Publications of projects that have featured in ESPAUR report between 2013 and 2019

Chapter 2: Antimicrobial resistance


Chapter 3: Carbapenemase-producing Enterobacterales


Cusack TP, Phimolsarnnousith V, Duangmala K et al. Molecular characterization of carbapenem-resistant Escherichia coli and Acinetobacter baumannii in the Lao People’s Democratic Republic. J Antimicrob Chemother 2019; 74; 2810-1821


Roulston KJ, Bharucha T, Turton JF *et al.* A case of NDM-carbapenemase-producing hypervirulent *Klebsiella pneumoniae* sequence type 23 from the UK. *JMM Case Rep* 2018; 5(9):e005130.


**Chapter 4: Antibiotic Consumption**


Chapter 6: Antifungal resistance, prescribing and stewardship


**Chapter 7: Antimicrobial Stewardship:**

Allison R, Lecky DM, Beech E et al. Local implementation of national antimicrobial stewardship initiatives: findings of a mixed-methods national study. *Br J Gen Pract* 2018; 68 (suppl1): bjgp18X697025.


**Chapter 8: Professional education and training and Public Engagement**


Eley CV, Sharma A, Lecky DM et al. Qualitative study to explore the views of general practice staff on the use of point-of-care C reactive protein testing for the management of lower respiratory tract infections in routine general practice in England. *BMJ Open* 2018; 8: e023925.


Antimicrobial resistance

Identification of optrA in linezolid-resistant Enterococcus faecalis isolated from companion animals in the UK
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Presented at: 29th European Congress of Clinical Microbiology and Infectious Diseases – April 2019

Background: Linezolid is licensed for the human treatment, often as a ‘last resort’, of Gram-positive infections including streptococci, vancomycin-resistant enterococci and methicillin-resistant staphylococci. Linezolid resistance is rare in enterococci but has been detected in isolates originating from humans and livestock. We report transmission of linezolid-resistant E. faecalis harbouring optrA between companion animals at a UK small-animal hospital.

Materials/methods: An E. faecalis isolate from a cat wound swab was referred by the veterinary diagnostic laboratory to Public Health England’s Antimicrobial Resistance and Healthcare Associated Infections Reference Unit for investigation of multidrug-resistance. Subsequently, three further E. faecalis isolates from other two cats and one dog from the same small-animal hospital (but different households) were referred. MICs were determined using BSAC agar dilution and interpreted using EUCAST criteria. Screening for the G2576T chromosomal 23S rRNA mutation and plasmid-borne cfr and optrA genes associated with linezolid resistance was performed by PCR, with strain typing by pulsed-field gel electrophoresis (PFGE).

Results: Four isolates from three wound swabs (two cats, one dog), and a third cat rectal swab were confirmed resistant to linezolid (MICs=8 mg/L) and gentamicin (MICs >512 mg/L), but susceptible to teicoplanin (MICs <=0.5 mg/L) and vancomycin (MICs=1-2 mg/L), and wild-type for daptomycin (MICs=1 mg/L). All four isolates were positive for optrA, but negative for cfr and the G2576T 23S rRNA mutation. PFGE typing revealed that the isolates consisted of two pairs with members of each pair sharing identical profiles.

Conclusions: We believe this is the first report of optrA-positive enterococci isolated from companion animals. Linezolid is not licensed for veterinary use in the UK, but optrA also confers resistance to florfenicol, which is used in animals. Standard protocols for management of colonized/infected animals should prevent transmission to veterinary staff, and therapeutic options (ampicillin or glycopeptides) remain should an infection occur. However, transmission of this organism to owners carries the potential
for plasmid-mediated spread to other bacteria, particularly in healthcare environments, and is of public health importance. A One-Health approach to monitoring emergence and dissemination of resistance mechanisms of public health importance is needed.

**Linezolid- and glycopeptide-resistant Enterococcus faecium isolated from a Haematology Unit**

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**Presented at:** Hospital Infection Society conference – November 2018

**Introduction:** Glycopeptides and linezolid are important antimicrobial agents used in Haematology to treat Gram-positive infections in neutropenic patients.

**Methods:** After isolating linezolid- and glycopeptide-resistant *Enterococcus faecium* (LGREFM) from Haematology patients during 2017, we reviewed the laboratory information system to identify all isolates confirmed as linezolid- (MICs = 8 mg/L) and vancomycin-resistant (MICs ≥ 32 mg/L) by the National Infection Service, PHE Colindale. The resistance mechanism for linezolid was determined by molecular investigations.

**Results:** LGREFM were isolated from nine patients on the Haematology Unit. These were mainly from faeces samples in patients with diarrhoea (where vancomycin-resistant enterococci are routinely sought for infection control purposes), however three patients had LGREFM isolated from urine samples and one from a blood culture. Resistance to linezolid was due to the chromosomal G2576T 23S rRNA mutation. Molecular typing by PFGE in seven patients demonstrated that four strains were unique, one patient had two similar isolates (but distinct from the others) and two patients had isolates with similar, but not identical, profiles. The monthly quantity of linezolid issued to the Haematology Unit showed an increase during the summer and autumn of 2017.

**Conclusion:** There was an increase in LGREFM isolates in the Haematology Unit from May 2017, which were associated with an increase in linezolid use, in part related to a shortage of vancomycin. PFGE typing demonstrated that most of the isolates were unique, so cross-infection probably played, at most, a minor part in this cluster of LGREFM.
Genomic investigation of linezolid-resistant *Enterococcus faecalis* carrying the *optrA* gene

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**Presented at:** 29th European Congress of Clinical Microbiology and Infectious Diseases – April 2019

**Background:** Linezolid is reserved for treating severe, antibiotic-resistant, Gram positive bacterial infections in humans. Linezolid resistance is caused by mutations in 23S rRNA or acquisition of *cfr, optrA, or poxtA* genes. Although enterococcal linezolid resistance remains rare (generally <1%), the plasmid-mediated *optrA* gene has been detected in many countries. We performed whole genome sequencing of linezolid resistant *Enterococcus faecalis* isolates to determine if the *optrA* gene was present in a single genetic clone and whether it was carried by transmissible genetic elements.

**Materials/methods:** Isolates were identified as linezolid- and chloramphenicol-resistant in routine diagnostic laboratories, and confirmed to carry the *optrA* gene by Public Health England AMRHI Reference Unit. Illumina MiSeq short reads were mapped to a reference strain with SMALT and a core genome phylogeny made. Hybrid assemblies of short reads and Oxford Nanopore MinION long reads were generated with Unicycler and annotated with Prokka.

**Results:** The *optrA* gene was found in six linezolid-resistant *E. faecalis* isolated between 2014 and 2017. All isolates were from genitourinary samples and were susceptible to amoxicillin and vancomycin. No direct epidemiological links were identified between patients, only one had recent linezolid exposure. Core genome phylogeny confirmed the isolates were genetically unrelated, belonging to distinct MLST profiles. The *optrA* gene was found on a plasmid in each isolate, and these plasmids had limited sequence similarity. It was notable that the *optrA* gene was always co-located with the *fexA* phenicol resistance gene and flanked by two copies of IS1216E. Four *optrA* amino acid sequence variants were detected, differing from each other at 1-3 amino acids. One of these variants had not been described previously.

**Conclusions:** This is the first genomic investigation of *optrA*-mediated oxazolidinone resistance in *E. faecalis* using hybrid assembly of short and long sequencing reads. Our sequencing approach allowed the assembly of complete bacterial genomes and investigation of plasmids carrying *optrA*. We report multiple *optrA* variants in diverse *E. faecalis* strain and plasmid backgrounds, suggesting multiple introductions into the population and/or ongoing transfer of the gene. The reservoir and mechanism of *optrA* selection in humans is unclear and requires investigation to avoid widespread linezolid resistance.
Visualizing current and potential future antibiotic resistance levels using Bayesian spatio-temporal models
Koen B. Pouwels¹, Berit Muller-Pebody¹, Susan Hopkins¹, Julie V. Robotham¹
¹ Public Health England

**Presented at:** 29th European Congress of Clinical Microbiology and Infectious Diseases – April 2019

**Background:** To facilitate optimal antibiotic prescribing it is important to know, before microbiological test results are available, the probability of antibiotic resistances for patients presenting to healthcare providers. To predict the resistance profile of a presenting infection, information about local resistance prevalences are needed, but often this is not known accurately due to insufficient local data and biases in routine surveillance. Here we propose to use Bayesian spatio-temporal models to overcome these limitations to provide more accurate estimates of local resistance prevalences and to show the predicted impact of changes in antibiotic prescribing on future resistance prevalences.

**Methods:** Monthly primary care prescribing data were obtained from NHS Digital. Positive Escherichia coli urinary and blood samples between January 2014 and April 2018 were obtained from PHE’s Second Generation Surveillance System (SGSS). Bayesian spatio-temporal models, taking into account various risk-factors including antibiotic use and the probability that a sample was taken from clinical cases, were used to estimate pre-test probabilities of antibiotic resistances against relevant antibiotics.

**Results:** More realistic estimates of local pre-test probabilities of antibiotic resistances could be produced using these models than when simply using the proportion of tested samples that were resistant to the antibiotic of interest. The Bayesian spatio-temporal models were especially advantageous in cases where there are few samples on which to base the local resistance prevalence or when it is not routine practice to test for antibiotic resistance, such as for urinary tract infections. Current and future predicted antibiotic resistances as a function of changes in antibiotic use were visualized using heat maps.

**Conclusions:** Bayesian spatio-temporal models can help to inform local pre-test probabilities of antibiotic resistances, thereby better informing empiric antibiotic prescribing.
A prospective surveillance study to determine the prevalence of 16S rRNA methyltransferases in the UK

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Presented at: 28th European Congress of Clinical Microbiology and Infectious Diseases – April 2018

Background: 16S rRNA methyltransferases (RMTases) are an emerging resistance mechanism, and cause high level resistance (MICs ≥256 mg/L) to all clinically-relevant aminoglycosides in Gram-negative bacteria. The aim of this study was to determine the prevalence of RMTases in the UK by conducting a six-month prospective surveillance study involving UK hospitals.

Materials/methods: Fourteen UK hospitals collected Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa isolates displaying amikacin resistance (MIC >16 mg/L) from 1st May to 31st October 2016, and completed anonymized questionnaires regarding patient travel history, medical care abroad and previous antibiotic use to identify possible risk factors for the acquisition of RMTase-positive bacteria. Isolates were submitted to PHE’s national reference laboratory, where they were: plated on Mueller-Hinton agar supplemented with 256 mg/L amikacin to detect high-level resistance, screened for RMTases using two multiplex PCRs, screened for carbapenemase genes blaKPC, blaNDM, blaOXA-48-like and blAVIM using a real-time PCR, and typed using variable-number tandem repeat (VNTR) analysis.

Results: A total of 218 amikacin-resistant isolates were sent from 14 UK hospitals: 147 (67.4%) Enterobacteriaceae, 55 (25.2%) P. aeruginosa and 16 (7.3%) A. baumannii. Of these, 106 isolates were high-level amikacin resistant (MIC >256 mg/L), of which 79 (74.5%) were identified as RMTase gene-positive (Table) with armA (43/79, 54.4%) the most common. A novel RMTase or other genes that confer high-level amikacin resistance may be present in the 27 RMTase-negative isolates. Carbapenemase genes were identified in 69/79 (87.3%) RMTase-positive isolates including blaNDM (45/79, 57%), blaOXA-48-like (11/79, 13.9%), blaNDM + blaOXA-48-like (7/79, 8.9%) blaKPC (1/79, 1.2%) and blAVIM (1/79, 1.2%). Sequence types (STs) were derived from VNTR profiles and demonstrated that RMTases are associated with high-risk bacterial clones such as K. pneumoniae ST14 (10/67, 15.9%) (Table) The overall period prevalence of RMTases
was 0.12% (79/68,610), ascertained from isolates screened for amikacin resistance in 14 laboratories.

**Conclusions**: The prevalence of RMTases was 0.12% amongst hospitals participating in this study. Their association with high-risk bacterial clones, and with carbapenemase producers in particular, means that the threat they pose may grow in the future, potentially removing existing aminoglycosides and the novel agent plazomicin, from treatment regimens for multidrug-resistant bacterial infections.

<table>
<thead>
<tr>
<th>16S RMTase</th>
<th>Species (No)</th>
<th>Number of Isolates</th>
<th>ST inferred from VNTR (No)</th>
<th>Carbapenemases (No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ArmA</td>
<td><em>K. pneumoniae</em> (n=22), <em>A. baumannii</em> (n=11), <em>Escherichia coli</em> (n=4), <em>Citrobacter freundii</em> (n=2), <em>Enterobacter cloacae</em> complex (n=2) and <em>Klebsiella oxytoca</em> (n=2)</td>
<td>43</td>
<td><em>A. baumannii</em>: ST2 (n=11); <em>K. pneumoniae</em>: ST14 (n=10), ST15 (n=2), ST147 (n=2), ST307 (n=1) and undetermined (n=7); not typed by VNTR (n=10)</td>
<td>NDM (n=18), OXA-23-like + OXA-51-like (n=11), negative (n=6), OXA-48-like (n=4), NDM + OXA-48-like (n=3) and KPC (n=1)</td>
</tr>
<tr>
<td>RmtB</td>
<td><em>E. coli</em> (n=7), <em>K. pneumoniae</em> (n=4), <em>P. aeruginosa</em> (n=2) and <em>Providencia stuartii</em> (n=1)</td>
<td>14</td>
<td><em>K. pneumoniae</em>: ST138 (n=1), ST231 (n=1) and undetermined (n=2); <em>P. aeruginosa</em>: ST773 (n=2); not typed by VNTR (n=8)</td>
<td>NDM (n=10), negative (n=2), NDM + OXA-48-like (n=1) and VIM (n=1)</td>
</tr>
<tr>
<td>RmtC</td>
<td><em>C. freundii</em> (n=4), <em>K. pneumoniae</em> (n=3), <em>E. coli</em> (n=2) and <em>E. cloacae</em> complex (n=1)</td>
<td>10</td>
<td><em>K. pneumoniae</em>: undetermined (n=2) and ST307 (n=1); not typed by VNTR (n=7)</td>
<td>NDM (n=9) and NDM + OXA-48-like (n=1)</td>
</tr>
<tr>
<td>RmtF</td>
<td><em>K. pneumoniae</em></td>
<td>11</td>
<td>ST147 (n=5), undetermined (n=3), ST231 (n=2) and ST383 (n=1)</td>
<td>OXA-48-like (n=6), NDM + OXA-48-like (n=2), negative (n=2) and NDM (n=1)</td>
</tr>
<tr>
<td>ArmA + RmtF</td>
<td><em>K. pneumoniae</em></td>
<td>1</td>
<td>ST231</td>
<td>OXA-48-like</td>
</tr>
<tr>
<td>Negative</td>
<td><em>P. aeruginosa</em> (n=53), <em>E. coli</em> (n=30), <em>K. pneumoniae</em> (n=28), <em>E. cloacae</em> complex (n=9), <em>A. baumannii</em> (n=5), <em>C. freundii</em> (n=4), <em>K. oxytoca</em> (n=3), <em>Serratia marcescens</em> (n=3), <em>C. amalonaticus</em> (n=1), <em>Hafnia alvei</em> (n=1), <em>Morganella morganii</em> (n=1) and <em>Proteus mirabilis</em> (n=1)</td>
<td>139</td>
<td><em>A. baumannii</em>: ST2 (n=5); <em>K. pneumoniae</em>: undetermined (n=13), ST101 (n=7), ST15 (n=3), ST258 (n=2), ST11 (n=1), ST20 (n=1) and ST405 (n=1); <em>P. aeruginosa</em>: undetermined (n=49), ST233 (n=3) and ST235 (n=1); not typed by VNTR (n=53)</td>
<td>Negative (n=93), OXA-48-like (n=16), NDM (n=15), VIM (n=5), OXA-23-like + OXA-51-like (n=3), GES-5 (n=2), KPC (n=2), KPC + NDM (n=1), OXA-23-like + OXA-51-like + NDM (n=1) and OXA-40-like + OXA-51-like (n=1)</td>
</tr>
</tbody>
</table>
OXA-1 beta-lactamase as the major cause of raised piperacillin/tazobactam MICs among ESBL-producing ST131 E. coli from bloodstream infections

David Livermore\(^1\), Michaela Day\(^2\), Paul Cleary\(^3\), Katie Hopkins\(^2\), Mark Alexander Toleman\(^4\), David Wareham\(^5\), Camilla Wiuff\(^6\), Neil Woodford\(^2\)

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Presented at: 28\(^{th}\) European Congress of Clinical Microbiology and Infectious Diseases – April 2018

**Background:** ST131 *E. coli* with ESBLs, principally CTX-M-15, have expanded globally since around year 2000 and present a major public health issue. Most are multi-resistant to fluoroquinolones, cephalosporins, antifolates and, often, aminoglycosides. Susceptibility to piperacillin-tazobactam (PTZ) is variable and has been suggested to relate to the co-production of other \(\beta\)-lactamases, notably OXA-1, though there is a lack of robust data to prove or refute this assertion.

**Materials/methods:** During a national study on *E. coli* we collected and sequenced, by Illumina methodology, 293 representative ESBL producers from bacteraemia. MICs were determined by BSAC agar dilution and reviewed against EUCAST breakpoints (PTZ S \(\leq\)8, R >16 mg/L).

**Results:** Among the 293 isolates, 187 belong to ST131 and its minor variants and 158 of these had CTX-M-15 ESBLs alone or in combination with other \(\beta\)-lactamases, principally TEM-1 or OXA-1. For these 158 organisms, there was a clear association (\(p<0.01\), chi squared test for proportion) between raised PTZ MICs, and co-carriage of OXA-1 enzyme such that the modal MIC was 8-16 mg/L for groups with OXA-1 but only 2 mg/L for groups lacking this enzyme. There was no such association for TEM-1. PTZ non-susceptibility nevertheless was seen in 2 isolates lacking OXA-1 enzyme, indicating that other mechanisms can be responsible.

<table>
<thead>
<tr>
<th>(\beta)-lactamases co-carried with CTX-M-15</th>
<th>PTZ mode MIC, mg/L</th>
<th>Non-susceptible to PTZ, 8 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2</td>
<td>1/13</td>
</tr>
<tr>
<td>TEM-1/191 only</td>
<td>2</td>
<td>1/29</td>
</tr>
<tr>
<td>OXA-1 only</td>
<td>8</td>
<td>19/74</td>
</tr>
<tr>
<td>OXA-1 plus TEM-1</td>
<td>16</td>
<td>17/38</td>
</tr>
<tr>
<td>Multiple (variously other CTX-M, CMY, OXA-9) plus OXA-1</td>
<td>16</td>
<td>3/4</td>
</tr>
</tbody>
</table>
The remaining 29/187 ST131 ESBL isolates lacked CTX-M-15 and variously had CTX-M-3, -14 or -27 enzymes; none co-produced OXA-1, though 4 had TEM-1; the modal PTZ MIC was 2 mg/L and all were susceptible.

**Conclusion:** Co-carriage of OXA-1, an inhibitor-resistant penicillinase, is the major arbiter of PTZ susceptibility or resistance in ST131 ESBL *E. coli*.


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**Presented at:** Public Health England Public Health Research and Science Conference 2019 –Manchester, UK; April 2019

**Background:** Urinary Tract Infections (UTIs) are one of the most common infections in both community and hospital settings and a risk factor for development of bloodstream infection. The National Institute for Health and Care Excellence (NICE) empirical treatment guidelines for UTIs include nitrofurantoin, trimethoprim, ciprofloxacin, fosfomycin and pivmecillinam. The aim of our study was to assess suitability of these recommendations for treating UTIs in acute and primary care in England.

**Materials/Methods:** Descriptive analyses were performed on UTI specimen results submitted to PHE’s Second Generation Surveillance System (SGSS) from England between 1st January 2015 and 31st December 2017. Only the first patient specimen within a 14-day period was included. UTI samples are not cultured routinely for uncomplicated UTI in adult women.

**Results:** Between 2015 and 2017, 128 genera of bacteria were identified from 6,096,670 urine isolates: 43% of urine isolates were reported from acute healthcare (2,612,091); 53% from GPs (3,252,752), with 4% from other community care settings (231,827). The most prevalent bacterial genera isolated in acute care were *Escherichia* (54% of isolates), *Enterococcus* (9%), *Proteus* (5%), *Klebsiella* (4%), *Pseudomonas* (4%) and *Staphylococcus* (3%). A similar distribution was recorded in GP specimens. In acute care isolates resistance was 37% for trimethoprim, 13% for nitrofurantoin, 16% for ciprofloxacin, 14% for (piv-)-mecillinam and 12% for fosfomycin. Comparable GP isolate resistances were 34%, 10%, 11%, 10% and 9%, respectively.

