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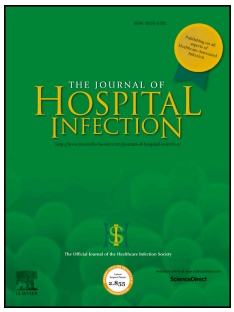
Accepted Manuscript



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PII: S0195-6701(16)30579-5

DOI: 10.1016/j.jhin.2016.12.008

Reference: YJHIN 4985

To appear in: *Journal of Hospital Infection*

Received Date: 10 October 2016

Accepted Date: 9 December 2016

Please cite this article as: Abernethy J, Guy R, Sheridan EA, Hopkins S, Kiernan M, Wilcox MH, Johnson AP, Hope R, on behalf of the E. coli bacteraemia sentinel surveillance group, Epidemiology of *Escherichia coli* bacteraemia in England: Results of an enhanced sentinel surveillance programme, *Journal of Hospital Infection* (2017), doi: 10.1016/j.jhin.2016.12.008.

Epidemiology of *Escherichia coli* bacteraemia in England: results of an enhanced sentinel surveillance programme

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Abstract

Background*: Escherichia coli* causes over one third of the bacteraemia cases in England each year, and the incidence of these infections is increasing.

Aim*:* To determine the underlying risk factors associated with *E. coli* bacteraemia.

Methods*:* A three month enhanced sentinel surveillance study involving 35 National Health Service hospitals was undertaken in the winter of 2012/13 to collect risk factor information and further details on the underlying source of infection to augment data already collected by the English national surveillance programme. Antimicrobial susceptibility results for *E. coli* isolated from blood and urine were also collected.

Findings*:* A total of 1,731 cases of *E. coli* bacteraemia were included. The urogenital tract was the most commonly reported source of infection (51.2% of cases) with prior treatment for a urinary tract infection being the largest independent effect associated with this infection source. Half of all patients had prior healthcare exposure in the month prior to the bacteraemia with antimicrobial therapy and urinary catheterisation being reported in one third and one fifth of these patients. Prior healthcare exposure was associated with a higher proportion of antibiotic non-susceptibility in the blood culture isolates (P=0.001).

Conclusion*:* Analysis of risk factors suggests potential community and hospital-related interventions particularly better use of urinary catheters and improved antibiotic management of urinary tract infections. As part of the latter strategy, antibiotic resistance profiles need to be closely monitored to ensure treatment guidelines are up to date to limit inappropriate empiric therapy.

Keywords:

Urinary Tract Infection, Risk Factors, Healthcare Associated, Community

Introduction

Voluntary surveillance identified *Escherichia coli* as the leading cause of bacteraemia in England, with increasing incidence over time despite the overall incidence of bacteraemia being in decline[1]. In 2015, 37,273 cases of *E. coli* bacteraemia were reported to the English mandatory surveillance programme[2]. Thirty-day all-cause mortality in England for this infection was recently estimated as 18.2% (17.8-18.7%), equating to 5,220 deaths over a 12-month period[3]. Thus appropriately targeted interventions are required to reduce morbidity and mortality associated with *E. coli* bacteraemia. Whilst English mandatory surveillance of *E. coli* bacteraemia (initiated in 2011) allows better estimation of *E. coli* bacteraemia incidence than previously possible, detailed epidemiological information is needed to elucidate the reasons behind observed trends.

Following a recommendation from the UK government's Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), a sentinel surveillance scheme was initiated to augment existing mandatory surveillance.[4] The sentinel programme aimed to gather more detailed risk factor information for patients in the hospital and community settings. Specific data collected included antibiotic consumption, use of urinary catheters, indwelling vascular access and other devices, and invasive procedures prior to the bacteraemia. Additionally we aimed to gather detailed information regarding the clinically identified focus or cause of bacteraemia and antibiotic susceptibility data for the *E. coli* blood and urine cultures.

Methods

Study design

The sentinel study ran in participating English NHS Trusts (hospitals under the same management board) over the winter of 2012/13. The study was powered to detect with 95% confidence the prevalence of an underlying infection focus or risk factor with a true frequency of at

least 10%, based on estimates of the prevalence of the second commonest focus (hepatobiliary) reported via mandatory surveillance.[5] As the sampling strategy was clustered (by NHS Trust and not patient) a design effect was included. This equated to a sample size of 2,625 *E. coli* bacteraemia cases; we therefore aimed to recruit 40 Trusts with data collection running over 3 months. Participating Trusts were selected using simple random sampling. Additionally, two specialist cancer Trusts and six interested Trusts were included post-hoc.

Cases from the sentinel study were linked to mandatory *E. coli* bacteraemia reports (linked using NHS number, a unique personal identifier), to obtain further patient and specimen information, and to voluntary laboratory reports [6] (linked using a combination of available personal identifiers [NHS number, hospital number, date of birth, gender, encrypted surname]) to obtain antibiotic susceptibility data for both *E. coli* blood culture (if not reported by sentinel sites) and urine cultures, one month and one year before the date of the blood culture. Duplicate entries for the same patient within the same episode (considered as 14 days), were removed from analysis with data relating to the earliest specimen retained. This study focused on *E. coli* bacteraemia and for cases of polymicrobial bacteraemia only information pertaining to the *E. coli* isolate was retained.

Data items relating to healthcare exposure prior to the bacteraemia were collected. Specifically, in the prior three days: indwelling vascular access devices (in situ or removed), including the type of intravascular device; in the prior 7 days: urinary catheterisation (in situ, inserted, removed or manipulated), including the type of catheter, insertion method and primary indication for catheterisation; in the prior 4 weeks: other devices (in situ or removed), including the type of device and date of insertion; other procedures, including the type and date of procedure; and antimicrobial chemotherapy, including antibiotic name(s), indication and the treatment area. Patients with more than one healthcare exposure reported or more than one occurrence of a specific healthcare exposure were included in the study. Prior healthcare exposure in either the community or hospital in the 4 weeks and 1 week before bacteraemia was categorised as “Yes” if at

least one of the above data items were selected as “Yes” or as “No” if all of the above items were selected as “No”; otherwise it was coded as “Not known”. In addition to these data items, the primary focus or reason for the bacteraemia was collected. More detail on data collection can be found in Supplementary Information 1.

