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

Findings: From 1998-2016, 5706 EC-BSIs occurred in 5215 patients, and 228376 EC-UTIs in 137075 patients. 1365(24%) EC-BSIs were nosocomial (onset >48h post-admission), 1863(33%) were community (>365 days post-discharge), 1346(24%) were quasi-community (31-365 days post-discharge), and 1132(20%) were quasi-nosocomial (≤30 days post-discharge). 1413(20%) EC-BSIs and 36270(13%) EC-UTIs were co-amoxiclav-resistant (41% and 30%, respectively, in 2016). Increases in EC-BSIs were driven by increases in community (10%/year (95% CI:7%-13%)) and quasi-community (8%/year (95% CI:7%-10%)) cases. Changes in EC-BSI-associated 30-day mortality were at most modest (p>0*03), and mortality was substantial (14-25% across

groups). By contrast, co-amoxiclav-resistant EC-BSIs increased in all groups (by 11%-19%/year, significantly faster than susceptible EC-BSIs, pheterogeneity<0*001), as did co-amoxiclav-resistant EC-UTIs (by 13%-29%/year, pheterogeneity<0*001). Co-amoxiclav use in primary-care facilities was associated with subsequent co-amoxiclav-resistant EC-UTIs (p=0*03) and all EC-UTIs (p=0*002).

Interpretation: Current increases in EC-BSIs in Oxfordshire are primarily community-associated, with high rates of co-amoxiclav resistance, nevertheless not impacting mortality. Interventions should target primary-care facilities with high co-amoxiclav usage.

Funding: National Institute for Health Research.

Trends in *Escherichia coli* bloodstream infection, urinary tract infections and antibiotic susceptibilities in Oxfordshire, 1998-2016: an observational study

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Abstract

Background: The incidence of *Escherichia coli* bloodstream infections (EC-BSIs), particularly those caused by antibiotic-resistant strains, is increasing in the UK and internationally. This is a major public health concern but the evidence base to guide interventions is limited.

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

Findings: From 1998-2016, 5706 EC-BSIs occurred in 5215 patients, and 228376 EC-UTIs in 137075 patients. 1365(24%) EC-BSIs were nosocomial (onset >48h post-admission), 1863(33%) were community (>365 days post-discharge), 1346(24%) were quasi-community (31-365 days post-discharge), and 1132(20%) were quasi-nosocomial (≤30 days post-discharge). 1413(20%) EC-BSIs and 36270(13%) EC-UTIs were co-amoxiclav-resistant (41% and 30%, respectively, in 2016). Increases in EC-BSIs were driven by increases in community (10%/year (95% CI:7%-13%)) and quasi-community (8%/year (95% CI:7%-10%)) cases. Changes in EC-BSI-associated 30-day mortality were at most modest (p>0·03), and mortality was substantial (14-25% across groups). By contrast, co-amoxiclav-resistant EC-BSIs increased in all groups (by 11%-19%/year, significantly faster than susceptible EC-BSIs, $p_{heterogeneity}$<0·001), as did co-amoxiclav-resistant EC-UTIs (by 13%-29%/year, $p_{heterogeneity}$<0·001). Co-amoxiclav use in primary-care facilities was associated with subsequent co-amoxiclav-resistant EC-UTIs (p=0·03) and all EC-UTIs (p=0·002).

Interpretation: Current increases in EC-BSIs in Oxfordshire are primarily community-associated, with high rates of co-amoxiclav resistance, nevertheless not impacting mortality. Interventions should target primary-care facilities with high co-amoxiclav usage.

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Research in context

Evidence before this study

We searched PubMed for publications from inception up until October 26, 2017, with the terms "*Escherichia coli*", "*E. coli*", "bacteraemia", "bloodstream infection", restricting the search to English language articles, and also reviewed references from retrieved articles. *Escherichia coli (E. coli)* is the most common cause of bloodstream infection, and the incidence of *E.* coli bloodstream infection, and particularly antibiotic-resistant infections, is increasing in the UK and internationally. Although the UK government aims to reduce healthcare-associated *E. coli* bloodstream infection, there is only limited evidence to inform appropriate interventions.

Added value of this study

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

- Increases in the incidence of *E. coli* bloodstream infections were driven mainly by non-hospital-associated cases; however, neither patients with previous urinary tract infections nor having previously had urine specimens sent from catheters appeared to be driving the increases

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

- Higher co-amoxiclav use in primary care was associated with higher rates of both co-amoxiclav-resistant *E. coli* urinary tract infections and *E. coli* urinary tract infections overall, supporting drives to reduce broad-spectrum and inappropriate antibiotic use in primary care

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

Implications of all available advice

This suggests that government strategies to effectively reduce *E. coli* bloodstream infections should target community settings, as well as healthcare-associated settings. The absence of an increased mortality signal suggests that co-amoxiclav resistant *E. coli* infections are either being successfully treated by dual empiric therapy in severe cases (e.g. with concomitant gentamicin), can be "rescued" once isolate susceptibilities become available, or currently deployed phenotypic susceptibility testing breakpoints do not adequately correlate with clinical outcome.

Introduction

Escherichia coli is a major cause of bloodstream infection (BSI)[1] and a critical antimicrobial resistance (AMR) concern;[2] rates are rising worldwide.[3] For example, *E. coli* bloodstream infections (EC-BSIs) reported (voluntarily) to Public Health England rose by 44% between 2003-2011;[4] a similar 68% increase between 1999-2011 was seen in Oxfordshire, UK.[5] Mandatory reporting was introduced in England in July 2011*;* a further 28% increase in EC-BSI incidence occurred by July-September 2016, to 78·8 cases/100,000 population.[6]

In the UK, as elsewhere, most (>70%) EC-BSIs are identified within two days of hospital admission.[6] However, the impact of previous hospital-exposure on trends in EC-BSI has not been comprehensively investigated, with only two relevant previous studies, one in the Calgary Health Region 2000-2006[7], and another in Oxfordshire in 2011[5] considering only whether blood cultures were taken outside or inside hospital. EC-BSI source may also differ by hospital-exposure. In a recent study, ~50% of UK EC-BSIs were considered most likely due to urinary tract infections (UTIs);[8] gastrointestinal foci are however more common in inpatients.[6]

30-day all-cause mortality following EC-BSI is ~16%;[9] and could rise given the impact of increasing AMR on treatment options.[2] In Oxfordshire, EC-BSI incidence rises through 2011 were essentially confined to ciprofloxacin-, co-amoxiclav-, cefotaxime- and/or aminoglycoside-resistant organisms.[5] The reasons for rising EC-BSI more generally are unclear, with increased antibiotic usage implicated in some, but not all, studies.[10–15] In the UK and internationally, co-amoxiclav is used as empiric treatment for many infection syndromes and for prophylaxis.[10,16] Hence, trends in co-amoxiclav resistance are particularly important.

We therefore aimed to investigate possible drivers of changes in EC-BSI incidence and antibiotic susceptibilities in Oxfordshire over the last two decades, while stratifying for hospital-exposure. We hypothesized that increases may be due to features of the at-risk population (therefore exploring demographics, recurrent infections, increased ascertainment), healthcare-history (previous urine cultures, and specifically previous catheter specimens, previous admission diagnoses, antibiotic usage), and/or the bacteria (exploring mortality/severity, AMR burden).

Methods

The Infections in Oxfordshire Research Database (IORD)[17] records all admissions to the Oxford University Hospitals National Health Service Foundation Trust (OUH), Oxfordshire, UK, from April 1997, linked by patient with microbiology and biochemistry/haematology results. The four hospitals within OUH provide all acute care, microbiology and pathology services in the region (~680,000 individuals). Out-of-hospital mortality was determined by updates from a national information system recording all UK deaths. IORD has generic Research Ethics Committee and Health Research Authority approvals (14/SC/1069, ECC5-017(A)/2009). Data on antibiotic prescribing and numbers of registered patients for each general practice were obtained from the Health and Social Care Information Centre (available January 2011-December 2016 only).

The primary study outcome was EC-BSI, defined as *E. coli* isolated from blood cultures taken 01/Jan/1998-31/Dec/2016 inclusive, including polymicrobial cultures (13%), without age restriction and de-duplicated within 14-days of each index positive.[18] For context we also analysed *E. coli* UTIs (EC-UTIs), defined as pure culture from urine of $>10^4$ colony-forming-units/ml, de-duplicated within 90-days. We classified EC-BSIs/EC-UTIs as 'nosocomial' if samples were taken >48h post-admission until discharge.[19] All other EC-BSIs/EC-UTIs were classified as 'community', 'quasi-community' or 'quasi-nosocomial' if the last hospital discharge was >1 year, 31-365 days, or 0-30 days previously. We also calculated incidences of first ever and recurrent EC-BSIs. See Supplementary Methods for further details.

To account for the contribution of ageing and population growth, we standardised incidence for age and sex against the 1998 Oxfordshire population distribution (estimates from the UK Office for National Statistics). To assess ascertainment, we considered the incidence of blood/urine cultures, regardless of result, and also additionally standardised for culture rates.

As a proxy for changes in bacterial virulence, we considered 30-day mortality after, and levels of monocytes, neutrophils, lymphocytes, C-reactive protein (CRP), creatinine and urea at (closest value within [-2,+2] days) sample collection. To investigate AMR burden, which might also affect treatment outcomes, we assessed resistance to drugs consistently tested throughout the study period. Susceptibility testing was performed using disk-diffusion to 31/Jan/2013, then by microbroth dilution (BD Phoenix™ Automated Microbiology System, Beckton Dickinson, Franklin Lakes, NJ, USA) (see Supplementary Methods).

Guidelines recommend empirical treatment for uncomplicated UTIs and for urine samples to be sent to the laboratory only from individuals with clinical treatment failure, frequent or recurrent UTI or with a possibly resistant infection.[16] To investigate this patient group, we first classified EC-BSIs according to whether the patient had ever had an EC-UTI identified by the laboratory ≥3 days previously. To investigate the contribution of UTI around the time of the EC-BSI, including where *E. coli* was not isolated, we classified EC-BSIs as 'likely urine-associated' (urine sample taken 3-30 days previously; EC-UTI or mixed growth/negative but UTI suspected clinically from request codes), 'urosepsis' (defined as for likely urine-associated BSIs but urine samples within (-3,+2] days of the EC-BSI), 'unlikely urine-associated' (UTI with non-*E. coli* pathogen or no urine sample), or 'unknown' (other) (details in Supplementary Methods). To investigate the contribution of catheters, we classified EC-BSIs according to whether the patient had ever had a catheter urine specimen submitted up to and including the day of blood collection (regardless of result).

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

Statistical analysis

Incidence was modelled using negative binomial regression of counts per month, binary outcomes using poisson regression of monthly counts (to estimate analogous rate ratios) and test results using median quantile regression of absolute values against sample date. Test results and mortality were adjusted for age and sex. Changes in trends in these outcomes were estimated using iterative sequential regression (Supplementary Methods),[20] and compared between outcomes using stacked regression.[21] To estimate associations with primary care co-amoxiclav prescribing, co-amoxiclav defined-daily-doses (DDDs) per 1000 registered patients in the previous or current year and general practice were included as explanatory variables (Supplementary Methods).

Analyses were conducted using R 3.2.2, and STATA 14.1 for stacked regression and probability weighted analyses.

Results

After 14-day de-duplication, from 1998-2016 5706 EC-BSIs occurred in 5215 patients (i.e. 9% recurrences (relapse and/or reinfection)). Recurrences occurred a median(IQR) 144(39-577) days apart: of 391 patients with recurrences, 324(83%) had one and 52(13%) had two (range 1-8). Overall incidence increased year-on-year (annual incidence rate ratio (IRR)=1·06 (95% CI 1·05-1·06)). For most EC-BSI (5393(95%)) patients were admitted to OUH before or within the 24h following the blood culture (remainder mostly taken in emergency departments or community hospitals). Only 1365(24%) EC-BSIs were 'nosocomial' (≥48h post-admission). A further 1132(20%) were 'quasi-nosocomial' (discharged up to 30 days previously), 1346(24%) were 'quasi-community' (discharged 31-365 days previously) and 1863(33%) were 'community' cases (discharged >1 year previously or never previously admitted to OUH).

Incidence trends for EC-BSIs varied substantially with hospital-exposure (**Figures 1A&2A**, **Supplementary Table 1**), with overall increases clearly driven by community and quasi-community hospital-exposure groups, and no evidence of different incidence trends between these two groups in 2016 ($p_{heterogeneity}$=0·27). By contrast, quasi-nosocomial and nosocomial EC-BSIs increased more slowly. Considering only the first EC-BSI per patient or subsequent EC-BSIs (**Figure 2A**, **Supplementary Figure 1**) gave broadly similar results. Year-on-year increases in first EC-BSI became smaller (but still significant) the more recent the hospital exposure. Quasi-community recurrent EC-BSI were rising faster than first EC-BSIs ($p_{heterogeneity}$<0·001) and the stable current trend in all quasi-nosocomial BSIs appeared to be driven by reduced recurrences in this group.

After 90-day de-duplication, 228376 EC-UTIs occurred in 137075 patients (i.e. 40% recurrences (relapse/re-infection)). Recurrences occurred a median(IQR) 457(200-1119) days apart: of the 41371(30%) patients with recurrences, 22011(53%) had one and

8742(21%) had two (range 1-33). 12898(9%) patients had two EC-UTI within six months. EC-UTIs were predominantly community (160359,70%), and less commonly quasi-community (44283,19%), quasi-nosocomial (12764,6%) or nosocomial (10970,5%) in origin. Rates of EC-UTI increased over 1998-2016 in community, quasi-community and quasi-nosocomial groups, although current trends were fairly stable, but declined significantly in the nosocomial group (**Figure 1B&2B**). Furthermore, increases were accounted for entirely by substantial increases in recurrent UTI episodes, with decreasing overall trends in first EC-UTI per patient (**Supplementary Figure 2**).

In 2016, therefore, recurrences accounted for at least half of community, quasi-community and quasi-nosocomial EC-UTIs, and around a fifth of quasi-community and quasi-nosocomial EC-BSIs (**Supplementary Table 2**).

Impact of population and sampling on EC-BSI

Blood culture submission rates increased substantially from 1998-2016 for community/quasi-community/quasi-nosocomial groups (**Figure 2A**, **Supplementary Figure 3**), raising the possibility that observed increases in EC-BSIs were driven by increases in the use of blood cultures as a diagnostic test. However, there was no suggestion that the indications for blood culture changed with time: neutrophils and CRP when cultures were taken did not meaningfully change and there was no change in the 30-day mortality post blood culture sampling (**Supplementary Figure 4**). Further, increases in community blood culture submission rates were significantly smaller than increases in community EC-BSIs ($p<0{\cdot}001$, **Figure 2A**). Standardising for age and sex explained only 10-26%, and standardising additionally for number of blood cultures taken 9-28%, of the increase in overall or first-per-patient EC-BSIs, with the greatest percentage explained in nosocomial EC-BSIs and the least in community EC-BSIs (**Supplementary Tables 3,4**). In contrast, urine sample submission was more stable over time (**Supplementary Figure 5**).

Disease severity of EC-BSIs

30-day mortality following EC-BSI declined slightly (IRR=0·98) in the nosocomial (p=0·03) and quasi-nosocomial (p=0·06) groups, but there was no evidence for changes in quasi-community and community groups (p>0·21, adjusting for age and sex, **Supplementary Figure 6**). Mortality was substantial at 25%, 30%, 16% and 14% across the groups, respectively. Changes in haematology/biochemistry test results over time were small and/or non-significant (**Supplementary Figure 6**), and did not indicate that less severe infections were being identified, or that there were any changes in pathogen virulence.

Impact of previous illness on EC-BSI

1755(31%) EC-BSI occurred in patients with an EC-UTI ≥3 days previously (median(IQR) 213(43-918) days previously). However, incidence trends were broadly similar for EC-BSIs with or without EC-UTIs ≥3 days previously, although quasi-community EC-BSIs were rising particularly fast in those with previous EC-UTIs ($p_{heterogeneity}$<0·001, **Figure 2A**, **Supplementary Figure 7**). We next explored whether EC-BSI increases were associated with past symptomatic urinary disease, including those without positive urine cultures. Considering urine samples/results taken within 30 days before the EC-BSI, and incorporating information on mixed growth and request codes, only 760(13%) EC-BSIs were 'likely urine-associated', with 1613(28%) 'urosepsis', 1613(28%) 'unlikely urine-associated' (of which 181[11%] had a contemporaneous urine specimen positive for another pathogen), and 1720(30%) unknown. However, the relative proportions of these did not vary substantially over time (**Figure 3**), suggesting no specific subgroup was associated with incidence increases. Percentages of EC-BSIs with a previous catheter urine specimen (CSU) increased with recency of hospital-exposure, being present in 365(20%) community, 364(32%) quasi-community, 541(40%), quasi-nosocomial, 584(43%) nosocomial. However,

incidence trends were broadly similar for EC-BSIs with or without a previous CSU (**Figure 2A**, **Supplementary Figure 8**), although quasi-nosocomial EC-BSIs were rising particularly fast in those with previous CSUs ($p_{heterogeneity}$<0·001), while increases in nosocomial EC-BSIs were restricted to those without previous CSUs ($p_{heterogeneity}$=0·03).

