Journal of Hospital Infection 101 (2019) 120–128

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Factors that impact on the burden of *Escherichia coli* bacteraemia: multivariable regression analysis of 2011–2015 data from West London

O. Blandy [a], K. Honeyford [a], M. Gharbi [a], A. Thomas [a], F. Ramzan [a], M.J. Ellington [b], R. Hope [b], A.H. Holmes [a], A.P. Johnson [a,b], P. Aylin [a,c], N. Woodford [a,b], S. Sriskandan [a,*]

[a] *NIHR Health Protection Research Unit for Healthcare-Associated Infections and Antimicrobial Resistance, Imperial College, London, UK*
[b] *National Infection Service, Public Health England, UK*
[c] *Department of Primary Care and Public Health, Imperial College, London, UK*

ARTICLE INFO

Article history:
Received 7 September 2018
Accepted 30 October 2018
Available online 4 November 2018

Keywords:
Escherichia coli
Bacteraemia
Gram negative
Risk factor
Burden of disease

SUMMARY

Background: The incidence of *Escherichia coli* bacteraemia in England is increasing amid concern regarding the roles of antimicrobial resistance and nosocomial acquisition on burden of disease.

Aim: To determine the relative contributions of hospital-onset *E. coli* bloodstream infection and specific *E. coli* antimicrobial resistance patterns to the burden and severity of *E. coli* bacteraemia in West London.

Methods: Patient and antimicrobial susceptibility data were collected for all cases of *E. coli* bacteraemia between 2011 and 2015. Multivariable logistic regression was used to determine the association between the category of infection (hospital or community-onset) and length of stay, intensive care unit admission, and 30-day all-cause mortality.

Findings: *E. coli* bacteraemia incidence increased by 76% during the study period, predominantly due to community-onset cases. Resistance to quinolones, third-generation cephalosporins, and aminoglycosides also increased over the study period, occurring in both community- and hospital-onset cases. Hospital-onset and non-susceptibility to either quinolones or third-generation cephalosporins were significant risk factors for prolonged length of stay, as was older age. Rates of mortality were 7% and 12% at 7 and 30 days, respectively. Older age, a higher comorbidity score, and bacteraemia caused by strains resistant to three antibiotic classes were all significant risk factors for mortality at 30 days.

Conclusion: Multidrug resistance, increased age, and comorbidities were the main drivers of adverse outcome. The rise in *E. coli* bacteraemia was predominantly driven by community-onset infections, and initiatives to prevent community-onset cases should be a major focus to reduce the quantitative burden of *E. coli* infection.

* Corresponding author. Address: Section of Infectious Diseases and Immunity, Du Cane Road, Imperial College London, London W12 0NN, UK. Tel.: +44 (0)208 383 3135.
E-mail address: s.sriskandan@imperial.ac.uk (S. Sriskandan).

https://doi.org/10.1016/j.jhin.2018.10.024

Introduction

Escherichia coli is the most common pathogen causing bacteraemia in the UK and a major cause of morbidity and mortality [1,2]. *E. coli* bacteraemia is considered to represent the extreme end of a continuum that often commences with more localized *E. coli* infection, most commonly within the urinary tract, and propagates due to a number of different factors including bacterial virulence, antimicrobial resistance (AMR), suboptimal treatment of urinary tract infection (UTI), and poor catheter care [3].

E. coli bacteraemia incidence in England increased by 14% between 2011 and 2015, rising by a further 10% to 2017/18 when 41,060 cases were reported and is associated with an 18% 30-day all-cause mortality [4–6]. The cause of the sustained increase in *E. coli* bacteraemia is incompletely understood, although there is evidence that it may reflect increased dissemination of antibiotic-resistant strains; a UK-based study found that an increase in *E. coli* bacteraemia between 1999 and 2011 was accounted for by predominantly antimicrobially resistant, not susceptible, organisms [7]. The contribution of internationally disseminated resistant *E. coli* clonal lineages, for example ST131, to the overall burden of *E. coli* bacteraemia in the UK is unknown [8,9]. In the UK, around 40% of *E. coli* are trimethoprim-resistant, and failure to alter prescribing practice for UTI in response to such patterns of AMR may have contributed to the rise in *E. coli* bacteraemia [3].

To combat the rising *E. coli* bacteraemia burden, the UK Department of Health and Social Care announced an ambition to halve healthcare-associated Gram-negative bacteraemia incidence by 2021, including *E. coli* bacteraemia [10]. Although hospital-onset infections account for around 23% of *E. coli* bacteraemia, around 50% of *E. coli* bacteraemia cases have some type of healthcare contact in the preceding four weeks [6,11]. The varying contribution of underlying factors across the healthcare/care economy and their relative impact on disease burden and severity is, however, poorly quantified. Such data are required to shape prevention strategies and to improve clinical outcomes.

The aim of this study was to use routinely collected longitudinal healthcare data to investigate *E. coli* bacteraemia in a large urban setting over 4.5 years, to determine the contribution of specific *E. coli* AMR patterns to the burden and severity of *E. coli* bacteraemia, and to understand both the relative contribution and the risks associated with community- and hospital-onset *E. coli* bloodstream infection.

Methods

A retrospective study was conducted using data from three sites of a large teaching NHS Trust in London, between January 1st, 2011 and June 30th, 2015. The NHS Trust and diagnostic laboratory serve a wide population catchment of ~2,000,000 in west London.

