# Are resistance rates among bloodstream isolates a good proxy for other infections? Analysis from the BSAC Resistance Surveillance Programme

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**Short running title:** bacteraemia versus respiratory resistance rates

# Synopsis

**Background:** Bacteraemia data are often used as a general measure of resistance prevalence but may poorly represent other infection types. We compared resistance prevalence between bloodstream (BSI) and lower respiratory (LRTI) isolates collected by the BSAC Resistance Surveillance Programme. **Methods:** BSI isolates (n=8912) were collected during 2014 - 2018 inclusive and LRTI isolates (n=6280) between Oct 2013 to Sept 2018 from participating laboratories in the UK and Ireland, to a fixed annual quota per species group. LRTI isolates, but not BSI, were selected by onset: community for *Streptococcus pneumoniae*; hospital for *Staphylococcus aureus*, *Pseudomonas aeruginosa*, Enterobacterales. MICs were determined centrally by agar dilution; statistical modelling adjusted for ICU location and possible clustering by collection centre. **Results:** Resistance was more prevalent among the LRTI isolates, even after adjusting for a larger proportion of ICU patients. LRTI *P. aeruginosa* and *S. pneumoniae* were more often resistant than BSI isolates for most antibiotics, and the proportion of MRSA was higher in LRTI. For *S. pneumoniae*, the observation reflected different serotype distributions in LRTI and BSI. Relationships between LRTI and resistance were less marked for Enterobacterales, but LRTI *Escherichia coli* were more often resistant to β-lactams, particularly penicillin/β-lactamase inhibitor combinations, and LRTI *Klebsiella pneumoniae* to piperacillin/tazobactam. For *Enterobacter cloacae* there was a weak association between LRTI, production of AmpC enzymes and cephalosporin resistance. **Conclusions:** Estimates of resistance prevalence based upon bloodstream isolates underestimate the extent of the problem in respiratory isolates, particularly for *P. aeruginosa, S. pneumoniae*, *S. aureus* and, less so, for Enterobacterales.

# Introduction

Surveillance of the national and international prevalence of antimicrobial resistance is widely predicated on isolates from bacteraemia, as in EARS-NET and most PHE surveillance.[1, 2] The rationale is that bacteraemia isolates represent invasive infection, not colonisation, raising confidence in their significance. The bacterial strains able to cause bloodstream infection (BSIs) may not, however, be representative of those causing other infections, where resistant lineages may be more or less prominent. This point is pertinent, for example, for *Escherichia coli*, where around half the bacteraemias are attributable to five sequence types, one of which (ST131) accounts for most multi-resistant cases.[3] In the case of *Streptococcus pneumoniae* the predominant serotypes from bacteraemias overlap but do not precisely match those prevalent in respiratory infection.[4, 5]

A further vital point is that bacteraemias may develop because prior treatment of a more localised infection fails. This hazard seems more likely when the initial infection is due to a multi-resistant organism. If so, resistance rates for bloodstream isolates may exceed those for isolates from other sites. Lastly, the prevalence of resistance in acute infections, including bacteraemias is widely acknowledged to be less than that among isolates from chronic infections, which are exposed to multiple rounds of antibiotic selection as, for example with *Pseudomonas aeruginosa* from cystic fibrosis and non-CF bronchiectasis.

The BSAC Resistance Surveillance Programme has monitored the antimicrobial susceptibility of isolates collected from BSIs and lower respiratory tract infections (LRTIs) from laboratories throughout the UK and Ireland. Here we compare resistance rates between bloodstream and respiratory isolates collected over the five most recent surveillance seasons.

# Methods

*Isolates*

The BSAC Resistance Surveillance Programme has been described previously.[6] It collected fixed quotas of BSI and LRTI isolates (n = 7 – 40 per species/bacterial group annually) from sentinel UK and Irish microbiology laboratories. Between 21 and 39 sites have participated each year over the five-year period reviewed here, with some turnover of sites between years. BSI isolates were collected on a calendar year basis; those from the five years 2014 – 2018 inclusive are reviewed here. LRTI isolates were collected on an October to September year, so that winter peaks were not split across collection years; the isolates reviewed here were collected between Oct 2013 - Sept 2018. Respiratory *S. pneumoniae* were from community-onset LRTIs (i.e. evident at hospital admission or arising within 48h of admission), whereas LRTI Enterobacterales, *P. aeruginosa* and *Staphylococcus aureus* were collected from hospital-onset LRTI (i.e. arising >48 hours after admission). BSI isolates were collected without reference to the time or place of onset. Isolates from cystic fibrosis patients were excluded, as were repeat isolates from the same patient within 14 days.

*Laboratory methods*

The species identity of most isolates was confirmed centrally by MALDI-TOF MS (Bruker Biotyper, Bruker, Bremen, Germany), exceptions being *E. coli,* which was identified using CHROMagar™ Orientation (CHROMagar, Paris, France) with or without confirmation by MALDI-TOF; *S. aureus*, identified using CHROMagar™ Staphylococcus (CHROMagar Paris, France) with or without confirmation by MALDI-TOF, and pneumococci, which were identified based upon colonial appearance and optochin susceptibility.[7] Pneumococci were serotyped as previously described.[5]

The BSAC agar dilution method was used to determine MICs for the collected isolates.[6] Breakpoints followed EUCAST criteria (v11.0, 2021).[8] Regarding pneumococci, ciprofloxacin was the only fluoroquinolone tested; however, as there are no EUCAST breakpoints for this agent further analysis was not possible. Pneumococci were tested against amoxicillin and results were interpreted according to the EUCAST breakpoint (R>1 mg/L) for oral dosing.

Methicillin resistance was defined by the presence of *mec*A, as detected by PCR.[9] Enterobacterales with ceftazidime and/or cefotaxime MICs ≥1 mg/L were tested for ESBL production based on synergy between oxyimino-cephalosporins and clavulanate, and for AmpC activity based upon cefoxitin resistance and synergy between oxyimino-cephalosporins and cloxacillin.[6] Isolates thereby inferred to have ESBLs were tested for *bla*$_{\text{CTX-M}}$ by type-specific PCR;[10] those inferred to have AmpC were tested by PCR for plasmid-mediated AmpC.[11] Carbapenem-non-susceptible Enterobacterales were tested for carbapenemase genes by specific PCR[12] or microarrays. *P. aeruginosa* isolates with resistance to all β-lactams and with ceftazidime MIC ≥128 mg/L or imipenem ≥64 mg/L, were tested by PCR for carbapenemase[12, 13] and ESBL genes.[14 15] *P. aeruginosa* isolates with upregulated AmpC were categorised according to their relative susceptibility to piperacillin-tazobactam, ceftazidime and carbenicillin.[16, 17] Multiresistance has been defined as resistance to three or more different classes of antimicrobial agent.

*Statistical analysis*

We employed Stata 15.1 (2017, StataCorp LLC, College Station, TX) for all analyses. Cluster-robust standard errors were used throughout to adjust for possible clustering by collection centre.

For the most part, isolates with MICs in the EUCAST 'susceptible' (S) and 'susceptible, increased exposure' (I) categories[8] were pooled and compared with those found resistant (R); an exception being *S. pneumoniae* and penicillin, where 'susceptible, increased exposure' (I) and resistant (R) isolates were pooled. We describe proportions resistant in four categories: BSI non-ICU, BSI ICU, LRTI non-ICU, LRTI ICU, with 95% CIs estimated by the logit method for each organism/test combination.

We estimated risk ratios (RRs) and their 95% CIs using binomial generalised linear regression with a log link function. Our primary model estimated the overall RR for LRTI (compared with BSI as a baseline) adjusted for ICU, including infection site and ICU/non-ICU treatment speciality as predictors. We estimated RRs for LRTI in non-ICU and ICU treatment groups (and a P value for the difference between them) in a second model including infection site, ICU/non-ICU treatment speciality, and their interaction. We also fitted unadjusted models, with LRTI as the only predictor, for comparison with the primary model.

*Exclusions - isolates and tests*

Antibiotics were considered for inclusion in the present analysis if they were tested for three or more consecutive seasons, with an exception for ceftazidime/avibactam, which was tested in the 2014, 2017 and 2018 bacteraemia surveillances but only in the 2016/17 and 2017/18 respiratory surveillances. Where an antimicrobial was tested for isolates from only one infection site (i.e. BSI or LRTI) in a season, data from the other site were excluded to avoid any confounding by temporal trends. Where details on the patient's location were missing or stated as 'not known', we deduced non-ICU if the care setting was recorded as community/out-patients; otherwise, isolates where the speciality remained unknown were excluded from analysis (Table 1).