For the 1132 quasi-nosocomial EC-BSI patients discharged in the preceding 30 days, the most common reasons for the antecedent admission were malignancy (395,35%), gastrointestinal disorders (177,16%), and renal/urological disorders (164,14%) (**Supplementary Table 5**), with no major temporal variability (**Supplementary Figure 9A**). There was no evidence that the antecedent admission was shorter than the quasi-community group (median 2·0 (IQR:0·3-7·9) days vs 2·3 (0·3-8·2) respectively, ranksum p=0·15). There was strong evidence that quasi-nosocomial EC-BSIs with a UTI diagnostic code or an infectious primary diagnostic code for the antecendent admission were rising faster than those without (heterogeneity p=0·005, p<0·001 respectively, **Supplementary Figure 9B&C**), but these still comprised <25% of quasi-nosocomial EC-BSIs.

Antimicrobial susceptibility

Exploring the possibility that EC-BSI increases were associated with the development of AMR, the only EC-BSI antibiotic-resistant phenotype that consistently increased across all groups was co-amoxiclav (p<0·001; **Figures 2A&4**), with 212(41%) of 515 EC-BSIs in 2016 being co-amoxclav resistant (**Supplementary Table 6**). Co-amoxiclav-resistant EC-BSIs increased significantly faster than co-amoxiclav-susceptible EC-BSIs ($p_{heterogeneity}$<0·001), but community and quasi-community co-amoxiclav-susceptible EC-BSIs were still increasing significantly in 2016. Most (942/1412, 67%) co-amoxiclav-resistant EC-BSIs remained susceptible to gentamicin and ciprofloxacin (**Figure 4**).

Increases in other antibiotic-resistant EC-BSIs were most notable in the community and quasi-community groups, with significant year-on-year increments in all but trimethoprim-

resistant EC-BSIs, which remained stable in these groups (**Supplementary Figure 10**). Co-amoxiclav-resistant EC-UTIs also rose consistently and significantly regardless of healthcare-exposure, but trends were more variable for other antibiotics (**Supplementary Figure 11**). In 2016, 3921/13792(28%) EC-UTIs were co-amoxiclav-resistant.

Given the substantial increase in co-amoxiclav resistant EC-BSIs, we investigated whether there was any evidence of differential severity in susceptible and resistant cases. There was no strong evidence that co-amoxiclav-resistant EC-BSIs were associated with higher neutrophil counts in any hospital-exposure group (p>0·04, adjusting for age and sex), or that neutrophil counts were changing differently over time compared with co-amoxiclav-susceptible EC-BSI ($p_{heterogeneity}$>0·67; **Supplementary Figure 12**). Mortality was higher (32% (95% CI 13%-46%); p=0·002, adjusting for age and sex) for co-amoxiclav-resistant vs co-amoxiclav-susceptible nosocomial EC-BSIs, but not community/quasi-community/quasi-nosocomial EC-BSIs (p>0·48), and mortality did not change differently over time in any group ($p_{heterogeneity}$>0·35; **Supplementary Figure 12, Figure 2C**).

Over financial years 2003-2014, the strongest associations with nosocomial co-amoxiclav-resistant EC-BSIs were with hospital co-amoxiclav (cross-correlation 0·75) and third-generation cephalosporin (0·80) use (**Supplementary Table 7**). Community prescribing data was only available from 2011, and co-amoxiclav-resistant EC-BSIs were too few to consider relationships with co-amoxiclav use. However, from 2012-2016, primary care facilities prescribing more co-amoxiclav in the previous year had higher rates of subsequent co-amoxiclav-resistant-community-EC-UTIs (IRR (per 100DDD higher)=1·05 (95% CI 1·02-1·08) p=0·003, **Figure 5**), and co-amoxiclav use in the previous year was a stronger predictor of current rates than co-amoxiclav use in the current year (p=0.003 vs p=0.64). Co-amoxiclav use in the current year was a stronger predictor of all community-EC-UTIs (p=0.01 vs p=0.11) and urine specimen submission (p=0.0001 vs p=0.006), and was associated with higher rates of both (IRR=1·02 (1·00-1·04) p=0·01 and 1.02 (1·01-1·03)

p=0·002 respectively). Co-amoxiclav use was not associated with the proportions of *E. coli*-positive specimens (p=0·68). Similar results were seen across all samples regardless of hospital-exposure group (**Supplementary Figure 13**), and also when adjusting instead for the proportion aged over 65 and male in 2017 per practice.

Discussion

We have explored potential explanations for continuing increases in EC-BSI in Oxfordshire over 19 years using extensive, routinely-collected data, including diagnostic codes and laboratory/microbiology results. Incidence varied dramatically according to hospital-exposure, with increases notably being driven by community/quasi-community cases. This is important given a new National Health Service ambition aiming to reduce Gram-negative BSIs by targeting healthcare-associated cases; previous successful campaigns to reduce methicillin-resistant *Staphylococcus aureus* (MRSA) BSI and *Clostridium difficile* infections also focussed on nosocomial risk factors. Our data suggest that defining appropriate strategies targeting community/quasi-community associated EC-BSIs might have a greater impact. Crucially, co-amoxiclav-resistant EC-BSIs rose significantly faster than co-amoxiclav-susceptible EC-BSIs, regardless of hospital-exposure, with the greatest number of co-amoxiclav-resistant EC-BSIs in 2016 being community/quasi-community EC-BSIs. The association between primary care co-amoxiclav prescribing and co-amoxiclav-resistant EC-UTIs implicates co-amoxiclav prescribing as a key driver behind these rises. Co-amoxiclav is one of the most commonly prescribed antibiotics nationally in both the community and hospitals.[16,22] Our findings indicate that reduced prescribing of co-amoxiclav could reduce the selection pressure for EC-BSI. Despite co-amoxiclav being used for empiric BSI treatment, there were no clinically important changes in mortality.

EC-BSI is generally considered ‘community-acquired’ although the true apportionment to community- vs healthcare-associated categories remains unclear, and there are differing definitions of healthcare-associated BSI.[6,23] By linking to previous hospital admissions, one major study strength is that we could identify that incidence trends for non-nosocomial EC-BSIs varied significantly by proximity to hospital-exposure. Blood sample submission also increased significantly, potentially increasing ascertainment of ‘mild’ cases. However, blood cultures are key to the assessment of unwell patients whenever infection is suspected, and there were no clinically important changes in EC-BSI-associated severity at presentation or

mortality, despite substantially increasing incidence, suggesting major ascertainment bias is unlikely.

The increasing trend in nosocomial EC-BSI was significantly smaller than for community/quasi-community EC-BSI in Oxfordshire, as observed nationally.[8] Multiple infection control interventions were rolled out in UK hospitals from 2005-2010[24,25] in response to MRSA/*C. difficile*, and horizontal components of these initiatives could have contributed to these lower nosocomial rates. Consistent with this, increases in hospital-onset BSI caused by Gram-negative bacilli reversed after a MRSA Prevention Initiative was introduced in the US, while community-acquired incidence did not change.[26]

Epidemiological differences between *E. coli* , MRSA and *C. difficile* also highlight the potential need for different interventions, particularly in primary care.[6] In particular, recurrences explain relatively little of the ongoing increases in EC-BSIs, and both co-amoxiclav-resistant and co-amoxiclav-susceptible EC-BSI are rising. Overall, 42% of EC-BSI appeared to be more likely amenable to urinary-focussed intervention, similar to a England-wide study that found 51% of EC-BSIs had an underlying urogenital tract focus, with the largest independent risk factor for these being treatment for UTI in the prior four weeks.[8] In our study, 13% of EC-BSIs were likely urine-associated and 28% presented as urosepsis; the first group may be most tractable for prevention but was smallest in both community and quasi-community EC-BSI, whereas urosepsis was the largest. One limitation is lack of data on visits to general practice; therefore, some patients may have had UTI symptoms and been treated empirically without a urine culture being sent, although successfully treated UTIs should not cause bacteraemia. Guidelines recommend urine samples be submitted from individuals with clinical treatment failure, frequent or recurrent UTI or with a possibly resistant infection;[16] therefore bacteraemias due to UTI treatment failure should be ascertained within our data. It is hypothesised that much of the burden of EC-BSIs, and especially the rising incidence (in all hospital-exposure groups), arises from poor urinary

catheter care. However, only 20% and 30% of the community and quasi-community groups, where incidence is increasing fasted, had a previous CSU, and there was no evidence that incidence was increasing faster in those with a previous CSU versus without. One key limitation is that we did not have records of the presence of a catheter, but only urine specimens recorded as being taken from a catheter, arguing that if a catheter was present and causing infection, a specimen would likely have been taken from it at some time.

Interestingly, there was strong evidence that quasi-nosocomial EC-BSIs with UTI or infectious diagnostic codes in the previous admission were rising faster than those without. This may reflect underlying predisposition to infection (e.g. chronic illnesses), or that prior antibiotic use adversely affects a patient's microbiota potentially leading to colonisation/overgrowth by more pathogenic *E. coli*, thus predisposing to EC-BSI.

A limitation of surveillance studies is changes in antimicrobial susceptibility testing methodology (here in February 2013). Whilst the proportion of isolates classified as resistant can vary by testing protocol,[27,28] crucially changes in co-amoxiclav resistance around this time occurred regardless of method (**Supplementary Figure 14**). Recent data suggest that broth dilution (BD-Phoenix) and the gold standard agar dilution have high agreement;[29] thus, rising rates of co-amoxiclav-resistant (as defined by EUCAST breakpoints) EC-BSI/EC-UTI are likely correct.

For the first time, we have shown that GP practices with higher co-amoxiclav prescribing rates were more likely to have patients diagnosed with co-amoxiclav resistant EC-UTIs. Similar associations between trimethoprim use and trimethoprim-resistant urine-associated EC-BSI have been reported in adult women in England.[15] Assessing usage-resistance associations is complicated, since changes in use of one antibiotic are generally accompanied by compensatory prescribing, and may be compounded by multi-drug resistance. Our results may therefore not be generalizable; for example, although the region

we studied is sizeable (~1% of the UK), we did not observe a uniform decrease in cephalosporin-resistant and quinolone-resistant EC-BSIs as seen in BSI caused by *Enterobacteriaceae*.[14] Such differences likely reflect a complex interplay of selection pressures.

A key limitation is that co-amoxiclav-resistant EC-BSI were too few over the period with contemporary prescribing data to investigate associations with antibiotic prescribing within the community. We were unable to assess associations between individual-patient antibiotic use (not available in the research database) and risk of resistant infections or between specific empiric regimens and outcome. However, there were no clinically important changes in mortality overall, by co-amoxiclav-susceptible/resistant phenotype, or by hospital-exposure across the study period. Co-amoxiclav remains our recommended first-line empiric treatment for most severe infections, so the substantial increase in incidence of co-amoxiclav-resistant bacteraemias suggests either that initial inappropriate treatment can be successfully rescued,[30] or that the current definition of co-amoxiclav breakpoints may be suboptimal.[31] Crucially, neither scenario supports a move towards broader empiric antibiotic treatment, consistent with prevailing antimicrobial stewardship messages.

In summary, on-going increases in EC-BSI were driven by community and quasi-community cases, and cannot be attributed only to increased recurrences or an aging population. Absence of changes in mortality and severity do not support ascertainment bias playing a major role, although this cannot be excluded. Whilst urinary foci are clearly important, at present the scope for intervening to prevent UTIs progressing to bacteraemia could be limited. Notably, higher co-amoxiclav use in primary care was associated with higher rates of both EC-UTI and co-amoxiclav-resistant EC-UTI, supporting drives to reduce broad-spectrum and inappropriate antibiotic use. However, despite substantial increases in co-amoxiclav-resistant EC-BSI, evidence that patient clinical outcomes are no worse does not support broadening empiric antibiotic prescribing from co-amoxiclav.[9]

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Contributions: KDV, NS, DHW, TEAP, and ASW designed the study. TPQ prepared extracts from the IORD database, KDV obtained data from the HSCIC. KDV and ASW analysed the data. KDV, TEAP and ASW prepared the figures. KDV, NS, and ASW prepared the first draft of the manuscript. All authors commented on the data and its interpretation, revised the content critically and approved the final version.

Figure legends

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

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

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

Footnote: IRR=annual incidence rate ratio in 2016. See Supplementary Table 1 for numbers and heterogeneity tests

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

Footnote: See Supplementary Methods for definitions.

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

Footnote: IRR=annual incidence rate ratio in 2016.

Figure 5. Number of community co-amoxiclav-resistant EC-UTIs (A), community EC-UTIs (B) and community urine samples (C) submitted regardless of result per 1000 patients per GP practice 2012-2016 compared with co-amoxiclav DDD per 1000 patients per general practice in the previous year for the first and the current year for the last two.

Footnote: showing one record per year per GP practice. Spearman rho (and models) for each panel excludes 5 which submitted less than 151 samples over 2011-2016 (all others

submitted over 308). Speraman rho for previous vs current for the 3 groups (ρ=0.20 vs ρ=0.04, ρ=0.33 vs ρ=0.35, ρ=0.37 vs ρ=0.40)

Figure 1

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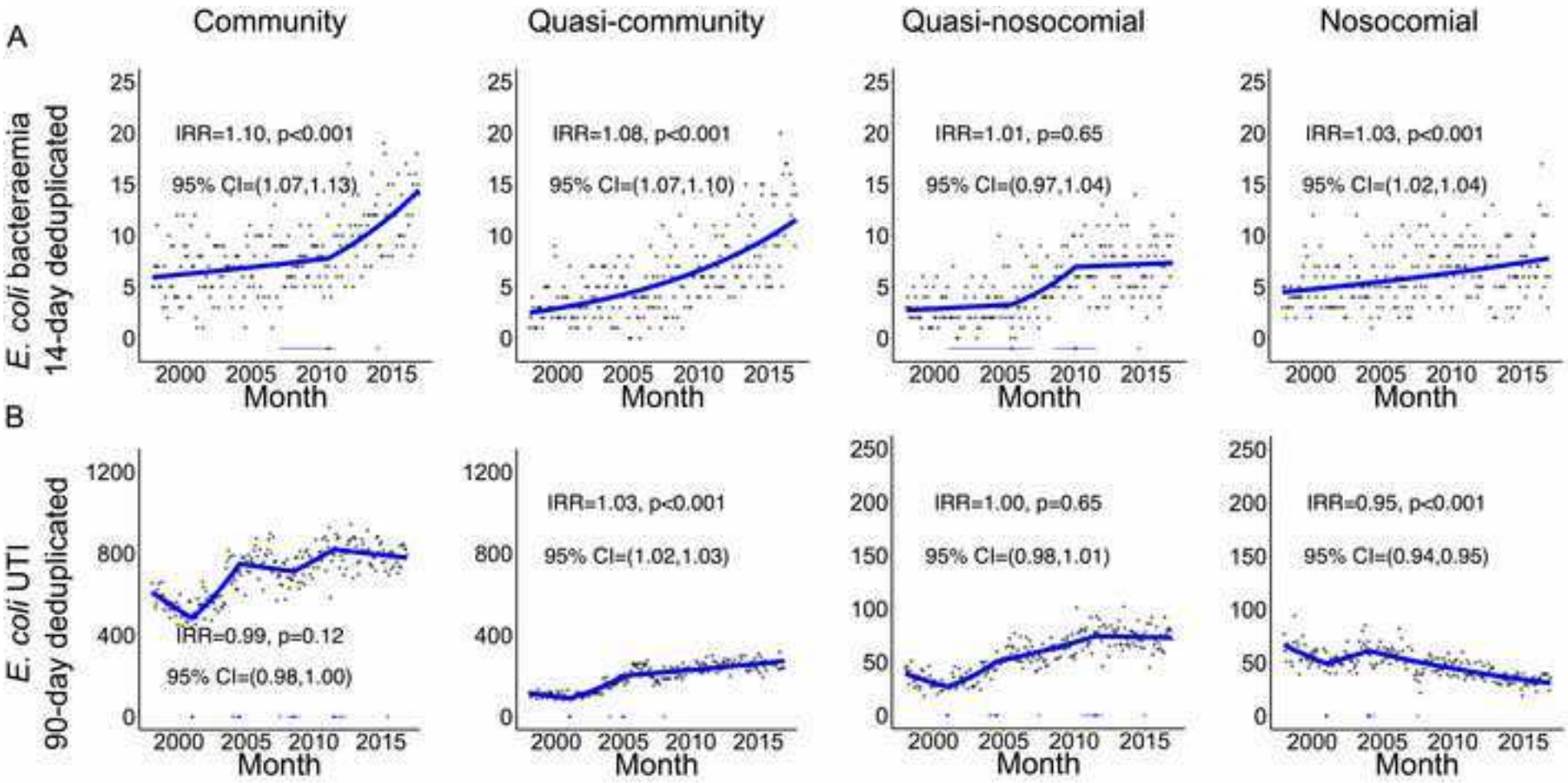