As this was a retrospective study using routinely collected, linked and anonymized electronic healthcare patient data, the study did not impact patient care and did not require patient consent. The study was approved by an independent research ethical review board (15/LO/0746).

Cases of *E. coli* bacteraemia were all adult patients (aged >18 years) with a blood culture that tested positive for *E. coli* in the pathology department. Any unique *E. coli* bacteraemia occurring more than 30 days after prior bacteraemia was considered to represent a new infection. *E. coli* bacteraemia cases were considered to be hospital-onset if a blood culture yielding *E. coli* had been taken after the second calendar day of admission to hospital; cases were considered community-onset if a positive blood culture was taken on the first or second day of admission [12]. Each unique *E. coli* bacteraemia episode was recorded; any duplicate *E. coli* bacteraemia results obtained within 30 days of the initial blood culture were removed from the dataset. Cases of *E. coli* bacteraemia were linked to the associated *E. coli* bacteraemia isolate antimicrobial susceptibility data. Positive urine *E. coli* results from *E. coli* bacteraemia cases were linked if isolated up to 14 days prior to, and two days after, the relevant *E. coli* bacteraemia isolate collection date.

Microbiologically confirmed *E. coli* bacteraemia cases were identified from the NHS Trust microbiology data warehouse. Demographic and comorbidity data were extracted from the patient administration system (PAS) and linked to each individual case. PAS data provided ICD-10 (diagnostic) codes and OPCS (procedure) codes, from which comorbidities were selected for analysis. We selected these based on reported risk factors for bacteraemia; comorbidities identified by Elixhauser *et al.*; procedures linked to immunocompromised status; and confirmed UTI, which was identified using the ICD-10 code and urine microbiology results [13–23]. A modified Elixhauser index was calculated as an indication of overall morbidity [24]. Index of Multiple Deprivation, as classified by the Department for Communities and Local Government, was derived using partial postcodes [25]. Cases were excluded if a patient link between the microbiology and PAS datasets could not be established.

Susceptibilities of *E. coli* bacteraemia isolates were obtained from the microbiology data warehouse and were previously determined by European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology to fluoroquinolones (ciprofloxacin), third-generation cephalosporins (ceftazidime, cefotaxime, and ceftriaxone), carbapenems (imipenem, meropenem, ertapenem) and aminoglycosides (gentamicin) [26]. Urinary isolate susceptibilities to trimethoprim, nitrofurantoin, cephalexin, and ciprofloxacin were similarly recorded. For our analysis, intermediate and resistant isolates were combined and classified as 'non-susceptible'. For practical purposes of analysis only, if an organism was non-susceptible to at least one of the antibiotics within a class, the isolate was considered non-susceptible to the class as a whole. Isolates non-susceptible to all three of the microbial classes (ciprofloxacin, third-generation cephalosporins or gentamicin) were classed as multidrug-resistant (MDR).

Three main outcomes were considered: (a) post-infection length of stay (LOS); (b) intensive care unit (ICU) admission; and (c) mortality. Mortality data were obtained from the national repository of death registrations. Mortality at 7, 30 and 365 days post infection was considered. Post-infection LOS was defined using the difference in time between the date on which *E. coli* bacteraemia-positive blood culture was collected and date of patient discharge or death. Patients with LOS >75th percentile were considered to have a long LOS. ICU admission data were obtained using a Trust database.

Initially the characteristics of hospital- and community-onset *E. coli* bacteraemia patients were compared.

Differences in categorical variables were assessed using χ^2-test. $P < 0.05$ was considered statistically significant. Non-normally distributed variables were reported as medians with interquartile ranges (IQRs) and compared for significance using the rank-sum test.

Trends in monthly cases of *E. coli* bacteraemia, stratified by category of infection (hospital-onset or community-onset), were determined using linear regression. The same approach was used to determine trends in MDR *E. coli* bacteraemia isolates and for non-susceptibility to each of the three classes of antimicrobials (third-generation cephalosporins, fluoroquinolones, and aminoglycosides).

Multivariable logistic regression models were developed to separately determine the association between category of infection (hospital or community-onset) and (i) LOS, (ii) ICU admission, and (iii) 30-day all-cause mortality, after adjusting for patient characteristics. Factors found to be significant ($P < 0.2$) and a-priori confounders were included in the initial model, and a backward stepwise elimination was performed to develop the final models. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. Interaction terms were tested to minimize the risk of moderation between variables. Odds ratios (ORs) were reported with 95% confidence intervals (CIs) and *P*-values. Kaplan–Meier analyses were conducted to evaluate hospital-onset as predictor of all-cause 30- and 365-day mortality. Log-rank tests were used to summarize differences between groups and to calculate significance.

Data processing and analyses were performed using Stata v14.1 (Stata Corp., College Station, TX, USA).

Results

A total of 1626 *E. coli*-positive blood cultures from 1204 individual patients were recorded between 2011 and 2015. A total of 978 *E. coli* bacteraemia cases from 954 individual patients that had complete data records and were included for study (Supplementary Figure S1); from these, 24% of the episodes were categorized as hospital-onset.

The median patient age was 68 years (Table I); 46.2% were male and 45.3% were non-Caucasian. Overall 7-day mortality was 7%, and 30-day mortality was 12%; 9.4% of patients were transferred to ICU, and the mean post-infection LOS was 8.3 days.

The overall monthly *E. coli* bacteraemia incidence increased ($P < 0.001$) from 71 cases in the first six months of 2011 to 125 cases in the first six months of 2015. This increase was almost entirely attributable to significantly increased numbers of community-onset *E. coli* bacteraemias (Figure 1).