**Conclusion:** High levels of resistance to trimethoprim in both acute and community healthcare settings risk high rates of empirical treatment failure of UTIs with trimethoprim. Resistance to nitrofurantoin, ciprofloxacin, (piv-)mecillinam and fosfomycin generally remains lower, however, high levels of resistance to nitrofurantoin were observed in *Klebsiella* in both acute and community settings.

Further characterisation of organisms and resistance by setting and patient demographics is required to help inform decision tools to aid empirical UTI treatment based on patient characteristics.
Carbapenemase Producing Enterobacterales; Research outputs, 2013 – 2019

Routine identification of carbapenemase-producing Gram-negative bacteria by diagnostic laboratories in England demands surveillance modernisation


Presented at: Don’t Panic! Conference, 2019

Background: The electronic reporting system (ERS) for the enhanced surveillance of carbapenemase-producing Gram-negative bacteria was introduced in 2015 to capture data on isolates referred for confirmation of carbapenemase production to Public Health England’s (PHE) Antimicrobial Resistance and Healthcare Associated Infections Reference Unit. However, an increasing number of diagnostic laboratories are introducing methods to routinely identify carbapenemases.

Methods: A questionnaire was sent to PHE Field Service Information Managers. Information Managers conducted telephone interviews with senior laboratory staff and responses were collected and submitted electronically. The survey was open between 11th July – 19th August 2018. Survey responses were cleaned and analysed in Stata version 15.

Results: 113/120 (94%) laboratories participated. Eighty (70.8%) laboratories used phenotypic methods for the detection of carbapenemase activity; these results were stored on laboratory information management system (LIMS) in 88.3% of laboratories. However, only 29.6% of laboratories reported using EUCAST screening cut-offs for carbapenem susceptibility testing to determine whether to proceed to local or reference laboratory referral for carbapenemase testing. Fifty-five (48.7%) laboratories reported use of molecular testing for carbapenemase identification. The most commonly adopted methods were commercial PCR (60.0%) and immunochromatographic assays (43.6%). The majority (>90%) of laboratories could identify isolates harbouring KPC, OXA-48-like or NDM; VIM and IMP could be identified by fewer laboratories (76.4% and 65.5%, respectively). Nearly all (98.1%) laboratories performing molecular testing recorded the results on their LIMS.

Conclusions: Survey participation was high and identified that nearly half of diagnostic laboratories were performing molecular identification of carbapenemases, with more using phenotypic methods to detect carbapenemase activity. However, less than one-third of laboratories were using EUCAST screening cut-offs as recommended in the UK Standards for Microbiology Investigations to identify bacteria requiring further screening for carbapenemases.

With diagnostic laboratories identifying carbapenemases using molecular tests PHE has altered its approach to surveillance. The ERS was decommissioned in April 2019 and modifications were made to PHE’s Second Generation Surveillance System (SGSS) to allow diagnostic laboratories to automatically report carbapenemase producers and
capture AMR HAI results. This will facilitate linkage to other datasets and will be vital in improving our understanding of the epidemiology of carbapenemases in England, without increasing the data burden on the NHS.

**A mathematical model of carbapenemase-producing Enterobacteriaceae transmission and control in the English hospital setting**


Presented at Spread of Pathogens in Healthcare Institutions and Networks: a modeling conference, 2019

**Background:** Carbapenemase-producing Enterobacteriaceae (CPE) are a growing threat across Europe, and in England CPE detections are increasing year-on-year. However, understanding of these organisms' transmission dynamics and effectiveness of potential control measures is severely lacking and mathematical models scarce. We present a data-driven mathematical model of CPE transmission within hospitals to fill this gap and inform decision-making on interventions to reduce this emerging threat.

**Methods:** We developed an individual-based mathematical model simulating CPE transmission within hospitals including (re)admissions from the community population. Transmission was modelled considering colonised and infected patients, as well as environmental contamination. Dynamics on applying Public Health England’s ‘CPE Toolkit’ (see Figure) were explored, in settings where CPE is emerging or is endemic. Parameterisation used primary data wherever possible, including estimating transmission (patient-patient and environment-patient) through application of Markov chain Monte Carlo algorithms to individual-level prospective hospital study data.

**Results:** Model outputs include incidence/prevalence over time, numbers screened (and identified positive), imported cases, transmission events, control measures initiated. Analysis of existing screening criteria indicates 21% of CPE carriers admitted to settings in non-endemic areas are not identified as suspected positives, and thus neither subject to additional control measures nor CPE screening tests. Over 40% of those screened are discharged before a final outcome is known and recorded for future use; estimation of CPE clearance rates (analysis of real hospital data, 2009-2016) predicts that 33% of patients colonised at discharge would still have CPE carriage a year later.

**Conclusions:** Our model provides insight into unobserved colonisations and associated transmission. In addition to quantifying the efficiency/effectiveness of existing screening criteria and pre-emptive control measures, our model evaluates alternative interventions to improve these indicators, and to reduce transmissions.
Evaluation of temocillin and meropenem MICs as diagnostic markers for OXA-48-like carbapenemases
Hopkins KL, Meunier D, Pike R, Woodford N.

Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2019.

Background: OXA-48-like non-metallo-carbapenemases are rapidly spreading in European countries and are the most common carbapenemase family identified in the UK. Following detection of reduced susceptibility to meropenem (MIC >0.12 mg/L), high-level temocillin resistance (MICs >128 mg/L) in the absence of synergy in combination disk testing has been proposed by EUCAST as a putative phenotypic marker for OXA-48-like production. We evaluated temocillin and meropenem MICs as diagnostic markers for prediction of OXA-48-like production.

Methods: MIC data for isolates of Escherichia coli (n=471), Klebsiella spp. (n=694) and Enterobacter spp. (n=172) with OXA-48-like enzymes were reviewed from submissions made to Public Health England’s Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit between 1st January 2014 and 30th September 2018 by English diagnostic laboratories. Temocillin and meropenem MICs were determined by agar dilution and interpreted using EUCAST criteria. blaOXA-48-like genes were sought by PCR.

Results: Meropenem MICs were below the EUCAST screening cut-off (MICs ≤0.12 mg/L) for 59 (12.5%) E. coli isolates, 1 (0.6%) Enterobacter spp. and 6 (0.9%) Klebsiella spp. Temocillin MICs were below the EUCAST cut-off (MICs ≤128 mg/L) for 60 E. coli (12.7%; MICs 32-128 mg/L), 12 Enterobacter spp. (7%; MICs 64-128 mg/L) and 95 Klebsiella spp. (13.7%; MICs 8-128 mg/L). Both meropenem and temocillin MICs were below EUCAST cut-off values for 19 (4%) E. coli and 2 (0.3%) Klebsiella spp. E. coli with meropenem MICs ≤0.12 mg/L were referred by 28 laboratories representing all nine regions within England.

Conclusions: These data highlight the problems with phenotypic detection of OXA-48-like producers and indicate that multiple tests are needed to maximise sensitivity as per EUCAST guidance. Phenotypic screening criteria could be improved by changing the temocillin cut-off to >16 mg/L but meropenem MICs ≤0.12 mg/L for >10% E. coli referred to AMRHAI indicates that E. coli producing OXA-48-like carbapenemases are still particularly likely to be under-reported.

A prospective multi-centre evaluation of the NG-test Carba5, a multiplex immunochromatographic assay for the rapid detection of carbapenemase-producing Enterobacteriaceae in culture

Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2019.
Background: The spread of carbapenemase-producing Enterobacterales (CPE) is a public health concern. Rapid detection and identification of CPE is essential to prevent further spread and inform appropriate antimicrobial therapy. During a prospective multi-centre study, we have evaluated the NG-test Carba5 (NGBiotech), a multiplex Lateral Flow ImmunoAssay (LFIA) allowing the detection of NDM, OXA-48-, KPC-, VIM- and IMP-like carbapenemases from bacterial culture in less than 15 minutes.

Methods: The NG-test Carba5 (NGBiotech) was used to prospectively screen isolates sent to three national reference centres (Belgium, UK, France), a regional referral laboratory (Andalusia, Spain), and a clinical microbiology laboratory (Careggi University Hospital, Florence, Italy) for CPE detection. The NG-test Carba5 was used as recommended by the manufacturer in parallel with the local workflow in place for the detection of CPE. The time to a positive result was recorded.

Results: A total of 1095 isolates was tested between February - October 2018. KPC (n=151; 62% were from Italy), OXA-48-like (n=231; 43%, 26%, 21% came from France, Belgium and UK, respectively), NDM (n=119; 52% and 36% were from UK and France, respectively), VIM (n=94; 61% were from Spain), IMP (n=28; 79% were from Spain) and multiple carbapenemase producers (n=26) were all detected in a time-to-positivity average of 2-3 minutes (Table 1). Only 3/652 CPE (IMI-1, OXA-427 and OXA-23) were not detected, illustrating that the NG-test Carba5 was able to detect 99.5% of CPE circulating in the countries involved in the study. Of note, the NG-test Carba5 detected 12 IMP-8-positive isolates not detected by the Xpert® Carba-R assay (Cepheid).

Conclusions: The NG-test Carba5 is able to detect the ‘big 5’ carbapenemase families on their own or in combination with other carbapenemases. The overall sensitivity and specificity were nearly 100%. It requires minimum hands-on-time (<1 min), is easy to implement and has a time-to-positivity of less than 3 mins, in most of the cases. This tool is critical for implementing rapid infection control measures and is also relevant in areas with a high prevalence of NDM-, OXA-48-, KPC-, VIM- or IMP-like producers to discriminate between the carbapenemase families, especially with novel avibactam-based treatments.

**Longitudinal sampling of patients and wastewater sites in an endemic blaKPC-carbapenemase context demonstrates high levels of colonisation, genetic diversity and rapid genetic flux**

**Presented at:** The European Congress of Clinical Microbiology and Infectious Diseases, 2019.

**Background:** Carbapenemase-producing Enterobacteriaceae (CPE) are a global health threat; genes encoding carbapenem resistance, e.g. blaKPC, can be disseminated readily on mobile genetic elements (MGEs). Hospital wastewater sites have been recognized as potential CPE reservoirs and niches for gene exchange; however,
detailed knowledge of CPE diversity in these reservoirs and their contribution to transmission is lacking.

**Methods:** Standardised, prospective longitudinal sampling of wastewater sites (n=351) across six wards was carried out biweekly over 6-12 months (2016) in a hospital in Manchester, UK, which has experienced a poly-species KPC-CPE outbreak since 2009. Rectal screens were performed on patients admitted to these wards as part of hospital-wide CPE infection control. Linked, pseudo-anonymised patient admission and microbiology data were retrospectively analysed to characterise extent of patient capture from prospective sampling and patient movements. Samples were selectively cultured for CPE; ~5 colonies/sample were sub-cultured and whole genome sequenced. Phylogenetic analyses and resistance gene/Tn4401/target site sequence (TSS)/plasmid replicon typing were undertaken (ClonalFrameML; mapping/BLAST-based identification/characterization of target loci).

**Results:** 264/6496 (4.1%) patients admitted to the study wards and 310/4760 (6.5%) wastewater samples were CPE-positive during the study period. Mixed colonization (i.e. genetic differences at any level) at any given sampling time-point was common (>20%) in both wastewater sites and patients. 1755 CPE isolates (environment/patient) were successfully sequenced. All isolates contained blaKPC-2, estimated copy number varied (median=1.76; maximum=9.8). In 1510 (86%) isolates blaKPC-2 was in Tn4401a; 19 different Tn4401a variants were observed, two of which predominated (1342/1510 [88%] isolates). The two predominant Tn4401a variants were found with at least 24 different TSS combinations, consistent with significant Tn4401a mobility. Major species included *Klebsiella* (n=813 isolates), *Enterobacter* (563), *Citrobacter* (147) and *Escherichia* spp. (73), with 1-56 (*Raoultella* vs *Klebsiella*) genomic clusters identified.

**Conclusions:** Dense sampling of patient and wastewater sites in an endemic nosocomial blaKPC context and high-resolution genomic analysis demonstrated significant colonisation, genetic diversity and flux. Analysis of single isolates from patients inadequately reflects complexity; tracking transmission events at any genetic level is difficult. Different dynamics were observed for different species, strains and MGEs; further work estimating statistical associations between genetically linked isolates and specific sites is ongoing.

**Epidemiology of carbapenemase-producing bacteria in England, 2016–2018: results from the national enhanced surveillance system**

**Presented at:** The European Scientific Conference on Applied Infectious Disease Epidemiology, 2018

**Background:** In May 2015, following an increase in reported cases, Public Health England launched an enhanced surveillance system to electronically capture data on patients infected/colonised with carbapenemase-producing Gram-negative bacteria. Our study aimed to identify high risk groups to inform infection prevention and control interventions.
Methods: Cases were defined as patients with a carbapenemase-producing organism isolated from a screening or clinical specimen in England between April 2016–March 2018. Cases were de-duplicated by patient, bacterial species, specimen site and resistance mechanism for each year of surveillance.

Results: There were 3953 cases reported via the system. 1786 (45.2%) patients were female and 2163 (54.7%) were male. The median age of patients was 69.5 years. Most cases were hospital inpatients (3436, 86.9%). Enhanced fields including foreign travel and clinical specialty were poorly completed (14% and 21%, respectively). The majority of organisms reported were from screening specimens (3151, 79.7%), with 798 clinical cases recorded (20.2%). Of the clinical specimens, the most common specimen types were urine (330, 41.4%), blood (102, 12.8%) and sputum (57, 7.1%). Carbapenemase enzymes were identified in 15 different genera. The most common species were *Klebsiella pneumoniae* (1424, 36.0%) and *Escherichia coli* (1119, 28.3%). Nine resistance mechanisms were identified; OXA-48-like enzymes were the most frequently identified (2076, 52.5%), followed by NDM (904, 22.9%) and KPC (890, 22.5%).

Conclusions: The enhanced surveillance system is voluntary and poor completion of enhanced data fields is limiting our ability to identify high risk patient groups to inform public health action. However, the system does capture comprehensive patient demographic data and functions as an electronic referral system. Future work will involve data linkage to allow us to identify groups at greater risk and focus control and prevention efforts.

**Diversity of Carbapenemase-Producing Enterobacteriaceae in England As Revealed By Whole Genome Sequencing**

Hopkins KL, Doumith M, Mustafa N, Meunier D, Ellington M, Woodford N.

**Presented at:** ASM Microbe, 2018.

**Background:** Increasing numbers of carbapenemase-producing Enterobacteriaceae (CPE) have been referred to the national reference laboratory since screening started in the early 2000s. Whole genome sequencing (WGS) was applied over 30 months to inform our understanding of CPE epidemiology in England.

**Methods:** WGS was applied to the first confirmed CPE from each new patient referred by an English laboratory between 1st Jan ’14 and 30th June ’16. Multiple isolates from the same patient were included if of different species, or the same species with a different carbapenemase. Illumina HiSeq 2500 WGS data was analysed using an in-house bioinformatics pipeline that determines species identification, MLST profile and antimicrobial resistance gene content.

**Results:** WGS data were obtained for 2658 CPE, representing 60% of CPE received from an English laboratory over this period. CPE were referred from all regions but North West England (NWE, n=941) and London (n=927) were particular foci. OXA-48-like (n=1119, variants OXA-48, -181, 204, -232, -244 and -484), NDM (n=691, NDM-1, -3, -4, -5 and -7 ), KPC (n=570, KPC-2, -3, -4 and -23), VIM (n=100, VIM-1, -4 and -19) and IMP (n=33, IMP-1, -4 and -14) predominated with 1 - 21 isolates harbouring FRI,
IMI, NMC-A, SME, GES-5 or various two carbapenemase gene combinations. *Klebsiella pneumoniae* (Kpn, n=1380), *Escherichia coli* (Esc, n=723) and *Enterobacter cloacae* (Ent, n=294) accounted for most isolates. Host species showed significant diversity with 151, 115 and 63 STs amongst *K. pneumoniae*, *E. coli* and *E. cloacae*, respectively. A further 126/1380 *K pneumoniae*, 45/723 *E. coli* and 49/294 *E. cloacae* could not be assigned to a previously defined ST. The top three STs per species were 14 (n=168), 11 (n=160) and 147 (n=105) amongst *K. pneumoniae*, 38 (n=158), 410 (n=63) and 167 (n=50) amongst *E. coli* and 108 (n=42), 104 (n=29) and 66 (n=22) amongst *E. cloacae*. Some clones represented local outbreaks (e.g. all Ent-ST108 with OXA-48 from NWE, 37/42 from one laboratory) whilst others were associated with multiple carbapenemases and referred from all nine regions (e.g. 155/158 Esc-ST38 with OXA-48, -181 and -244 from 66 laboratories). Global high-risk clones Kpn-ST258 (n=39, carrying KPC-2, -3 and -23) and Esc-ST131 (n=39, carrying KPC-2, NDM-1, OXA-48, -181, VIM-1 and -4) were each referred by 8/9 regions.

**Conclusions:** WGS has provided us with unprecedented data on the CPE clones circulating within England and their carbapenemase genes. The diversity suggests a role for clonal spread and carbapenemase gene transfer between STs.

**Carbapenemase-producing Escherichia coli ST131 emerged from pandemic (H30R) subclades**

Ellaby E, Doumith M, Hopkins K, Woodford N, Ellington M.

**Presented at:** the European Congress of Clinical Microbiology and Infectious Diseases, 2018.

**Background:** Increased antimicrobial resistance (AMR) rates and the emergence multidrug-resistant (MDR) *E. coli* threaten public health. A major pandemic extra-intestinal sequence type (ST)131, is associated with MDR urinary tract and bloodstream infections. Resistant ST131 typically harbour chromosomal mutations and acquired genes (e.g. CTX-M ESBLs) that encode resistance. These resistances associate with the fimH30 allotype ST131 sub-clades C1 and C2. We assessed the onwards development of ST131 sub-clades, as carbapenemases were acquired, and examined the geographical and temporal distribution in order to evaluate clinical and public health risks.

**Methods:** Submissions of carbapenemase-producing Enterobacteriaceae to PHE’s AMRHI Reference Unit were reviewed, along with clinical and demographic data. Kmer-ID and MLST identified ST131 *E. coli* (illumina HiSeq 2500, WGS) of the first submission for each confirmed case (January 2014 to June 2016). Carbapenemase-producing *E. coli* (CPE. *coli*) ST131 isolates were incorporated into a published phylogenetic framework and dataset, a RAxML SNP-based phylogeny was calculated after read alignments against the EC958 reference strain (PHEnix). Genes/loci were detected (AMRHI’s GeneFinder).

**Results:** Thirty-nine colistin susceptible ST131 isolates from 8/9 English regions produced carbapenemases; they represented 4.5% of CPE. *coli* sequenced by
AMRHAI. Over half (23/38) belonged to FQ-R ST131 clades C1 or C2 (8 and 15, respectively), whilst 10 and 6 ST131 CPE. coli belonged to FQ-S clades A and B, respectively. KPC-2 was the most common carbapenemase (N=21), associated mainly with clade C isolates (N= 14), followed by B (N=4) and A (N=3); they were geographically widespread (6 regions). OXA-48- producing ST131 (N=10) were predominantly clade A (N=5), two isolates in clades C1 and C2 and one in clades B; they were also geographically widespread (3 regions). The eight remaining ST131 CPE. coli producing NDM-1, -5, VIM-1, -4 or OXA-181, were referred from six regions and were primarily clade C (N=5).

Conclusions: Distinct carbapenemases have been acquired by genetically and geographically diverse ST131 isolates submitted to PHE’s national reference laboratory from English laboratories. Our data highlight the ongoing success and diversification of clade C ST131 as CPE. coli emerge, emphasising the need for ongoing monitoring of this ‘high-risk’ lineage, which has known pandemic potential.

WGS investigation of three OXA-48 carbapenemase bacteraemias and sink colonization in a haematology unit


Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2018.

Background: Carbapenemase-producing Enterobacteriaceae (CPE) are a serious healthcare challenge. Since ward sinks are potential CPE reservoirs contributing to patient colonisation/infection, we investigated CPE colonization of sinks following a small outbreak of blaOXA-48 associated CPE infections on the Haematology ward at a hospital in Oxford, UK.