Figure 2

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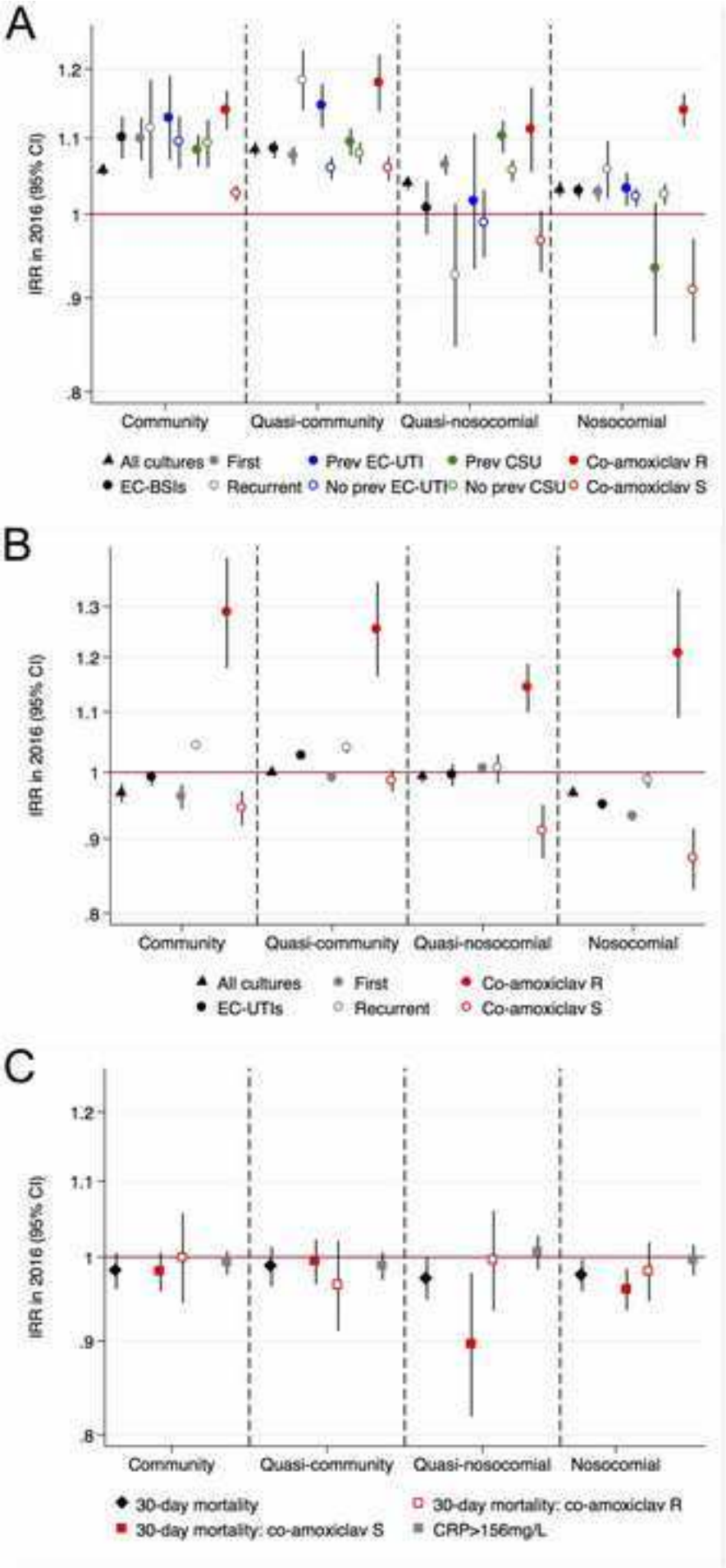

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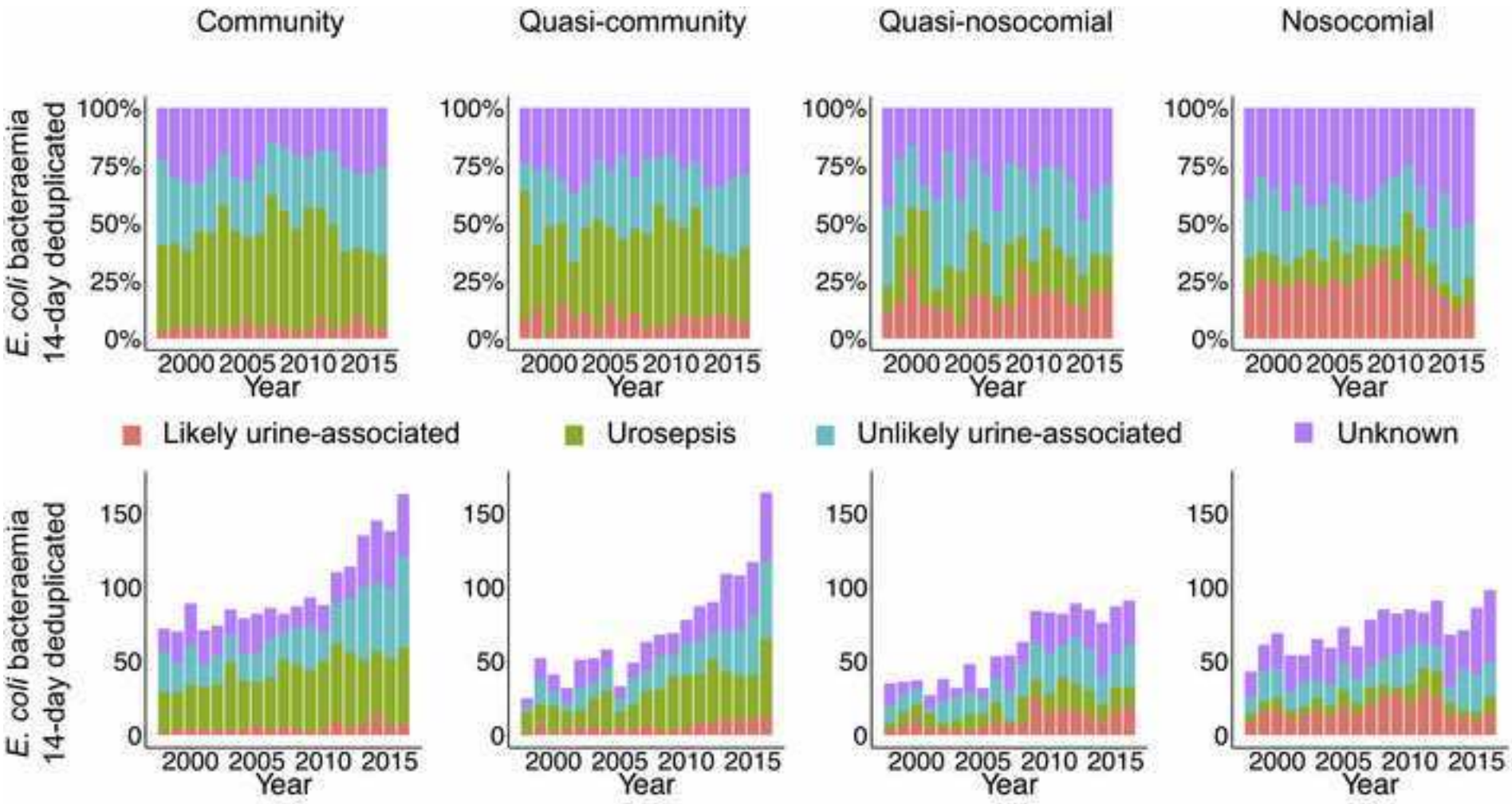

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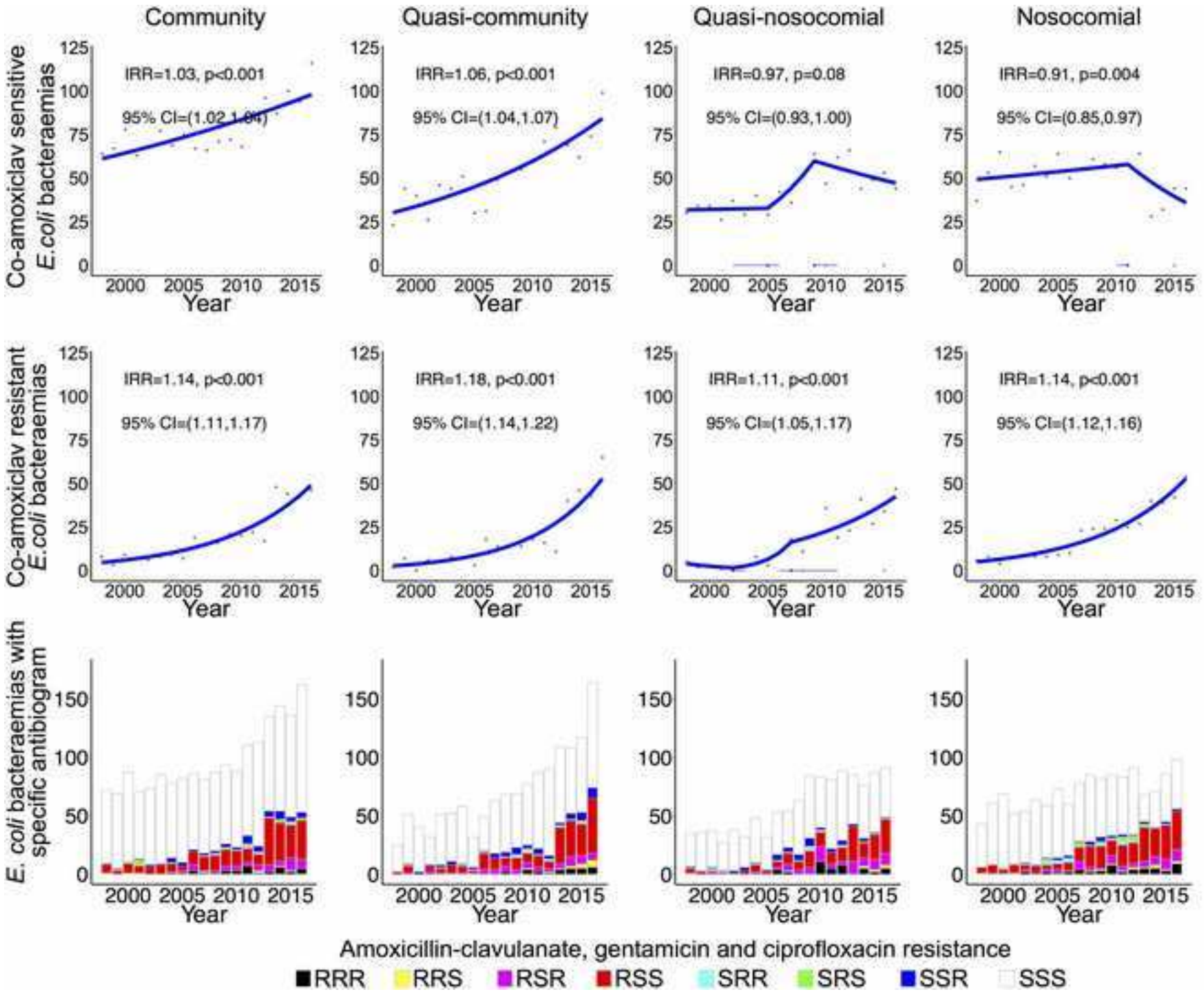

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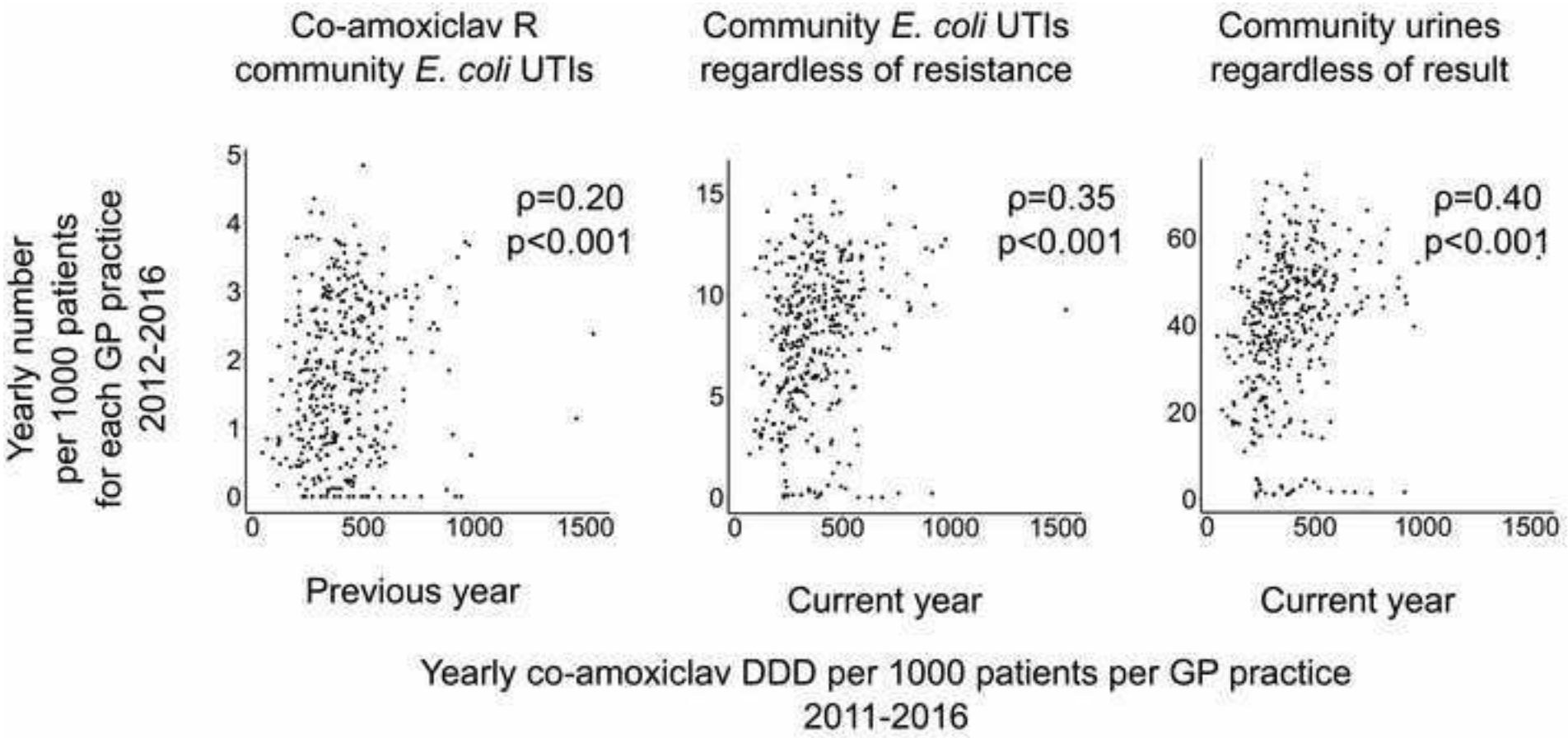

Supplementary Material

Supplementary Methods

(a) Further details of population

We included *Escherichia coli* isolated from blood from pure and mixed/polymicrobial cultures in our primary outcome in case differences in identification of polymicrobial infections were affecting incidence trends. Mixed/polymicrobial cultures comprised 763/5706 (13%) EC-BSI over the study. Of these, 187/763 (25%) were infections with *E. coli* and only plausible contaminants, including Coagulase negative staphylococcus; Streptococcus viridans, oralis, salivarius, mitis, viridans, and unspecified; diphtheroids; Propionibacterium species; and Bacillus species. Of the 576 EC-BSI with at least one other plausible pathogen, 412 (72%) other pathogens were likely gastrointestinal including Klebsiella pneumoniae and oxytoca, Enterococcus species, Enterococcus faecalis group D, Proteus mirabilis, Bacteroides fragilis, Enterobacter species, gastrointestinal anaerobes, and yeast. Percentages of polymicrobial infections did not vary over calendar time.

We used a strict definition of nosocomial EC-BSI ending at discharge in order to investigate the group whose EC-BSI had not actually been identified during hospitalisation. A relatively small number, 44/1132 (4%), of quasi-nosocomial EC-BSI cases were discharged in the 24 hours preceding the blood culture being taken: 147/1132 (13%) were discharged in the last 48 hours.