Patients with community-onset *E. coli* bacteraemia were significantly older than hospital-onset cases (median ages of 69 and 65 years, respectively; $P = 0.002$) and were more likely to be from the two most deprived quintiles than those with hospital-onset *E. coli* bacteraemia. Almost all patients with community-onset *E. coli* bacteraemia (91%) were admitted to hospital as emergencies. However, almost one-third of hospital-onset *E. coli* bacteraemia cases followed an elective admission. Hospital-onset cases were more likely to be immunocompromised, have cancer, diabetes, or have had at least one procedure during the *E. coli* bacteraemia episode. Endoscopies or surgical procedures on the gastrointestinal or urinary tracts were more freqently identified during hospital-onset *E. coli* bacteraemia episodes compared with community-onset *E. coli* bacteraemia episodes (Supplementary Table S1). Patients admitted via elective routes were more likely to have an endoscopic procedure compared to cases with emergency admission. However, no differences were found between the groups for gastrointestinal or urinary tract surgery (Supplementary Table S2). UTI was identified in 27% of all patients with no significant differences in occurrence between the groups.

Antimicrobial resistances were common; 36% of *E. coli* bacteraemia isolates overall were non-susceptible to ciprofloxacin and 23% were non-susceptible to third-generation cephalosporins. Univariable analysis showed that resistance to individual antimicrobials was associated with hospital-onset infection. MDR isolates accounted for 11% of episodes and were more common in males and patients with diabetes, and/or renal failure. MDR was not associated with hospital-onset *E. coli* bacteraemia (Supplementary Table S3). During the study period, the number of isolates resistant to each of ciprofloxacin, gentamicin, and third-generation cephalosporins increased in both hospital-onset and community-onset cases. The incidence of MDR isolates also increased, although this was not significant ($P = 0.07$). Although rare (2.9%), non-susceptibility to carbapenems increased significantly over the study period in hospital-onset patients only (Supplementary Table S4).

Sub-analysis of the 209 *E. coli* bacteraemia episodes with urine samples that had yielded *E. coli* demonstrated that *E. coli* urine isolates resistant to any of the indicator antimicrobials tested routinely were associated with MDR *E. coli* bacteraemia (Supplementary Table S5).

Multivariable logistic regression of post-infection LOS (for patients who survived more than 30 days from onset of *E. coli* bacteraemia) suggested that hospital-onset, older age, and non-susceptibility to third-generation cephalosporins or to ciprofloxacin were significantly associated with prolonged LOS. Hospital-onset *E. coli* bacteraemia was associated with 3.6-fold increased risk of increased LOS, and patients aged ≥80 years had a five-fold increased risk of longer post-infection LOS (Table II and Supplementary Table S6). *E. coli* bacteraemia isolate non-susceptibility to third-generation cephalosporin and ciprofloxacin were both associated with longer LOS (OR: 1.7).

Intensive care unit admission was associated with an elevated weighted Elixhauser comorbidity index, patients having undergone a procedure, and younger age, after adjusting for covariates in a multivariable model. *E. coli* bacteraemia patients aged ≥80 years had five-fold lower odds of ICU admission than *E. coli* bacteraemia patients aged 18–39 years, whereas having a weighted Elixhauser comorbidity score of >14 increased the odds of ICU admission by ten-fold compared to having a score of 0 (Table II and Supplementary Table S6).

Reduced survival for hospital-onset *E. coli* bacteraemia compared with community-onset *E. coli* bacteraemia patients was significant after 30 days, and the effect remained at 365 days (Figure 1). After adjusting for covariates, however, multivariate analysis indicated that older age, a higher weighted Elixhauser comorbidity index score, ICU admission,

Table I
E. coli bacteraemia patient characteristics split by hospital and community-onset of disease