Time of bacteraemia onset based on the days between hospital admission and the taking of a positive blood culture was categorised as follows: on or day after admission (a proxy for community-onset infection); 2-6 days after admission (proxy for early healthcare-onset infection); 7 days or more after admission (proxy for late healthcare-onset infection); from a non-admitted patient.

Information on susceptibility of the *E. coli* blood culture and urine isolates to ciprofloxacin, trimethoprim, co-amoxiclav, third-generation cephalosporins (cefotaxime/ceftazidime), carbapenems (imipenem/meropenem), gentamicin, nitrofurantoin and piperacillin/tazobactam was ascertained using laboratory data reported via the national voluntary surveillance system. The presence of a urine culture in the linked laboratory dataset was taken as a proxy for urinary tract infection (UTI) in the month or year prior to the *E. coli* bacteraemia. Combined susceptibility for blood cultures, using the above antibiotics, was categorised as: “non-susceptible” if the blood culture was recorded as non-susceptible to at least one of the aforementioned antibiotics; and “susceptible” if the blood culture was recorded as susceptible to all of the aforementioned antibiotics.

Statistical analysis

General associations between two variables were examined using the Chi^2 test. Multivariable logistic regression was used to estimate the independent effects of prior UTI, prior treatment of a urogenital tract infection and urinary catheterisation, on having a urogenital tract focus of bacteraemia, controlled for the effects of age, gender, (both of which were considered a priori confounders thus

automatically included in the model) treatment specialty and timing of bacteraemia onset. Only the presence of a UTI in the month prior to the bacteraemia was used in the model as it was considered more directly relevant than a UTI one year prior. A random effects term was used to control for clustering by reporting Trust. Variables that were not significant in the final model were omitted, even if the crude odds ratios showed a significant effect. All data management and analyses were performed using Stata 13.0.[7]

Results

Thirty-five NHS acute Trusts submitted data to the sentinel programme, representing 1,731 cases of *E. coli* bacteraemia. Thirty-seven cases could not be linked to the mandatory surveillance dataset and were excluded from analysis and six cases were removed as within-episode duplicates. We achieved 90% power in our estimate of a risk factor or focus with a frequency of 10%. Distributions of cases from this sentinel study compared to the national mandatory data by patient sex or age and by time of onset or focus of bacteraemia were not statistically distinct P>0.05 (data not shown).

Description of the study participants

Half of the bacteraemias (n= 833; 49.3%) were in patients aged ≥75 years, and around half were in women (n=901; 53.4%) (Table 1). Over two-thirds of patients had a positive blood culture taken 0-1 day after admission (n=1,153; 68.3%). The underlying infection focus was reported as the 'urogenital tract' in 51.2% (n=865) of patients. The next most frequent foci were 'hepatobiliary' (15.6%; n=264), and 'unknown' (14.9%; n=252).

Healthcare exposure prior to the bacteraemia

Half (n=930) of the patients had a healthcare exposure, as defined in the Methods section, in the four weeks prior to the bacteraemia and one third (n=584) had a healthcare exposure in the

week prior to the bacteraemia. The percentage of patients with prior healthcare exposure increased as the time of bacteraemia onset after hospital admission increased (Figure 1). Of the patients diagnosed 0-1 day after admission, 46.7% (n=538) had a healthcare exposure in the month prior to the bacteraemia, increasing to 85.4% (n=251) in patients in hospital for ≥7 days prior to the bacteraemia reflecting the increased opportunity of healthcare exposure for admitted patients as well as potentially more comorbidities. Stratification by age showed some variation in prior healthcare exposure four weeks prior to the bacteraemia, with 26.9% (n=7) of 0-1 year olds, 54.3% (n=95) of 1-44 year olds, 57.5% (n=651) of 45-84 year olds and 49.9% (n=177) of patients 85 years or more having had a prior healthcare exposure (details not shown).

Antimicrobial therapy was the most commonly reported prior healthcare exposure in one third (n=546) of patients (Table 1);-of these 546 patients 58.4% (n=319) received one antibiotic, 23.1% (n=126) received two and the remaining 101 received three or more. Seventy-nine percent (721/907) of the antibiotic prescriptions were for treatment of infection. Treatment for infection of the urogenital tract was most commonly reported (n=229; 31.8%), followed by treatment of the respiratory tract (n=123; 17.1%). For patients treated for urogenital tract infection, trimethoprim and co-amoxiclav were most commonly prescribed (n= 50 [21.8%] and n= 47 [20.5%], respectively). Fourteen percent (125/907) of prescriptions were for medical or surgical prophylaxis; where the site was reported (n=115), 26.1% (n=30) of prescriptions were for a genito-urinary site. Twelve of these patients were catheterised in the three days prior to the bacteraemia. It was not possible to determine if these patients were also treated for a UTI as treatment and prophylaxis were mutually exclusive options.

Twenty-two percent of patients (n=373) had an indwelling intravascular device that either remained in situ at the onset of the bacteraemia, or had been removed within the 3 days prior to the bacteraemia (Table 1). Of these patients, 88.2% (n=329) had one indwelling intravascular device and 8.0% (n=30) had two with the remainder having between three and six. Where reported (n=444), the

most common catheter types were peripheral (41.6%; n=184), and central venous catheters (11.8%; n=52).