(b) Further details of classifications

Urinary specimens should only be sent for microbiological testing on clinical suspicion of a UTI;[1] however, 43% of mixed growth or culture-negative urine samples taken within [-30,+2] days of an *E. coli* bloodstream infection (EC-BSI) did not have a completed request code making it difficult to assess whether there really was clinicial suspicion of urinary infection before the bacteraemia. To investigate the contribution of antecedent UTIs to rising *E. coli* bacteraemia incidence, we therefore hierarchically classified *E. coli* bacteraemias as

(i) 'likely urine-associated', if they either had an *E. coli*-positive urine culture, or if they had mixed growth or negative urine culture with a relevant request code (mentioning UTI or other urinary symptoms, dysuria, urosepsis, pyelonephritis, positive dipstick), within [-30,-3] days of the EC-BSI sample

(ii) 'urosepsis', if they either had an *E. coli*-positive urine culture, or if they had mixed growth or negative urine culture with a relevant request code within (-3,+2] days of the bacteraemia sample (but not (i), i.e. no pre-existing evidence of a urine infection which could have potentially been prevented from becoming urosepsis)

(iii) 'unlikely urine-associated', if they had a urine culture positive for other pathogens within [-30,+2] days of the EC-BSI sample, or if no urine culture was taken within [-30,+2] days of the EC-BSI sample (but not (i) or (ii))

(iv) 'unknown', if they had a mixed growth or negative urine culture and either an irrelevant or no request code within [-30,+2] days of the EC-BSI sample (but not (i), (ii) or (iii))).

Sensitivity analyses included definitions based on urine cultures up to 100 days before the EC-BSI sample rather than 30 days, with similar results (data not shown).

For quasi-nosocomial bacteraemias, primary diagnostic codes from the antecedent admission were grouped as 'cardiovascular disorder', 'neurological disorder', 'dermatological/rheumatological disorders', 'endocrine disorder', 'obstetrics and gynaecology disorder', 'haematological disorder', 'malignancy', 'gastrointestinal disorder', 'orthopaedic disorders including trauma', 'poisoning', 'renal and urological disorders', 'respiratory disorder', 'other'.

(c) Antimicrobial susceptibility testing

To investigate AMR burden, we assessed *E. coli* isolated from blood for resistance reported by the diagnostic laboratory to amoxicillin, co-amoxiclav, trimethoprim, gentamicin, ciprofloxacin, ceftriaxone, ceftazidime, piperacillin-tazobactam and meropenem, and *E. coli*

isolated from urine for resistance to amoxicillin, co-amoxiclav, trimethoprim, ciprofloxacin, nitrofurantoin and cefalexin (the only drugs consistently tested throughout the study period). Before February 2013, in the OUH microbiology service laboratory antimicrobial susceptibility was tested using disk diffusion in an uncontrolled inoculum using a control; in February 2013 this was replaced by the automated susceptibility testing with the Phoenix BD system using European Committee on Antimicrobial Susceptibility testing (EUCAST) breakpoints, using disk diffusion direct from blood in an uncontrolled inoculum as an early flag. In December 2013, disk diffusion in a controlled inoculum using the British Society for Antimicrobial Chemotherapy (BSAC) diameter zones was introduced for selected samples in addition to BD-Phoenix. Where multiple results were available for one sample, the Phoenix result was used in preference to the disk diffusion result as most disk diffusion results were uncontrolled; otherwise any resistant result was used in preference to susceptible results. Agreement between disk diffusion and Phoenix in samples where both were done was reasonable (**Supplementary Figure 14**).

(d) Changes in co-amoxiclav formulation in hospital prescribing

In July 2010, the hospital co-amoxiclav formulation changed from 250mg amoxicillin and 125mg clavulanate to 500mg amoxicillin and 125mg clavulanate affecting defined daily doses (DDD) because of the different strengths. Hospital practice was to prescribe an additional 250mg amoxicillin with the original formulation prior to July 2010, supported by a concurrent decrease in raw amoxicillin DDDs in July 2010 (because it was no longer being prescribed with the original co-amoxiclav formulation) and increase in co-amoxiclav DDDs in July 2010 (as an additional 250mg amoxicillin was being counted as a co-amoxiclav DDD rather than an amoxicillin DDD). We therefore adjusted raw co-amoxiclav and amoxicillin DDDs before July 2010 to count the additional amoxicillin prescribed with the old co-amoxiclav formulation as a co-amoxiclav DDD, making assignment consistent over the whole study period.

(e) Further details of statistical analyses

Changes in trends in outcomes were estimated using iterative sequential regression (ISR).[2] The ISR algorithm first modelled the outcome using samples taken between 1 January 1998 and 1 January 1999, and compared a model with one trajectory over calendar time in the outcome to a model allowing this trajectory to change 6 months after the start of observation. If the model with two trajectories was not a better fit (determined by a Bayesian Information Criterion being lower by at least 3.84 [the critical value to detect a significance level of 0.05 with a $\chi 2$ test and one degree of freedom]), an additional six month's observations (to June 1999) were included. Then the model with one trajectory was compared to models with 2 trajectories with either June 1998 or January 1999 as the changepoint, again considering whether any model with a change in trajectory substantially improved model fit. Any changepoint that improved model fit was fixed, and then an additional six month's data included. This process was iterated up to January 2017. For antibiotic resistance trends, due to the smaller number of observations counts per year (rather than per month) were modelled, first considering samples taken between 1 January 1998 and 1 January 2002, and then successively every year through 1 January 2017. Incidence trends in different subgroups or for different outcomes using stacked regression.[3]

For standardization to the population of Oxfordshire in 1998, we used estimates from the UK Office for National Statistics. These were not available for 2016 so we used a linear extrapolation of the previous two years.

Under 1% of susceptibility results were missing for each antibiotic tested, with the exception of trimethoprim for which blood cultures were not tested October-December 2014. Analyses therefore used a probability weight of 4/3 for the incidence of trimethoprim-resistant *E. coli* bacteraemias in 2014; all other analyses of incidence of resistant bacteraemias/UTIs were based on observed data only (i.e. complete cases).

Continuous test results were truncated at the 1st and 99th percentile; median values were modelled using quantile regression to avoid influence from outliers. All analyses of test results were restricted to complete cases; for EC-BSI completeness was 93% for neutrophils, 93% for C-reactive protein (CRP) (post-2000 only), 95% for creatinine and 93% for urea. CRP was reported with different upper thresholds over the study period, and approximately half the values were consistently above the upper threshold. CRP was therefore considered as a binary rather than continuous outcome, namely CRP≥156 mg/L (minimum upper threshold used over 1998-2016). In January 2009 the creatinine analysis method changed in the laboratory,[2] models adjusted for this change using a step-function. All analyses of laboratory parameters adjusted for age and sex.

In order to estimate a simple univariable association between hospital antimicrobial prescribing and co-amoxiclav resistant bacteremia incidence, analogous to a Spearman rho for two continuous factors, we calculated a bivariate cross-correlation, i.e. the correlation between one series at time t and another series at time t - k as a function of the time t and lag k. Because of differences in the time periods in which (quarterly) antibiotic prescribing data were available, we included only financial years 2003-2014. For each class of antibiotics, and all antibiotics combined, we considered a time lag of 0 (ie same quarter), and all quarters up to -3 and +3, (where -1/4 means antibiotic use in previous quarter against bacteraemias in current quarter).

To estimate associations between annual community urine sample submission, community EC-UTI and community co-amoxiclav-resistant EC-UTI incidence, and co-amoxiclav use in primary care, we used backwards elimination to identify the most parsimonious model including co-amoxiclav defined-daily-doses (DDD) per 1000 registered patients in the current and previous year together with their interaction with the calendar year trend, adjusting for general practice. We did not consider co-amoxiclav resistant EC-BSI incidence as numbers

were too small over the period where antibiotic data were available. As antibiotic usage was only available 2011-2016, we considered annual outcomes from 2012-2016 only. Because incidence of co-amoxiclav resistant EC-UTIs were lower than the predicted time trend in 2012 (**Supplementary Figure 11**) we allowed for this using a step function, and estimated time trends in addition to this. All models excluded 13 practices, 8 which had missing data for at least one of the years and 5 which submitted less than 151 samples over 2011-2016 (all others submitted over 308 samples). For the outcome co-amoxiclav-resistant EC-UTI, the best predictor was usage in the previous year and there was no evidence of interactions with the calendar time trend (p=0.22). For EC-UTIs and all urines, usage in the current year was the better predictor and there was no evidence of interactions with the calendar time trend (p=0.55). The same models were chosen when including all samples regardless of hospital-exposure group. We also obtained 2017 demographics from the Health and Social Care Information Centre and included proportion aged over 65 and proportion males per GP practice as explanatory variables, without GP practice.

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Supplementary Table 1 Summary of current (2016) annual rate ratios

	Insert	Community	Quasi-community	Quasi-nosocomial	Nosocomial
		aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)
All EC-BSI	Fig. 1	**1.10 (1.07-1.13)**	**1.08 (1.07-1.10)**	1.01 (0.97-1.04)	**1.03 (1.02-1.04)**
According to previous EC-BSI					
First EC-BSI *	Supp. Fig. 1	**1.10 (1.07-1.13)**	**1.08 (1.06-1.09)**	**1.06 (1.05-1.08)**	**1.03 (1.02-1.04)**
Recurrent EC-BSI	Supp. Fig. 1	**1.11 (1.05-1.18)**	**1.18 (1.14-1.23)**	0.93 (0.85-1.01)	1.06 (1.02-1.10)
Heterogeneity first vs recurrence EC-BSI		p=0.70	p<0.001	p=0.004	p=0.14
All blood cultures (regardless of result)	Supp. Fig. 3	**1.06 (1.05-1.07)**	**1.08 (1.07-1.09)**	**1.04 (1.03-1.05)**	**1.03 (1.02-1.04)**
Heterogeneity EC-BSI vs all blood cultures		p<0.001	p=0.92	p=0.05	p=0.76
According to previous EC-UTI					
All EC-BSI with previous EC-UTI **	Supp. Fig. 6	**1.13 (1.07-1.19)**	**1.15 (1.11-1.18)**	1.02 (0.93-1.11)	1.03 (1.01-1.05)
All EC-BSI with no previous EC-UTI	Supp. Fig. 6	**1.09 (1.06-1.13)**	**1.06 (1.04-1.07)**	0.99 (0.95-1.03)	**1.02 (1.01-1.03)**
Heterogeneity by previous EC-UTI		p=0.66	p<0.001	p=0.73	p=0.02
According to previous CSU					
All EC-BSI with previous CSU	Supp. Fig. 7	**1.08 (1.06-1.10)**	**1.09 (1.08-1.11)**	**1.10 (1.08-1.12)**	0.93 (0.86-1.01)
All EC-BSI with no previous CSU	Supp. Fig. 7	**1.09 (1.06-1.13)**	**1.08 (1.06-1.09)**	**1.06 (1.04-1.07)**	**1.03 (1.01-1.04)**
Heterogeneity by previous CSU		p=0.61	p=0.18	p<0.001	p=0.03

	Insert	Community	Quasi-community	Quasi-nosocomial	Nosocomial
		aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)
According to co-amoxiclav susceptibility					
Co-amoxiclav resistant EC-BSI	Fig. 3	**1.14 (1.11-1.17)**	**1.18 (1.14-1.22)**	**1.11 (1.05-1.17)**	**1.14 (1.12-1.16)**
Co-amoxiclav susceptible EC-BSI	Fig. 3	**1.03 (1.02-1.04)**	**1.06 (1.04-1.07)**	0.97 (0.93-1.00)	0.91 (0.85-0.97)
Heterogeneity		p<0.001	p<0.001	p<0.001	p<0.001
30-day mortality: all EC-BSI	Supp. Fig 9	0.99 (0.96-1.01)	0.99 (0.96,1.01)	0.98 (0.95,1.00)	0.98 (0.96,1.00)
CRP >156 mg/L: all EC-BSI	Supp. Fig 9	0.99 (0.98,1.01)	0.99 (0.97,1.01)	1.01 (0.98,1.03)	1.00 (0.98,1.02)
30-day mortality: co-amoxiclav sensitive EC-BSI	Supp. Fig 12†	0.98 (0.96,1.01)	0.99 (0.97,1.02)	0.97 (0.94,1.00)	0.96 (0.94,0.99)
30-day mortality: co-amoxiclav resistant EC-BSI	Supp. Fig 12†	1.00 (0.94,1.06)	0.96 (0.91,1.02)	1.00 (0.93,1.06)	0.98 (0.95,1.02)
All EC-UTI	Fig. 1	0.99 (0.98-1.00)	**1.03 (1.02-1.03)**	1.00 (0.98-1.01)	**0.95 (0.94-0.95)**
According to previous EC-UTI					
First EC-UTI *	Supp. Fig. 2	**0.96 (0.94-0.98)**	0.99 (0.98-1.00)	1.01 (1.00-1.01)	**0.93 (0.93-0.94)**
Recurrent EC-UTI	Supp. Fig. 2	**1.04 (1.04-1.05)**	**1.04 (1.03-1.05)**	1.01 (0.98-1.03)	0.99 (0.97-1.00)
Heterogeneity		p<0.001	p<0.001	p=0.99	p<0.001
All urine cultures (regardless of result)	Supp. Fig. 5	**0.99 (0.98-0.99)**	**1.01 (1.01-1.01)**	**1.02 (1.01-1.02)**	1.02 (1.01-1.04)
According to co-amoxiclav susceptibility					
Co-amoxiclav resistant EC-UTI	Supp. Fig. 11	**1.29 (1.18-1.40)**	**1.25 (1.16-1.35)**	**1.14 (1.10-1.19)**	**1.21 (1.09-1.34)**

	Insert	Community	Quasi-community	Quasi-nosocomial	Nosocomial
		aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)
Co-amoxiclav susceptible EC-UTI	Supp. Fig. 11	**0.94 (0.92-0.97)**	0.99 (0.97-1.00)	**0.91 (0.87-0.95)**	**0.87 (0.83-0.91)**
Heterogeneity		p<0.001	p<0.001	p<0.001	p<0.001

* First ever recorded per patient between 1998-2016; all other subsequent cases counted as recurrences

** Any EC-UTI 3 or more days prior to the EC-BSI.

† No evidence of heterogeneity therefore Supplementary Figure 11 shows pooled mortality trends across susceptible and resistant EC-BSI

Note: showing annual rate ratios estimated by ISR in 2016; bold p<0.001, underline p between 0.001-0.05

Supplementary Table 2 Relative contribution of recurrent EC-BSIs and EC-UTIs to total numbers in 2016 by recent hospital-exposure

	Community	Quasi-community	Quasi-nosocomial	Nosocomial
	Recurrent/total (%)	Recurrent/total (%)	Recurrent/total (%)	Recurrent/total (%)
Bacteraemias	4/163 (2%)	24/164 (15%)	17/91 (19%)	11/98 (11%)
UTIs	4682/9464 (49%)	2003/3097 (65%)	472/885 (53%)	148/416 (36%)

Supplementary Table 3 Overall EC-BSI incidence trends in 2016, unadjusted and standardized to the sex and age population of Oxfordshire 1998

	Community aRR (95% CI) (with breakpoint)	Quasi-community aRR (95% CI)	Quasi-nosocomial aRR (95% CI)	Nosocomial aRR (95% CI)
Unstandardized	1.10 (1.04-1.17)	**1.08 (1.06-1.10)**	**1.07 (1.05-1.09)**	**1.03 (1.01-1.05)**
Standardized	1.09 (1.02-1.16)	**1.07 (1.05-1.09)**	**1.06 (1.04-1.08)**	1.02 (1.01-1.04)
Percentage change in regression coefficient*	10%	14%	12%	23%
Also standardized for number of samples taken per month	1.09 (1.02-1.16)	**1.07 (1.04-1.09)**	**1.06 (1.04-1.08)**	1.02 (1.01-1.04)
Percentage change in regression coefficient*	9%	17%	12%	23%

* difference in coefficients from standardised and unstandardized estimates expressed as a percentage of the unstandardized estimate.

Note: only fitting a single trajectory to incidence for the quasi-nosocomial hospital-exposure group, approximating Figure 1. aRR=annual rate ratio per year in 2016; bold p<0.001, underline p between 0.001-0.05

Supplementary Table 4 First per patient EC-BSI incidence trends, unadjusted and standardized to the sex and age population of Oxfordshire 1998

	Community aRR (95% CI) (with breakpoint)	Quasi-community aRR (95% CI)	Quasi-nosocomial aRR (95% CI)	Nosocomial aRR (95% CI)
Unstandardized	1.10 (1.03-1.17)	**1.07 (1.05-1.10)**	**1.06 (1.04-1.08)**	1.03 (1.01-1.05)
Standardized	1.09 (1.02-1.16)	**1.06 (1.04-1.08)**	**1.05 (1.04-1.07)**	1.02 (1.00-1.04)
Percentage change in regression coefficient*	10%	15%	14%	26%
Also standardized for samples taken per month	1.09 (1.02-1.16)	**1.06 (1.04-1.08)**	**1.05 (1.04-1.07)**	1.02 (1.00-1.04)
Percentage change in regression coefficient*	9%	19%	13%	28%

* difference in coefficients from standardised and unstandardized estimates expressed as a percentage of the unstandardized estimate.