Patient characteristics	Total ($N = 978$)	Hospital-onset *E. coli* bacteraemia ($N = 236$)	Community-onset *E. coli* bacteraemia ($N = 742$)	*P*-value[a]
Age (years) (median, IQR)	68 (51–79)	65 (46–77)	69 (53–80)	0.0019
18–39	132 (13.5%)	42 (17.8%)	90 (12.1%)	
40–59	197 (20.1%)	48 (20.3%)	149 (20.8%)	
60–79	424 (43.4%)	107 (45.3%)	317 (42.7%)	
≥80	225 (23.0%)	39 (16.5%)	186 (25.1%)	0.017
Male	452 (46.2%)	118 (50.0%)	334 (45.0%)	0.181
Ethnicity				
White	535 (54.7%)	119 (50.4%)	416 (56.1%)	
Mixed	17 (1.7%)	8 (3.4%)	9 (1.2%)	
Asian	154 (15.8%)	41 (17.4%)	113 (15.2%)	
Black	99 (10.1%)	22 (9.3%)	77 (10.4%)	
Chinese	5 (0.5%)	3 (1.3%)	2 (0.3%)	
Other	109 (11.2%)	29 (12.3%)	80 (10.8%)	
Not stated	59 (6.0%)	14 (5.9%)	45 (6.1%)	0.102
IMD, median (IQR)	3 (3–4)	4 (3–5)	3 (3–4)	<0.0001
Admission method				
Elective	107 (10.9%)	72 (30.5%)	35 (4.7%)	
Emergency	826 (84.5%)	149 (63.1%)	677 (91.2%)	
Maternity	34 (3.5%)	10 (4.2%)	24 (3.2%)	
Other	11 (1.1%)	5 (2.1%)	6 (0.8%)	<0.0001
Elixhauser comorbidity present	595 (60.8%)	198 (83.9%)	397 (53.5%)	<0.0001
Diabetes	196 (20.0%)	60 (25.4%)	136 (18.3%)	0.018
Renal failure	178 (18.2%)	38 (16.1%)	140 (18.9%)	0.337
Liver disease	68 (6.9%)	22 (9.3%)	46 (6.2%)	0.1
Cancer	163 (16.7%)	80 (33.9%)	83 (11.2%)	<0.0001
Immunocompromised	64 (6.5%)	59 (15.4%)	5 (0.67%)	<0.0001
Urinary tract infection	376 (38.5%)	91 (38.6%)	285 (38.4%)	0.967
Elixhauser comorbidity score				
<0	17 (1.7%)	2 (0.9%)	15 (2.0%)	
0	437 (44.7%)	50 (21.2%)	387 (52.2%)	
1–5	183 (18.7%)	48 (20.3%)	135 (18.2%)	
6–13	192 (19.6%)	78 (33.1%)	114 (15.4%)	
≥14	149 (15.2%)	58 (24.6%)	91 (12.26%)	<0.0001
Any procedure (yes)	511 (52.3%)	213 (90.3%)	298 (40.2%)	<0.0001
No. of different procedures				
0	759 (77.6%)	147 (62.3%)	612 (82.5%)	
1	142 (14.5%)	45 (19.1%)	97 (13.1%)	
2	52 (5.3%)	29 (12.3%)	23 (3.1%)	
3	19 (1.9%)	10 (4.2%)	9 (1.2%)	
4	5 (0.5%)	5 (2.1%)	0 (0.0%)	
5	1 (0.1%)	0	1 (0.1%)	<0.0001
Bacterial antimicrobial non-susceptibility				
Ciprofloxacin	356 (36.4%)	113 (47.9%)	243 (32.8%)	<0.0001
Gentamicin	167 (17.8%)	51 (21.7%)	116 (15.7%)	0.032
Third-generation cephalosporin	219 (23.4%)	77 (32.6%)	142 (19.1%)	<0.0001
Multidrug-resistant	112 (11.4%)	34 (14.4%)	78 (10.5%)	0.102
Carbapenem	29 (2.9%)	15 (6.4%)	14 (1.9%)	<0.0001
Adverse outcome				
Post-infection mortality				
≤7 days	70 (7.3%)	20 (8.8%)	50 (6.9%)	0.33
≤30 days	117 (12.2%)	41 (17.6%)	76 (10.5%)	0.004
Post-infection LOS (>30 survivors), median (IQR)	8.3 (4.5–16.1)	14.3 (8.7–25.8)	6.8 (4.2–14.4)	<0.0001
ICU admission	90 (9.2%)	45 (19.1%)	45 (6.1%)	<0.0001

IQR, interquartile range; IMD, Index of Multiple Deprivation; LOS, length of stay.
[a] χ^2-Test.