For data plots (see Results, Figures 1-4), we excluded combinations of organism and antibiotic if the resistance prevalence was <1% in all categories (BSI ICU, BSI non-ICU, LRTI ICU and LRTI non-ICU). For modelling, we additionally excluded combinations with no resistant isolate(s) detected in one or more of these four categories.

# Results

*Total number of organisms received and available for analysis*

A total of 15,192 isolates were initially identified for inclusion in the analysis, comprising 8912 from BSIs and 6280 from LRTIs (Table 1). After excluding those with unknown ICU/non-ICU location, analysis included 2907 *S. pneumoniae*; 3311 *S. aureus,* of which 308 (9%) were MRSA; 2023 *P. aeruginosa*; 3679 *E. coli*; 1614 *Klebsiella pneumoniae* and 1205 *Enterobacter cloacae* complex (Table 1); effective totals are lower for those antibiotics that were not tested every year.

*Patient demographics and location*

The proportion of isolates from men exceeded that from women for both BSIs and LRTIs for most species, exceptions being respiratory *P. aeruginosa*, bloodstream *E. coli,* and both bloodstream and respiratory *S. pneumoniae*, where the proportions from male and female patients were similar (Table 1). The modal age group was most often 80+ years for BSI and 70-79 years for LRTI. Exceptions were bloodstream *E. cloacae* complex and *K. pneumoniae* isolates, which both were associated with a younger modal age group (70-79), also respiratory *E. cloacae* complex and *S. pneumoniae*, again associated with a lower modal age group (60-69 years) (Table 1).

For all species groups except *S. pneumoniae,* a far larger proportion of the LRTI isolates were from ICU patients than was the case for BSI isolates (31-50% versus 4-

13%, varying according to species) (Table 1). In the case of *S. pneumoniae* the proportions of ICU patients were small (2-4%) for both BSI and LRTIs.

*Prevalence of resistance in BSI compared with LRTI*

We describe resistance prevalence for all organism/test combinations that were pre-defined as 'priority' on grounds of clinical importance and availability of data. Thirteen organism-antibiotic combinations were excluded from the models (summarised in Table 2) but not the plots (Figures 1-4) owing to the absence of any resistant isolate in one or more of the analysis categories. For 12 of these 13, resistance was estimated to be more prevalent overall in LRTI than in BSI, but this was not strong evidence for a genuine difference, as the prevalence of resistance was low for both infection sites (mostly <1%; maximum 2.7%).

Our statistical models sought to control for any effect due to the much larger proportion of ICU cases in the LRTI group. They did not adjust for trends over time; however, no major resistance trends were evident during the surveillance period (data not shown). Comparison between the primary and unadjusted models showed that simple adjustment for ICU had little impact on the estimated RR for LRTI.

For *S. pneumoniae* the prevalence of resistance was two- to three-fold greater among LRTI than BSI isolates for all the antibiotics reviewed, i.e. penicillin (MIC >0.06 mg/L), amoxicillin, erythromycin and tetracycline (Figure 1, Table 2). There was no evidence of a difference between ICU and non-ICU settings (Table 2), although it should be cautioned that very few *S. pneumoniae* isolates were obtained from ICU patients regardless of infection type. Serotype distributions differed between the BSI and LRTI pneumococci (Table 3). The top five bacteraemia serotypes, accounting for 49% of BSI isolates (532/1092) were 8, 12F, 22F, 3 and 9N; the top five pulmonary

serotypes, comprising 34% of LRTI isolates (617/1815) were 15A, 11A, 3, 23B and 23A. Serotype 15A, which includes a sizeable proportion of multi-resistant isolates was among the top three LRTI isolates in all years, whereas serotypes associated with multiresistance (15A and 19A) only ever achieved fourth or fifth rank among the BSI isolates.

For *S. aureus* there was strong evidence that MRSA, indicated by the presence of *mecA*, was more prevalent among LRTI isolates than among those from BSIs. There was weaker evidence that the prevalence of resistance to ciprofloxacin and erythromycin was more prevalent in LRTI isolates (Figure 2, Table 2). These resistances are common traits among the long-prevalent ST22/EMRSA-15 and ST30/EMRSA-16 lineages of MRSA, potentially explaining the association.[18] Clindamycin and erythromycin (but not *mecA*) showed strong evidence of a difference in the RR of LRTI between ICU and non-ICU settings (Table 2).

For *P. aeruginosa* there was strong evidence that the prevalence of resistance was higher in LRTI than BSI for piperacillin/tazobactam, ceftazidime, meropenem, imipenem and ciprofloxacin, typically with a RR of 2–3; there was a weaker signal for tobramycin (Figure 3, Table 2). The point estimates are consistent with a stronger effect of LRTI outside the ICU, but the evidence for this is very weak.

Among Enterobacterales there was clear evidence of greater resistance prevalence in LRTI isolates compared with those from BSI only for some β-lactams, with the particular compounds affected varying according to species (Figures 4A-C, Table 2). Among *E. coli,* there was strong evidence of a higher prevalence of resistance in LRTI than BSI for amoxicillin, amoxicillin/clavulanate, piperacillin/tazobactam and for a larger proportion of isolates expressing AmpC β-

lactamases. There was weaker evidence of a positive association with LRTI for resistance to oxyimino cephalosporins and production of ESBLs (Figure 4A, Table 2). For all antimicrobials modelled, including ciprofloxacin, gentamicin and tobramycin as well as β-lactams, the estimated RR for LRTI was greater outside the ICU, meaning that the overall RR underestimates of the effect of LRTI outside ICU (Table 2).

For *K. pneumoniae* there was evidence of higher prevalence of resistance in LRTI isolates than BSI for piperacillin/tazobactam only. Unlike for *E. coli*, there was no good evidence of a differential effect of LRTI on resistance between ICU and non-ICU isolates (Figure 4B, Table 2); there were, however, relatively few BSI ICU isolates compared with *E. coli* (Table 1), reducing the robustness of this comparison.

Among *E. cloacae* complex isolates there was weak evidence of increased resistance to cefotaxime and ceftazidime, as well as of increased AmpC production, in LRTI than BSI, particularly for non-ICU isolates (Figure 4C, Table 2). This was a broadly similar pattern to that for *E. coli*; however, there were fewer isolates than for *E. coli* and so the evidence is weaker.

Just 24 carbapenemase producers were identified, these comprised 17 Enterobacterales (13 from LRTI and 4 from BSI) and seven *P. aeruginosa* (5 LRTI and 2 BSI). No single carbapenemase type dominated. Given the small numbers and diversity, no useful comparisons could be performed. Likewise, too few ESBL-producing *P. aeruginosa* or AmpC-producing *K. pneumoniae* were collected for robust analysis (Figures 3 and 4B).

## Discussion

Resistance among bloodstream isolates is often used as a general proxy for resistance prevalence, including by the ECDC and PHE. The present analysis shows

this approach substantially underestimates the burden of resistance in LRTI, which accounts for the largest single fraction of hospital antibiotic prescribing.[19] For *S. pneumoniae* and *P. aeruginosa*, resistance rates were higher in LRTI for most or all antibiotics reviewed. For *S. aureus* the prevalence of MRSA was 1.75-fold greater in LRTI. Differences were less marked among Enterobacterales but, according to the species, a greater prevalence of resistance among LRTI isolates was seen for various β-lactams and penicillin/β-lactamase inhibitor combinations, linked with correspondingly higher rates of β-lactamase expression. We saw no case with good evidence of lower prevalence of resistance in LRTI isolates than in those from BSI. A possible confounder, recognised when this analysis was being initiated, was that the proportions of ICU patients were higher in the case of LRTI; others have previously shown an excess of resistance associated with ICU infections.[20] However, extensive statistical modelling indicated that the site of infection, rather than the ICU/non-ICU location of the patient, was an independent and stronger predictor of increased resistance. These findings have important implications for national surveillance of antimicrobial resistance.