Methods: Wastewater was aspirated from all sink U-bends and sub-cultured onto selective agar (CHROMagarTM Orientation) at serial dilutions 10-2, 10-3 and 10-4 with cefpodoxime (CPD) and ertapenem (ERT) discs. Based on colony morphology and proximity to CPD/ERT antibiotic discs, suspected CPD/ERT- resistant Enterobacteriaceae underwent MALDI-ToF species identification and confirmatory phenotypic testing (Carbapenem Inactivation Method). DNA was extracted from confirmed carbapenem-resistant organisms (CRO)(Kurabo QuickGene DNA tissue kit); WGS was performed using the Illumina Hiseq 4000 (150bp paired-end reads). Clinical outbreak isolates were also sequenced. Sequencing reads were mapped to species-specific references and single nucleotide variants (SNV) called to assess genetic relatedness of strains from sinks/clinical specimens. Reads were assembled de novo in order to perform MLST/plasmid/resistance gene typing (https://cge.cbs.dtu.dk/services/) and investigate genetic structures associated with blaOXA-48.

Results: Two OXA-48 E. cloacae (Mar, Apr/2017) and one K. pneumoniae (Mar/2017) were isolated from blood cultures of three patients. 65 colonies from 19/59 (32%) sinks were confirmed as Enterobacteriaceae; 4/59 (7%) sinks were colonised by multiple
species. Two isolates from the same sink were carbapenem-resistant *Enterobacter cloacae*. From 9/59 (15%) sinks, 11 non-Enterobacteriaceae CRO were found: *Sphingobium cloacae* (n=1), *Microbacterium liquefaciens* (n=1), and unidentified species (n=9). The two clinical OXA-48-*E. cloacae* strains were genetically indistinguishable (0 SNVs, ST-118), consistent with direct/indirect transmission between patients; the genetic data were too limited to infer horizontal transmission between these isolates and the OXA-48-*K. pneumoniae*. The sink *E. cloacae* were of a different sequence type (ST-837), and harboured multiple resistance genes (including several beta-lactamases, fosA, aac6'-Ib-cr, qnrA1, sul1/2, catA2, mcr-4), but not blaOXA-48.

**Conclusions**: Although there was no evidence of sink-associated transmission of blaOXA-48 in the unit, highly drug-resistant *E. cloacae* were found in 1/59 (2%) ward sinks and ~32% of sinks were colonised with Enterobacteriaceae. Non-Enterobacteriaceae CRO were also common; this may reflect unit-specific environmental/population attributes or antibiotic selection pressures.

**Studies from the TRACE rig: a unique model system to investigate the Transmission of Carbapenemase-producing Enterobacteriaceae in hospital drains**

Paton S, Moore G, Walker J, Bennett A.

**Presented at**: the Infection Prevention Society Annual Conference, 2017.

**Background**: Carbapenemase-producing Enterobacteriaceae (CPE) are increasingly important causes of healthcare-associated infection. Suspected reservoirs include hospital sinks, waste traps and drains. At PHE Porton a unique laboratory model incorporating stainless-steel utility sinks (SSUS), clinical hand-wash basins (CHWB) and appropriate fixtures, fittings, water temperature and hardness levels to simulate a clinical setting has been designed and built. This controlled environment was used to investigate factors facilitating the colonisation, proliferation and dispersal of CPE.

**Methods**: Waste traps, known to be contaminated with CPE-containing biofilms were removed from hospital wards and installed within the model system. Taps associated with each SSUS and CHWB were flushed four times a day. Water and biofilm samples were taken from each waste trap to monitor the type and level of organisms (both CPE and non-CPE) before, during and after interventions. The effect of adding or removing hand-wash soap, detergent and synthetic dishwater to the flushing regimen was determined. The potential for aerosols to be released from contaminated waste traps was also assessed.

**Results**: Removing detergent from the flushing regimen significantly decreased the number of bacteria recovered from the waste traps. In contrast, the presence/absence of hand-wash soap had little effect on bacterial numbers. Twice-daily enrichment with synthetic dishwater led to a rapid increase in both the number and diversity of microorganisms isolated from the trap water, including CPE previously only isolated from the trap biofilms. Aerobiological sampling did not detect the presence of CPE in aerosols released during normal sink use.
Conclusions: The TRACE rig provides a safe self-contained system for studying contaminated traps in situ. Regular addition of nutrients resulted in a proliferation of organisms and the results suggest that aerosolisation of these organisms is minimal. This work demonstrates that sink trap microbiomes are influenced by the nutrient sources introduced to them, enforcing the importance of appropriate discard of hospital waste.

The evolving face of carbapenemase-producing Enterobacteriaceae: a 5-year review of a London teaching hospital’s experience
Bharathan B, Cummins M, Hopkins K, Sivaramakrishnan A.

Background: The incidence of Carbapenemase-producing Enterobacteriaceae (CPE) has steadily increased over the last decade. However, data regarding risk factors associated with CPE acquisition and the best method of CPE detection is lacking. In the United Kingdom, the Public Health England CPE toolkit has been used to identify potential cases. We review our experience, as a large London hospital, looking at the epidemiology and evolving detection methods of CPEs within our trust.

Methods: We conducted a search of all Barts Health CPE isolates from the period of April 2011 to August 2016 in conjunction with the Antimicrobial Resistance and Healthcare and Associated Infections (AMRHAI) Reference Unit, Public Health England. We reviewed the susceptibility patterns for the 136 CPE cases isolated during this period, to highlight patterns of resistance for different carbapenamase classes, detection methods and identify potential risk factors. Organisms were identified by MALDI-TOF (Bruker, Germany) and automated sensitivity testing performed (Microscan Walk Away System, Siemens Healthcare). All Enterobacteriaceae isolates reported as carbapenem resistant underwent confirmatory testing to determine Ertapenem Minimum Inhibitory Concentration (MIC) by means of an E-test (Biomerieux Clinical Diagnostics). The presence of a carbapenemase was confirmed by multiplex PCR by AMRHAI.

Results: We identified 136 CPE cases during the study period. Of these 60 (44%) were Klebsiella pneumoniae, 15 (11%) Klebsiella species, 35 (26%) Escherichia coli, 18 (13%) Enterobacter species, 4 (3%) Citrobacter species and 4 (3%) Serratia species. AMRHAI confirmed the presence of 92 (68%) OXA-48, 35 (26%) NDM, 6 OXA-48 with concurrent NDM (4%), and 3 (2%) SME carbapenemases. These were isolated across a wide range of clinical specimens. Detection of OXA-48 improved during our study period, in response to an outbreak in 2016. Colorex Supercarba agar was introduced as a screening medium. Review of antibiotic susceptibility patterns demonstrated the previous standard of operation whereby only isolates with an ertapenem MIC >1 were flagged as possible CPEs was an insensitive method for detection of OXA-48 carbapenemases, which can often test susceptible to carbapenems. Isolates resistance to temocillin and tazobactampiperacillin with or without a reduced MIC to ertapenem were flagged as possible CPEs and sent to ARMHAI for confirmation of a OXA-48
enzyme. Contrary to the CPE toolkit guidelines, a history of hospitalisation abroad was not a significant risk factor in the majority of cases, with prolonged length of stay and prior antibiotic use being more prevalent risk factors.

**Conclusions:** We detected CPEs from a wide range of specimens in patients lacking the convention risk factors for CPE acquisition. OXA-48 and NDM isolates formed the majority of our carbapenemases. As recognition of CPEs has increased, laboratory methods have improved. The use of reduced susceptibility to both temocillin and tazobactam-piperacillin significantly improved detection of OXA-48 carbapenemases.

**WGS reveals the diversity that dominated CPE in the United Kingdom during 2014 and 2015**

Ellington M, Hopkins K, Doumith M, Meunier D, Turton J, Woodford N.

**Presented at:** the European Congress of Clinical Microbiology and Infectious Diseases, 2016.

**Background:** Carbapenemase-producing *Enterobacteriaceae* (CPE) are fast emerging globally. They are multidrug resistant often with few treatment options. Their spread threatens modern healthcare. Better understanding of their epidemiology and mode(s) of spread is an international priority. Whole genome sequencing (WGS) offers unprecedented amounts of data from a single assay.

**Materials and methods:** PHE’s AMRHAI Reference Unit seeks the referral of all isolates of suspected CPE in England, along with clinical and demographic data. Since January 2014, WGS of the first referred CPE isolate of each species from each confirmed case has been performed on a HiSeq 2500 (Illumina). Species ID via Kmer-ID, MLST and resistance gene compliments (via BLAST), were determined from VelvetOptimiser assemblies.

**Results:** In 2014 AMRHAI confirmed 802 first isolates of a given species from 786 patients, this rose to 884 isolates from 850 patients in the first three quarters of 2015. For 2014-15 the OXA-48-like, KPC, NDM and VIM carbapenemase families predominated among UK CPE (1613/1686 isolates). *Klebsiella pneumoniae* was the most frequent host species (n=950), followed by *E. coli* (n=410) and *Enterobacter cloacae* complex (n=195). There was remarkable genetic (MLST) diversity amongst *K.pneumoniae* and *E. coli*, except where stated below. Classic OXA-48-producers (n=464) were evenly comprised of *K. pneumoniae*, *E. coli* and other species; 40% of the *E. coli* with OXA-48 were ST38. OXA-181 producers (n=113) were *K. pneumoniae* or *E. coli*, whilst blaOXA-204, -232, -244 and -484 were each limited to one species, but were not associated with clonal associations. KPC producers (n=432) encoded KPC-2 (n=392), KPC-3 (n=27) or -4 (n=4) and were mostly *K. pneumoniae* (78%). NDM-1 was the most frequent NDM variant (331/423) followed by NDM-5, -7 and -4. Amongst *K. pneumoniae* with NDM-1 (n=228), 61% (n=141) belonged to one of five MLSTs (11, 14, 15, 147, 231), one isolate was ST258. Of 91 VIM positive isolates 50 were *K. pneumoniae*. IMP (n=12), IMI (n=6) and GES (n=6) enzymes were rare and single isolates had DIM, SME or NMC-A. Of 45 isolates with two carbapenemases, 43 had
NDM (-1, -4, -5 or -7) and OXA-48, -181 or -232 alleles; NDM-1 and OXA-232 were found together most frequently (n=16). Single isolates harboured KPC-2 with OXA-48 or NDM-1. CPE were widely disseminated in England, but with foci in the North-West and London areas. Simpsons index indicated bacteria isolated in both areas were highly MLST diverse (0.028 in London and 0.040 in North-West, where 0 = infinite diversity). CPE were isolated from screening swabs and clinical specimens from hospital patients and from GP urine samples.

Conclusions: The resolution provided by WGS has highlighted the genetic diversity and wide dissemination of CPE in the UK. This and the increased numbers detected signal CPE as a major public-health challenge.

Is an assay specific for detection of OXA-48-like carbapenemase genes a useful addition to front-line diagnostics?
Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2016.

Background: Enzyme-mediated carbapenem resistance is an increasing global problem. Rapid detection of patients infected or colonised with carbapenemase-producing bacteria is necessary for correct treatment and appropriate infection control procedures. Bacterial culture and phenotypic detection of carbapenemases can take over 48 hours with no specific phenotypic confirmatory test available for OXA-48-like enzymes. Current methods for confirmation of OXA-48-like producers rely on PCR from culture. This method describes detection of OXA-48-like genes by Recombinase Polymerase Amplification (RPA) from bacterial isolates in 30 minutes and direct from urine samples in less than 60 minutes.

Methods: Real-Time Recombinase Polymerase Amplification kits (TwistAmp® Exo) were obtained from TwistDx, Cambridge. RPA primers and probes were developed against an alignment of OXA-48-like sequences. These were tested against a range of control isolates consisting of 165 OXA-48-like Enterobacteriaceae clinical isolates confirmed using PCR by the Antimicrobial Resistance and Healthcare Acquired Infection reference laboratory (AMRHAI, PHE Colindale, UK), as well as a range of non-OXA-48-like carbapenemase-producing isolates. An OXA-48-positive isolate was serially diluted in urine to determine the limit of detection in a clinically-relevant sample matrix, using a simple boiled-lysis protocol for sample preparation.

Results: From 165 OXA-48-like isolates received from the reference laboratory, 164 were detected by RPA (99.4% sensitivity). The reason for the failure to detect one clinical isolate was also investigated. The RPA was also tested against 165 strains producing other carbapenemases and clinical isolates that were negative for OXA-48-like carbapenemases; no false-positives were seen (100% specificity). The limit of detection in spiked healthy human urine following a crude extraction method was 1050 cfu/ml.
Conclusions: This highly specific, highly sensitive method can potentially improve detection of OXA-48-like carbapenemases in diagnostic laboratories and the use of isothermal amplification methods potentially allows simple instrumentation suitable for near-patient settings. This assay has been shown to detect OXA-48-like carbapenemases from bacterial isolates, and direct from urine samples with a detection limit of 103 cfu/ml, enabling detection of colonisation as well as infection. The ability to screen direct from patient samples enables rapid results to instruct potential infection control procedures in high-risk environments.

Development of rapid isothermal recombinase polymerase amplification assays for the detection of carbapenemase genes


Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2016.

Background: Acquisition of transferable carbapenemase genes has been recognized internationally as a major public health threat. The so called ‘big five’ carbapenemase families include the KPC and OXA-48-like non-metallo-enzymes and the NDM, VIM and IMP metallo-enzymes. Rapid detection of these is crucial, not only for patient management but also for infection prevention and control of further transmission. Recombinase polymerase amplification (RPA) is an isothermal nucleic acid amplification method that is an alternative to real-time polymerase chain reaction (qPCR). Such assays are amenable to miniaturization on a digital microfluidic platform (Kalsi et al. 2015. Lab Chip. 15:3065-75). Here we describe the development of rapid RPA assays for the detection of five carbapenemase targets and relate this to sensitivity and specificity of detection using clinical isolates.

Methods: RPA assays were developed against KPC, NDM, OXA-48-like, VIM and IMP targets. Assay limit of detection (LoD) and time to positivity (TTP) were established for each of the assays using purified genomic DNA (gDNA) from relevant clinical strains and/or plasmid constructs containing representative genes of the individual carbapenemase families. Cross-reactivity of the assays was determined by testing against a panel of bacteria that are frequently encountered clinically, other carbapenemase/antibiotic resistance genes and background human DNA. Specificity was also assessed by evaluating against a panel of approximately 450 clinical isolates with previously defined carbapenem resistance mechanisms.

Results: All assays reported a LoD of between 10 and 100 genome copies with TTP of less than 20 minutes. No cross-reactivity was observed with non-target bacteria or other antibiotic resistance genes (100% specificity). No false-positives occurred in the presence of human DNA and the assay LoD was unaffected in the presence of a high concentration of non-target DNA. Of the 450 clinical isolates tested, >95% were identified correctly with the relevant assays with no false-positives observed and reasons for discrepant results will be described.
Conclusions: We successfully developed isothermal RPA assays that showed high levels of sensitivity and specificity against the five major carbapenemase families. We aim to transfer these tests onto a microfluidic platform as a proof of concept to demonstrate their utility within a point-of-care device which could allow diagnosis of carbapenemase-producing bacteria, potentially allowing clinicians to manage patient antibiotic treatment options more effectively. The potential for the use of the devices for applied infection control will also be evaluated.

Establishment of a rapid screening network for carbapenemase-producing Enterobacteriaceae (CPE)


Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2016.

Background: Carbapenemase-producing Enterobacteriaceae (CPE) are increasingly reported worldwide and are a major cause of nosocomial but also community-acquired infections. As carbapenemases are often the last resort treatment for infections caused by multidrug-resistant Enterobacteriaceae, rapid identification of patients with CPE is crucial to avoid dissemination and to implement control measures. The aim of the study was to establish a rapid response network to enable rapid CPE management.

Methods: All Enterobacteriaceae isolates from the West Midlands (England) region (population 5.6 M) that were non-susceptible to any carbapenem were submitted to the regional Public Health Laboratory (Birmingham) for CPE testing using a newly created Electronic Reporting System that allows rapid bilateral communication. The isolates were screened for carbapenemase genes (blaOXA-48-like, blaKPC, blaNDM and blaVIM) by real-time PCR. DNA was extracted by boiling a suspension of the internal positive control (B. thuringiensis) spiked with each testing isolate. A positive control for each of the four gene families sought was processed on each run. Platinum Quantitative PCR SuperMix–UDG (Invitrogen) and specific primers and probes were included in the reaction mix. Species identification was confirmed using MALDI-ToF MS (Bruker Daltonics) and isolates were forwarded to the national reference laboratory (AMRHAi Reference Unit) for further investigations. Results were reported back to the sending laboratories within 24-48 hours.

Results: A working network was established across the West Midlands for the rapid detection of CPE using an enhanced surveillance approach. During the 9 months (19th Jan-19th Oct 2015) we analysed a total of 201 isolates from 12 different labs. PCR results were issued within 24 hours for most (89.2%) of the isolates. One or more carbapenemase genes targeted by the multiplex real-time PCR was amplified from one-third (65/201) of carbapenem-non-susceptible isolates (34 K. pneumoniae, 18 E.coli, 9 E. cloacae complex and 4 K. oxytoca). KPC was the most frequently identified carbapenemase family (27/201; 13.4%) followed by OXA-48-like (25/201; 12.4%) and NDM (16/201; 8%). Three isolates carried two different carbapenemases; OXA-48-like
plus NDM (n=2) and OXA-48-like plus KPC (n=1). VIM genes were not detected in any of the isolates. Two-thirds of carbapenem-nonsusceptible isolates were PCR-negative for carbapenemase genes. The majority of the samples received for analysis were urines (n=103; 51.2%) and screening swabs (n=57; 28.4%). Among those yielding CPE, 33 were screening samples (50.8%) and 32 clinical samples (20 urines, 4 blood cultures, 4 sputum, 2 tissues and 2 surgical wounds). Carbapenemase rates remained constant in time and no outbreaks were detected in the region during the study period.

Conclusions: The rapid response network for CPE screening, with fast turnaround times, enables local infection control teams to take timely action to limit the onward spread of CPE. This new enhanced surveillance approach also allows monitoring of CPE trends.

GES-5 carbapenemase-producing Klebsiella oxytoca causing clinical infection in a UK haematopoietic stem cell transplantation unit


Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2016.

Background: Carbapenemase-producing Enterobacteriaceae (CPE) are a particular threat to the immunosuppressed, including haematopoietic stem-cell transplant (HSCT) recipients. Rapid identification is imperative to optimise care and curtail nosocomial outbreaks. However, this is challenged by emerging carbapenemases and non-enzymatic resistance, resulting in inconsistent \textit{in vitro} phenotyping. GES-5 is an Ambler Class-A carbapenemase, relatively rare in Enterobacteriaceae. We report our experience of identifying a GES-5-producing (GES-5+) \textit{Klebsiella oxytoca} in a UK HSCT unit, identified via carbapenem therapeutic failure.

Methods: In-house laboratory: CPE screening was undertaken in all HSCT patients in our unit by plating rectal swabs onto a CPE-selective chromogenic medium (Colorex® mSuperCARBA®, E&O Laboratories, UK). Suspicious colonies were sub-cultured on MacConkey agar, and identified using MALDI-TOF. EUCAST antimicrobial disc susceptibility was supplemented by gradient-diffusion susceptibility to confirm carbapenem-resistance. Following carbapenemase gene-detection by PCR (Xpert® Carba-R, Cepheid Inc, USA), isolates were sent for analysis at the Reference Laboratory, Public Health England (PHE). Reference Laboratory: Extended MIC profiling using agar-dilution was undertaken for interpretive reading. Specific PCR for carbapenemase-encoding genes was employed, and Sanger sequencing of the amplicons of each isolate was sent for whole-genome sequencing (WGS) (HiSeq 2500®, Illumina Inc., USA). WGS data were analysed using an in-house bioinformatics pipeline, which determined the multi-locus sequence type (MLST) and resistance gene-complement. Pulsed-field gel electrophoresis (PFGE) was performed on XbaI-digested genomic DNA.
Results: Clinical: The *K. oxytoca* became apparent clinically in August 2015, having been isolated in the urine of a neutropenic female HSCT patient. Intravenous (IV) meropenem and amikacin were started, in line with *in-vitro* sensitivities; nevertheless, bacteraemia occurred three days later. Despite combination antimicrobials, *K. oxytoca* bacteraemia persisted. Infection control measures were implemented. Bacteraemia with other organisms supervened, and the patient succumbed to neutropenic sepsis. Identification: This organism was referred to PHE for ertapenem resistance and a negative carbapenemase PCR. Initially, resistance was attributed to an ESBL plus porin-loss; first-line carbapenemase reference PCR was negative. WGS confirmed subsequently that this isolate harboured *blaGES*-5 and also the ESBLs, CTX-M-15 & SHV-12. Epidemiological review: 430 *K. oxytoca* isolates were identified in our Trust since 1st April 2014. 31 isolates (from 17 patients) were ertapenem-resistant. Of these, 14 (from 9 patients) were GES-5+; these isolates shared homologous PFGE profiles (SMAR45KL-5) and belonged to MLST 138, comparable to the index isolate. All patients had proven links with the HSCT unit. Three similar isolates (from patients with unclear epidemiological links) were also identified on retrospective review.