Note: aRR=annual rate ratio per year in 2016; bold p<0.001, underline p between 0.001-0.05

Supplementary Table 5 Primary diagnostic code for the antecedent admission for quasi-nosocomial EC-BSIs

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Cardiovascular disorder	1	2	3	2	2	4	3	1	4	3	8	7	5	3	13	4	2	4	4	75
Neurological disorder	1	0	2	2	1	1	2	0	0	1	2	4	2	5	3	0	2	3	3	34
Dermatological or rheumatological disorders	0	1	1	0	1	1	2	0	1	2	3	1	0	3	1	2	1	2	1	23
Endocrine disorder	1	1	1	0	0	0	0	0	1	0	1	0	0	0	1	2	0	1	0	9
Gastrointestinal disorder	7	7	2	3	4	2	4	6	13	4	13	10	17	7	11	12	15	17	23	177
Gynaecological or obstetric disorder	1	1	1	3	1	1	4	1	2	1	1	0	1	3	0	2	4	2	1	30
Haematological disorder	1	0	0	1	2	0	1	0	0	0	2	2	3	2	4	2	0	1	0	21
Malignancy	15	13	15	9	16	11	23	14	15	23	22	35	26	30	29	32	26	24	17	395
Orthopaedic disorders including trauma	0	0	3	0	0	2	1	2	1	2	2	2	5	4	1	4	5	7	3	44
Poisoning	0	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	3
Renal and urological disorders	3	7	3	4	7	4	5	6	7	11	4	10	13	12	15	11	12	13	17	164
Respiratory disorder	2	1	0	3	2	4	0	1	3	4	3	7	4	5	3	4	5	7	12	70
Dermatological disorder	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
Other	3	2	5	0	2	2	3	1	5	3	1	6	7	8	8	10	4	6	9	85

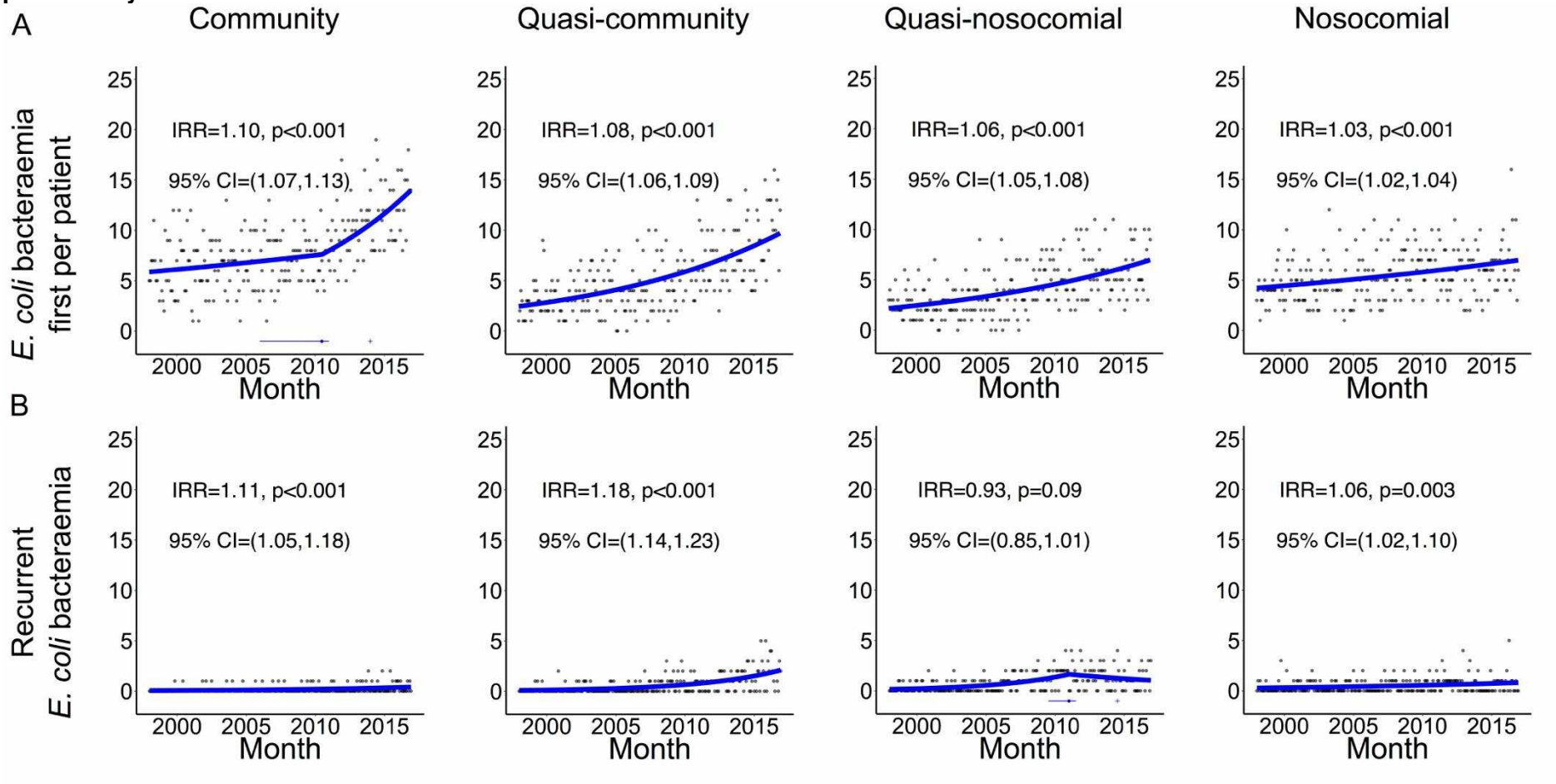
Supplementary Table 6 Total number and percentage of EC-BSIs and EC-UTIs tested for each antibiotic and resistant to each antibiotic over the whole period and in 2016

		Tested(%)	Resistant(%)	Tested in 2016(%)	Resistant in 2016(%)
Bacteraemias					
	Amoxicillin	5689(100%)	3357(50%)	515(100%)	294(57%)
	Co-amoxiclav	5691(100%)	1413(20%)	515(100%)	212(41%)
	Trimethoprim	5362(94%)	2230(35%)	515(100%)	168(33%)
	Piptaz	5490(96%)	434(7%)	516(100%)	37(7%)
	Gentamicin	5695(100%)	327(5%)	516(100%)	40(8%)
	Ciprofloxacin	5694(100%)	672(10%)	516(100%)	77(15%)
	Ceftriaxone	5474(96%)	364(5%)	516(100%)	45(9%)
	Ceftazidime	5686(100%)	352(5%)	515(100%)	53(10%)
	Meropenem	5555(97%)	6(0%)	516(100%)	0(0%)
	Amikacin	1003(18%)	27(2%)	514(100%)	12(2%)
	Aztreonam	1703(30%)	166(9%)	515(100%)	54(10%)
	Cefalexin	844(15%)	211(22%)	0(0%)	0(NaN%)
	Cotrimoxazole	1694(30%)	484(26%)	512(99%)	140(27%)
	Ertapenem	2605(46%)	3(0%)	515(100%)	0(0%)
	Fosfomycin	918(16%)	4(0%)	512(99%)	3(1%)
UTIs					
	Amoxicillin	228183(100%)	108507(39%)	13829(100%)	6329(46%)
	Co-amoxiclav	228054(100%)	30041(11%)	13792(99%)	3921(28%)
	Trimethoprim	228094(100%)	97281(35%)	13825(100%)	4193(30%)
	Piptaz	59394(26%)	6098(8%)	13798(100%)	366(3%)
	Gentamicin	59917(26%)	4305(6%)	13794(100%)	730(5%)
	Ciprofloxacin	228128(100%)	14221(5%)	13826(100%)	1285(9%)
	Ceftriaxone	55798(24%)	3830(6%)	13815(100%)	720(5%)
	Ceftazidime	59615(26%)	4098(6%)	13815(100%)	683(5%)
	Meropenem	59559(26%)	103(0%)	13793(100%)	6(0%)
	Cefalexin	223197(98%)	45324(17%)	13780(99%)	1932(14%)
	Cotrimoxazole	51033(22%)	13265(21%)	13746(99%)	3552(26%)
	Ertapenem	51837(23%)	135(0%)	13787(99%)	32(0%)
	Fosfomycin	50804(22%)	499(1%)	13777(99%)	90(1%)
	Nitrofurantoin	226236(99%)	12032(4%)	13790(99%)	236(2%)
	Pivmecillinam	28087(12%)	7514(22%)	13772(99%)	1346(10%)

Supplementary Table 7 Highest cross-correlation between hospital antimicrobial prescribing and co-amoxiclav resistant bacteremia incidence

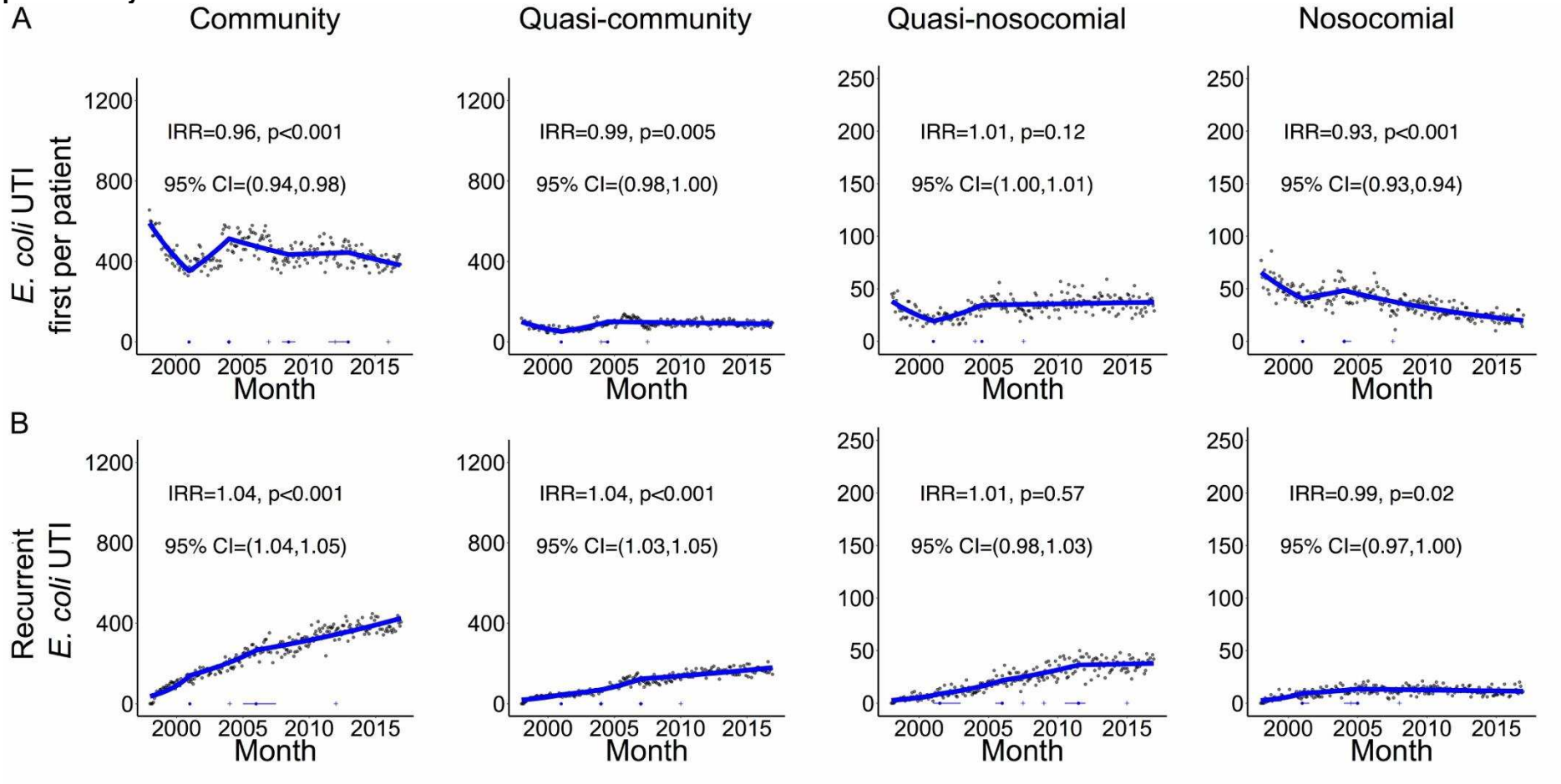
Antibiotic	Highest cross-correlation and lag
Co-amoxiclav	0.75 at lag 0
First generation cephalosporins	-0.44 at lag 3/4
Second generation cephalosporins	-0.71 at lag 0
Third generation cephalosporins	0.80 at lag 0
Piptaz	0.62 at lag 0
All cephalosporins	-0.59 at lag 1/4
Imidazole	-0.51 at lag 1/4
Lincosamide	0.69 at lag 0
Macrolide	-0.31 at lag -3
Beta lactamase resistant penicillins	-0.49 at lag -2 1/4
Beta lactamase sensitive penicillins	-0.28 at lag 1 1/4
Penicillins with extended spectrum	-0.54 at lag 1/4
Quinolone	-0.45 at lag -2 1/2
Combinations of sulfonamides and trimethoprim, including derivatives	0.35 at lag 3 1/4

Supplementary Figure 1. Monthly EC-BSI according to recent hospital-exposure (A) first per patient only (B) recurrences within a patient only



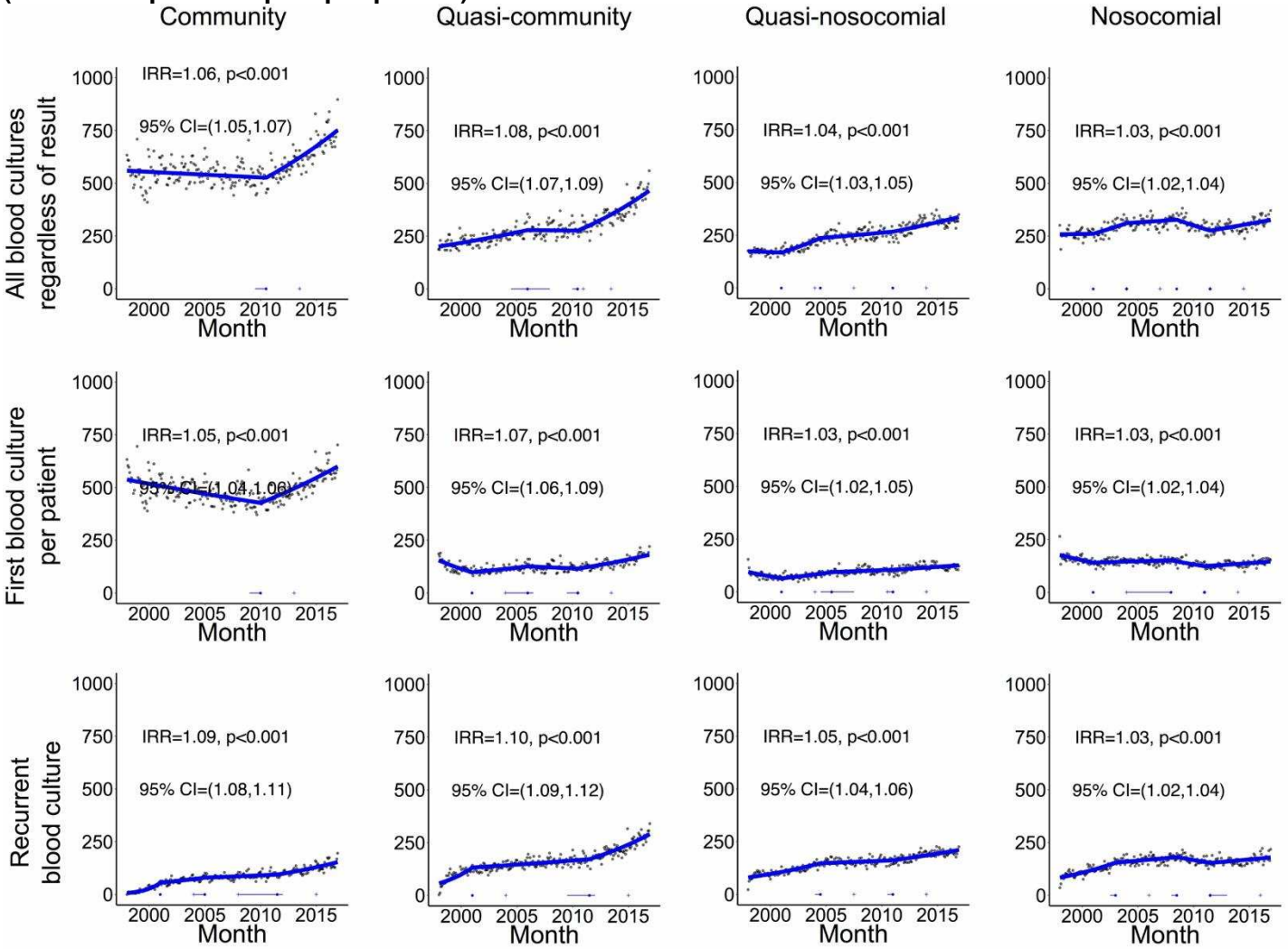
Footnote: IRR=annual incidence rate ratio in 2016. See Table 1 for heterogeneity tests between first vs subsequent EC-BSIs.