*S. pneumoniae* was the only community-onset respiratory pathogen considered; other community pathogens collected in the BSAC respiratory surveillance (*Haemophilus influenzae* and *Moraxella catarrhalis*) rarely cause BSIs. Greater resistance among pneumococci from LRTI rather than BSI recapitulates the findings of an earlier study from Spain, where penicillin-resistant pneumococci were (and are) more prevalent than in the UK.[21] The present finding probably reflects the association of particular serotypes with resistance and/or with the ability to initiate invasive infection. None of the most prevalent serotypes associated with BSI here (8, 12F, 22F, 3, 9N) is commonly resistant, whereas 15A, as the most prevalent serotype

from LRTI, includes a sizeable subgroup of ST63 isolates with resistance to tetracyclines and macrolides and reduced susceptibility to β-lactams.[22] Notably, this serotype is not covered either by modern conjugate vaccines, nor by the 23-valent polysaccharide pneumococcal vaccine used to protect the elderly in the UK.

In the case of *S. aureus*, there was an association between MRSA/*mecA* and LRTI, extending more weakly to resistances to ciprofloxacin, erythromycin and clindamycin, all of which are prevalent traits in the ST22/EMRSA-15 and ST30/EMRSA-16 lineages that dominate among MRSA in the UK. Reasons for a higher MRSA prevalence in LRTI remain unknown but it is plausible that bloodstream infections by MRSA have been particularly reduced by national guidelines that emphasised the prevention of line-associated infections, which previously accounted for over half of all MRSA bacteraemias.[23, 24] Different interventions, including head-of-bed elevation, oral chlorhexidine gel, sedation holds and a weaning protocol[25] are asserted to be more important to the prevention of MRSA pneumonias, and these may have been less successful or less widely adopted.

Excesses of resistance among LRTI isolates in the case of *P. aeruginosa* seem likely to reflect associations with chronic pulmonary conditions. The BSAC Respiratory Programme primarily sought isolates from acute hospital-onset LRTIs. However, the reality is that these infections often arise in patients with underlying pulmonary disease including asthma, bronchiectasis, and COPD, which are frequent and under-diagnosed causes of morbidity in the UK.[26] Individuals with underlying pulmonary disease are prone to become colonised with *P. aeruginosa*, to experience exacerbations involving infection, and to receive frequent therapeutic or prophylactic antibiotics, selecting for resistance. These infections rarely progress to invasive disease, meaning that the resistances of the strains involved are not reflected in

bacteraemia data. Rather, *P. aeruginosa* bacteraemias mostly arise in a different, vulnerable hospital population, notably those with haematological malignancy, and immunosuppression. The strains responsible are clonally diverse, often being acquired from the environment,[27] and having less prior exposure to antibiotics than the organisms from much-treated respiratory patients. Since nosocomial pneumonias occur in *c.* 1.5% of England's by 16 million admissions per annum,[28, 29] with around 25% involving *P. aeruginosa*,[30] we estimate 60,000 *P. aeruginosa* hospital LRTIs annually. Meanwhile, mandatory surveillance indicates 4000–5000 *P. aeruginosa* BSI cases annually in England.[31] With LRTIs outnumbering BSIs 12-fold, it seems inappropriate to predicate national surveillance solely on BSIs and their lower resistance rates.

Higher resistance prevalence rates among LRTI isolates of Enterobacterales were specific to particular combinations of organism and antibiotic. Compared with BSI isolates, *E. coli* from LRTI were more often resistant to amoxicillin, amoxicillin/clavulanate, and piperacillin/tazobactam, with weaker evidence for a higher prevalence of resistance to third-generation oxyimino cephalosporins (ceftazidime or cefotaxime). This cephalosporin resistance corresponded with a higher prevalence of AmpC (strong evidence) and ESBLs (weak evidence) in LRTI. Resistance to penicillin/β-lactamase inhibitor combinations in *E. coli* is most often a correlate of co-carriage of OXA-1 β-lactamases[32] or of β-lactamase quantity[33] but any relationship between these characteristics, which were not examined here, and lineages prevalent in LRTI versus BSIs remain unknown. Most *E. coli* BSIs originate from a urinary or intra-abdominal source[34] and multiresistance, particularly ESBL production, is associated with the global ST131 lineage.[3] *E. coli* is less prominent as a respiratory pathogen and the role of ST131 is less clear in LRTI, though the lineage has been

linked with pneumonias in East Asia.[35] The present isolates were not typed. However, among ESBL producers with a Group 1 *bla*$_{CTX-M}$ β-lactamase gene (as typical in ST131), 70/212 (33.0%) from BSIs and 27/94 (28.7%) from LRTIs had antibiograms typical of multiresistant ST131,[36] with resistance to cephalosporins, ciprofloxacin and tobramycin, but not gentamicin; whilst a further 81/212 (38.2%) and 42/94 (44.7%), respectively, had possible ST131, with additional resistance to gentamicin, as occurs if a further aminoglycoside-modifying enzyme is acquired.

Notably, differences in resistance rates have also been reported between UTI and BSI isolates for *E. coli*, though with the direction being variable. In general, UTI isolates are less resistant than those from BSIs,[37] supporting the view that many *E. coli* BSIs arise following resistance-associated treatment failures in UTIs.[38] Nonetheless this pattern may reverse for isolates from complicated UTIs, putatively exposed to previous rounds of antibiotics.[39]

*K. pneumoniae* and *E. cloacae* are opportunistic Enterobacterales groups commonly responsible for nosocomial pneumonia, and it is plausible (though unproven) that more bacteraemias for these species have a respiratory origin than for *E. coli*. A raised prevalence of resistance among LRTI isolates was seen only for piperacillin/tazobactam in the case of *K. pneumoniae*. Reasons remain uncertain and the genetic correlates of resistance to piperacillin/tazobactam remain poorly defined in the species.[40] Lastly, for *E. cloacae*, we found weak evidence that AmpC hyperproduction and (probably contingent) resistance to cefotaxime and ceftazidime was more prevalent in LRTI isolates, at least outside the ICU; there was no such association for ceftobiprole, which largely evades AmpC enzymes.[41]

It should be added that LRTI presents further challenges beyond higher resistance prevalence. In particular, achieving adequate drug exposure is more difficult than in the blood. This aspect is further complicated by the fact that lung pharmacokinetic data for antimicrobial agents are often derived from healthy volunteers during Phase 1 development.[42] These individuals may not adequately reflect ICU patients with augmented renal clearance, where inadequate levels may be associated with significant mortality.[43] Further challenges include a relatively high bacterial burden in LRTI and slow bacterial killing/clearance due to saturation of alveolar macrophages. Lastly, the lung is a primary site of infection, whereas bacteraemias may resolve spontaneously if source control is established elsewhere. It is arguable that breakpoints should be infection-site specific. Neither EUCAST nor the BSAC has yet adopted this approach but, were they to do so, LRTI breakpoints would certainly be lower than for many other sites, increasing the impact of the greater resistance prevalence rates seen here.

A limitation to this analysis is that, for all species except *S. pneumoniae*, the LRTI isolates were from hospital-onset infections whereas the bacteraemia isolates included a mixture of hospital- and community-onset infections. It remains possible that we primarily found a hospital/community difference rather than a BSI/LRTI one. Unfortunately, this is not testable without detailed review of individual patient notes because: (i) patients with ‘community-onset’ bacteraemias may recently have been hospitalised and (ii) because ‘hospital-onset bacteraemia’ may be a late consequence of community-onset infection at another body site.

In conclusion, we urge those involved in the coordination of national surveillance of antimicrobial resistance to extend their activity beyond bloodstream

infections. This is particularly important for *S. pneumoniae, S. aureus*/MRSA and *P. aeruginosa,* where BSI data underestimate resistance for multiple antibiotics. Relying too heavily on surveillance data from bacteraemia reports alone may lead to inappropriate or sub-optimal empirical treatment. This may be of particular importance for LRTI, which is the commonest reason for hospital antibiotic prescribing and which involves a body site where source control cannot easily be performed, increasing the demand placed on the antibiotic component.