Twenty-one percent of patients (n=354) either had a urinary catheter in place at the time of the bacteraemia, or had one inserted, removed or manipulated in the 7 days prior to the bacteraemia (Table 1); of these, 96.9% (n=343) were catheterised just once. Where reported (92.7%; n=328) urinary retention (27.1%; n=89) and fluid balance (21.6%; n=71) were the primary reasons for catheterisation. Eleven percent (n=36) of patients had a catheter inserted for incontinence. The reason for catheterisation was unknown in 19.2% (n=63) of instances. The primary insertion type was urethral (91.8%; n=302). Long term (in situ ≥28 days) and short term (in situ <28 days) catheters predominated (41.3%; n=152 and 38.3%; n=141, respectively), the remaining 20% were reported as temporary catheters. Among the patients whose bacteraemia was detected ≥7 days after hospital admission (n=294) 40.1% (n=118) had been subject to urinary catheterisation in the 7 days before bacteraemia. The equivalent figure for patients with a bacteraemia detected 2-6 days after admission was 36.4% (n=47/129) and for those detected on admission it was 15.4% (n=178/1,153).

Twelve and seven percent (n=209 and n= 123, respectively) of patients had another procedure or device in the four weeks before bacteraemia. Of the available procedure categories, 'other' was most frequently selected (64.3%), of which approximately half were surgical procedures.

Patients with an underlying urinary focus of bacteraemia

Six-hundred and ninety (79.8%) of the 865 patients where the underlying infection focus was reported as the 'urogenital tract' were recorded as having a UTI. Amongst those patients with a urogenital tract focus where the date of infection onset was recorded (n=510), 48.4% (n=248) had the blood culture taken on the day of onset, while for a further 214 patients (41.8%) the onset of infection occurred up to 7 days before the positive blood culture was taken. Where the urogenital

infection was reported as catheter-, procedure-, or device-related (n=171), 84.2% (n=144) were related to a urinary catheter, 12.3% (n=21) to a procedure and the remainder (3.5%; n=6) to a device. Where information on prior UTIs was reported, two thirds of patients (62.4% n=176/282) had at least one prior UTI. Of patients with a urogenital tract focus with at least one antibiotic prescribed in the four weeks prior to bacteraemia, 51.6% (145/281) of antibiotics were prescribed for treatment of urogenital system-associated infection. Where reported co-amoxiclav (23.1%; n=29/212) and trimethoprim (22.2%; n=47) were most commonly prescribed, whilst 9.9% (n=21) were prescribed nitrofurantoin.

Regression analysis of factors associated with urinary tract focus of infection

The largest independent risk factor for a bacteraemia's underlying focus being the urogenital tract was prior treatment for urogenital tract infection within 4 weeks of the bacteraemia onset: adjusted OR (aOR) 10.7 (95% confidence interval (CI): 6.3-18.1) (Table 2). Having had a UTI in the month prior to bacteraemia increased the odds of urogenital tract-related bacteraemia 5-fold (aOR 5.4; 95% CI 3.6-8.1). Having a catheter inserted for incontinence (versus 'other') and surgical specialty (versus medical specialty) also increased the odds of a urogenital tract focus (aOR 5.2; 95% CI: 1.5-18.1 and aOR 4.3; 95% CI 2.0-9.3, respectively). Several factors were associated with a reduction in the odds of a urogenital tract focus of infection including male gender, unknown presence of catheter, general specialty and bacteraemia detected 2-6 days or ≥7 days post admission.

Antibiotic susceptibility

Where tested, the highest levels of antibiotic non-susceptibility among isolates from blood were to co-amoxiclav (43.0% [n=511/1,188]) or trimethoprim (40.5% [n=317/783]) (Figure 2). Ciprofloxacin non-susceptibility was seen in 17% of tested isolates (n=187/1,100). Carbapenem non-

susceptibility was only observed in two isolates out of 1,060 tested. There was an association between timing of bacteraemia onset and co-amoxiclav (p=0.027) and piperacillin/tazobactam (p=0.008) susceptibilities, both of which showed a greater proportion of non-susceptible isolates from patients with bacteraemia detected 2 or more days after hospital admission (Table 3). Ciprofloxacin (p=0.02) and trimethoprim (p<0.001) non-susceptibility were associated with different foci of infection with a greater percentage of isolates non-susceptible to ciprofloxacin found in patients with "pneumonia" reported as the underlying infection focus (23.7%; 9/38), whilst trimethoprim non-susceptibility was most commonly observed in patients with an underlying urogenital tract focus (48.1%; 198/412) (Table 4). There was an association between antibiotic non-susceptibility of blood culture isolates and healthcare exposure in the four weeks prior to the bacteraemia (P=0.001), with 60.9% (n=406/667) of isolates from patients with prior healthcare exposure showing non-susceptibility to at least one of the antibiotics tested versus 50.7% (n=165/330) of isolates without a prior healthcare exposure (data not shown). Antibiotic non-susceptibility was also associated with antibiotic exposure in the four weeks prior to bacteraemia (P<0.001), the rates of non-susceptibility being 66.5% (n=262/394) and 51.4% (n=244/475), in those with and without prior antibiotic exposure respectively (data not shown).

Urine cultures with antibiotic susceptibilities one year and four weeks prior to the *E. coli* bacteraemia were identified for 340 (20.1%) and 230 (13.6%) patients, respectively. The highest levels of non-susceptibility in isolates from urine at both time points were for trimethoprim (47.7% [n=162/340] at one year and 46.3% [n=106/229] at four weeks (not shown). Co-amoxiclav non-susceptibility was also common at around 30% at both time points. Ciprofloxacin non-susceptibility was seen in 20.4% (n=47/231) and 15.5% (n=23/148) of urinary isolates in the year and four weeks prior to the bacteraemia. The levels of non-susceptibility to third-generation cephalosporins at the same time points were 21.3% (29/136) and 13.8% (12/87), respectively. Non-susceptibility to piperacillin/tazobactam was 22.1% (28/127) at one year and 24.4% (20/82) at four weeks prior to the bacteraemia. Non-susceptibility to nitrofurantoin was low, being reported in 6.9% (22/321) of

isolates at one year and 4.6% (10/216) at one month. Only one patient's infection was caused by *E. coli* non-susceptible to carbapenems at both time points.