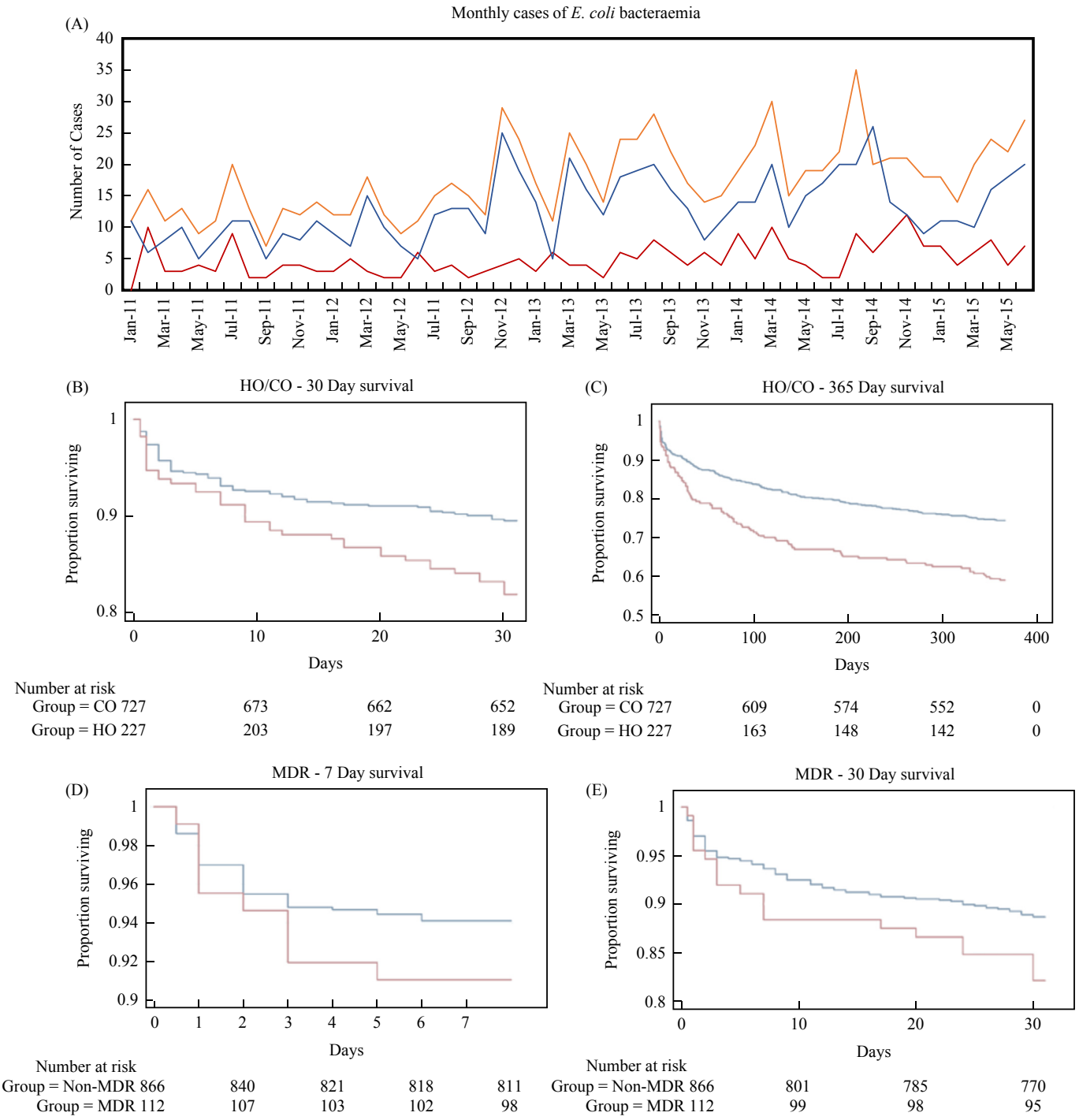

Figure 1. Trends in *E. coli* bacteraemia case presentations and mortality comparing hospital- (HO) and community-onset (CO) *E. coli* bacteraemia cases. (A) Total number of monthly *E. coli* bacteraemia cases by onset setting over the study period (January 2011 to May 2015). Orange Line indicates total number of cases; blue line represents community-onset; red line indicates hospital-onset cases. (B) Patient 30-day survival with *E. coli* bacteraemia in either hospital- or community-onset setting. (C) Patient 365-day survival with *E. coli* bacteraemia cases in either hospital- or community-onset settings. For (B) and (C) hospital-onset indicated by red line; community-onset indicated by blue line. (D) Patient 7-day survival of *E. coli* bacteraemia cases with either multidrug- or non-multidrug-resistant *E. coli* isolates. (E) Patient 30-day survival of *E. coli* bacteraemia cases with either multidrug- or non-multidrug-resistant *E. coli* isolates. For (D) and (E) blue line indicates non-MDR; red line indicates MDR infection.

and MDR *E. coli* bacteraemia isolates were significant risk factors for 30-day mortality in the model (Table II). Patients with *E. coli* bacteraemia aged >60 years had a five-fold increase in risk of death compared with the youngest age group (18–39 years), whereas those with an MDR *E. coli* isolate had a two-fold increased risk. Conversely, the odds of mortality at 30 days were halved for patients with a detected UTI.

Table II
Adjusted odds ratios for exposures associated with post-infection length of stay, intensive care unit admission and 30-day mortality among *E. coli* bacteraemia cases

Variable	Post-infection LOS (30-day survivors)			ICU admission			30-day mortality (from infection)		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Exposure									
Community-onset	1			1			1		
Hospital-onset	3.6	2.47–5.25	<0.0001	1.31	0.80–2.14	0.285	1.49	0.93–2.38	0.097
Covariate									
Age (years)									
18–39	1			1			1		
40–59	1.69	0.87–3.30	0.122	0.79	0.37–1.67	0.535	1.96	0.67–6.92	0.196
60–79	2.43	0.83–4.44	0.004	0.39	0.19–0.82	0.012	4.89	1.69–14.13	0.003
≥80	5.41	2.85–10.30	<0.0001	0.2	0.08–0.53	0.001	4.72	1.58–14.13	0.006
Gender									
Female	1			1					
Male	1.16	0.83–1.63	0.391	0.99	0.61–1.61	0.966	0.86	0.56–1.30	0.467
Index of Multiple Deprivation	1.03	0.95–1.13	0.395						
UTI							0.5	0.31–0.79	0.003
Elixhauser comorbidity score									
<0				2.86	0.52–15.52	0.223	–	–	–
0				1			1		
1–5				3.4	1.43–8.06	0.005	0.58	0.27–1.21	0.148
6–13				3.03	1.29–7.10	0.01	2.07	1.18–3.62	0.011
≥14				4.42	1.81–10.81	0.001	3.18	1.84–5.49	<0.0001
Procedure (yes/no)				17.1	5.15–56.83	<0.0001			
Bacterial antimicrobial non-susceptibility									
Third-generation cephalosporin	1.68	1.07–2.64	0.025						
Ciprofloxacin	1.68	1.12–2.53	0.013						
Gentamicin									
Carbapenem									
Multidrug-resistant							2	1.12–3.58	0.02

LOS, length of stay; ICU, intensive care unit; OR, odds ratio.

Discussion

This study examined trends in almost 1000 episodes of *E. coli* bacteraemia over a 4.5-year period, during which time there was a 76% increase in *E. coli* bacteraemia. Although hospital-onset *E. coli* bacteraemia accounted for one-quarter of all *E. coli* bacteraemia cases, the increase in incidence was almost entirely accounted for by community-onset infections. During this time, there was a parallel increase in resistance to ciprofloxacin, gentamicin, and cephalosporins. These changes were seen equally in both hospital- and community-onset cases. Resistance to carbapenems was observed, but this was rare, and primarily seen among hospital-onset cases.