Supplementary Figure 2. Monthly EC-UTIs according to recent hospital-exposure (A) first per patient only (B) recurrences within a patient only



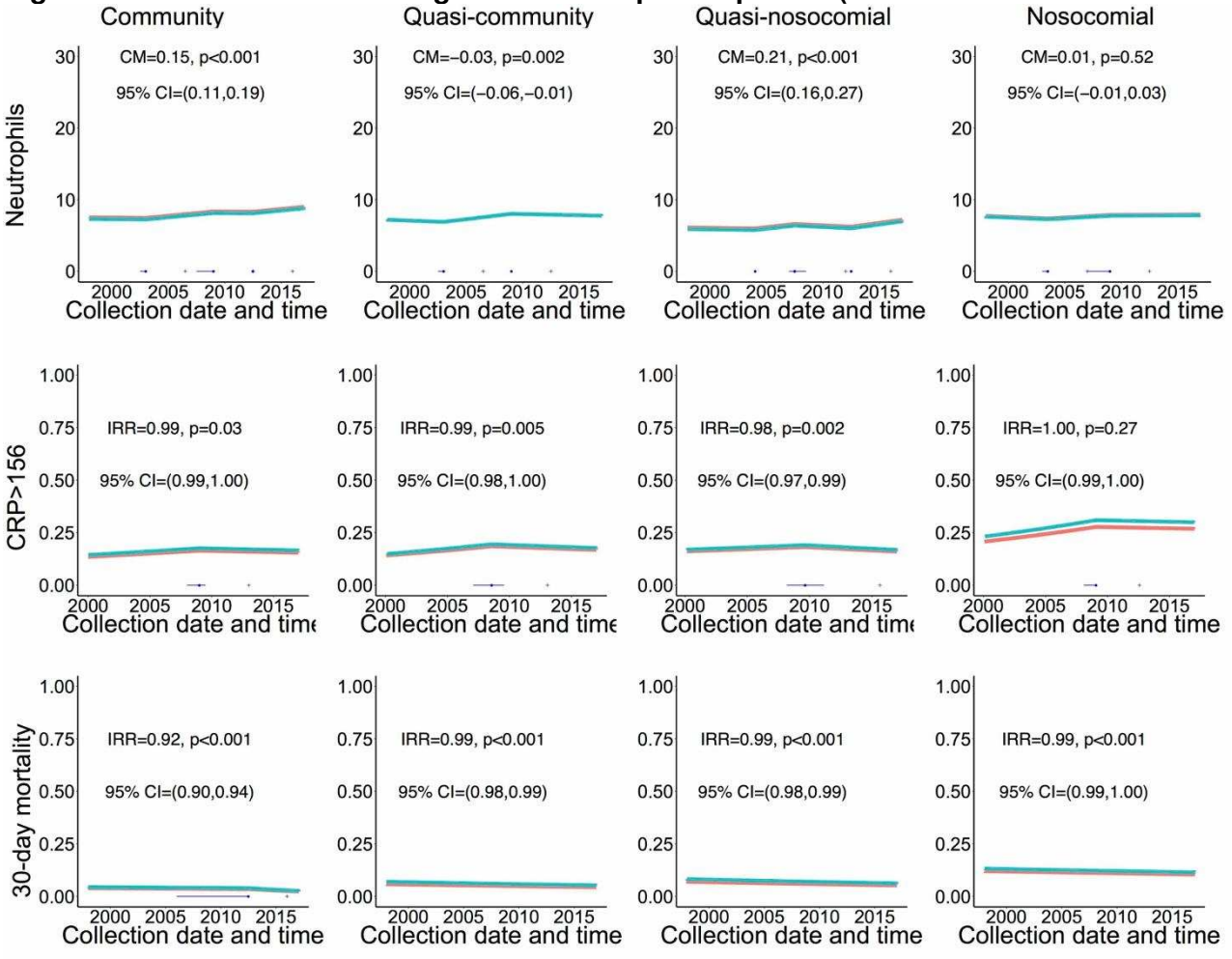
Footnote: IRR=annual incidence rate ratio in 2016. See Table1 for heterogeneity tests between first vs subsequent EC-UTIs.

Supplementary Figure 3. Monthly blood samples submitted for culture regardless of result according to recent hospital-exposure (first and repeat samples per patient)



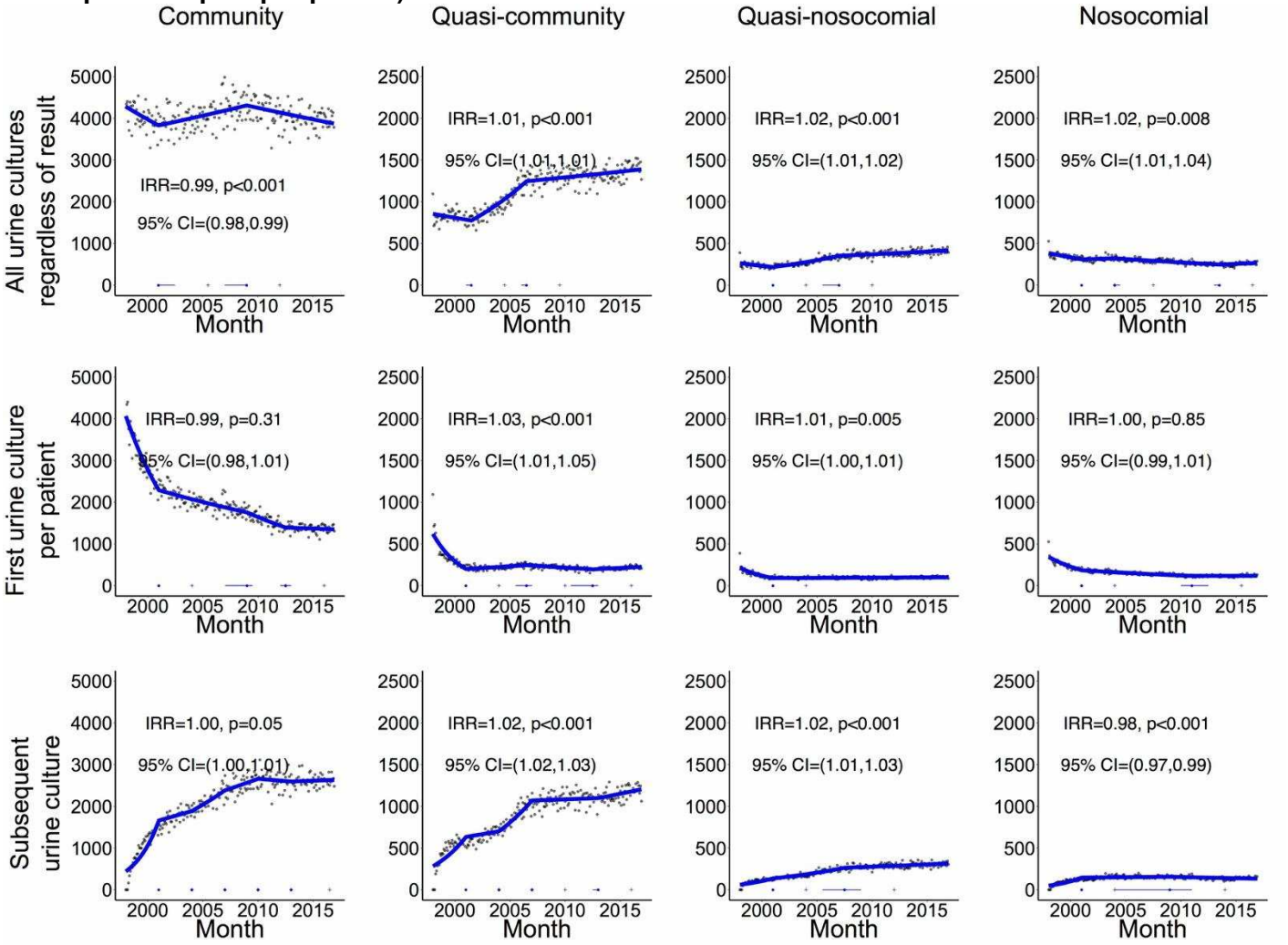
Footnote: including repeat samples submitted >14 days after an index sample. IRR=annual incidence rate ratio in 2016.

Supplementary Figure 4. Trends in haematology/biochemistry test results and 30-day mortality following a blood culture being taken regardless of its result according to recent hospital-exposure (first and recurrent infections).



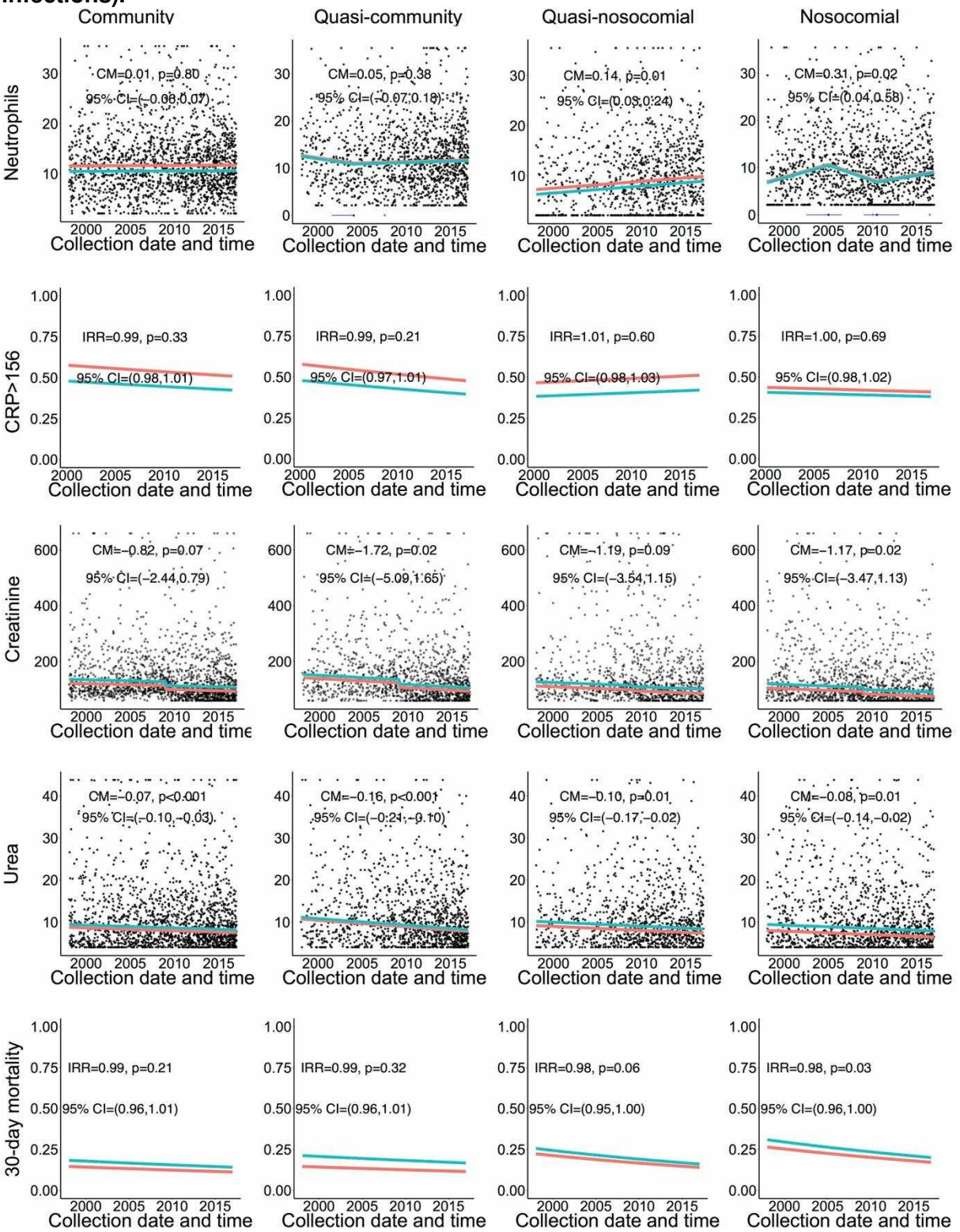
Footnote: including repeat samples submitted >14 days after an index sample. Fitted lines are for men (blue) and women (red) at mean age, IRR=annual incidence rate ratio in 2016. CM=change in median in 2016

Supplementary Figure 5. Monthly urine samples submitted for culture regardless of result according to recent hospital-exposure (first and repeat samples per patient)



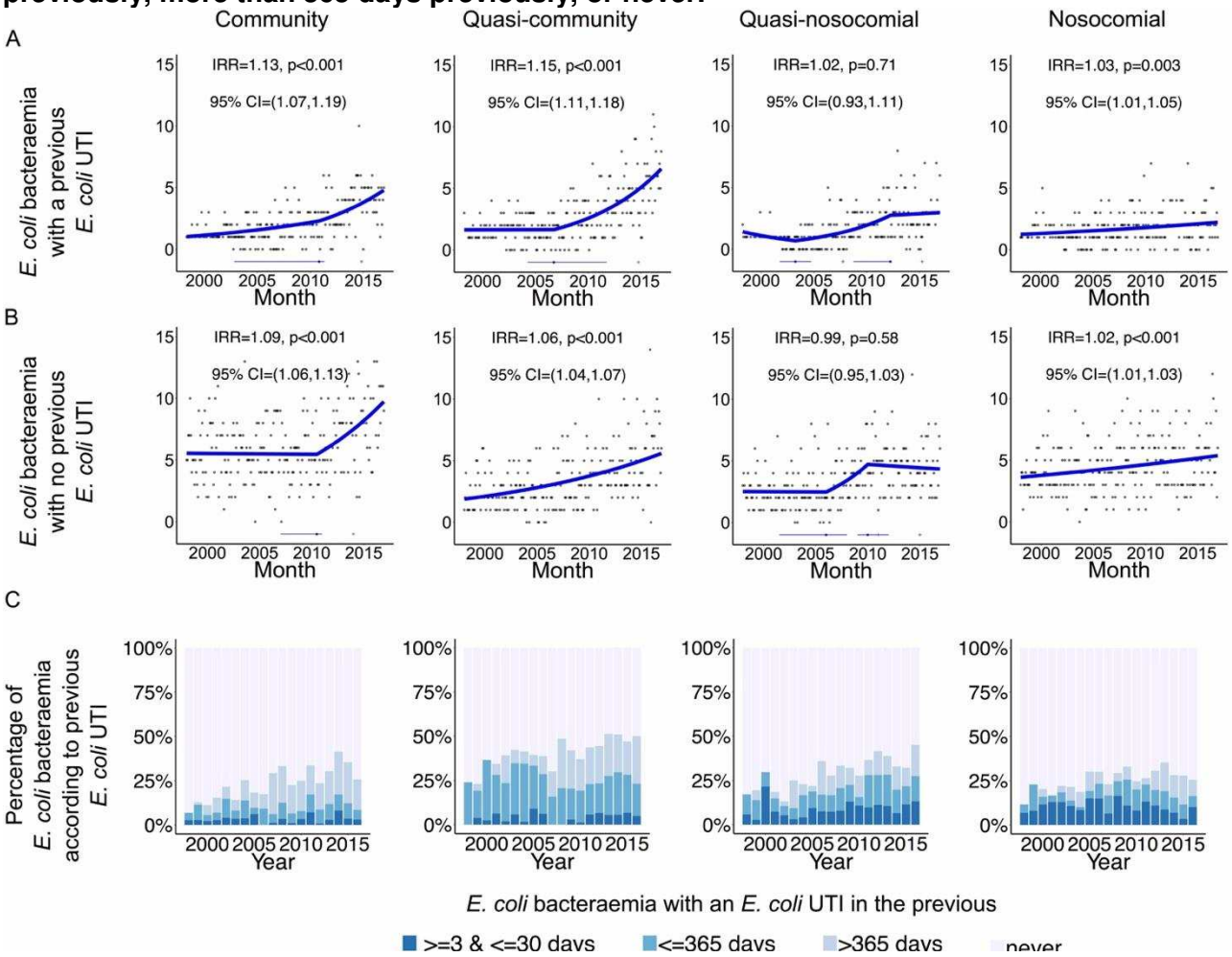
Footnote: including repeat samples submitted >90 days after an index sample. IRR=annual incidence rate ratio in 2016.