Where antibiograms were available for both urine and blood isolates from the same patient, there was a significant association between non-susceptibility in urine and the subsequent blood culture for each of the antibiotics examined, the association being stronger for isolates taken up to four weeks prior to the bacteraemia compared with the association at one year (data not shown).

Discussion

While large declines in infections such as methicillin-resistant *Staphylococcus aureus* bacteraemia occurred concomitant with healthcare-based interventions (e.g. intravascular device-related care bundles; screening/decolonisation of high risk patients), E. *coli* bacteraemia is frequently considered a community-associated infection with lesser scope for reducing incidence.[8-10] All potential areas for reducing *E. coli* bacteraemia incidence do, however, need to be investigated given the high burden of this infection (37,273 cases reported for 2015[2]) as even small reductions in incidence could equate to thousands of patients a year. The data presented here highlight potential interventions for reducing *E. coli* bacteraemia incidence, such as improved urinary catheter care and UTI diagnosis and management.

Several of our findings suggest treatment failure in UTIs is an important risk factor for the development of *E. coli* bacteraemia. Hence prompt diagnosis and appropriate treatment of UTIs, the commonest underling focus of *E. coli* bacteraemia identified here and elsewhere,[11, 12] with antibiotics to which the organism is susceptible are key in limiting progression from UTI to bacteraemia and severe sepsis. Antibiotic therapy in the four weeks before bacteraemia was the most commonly reported healthcare exposure (one third of patients), and of these patients almost one third were prescribed antibiotics for treatment of a genito-urinary infection. Notably the most

commonly prescribed antibiotics for these patients were trimethoprim and co-amoxiclav, where non-susceptibility in urine isolates was common (around 47% and 30%). Furthermore, trimethoprim non-susceptibility was common (40.5%) in *E. coli* blood isolates. This may reflect prior trimethoprim exposure in the treatment of the patient's UTI with subsequent selection of resistant strains leading to treatment failure and progression to bacteraemia, or UTI caused by uropathogenic strains already resistant to trimethoprim. These findings are concerning in relation to trimethoprim as this antibiotic typically dominated first-line treatment recommendations for uncomplicated UTI in primary care,[13] and thus is commonly prescribed,[14] as supported by our findings. However it is reassuring that recent guidelines now advocate nitrofurantoin therapy with trimethoprim use dependant on local resistance patterns.[15] This reiterates that guidelines for empiric UTI therapy need constant review and updating. Whilst nitrofurantoin non-susceptibility was lower at around 5-7%, trends need to be monitored given its increasing importance in empiric UTI therapy. Non-susceptibility to third-generation cephalosporins in urine was higher than typically seen in *E. coli* blood isolates, especially in patients with a history of UTIs within a year before bacteraemia; these patients may represent UTI treatment failures or those carrying multi-drug resistant, but not especially virulent, isolates. Furthermore, the association between resistance in urine before bacteraemia is consistent with a recent meta-analysis showing that prior antibiotic exposure increased the odds of antibiotic non-susceptibility.[16] Whilst ciprofloxacin, third-generation cephalosporins, gentamicin and carbapenems are less frequent first-line therapies for UTIs,[14] they are important for treating more severe infections, thus non-susceptibility trends should be monitored.

Prior healthcare exposure, regardless of whether it was one week or month prior to the bacteraemia case, primarily equated to antibiotic prescribing and was perhaps an important factor for subsequent non-susceptible *E. coli* bacteraemia. This highlights patient groups with *E. coli* bacteraemia who may be more likely to have a non-susceptible infection and justifies the current focus on antibiotic prescribing and antimicrobial resistance. We noted a general trend for increased non-susceptibility with healthcare-onset bacteraemia cases; however this was only significant for co-

amoxiclav and piperacillin/tazobactam. This is most likely due to these being common first-line therapy for patients presenting at hospital with an infection and where these infections subsequently progress to a bacteraemia resistant isolates will be selected for. A larger study may have also identified significant associations for other antibiotics.

Regression analysis somewhat predictably identified prior urogenital tract infection treatment and having a UTI in the month prior to the bacteraemia as the most important risk factors for the development of a (presumed) urogenital tract focus bacteraemia, increasing the odds of a urogenital tract focus 10.7 and 5.4 fold, respectively. We hypothesise that patients with urine samples sent for antimicrobial testing would more likely have experienced treatment failure or had a complicated UTI, as most uncomplicated UTIs are typically treated empirically in primary care.[17] Furthermore, three quarters of patients with a urogenital tract focus had their bacteraemia detected on admission. This implies either a failure in diagnosis and treatment of UTI in the community or patients presenting directly to the hospital with bacteraemia who have not visited their primary care physician for treatment of their symptoms. Greater awareness of the patient groups at risk of UTIs developing into bacteraemia in the community and hospital could reduce treatment failure or unrecognised complicated UTIs progressing to bacteraemia, through for example enhanced monitoring of patients with suspected UTI and prompt intervention when empirical treatment fails. Mid-stream urine sampling of all patients with symptomatic UTI, or where otherwise indicated in the guidance for susceptibility screening would also allow appropriate antibiotic therapy to be prescribed. [17] Further studies are warranted to gain a better understanding of who these patients are and what the potential intervention opportunities may be. Near patient testing for antimicrobial resistance may be a future option to improve management. Furthermore reduction of UTI incidence would limit the largest underlying focus of *E. coli* bacteraemia; studies are required to understand how this can be achieved.