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## Transparency Declaration

MA: is a Trustee of the BSAC Council and is employed by Merck Sharp & Dohme (UK) Limited, London, UK. DML: Advisory Boards or ad hoc consultancy Accelerate, Antabio, Centauri, Entasis, Integra-Holdings, Meiji, Menarini, Mutabilis, Nordic,

ParaPharm, Pfizer, QPEX, Shionogi, Summit, T.A.Z., VenatoRx, Wockhardt, Zambon, Paid lectures – bioMérieux, Beckman Coulter, Cardiome, Merck/MSD, Menarini, Nordic, Pfizer and Shionogi. Relevant shareholdings or options – Dechra, GSK, Merck and Pfizer, amounting to less than 10% of portfolio value. He also has nominated holdings in Avacta, Byotrol, Destiny, Diaceutics, Evgen, Fusion Antibodies, Genedrive, Hardide, Renalytics, Scancell and Synairgen (all of which have research/products pertinent to COVID-19) through Enterprise Investment Schemes but has no authority to trade these shares directly. CL: is a Trustee of the BSAC Council and is employed by Shionogi B.V., London, UK. CH, SM and RR have no conflicts of interest.

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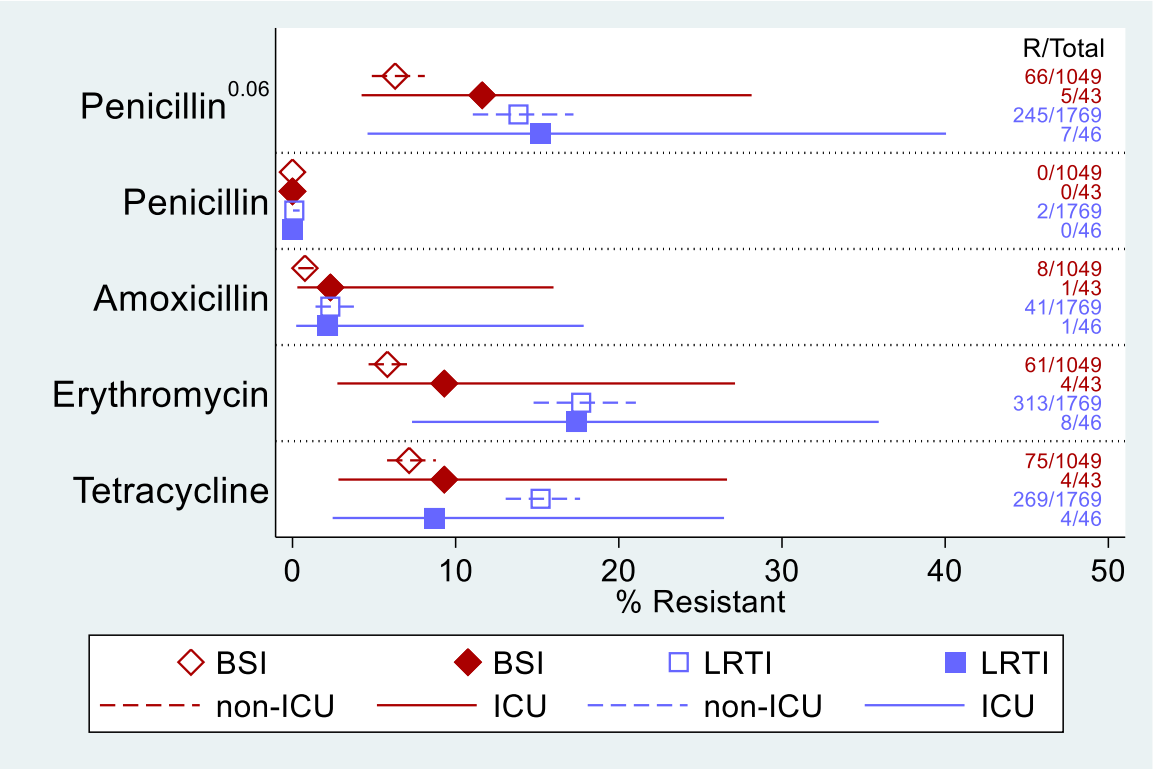
**Table 1.** Isolates tested by species and patient demographics

| Organism | Source | n | Sex (%) male | Sex (%) female | Modal age group (years) | ICU Location n (%) [N missing ICU data] |
|---|---|---|---|---|---|---|
| *S. pneumoniae* | BSI | 1127 | 51 | 49 | >80 | 43 (4) [35] |
| (n = 2959) | LRTI | 1832 | 53 | 47 | 60-69 | 45 (2) [17] |
| *S. aureus* | BSI | 2405 | 63 | 37 | >80 | 190 (8) [86] |
| (n = 3441) | LRTI | 1036 | 62 | 38 | 70-79 | 409 (40) [44] |
| *P. aeruginosa* | BSI | 1073 | 65 | 35 | >80 | 94 (9) [25] |
| (n = 2105) | LRTI | 1032 | 56 | 44 | 70-79 | 329 (31) [57] |
| *E. coli* | BSI | 2543 | 50 | 50 | >80 | 103 (4) [75] |
| (n = 3790) | LRTI | 1247 | 67 | 33 | 70-79 | 489 (40) [36] |
| *K. pneumoniae* | BSI | 924 | 60 | 40 | 70-79 | 59 (6) [29] |
| (n = 1664) | LRTI | 740 | 70 | 30 | 70-79 | 280 (38) [21] |
| *E. cloacae*[a] | BSI | 840 | 60 | 40 | 70-79 | 112 (13) [19] |
| (n = 1233) | LRTI | 393 | 64 | 36 | 60-69 | 195 (50) [9] |

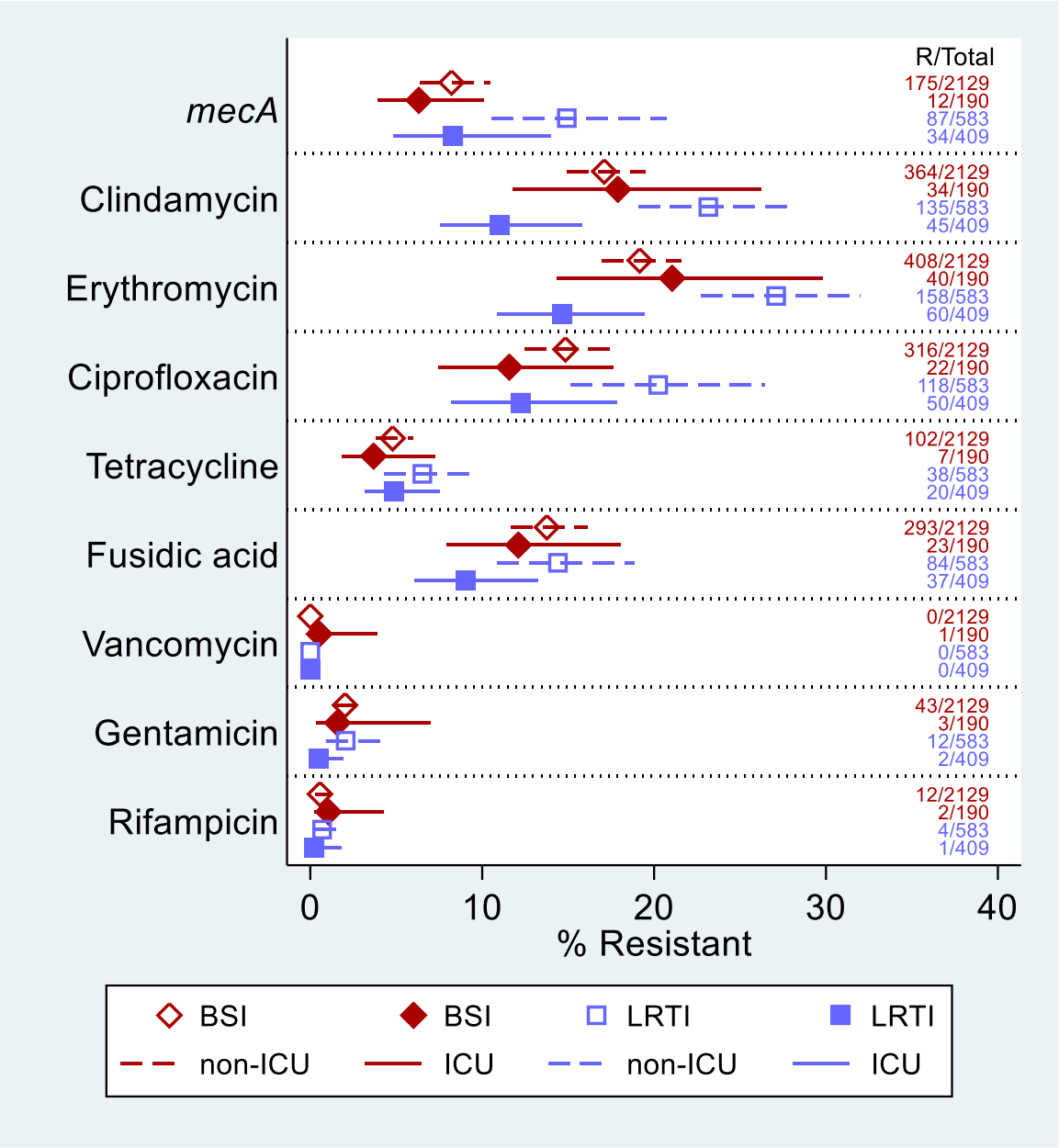
Key: [a]*E. cloacae* complex comprises *Enterobacter cloacae*, *E. asburiae*, *E. hormaechei*, *E. kobei*, *E. ludwigii* and *E. nimipressuralis*; BSI, bloodstream infection; LRTI, respiratory isolates. Age groups were categorised as: <5, 5-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, >80 years.

