
406 response to MRSA/*C. difficile*, and horizontal components could have contributed to lowering  
407 nosocomial rates. Consistent with this, increases in hospital-onset Gram-negative BSI  
408 reversed after introducing a MRSA Prevention Initiative in the US, while community-acquired  
409 incidence remained unchanged.<sup>38</sup>

410

411 Whereas MRSA and *C. difficile* are predominantly hospital-associated pathogens,  
412 differences in EC-BSI epidemiology highlight the need for different interventions, particularly  
413 in primary care.<sup>7</sup> In particular, recurrences explain relatively little of the ongoing increases in  
414 EC-BSIs, and both co-amoxiclav-resistant and co-amoxiclav-susceptible EC-BSI are rising.  
415 Overall, 42% of EC-BSI appeared to be more likely amenable to urinary-focussed  
416 intervention, similar to an England-wide study that found 51% of EC-BSIs had an underlying  
417 urogenital tract focus, with UTI treatment in the prior four weeks the largest independent risk  
418 factor.<sup>10</sup> In our study, 13% of EC-BSIs were likely urine-associated and 28% presented as  
419 urosepsis; the first group may be most tractable for prevention but was smallest in both  
420 community and quasi-community EC-BSI, whereas urosepsis was the largest. One key  
421 limitation is lack of data on visits to primary-care facilities, meaning our assessment of

422 urinary sources relied on samples being submitted for microbiological testing, and may  
423 therefore underestimate the true burden of urinary-associated EC-BSI, since some patients  
424 may have had UTI symptoms and either did not present to primary-care facilities or were  
425 treated empirically without a urine sample being submitted. Changes in patient health-  
426 seeking behaviour or sample submission over time could lead to bias in attributing EC-BSIs  
427 to different sources. However, successfully treated UTIs, and those resolving without  
428 intervention, should not cause bacteraemia, and bacteraemias due to UTI treatment failure  
429 should be ascertained within our data since guidelines recommend urine samples be  
430 submitted from individuals with clinical treatment failure, frequent or recurrent UTI or with a  
431 possibly resistant infection.<sup>20</sup> . Much of the burden of EC-BSIs, and especially the  
432 rising incidence, is hypothesized to arise from poor urinary catheter care. However, only  
433 20% and 30% of the community and quasi-community groups, where incidence is increasing  
434 fastest, had a previous CSU, and there was no evidence that incidence was increasing  
435 faster in those with a previous CSU versus without. One key limitation is that we did not have  
436 records of the presence of a catheter, but only urine specimens recorded as being taken  
437 from a catheter, arguing that if a catheter was present and causing infection, a specimen  
438 would likely have been taken from it at some time. Similarly, we did not have direct  
439 information on the source of each individual EC-BSI. Interestingly, there was strong  
440 evidence that quasi-nosocomial EC-BSIs with UTI or infectious diagnostic codes in the  
441 previous admission were rising faster than those without (**Supplementary Figure 1**). This  
442 may reflect underlying predisposition to infection (e.g. chronic illnesses), or that prior  
443 antibiotic use adversely affects a patient's microbiota potentially leading to  
444 colonisation/overgrowth by more pathogenic *E. coli*, thus predisposing to EC-BSI.

445

446 A limitation of surveillance studies is changes in antimicrobial susceptibility testing  
447 methodology (here in February 2013). Whilst testing protocol can affect results,<sup>39,40</sup> crucially  
448 changes in co-amoxiclav resistance around this time occurred regardless of method

449 **(Supplementary Figure 14)**. Recent data suggest that broth dilution (BD-Phoenix) and the  
450 gold standard agar dilution have high agreement;<sup>41</sup> thus, rising rates of co-amoxiclav-  
451 resistant (as defined by EUCAST breakpoints) EC-BSI/EC-UTI are likely correct.

452

453 We also found that primary-care facilities with higher co-amoxiclav prescribing rates in the  
454 previous year were more likely to have patients diagnosed with co-amoxiclav resistant EC-  
455 UTIs in the subsequent year. Similar associations between trimethoprim use and  
456 trimethoprim-resistant urine-associated EC-BSI have been reported in adult women in  
457 England,<sup>16</sup> and recently more generally across multiple antibiotic classes for EC-UTI.<sup>17</sup> Over  
458 the period with contemporary prescribing data, co-amoxiclav-resistant EC-BSI were too few  
459 to investigate associations with antibiotic prescribing within the community. Assessing  
460 usage-resistance associations is complicated, since changes in use of one antibiotic are  
461 generally accompanied by compensatory prescribing, and may be compounded by multi-  
462 drug resistance. Comparisons are ecological, which is a key limitation. Our results may also  
463 not be generalizable; for example, although the region we studied is sizeable (~1% of the  
464 UK), we did not observe a uniform decrease in cephalosporin-resistant and quinolone-  
465 resistant EC-BSIs as seen in BSI caused by *Enterobacteriaceae*.<sup>15</sup> Such differences likely  
466 reflect a complex interplay of selection pressures.