Urinary catheter use was also identified as an important risk factor. We found that 21% of patients had a urinary catheter inserted, removed or manipulated in the week before bacteraemia; 144 reported bacteraemias were likely related to a urinary catheter in the study. Urinary catheters inserted for incontinence were associated with a 5.2-fold increase in the risk of a urinary focus of infection. Whilst incontinence and the other main reasons for catheterisation (urinary retention and fluid balance) could be considered appropriate indications,[18] without more detailed patient medical history it is not possible to determine whether each catheter was appropriately used. Additionally, it is concerning that for one in five catheterised patients the indication for catheterisation was not known/recorded, indicating a lack of optimised patient management , possibly increasing the risk of complications. Furthermore, almost half of the catheterised patients had a long-term catheter. Although this may have been appropriately indicated, it nonetheless increases the risk of infection compared to short-term catheters as the risk of infection developing from catheters increases with catheterisation duration.[19] Periodic review of patients with long term catheters is advised [20] and should be followed. Further research is required to determine if suprapubic versus urethral long term catheters would present a lower infection risk both of which may reduce urinary catheter-related infections.

There is considerable literature highlighting high levels of catheter use in healthcare,[14, 21, 22] with evidence for a large proportion of such usage being inappropriate and/or poorly monitored.[23, 24] We identified that the percentage of patients with a urinary catheter increased from 15.4% in those diagnosed around admission to 40.1% in those diagnosed ≥ 7 days after admission. This identifies the importance of appropriate catheter care in the community as well as close monitoring in hospitalised patients. The latter represent a patient group where device-related hospital-based interventions could be targeted to reduce *E. coli* bacteraemia incidence, although it is worth noting that the present data is unable to identify which patients may be catheterised as part of the sepsis pathway for monitoring of urinary output.

Urinary catheter use is associated with an increased risk of complications, notably catheter-associated UTI.[22, 25, 26] Given the urinary tract is the predominant underlying focus of *E. coli* bacteraemia, appropriate catheter use and management are obvious interventions, particularly when the catheter is used solely for incontinence where non-invasive treatment options exist. As with the management of UTIs, any such intervention must be targeted at the community and hospital setting as many catheterised patients reside in the former [21] supported by the data here.

These sentinel data are representative of the national picture of *E. coli* bacteraemia, based on comparisons of age, gender, timing of bacteraemia onset and underlying focus of infection. Despite a smaller sample size than intended, the power of the sentinel study was 90% to detect a risk factor or focus with a frequency of 10%. There are, however, several limitations to the present study. Our study has only collected information on patients with *E.coli* bacteraemia therefore it is not possible to compare the population with and without infection, nor to estimate the impact of interventions on reducing *E.coli* bacteraemia incidence. The susceptibility results relate to antimicrobials tested which were not necessarily those received by the patient. Thus, it is not possible to determine the effects of antimicrobial exposure for the treatment of UTI on subsequent non-susceptibility in blood cultures. Additionally antimicrobial testing practices vary by laboratory and some antibiotics are less frequently tested which may impact on the linked urine antimicrobial results. Robust information on the management and treatment of prior UTIs and catheter use would provide further resolution on specific risk factors.

It is clear from this study that *E. coli* bacteraemia is often secondary to an earlier UTI. Therefore, prevention of UTIs, particularly in the elderly, may reduce bacteraemia developing. We have highlighted potential interventions and further research to reduce the incidence of *E. coli* bacteraemia in England: 1) close monitoring and effective treatment of patients with suspected UTI; 2) awareness of local antibiotic resistance profiles with early recognition of UTI treatment failure with prompt initiation of effective antimicrobial therapy; 3) early identification of suspected

bacteraemia secondary to UTI, primarily in the community; 4) appropriate use and management of urinary catheters in the hospital and community with monitoring for signs of infection; 5) further research on UTI incidence in England, infection rates in suprapubic versus long term catheters, and antibiotic consumption patterns.

Whilst interventions targeted at the community setting may be harder to implement and monitor than hospital-based interventions, this should not be a reason for not trying, given the high burden of *E. coli* bacteraemia.

Transparency declaration

This work was funded in its entirety by Public Health England.

MHW has received: consulting fees from Actelion, Astellas, Astra-Zeneca, Bayer, Cerexa, Cubist, Durata, The Medicines Company, MedImmune, Merck, Motif Biosciences, Nabriva, Optimer, Paratek, Pfizer, Roche, Sanofi-Pasteur, Seres, Summit, and Synthetic Biologics; lecture fees from Abbott, Alere, Astellas, Astra-Zeneca, Pfizer & Roche; and grant support from Abbott, Actelion, Astellas, bioMerieux, Cubist, Da Volterra, Merck, Paratek, Pfizer, Sanofi-Pasteur and Summit. SH is affiliated with the National Institute for Health Research Health Protection Research Units (NIHR HPRU) in Healthcare Associated Infection and Antimicrobial Resistance at Imperial College London and University of Oxford in partnership with Public Health England (PHE). The other authors had nothing to disclose. The views expressed in this article are those of the authors and not necessarily shared by their organisations or affiliates.

JKA lead on the scientific writing and analysis, RJH and APJ edited initial drafts and gave feedback on early analysis, JKA, ES, SH, MK, MHW, APJ and RJH designed the surveillance programme and associated questionnaire. RG performed the linkage work required for the antibiotic susceptibility data and the identification of urinary cases. All authors commented on the final edits of the manuscript.

Acknowledgements

The *E. coli* bacteraemia sentinel surveillance group comprised of the following NHS acute Trusts and collaborators who we thank for participating in the study:

Aintree University Hospitals, Dr Rachel A Sen; Barts & the London, Dr Albert Mifsud; Buckinghamshire Healthcare, Dr Jean O'Driscoll; Cambridge University Hospitals, Dr Nick Brown/Cheryl Trundle; County Durham & Darlington, Dr David Allison; Croydon Health Services, Dr Mary Twagira; Derby Hospitals, Dr Gnanarajah; East & North Hertfordshire, Dr Fatih Awad-El Kariem; East Cheshire, Dr Rajesh Rajendran; East Sussex Healthcare, Dr S Umashankar; Gateshead Health, Dr Glenda Horne; Homerton University Hospital, Dr Alleyna Claxton; Lancashire Teaching Hospitals, Dr John Cheesbrough; Leeds Teaching Hospitals, Dr Andrew Kirby; Luton & Dunstable Hospital, Dr Rohinton Mulla; Mid Essex Hospital Services, Dr Louise Teare; Newham University Hospital, Dr Caryn Rosmarin; North West London Hospitals, Dr G Gopal Rao; Northern Devon Healthcare, Dr David Richards; Nottingham University Hospitals, Dr Tim Boswell; Oxford University Hospitals, Dr Ian Bowler/Lilly O'Connor; Plymouth Hospitals, Dr Peter Jenks; Portsmouth Hospitals, Dr Sarah Wyllie; Royal Berkshire, Dr Nilangi Virgincar; Royal Free Hampstead, Dr Susan Hopkins; South London Healthcare, Dr Martino Dallantonia; South Tyneside, Dr Alan Rodgers/Dr Richard Ellis; Southport & Ormskirk Hospital, Dr Judith Bowley/Martin Kiernan; Surrey & Sussex Healthcare, Dr Karen Knox; The Royal Marsden, Dr Unell Riley; The Whittington Hospital, Dr Michael Kelsey; University College London Hospitals, Dr Peter Wilson/Dr Nan Shetty; University Hospital of North Staffordshire, Dr Jeorge Orendi; University Hospitals of Morecambe Bay, Dr Monika Pasztor

We would also like to acknowledge: the UK government's Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection *E. coli* sub-group (Martin Kiernan; Dr Cliodna McNulty; Professor Peter Hawkey; Professor Heather Loveday; Dr Carol Pellowe; Dr Russell Hope; Ann Moore; Dr Stuart Bruce; Catherine Williams; Zara Head; Dr Ruth Milton; Jennie Wilson) for their support for the sentinel study; Dean Ironmonger for technical support in the development of the software; and Sobia Wasti and Angela Falola for assisting in recruitment of the sentinel sites.

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Table 1.Description of the *E. coli* bacteraemia sentinel study participants

Patient and specimen characteristics			**N**	**%**
		Total study participants	1,688	
Patient and specimen details	Age group (years)	0-<1	26	1.5
		1-14	14	0.8
		15-44	161	9.5
		45-64	312	18.5
		65-74	342	20.3
		75-84	478	28.3
		85+	355	21.0
	Gender	Female	901	53.4
		Male	753	44.6
		Unknown	34	2.0
	Timing of *E. coli* bacteraemia onset	0-1 after admission	1,153	68.3
		2-6 days	129	7.6
		>=7 days	294	17.4
		Not admitted	110	6.5
		Not reported	2	0.1
	Specialty	Medical	1,162	68.8
		General	236	14.0
		Surgical	60	3.6
		Not known	59	3.5
		Not reported	171	10.1
	Underlying focus of infection	Bone and joint infection	7	0.4
		Central nervous system	1	0.1
		Contaminant	5	0.3
		Febrile neutropenia	54	3.2
		Gastrointestinal tract	118	7.0
		Hepatobiliary	264	15.6
		Indwelling intravascular device	19	1.1
		Other	29	1.7
		Pneumonia	54	3.2
		Skin/soft tissue infection	18	1.1
		Unknown	252	14.9
		Urogenital tract	865	51.2
		Not reported	2	0.1
Healthcare exposure	Any exposure in the week prior to bacteraemia	Yes	584	34.6
		No	949	56.2
		Not known	155	9.2
	Any exposure in the month prior to bacteraemia	Yes	930	55.1
		No	458	27.1
		Not known	300	17.8

	Antibiotics in the 4 weeks prior to the bacteraemia	Yes	546	32.4
		No	681	40.3
		Not known	459	27.2
		Not reported	2	0.1
	Urinary catheter in situ, inserted, removed, manipulated in the 7 days prior to the bacteraemia	Yes	354	21.0
		No	1,206	71.5
		Not known	128	7.6
	Indwelling vascular access device in situ, or removed in the 3 days prior to the bacteraemia	Yes	373	22.1
		No	1,190	70.5
		Not known	125	7.4
	Other devices in situ or removed in the 4 weeks prior to the bacteraemia	Yes	123	7.3
		No	1,332	78.9
		Not known	233	13.8
	Other procedures in the 4 weeks prior to the bacteraemia	Yes	209	12.4
		No	1,213	71.9
		Not known	265	15.7
		Not reported	1	0.1

Table 2. Crude and adjusted1 odds ratios for risk factors for genito-urinary focus of *E. coli* bacteraemia

Variable		Crude OR	95% Confidence interval		P value	Adjusted OR	95% confidence interval		P value
Gender	Female	1							
	Male	0.7	0.6	0.9	0.0018	0.7	0.5	0.9	0.001
Age group (years)	1-44	1							
	0<1	0.7	0.3	1.5	0.3201	1.2	0.5	2.9	0.748
	45-84	0.7	0.5	1.0	0.0603	0.8	0.6	1.2	0.358
	>=85	1.0	0.7	1.4	0.9594	1.0	0.6	1.5	0.948
UTI in the month prior to bacteraemia	None	1							
	>=1	4.1	2.9	5.7	<0.001	5.4	3.6	8.1	<0.001
Urinary catheterisation in the 7 days prior to the bacteraemia	No	1							
	Yes	2.2	1.7	2.9	<0.001	1.8	0.9	3.8	0.108
	Not known	0.5	0.4	0.8	0.0015	0.4	0.3	0.7	0.001
Duration of catheterisation	No catheters	1							
	Short term	1.6	1.1	2.2	0.0062				
	Long term	5.0	3.2	7.7	<0.001				
	Not known	1.3	0.7	2.3	0.4867	Omitted due to collinearity with "Urinary catheterisation in the 7 days prior to the bacteraemia"			
Insertion method of urinary catheter	No catheter	1							
	Suprapubic	5.6	1.2	25.8	0.0123				
	Urethral	2.6	2.0	3.4	<0.001				
	Don't know	1.1	0.4	3.2	0.8282				Not included
Reason for urinary catheterisation	Not reported	1							
	Other	2.0	1.5	2.7	<0.001	2.0	0.9	4.4	0.09
	Incontinence	7.0	2.7	18.2	<0.001	5.2	1.5	18.1	0.009
	Not known	3.9	2.1	7.2	<0.001	2.6	1.0	7.1	0.061
Treatment for a UTI in the month prior to the *E. coli* bacteraemia	No	1							
	Yes	7.7	4.7	12.5	<0.001	10.7	6.3	18.1	<0.001
Specialty	Medical	1							
	General	0.5	0.4	0.7	<0.001	0.6	0.4	0.9	0.016
	Surgical	4.1	2.1	8.0	<0.001	4.3	2.0	9.3	<0.001
	Not known	1.3	0.8	2.3	0.2821	1.8	0.9	3.4	0.074
	Not reported	1.0	0.7	1.4	0.9066	1.2	0.7	1.9	0.578
Timing of *E. coli* bacteraemia onset	0-1 day after admission	1							
	2-6 days	0.6	0.4	0.8	0.0023	0.4	0.2	0.6	<0.001
	>=7 days	0.5	0.4	0.6	<0.001	0.3	0.2	0.4	<0.001
	not admitted	0.8	0.6	1.3	0.4059	1.0	0.6	1.8	0.987
	Not reported	0.8	0.0	12.6	0.8658	0.5	0.0	9.6	0.639