Supplementary Figure 6. Trends in haematology/biochemistry test results and 30-day mortality following EC-BSI according to recent hospital-exposure (first and recurrent infections).



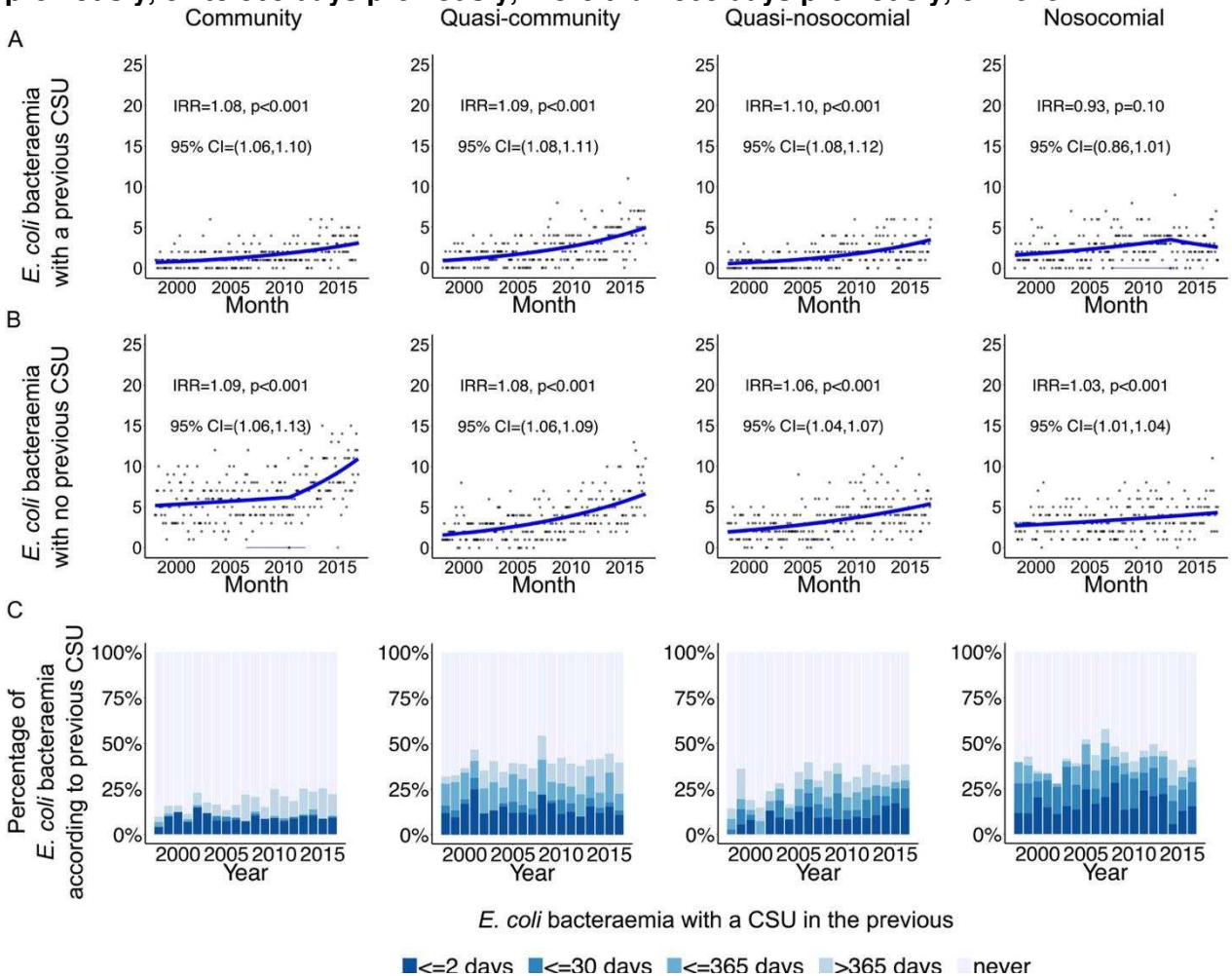
Footnote: CM=change per year in median value in 2016. Adjusted for age and gender. Fitted lines are for men (blue) and women (red) at mean age, IRR=annual rate ratio in 2016.

Supplementary Figure 7. Monthly EC-BSIs according to whether (A) patient had had an EC-UTI ≥3 days previously (B) patient had not had an EC-UTI ≥3 days previously (C) Annual EC-BSIs according to time from previous EC-UTI: 3-30 days previously, 31 to 365 days previously, more than 365 days previously, or never.



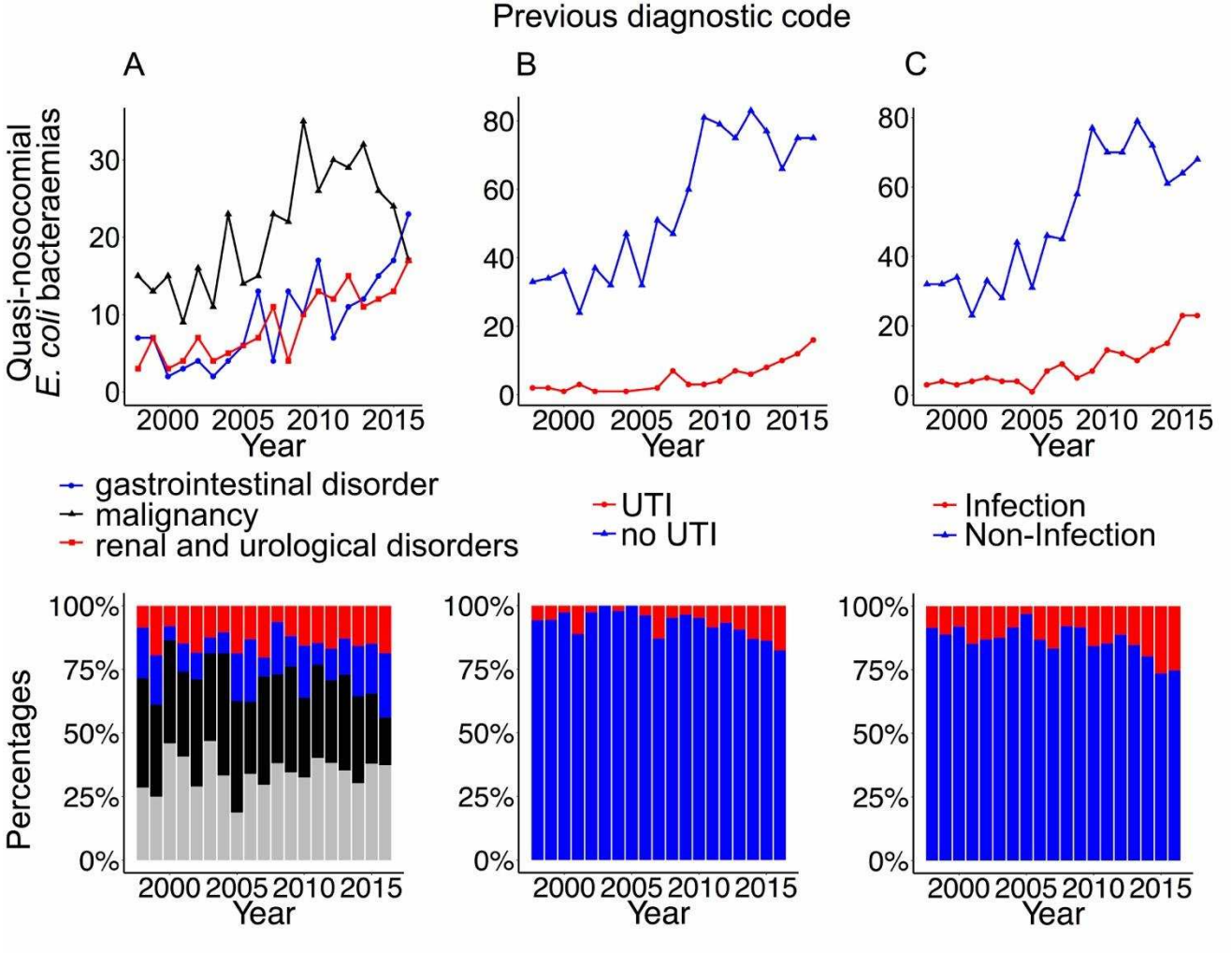
Footnote: IRR=annual incidence rate ratio in 2016. See Supplementary Table 1 for heterogeneity tests between patients with and without an EC-UTI ≥3 days previously. Results similar restricting to EC-UTIs within the last year or 4 years.

Supplementary Figure 8. Monthly EC-BSIs according to whether (A) patient had had a catheter urine specimen (CSU) previously (B) patient had not had a CSU previously (C) Annual EC-BSIs according to time from previous CSU: in the previous 2 days, 3-30 days previously, 31 to 365 days previously, more than 365 days previously, or never.



Footnote: IRR=annual incidence rate ratio in 2016. See Supplementary Table 1 for heterogeneity tests between patients with and without a CSU previously.

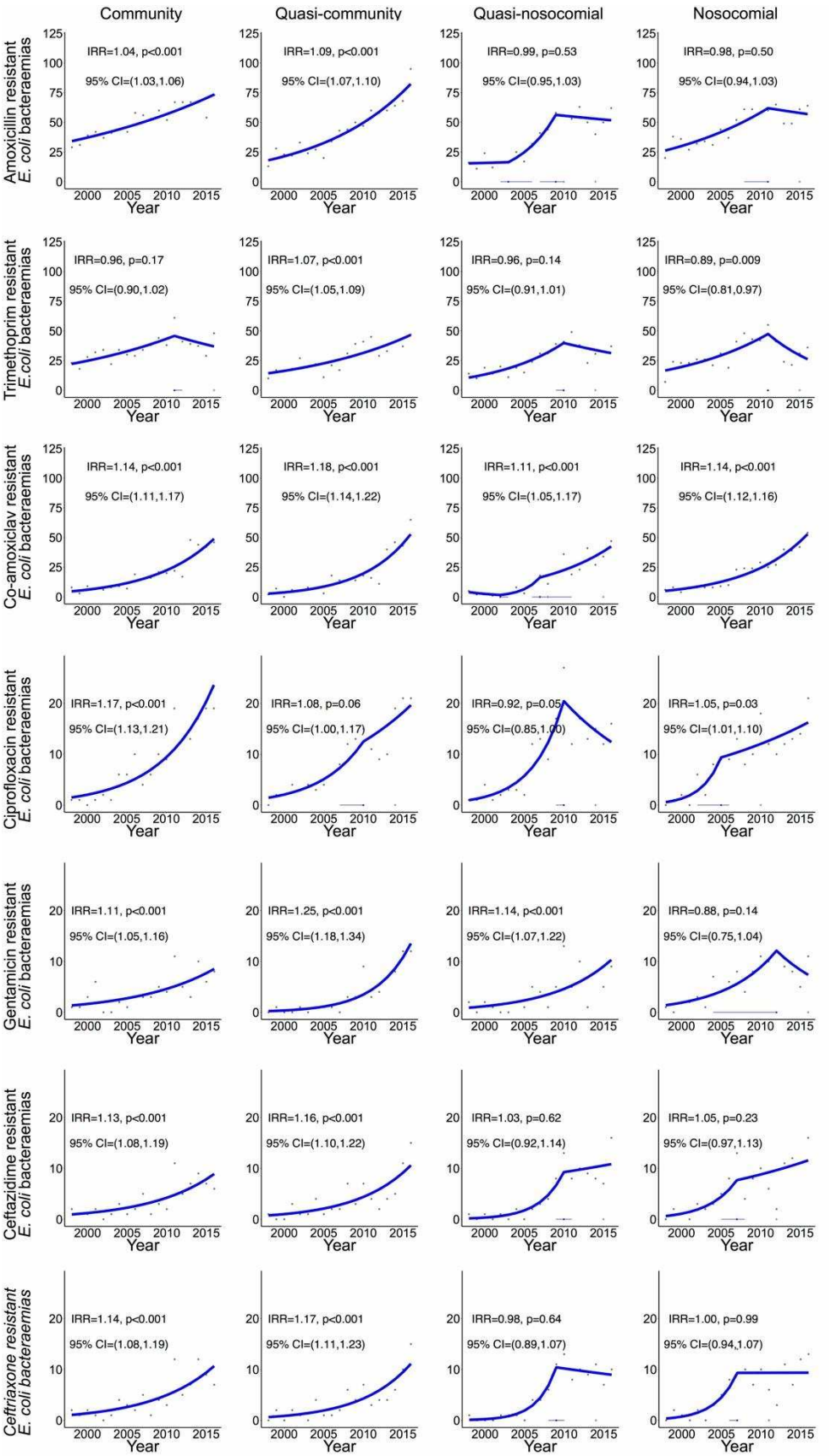
Supplementary Figure 9. Annual quasi-nosocomial EC-BSIs according to (A) for the three main categories of primary diagnostic codes for the antecedent admission, (B) having a UTI in any of the diagnostic codes of the previous admission to the EC-BSI, and (C) having the primary diagnostic code of the previous admission as an infection versus non-infection.



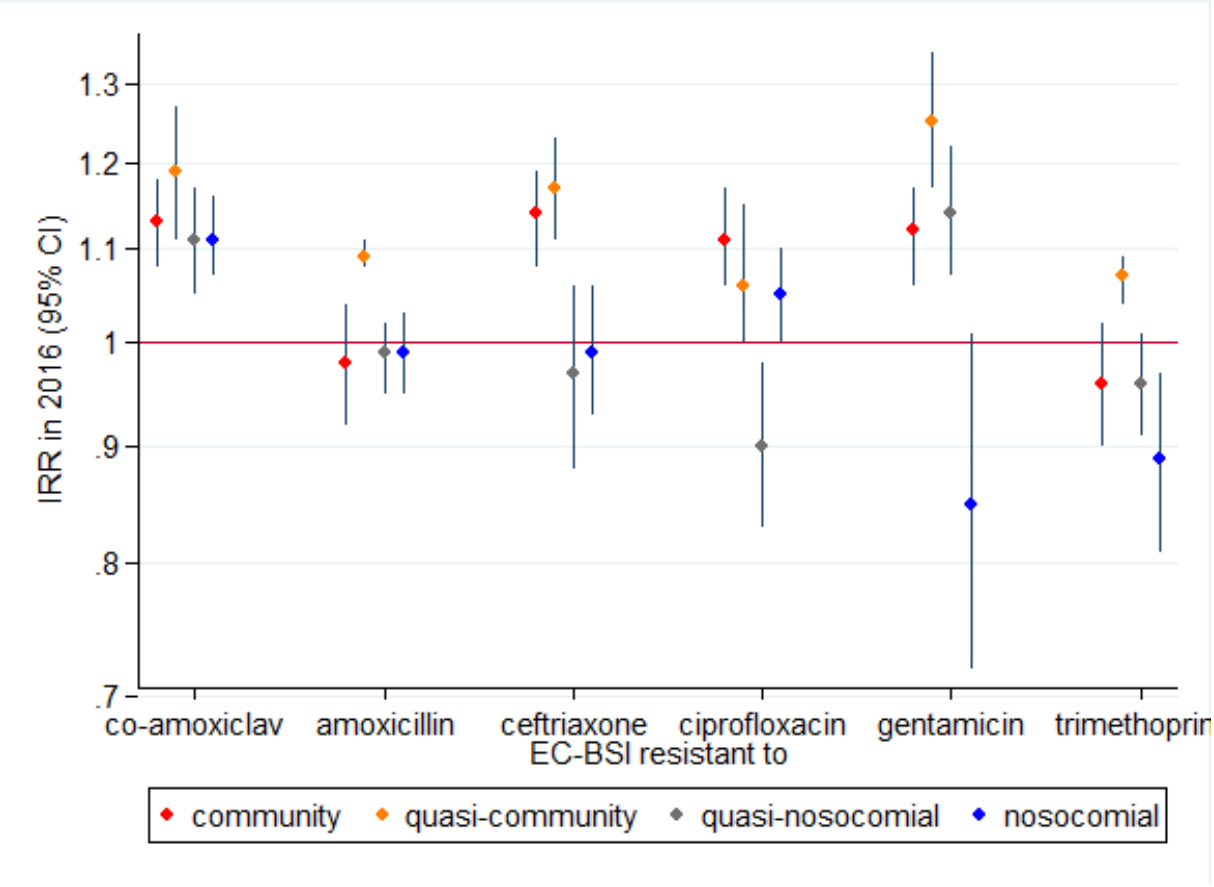
Footnote: see Supplementary Table 5 for all diagnostic code categories.