Conclusions: To the best of our knowledge, we believe this represents the first-ever documented UK GES-5+ *K. oxytoca* outbreak, causing clinical infection. Diagnosis was hampered by an emerging carbapenemase, absent from commercial and first-line reference assays, and ambiguous *in-vitro* sensitivities. Early CPE case-identification is critical to attenuate outbreaks and to facilitate retrospective screening.

Characterization of recent OXA-48-like and NDM-producing Enterobacteriaceae from the UK using whole-genome sequencing
Hopkins K, Doumith M, Staves P, Meunier D, Woodford N.
Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2015.

Objectives: We analysed whole-genome sequencing (WGS) data of carbapenemase-producing Enterobacteriaceae (CPE) confirmed by the Antimicrobial Resistance & Healthcare-Associated Infections Reference Unit (AMR/HA) in 2014 to see if an underlying explanation could be found for the recorded year-on-year increases in OXA-48-like and NDM CPE.

Methods: Isolates submitted for investigation of carbapenem resistance were screened for OXA-48-like and NDM genes (amongst others) by PCR. The first confirmed *bla*OXA-48-like- or *bla*NDM-positive Enterobacteriaceae isolate from each patient was sent for WGS on the Illumina HiSeq. *bla*OXA-48-like- and *bla*NDM-positive isolates from the same patient with a different bacterial identification were also included. WGS data were analysed using an in-house bioinformatics pipeline, which determined the bacterial identification and, where applicable, multi-locus sequence type (MLST), and identified plasmid replicon types and antimicrobial resistance genes.

Results: During the first 9 months of 2014 we observed a 115% increase (n=124 to n=266) in OXA-48-like CPE and a 109% increase (n=117 to n=244) in NDM CPE.
compared with the same time period in 2013. Seventeen isolates produced both OXA-48-like and NDM carbapenemases compared with one in 2013. WGS data were available for 115 (43%) OXA 48-like- and 121 (50%) NDM-producers, and 11 (65%) isolates producing both carbapenemases. Overall, *Klebsiella pneumoniae* (56%), *E. coli* (28%) and *Enterobacter cloacae* complex (9%) were the most common hosts. MLST data indicated that the isolates were diverse (Table). Clones such as *K. pneumoniae* ST147 carrying blaNDM-1 and *E. coli* ST38 carrying blaOXA-48 were referred by multiple laboratories, compared with *E. cloacae* ST108 carrying blaOXA-48 sent by one laboratory (Table). One or more plasmid replicon types were detected in 91% isolates. IncL/M plasmids were detected in 83% blaOXA-48 isolates, though not in 10/14 *E. coli* ST38 isolates. Other transferable mechanisms of public health concern including ESBLs, acquired AmpCs, 16S rRNA methylases, plasmid-mediated quinolone and fosfomycin resistance genes were detected.

**Conclusion:** The incidence of OXA-48-like and NDM CPE is increasing in the UK. The majority of these isolates belong to diverse clones but hospital specific clusters and clones previously reported internationally are also contributing.

<table>
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<tr>
<th>In-house PCR</th>
<th>Most common hosts</th>
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<th>Most common MLST</th>
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<td>E. coli (n=30)</td>
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<td>NDM-1 (n=2)</td>
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<td><em>K. pneumoniae</em> (n=5)</td>
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<td>ST14 (n=3)</td>
<td>NDM-1 + OXA-232 (n=3)</td>
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<td>NDM-4 + OXA-181 (n=3)</td>
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<td>ST93 (n=2)</td>
<td>NDM-1 + OXA-48 (n=2)</td>
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Evaluation of the Check-Direct CPE assay for detecting carbapenemase genes in multidrug-resistant Gram-negative bacteria
Meunier D, Hopkins KL, Findlay J, Woodford N.

Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2015.

Objective: Limiting the impact of carbapenemases requires rapid detection by the clinical laboratory, to identify infected and colonized patients so that infection prevention and control practices can be implemented. We evaluated the Check-Direct CPE assay for detection of \textit{bla}KPC, \textit{bla}OXA-48, \textit{bla}NDM/\textit{bla}VIM genes (the latter two genes not differentiated by the assay) among diverse species of Enterobacteriaceae.

Methods: Enterobacteriaceae isolates (n=100) submitted for investigation of carbapenem resistance to PHE’s Antimicrobial Resistance and Healthcare Associated Infections Reference Unit were tested. Submissions included isolates with carbapenemases or where carbapenem resistance was mediated by combinations of ESBL/AmpC plus porin loss. The Check-Direct CPE assay was applied to colonies picked directly from the submitted slope and from overnight cultures. DNA extractions were performed by vertically picking one colony with a sterile wooden toothpick. The colony was suspended in 200 μl of extraction buffer and the suspension was mixed briefly. Ten μl of the internal control solution was added to the tube before heating at 98°C for 10 minutes. The supernatant obtained after centrifugation was used as the assay template. The Check-Direct CPE assay was performed on an ABI Prism 7500 Real-Time PCR machine. Results were interpreted according to the protocol including visual inspection of amplification curves. All isolates were tested using the Modified Hodge Test (MHT) assay according to CLSI guidelines. The Check-Direct CPE results were compared with those generated using in-house PCRs and the MHT.

Results: Fifty-five isolates were positive for genes encoding KPC, OXA-48, VIM or NDM enzymes by in-house PCR. By interpreting Check-Direct CPE CT values >31 as invalid for KPC, OXA-48 and NDM/VIM, the same 55 true-positives were detected whether testing bacterial cells from slopes or overnight cultures. There were no false-positives and no false-negatives. The overall sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of the assay were therefore 100%. The MHT detected carbapenemase activity in 51/55 carbapenemase producers. Amongst isolates negative for KPC, OXA-48-like, VIM and NDM by in-house PCR, 7/45 (15.6%) were positive in the MHT. The overall sensitivity and specificity of the MHT assay were therefore 92.7% and 84.4%, with PPV and NPV of 87.9% and 90.5%, respectively.

Conclusions: The Check-Direct CPE assay detected all known (n=55) KPC, OXA-48-like, VIM and NDM producers. There were no false-positive or falsenegative results. Results were comparable whether testing bacterial growth harvested direct from the slope or following overnight subculture, offering potential for reducing the turnaround time. Interpretation of the Check-Direct CPE assay was easier and less subjective than the MHT. The Check-Direct CPE assay was also more sensitive and specific, with higher PPV and NPV compared with the MHT.
Evaluation of the BD MAX™ CRE assay for the detection of blakpc, blandm and blaoxa-48 carbapenemase genes in multidrug-resistant Gram-negative clinical isolates.

Meunier D, Hopkins K, Paule S, Babini G, Woodford N.

Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2014.

Objective: Acquired carbapenemases are a public health concern and have been described as the Gram-negative resistance issue for the next 5-10 years. Limiting the impact of carbapenemases requires rapid detection by the clinical laboratory, to identify infected and colonized patients so that infection control practices can be implemented to prevent or minimize onwards transmission. We evaluated the BD MAX™ CRE (Research Use Only) assay for detection of blakPC, blanDM and blaoXA-48 genes among diverse species of Gram-negative clinical isolates.

Methods: Isolates with defined carbapenem resistance mechanisms (n=151) were tested, as were suspected carbapenemase-producers (n=175) submitted from UK laboratories to PHE’s AMRHAI Reference Unit. Each isolate was prepared by adding to a Sample Buffer Tube (SBT) either (a) 200 μl of a 0.5 McFarland suspension diluted 1:100, or (b) 10 μl of cell suspension prepared by suspending 1-5 colonies in 100 μl distilled water. The SBT were then processed using the BD MAX™ assay according to the manufacturer's protocol. Results were compared with those generated by in-house PCR assays for the detection of class A, class B and class D carbapenemases.

Results: The BD MAX™ assay identified the correct carbapenemase gene in all of 118 previously-characterised isolates harbouring blakPC, blanDM and/or blaoXA-48, and correctly identified as negative 10/10 noncarbapenemase producers, 5/5 OXA-type carbapenemases (not blaoXA-48) and 16/18 VIM/IMP producers. False-positive results for blakPC, blanDM or blaoXA-48 genes were obtained for 2/18 VIM/IMP producers, and for 5/118 isolates harbouring blakPC, blanDM and/or blaoXA-48 a second target not confirmed by inhouse PCR was also detected. The BD MAX™ assay was then performed on 175 suspected carbapenemase producers, 79 of which were confirmed to produce blakPC, blanDM or blaoXA-48 by in-house PCR and the BD MAX™ assay. Ten blavIM producing isolates were correctly identified as negative by the assay. However, false-positive results were observed in 1/86 isolates found as non-carbapenemase producers and an additional gene not confirmed by the in-house PCRs was also detected in 3/79 carbapenemase-producers. The BD MAX™ assay is designed for testing rectal swabs. When used with colony suspensions the overall sensitivity and specificity of the BD MAX™ assay were 100% and 92%, respectively, with positive and negative predictive values of 94.7% and 100%, respectively.

Conclusions: The BD MAX™ CRE RUO assay was able to detect blakPC, blanDM or blaoXA-48 genes in all the carbapenemase-producing isolates confirmed by in-house PCR. The preparation of the sample has been shown as a critical point, with direct use of colonies suspended in water reducing the number of false-positives and increasing the specificity of the assay.
Are carbapenemases really pre-requisite for carbapenem-resistance in Enterobacteriaceae?: analysis of isolates submitted to a national Reference laboratory in 2012.
Presented at: the European Congress of Clinical Microbiology and Infectious Diseases, 2014.

Objectives: Concern about the inexorable rise in carbapenem-positive Enterobacteriaceae (CPE) led us to undertake a proportionate analysis of carbapenem-resistant isolates received in 2012 from hospital laboratories throughout England.

Methods: Isolates were batched for weekly testing. All carbapenem-resistant Enterobacteriaceae (CRE) had MICs (mg/L) of imipenem (+/- EDTA), meropenem and ertapenem determined by agar dilution, along with MICs of cephalosporins and other beta-lactams (+/- clavulanate or cloxacillin), aminoglycosides, ciprofloxacin, tigecycline and colistin. BSAC breakpoints were used to interpret MICs; carbapenem-resistance was defined as an MIC of ertapenem => 2. Carbapenemases were identified by PCR; species by MALDI-TOF.

Results: A total of 1374 CRE were submitted in 2012. 841 (61.2%) were CPE compared to 533 (38.8%) that were carbapenem-resistant without a carbapenemase, associated with porin mutation and/or loss combined with AmpC or other beta-lactamase activity. 55.9% of carbapenem-resistant but carbapenemase-negative isolates were resistant to ertapenem only, something only seen in CPE with an OXA-48. However, in any one week of submissions, up to 54.5% of carbapenem-resistant carbapenemase-negative Enterobacter spp. had an MIC of ertapenem >4, consistent with AmpC activity combined with changes in the porin profile. Of the CPE, 240 (28.5%) were MBLs, compared to 601 (71.5%) that were non-metallo beta-lactamases. MBLs were typically resistant to all three carbapenems across species and identified by potentiation of imipenem by EDTA > 3 log2 dilutions with an error rate below 1%. For KPC producers, MICs of ertapenem and imipenem for E. coli could be as low as 4 with meropenem at 2. MICs of meropenem ranged from 8 to >32 for KPC Klebsiella pneumoniae and Enterobacter spp. MICs of cefotaxime ranged from 8 to > 256 for KPC producing K. pneumoniae and 64 to >256 for Enterobacter spp. Some potentiation of cefotaxime by clavulanate was observed for KPC K. pneumoniae. OXA-48 producing K. pneumoniae usually only had resistance to ertapenem plus elevated MICs of cephalosporins in the presence of an ESBL.

Conclusions: Carbapenemases are not the sole means of producing resistance to carbapenems but were the commonest mechanism among isolates from hospitals in England. Just over half of the non-CPEs were only resistant to ertapenem (i.e. sensitive to meropenem and imipenem) but carbapenemresistance was more frequent in Enterobacter spp. Although carbapenem-resistance without a carbapenemase is not commonly of the same magnitude as that associated with carbapenemases (except OXA-48), resistance in these isolates can be significant.
Antimicrobial consumption

Impact of the trimethoprim-to-nitrofurantoin Quality Premium on the incidence of Escherichia coli bloodstream infection in England
Amelia Au-Yeung*, Ayoub Saei, André Charlett, Graeme Rooney, Simon Thelwall, Berit Muller-Pebody, Russell Hope, Susan Hopkins, Rachel Freeman
1 Public Health England
Presented at: PHE Public Health Research and Science Conference – April 2019

Background: Escherichia coli (E. coli) is the most common cause of urinary tract infection (UTI). Unsuccessful treatment of UTI may allow progression to an invasive bloodstream infection (BSI).
An increase in trimethoprim resistance detected in E. coli UTI informed the recommendation to use nitrofurantoin as first-line treatment for UTI in primary care from November 2014. To improve compliance with this recommendation, NHS England introduced a Quality Premium (QP) in 2017/18 to measure trimethoprim-to-nitrofurantoin prescribing from April 2017.
The aim of the study was to investigate the impact of changing trimethoprim-to-nitrofurantoin prescribing on the incidence of E. coli community-onset BSI (COBSI).

Methods: The ratio of trimethoprim-to-nitrofurantoin items prescribed was calculated from PHE’s Antimicrobial Prescribing Data Warehouse. E. coli COBSI were defined as infection episodes occurring within 48 hours of admission to a hospital in England. Data were extracted from the national mandatory surveillance system. Population data were obtained from the Office for National Statistics and the E. coli COBSI rate was expressed as cases per 100,000 population. Interrupted time-series analysis was performed, adjusting for seasonality, secular trend and changes in guidelines. The pre-intervention and post-intervention periods were defined as November 2012 to March 2017 and April 2017 to March 2018, respectively. Incidence rate ratios (IRR) were estimated using negative binomial regression.

Results: The mean trimethoprim-to-nitrofurantoin ratio pre-intervention was 1.64, falling to 0.70 post-intervention. The observed incidence of E. coli COBSI increased from 4.44 to 5.01 per 100,000 population.
After adjustments, reduction in trimethoprim-to-nitrofurantoin prescribing was associated with an 11% decrease in E. coli COBSI (IRR: 0.89, 95% CIs: 0.84-0.94, p<0.001).

Conclusion: The results demonstrate that changes in trimethoprim-to-nitrofurantoin prescribing during the QP had a significant impact on the rate of E. coli COBSI. Further work will explore differential impact across the country and the impact on antibiotic resistance detected in COBSI.
Relation between reduced piperacillin/tazobactam use and Pseudomonas aeruginosa bloodstream infections in England, 2015 to 2017
Graeme Rooney*, Simon Thelwall, Rachel Freeman, Rebecca Guy, Andre Charlett, Ayoub Saei, Amelia Au-Yeung, Kate Wilson, Berit Muller-Pebody, Alan Johnson, Susan Hopkins, Russell Hope

Presented at: PHE Public Health Research and Science Conference – April 2019

Background: Piperacillin with tazobactam is a first line treatment for infections caused by Pseudomonas aeruginosa. From April 2017 there was an international shortage of piperacillin-tazobactam resulting in sharp reductions in consumption. During the same period, we observed an increase in P. aeruginosa bloodstream infections (BSI). The aim of our study was to explore the relationship between piperacillin-tazobactam consumption and P. aeruginosa BSI.

Methods: Piperacillin-tazobactam consumption was quantified in terms of defined daily doses (DDD), a standardised measure of drug consumption. DDD data for antibiotics prescribed in hospital were downloaded from the antimicrobial prescribing data supplier, IQVIA. P. aeruginosa BSIs were quantified in terms of 14 day de-duplicated patient episodes. P. aeruginosa BSI data were extracted from PHE’s voluntary national microbiological surveillance database. Episodes and DDDs were aggregated for England by month from January 2015 to December 2017.

Negative binomial regression was used to assess the association between incidence of P. aeruginosa BSI and total DDD of piperacillin-tazobactam, controlling for seasonality and secular trends. Analyses were performed using Stata 15.

Results: Following the shortage, the mean monthly piperacillin-tazobactam consumption (in 10,000 DDDs) declined from 17.3 (April to December mean for 2015 and 2016) to 9.2 between April and December 2017. Over the same periods, the mean monthly counts of P. aeruginosa BSI increased from 271.5 to 318.8. There was evidence that lower levels of piperacillin-tazobactam consumption were associated with higher incidences of P. aeruginosa (incidence rate ratio = 0.987 per 10,000 DDD, 95% CI: 0.977–0.997, p=0.015).

Conclusions: We identified an association between decreasing piperacillin-tazobactam usage and increasing P. aeruginosa BSI. This may explain the large increase in P. aeruginosa BSI and is a cautionary example of the effects of uncontrolled changes to antibiotic prescribing.
Trimethoprim and nitrofurantoin resistance for Escherichia coli urinary tract infection in the North East England
Helen Bagnall, Dr Petra Manley

**Background:** Urinary tract infections (UTIs) are one of the most common indications for antibacterial prescribing in primary care. The majority of UTIs are caused by Escherichia coli and can lead to E. coli bacteraemias. In the North East, the incidence of bloodstream infections has been consistently above the national average with E. coli bacteraemia rates being the highest of all England. In April 2017, the North East and Cumbria Clinical Commissioning Groups (CCGs) recommended nitrofurantoin (replacing trimethoprim) as first line antibiotic for treatment of UTIs in the general adult population. At the same time, the 2017/18 Quality Premium (QP) was introduced requiring CCGs to reduce trimethoprim prescriptions. This study aimed to estimate the resistance of E. coli UTIs to trimethoprim and nitrofurantoin in the general population in the North East, 2012 to 2018. The secondary aim was to assess the impact of antibiotic prescribing guidance on trimethoprim and nitrofurantoin consumption for UTIs in primary care.

**Methods:** We conducted a retrospective ecological study. Data for urine specimens with trimethoprim and nitrofurantoin antimicrobial sensitivity tests were obtained from the PHE Second Generation Surveillance System from March 2012 to February 2018 for North East residents aged ≥15 years. Prescribing data for the same time period were obtained from the PHE Primary Care prescribing data warehouse for trimethoprim and nitrofurantoin. General practice characteristics (e.g. % male, % aged 64, IMD score) data were obtained from NHS Digital and ONS.

We described trimethoprim:nitrofurantoin prescribing ratio, UTIs over time by age and sex, and conducted multi-level mixed effects linear regression to assess variation in prescribing by general practice characteristics, and trends before/after the QP was introduced. Generalized estimating equations were used to investigate the association between non-susceptibility and general practice characteristics, and between prescribing and subsequent non-susceptibility.

**Results:** A total of 286,366 UTIs were reported in the study period in patients aged ≥15 years. Of these, 72% were caused by E. coli, corresponding to 111,738 individuals. The average number of E.coli infections per individual was 1.8 (range 1 - 26).

The ratio of trimethoprim:nitrofurantoin prescriptions remained constant between 1.5 and 1.6 until 2017 when it started to decrease to approximately 0.5 by 2018. There was a gradual decrease in trimethoprim prescriptions followed by a steep decline from spring 2017. Nitrofurantoin prescriptions remained constant until spring 2017 when they increased significantly.

98% of E. coli isolates had antimicrobial susceptibility results available. The overall proportion of non-susceptible isolates was 34% for trimethoprim and 3% for nitrofurantoin, with little variation in non-susceptibility by season. Trimethoprim non-susceptibility remained stable until spring 2017 when it started to decrease to
approximately 31% in 2018. Non-susceptibility to nitrofurantoin peaked at 5% in 2014 but since summer 2016 has decreased year on year to 1.9% in 2018. 

Trimethoprim non-susceptibility was higher in females with a greatest difference in the 45-54 year age group (32% in females vs 24% in males) and increased with age (40% and 39% for females and males respectively in those aged ≥75 years). Nitrofurantoin non-susceptibility was also highest in those aged ≥75 years, however it was higher in males across all age groups with the greatest difference in the 15-24 year age group.

In the multivariable analysis, we found increased trimethoprim and nitrofurantoin prescribing with increased deprivation and higher number of patients registered per practice. Trimethoprim non-susceptibility was higher in urban areas, and nitrofurantoin non-susceptibility was higher in practices with a higher proportion of ≥65 year olds and higher number of patients per doctor. Trimethoprim non-susceptibility increased following higher prescribing in previous and third lagged quarters, and nitrofurantoin non-susceptibility increased following higher prescribing in previous quarters.