**Figure 1.** Rates of resistance (with 95% CI) among *Streptococcus pneumoniae* from bloodstream (BSI) and respiratory infections (LRTI), from patients in ICU versus non-ICU.



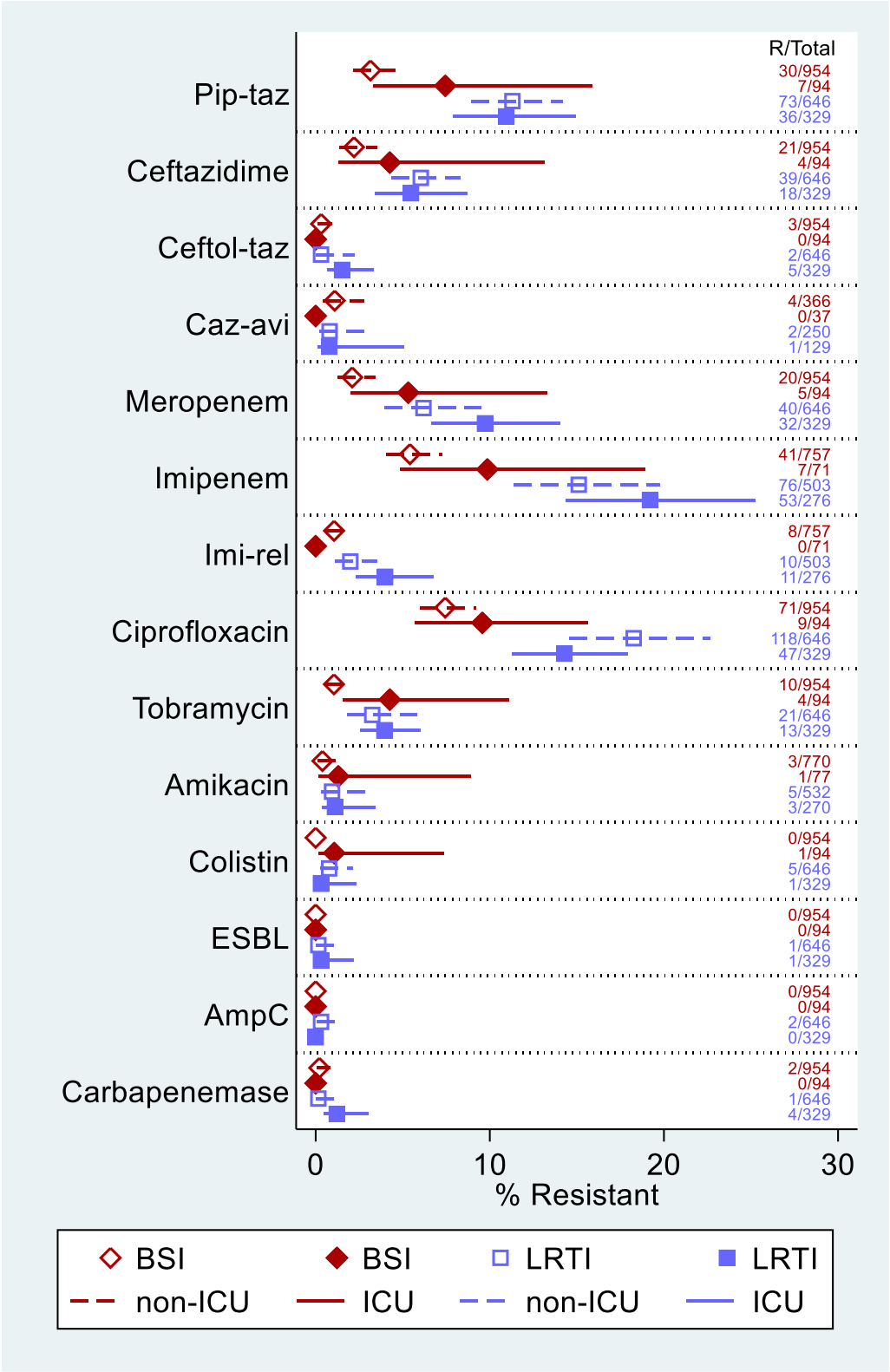

Key: Penicillin$^{0.06}$: penicillin analysed at a ≥0.06 mg/L breakpoint for pneumococci (i.e., combining resistant and 'susceptible dose-dependent' categories). Not shown: cefotaxime, ceftobiprole, ceftaroline (<1% resistant in all categories). This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

**Figure 2.** Rates of resistance (with 95% CI) among *Staphylococcus aureus* from bloodstream (BSI) and respiratory infections (LRTI), from patients in ICU versus non-ICU