Supplementary Figure 10. Annual EC-BSIs according to recent hospital-exposure and antibiotic susceptibility (A) by antibiotic (B) summary

(A) by antibiotic

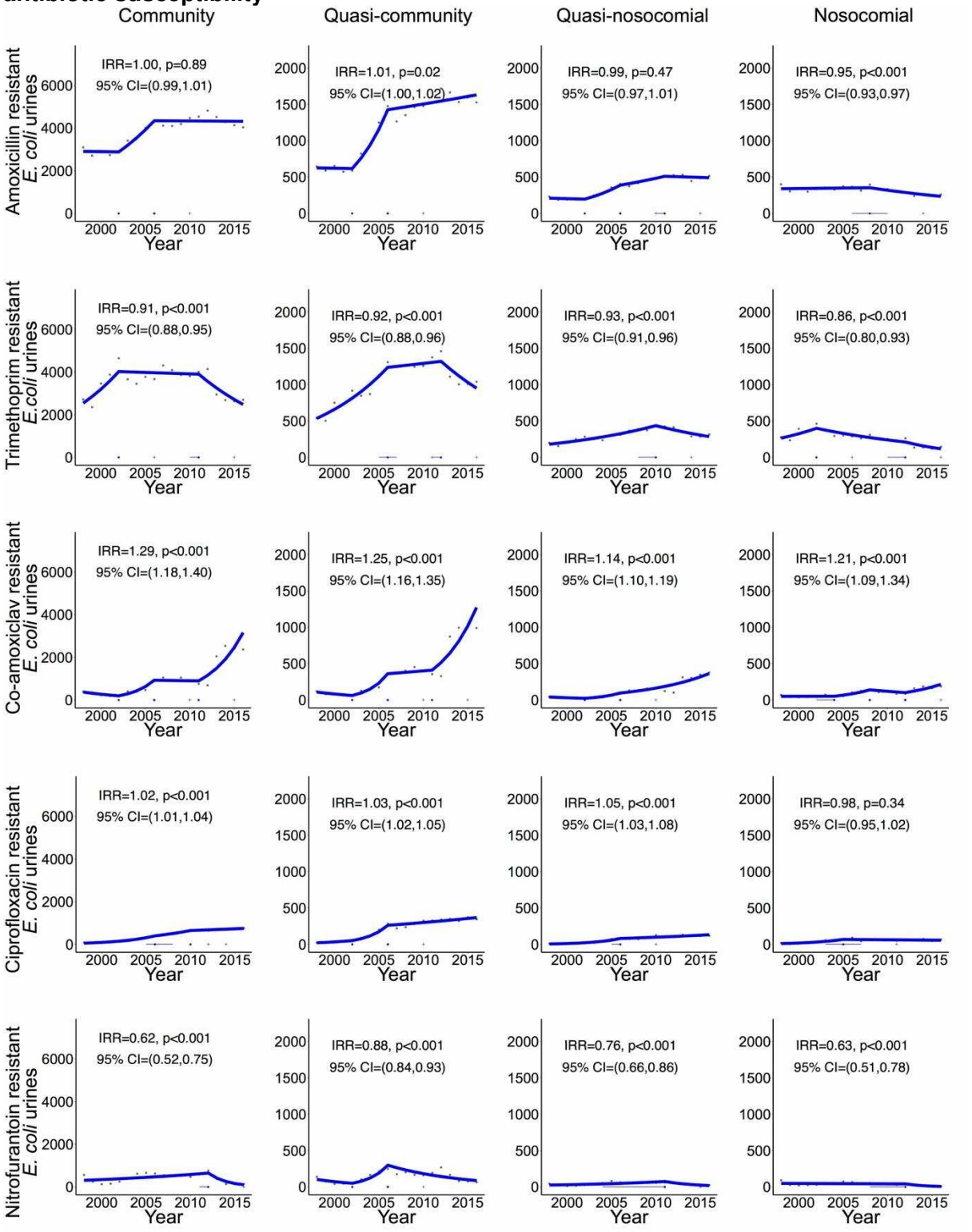


(B) summary



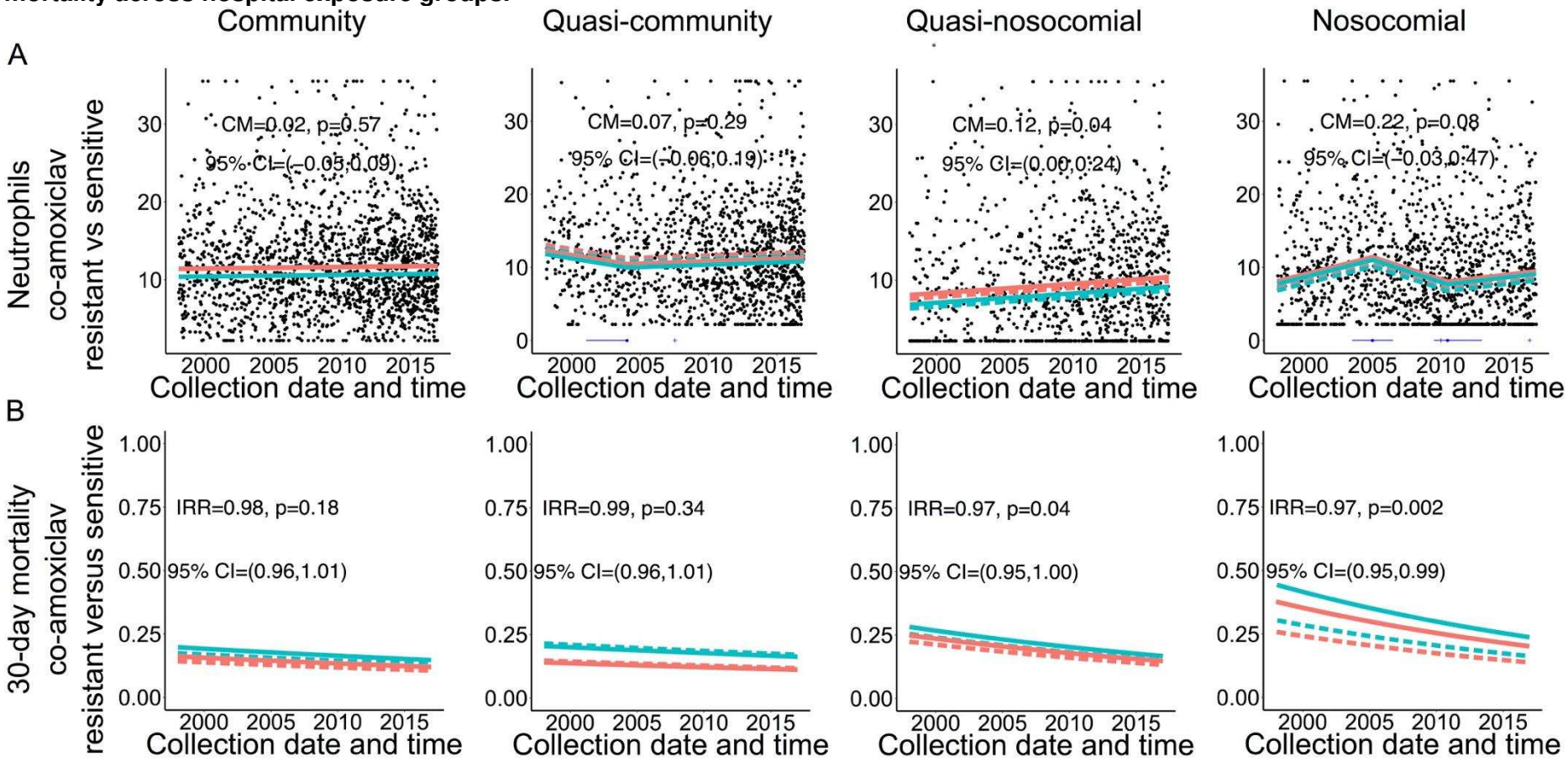
Footnote: IRR=annual incidence rate ratio in 2016.

Supplementary Figure 11. Annual EC-UTIs according to recent hospital-exposure and antibiotic susceptibility



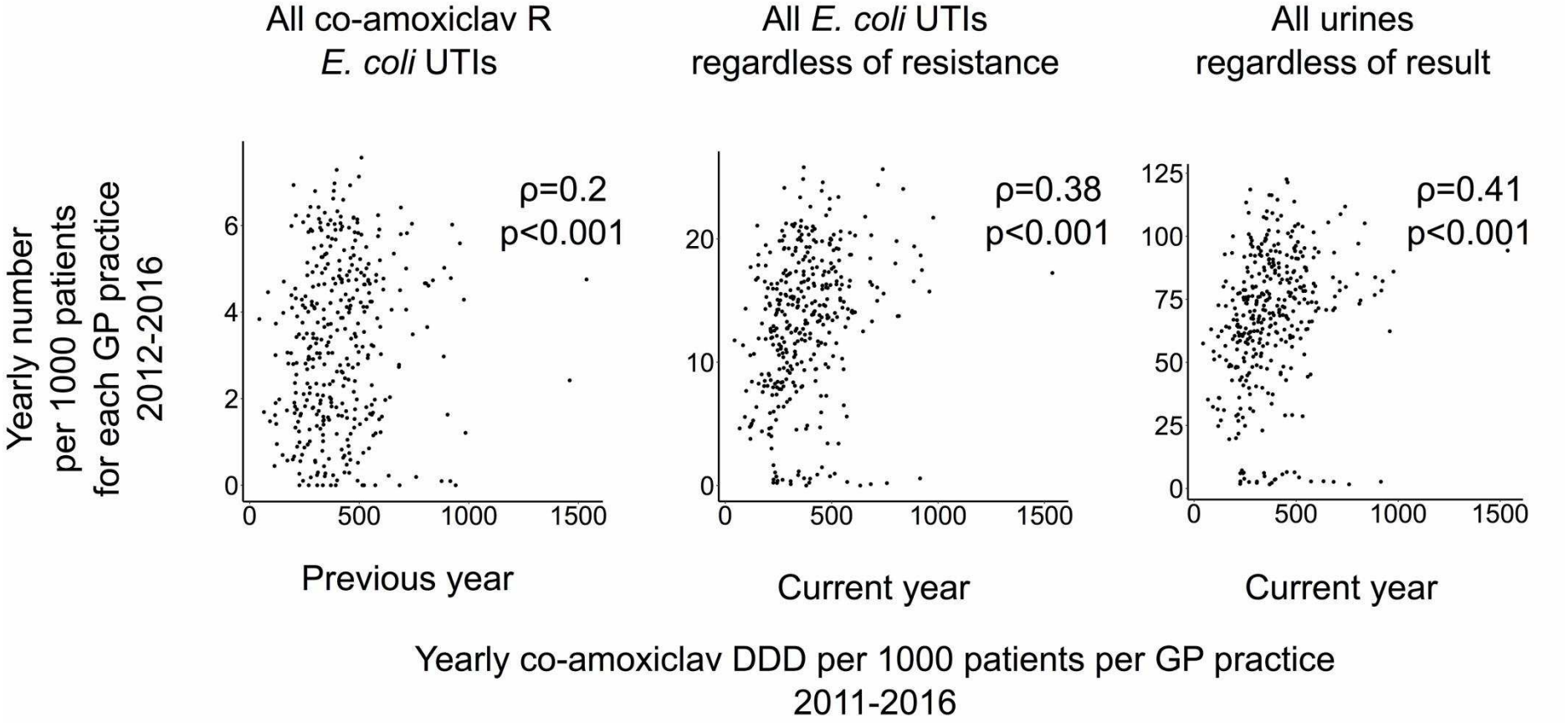
Footnote: IRR=annual incidence rate ratio in 2016.

Supplementary Figure 12: Severity of co-amoxiclav-resistant vs susceptible EC-BSIs, by (A) neutrophil counts and (B) 30-day mortality across hospital exposure groups.



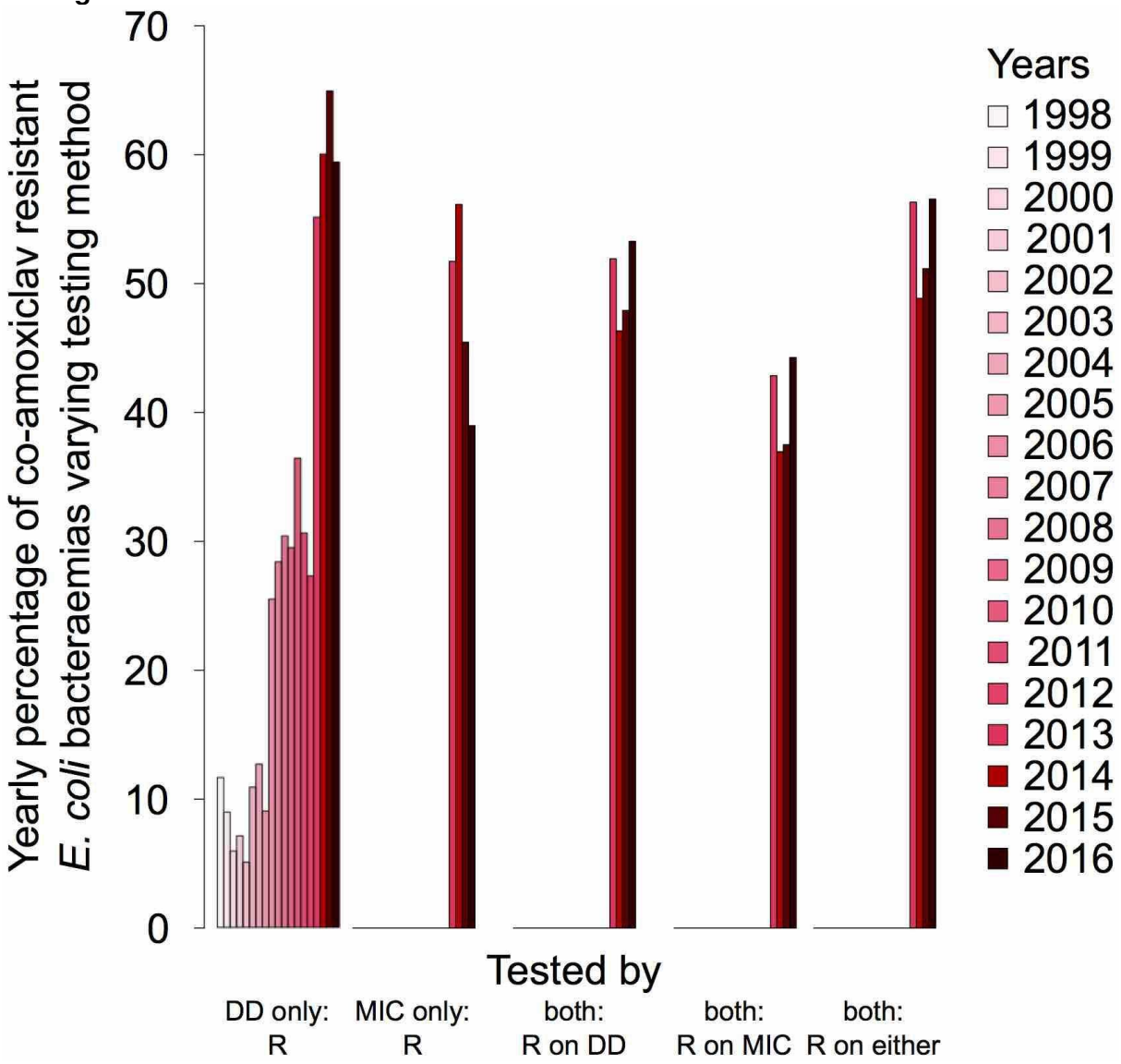
Footnote: CM=change per year in median value in 2016. Fitted lines are for co-amoxiclav susceptible women (red and dashed), co-amoxiclav susceptible men (blue and dashed), co-amoxiclav resistant women (red and solid), and co-amoxiclav resistant men (blue and solid) at mean age. IRR=annual rate ratio in 2016. Neutrophils and mortality are both also adjusted for age and sex. No evidence of different trends between co-amoxiclav susceptible and co-amoxiclav resistant for either neutrophils ($p_{heterogeneity}>0.67$) or 30-day mortality ($p_{heterogeneity}>0.35$).

Supplementary Figure 13. Number of urine samples submitted regardless of result, EC-UTIs and co-amoxiclav-resistant EC-UTIs per 1000 patients per GP practice 2012-2016 compared with co-amoxiclav DDD per 1000 patients per general practice in the previous year for the first and the current year for the last two (community, quasi-community, quasi-nosocomial, nosocomial groups combined)



Footnote: showing one record per year per GP practice. Spearman rho (and models) for each panel excludes 5 which submitted less than 151 samples over 2011-2016 (all others submitted over 308). Speraman rho for previous vs current for the 3 groups (ρ=0.2 vs ρ=0.05, ρ=0.36 vs ρ=0.38, ρ=0.38 vs ρ=0.41)

Supplementary Figure 14: Co-amoxiclav resistance in EC-BSIs according to different testing methods



Footnote: DD=disc diffusion. MIC=median inhibitory concentration by microbroth dilution (Phoenix)