Hospital-onset *E. coli* bacteraemia is a major target for current national initiatives to drive down the healthcare-associated Gram-negative bacteraemia burden across England. Our hospital group recently reported that just 12% of hospital-onset infections were associated with urinary catheters [27], while we noted such patients were more likely to have had an endoscopy than community-onset patients; association with timing of endoscopy will be important to investigate in future prospective studies [27]. In our longitudinal study, which focused on burden and outcome, hospital-onset *E. coli* bacteraemia was independently associated with prolonged LOS. Hospital-onset infection was not associated with increased risk of ICU admission or with increased risk of 30-day mortality after adjusting for cofactors. Comorbidities and older age were associated with risk of mortality, as was multidrug resistance. All-cause mortality associated with *E. coli* bacteraemia was low in this study, compared with rates reported from Public Health England's national mandatory surveillance data [6].

The increase in AMR among *E. coli* isolates over the course of the study period was concerning and raises the possibility that resistance may have contributed to the overall increase in *E. coli* bacteraemia cases, particularly when one considers that 54% of all urine *E. coli* isolates were resistant to trimethoprim, the antibiotic most frequently used during the study period to treat UTIs in the community. AMR in *E. coli* bacteraemia isolates was associated with prolonged LOS (third-generation cephalosporin resistance) and increased mortality (MDR isolates).

The frequency and increase in fluoroquinolone resistance among *E. coli* bacteraemia isolates was entirely unexpected, as a national reduction in ciprofloxacin use occurred between 2012 and 2016 [28]. Ciprofloxacin resistance in *E. coli* bacteraemia in England was previously reported to be around 18–20%, whereas the rates observed in the current study were 36% overall [3,6,11]. Urinary tract isolates showed a similar 35%

prevalence of ciprofloxacin resistance. The rates may reflect the emergence of specific *E. coli* lineages in our urban population that carry additional resistances that can be selected through use of other antimicrobials. Alternatively, increasing use of fluoroquinolones such as levofloxacin for lower respiratory tract infections may lead to an increase in the reservoir of quinolone-resistant *E. coli* in the enteric microbiota [28]. The increase in ciprofloxacin resistance mandates genomic analysis of *E. coli* isolates to detect the emergence of resistant lineages, as well as epidemiological analysis of the impact of levofloxacin exposure on the carriage of quinolone-resistant *E. coli*. After adjustment of covariates, cases of *E. coli* bacteraemia with MDR *E. coli* isolates were associated with increased likelihood of dying within 30 days of infection, though this effect was smaller than that found by Peralta *et al.* [29]. There was little difference in 7-day all-cause mortality between patients with MDR and non-MDR *E. coli* bacteraemia, suggesting that the initial illness severity and early treatment outcome is unaffected by MDR.

Having a microbiologically confirmed UTI was associated with reduced mortality risk following *E. coli* bacteraemia; this observation is consistent with other studies [6,30]. Bloodstream infections that are not linked to UTI may be associated with more complex anatomical, surgical, or medical problems that represent significant comorbidities or challenges to source control. Another explanation may be that documentation of UTI, through urine culture or audit, represents a marker of good clinical practice [31].

The implications of this study are that reductions in hospital-onset *E. coli* bacteraemia may do little to halt the observed year-on-year increase in *E. coli* bacteraemia caseload or the adverse mortality of *E. coli* bacteraemia. This finding was recently echoed by a study from Oxfordshire, a smaller, less urban population [32]. In our study, hospital-onset *E. coli* bacteraemias were not inherently more severe than community-onset infection, with similar 7-day mortality rates, and, after adjustment for covariables, were not associated with increased risk of 30-day mortality. However, reducing hospital-onset *E. coli* bacteraemia may result in cost savings, as hospital-onset *E. coli* bacteraemia patients remained in hospital for twice as long as community-onset *E. coli* bacteraemia patients following bacteraemia. It is not possible to determine the number of hospital-onset *E. coli* bacteraemia cases that were preventable in our study, but others have estimated the preventable proportion of all cases to be under 5% [33].

Our results suggest that a greater impact on *E. coli* bacteraemia case number will be achieved by prevention of community-onset cases. As UTI is reported to underlie a majority of such cases, prompt (and successful) antimicrobial treatment of UTI can be predicted to reduce community-onset *E. coli* bacteraemia [6,34]. Recent recommendations to use nitrofurantoin rather than trimethoprim for UTI may therefore result in an overall reduction in *E. coli* bacteraemia caseload, albeit that further investigation to explore the 5% of UTI isolates that were reported to be non-susceptible to nitrofurantoin is required (Supplementary Table S5) [35]. Current guidelines do not recommend routine microbiological testing of urine in uncomplicated UTI; since a high proportion of *E. coli* bacteraemias may be due to UTI treatment failures, culture of urine to determine antimicrobial susceptibilities could reduce time to appropriate antimicrobial therapy, and therefore reduce *E. coli* bacteraemia incidence, although delays in test results may be a barrier [36]. Whereas a recent evaluation of point-of-care tests for UTI assessed cost-effectiveness, the impact of such tests on complications such as *E. coli* bacteraemia remains unquantified [37].