467

468 A key limitation is that we were unable to assess associations between individual-patient  
469 antibiotic use (not available in the research database) and risk of resistant infections or  
470 between specific empiric regimens and outcome; these are important future research  
471 priorities. However, there were no clinically important changes in mortality overall, by co-  
472 amoxiclav-susceptible/resistant phenotype, or by hospital-exposure. Co-amoxiclav remains  
473 our recommended first-line empiric treatment for most severe infections, so the substantial  
474 increase in incidence of co-amoxiclav-resistant bacteraemias suggests either that initial  
475 inappropriate treatment can be successfully rescued,<sup>42</sup> or that the current definition of co-  
476 amoxiclav breakpoints may be suboptimal.<sup>43</sup> Crucially, neither scenario supports a move

477 towards broader empiric antibiotic treatment, consistent with prevailing antimicrobial  
478 stewardship messages.

479

480 Another inherent limitation is restriction to the routinely collected data available, in particular  
481 lack of information on prognostic factors such as illness severity scores, lack of individual  
482 antibiotic prescribing data (as above), and having only antibiograms since strain typing was  
483 not routinely performed. Representative isolates from 2008-present have been selected for  
484 whole genome sequencing and their analysis may increase our understanding of the  
485 pathogenesis of EC-BSI. For example, the distinct change in the monthly incidence of  
486 community EC-BSI in July 2010 could reflect the introduction and proliferation of a new  
487 strain of *E. coli* to the region.<sup>44</sup>

488

489 In summary, on-going increases in EC-BSI were driven by community and quasi-community  
490 cases, and cannot be attributed only to increased recurrences or an aging population.

491 Absence of changes in mortality and severity do not support ascertainment bias playing a  
492 major role, although this cannot be excluded. Whilst urinary foci are clearly important, at  
493 present the scope for intervening to prevent UTIs progressing to bacteraemia could be  
494 limited. Notably, higher co-amoxiclav use in primary care was associated with higher  
495 subsequent rates of co-amoxiclav-resistant EC-UTI, supporting drives to reduce broad-  
496 spectrum and inappropriate antibiotic use. However, despite substantial increases in co-  
497 amoxiclav-resistant EC-BSI, evidence that patient clinical outcomes are no worse does not  
498 support broadening empiric antibiotic prescribing from co-amoxiclav.<sup>11</sup>

499

500

501 *Contributors*

502 KDV, NS, DHW, TEAP, and ASW designed the study. TPQ prepared extracts from the IORD  
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504 TEAP and ASW prepared the figures. KDV, NS, and ASW prepared the first draft of the  
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507

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652

653

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677 content critically and approved the final version.

678 Please contact the corresponding author for questions regarding the analysis, data or code.

679

## 680 Figure legends

681 Figure 1. Monthly (A) EC-BSI and (B) EC-UTI according to recent hospital-exposure (first  
682 and recurrent infections).

683 Footnote: only counting EC-BSI recurrences occurring >14 days after an index positive, and  
684 EC-UTI recurrences occurring >90 days after an index positive. Thick blue line represents  
685 the estimated incidence by iterative sequential regression (ISR). Blue lines at the base of the  
686 graph represent 95% CI around the breakpoints estimated by the ISR model. IRR=annual  
687 incidence rate ratio in 2016, that is the relative increase in rate per year as estimated in  
688 2016.

689

690 Figure 2. Summary of incidence trends in 2016 for (A) EC-BSIs, (B) EC-UTIs, and (C)  
691 severity of co-amoxiclav resistant and sensitive EC-BSIs.

692 Footnote: IRR=annual incidence rate ratio in 2016, that is the relative increase in rate per  
693 year as estimated in 2016. See Supplementary Table 1 for numbers and heterogeneity tests.

694

695 Figure 3. Annual EC-BSI according to recent hospital-exposure and urine sample  
696 submission/results.

697 Footnote: See Supplementary Methods for definitions.

698

699 Figure 4. Annual EC-BSI susceptible and resistant to co-amoxiclav, with and without  
700 resistance to gentamicin and ciprofloxacin, according to recent hospital-exposure.

701 Footnote: IRR=annual incidence rate ratio in 2016, that is the relative increase in rate per  
702 year as estimated in 2016.

703

704 Figure 5. Community co-amoxiclav-resistant EC-UTIs (A), community EC-UTIs (B) and  
705 community urine samples submitted regardless of result (C) per 1000 patients per primary-  
706 care facility 2012-2016 compared with co-amoxiclav usage.

707 Footnote: showing one record per year per primary-care facility. For (A) the strongest  
708 predictor was co-amoxiclav DDD per 1000 patients per general practice in the previous year;  
709 for (B) and (C) the strongest predictor was co-amoxiclav DDD per 1000 patients per general  
710 practice in the current year. Spearman rho (and models) for each panel excludes 5 facilities  
711 which submitted less than 151 samples over 2011-2016 (all others submitted over 300).  
712 Spearman rho for univariable associations with previous vs current co-amoxiclav usage for  
713 the 3 outcomes left to right  $\rho=0.20$  vs  $\rho=0.04$ ,  $\rho=0.33$  vs  $\rho=0.35$ ,  $\rho=0.37$  vs  $\rho=0.40$   
714 respectively.