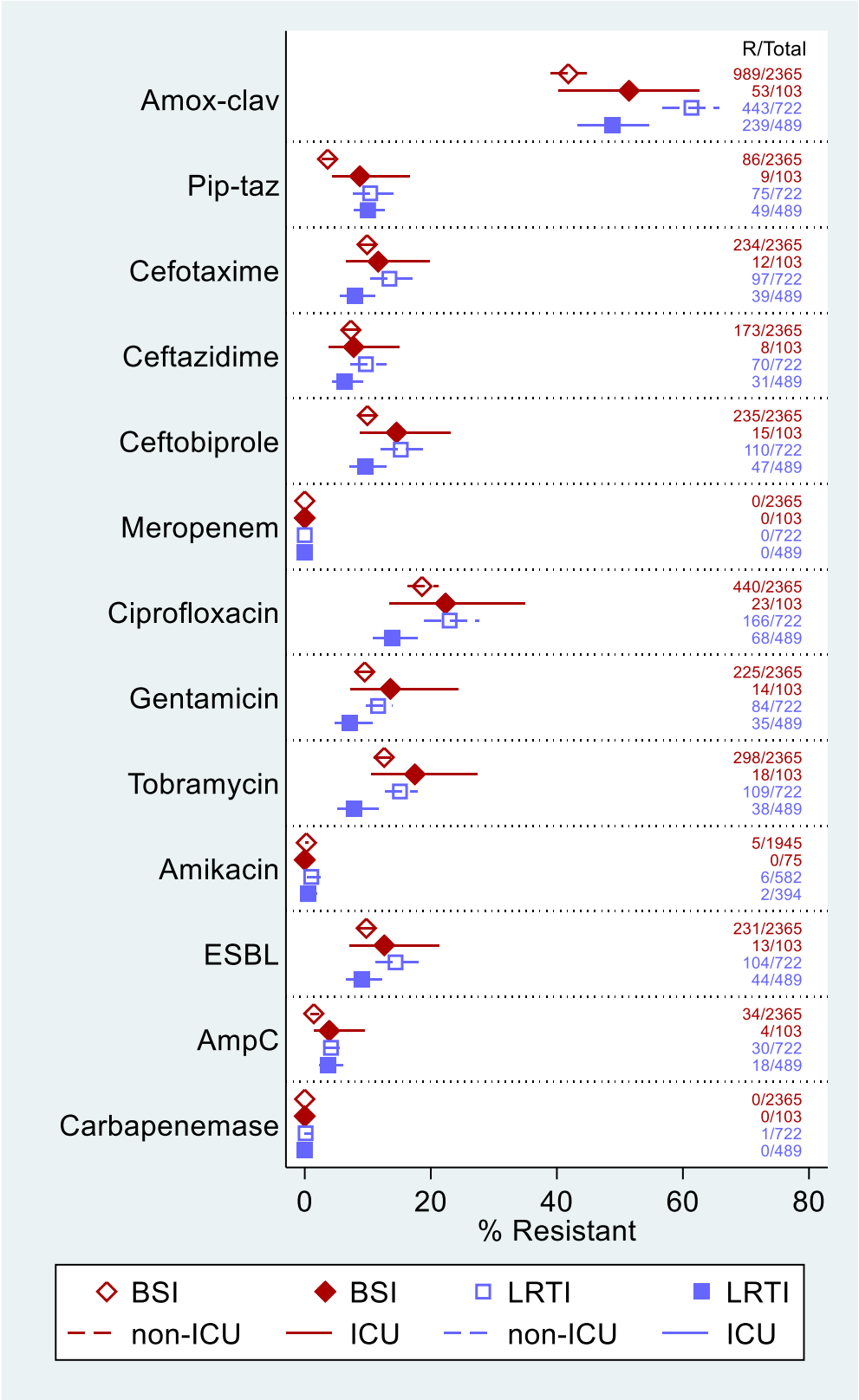

Key: *mecA*: isolates positive for the *mec*A gene, representing MRSA. Not shown: Ceftobiprole, ceftaroline, teicoplanin and tedizolid (<1% resistant in all categories). This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

**Figure 3.** Rates of resistance (with 95% CI) among *Pseudomonas aeruginosa* from bloodstream (BSI) and respiratory infections (LRTI), from patients in ICU versus non-ICU



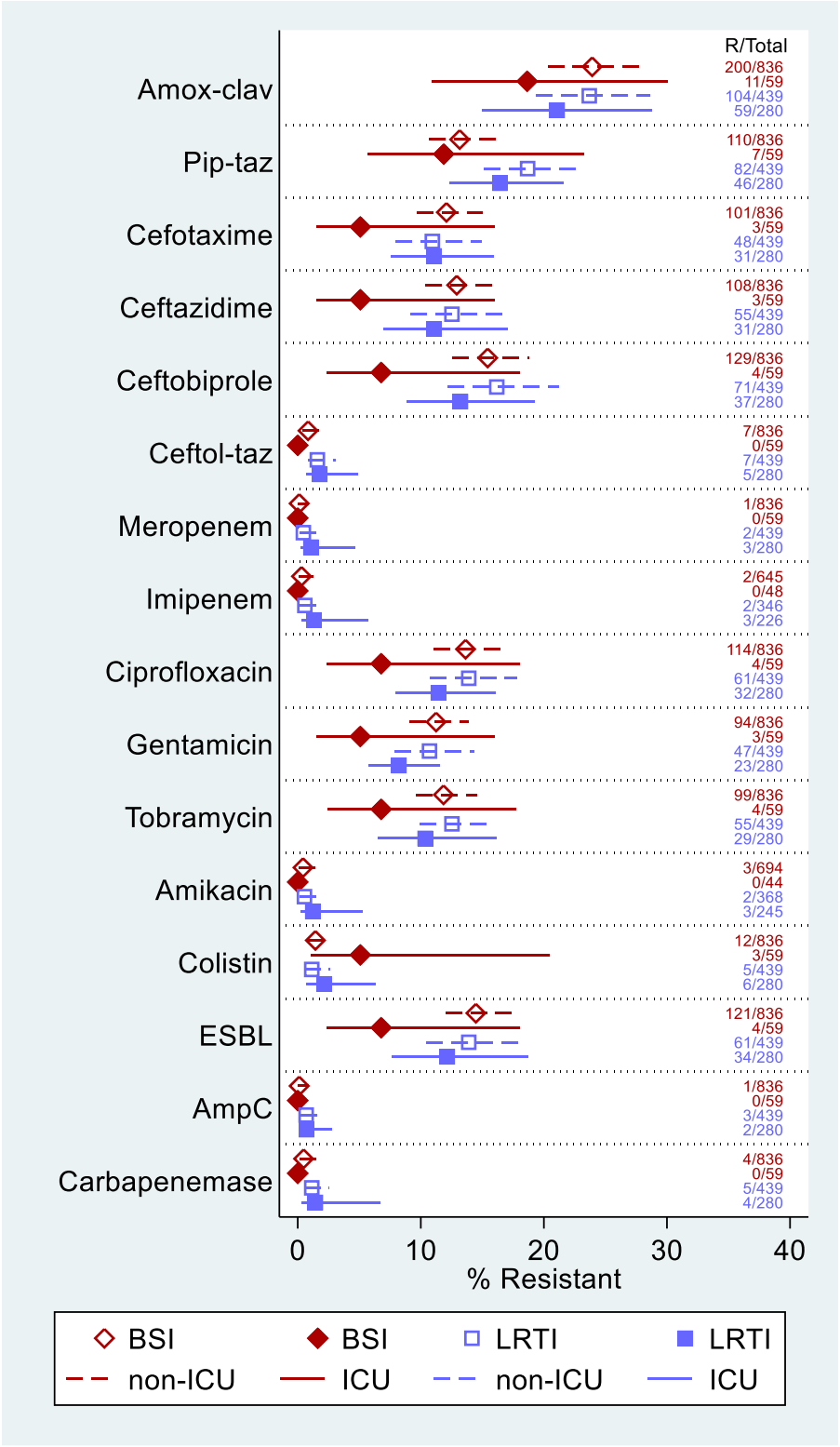
Key: Pip/taz: piperacillin/tazobactam; ceftol/taz: ceftolozane/tazobactam; caz/avi: ceftazidime/avibactam; imi/rel: imipenem/relebactam. This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

**Figure 4A.** Rates of resistance (with 95% CI) among *Escherichia coli* from bloodstream (BSI) and respiratory infections (LRTI), from patients in ICU versus non-ICU



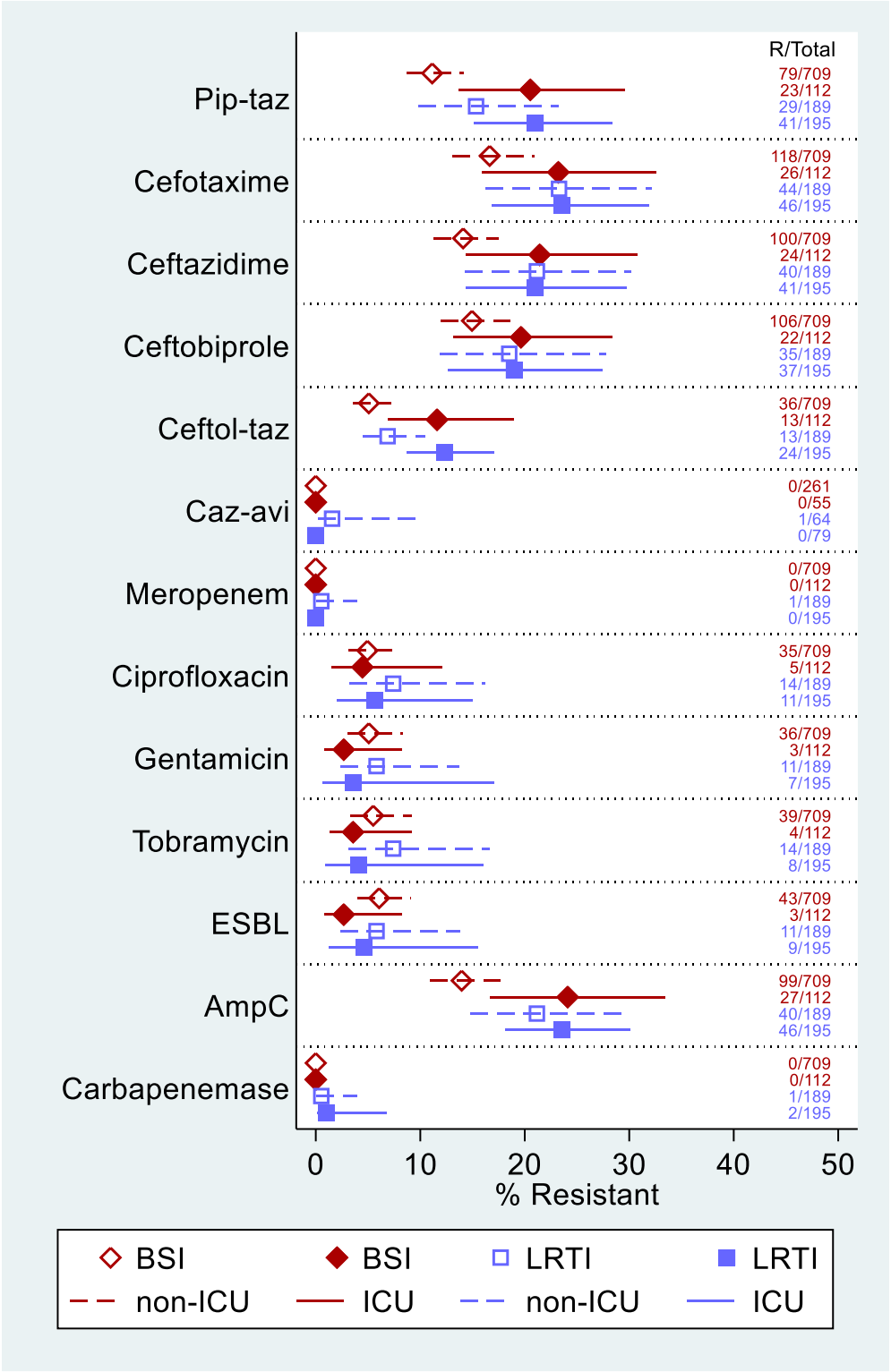
Key: Amox/clav: amoxicillin/clavulanate; pip/taz: piperacillin/tazobactam. Not shown: Amoxicillin (to avoid compressing scale): resistance rates were as follows: 63%, BSI non-ICU; 71%, BSI ICU; 78%, LRTI non-ICU, and 67%, LRTI ICU; ceftolozane/tazobactam, ceftazidime/avibactam, imipenem, imipenem/relebactam, ertapenem, and colistin (<1% resistant in all categories). This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