Although 30-day all-cause mortality from *E. coli* bacteraemia in our study was lower than that reported nationally, it was evident that the risk of death was closely related to older age and comorbidity. Some studies have used 30-day mortality as a measure of disease severity; however, few studies have used other indicators such as 7-day mortality, ICU admission and LOS. Such data are readily available and provide greater context for the overall burden and cost of infections such as *E. coli* bacteraemia. Paradoxically, and despite increased mortality, the elderly were less likely to be admitted to the ICU, probably related to physician selection of candidates for level-3 beds. We considered the possibility that elderly patients had greater comorbidity, but comorbidity was associated with a greater risk of ICU admission. This illustrates a limitation when using ICU admission as a marker of severity, since, in countries such as the UK, admission is heavily influenced by factors other than illness severity, such as patient and physician choice, and bed availability.

The study was observational and retrospective, therefore causality of results can only be inferred. Since the study used routinely collected electronic data, several potential risk factors for *E. coli* bacteraemia could not be assessed — for example, urinary catheterization, travel, and recent healthcare history; prospective studies are required to capture such risk factors that are not routinely collected. Classification of cases as community- or hospital-onset may be challenging when using such data resources. The time lag between admission and taking of positive blood culture was calculated using calendar dates, and this will have led to some overlap in biological characteristics of a small number of community- and hospital-onset cases. Additionally, due to ethical constraints, it was not possible to evaluate recent patient healthcare contact both from within and outside of the Trust, therefore there is a possibility that a proportion of *E. coli* bacteraemia episodes that were classified as community-onset infections may be healthcare-associated. The proportions of patients within each category of infection were, however, similar to those reported by others [3,6,11].

In conclusion, this study found a significant increase in *E. coli* bacteraemia between January 1st, 2011 and June 30th, 2015, due mainly to a significant increase in community-onset cases, coupled with increasing non-susceptibility to major classes of antimicrobials in both hospital- and community-onset cases. Interventions targeting community-onset *E. coli* bacteraemia patients are likely to have the greatest impact on *E. coli* bacteraemia incidence.

Acknowledgements

We would like to thank colleagues from the NHS Departments of Microbiology and Infection Prevention and Control for helpful discussions and advice during this project. The authors also acknowledge the support of the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre.

Conflict of interest statement
None declared.

Funding sources
This research was funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at Imperial College London in partnership with Public Health England (PHE). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health, or PHE.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2018.10.024.

References

[1] Oppenheim B. *Escherichia coli* bacteraemia papers. J Hosp Infect 2017;95:363—4.
[2] Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309—17.
[3] Abernethy J, Guy R, Sheridan EA, Hopkins S, Kiernan M, Wilcox MH, et al. Epidemiology of *Escherichia coli* bacteraemia in England: results of an enhanced sentinel surveillance programme. J Hosp Infect 2017;95:365—75.
[4] Public Health England. Voluntary surveillance of bacteraemia caused by *Escherichia coli* in England: 2008—2015 Health Protection Report Volume 10 Number 19 17 June 2016. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/531989/hpr1916.pdf [last accessed August, 2018].
[5] Public Health England. Annual epidemiological commentary: Gram-negative bacteraemia, MRSA bacteraemia, MSSA bacteraemia and *C. difficile* infections, up to and including financial year April 2017 to March 2018 . Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/724030/Annual_epidemiological_commentary_2018.pdf [last accessed August, 2018].
[6] Abernethy JK, Johnson AP, Guy R, Hinton N, Sheridan EA, Hope RJ. Thirty day all-cause mortality in patients with *Escherichia coli* bacteraemia in England. Clin Microbiol Infect 2015;21. 251.e1—8.
[7] Schlackow I, Stoesser N, Walker AS, Crook DW, Peto TEA, Wyllie DH, et al. Increasing incidence of *Escherichia coli* bacteraemia is driven by an increase in antibiotic-resistant isolates: electronic database study in Oxfordshire 1999—2011. J Antimicrob Chemother 2012;67:1514—24.
[8] Kim S-Y, Park Y-J, Johnson JR, Yu JK, Kim Y-K, Kim YS. Prevalence and characteristics of *Escherichia coli* sequence type 131 and its H30 and H30Rx subclones: a multicenter study from Korea. Diagn Microbiol Infect Dis 2016;84:97—101.
[9] Livermore DM, Hope R, Reynolds R, Blackburn R, Johnson AP, Woodford N. Declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream Enterobacteriaceae from the UK: links to prescribing change? J Antimicrob Chemother 2013;68:2667—74.
[10] Global and Public Health Group. UK 5 Year Antimicrobial (AMR) Strategy 2013—2018 — third annual progress reoprt, 2016. 2017. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/662189/UK_AMR_3rd_annual_report.pdf [last accessed August 2018].
[11] Bou-Antoun S, Davies J, Guy R, Johnson AP, Sheridan EA, Hope RJ. Descriptive epidemiology of *Escherichia coli* bacteraemia in England, April 2012 to March 2014. Eurosurveillance 2016;21:30329.
[12] Davies J, Johnson AP, Hope R. Identifying hospital-onset *Escherichia coli* bacteraemia cases from English mandatory surveillance: the case for applying a two-day post-admission rule. J Hosp Infect 2017;97:207—11.
[13] Marín M, Gudiol C, Garcia-Vidal C, Ardanuy C, Carratalà J. Bloodstream infections in patients with solid tumors. Medicine (Baltimore) 2014;93:143—9.
[14] Lin J-N, Chen Y-H, Chang L-L, Lai C-H, Lin H-L, Lin H-H. Clinical characteristics and outcomes of patients with extended-spectrum β-lactamase-producing bacteremias in the emergency department. Intern Emerg Med 2011;6:547—55.
[15] Fennell J, Vellinga A, Hanahoe B, Morris D, Boyle F, Higgins F, et al. Increasing prevalence of ESBL production among Irish clinical Enterobacteriaceae from 2004 to 2008: an observational study. BMC Infect Dis 2012;12:116.
[16] Al-Hasan MN, Juhn YJ, Bang DW, Yang H-J, Baddour LM. External validation of bloodstream infection mortality risk score in a population-based cohort. Clin Microbiol Infect 2014;20:886—91.
[17] Park YS, Bae IK, Kim J, Jeong SH, Hwang S, Seo Y-H, et al. Risk factors and molecular epidemiology of community-onset extended-spectrum β-lactamase-producing *Escherichia coli* bacteremia. Yonsei Med J 2014;55:467.
[18] Lopez-Cerero L, Navarro MD, Bellido M, Martin-Pena A, Vinas L, Cisneros JM, et al. *Escherichia coli* belonging to the worldwide emerging epidemic clonal group O25b/ST131: risk factors and clinical implications. J Antimicrob Chemother 2014;69:809—14.
[19] Kaya O, Akcam FZ, Gonen I, Unal O, Ceylan T. Risk factors for bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli* in a Turkish hospital. J Infect Dev Ctries 2013;7:507—12.
[20] Falcone M, Vena A, Mezzatesta ML, Gona F, Caio C, Goldoni P, et al. Role of empirical and targeted therapy in hospitalized patients with bloodstream infections caused by ESBL-producing Enterobacteriaceae. Ann Ig 2014;26:293—304.
[21] Chen LF, Chiu C-T, Lo J-Y, Tsai S-Y, Weng L-S, Anderson DJ, et al. Clinical characteristics and antimicrobial susceptibility pattern of hospitalized patients with community acquired urinary tract infections at a regional hospital in Taiwan. Healthcare Infect 2013;19:20—5.
[22] Roubaud Baudron C, Panhard X, Clermont O, Mentré F, Fantin B, Denamur E, et al. *Escherichia coli* bacteraemia in adults: age-related differences in clinical and bacteriological characteristics, and outcome. Epidemiol Infect 2014;142:2672—83.
[23] Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36:8—27.
[24] van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care 2009;47:626—33.
[25] Ministry of Housing Communities and Local Government. English indices of deprivation 2015. 2015. Available at: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 [last accessed August 2018].
[26] European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. 2017., 7.1. Available at: http://www.eucast.org/ast_of_bacteria/previous_versions_of_documents [last accessed August 2018].
[27] Otter JA, Galletly TJ, Davies F, Hitchcock J, Gilchrist MJ, Dyakova E, et al. Planning to halve Gram-negative bloodstream infection: getting to grips with healthcare-associated *Escherichia coli* bloodstream infection sources. J Hosp Infect 2018 Jul 27 [Epub ahead of print].
[28] Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report. 2017. Available at: https://assets.publishing.service.gov.uk/government/