**Conclusion:** We used routinely collected laboratory and prescribing data to monitor changes in prescribing and non-susceptibility following interventions, and association with other factors such as general practice characteristics. Following the guidance change and 2017 QP, there was a significant change in trimethoprim/ nitrofurantoin consumption. We only analysed a year of data post-intervention but observed substantial decrease in trimethoprim use and non-susceptibility. Nitrofurantoin use has increased replacing trimethoprim, whilst nitrofurantoin non-susceptibility showed a slight decrease. Levels of prescribing and non-susceptibility varied by general practice size and their population socio-demographics.

Primary care services and PHE should continue to monitor the use and susceptibility of nitrofurantoin and trimethoprim in order to understand the impact of changes in prescribing practice on non-susceptibility of both agents and clinical outcomes. Further work with general practices would be needed to better understand characteristics that influence prescribing practices.
Harmonised antimicrobial resistance and use indicators - how useful are they?
Berit Muller-Pebody¹*, Marian Bos², Rebecca Guy¹, Amelia Au-Yeung¹, Susan Hopkins¹, Ana Vidal²
¹ Public Health England, ² Veterinary Medicines Directorate

Presented at: International Conference on One Health Antimicrobial Resistance (ICOHAR) – April 2019

Background: Harmonised surveillance indicators for antimicrobial resistance (AMR) and use (AMU) have been developed by the European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and European Medicines Agency (EMA) to assist countries in assessing progress in reducing AMR and AMU in humans and food-producing animals. We present outcomes for harmonised AMR and AMU indicators for the United Kingdom.

Methods: National data captured by UK surveillance or monitoring programmes from the human sector and animal sector between 2013 and 2017 were used to produce AMR and AMU indicators in humans and food-producing animals.

Results: Primary AMR indicators showed 50% reduction in methicillin-resistant Staphylococcus aureus (humans), 29% decrease in Escherichia coli resistant to 3rd generation cephalosporins (humans) and 30% increase in fully susceptible E. coli (food-producing animals) between 2013 and 2017. Secondary AMR indicators (humans) demonstrated reduced resistance to key antibiotics for Klebsiella pneumoniae and Streptococcus pneumoniae but increased carbapenem (K. pneumoniae) and penicillin (S. pneumoniae) resistance. Resistance to key antibiotics and proportion of ESBL-/AmpC-producing isolates decreased in indicator E. coli (food-producing animals).

For AMU, primary indicators demonstrated 5% reduction of total consumption of systemic antibiotics (humans) and 41% reduction of sales of veterinary antibiotics. Secondary AMU indicators showed increased use of broad-spectrum antibiotics in hospitals (humans) and decreased sales of quinolones, 3rd/4th generation cephalosporins and colistin (veterinary sector).

Conclusions: Harmonised AMR and AMU surveillance indicators are valid tools for monitoring progress and areas where increased effort is needed to tackle AMR and reduce antimicrobial usage.
The importance of monitoring a novel antibiotic: National surveillance of ceftazidime-avibactam resistance and usage in England, 2018
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Background: Ceftazidime-avibactam (CAZ-AVI), a novel cephalosporin/β-lactamase inhibitor combination, is licensed to treat complicated and hospital-acquired infections, particularly those caused by multi-drug resistant Gram-negative bacteria (MDR-GNB). Since the antibiotic’s approval in 2015, concerning reports of emerging CAZ-AVI-resistant GNB have been published. We investigated the current situation of CAZ-AVI use and resistance in England to inform activities aimed at conserving the antibiotic’s effectiveness.

Methods: Routine laboratory records with CAZ-AVI susceptibility data and reference laboratory data on CAZ-AVI MICs and carbapenemase genes for GNB from March 2016-September 2018 and April 2016-March 2018 respectively were extracted from Public Health England’s surveillance systems. National CAZ-AVI usage by National Health Service (NHS) hospitals was obtained for January 2017–April 2018. Temporal distribution of CAZ-AVI use, resistance and mechanisms, and patient demographics were analysed.

Results: Reports of routine susceptibility test results for CAZ-AVI increased from 5 in 2015/16 to 4287 in 2018. Twelve percent (74/618) of Klebsiella spp. isolates tested, 4.7% (48/1026) of Escherichia coli and 14.8% (224/1516) of Pseudomonas aeruginosa were reported as CAZ-AVI-resistant in 2018. The proportion of CAZ-AVI resistance was highest in tested isolates from young adults (25 – 40 years). Of 5640 GNB isolates tested at the national reference laboratory, 12.6% were CAZ-AVI-resistant; metallo-β-lactamase activity was detected in 87.3% of isolates. CAZ-AVI resistance was observed in twelve K. pneumoniae isolates producing both KPC and OXA-48, one Citrobacter freundii and one E. coli both producing OXA-48-like. CAZ-AVI was used by 30% (46/151) of trusts since its launch and national monthly usage increased from 21 Daily Defined Doses (DDD) in March 2017 to 306 DDDs in March 2018. Five specialties (intensive/critical care, respiratory/general medicine, and haematology) prescribed almost half of the total DDDs.

Conclusions: Routine and reference laboratory testing have highlighted the presence of CAZ-AVI resistance in England emphasising the importance of vigilance by clinicians and microbiologists and the requirement for national surveillance. Clinical specialties with current highest use of CAZ-AVI where resistance is most likely to be encountered were determined. Detailed information on risk factors for development of resistance and resistance mechanisms is needed to better inform clinical decision-making, infection prevention and surveillance.
New antibiotics monitoring – Ceftazidime/avibactam summary
Caitlin Pley*, Berit Muller-Pebody
1 Public Health England

Background: Public Health England collects surveillance data for new antibiotics or antibiotic combinations from the outset of their clinical use as an essential measure to detect early resistance and correlate this with usage trends. The novel cephalosporin/β-lactamase inhibitor combination, ceftazidime/avibactam, is a last-resort treatment for complicated and hospital-acquired infection with multi-drug resistant Gram-negative bacteria, including ESBL-producing and carbapenem-resistant organisms. It is active against KPC and OXA-48 carbapenemases, but not against the metallo-β-lactamases (including NDM and VIM). Since its launch in the UK in March 2017, national monthly usage has steadily increased from 21 Daily Defined Doses (DDDs) in March 2017 to 588 DDDs in September 2018, although consumption levels remain low in comparison to similar drug combinations in routine use.

An ECDC risk assessment in 2018 concluded that emerging ceftazidime/avibactam resistance posed a significant public health threat due to the exchange of resistance determinants between species, the risk of nosocomial transmission and potential adverse clinical outcomes for patients. Since its approval, ceftazidime/avibactam has been subject to routine antimicrobial susceptibility tests for isolates of Gram-negative bacteria at the AMRHI Reference Unit.

Results: Between April 2016 and March 2018, 5,640 isolates of Enterobacterales were tested for ceftazidime/avibactam susceptibility and the presence of carbapenemase genes. 12.6% of isolates were found to be resistant to the drug combination, of which 87.3% were intrinsically resistant due to the presence of metallo-β-lactamases against which ceftazidime-avibactam has no activity. Acquired resistance to ceftazidime/avibactam has established itself as a threat for transmission in healthcare settings and further limits treatment options for patients with multi-drug resistant Gram-negative infections.

Conclusion: As ceftazidime/avibactam data has shown, clinical vigilance and national surveillance should be routinely implemented from the very start of an antibiotic's lifespan. Further, heightened monitoring of new antibiotics should be complemented with clinical guidelines for rational use, antimicrobial stewardship programmes and effective infection prevention and control measures, both in healthcare settings and in the community.
Scanning the horizon for new antibiotics
Caitlin Pley*, Berit Muller-Pebody
1 Public Health England

Background: The development of new antibiotics is fraught with scientific complexity and economic disincentives. The difficulty of discovering new molecules that defy existing resistance mechanisms, as well as unfavourable profit margins, because new antibiotics are often reserved as last-resort treatments, discourage companies from investing in antibiotics research and development (R&D). Despite these challenges, a number of promising drug candidates, of which three are highlighted below, are currently in the clinical phases of development and are preparing to seek approval by the European Medicines Agency (EMA).

Results: Cefiderocol is a new 4th generation cephalosporin with an iron-binding moiety, which enables its ‘Trojan Horse’ cell entry strategy. This siderophore cephalosporin can bypass the usual mechanism by which cephalosporins enter Gram-negative bacteria, through porin channels in the outer membrane which are increasingly mutated to confer cephalosporin resistance. Rather, by binding an iron atom outside of the cell, cefiderocol enters the periplasm of Gram-negative bacteria through their iron uptake mechanism. Bacteria require iron to fulfil the essential metabolic functions required for survival and replication. The body’s innate immune response to infection decreases the availability of free iron, which leads to bacteria upregulating the transport mechanisms by which cefiderocol enters the cell. In vitro studies have demonstrated stability of cefiderocol against Class A, B, C and D β-lactamases, including KPC, OXA, IMP, VIM and NDM carbapenemases1. Although cefiderocol is not active against Gram-positive organisms and anaerobes, it holds promise for the treatment of multi-drug resistant Gram-negative infections. Cefiderocol is currently in two Phase 3 trials, APEKS-NP for healthcare-associated pneumonia, and CREDIBLE-CR for carbapenem-resistant organisms in a variety of infection sites2. In a Phase 2 trial of complicated urinary tract infection, cefiderocol was superior to imipenem/cilastatin (73% in the cefiderocol group vs 55% in the imipenem/cilastatin group) for the achievement of composite clinical and microbiological cure3. Cefiderocol may be the first antibiotic to be effective against all three WHO critical priority organisms, however, there have been first reports of adaptive resistance from in vitro and in vivo studies4,5.

Plazomicin is a next-generation aminoglycoside that gained approval from the US Food and Drug Administration (FDA) for the treatment of complicated urinary tract infections in July 2018. The EPIC Phase 3 trial positioned plazomicin as superior to meropenem for the treatment of complicated urinary tract infection, including acute pyelonephritis, with the two treatment groups achieving composite clinical and microbiological cure at Test of Cure in 81.7% and 70.1% of patients respectively. Plazomicin shares some of the adverse effects of other aminoglycosides, including nephrotoxicity and ototoxicity. Plazomicin is principally excreted through the kidney, and thus renal impairment significantly affects the plasma concentration and toxicity of plazomicin. In vitro, plazomicin has shown activity against organisms with aminoglycoside-modifying enzymes, ESBLs and carbapenemases. Like cefiderocol, plazomicin provides some hope for the treatment of multi-drug resistant Gram-negative infections.

There are few new classes of antibiotics in development, and murepavadin, a new Outer Membrane Protein Targeting Antibiotic (OMPTA), offers new hope in treating serious infections with Pseudomonas aeruginosa. Murepavadin is a cyclic hairpin peptidomimetic of the protein Protegrin-1, a broad-spectrum immune protein discovered in porcine immune cells, that achieved a better safety profile and selectivity for Pseudomonas through iterative cycles of lead optimisation. The target protein of murepavadin is LptD, a lipopolysaccharide transporter in the outer membrane of Pseudomonas, and inhibition results in the cessation of cell wall synthesis. Animal studies have shown efficacy of murepavadin against MDR and XDR Pseudomonas strains. A Phase 2 trial offered encouraging results for the treatment of ventilator-associated pneumonia caused by Pseudomonas aeruginosa. However, two ongoing Phase 3 trials were temporarily halted in May 2019 due to a higher incidence of acute kidney injury in the murepavadin arm of one of the studies, and a decision was taken in July 2019 to abandon both trials and to return to preclinical studies to investigate other formulations. Murepavadin is an example of a precision medicine approach to the treatment of infection; where a concomitant decrease in the use of broad-spectrum

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antibiotics would reduce the risk of co-selection for resistance in other organisms and have a less disruptive effect on the gut microbiome. However, to enable the clinical use of selective antibiotics as mono-therapy, new rapid diagnostics will be needed.

**Conclusion:** Antibiotics, both old and new, are precious public goods that must be safeguarded so that infections remain treatable into the future. Fostering innovation and incentivising investment into antibiotic R&D are urgently needed to offer new treatment options for drug-resistant infections.
Antifungal resistance, prescribing and stewardship

Candidaemia 30-day all-cause mortality in England: A retrospective review of clinical characteristics, epidemiology and risk factors, 2009 to 2016
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Introduction and Aim: Invasive fungal diseases are an emerging global concern with some countries reporting Candida spp. as one of the top three causes of bloodstream infection. England reports candidaemia as being the 10th most common laboratory reported bloodstream infection in recent years. Following concerns of high mortality rates internationally caused by the multi-resistant pathogen Candida auris, we have reviewed the all-cause mortality rate associated with candidaemia in England. This study describes candidaemia patient characteristics and determines factors that impact candidaemia 30-day all-cause mortality, focusing on antifungal resistance, age and pathogen species.

Methods: Candidaemia cases in England were identified from routine laboratory surveillance reports between 2009 and 2016. Mortality outcome at 30-days post-specimen date was ascertained by linking the patients to the National Health Service (NHS) Spine (centralised repository of patient information); patients were lost to follow up if they could not be linked. A proportion of 30-day all-cause mortality was calculated and relative risks (RR) for Candida species, patient demographics and antifungal susceptibility results were assessed.

Results: A total of 10,135 candidaemia patients were identified and linked to the NHS Spine. Seventeen different species of Candida were identified from blood cultures, 10% were not identified beyond genus. Overall candidaemia 30-day mortality was 33.6% (95% CI:32.7-34.6%), with a median time-to-death of 6 days. Mortality varied by gender (35.1% males, 31.7% females), and increased with age, with two times greater risk of death within 30 days for those aged 75y compared with those aged <1y (48.3% vs. 19.6%; RR 2.0 (95% CI:1.6-2.5) P<0.0001). Patients with recorded antifungal susceptibility test results had reduced risk of mortality compared to those without (RR 0.8 (0.75-0.85); 29.2% vs 36.4%). Mortality was highest for candidaemia isolates identified to genus only (36.5%), followed by C. albicans (36.1%) and C. glabrata (35.2%); the lowest was C. auris (12.5%).

Conclusions: This is the first national study on 30-day all-cause mortality from candidaemia in England. The limited capacity to identify yeasts is concerning, given the increased likelihood of yeast misidentification and resistance to first-line antifungal agents in non-Candida genera. Interventions to reduce mortality need to be
multifaceted and include improved diagnostics and monitoring of antifungal susceptibility.

**Candida auris in England; a picture of a national incident**
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**Presented at:** 29th European Congress of Clinical Microbiology and Infectious Diseases – April 2019

**Background:** *Candida auris*, an often multi-drug resistant fungal pathogen, increasingly causes global nosocomial outbreaks with reports of high mortality. We present the national incident response following increasing incidence and evidence of transmission in England.

**Materials/methods:** Patient demographics, prevalence on admission to ICU, antifungal susceptibility, and strain typing of *C. auris* in England were reviewed. Follow up of thirty-day mortality was assessed. Organism lineages and morphology were determined, and environmental spread and skin decontamination products evaluated.

**Results:** Between June 2013 and March 2018, twenty English hospitals reported 226 *C. auris* patient detections, the majority were patient-patient transmissions reported in 4 hospitals (1st outbreak case in January 2015). Thirty further UK hospitals received colonised patients via transfer. Seven patients were known transfers from hospitals abroad. Sixty-one detections were clinical infections (including 31 candidaemia). The median patient age was 58; 64% cases were male. Thirty-day all-cause mortality was 16%, but no directly attributable mortality.

Three clonal lineages of *C. auris* have been introduced since 2013: South Asian (121 cases; single cell strain), East Asian (1) and African (66; both aggregating strain-types). All isolates tested were fluconazole resistant and 32% (46/144) were resistant to at least 3 of fluconazole, echinocandin, amphotericin B, 5-flucytosine and/or voriconazole.

*C. auris* was found in the immediate environment and on monitoring equipment of colonised patients. Chlorine-based disinfectants and iodine-based skin antiseptics were effective against *C. auris* test strains; chlorhexidine-based product effectiveness depended on alcohol formulation.

No cases were identified in the admission to ICU point prevalence study (n=984).

**Conclusions:** The precise mode of transmission is unclear and likely to be multi-modal. The English experience shows that *C. auris* is difficult to eradicate, that environment and equipment contamination occurs surrounding colonised patients, there is relatively low case fatality, and chlorhexidine-based hand/body washes may not be effective in
removing *C. auris* from staff or from colonised patients. The low prevalence suggests widespread screening on admission to ICU should not currently be recommended. This multifaceted response to *C. auris* in England has involved public health, microbiology, mycology, epidemiology, and infection prevention and control experts. International collaboration enabled us to rapidly disseminate knowledge.

**Recovery and survival of airborne *Candida auris***

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**Presented at:** 29th European Congress of Clinical Microbiology and Infectious Diseases – April 2019

**Background:** *Candida auris* infections have been reported globally with many hospitals experiencing prolonged outbreaks despite enhanced infection control practices. *C. auris* has been recovered from multiple surfaces implying widespread environmental contamination. Rapid and persistent skin colonisation among affected patients is common and it is likely that any activity that disturbs dust and/or liberates skin squamae will increase air bioburden. However, airborne survival of *C. auris* and the potential for dispersal via airborne particles are still not fully understood.

**Materials/methods:** Active air sampling was carried out by placing samplers at the bedside of colonised and non-colonised patients. Type and level of activity within each bed space was recorded. A Goldberg drum was used to investigate, for the first time, the airborne survival of three *C. auris* isolates (each representing a different geographic clade) under controlled laboratory conditions. Survival was assessed over 2 h and compared to that of *C. parapsilosis* (a common commensal of human skin) and *Bacillus atrophaeus* (an aerostable biological tracer).

**Results:** In general, staff and patient activity within each bed space was minimal and no *C. auris* (< 1 cfu/m³) was recovered from the majority of air samples (n = 8). However, on one sampling occasion airborne *C. auris* was detected (6 cfu/m³) and was recovered from the room of a colonized patient when the bedsheets were being changed. When aerosolized under laboratory conditions, the survival of *C. auris* differed with clade and after 2 h, ranged from 15% (E. Asian) to 40% (S. African and S. Asian); similar to that of *C. parapsilosis* (45%).

**Conclusions:** These results suggest that *C. auris* has the potential to become airborne during high turbulence activities such as bed making and, if attached to particles < 5µm in diameter, could survive and remain suspended in the air. This risk appears to be lower for the East Asian clade.
Antimicrobial stewardship

Antibiotic resistance and managing infections in pharmacy: a cross-sectional com-b survey
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Presented at: 78th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2018

Background: Community pharmacy teams are key in contributing to tackling antimicrobial resistance (AMR).

Purpose: The study aimed to explore determinants of pharmacy team members’ behaviour in managing self-limiting infections using the COM-B (capability, opportunity, motivation and behaviour) model.

Methods: The study was conducted as part of implementing an infection management leaflet (TARGET). A questionnaire measuring COM-B in relation to management of self-limiting infections was distributed to 133 pharmacies.

Results: 158 questionnaires were completed by 84 pharmacies (63%). Primary descriptive COM-B analysis:

C: >90% agreed/strongly agreed that they knew how long common infections last, what self-care advice to provide and what antibiotic resistance is. 26% found it difficult to explain to patients why antibiotics were not needed.

O: 41% respondents agreed that they did not get the opportunity to provide all the self-care advice they wanted due to time pressures.

M: 73% believed they have a key role in helping control antibiotic use and 94% believe it is important they give self-care advice.

B: 56% reported that on a typical day they would often or very often have self-care conversations. 35% would often or very often give out self-care resources, information and advice; 25% reported that they would have liked to give self-care resources, information or advice, but were unable to.

Conclusion: Whilst pharmacy professionals generally have good self-reported capability, opportunity and motivation for managing self-limiting infections, there is need for further intervention to assist pharmacy staff in explaining to patients why antibiotics are not needed and how to deliver self-care advice under time pressure.
Introduction: Community pharmacy staff have the opportunity to influence patients’ use of antibiotics by advising patients on effective self-care option, appropriateness of antibiotics, antibiotic adherence and the consequences of using antibiotics incorrectly. 

Aims: To improve self-care and adherence advice given to patients/carers collecting antibiotics.

Methods: Community pharmacies in Gloucestershire were invited to participate in an antimicrobial stewardship (AMS) intervention, developed collaboratively with community pharmacists and pharmacy users. The intervention was centred around an Antibiotic Checklist that follows the antibiotic prescription journey, completed by patients and pharmacists, facilitating individualised advice to the patient. Patients completing checklists were invited to feed back.