**Figure 4B**. Rates of resistance (with 95% CI) among *Klebsiella pneumoniae* from bloodstream (BSI) and respiratory infections (LRTI), from patients in ICU versus non-ICU



Key: Amox/clav: amoxicillin/clavulanate; pip/taz: piperacillin/tazobactam; ceftol/taz: ceftolozane/tazobactam. Not shown: ceftazidime/avibactam and imipenem/relebactam (<1% resistant in all categories). This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

**Figure 4C**. Rates of resistance (with 95% CI) among isolates of *Enterobacter cloacae* complex from bloodstream (BSI) and respiratory infections (LRTI), from patients in ICU versus non-ICU



Key: Pip/taz: piperacillin/tazobactam; ceftol/taz: ceftolozane/tazobactam; caz/avi: ceftazidime/avibactam. Not shown: imipenem, imipenem/relebactam, and amikacin (<1% resistant in all categories). This figure appears in colour in the online version of *JAC* and in black and white in the printed version of *JAC*.

582 **Table 2**. Risk ratios for resistance in LRTI isolates compared with BSI isolates

583 among Gram-positive and Gram-negative bacteria

| Organism and antimicrobial | Risk ratio for resistance: LRTI versus BSI (95% CI) | | | P-values | |
|---|---|---|---|---|---|
| ***S. pneumoniae*** | *Overall*[1] | *non–ICU*[2] | *ICU*[3] | *Overall*[4] | *Interact*[5] |
| Penicillin 0.06[6] | 2.14 (1.70–2.71) | 2.20 (1.72–2.82) | 1.31 (0.41–4.13) | <0.001 | 0.387 |
| Amoxicillin | 2.82 (1.31–6.09) | 3.04 (1.42–6.52) | 0.93 (0.49–1.80) | 0.008 | 0.840 |
| Erythromycin | 2.98 (2.47–3.58) | 3.04 (2.54–3.65) | 1.87 (0.65–5.35) | <0.001 | 0.244 |
| Tetracycline | 2.07 (1.67–2.57) | 2.13 (1.71–2.64) | 0.93 (0.40–2.18) | <0.001 | 0.876 |
| ***S. aureus*** | *Overall*[1] | *non–ICU*[2] | *ICU*[3] | *Overall*[4] | *Interact*[5] |
| *mecA* | 1.75 (1.27–2.40) | 1.82 (1.30–2.53) | 1.32 (0.66–2.63) | 0.001 | 0.404 |
| Clindamycin | 1.21 (0.96–1.52) | 1.35 (1.09–1.68) | 0.61 (0.38–1.00) | 0.109 | 0.002 |
| Erythromycin | 1.27 (1.04–1.56) | 1.41 (1.16–1.72) | 0.70 (0.45–1.09) | 0.021 | 0.004 |
| Ciprofloxacin | 1.32 (1.00–1.74) | 1.36 (1.03–1.80) | 1.06 (0.60–1.86) | 0.053 | 0.377 |
| Tetracycline | 1.36 (0.88–2.08) | 1.36 (0.86–2.15) | 1.33 (0.64–2.75) | 0.164 | 0.949 |
| Fusidic Acid | 0.99 (0.76–1.29) | 1.05 (0.82–1.34) | 0.75 (0.42–1.34) | 0.935 | 0.236 |
| Gentamicin | 0.89 (0.46–1.70) | 1.02 (0.50–2.09) | 0.31 (0.04–2.21) | 0.715 | 0.303 |
| Rifampicin | 0.86 (0.23–3.18) | 1.22 (0.38–3.92) | 0.23 (0.02–2.66) | 0.822 | 0.220 |

584

| Organism and antimicrobial | Risk ratio for resistance: LRTI versus BSI (95% CI) | | | P–values | |
|---|---|---|---|---|---|
| ***P. aeruginosa*** | *Overall*[1] | *non–ICU*[2] | *ICU*[3] | *Overall*[4] | *Interact*[5] |
| Pip/taz | 3.09 (2.19–4.36) | 3.59 (2.36–5.47) | 1.47 (0.68–3.16) | <0.001 | 0.076 |
| Ceftazidime | 2.43 (1.36–4.34) | 2.74 (1.54–4.89) | 1.29 (0.40–4.18) | 0.003 | 0.240 |
| Meropenem | 2.66 (1.63–4.34) | 2.95 (1.59–5.48) | 1.83 (0.67–4.97) | <0.001 | 0.478 |
| Imipenem | 2.62 (1.88–3.67) | 2.79 (1.90–4.10) | 1.95 (0.98–3.87) | <0.001 | 0.390 |
| Ciprofloxacin | 2.31 (1.75–3.04) | 2.45 (1.81–3.32) | 1.49 (0.86–2.58) | <0.001 | 0.144 |
| Tobramycin | 2.30 (1.05–5.05) | 3.10 (1.33–7.21) | 0.93 (0.33–2.59) | 0.038 | 0.052 |
| Amikacin | 1.88 (0.41–8.58) | 2.41 (0.47–12.36) | 0.86 (0.09–7.98) | 0.413 | 0.453 |
| ***E. coli*** | *Overall*[1] | *non–ICU*[2] | *ICU*[3] | *Overall*[4] | *Interact*[5] |
| Amoxicillin | 1.22 (1.16–1.29) | 1.25 (1.19–1.31) | 0.94 (0.83–1.07) | <0.001 | <0.001 |
| Amox/clav | 1.41 (1.29–1.55) | 1.47 (1.35–1.59) | 0.95 (0.73–1.23) | <0.001 | 0.001 |
| Pip/taz | 2.55 (1.77–3.68) | 2.86 (2.01–4.06) | 1.15 (0.59–2.21) | <0.001 | 0.008 |
| Cefotaxime | 1.27 (0.98–1.64) | 1.36 (1.04–1.77) | 0.68 (0.35–1.32) | 0.065 | 0.074 |
| Ceftazidime | 1.26 (0.96–1.67) | 1.33 (0.99–1.77) | 0.82 (0.40–1.66) | 0.099 | 0.229 |
| Ceftobiprole | 1.40 (1.08–1.82) | 1.53 (1.18–1.98) | 0.66 (0.38–1.14) | 0.01 | 0.007 |
| Ciprofloxacin | 1.15 (0.97–1.37) | 1.24 (1.03–1.49) | 0.62 (0.36–1.08) | 0.099 | 0.032 |