uploads/system/uploads/attachment_data/file/656611/ESPAUR_report_2017.pdf [last accessed August 2018].

[29] Peralta G, Sanchez MB, Garrido JC, De Benito I, Cano ME, Martinez-Martinez L, et al. Impact of antibiotic resistance and of adequate empirical antibiotic treatment in the prognosis of patients with *Escherichia coli* bacteraemia. J Antimicrob Chemother 2007;60:855—63.

[30] Kennedy KJ, Roberts JL, Collignon PJ. *Escherichia coli* bacteraemia in Canberra: incidence and clinical features. Med J Aust 2008;188:209—13.

[31] Public Health England. National enhanced mandatory surveillance of Gram-negative Bacteraemia. 2017. Available at: https://hcaidcs.phe.org.uk/ContentManagement/LinksAndAnnouncements/HCAIDCS_Gram_Negative_2017_Submission_Form.pdf [last accessed August 2018].

[32] Vihta K-D, Stoesser N, Llewelyn MJ, Quan TP, Davies T, Fawcett NJ, et al. 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. Lancet Infect Dis 2018.

[33] Melzer M, Welch C. Is *Escherichia coli* bacteraemia preventable? Lancet Infect Dis 2012;12:103—4.

[34] Laupland KB, Gregson DB, Church DL, Ross T, Pitout JDD. Incidence, risk factors and outcomes of *Escherichia coli* bloodstream infections in a large Canadian region. Clin Microbiol Infect 2008;14:1041—7.

[35] Public Health England. Management and treatment of common infections — antibiotic guidance for primary care: for consultation and local adaptation. 2017. Available at: https://www.gov.uk/government/consultations/managing-common-infections-guidance-for-primary-care [last accessed August 2018].

[36] Public Health England. Diagnosis of urinary tract infections (UTIs) Quick reference guide for primary care: for consultation and local adaptation. 2017. Available at: https://webarchive.nationalarchives.gov.uk/20171111073406/https://www.gov.uk/government/publications/urinary-tract-infection-diagnosis [last accessed August 2018].

[37] Butler CC, Francis NA, Thomas-Jones E, Longo M, Wootton M, Llor C, et al. Point-of-care urine culture for managing urinary tract infection in primary care: a randomised controlled trial of clinical and cost-effectiveness. Br J Gen Pract 2018;68:e268—78.