Results: Twelve Gloucestershire pharmacies participated. Over four weeks, 931 Antibiotic Checklists were completed, enabling tailored antibiotic advice to be given to these patients/carers. 82% (595/724) of patients/carers that completed the Antibiotic Checklist reported knowing whether the antibiotics should be taken with or without food, whereas 18% (129/742) did not. 49% (340/701) reported that their antibiotic was for a RTI; 22% (157/701) UTI; 14% (98/701) dental; 9% (62/701) skin. 34% (68/201) of patients that left contact details provided feedback: all now intend to or reported already taking their antibiotics as advised by their doctor, nurse or pharmacist.

Conclusions: The Antibiotic Checklist provided valuable information on antibiotic indication and patient knowledge, to individualise AMS. Community pharmacy staff reported that this facilitated their role to Keep Antibiotics Working. We suggest the intervention is incorporated into KAW.

Funding: This project was supported by a HEE innovation fund.
Effectiveness of Behavioural Interventions to Reduce Urinary Tract Infections and E. coli Bacteraemia for Older Adults Across all Care Settings: A Systematic Review.

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Background: Escherichia coli bacteraemia rates in the UK have risen; rates are highest among older adults. Previous urinary tract infections (UTIs) and catheterization are risk factors. This research aimed to examine the effectiveness of behavioural interventions to reduce E. coli bacteraemia and/or symptomatic UTIs for older adults.

Methods: Sixteen databases, grey literature, and reference lists were searched. Titles and/or abstracts were scanned and selected papers were read fully to confirm suitability. Quality was assessed using Critical Appraisal Skills Programme guidelines and Scottish Intercollegiate Guidelines Network grading. Twenty-one studies were reviewed, and all lacked methodological quality. Six multi-faceted hospital interventions including education, with audit and feedback or reminders reduced UTIs but only three supplied statements of significance. One study reported decreasing catheter-associated UTI (CAUTI) by 88% ($F(1,20) = 7.25$). Another study reported reductions in CAUTI from 11.17 to 10.53 during Phase I and by 0.39 during Phase II ($\chi^2 = 254$). A third study reported fewer UTIs per patient week (risk ratio = 0.39). Two hospital studies of online training and catheter insertion and care simulations decreased CAUTIs from 33 to 14 and from 10.40 to 0. Increasing nursing staff, community continence nurses, and catheter removal reminder stickers reduced infection. There were no studies examining prevention of E. coli bacteraemias.

Conclusion: The heterogeneity of studies means that one effective intervention cannot be recommended. We suggest that feedback should be considered because it facilitated reductions in UTI when used alone or in multi-faceted interventions including education, audit or catheter removal protocols. Multi-faceted education is likely to be effective. Catheter removal protocols, increased staffing, and patient education require further evaluation.


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Infectious disease and primary care research: What GP staff say they need
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Background: The majority of UK antibiotics are prescribed in primary care. Whilst there have been many diagnostic advances and guidance development in recent years, this study aimed to identify where the perceived gaps in knowledge, guidance and research lie, from the prescriber perspective.

Method: A questionnaire survey and covering letter was disseminated to GPs between May and August 2017; 428 GP staff responded.

Results: Suspected Infection in the elderly (SIE), recurrent UTI (rUTI), surveillance of antibiotic resistance in the community (AMRsur), leg ulcers (LU), persistent cough (pC) and cellulitis (Cel) all fell into the top six conditions ranked in order of importance, and the top six most frequently named illnesses/conditions respondents felt required further research, evidence and guidance.

Across all six conditions, primary care respondent needs were ranked as follows:
- need for better evidence base for antibiotic treatment (SIE, AMRsur, Cel)
- need for better evidence base for self-care and non-antibiotic treatment (rUTI, pC)
- need for improved treatment guidelines for staff (LU)
- need for better point of care prognostic tests
- need for better clinical scores to help inform management
- need for better near patient antibiotic resistance test

Conclusion: This survey has highlighted broad areas for future involvement with primary care although further consultation with staff and other relevant bodies is required. For some conditions, this may be writing/updating/promoting antibiotic prescribing guidance whilst for others highlighting the current evidence base for, or more research into, self-care and non-antibiotic treatment is required.
Antimicrobial use in UK long-term care facilities: results of a point prevalence survey
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Presented at: 78th FIP World Congress of Pharmacy and Pharmaceutical Sciences

Background: The majority of people in long-term care facilities (LTCFs) are aged 65 years and older, and most of their care needs are provided by the LTCF staff. Our aim was to understand the use of antibiotics in LTCFs across the UK and to identify potential gaps in knowledge and support for carers and residents when using antibiotics, in order to determine how community pharmacy teams can provide additional support.

Methods: A point prevalence survey (PPS) was conducted by community pharmacists (\(n = 57\)) when they carried out visits to LTCFs across the UK between 13 November and 12 December 2017. Anonymized data were recorded electronically by the individual pharmacists.

Results: Data were analysed for 17,909 residents in 644 LTCFs across the UK. The mean proportion of residents on antibiotics on the day of the visit was as follows: 6.3% England (536 LTCFs), 7.6% Northern Ireland (35 LTCFs), 8.6% Wales (10 LTCFs) and 9.6% Scotland (63 LTCFs). The percentage of antibiotics prescribed for prophylactic use was 25.3%. Antibiotic-related training was reported as being available for staff in 6.8% of LTCFs and 7.1% of LTCFs reported use of a catheter passport scheme. Pharmacists conducting the PPS intervened during the survey for 9.5% of antibiotic prescription events; 53.4% of interventions were for clinical reasons and 32.2% were for administration reasons.

Conclusions: This survey identified high prophylactic use of antibiotics. There are opportunities for community pharmacy teams to improve antimicrobial stewardship in LTCF settings, including workforce education.

Full reference
Antibiotic prescribing for residents in long-term-care facilities across the UK
Thornley T1, Ashiru-Oredope D2, Normington A3, Beech E4, Howard P4
Presented at: 78th FIP World Congress of Pharmacy and Pharmaceutical Sciences

Background: Elderly residents in long-term-care facilities (LTCFs) are frequently prescribed antibiotics, particularly for urinary tract infections. Optimizing appropriate antibiotic use in this vulnerable population requires close collaboration between NHS healthcare providers and LTCF providers. Our aim was to identify and quantify antibiotic prescribing in elderly residents in UK LTCFs. This is part of a wider programme of work to understand opportunities for pharmacy teams in the community to support residents and carers.

Methods: This was a retrospective longitudinal cohort study. Data were extracted from a national pharmacy chain database of prescriptions dispensed for elderly residents in UK LTCFs over 12 months (November 2016–October 2017).

Results: Data were analysed for 341536 residents in LTCFs across the four UK nations, from which a total of 544796 antibiotic prescriptions were dispensed for 167002 residents. The proportion of residents prescribed at least one antibiotic over the 12 month period varied by LTCF, by month and by country.

Conclusions: Whilst national data sets on antibiotic prescribing are available for hospitals and primary care, this is the first report on antibiotic prescribing for LTCF residents across all four UK nations, and the largest reported data set in this setting. Half of LTCF residents were prescribed at least one antibiotic over the 12 months, suggesting that there is an opportunity to optimize antibiotic use in this vulnerable population to minimize the risk of AMR and treatment failure. Pharmacy teams are well placed to support prudent antibiotic prescribing and improved antimicrobial stewardship in this population.

Reference full publication:
Healthcare workers’ knowledge and attitudes about antibiotics and antibiotic resistance across 30 European Union and European Economic Area countries

Diane Ashiru-Oredope1*, Andrea Nilsson2, Eno Umoh1, Sagar Vasandani1, Olaolu Oloyede1, Susan Hopkins1, Dominique L. Monnet2 and the #ECDCAntibioticSurvey Project Advisory Group 3

1 Public Health England, 2 European Centre for Disease Prevention and Control, 3 A multi-disciplinary group consisting of representatives of each EU/EEA country as well as representatives of EU health professional organisations

Presented at: European Congress of Clinical Microbiology and Infectious Diseases 2019

Background: Whilst there have been a number of studies assessing the knowledge and attitudes of the general public and of health students about antibiotics and antibiotic resistance (AR) in Europe, there is a paucity of literature for healthcare workers (HCWs). This survey aimed to fill this gap.

Methods: An online questionnaire including 43 questions was developed through a modified-Delphi consensus process. The questionnaire was developed in consultation with a project advisory group (PAG) and pilot-tested across Europe. The questionnaire was distributed by PAG members to HCWs in each country and promoted via social media. Participation was voluntary, with the questionnaire being open between 28 January and 14 February 2019. Descriptive statistics were calculated and comparisons made using Chi-Squared test.

Results: There were 10,484 responses from HCWs across 30 EU/EEA countries (Figure 1). The respondents predominantly worked in hospitals (54%), while 12% worked in the community, 8% in pharmacies, 5% in long-term care facilities, 2% in public health institutes, 2% in academic settings and 4% in governmental organisations, industry or professional organisations; 13% of respondents selected other settings. Of all respondents, 96% were confident that they understood AR but only 60% answered the seven key knowledge questions correctly; the proportion varied by professional group (Figure 1). The majority (88%) of respondents agreed that there was a connection between their practices regarding antibiotics and the emergence/spread of antibiotic-resistant bacteria; and 57% agreed that they have a role in controlling AR, this was higher for medical doctors compared to any other HCW groups (p<0.001). Less than half (42%) of respondents agreed that there was good promotion of prudent antibiotic use and AR prevention in their country, and only 28% believed that national campaigns were effective in reducing unnecessary antibiotic use. Only 29% knew that the use of antibiotics to promote growth of farm animals was illegal in the EU.

Conclusions: This first Europe-wide survey highlights that HCWs across Europe have good awareness about antibiotics and AR. However, there are important knowledge gaps that need to be addressed. There is also a need to empower HCWs as key players in controlling AR.
Figure 1: Number of respondents who answered the seven key knowledge questions correctly, number of respondents who answered 6 or less key knowledge questions correctly and total number of respondents, by professional group.
Optimising interventions for Catheter Associated Urinary Tract Infections (CAUTI): behavioural analysis and stakeholders feedback

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Background: Catheter-associated urinary tract infections (CAUTI) are one of the most common device-related infections. Healthcare professionals (HCPs) play a key role in preventing CAUTI and interventions which target the influences on their behaviour are crucial in reducing the incidence of CAUTI. This study aimed to fill the gaps identified by previous behavioural analysis work in the national response to CAUTI in primary, secondary and care home settings.

Method: We conducted a mixed methods analysis involving: i) rapid review and behavioural analysis of effective research interventions using the Behaviour Change Wheel, Theoretical Domains Framework and the Behaviour Change Techniques (BCTs) Taxonomy; ii) mapping behavioural content of research interventions against the key influences on HCPs’ CAUTI-related behaviours and comparing this with national interventions; iii) developing new intervention components using a stakeholder focus group and survey.

Results: The rapid review identified 37 effective research interventions, which were multi-faceted and delivered through a broad range of BCTs and intervention functions. Based on research interventions, 38 potential intervention components were created and then refined during a focus group with 14 stakeholders. The survey identified seven intervention components judged to be feasible to implement which targeted key barriers such as lack of knowledge about risks of catheters or requests from patients and carers.

Conclusions: By drawing on behavioural theory and tools as well as expert stakeholder views and experiences, this project identified intervention components which can be considered when optimising individual national interventions to reduce CAUTI-related infections.
Optimising interventions to reduce antibiotic prescribing for respiratory tract infections in primary care: a mixed-methods study
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Accepted: Public Health England Conference 2019

Introduction: Most antibiotics in England are prescribed in primary care, with many prescribed inappropriately (i.e. unnecessarily or not according to guidelines) for respiratory tract infections. This study aimed to understand whether effective research interventions and national antimicrobial stewardship (AMS) interventions address the key theoretical and empirical barriers and facilitators to appropriate antibiotic prescribing, and to identify ways to improve these interventions.

Methods: We conducted two rapid reviews of studies in primary care: (i) qualitative studies of influences on antibiotic prescribing decisions, and (ii) research AMS interventions. We analysed the studies using the Theoretical Domains Framework, Behaviour Change Wheel and Behaviour Change Techniques (BCTs) Taxonomy. We compared the behavioural content of research interventions shown to be effective at changing prescribing and national interventions, and the extent to which they address key domains representing barriers and facilitators to appropriate prescribing. We conducted a focus group and survey with 15 stakeholders to identify suggestions to improve AMS interventions.

Results: We identified 13 qualitative and 17 intervention studies (UK-based). Analysis showed national interventions address key theoretical domains and use a range of theoretically-congruent intervention functions and BCTs. Intervention improvements were generated by stakeholders and using the research evidence for effective interventions. 14 new intervention components were considered by stakeholders as likely to be feasible, acceptable and effective.

Conclusion: Current AMS interventions have a good range of behavioural components which address key influences on behaviour but some barriers to appropriate antibiotic prescribing remain unaddressed. The intervention suggestions may offer further ways to optimise antibiotic prescribing.
Annexe Chapter 2 - Antimicrobial resistance

Annex 1: Methods and caveat

Data sources

Data on the antibiotic susceptibility of pathogens causing bacteraemia were obtained from SGSS (Second Generation Surveillance System), a national database maintained by Public Health England (PHE) that contains laboratory data supplied electronically by approximately 98% of hospital microbiology laboratories in England. SGSS comprises two modules, a communicable disease reporting (CDR; formerly CoSurv/LabBase2) module and an antimicrobial resistance (AMR; formerly AmSurv) module. The CDR module includes antimicrobial susceptibility test results for bloodstream isolates of the key pathogens being monitored as part of the UK 5-year AMR Strategy\textsuperscript{14} (Annex table 2a.1) covered in this report, although any test results suppressed from clinical reports by the sending laboratories are not captured when the data are submitted. In contrast the AMR module contains more comprehensive antibiogram information as it includes results for all antibiotics tested (including results suppressed from clinical reports) for isolates from all clinical sources. However, when SGSS was launched in 2014, the AMR module had lower laboratory coverage than the CDR module. Although there have been subsequent marked improvements in laboratory reporting to the AMR module of SGSS, analysis of trends in antimicrobial susceptibility for the period covered by this reporting were undertaken using data from the CDR module.

To date, hospital microbiology laboratories have reported antimicrobial susceptibility test results as “susceptible”, “intermediate” or “resistant”. These categories were defined as follows:

- susceptible: a bacterial strain is said to be susceptible to a given antibiotic when its growth is inhibited in vitro by a concentration of the drug that is associated with a high likelihood of therapeutic success
- intermediate: a bacterial strain is said to be intermediate when the concentration of antibiotic required to inhibit its growth in vitro is associated with an uncertain therapeutic outcome at standard antibiotic doses. It implies that an infection due

\textsuperscript{14} Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection Annual report 2015. Available on-line from:
to the isolate may be appropriately treated in body sites where the antibiotic is physically concentrated or when a high dosage of drug can be used

- resistant: a bacterial strain is said to be resistant to a given antibiotic when the concentration required to inhibit its growth in vitro is associated with a high likelihood of therapeutic failure

The breakpoint criteria for categorising clinical isolates as susceptible, intermediate or resistant to individual antibiotics will reflect those available at the time of the specimen. As noted in Box 2.1, in 2019 the EUCAST definitions were amended to regroup the ‘intermediate’ category with those that are susceptible (with the standard dose), as, dosed appropriately, the antibiotic should still work for treatment.\(^\text{15}\)

As patients may have more than one positive blood culture taken, blood cultures taken from the same patient that yielded growth of the same pathogen during a 14-day period from the initial positive blood culture were regarded as comprising the same episode of infection and were de-duplicated.

Annex table 2a.1 Drug/bug combinations monitored in support of the UK-5-year AMR Strategy 2013-18

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>ciprofloxacin, third-generation cephalosporins, gentamicin, carbapenems, co-amoxiclav, piperacillin/tazobactam*</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>ciprofloxacin, third-generation cephalosporins, gentamicin, carbapenems, co-amoxiclav, piperacillin/tazobactam*</td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
<td>ciprofloxacin, third-generation cephalosporins, gentamicin, carbapenems, piperacillin/tazobactam</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>ceftazidime, carbapenems</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.*</td>
<td>colistin</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>penicillin, erythromycin</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.*</td>
<td>glycopeptides</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>methicillin</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>ceftriaxone, azithromycin</td>
</tr>
</tbody>
</table>

*bacteria of antibiotics in the ‘shadow’ list

Data on the incidence of *E. coli*\textsuperscript{16} and *Staphylococcus aureus*\textsuperscript{17} bacteraemia were from the national mandatory surveillance schemes while data on the incidence of other pathogens were derived from cases reported to the CDR module of SGSS. As the latter data were provided on a voluntary basis, case ascertainment will have been incomplete. Data for resistance in *Neisseria gonorrhoeae* were from the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP),\textsuperscript{18} which comprises a network of sentinel genitourinary medicine clinics. Over a 3-month period each year, isolates from consecutive patients with gonorrhoea attending these clinics are referred to PHE’s national reference laboratory for antimicrobial susceptibility testing. Isolates are linked to demographic, clinical and behavioural data from the clinics for analysis of antimicrobial susceptibility trends in patient sub-groups.

Antibiotic groupings used in the BSI antimicrobial susceptibility analyses within the report are:

- third-generation cephalosporins comprised cefotaxime, ceftazidime, cefpodoxime and ceftriaxone, unless otherwise indicated
- carbapenems comprised meropenem or imipenem, except where neither were tested, in which cases results for ertapenem were used if available; the exception was for *Pseudomonas* spp. where ertapenem was excluded
- the only aminoglycoside included was gentamicin
- fluoroquinolones are ciprofloxacin, unless otherwise defined
- glycopeptides comprised vancomycin and/or teicoplanin
- colistin included results recorded as polymyxin

Data on isolates from urine between 2015 and 2018 were extracted from the AMR module of SGSS. Data items collated included source of specimen referral (GP, other community source, acute trust), age, sex and susceptibility to recommended agents for treatment of urinary tract infections (UTI).

Population data used within the chapter were taken from the Office for National Statistics annual mid-year population estimates published data for the corresponding geographic region and year.\textsuperscript{19}

Hospital-onset infections from the mandatory surveillance of *E. coli* bacteraemia were defined as any NHS patient specimens taken on the third day of admission onwards (e.g. day 3 when day 1 equals day of admission) at an acute trust (including cases with


\textsuperscript{19} Office for National Statistics. Mid-year Population Estimates.
unspecified specimen location) for in-patients, day-patients, emergency assessment, or unspecified patient category.

Records with an unknown admission date (where the specimen location is acute trust or unknown and the patient category is in-patient, day-patient, emergency assessment, or unspecified) are also included.

Community-onset infections from the mandatory surveillance *E. coli* bacteraemia were defined as any NHS patient specimens not determined to be hospital-onset. This will typically include the following groups:

- any acute trust specimens taken on either the day of admission or the subsequent day (e.g. days 1 or 2, where day 1 equals day of admission),
- any specimens from patients attending an acute trust who are not inpatients, day patients or under emergency assessment (i.e. non-admitted patients),
- any specimens from patients attending an identifiable healthcare location except an acute trust. This includes GP, nursing home, non-acute NHS provider, independent sector provider, mental health provider, residential home, penal establishment, unknown or other

### Statistical analyses

P values were calculated to assess the change in resistance over time. These were generated using an unadjusted binomial regression model for each drug/bug combination. Analyses were completed using Stata v15 (StataCorp).

### Limitations and caveats

In England, the mandatory surveillance scheme for *E. coli* bacteraemia does not include susceptibility testing data, which is collected through a parallel voluntary laboratory reporting system. Comparison of the incidence reported between the two systems indicated that the ascertainment achieved in the laboratory reporting system was 86% in 2018 (78% in 2014) and varied by local geography across the country (Annex table 2a.2).