| | | | | | |
|---|---|---|---|---|---|
| Gentamicin | 1.11 (0.90–1.36) | 1.22 (0.98–1.52) | 0.53 (0.27–1.02) | 0.339 | 0.028 |
| Tobramycin | 1.08 (0.87–1.33) | 1.20 (0.97–1.47) | 0.44 (0.25–0.79) | 0.505 | 0.002 |
| ESBL | 1.37 (1.04–1.81) | 1.47 (1.12–1.94) | 0.71 (0.39–1.31) | 0.026 | 0.031 |
| AmpC | 2.50 (1.51–4.16) | 2.89 (1.77–4.73) | 0.95 (0.33–2.71) | <0.001 | 0.035 |
| ***K. pneumoniae*** | *Overall*[1] | *non–ICU*[2] | *ICU*[3] | *Overall*[4] | *Interact*[5] |
| Amox/Clav | 1.01 (0.81–1.25) | 0.99 (0.79–1.24) | 1.13 (0.61–2.09) | 0.957 | 0.682 |
| Pip/taz | 1.42 (1.07–1.87) | 1.42 (1.07–1.89) | 1.38 (0.64–3.00) | 0.014 | 0.951 |
| Cefotaxime | 0.99 (0.73–1.34) | 0.91 (0.66–1.24) | 2.18 (0.66–7.24) | 0.942 | 0.132 |
| Ceftazidime | 1.04 (0.78–1.39) | 0.97 (0.71–1.32) | 2.18 (0.64–7.43) | 0.785 | 0.188 |
| Ceftobiprole | 1.10 (0.84–1.45) | 1.05 (0.79–1.39) | 1.95 (0.68–5.57) | 0.468 | 0.238 |
| Ciprofloxacin | 1.07 (0.80–1.42) | 1.02 (0.76–1.37) | 1.69 (0.59–4.84) | 0.655 | 0.350 |
| Gentamicin | 1.00 (0.73–1.36) | 0.95 (0.67–1.34) | 1.62 (0.49–5.28) | 0.989 | 0.406 |
| Tobramycin | 1.10 (0.84–1.44) | 1.06 (0.80–1.40) | 1.53 (0.55–4.21) | 0.507 | 0.479 |
| Colistin | 0.63 (0.23–1.76) | 0.79 (0.31–2.05) | 0.42 (0.07–2.42) | 0.380 | 0.535 |
| ESBL | 1.02 (0.78–1.33) | 0.96 (0.73–1.27) | 1.79 (0.60–5.32) | 0.893 | 0.255 |
| ***E. cloacae*** [7] | *Overall*[1] | *non–ICU*[2] | *ICU*[3] | *Overall*[4] | *Interact*[5] |
| Pip/taz | 1.21 (0.85–1.72) | 1.38 (0.88–2.15) | 1.02 (0.68–1.55) | 0.281 | 0.318 |
| Cefotaxime | 1.25 (0.95–1.66) | 1.40 (1.01–1.94) | 1.02 (0.70–1.48) | 0.112 | 0.201 |

| | | | | | |
|---|---|---|---|---|---|
| Ceftazidime | 1.29 (0.92–1.82) | 1.50 (1.04–2.16) | 0.98 (0.64–1.50) | 0.138 | 0.086 |
| Ceftobiprole | 1.14 (0.78–1.65) | 1.24 (0.81–1.89) | 0.97 (0.64–1.46) | 0.507 | 0.296 |
| Ceftol/tazo | 1.20 (0.77–1.89) | 1.35 (0.76–2.40) | 1.06 (0.63–1.80) | 0.424 | 0.490 |
| Ciprofloxacin | 1.44 (0.72–2.88) | 1.50 (0.81–2.78) | 1.26 (0.30–5.33) | 0.305 | 0.805 |
| Gentamicin | 1.18 (0.48–2.91) | 1.15 (0.51–2.55) | 1.34 (0.19–9.34) | 0.716 | 0.853 |
| Tobramycin | 1.30 (0.56–3.06) | 1.35 (0.63–2.90) | 1.15 (0.21–6.23) | 0.541 | 0.828 |
| ESBL | 1.09 (0.50–2.37) | 0.96 (0.46–2.00) | 1.72 (0.32–9.18) | 0.836 | 0.413 |
| AmpC | 1.28 (0.98–1.67) | 1.52 (1.09–2.11) | 0.98 (0.70–1.37) | 0.067 | 0.081 |

585 RR values >1 suggest that resistance is more prevalent in LRTI than BSI, and vice
586 versa for values <1.

587 Key: Amox/clav: amoxicillin/clavulanate acid; ceftol/taz: ceftolozane/tazobactam;
588 pip/taz: piperacillin/tazobactam; mecA: isolates positive for the *mec*A gene,
589 representing MRSA.

590 [1] The overall RR for LRTI is adjusted for ICU *assuming that the effects of LRTI and*
591 *ICU are independent* i.e., that the RR for LRTI is the same in ICU as in other
592 settings.

593 [2] The non-ICU RR is for comparison of LRTI with BSI in treatment settings other than
594 ICU.

595 [3] The ICU RR is for comparison of LRTI with BSI in intensive/critical care settings.

[4] The overall P-value refers to the overall RR. A low value gives evidence that the prevalence of resistance differs between LRTI and BSI (i.e., overall RR ≠1) after adjusting for ICU.

[5] The interaction P-value relates to a comparison of LRTI RRs between ICU and non-ICU. A low value gives evidence that the RR for LRTI differs between the two settings.

[6] Penicillin 0.06: Penicillin analysed at a ≥0.06 mg/L breakpoint for pneumococci (i.e., combining resistant and 'susceptible dose-dependent' categories).

[7] *E. cloacae* complex comprises *Enterobacter cloacae*, *E. asburiae*, *E. hormaechei*, *E. kobei*, *E. ludwigii* and *E. nimipressuralis*.

606 **Table 3.** Vaccine coverage and top five *Streptococcus pneumoniae* serotypes by

607 infection site and season

| Bloodstream | | | | | |
|---|---|---|---|---|---|
| | 2014<br>N=247 | 2015<br>N=244 | 2016<br>N=220 | 2017<br>N=208 | 2018<br>N=208 |
| Rank | Type (N) | Type (N) | Type (N) | Type (N) | Type (N) |
| 1 | 8 (43) | 8 (33) | 8 (39) | 8 (39) | 8 (36) |
| 2 | 22F (22) | 12F (26) | 12F (32) | 12F (19) | 12F (17) |
| 3 | 12F (20) | 22F (23) | 9N (19)[=3] | 3 (18) | 3 (16) |
| 4 | **15A** (19) | 9N (20) | 22F (19)[=3] | 10A (14) | 22F (14) |
| 5 | **19A** (16) | **19A** (19) | 3 (16) | **15A** (13) | 9N (13) |
| 13-valent vaccine % | 20.6 | 22.1 | 18.6 | 21.2 | 18.3 |
| 23-valent vaccine % | 68.6 | 80.1 | 80.5 | 75.7 | 72.6 |
| Respiratory | | | | | |
| | 2013–14<br>N=375 | 2014–15<br>N=429 | 2015–16<br>N=358 | 2016–17<br>N=345 | 2017–18<br>N=325 |
| Rank | Type (N) | Type (N) | Type (N) | Type (N) | Type (N) |
| 1 | **15A** (34) | **15A** (46) | 11A (38) | **15A** (31) | 3 (35) |
| 2 | 23B (26) | 11A (34) | **15A** (28) | 8 (28) | 11A (31) |
| 3 | 3 (22) | 23A (29) | 3 (22) | 3 (26) | **15A** (20) |
| 4 | 11A (21)[=4] | 3 (26) | 35F (20)[=4] | 11A (25) | 23B (19) |
| 5 | 23A (21)[=4] | 23B (21) | 10A (20)[=4] | **19F** (19) | 7C (18) |
| 13-valent vaccine % | 16.0 | 15.2 | 13.7 | 18.6 | 20.0 |
| 23-valent vaccine % | 45.3 | 46.6 | 54.9 | 53.2 | 52.3 |

608 Key: $^{=3}$ equal 3$^{rd}$ rank; $^{=4}$ equal 4$^{th}$ rank. **Bold** text indicates serotypes known to be

609 associated with high prevalence rates of multiresistance[22] (defined as resistance to

610 three or more classes of antimicrobial agent).