1. Final model includes risk factors identified from the literature and age and gender as a priori risk factors. Other variables were only included if they changed the effect of the main risk factors and were associated in the crude analysis. Adjusted ORs are adjusted for all other risk factors in the final model.

Table 3.Antibiotic susceptibilities of the *E.coli* blood culture by timing of bacteraemia onset in relation to hospital admission

		Timing of *E. coli* bacteraemia onset in relation to hospital admission								
		0-1 day after admission		**2-6 days**		**>=7 days**		**Not admitted**		
Antibiotic name	**Susceptibility result**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**P-value**
Ciprofloxacin	NS	124	16.6	13	16.9	36	19.7	14	15.4	
	S	623	83.4	64	83.1	147	80.3	77	84.6	
	Total	747	100	77	100	183	100	91	100	0.758
Trimethoprim	NS	210	40.3	22	40.0	55	45.1	28	33.7	
	S	311	59.7	33	60.0	67	54.9	55	66.3	
	Total	521	100	55	100	122	100	83	100	0.449
Co-amoxiclav	NS	326	40.5	48	54.6	96	48.2	41	44.1	
	S	480	59.6	40	45.5	103	51.8	52	55.9	
	Total	806	100	88	100	199	100	93	100	0.027
Third generation cephalosporins	NS	59	8.8	9	12.3	21	12.7	6	7.2	
	S	614	91.2	64	87.7	144	87.3	77	92.8	
	Total	673	100	73	100	165	100	83	100	0.311
Carbapenems	NS	1	0.1	0	0	1	0.5	0	0	
	S	706	99.9	80	100	183	99.5	88	100	
	Total	707	100	80	100	184	100	88	100	0.653
Gentamicin	NS	74	9.0	5	5.6	26	12.8	5	5.4	
	S	746	91.0	84	94.4	178	87.3	88	94.6	
	Total	820	100	89	100	204	100	93	100	0.105
Piperacillin/tazobactam	NS	77	9.9	15	18.1	34	17.3	13	14.1	
	S	704	90.1	68	81.9	163	82.7	79	85.9	
	Total	781	100	83	100	197	100	92	100	0.008
Nitrofurantoin	NS	5	4.6	0	0	0	0	0	0	
	S	103	95.4	9	100	22	100	5	100	
	Total	108	100	9	100	22	100	5	100	0.631

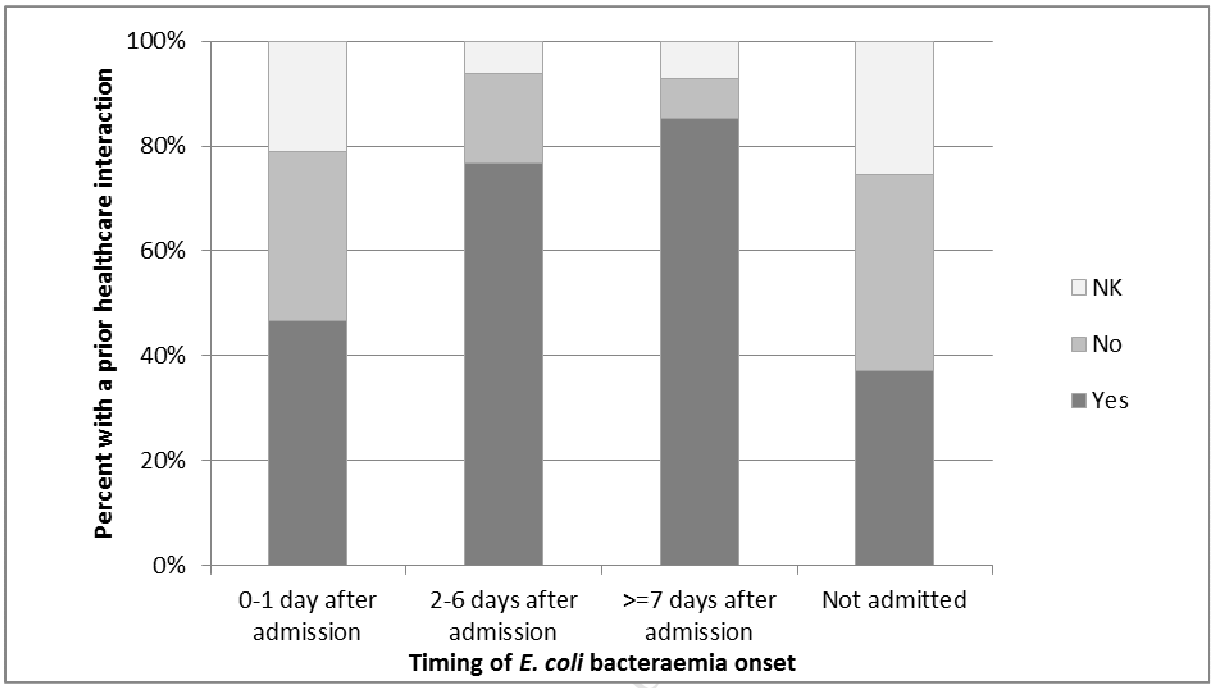
S, susceptible; NS, non-susceptible

Table 4. Antibiotic susceptibilities of the *E.coli* blood culture by underling focus of the *E. coli* bacteraemia