Since 2017 reporting of bacteraemia caused by *Klebsiella* spp. and *Pseudomonas aeruginosa* was also mandatory. Initial reviews of ascertainment between the mandatory and voluntary surveillance schemes for each pathogen were assessed for 2018 as 80% (*K. pneumoniae* only) and 84%, respectively.
Annex table 2a.2 a) Ascertainment factor applied to estimate total number of resistant bloodstream infection in England over time (2013 to 2018), and b) by region in England in 2018

<table>
<thead>
<tr>
<th>Year</th>
<th>Mandatory <em>E. coli</em> bacteraemia reports</th>
<th>SGSS <em>E. coli</em> bacteraemia reports</th>
<th>% ascertainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>33,497</td>
<td>27,150</td>
<td>81%</td>
</tr>
<tr>
<td>2014</td>
<td>35,685</td>
<td>27,746</td>
<td>78%</td>
</tr>
<tr>
<td>2015</td>
<td>37,401</td>
<td>30,430</td>
<td>81%</td>
</tr>
<tr>
<td>2016</td>
<td>40,328</td>
<td>33,716</td>
<td>84%</td>
</tr>
<tr>
<td>2017</td>
<td>41,310</td>
<td>35,330</td>
<td>86%</td>
</tr>
<tr>
<td>2018</td>
<td>42,535</td>
<td>36,552</td>
<td>86%</td>
</tr>
</tbody>
</table>

b)

<table>
<thead>
<tr>
<th>Region</th>
<th>Mandatory <em>E. coli</em> bacteraemia reports</th>
<th>SGSS <em>E. coli</em> bacteraemia reports</th>
<th>% ascertainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>London</td>
<td>6,238</td>
<td>5,132</td>
<td>82%</td>
</tr>
<tr>
<td>West Midlands</td>
<td>4,368</td>
<td>4,159</td>
<td>95%</td>
</tr>
<tr>
<td>North East</td>
<td>2,895</td>
<td>2,519</td>
<td>87%</td>
</tr>
<tr>
<td>Yorkshire &amp; Humber</td>
<td>4,822</td>
<td>3,766</td>
<td>78%</td>
</tr>
<tr>
<td>East Midlands</td>
<td>3,386</td>
<td>2,892</td>
<td>85%</td>
</tr>
<tr>
<td>East of England</td>
<td>4,348</td>
<td>3,997</td>
<td>92%</td>
</tr>
<tr>
<td>North West</td>
<td>6,117</td>
<td>4,447</td>
<td>73%</td>
</tr>
<tr>
<td>South East</td>
<td>6,085</td>
<td>5,868</td>
<td>96%</td>
</tr>
<tr>
<td>South West</td>
<td>4,276</td>
<td>3,772</td>
<td>88%</td>
</tr>
</tbody>
</table>

Estimating the burden of antibiotic-resistant bloodstream infections

Data used to update the key drug/bug summaries within the ESPAUR report have been utilised to generate a preliminary estimated burden of resistant bacteraemia in England. The total number of resistant infections is generated by calculating the proportion of each pathogen that were reported as resistant to a given antibiotic, and ensuring that that infection report is not counted in any subsequent antibiotic combinations to avoid double counting (process summarised in Annex figure 2a.1, with a full list of pathogen and antibiotic combinations in Annex table 2a.3). The pathogen and antibiotic combinations included in the report this year differ slightly from those presented in the 2017 ESPAUR report following the exclusion of colistin testing and resistance results due to poor coverage. In 2018 only 6% of *E. coli* bacteraemia reports, 8% of *K. pneumoniae* and *K. oxytoca* bacteraemia, 5% of *Acinetobacter* spp., and 13% of *Pseudomonas* spp. had a susceptibility test result for colistin.
For each year the ascertainment level of cases of *E. coli* bacteraemia reported on a voluntary basis to the CDR module of SGSS was estimated by comparison with mandatory surveillance reports (Annex table 2a.2 ). This value was then applied to the other pathogens under surveillance to estimate the total number of BSIs for each pathogen each year (except for *S. aureus* where the mandatory surveillance totals for both methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) were used).

The Charlson comorbidity Index is a method of categorising comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data, such as hospital abstracts data. Each comorbidity category has an associated weight (from 1 to 6), based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use.
ESPAUR Report 2019

Annex figure 2a.1. Flow diagram for generating the burden of resistant bloodstream infections (BSI) estimates

For relevant antibiotics for each pathogen

Is pathogen tested for Abx A? Yes No
Is pathogen resistant to Abx A? Yes No
Tested for Abx B? Yes No
Resistant to Abx B? Yes No
Tested for Abx C? Yes No
Resistant to Abx C? Yes No

Repeat until all pathogens have % resistance for each relevant antibiotic

Generate estimated No. resistant BSI * [calculation 5]

Calculated % resistant

Estimated no. for each pathogen and antibiotic +

No. resistant Abx A
No. resistant Abx B
No. resistant Abx C
Estimated No. resistant per combination

Add the estimates together

Estimated total resistant BSI

* full list of pathogens in annex table 2a.3 (next page); full list of numbered ‘Calculations’ in Annex Box 2.1
+ per pathogen and antibiotic combination, full list in annex table 2a.3 (next page), all estimates are for a given time frame
Annex table 2a.3 Bacteria and antibiotic resistance categories included in the AMR burden analysis

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Antibiotic resistance</th>
<th>Included in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cassini</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>Colistin- resistant</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Carbapenem-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Aminoglycoside-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem and/or third-generation cephalosporin)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem and/or third-generation cephalosporin and/or aminoglycoside)</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>Colistin- resistant</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Carbapenem-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Aminoglycoside-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem and/or third-generation cephalosporin)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem and/or third-generation cephalosporin and/or aminoglycoside)</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Klebsiella oxytoca</strong></td>
<td>Colistin- resistant</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Carbapenem-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Third-generation cephalosporin-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Aminoglycoside-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem and/or third-generation cephalosporin)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem and/or third-generation cephalosporin and/or aminoglycoside)</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Acinetobacter spp.</strong></td>
<td>Colistin- resistant</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Carbapenem-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Aminoglycoside- and fluoroquinolone-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem)</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Pseudomonas spp.</strong></td>
<td>Colistin- resistant</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Carbapenem-resistant (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Resistant to three or more antimicrobial groups (excluding isolates also resistant to colistin&lt;sup&gt;+&lt;/sup&gt; and/or carbapenem)</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Enterococcus spp.</strong></td>
<td>Glycopeptide-resistant</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>Meticillin-resistant</td>
<td>✓</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------</td>
<td>---</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>Penicillin- and macrolide-resistant (excluding isolates only resistant to penicillin)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Penicillin-resistant (excluding isolates also resistant to macrolides)</td>
<td>✓</td>
</tr>
</tbody>
</table>

### Annex Box 2.1 - Summary of calculations referenced in the flow diagram

All data used in each calculation should be for a comparable geography and time frame

- **Calculation 1**
  
  Total $S.\ aureus = no.\ MRSA\ mandatory\ reports + no.\ MSSA\ mandatory\ reports$

- **Calculation 2**
  
  Ascertainment factor (%) = \((no.\ E\coli\ mandatory\ reports \div no.\ E\coli\ voluntary\ reports) \times 100\)

- **Calculation 3**
  
  Estimated BSI reports = \(no.\ voluntary\ BSI\ reports \times \%\ ascertainment\ factor\)

- **Calculation 4**
  
  Resistance (%) = \((no.\ resistant\ reports\‡ \div no.\ tested\ reports\‡) \times 100\)

- **Calculation 5**
  
  Estimated no. resistant = \%\ resistance \times \([estimated]\ BSI\ reports\)

‡ per pathogen and antibiotic combination in each time frame (Annex table 2a.3)

For the improved estimation of the AMR burden and mortality assessment analyses, 30-day mortality was ascertained by linking bacteraemia reports to the NHS personal demographics service (NHS spine) to obtain date of death.\(^{20}\) Death within 30-days was derived based on the earliest specimen date of the 14-day episode, if there is more than one.

Hospital-acquired and community-acquired infections were defined through linking SGSS (CDR) bacteraemia episode data with acute trust admission (and discharge) date from hospital episode statistics data.\(^{21}\) Cases were categorised as hospital-acquired if the first patient specimen was identified two or more days after the admission date, or within 28 days after the hospital discharge date. Cases were categorised as community-associated for the remaining earliest patient specimens.

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Annexe Chapter 3 - CPE

Data sources and methods

Electronic reporting system for the enhanced surveillance of carbapenemase-producing Gram-negative bacteria

The system captured data on patients colonised and/or infected with Gram-negative bacteria suspected of having acquired carbapenemase expression. Data were captured via the electronic reporting system when isolates were submitted to regional or national reference laboratories for confirmatory testing, or locally confirmed isolates were reported, on a voluntary basis.

The system comprised compulsory and enhanced data fields. Compulsory questions were focused on: patient demographic information; laboratory details associated with the specimen; the healthcare setting the patient was in at time of specimen collection and; travel history in the previous 12 months (including healthcare abroad). Enhanced surveillance questions were to be completed for patients admitted to hospital on confirmation of colonisation or infection with a carbapenemase producer and included: admission details; clinical specialty; whether the patient was screened on admission and; previous contact with patients infected or colonised with carbapenemase-producing Gram-negative bacteria.

Data extraction and preparation

Data from the ERS were accessed from the main database via an ODBC database connection established in Microsoft Excel. Relevant data fields were extracted from the main database through the creation of standard views. The dataset was imported into a statistical software package for further manipulation. Incomplete isolate submissions were excluded, and exact duplicates were removed.

Variables for carbapenemase test results were re-coded to align both regional and national reference laboratory outputs. Local, regional and national results were combined to provide an overall result as to whether a carbapenemase was detected or not detected for each isolate submitted. In the event of a discrepancy between results, the national result superseded the local or regional result. New variables for isolates with more than one resistance mechanism detected were created.
Analysis

Cases were defined as patients with carbapenemase-producing Gram-negative bacteria isolated from a screening or clinical specimen in England between 5\textsuperscript{th} May 2015 to 31\textsuperscript{st} March 2019. Dates for inclusion were based on original specimen date rather than referral date since this information was not available. Cases were de-duplicated for each full year of surveillance by bacterial species reported, specimen site and resistance mechanism(s) identified.

Descriptive summary statistics for each variable were prepared; results from the analysis of enhanced surveillance variables are presented alongside the completeness each of these variables. Data cleaning, manipulation and analysis were conducted in Stata/SE version 13 (StataCorp., USA.)

Case fatality rate

Case fatality rate was estimated for cases of invasive disease, where invasive disease was defined as CPE isolated from a sterile site, as defined in in ‘Laboratory reporting to Public Health England: A guide for diagnostic laboratories’.\textsuperscript{22} A list of sterile sites are listed in the table below:

<table>
<thead>
<tr>
<th>BLADDER</th>
<th>LUNG</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOOD/BLOOD COMPONENTS</td>
<td>LYMPH NODE</td>
</tr>
<tr>
<td>BONE</td>
<td>OVARY/FALLOPIAN TUBE</td>
</tr>
<tr>
<td>BONE MARROW</td>
<td>OCULAR FLUID</td>
</tr>
<tr>
<td>BRAIN</td>
<td>PANCREAS</td>
</tr>
<tr>
<td>CSF</td>
<td>PERITONEUM</td>
</tr>
<tr>
<td>FASCIA/MUSCLE</td>
<td>PLEURA</td>
</tr>
<tr>
<td>GALL BLADDER</td>
<td>SURGICAL IMPLANT E.G VASCULAR SHUNT/ GRAFT</td>
</tr>
<tr>
<td>GLAND EG THYROID, PAROTID</td>
<td>SPINAL CORD</td>
</tr>
<tr>
<td>HEART</td>
<td>SPLEEN</td>
</tr>
<tr>
<td>HEART VALVE</td>
<td>TISSUE/TISSUE FLUID</td>
</tr>
<tr>
<td>JOINT</td>
<td>UTERUS</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>VASCULAR SYSTEM (VEIN/ARTERY)</td>
</tr>
<tr>
<td>LIVER</td>
<td></td>
</tr>
</tbody>
</table>

Mortality information was obtained by batch-tracing CPE cases against the NHS Spine. NHS number, date of birth, sex, first name and surname were submitted for tracing for CPE cases with invasive disease.

Data were submitted for tracing on 30th July 2019. For cases with a death recorded on the NHS Spine, the time in days between specimen date (the date which the specimen was collected) and date of death was calculated to identify whether it was within the 30-day window included in the case fatality calculations. For cases with multiple reports within the 30-day mortality window, the final specimen date was used to calculate 30-day all-cause CFR. CFR was calculated as follows:

30-day all-cause CFR = \( \frac{\sum 30\text{-day mortality traced reports}}{\sum \text{traced reports}} \times 100 \)

**Credible interval**

The point estimate and 95% credible interval (CRI) were estimated in a Bayesian framework, assigning a normal prior distribution with mean 0 and variance 1000 to the log odds of 30-day mortality and converting the resulting posterior estimates to probabilities. As the prior distribution is uninformative, the posterior probability is consequently largely based on data used in the analysis.
Annexe Chapter 4 - Antimicrobial consumption

Data source and methods

Primary care

Information on prescribing of antibiotics in the community was obtained from the PHE Antibiotic Prescribing Data Warehouse, a project initiated by the ESPAUR Oversight Group. Data is sourced from the NHS Digital database and are extracted each month as a snapshot in time from the GP payments system.

Age-group data for primary care was obtained from ePACT2 from NHSBSA.

Primary care prescribing data includes antibiotic prescribed from general practice and other community settings such as out-of-hours services and walk-in centres. The full list of primary care prescribing settings is provided in the annex.

Secondary care

Information on the use of antibiotics in secondary care was obtained from IQVIA (formerly QuintilesIMS, formed from the merger of IMS Health and Quintiles). The database held by IQVIA contains information from 99% of NHS hospital pharmacy systems for drugs dispensed to individual patients and wards. Data from all NHS acute Trusts were included and organisational changes are reflected up to the latest year of data provided in the report. Trusts can amend their prescribing data for up to a period of two years, hence data for the last two years is provisional and is subject to change.

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Dental care

Information on the use of antibiotics prescribed in NHS dental surgeries was obtained from NHSBSA through a data request.

All data presented in this chapter in Figures and Tables are available as a web Appendix in Excel format and a Figures slide set annex.
Classification of prescribing data

The classification of antibiotics for this report is based on the Anatomical Therapeutic Chemical / Daily Defined Dose (ATC/DDD) index 2019 managed by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology.\(^{23}\) Data covered all antibiotics in the ATC group ‘J01’, (antibiotics for systemic use) and three additional oral agents outside the ‘J01’ group used to treat *Clostridium difficile* infections, fidaxomicin (A07AA12), metronidazole (P01AB01) and vancomycin (A07AA09).

Third level pharmacological sub-grouping within ATC group ‘J01’:

- penicillins ("β-lactam antibacterials, penicillins") include extended-spectrum penicillins, β-lactamase sensitive and resistant penicillins, and β-lactamase inhibitors either alone or in combination with penicillins
- “other β-lactam antibacterials” includes cephalosporins, carbapenems, and monobactams.
- anti-*Clostridioides difficile* (formerly *Clostridium difficile*) agents include: oral vancomycin (ATC code: A07AA09) and fidaxomicin (ATC code: A07AA12). Oral metronidazole (ATC code: P01AB01) has been separated from this group, as opposed to previous years, following feedback from stakeholders
- “other antimicrobials” (ATC 3rd level pharmacological subgroup ‘J01X’) includes glycopeptides, polymyxins, steroid antibacterials, imidazole derivatives, nitrofuran derivatives, and other antimicrobials: fosfomycin, methenamine, linezolid, daptomycin and tedizolid

ATC/DDD methodology

The ATC system aims to identify the active therapeutic ingredient of all human medicines and assigns drugs a measure of use known as the DDD, which is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is important to note however that while the DDD is used as a unit of measurement of drug use, it does not necessarily reflect the recommended or prescribed daily doses used in practice as therapeutic doses for individual patients may vary depending on characteristics such as age, weight, ethnic differences, type and severity of disease and pharmacokinetic considerations.

---

**Denominators**

Mid-year populations (inhabitants) for each year were extracted from the Office National Statistics (ONS). Hospital admission data for each year was extracted from hospital episode statistics (HES) from NHS Digital.

**Trend analysis**

National trends in the consumption of antibiotics were assessed using linear regression; the dependent variable was antibiotic consumption in DDD per 1,000 inhabitants per day and the explanatory variable being year. A statistically significant trend (p<0.05) is denoted with the inclusion of †. Stata 15 was used in all analysis.

---


## Other community settings categories

Other community settings to category look up table.

<table>
<thead>
<tr>
<th>Other Community Settings</th>
<th>Setting Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>Other</td>
</tr>
<tr>
<td>Walk-in Centre</td>
<td>Walk-in Centre</td>
</tr>
<tr>
<td>Out-of-hours</td>
<td>Out-of-hours</td>
</tr>
<tr>
<td>WIC and OOH Practice</td>
<td>Out-of-hours</td>
</tr>
<tr>
<td>Public Health Service</td>
<td>PH Service</td>
</tr>
<tr>
<td>Community Health Service</td>
<td>Community Service</td>
</tr>
<tr>
<td>Hospital Service</td>
<td>Hospital</td>
</tr>
<tr>
<td>Optometry Service</td>
<td>Other</td>
</tr>
<tr>
<td>Urgent &amp; Emergency Care</td>
<td>Urgent Care</td>
</tr>
<tr>
<td>Hospice</td>
<td>Hospice</td>
</tr>
<tr>
<td>Care Home / Nursing Home</td>
<td>Nursing Home</td>
</tr>
<tr>
<td>Border Force</td>
<td>No data reported</td>
</tr>
<tr>
<td>Young Offender Institution</td>
<td>Custody</td>
</tr>
<tr>
<td>Secure Training Centre</td>
<td>No data reported</td>
</tr>
<tr>
<td>Secure Children’s Home</td>
<td>Custody</td>
</tr>
<tr>
<td>Immigration Removal Centre</td>
<td>Custody</td>
</tr>
<tr>
<td>Court</td>
<td>No data reported</td>
</tr>
<tr>
<td>Police Custody</td>
<td>No data reported</td>
</tr>
<tr>
<td>Sexual Assault Referral Centre</td>
<td>No data reported</td>
</tr>
<tr>
<td>Other – Justice Estate</td>
<td>No data reported</td>
</tr>
<tr>
<td>Prison</td>
<td>Custody</td>
</tr>
</tbody>
</table>
Trusts definitions

Trusts definitions in the ESPAUR report are based on the Estates Returns Information Collection (ERIC).\(^{26}\)

<table>
<thead>
<tr>
<th>Trust</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Small/Medium/Large</td>
<td>Sites that provides a range of inpatient medical care and other related services for surgery, acute medical conditions or injuries (usually for short-term illnesses or conditions). Treatment centres providing inpatient facilities are classed as general acute hospitals.</td>
</tr>
<tr>
<td>Acute Teaching</td>
<td>Sites that are a hospital that provides clinical education and training to future and current health professionals. Teaching hospitals work closely with medical students throughout their period of matriculation, and especially during their clerkship (internship) years.</td>
</tr>
<tr>
<td>Acute Specialist</td>
<td>Sites that undertake a single specialist function, inclusive of Oncology, Orthopaedics, Dental Hospital, Maternity Hospital, Children’s Hospital, and Cardio/Thoracic. This category excludes specialist hospitals in the Mental Health or Learning Disabilities sector.</td>
</tr>
<tr>
<td>Acute Multiservice</td>
<td>Sites where two or more functions are provided by the same provider. Such functions would include any combination of single speciality, acute services, community services, mental health services and learning disabilities services.</td>
</tr>
</tbody>
</table>

Department speciality to department group look up table.