		Underlying focus of the *E. coli* bacteraemia								
		Urogenital tract		Pneumonia		Other		Not known		
Antibiotic name	**Susceptibility result**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**P-value**
Ciprofloxacin	NS	108	18.5	9	23.7	55	17.6	15	9.0	
	S	475	81.5	29	76.3	257	82.4	152	91.0	
	Total	583	100	38	100	312	100	167	100	0.02
Trimethoprim	NS	198	48.1	3	13.6	79	38.0	37	26.2	
	S	214	51.9	19	86.4	129	62.0	104	73.8	
	Total	412	100	22	100	208	100	141	100	<0.001
Co-amoxiclav	NS	283	45.4	14	35.9	145	43.8	69	35.6	
	S	340	54.6	25	64.1	186	56.2	125	64.4	
	Total	623	100	39	100	331	100	194	100	0.08
Cephalosporins	NS	55	10.8	2	6.7	25	9.0	13	7.4	
	S	455	89.2	28	93.3	254	91.0	163	92.6	
	Total	510	100	30	100	279	100	176	100	0.521
Carbapenems	NS	1	0.2	0	0	1	0.3	0	0	
	S	542	99.8	38	100	304	99.7	174	100	
	Total	543	100	38	100	305	100	174	100	0.87
Gentamicin	NS	62	9.8	3	7.7	36	10.5	9	4.6	
	S	569	90.2	36	92.3	306	89.5	186	95.4	
	Total	631	100	39	100	342	100	195	100	0.108
Piperacillin/tazobactam	NS	83	14.0	5	13.2	37	11.3	14	7.3	
	S	512	86.1	33	86.8	292	88.8	178	92.7	
	Total	595	100	38	100	329	100	192	100	0.095
Nitrofurantoin	NS	2	2.2	0	0	3	8.3	0	0	
	S	89	97.8	2	100	33	91.7	15	100	
	Total	91	100	2	100	36	100	15	100	0.309

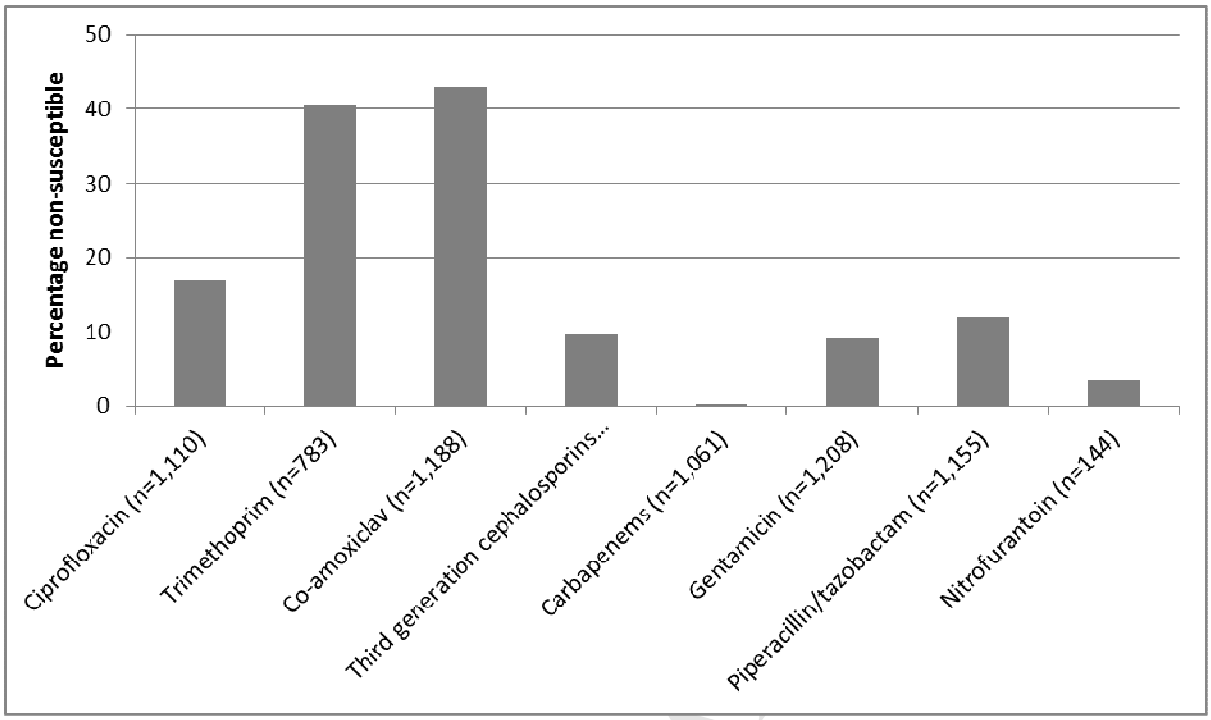
S, susceptible; NS, non-susceptible

Figure 1. Timing of *E. coli* bacteraemia onset and history of healthcare interaction in the month prior to the bacteraemia



Excludes 2 patients where admission status could not be ascertained

Figure 2. Antibiotic susceptibilities of the *E.coli* blood culture



Numbers in parentheses indicate the total number of isolates tested