<table>
<thead>
<tr>
<th>Department Speciality</th>
<th>Department Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed Outpatient Clinics</td>
<td>AE/Non-specific out-patient department</td>
</tr>
<tr>
<td>Aseptic unit</td>
<td>AE/Non-specific out-patient department</td>
</tr>
<tr>
<td>A &amp; E</td>
<td>AE/Non-specific out-patient department</td>
</tr>
<tr>
<td>Psychogeriatric</td>
<td>Geriatrics</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>Geriatrics</td>
</tr>
<tr>
<td>Intensive Care</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>Dermatology</td>
<td>General Medicine</td>
</tr>
<tr>
<td>Respiratory/ Chest/ Asthma clinic</td>
<td>General Medicine</td>
</tr>
<tr>
<td>Cardiology</td>
<td>General Medicine</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>General Medicine</td>
</tr>
<tr>
<td>Coronary care</td>
<td>General Medicine</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>General Medicine</td>
</tr>
<tr>
<td>Thoracic/ Chest medicine</td>
<td>General Medicine</td>
</tr>
<tr>
<td>General Medicine</td>
<td>General Medicine</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>General Medicine</td>
</tr>
<tr>
<td>Obstetrics &amp; Gynaecology</td>
<td>Obstetrics and gynaecology</td>
</tr>
<tr>
<td>Fertility /Genetics</td>
<td>Obstetrics and gynaecology</td>
</tr>
<tr>
<td>Orthopaedics</td>
<td>Orthopaedics</td>
</tr>
<tr>
<td>Pain Clinic</td>
<td>Other</td>
</tr>
<tr>
<td>Radiology</td>
<td>Other</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>Other</td>
</tr>
<tr>
<td>Physically Disabled</td>
<td>Other</td>
</tr>
<tr>
<td>Rehabilitation/Long stay unit</td>
<td>Other</td>
</tr>
<tr>
<td>Pathology Lab</td>
<td>Other</td>
</tr>
<tr>
<td>Mental Handicap</td>
<td>Other</td>
</tr>
<tr>
<td>Occupational Health</td>
<td>Other</td>
</tr>
<tr>
<td>Learning Disabilities</td>
<td>Other</td>
</tr>
<tr>
<td>Child Adolescent Psychiatry</td>
<td>Other</td>
</tr>
<tr>
<td>Other Wards/ Units</td>
<td>Other</td>
</tr>
<tr>
<td>Psychiatry / Mental Illness</td>
<td>Other</td>
</tr>
<tr>
<td>Psychiatric Day Hospital</td>
<td>Other</td>
</tr>
<tr>
<td>Paediatric ICU</td>
<td>Paediatrics</td>
</tr>
<tr>
<td>Neonatal Unit</td>
<td>Paediatrics</td>
</tr>
<tr>
<td>Paediatric / Paediatric Surgery</td>
<td>Paediatrics</td>
</tr>
<tr>
<td>Acute Internal Medicine</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>Medical Oncology</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>Service</td>
<td>Department</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Clinical Oncology (Radiotherapy)</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>A.I.D.S Unit</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>Infectious dis./Isolation</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>Renal Medicine</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>Liver Unit</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>Neurology</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>G.U.M</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>Haematology</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>GUM Medicine</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>Liver (failure) Unit</td>
<td>Specialist medicine</td>
</tr>
<tr>
<td>Transplantation Unit</td>
<td>Specialist Surgery</td>
</tr>
<tr>
<td>E.N.T.</td>
<td>Specialist Surgery</td>
</tr>
<tr>
<td>Cardio-thoracic Surgery</td>
<td>Specialist Surgery</td>
</tr>
<tr>
<td>Plastic Surgery</td>
<td>Specialist Surgery</td>
</tr>
<tr>
<td>Oral Surgery</td>
<td>Specialist Surgery</td>
</tr>
<tr>
<td>Vascular Surgery</td>
<td>Specialist Surgery</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Specialist Surgery</td>
</tr>
<tr>
<td>Urology</td>
<td>Specialist Surgery</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Specialist Surgery</td>
</tr>
<tr>
<td>General Surgery</td>
<td>General Surgery</td>
</tr>
<tr>
<td>Breast Treatment &amp; Care</td>
<td>General Surgery</td>
</tr>
<tr>
<td>Day Case Theatres</td>
<td>General Surgery</td>
</tr>
<tr>
<td>Theatre/ Anaesthetics</td>
<td>General Surgery</td>
</tr>
</tbody>
</table>
Annexe Chapter 5 – Use of NHS England levers to improve antimicrobial stewardship and reduce risk of antimicrobial resistant infections 2017 – 2019

Annex 5.1 Data source and methods

CQUIN 2c: Antibiotic review in patients with sepsis

Information on the percentage of antibiotic prescriptions reviewed as per CQUIN criteria was submitted by Trusts to PHE through the SelectSurvey.NET © Copyright 1998-2017 platform v4.166 and published on Fingertips. Data in this report was extracted from the October 2019 release of Fingertips from indicators 92516; Percentage of antibiotic prescriptions with evidence of review within 72 hours by quarter and 93460; Percentage of antibiotic prescriptions with evidence of review within 72 hours by an appropriate clinician with a documented outcome plus an IV to oral switch assessment for IV prescriptions by quarter. From this, data from Barnsley Hospital NHS Foundation Trust for Quarter 2 was removed for quality control reasons.

CQUIN 2d: Reduction in antibiotic usage per 1,000 admissions and proportion of antibiotic usage (for both inpatients and out-patients) within the Access AWaRe category

Information on antimicrobial prescribing 2016 baseline data, 2017/18 performance and 2018/19 targets were taken from published documents on NHS Improvement website pages Reducing the impact of serious infections CQUIN 2017/18\textsuperscript{27} and 2018/19.\textsuperscript{28}

Corrections were made to data published from NHS Improvement where necessary. Total antibiotic usage 2016 baseline data for Salford Royal NHS Foundation Trust (RM3) and The Royal Orthopaedic Hospital NHS Foundation Trust (RRJ) for which baseline data was not published but 2017/18 targets were given as well as for South Warwickshire NHS Foundation Trust (RJC) where data was corrected for data quality reasons were replaced with data from Fingertips or calculated from the target data


where this was not available. Total carbapenem usage 2016 baseline data for The Royal Orthopaedic Hospital NHS Foundation Trust (RRJ) for which baseline data was not published but 2017/18 targets were given was calculated from the target data. Access group 2016 baseline data for South Warwickshire NHS Foundation Trust (RJC) was corrected for data quality reasons using data from Fingertips.

Information on antimicrobial prescribing 2018/19 data was calculated from quarterly Trust prescribing data submissions to PHE with HES admissions data from NHS Digital where data for all four quarters was submitted. This data was extracted from the October 2019 release of Fingertips from indicators 92,201; Defined daily dose of antibiotics dispensed by Acute Trusts pharmacies to all inpatients and outpatients per 1,000 admissions- CQUIN data, 92,224 Defined daily dose of carbapenems dispensed by Acute Trusts pharmacies to all inpatients and outpatients per 1,000 admissions- CQUIN data and 93,317 Proportion of total antibiotic prescribing from the "Access" category of the WHO Essential Medicines List AWaRe index- CQUIN data.

Trust NHS region information was provided by NHS Improvement.

All acute trusts were considered as eligible to participate in the CQUIN schemes. Trusts were considered as having participated if they provided calendar year 2016 baseline data, were given targets and had all quarters of CQUIN financial year data for each indicator or a minimum of all quarters of CQUIN financial year data for the access group prescribing indicator.

Where there were trust reconfigurations targets were recalculated for merged trusts based on their combined annual admissions and antimicrobial consumption where data for both trusts was available.
Annex 5.2 Regional breakdown

Annex Figure 5.1 Reducing the impact of serious infections 2017/19 CQUIN scheme 2c indicator: antibiotic review. Boxplot showing the percentage of antibiotic prescriptions reviewed by the CQUIN criteria component 1 (appropriate clinical review) and met the CQUIN per region.
Annexe Chapter 6 - Antifungal resistance, prescribing and stewardship

Annex 1: Fungal subgroup membership

Fungal subgroup membership/collaborators:
Samir Agrawal; Diane Ashiru-Oredope; Richard Barton; Andy Borman; David Denning; David Enoch; Rebecca Guy; Philip Howard; Elizabeth Johnson; Rohini Manuel; Christianne Micallef; Caroline Moore; Berit Muller-Pebody (Chair); Katie Owens; Rakhee Patel; Riina Rautemaa-Richardson; Malcolm Richardson; Colin Richman; Silke Schelenz; Peter Stephens.
Annexe Chapter 7 - Antimicrobial stewardship

Annex 1: Draft Antimicrobial Prescribing and Stewardship Report (Template)

The aim of the report is to provide a summary of either CCG or hospital Trust data available on Fingertips- AMR Local Indicators. This information will provide clinicians and managers with an easily accessible resource, which can be disseminated or presented to commissioners, infection control team or antimicrobial committee, to highlight achievements and challenges that are vital to the antimicrobial stewardship strategy.

This example report is based on the NHS England initiatives, aggregated at trust type and sub-region level. This will be a dynamic/automated updated quarterly, in which the interpretation of the data generated and report narrative will be conditional to changes/fluctuations of the most recent data extract from PHE Fingertips profile. In addition, a separate report will be developed for CCGs, which will allow data to be aggregated at sustainability and transformation partnerships (STPs) level. The CCG report will include a section on resistance covering indicators on the susceptibility of *E. coli* to specific drug per quarter and healthcare-associated infection.

**Note:** Text highlighted in red within the draft template will be reflective of the Trust selected and the trend in the data.
1. Purpose

This report will summarise the intelligence on PHE fingertips to support the organisations AMS strategy and surveillance, in achieving the national AMR ambitions:

- reduce the number of specific drug-resistant infections in people by 10% by 2025;
- reduce UK antimicrobial use in humans by 15% by 2024;

This report will cover key data by Trust and region on:

- NHS England initiatives annual trend
- Antibiotic prescribing
- Infection rates
- Stewardship

2. National Background

The use of antimicrobials and burden on antimicrobial resistance has been well documented, highlighting the need more appropriate prescribing to keep antibiotics effective and reduce the spread and emergence of resistance [1]. Data collected indicates antibiotic consumption in secondary care in England increased by 7.7% between 2013 and 2017. Prescribing for hospital inpatients increased by only 2% but increased by 21% in hospital outpatient settings over the five-year period.

In 2017, the increased level of antibiotic prescribing in hospital inpatients also reflected a shortage in the supply of a key broad-spectrum antibiotic, piperacillin/tazobactam. The need to use two or more alternative antibiotics to give the same degree of antibacterial coverage resulted in an additional 2.2 million Defined Daily Doses (DDDs) being dispensed [2].

3. Notes of Caution on the Data

The figures produced for the indicators are raw and unadjusted for the confounding effects of both age and sex. Thus, comparison between different organisations should be treated with caution.

4. NHS England Initiatives

<table>
<thead>
<tr>
<th>Antimicrobial prescribing data</th>
<th>16/17 Q2</th>
<th>17/18 Q2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four quarter rolling rate of total antibiotic prescribing per 1000 admissions; by acute Trust</td>
<td>6,042</td>
<td>6,342</td>
</tr>
<tr>
<td>Four quarter rolling rate of carbapenem prescribing per 1000 admissions; by acute Trust and quarter</td>
<td>161.6</td>
<td>172</td>
</tr>
<tr>
<td>Proportion of total antibiotic prescribing from the &quot;Access&quot; category of the WHO Essential Medicines List AWaRe index (percent)</td>
<td>48</td>
<td>51.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital Care associated infection</th>
<th>16/17 Q2</th>
<th>17/18 Q2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of E. coli bacteraemia hospital-onset per 100,000 bed days by NHS acute Trust and financial year</td>
<td>33</td>
<td>30.2</td>
</tr>
<tr>
<td>Rate of C. difficile hospital-onset per 100,000 bed days by reporting acute Trust and financial year</td>
<td>19.5</td>
<td>20.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antimicrobial Stewardship data</th>
<th>16/17 Q2</th>
<th>17/18 Q2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of antibiotic prescriptions with evidence of review within 72 hours; by quarter</td>
<td>97.8</td>
<td>100</td>
</tr>
<tr>
<td>Percentage of frontline healthcare workers vaccinated with the seasonal influenza vaccine by NHS Acute Trust</td>
<td>79.9</td>
<td>80.8</td>
</tr>
</tbody>
</table>
5. Antibiotic Prescribing

5.1 Total antibiotic prescribing

**Figure 1:** Four quarter rolling rate of total antibiotic prescribing as DDD per 1000 admissions; Yorkshire and Humber Region

There is an increasing trend each quarter in the total prescribing of antibiotic per 1000 admissions, with an overall 12% increase in 2018/19 Q2 compared to 2017/2018 Q2. There is a two-fold variation of total antibiotic prescribing across the Trust in the NHS region name. **Trust name** has the highest rate of total antibiotic prescribing per 1000 admission in the region.

**Figure 2:** Four quarter rolling rate of total antibiotic prescribing DDD per 1000 admissions; Teaching Hospitals in England

There is a variation in antibiotic prescribing of 4-folds (1897 to 9034 per 1000 admissions) observed across Trust type in England (figure 2). The median rate of total antibiotic prescribing for teaching hospitals is 4672 DDDs per 1000 admissions. The total antibiotics prescribed within Trust name (6339 DDDs per 1000 admissions) in 2018/19 Q2 is greater than 75% of teaching hospitals in England.

**Figure 3:** Proportion of total antibiotic prescribing from the “Access” category of the WHO Essential Medicines List AWaRe index

Within **NHS region name** the prescribing of carbapenems (2018/19 Q2) varies about 9 fold (19 to 176 carbapenems per 1000 admissions) between acute Trusts. Prescribing of carbapenems in **Trust name** shows an increasing trend. There is a 20% increase in prescribing of carbapenem compared to same quarter (Q2) in the previous financial year.

**Figure 4:** Four quarter rolling rate of carbapenem prescribing DDD per 1000 admissions
In the most recent quarter there is 47% higher prescribing of carbapenems per 1000 admissions in Trust name compared to other Trust type across England.

6. Infection rates

Figure 5: E.coli bacteraemia hospital-onset counts and rates by financial year

There is a higher rate of hospital-onset E.coli bacteraemia within the Trust compared to the average rates of Trusts in NHS region name and Trust type in England. The rate of hospital-onset C. difficile infections shows a decreasing trend.

Figure 6: Hospital-onset C.difficile rates by financial year

7. Stewardship

The data (Figure 7) shows an increasing trend in the percentage of antibiotic prescriptions reviewed within 72 hours. The hospital reports a higher percentage of reviews compared to Trusts in the NHS region name and Trust type in England. The percentage of antibiotics stopped after review has decreased from the previous quarter.

Figure 7: Percentage of antibiotic prescriptions reviewed within 72 hours with a stop decision documented

Figure 8: Percentage of antibiotic prescriptions with evidence of review within 72 hours

8. Interventions

To support Trusts in making progress in addressing the challenges of antimicrobial resistance a number of organisations have published a range of guidance and toolkits accessible online. These resources provide a platform for generating evidence and clear actions to strengthen antimicrobial stewardship.

8.1 CQUIN

The Commission for Quality and Innovation (CQUIN) 2019/20 scheme on ‘Antimicrobial Resistance’ was split into two parts:

a. Lower Urinary Tract Infections in Older People

b. Antibiotic Prophylaxis in colorectal surgery

Details of each part of the indicator can be accessed here https://www.england.nhs.uk/publication/ccg-cquin-2019-20-indicatorsSpecifications/.
Annex 2: TARGET Treating Your Infection – Urinary Tract Infection leaflet for women under 65 years

<table>
<thead>
<tr>
<th>Possible urinary signs &amp; symptoms</th>
<th>The outcome</th>
<th>Recommended care</th>
<th>Types of urinary tract infection (UTI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysuria: Burning pain when passing urine (pee)</td>
<td>If none or only one of: dysuria, new nocturia, cloudy urine; UTI much less likely</td>
<td>Self-care and pain relief.</td>
<td>Kidneys (make urine)</td>
</tr>
<tr>
<td>New nocturia: Needing to pass urine in the night</td>
<td>You may need a urine test to check for a UTI</td>
<td></td>
<td>Infection in the upper urinary tract</td>
</tr>
<tr>
<td>Cloudy urine: Visible cloudy colour when passing urine</td>
<td>Antibiotic less likely to help</td>
<td>Delayed or backup prescription with self-care and pain relief</td>
<td></td>
</tr>
<tr>
<td>UTI more likely</td>
<td>Usually lasts 5 to 7 days</td>
<td>Start antibiotics if symptoms:</td>
<td><strong>Bladder (stores urine)</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Get worse</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Do not get a little better with self-care within 48 hours</td>
<td></td>
</tr>
<tr>
<td>Other severe signs/symptoms:</td>
<td>If 2 or more of: dysuria, new nocturia, cloudy urine; OR bacteria detected in urine AND NO vaginal discharge</td>
<td>Immediate antibiotic prescription plus self-care</td>
<td><strong>Urethra (takes urine out of the body)</strong></td>
</tr>
<tr>
<td>Frequency: Passing urine more often than usual</td>
<td>UTI more likely; antibiotics should help</td>
<td>If mild symptoms, delayed or back-up antibiotic prescription plus self-care</td>
<td></td>
</tr>
<tr>
<td>Urgency: Feeling the need to pass urine immediately</td>
<td>You should start to improve within 48 hours</td>
<td></td>
<td>Infection or inflammation in the urethra</td>
</tr>
<tr>
<td>Haematuria: Blood in your urine</td>
<td>Symptoms usually last 3 days</td>
<td></td>
<td><strong>Urethritis (inflammation of the urethra)</strong></td>
</tr>
<tr>
<td>Suprapubic pain: Pain in your lower tummy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other things to consider:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent sexual history</td>
<td>For women under 65 years with suspected lower urinary tract infections (UTIs) or lower recurrent UTIs (cystitis or urethritis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some sexually transmitted infections (STIs) can have symptoms similar to those of a UTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changes during menopause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some changes during the menopause can have symptoms similar to those of a UTI</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Self-care to help yourself get better more quickly

- Drink enough fluids to stop you feeling thirsty. Aim to drink 6 to 8 glasses including water, decaffeinated and sugar-free drinks.
- Take paracetamol or ibuprofen at regular intervals for pain relief, if you have had no previous side effects
- There is currently no evidence to support taking cranberry products or cystitis sachets to improve your symptoms
- Consider the risks factors in the Options to help prevent UTI column to reduce future UTIs

When should you get help?

Contact your GP practice or contact NHS

Options to help prevent a UTI

- The following symptoms are possible signs of serious infection and should be assessed urgently
- Phone for advice if you are not sure how urgent the symptoms are
- You have shivering, chills and muscle pain
- You feel confused, or are very drowsy
- You have not passed urine all day
- You are vomiting
- You see blood in your urine
- Your temperature is above 38°C or less than 36°C
- You have kidney pain in your back just under the ribs
- Your symptoms get worse
- Your symptoms are not starting to improve within 48 hours of taking antibiotics
- It may help you to consider these risk factors:
  - Stop bacteria spreading from your bowel into your bladder. Wipe from front (vagina) to back (bottom) after using the toilet. Avoid waiting to pass urine. Pass urine as soon as you need a wee. Go for a wee after having sex to flush out any bacteria that may be near the opening to the urethra. Wash the external vagina area with water before and after sex to wash away any bacteria that may be near the opening to the urethra. Drink enough fluids to make sure you are well hydrated throughout the day, especially during hot weather.
  - If you have a recurrent UTI the following may help:
    - Cranberry products and D-mannose: There is some evidence to say that these work to help prevent recurrent UTI.
    - After the menopause: Topical hormonal treatment may help; for example, vaginal creams.
    - Antibiotics at night or after sex may be considered

Antibiotics can be lifesaving. But antibiotics are not always needed for urinary symptoms.
Antibiotics taken by mouth, for any reason, affect our gut bacteria making some resistant.
Antibiotic resistance means that the antibiotics cannot kill that bacteria.
Antibiotic resistant bacteria can remain in your gut for at least a year after taking an antibiotic.

Common side effects to taking antibiotics include diarrhoea, nausea and vomiting. Seek medical advice if you are worried.

Keep antibiotics working: only take them when advised by a health professional. This way they are more likely to work for a future UTI.
Annex 3: Flowchart for women under 65 years with suspected UTI

Excludes women with recurrent UTI (2 episodes in last 6 months, or 3 episodes in last 12 months) or urinary catheter

**Urinary signs/symptoms**
- Do not treat asymptomatic bacteriuria in non-pregnant women as it does not reduce mortality or mortality.

First exclude vaginal and urethral causes of urinary symptoms:
- Vaginal discharge: 80% do not have UTI
- Urethritis - inflammation post sexual intercourse, irritants
- Check sexual history to exclude sexually transmitted infections
- Genitourinary syndrome of menopause (vulvovaginal atrophy)

Think sepsis - check for signs/symptoms using local/national tool such as NICE, RCGP or NEWS2.

Check for any new signs/symptoms of pyelonephritis - see box below

Does patient have any of 3 key diagnostic signs/symptoms?
- Dysuria (burning pain when passing urine)
- New nocturia (passing urine more often than usual at night)
- Urine cloudy to the naked eye

2 or 3 symptoms: NO

Does patient have any of 3 key diagnostic signs/symptoms?

YES

Perform Urine Dipstick Test

**POSITIVE nitrite or leukocyte and RBC POSITIVE**

YES

UTI likely

Send urine culture if risk of antibiotic resistance.
If not pregnant and mild symptoms, watch & wait with back-up antibiotic

OR

Consider immediate antibiotic using NICE/PHE guideline on lower UTI: antimicrobial prescribing.

NEGATIVE nitrite POSITIVE leukocyte

 Review time of specimen (morning is most reliable)
Send urine for culture to confirm diagnosis
Consider immediate or back-up antibiotic (if not pregnant) depending on symptom severity using NICE/PHE guideline on lower UTI: antimicrobial prescribing

NEGATIVE for all nitrite, leukocyte, RBC

UTI LESS likely

No urine culture
Reassure that UTI less likely
Consider other diagnosis

ALL PATIENTS: share self-care and safety-netting advice using TARGET UTI leaflet
If pregnant always send urine culture – follow national treatment guidelines if any bacteriuria

*Signs of pyelonephritis:
- Kidney pain/tenderness in back under ribs
- New/different myalgia, flu like illness
- Shaking chills (rigors) or temperature 37.9°C or above
- Nausea/vomiting

Key:
- Suspected sepsis alert
- UTI symptom
- Action advised
- Other advice