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'.[2]

(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).[3] 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 χ^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, were compared using stacked regression.[4] In brief, these methods "stack" the data for different regression models, for example for EC-BSI incidence in each of the four different healthcare exposure subgroups over calendar time, on top of each other. Individual model-specific trends are then calculated but across the entire stacked dataset, using robust variance adjustment to account for the same dependent variable (here month) occurring repeatedly in the stacked dataset. Because these model-specific trends are calculated within the same stacked dataset, they can then be compared using standard Wald tests.

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).

For analysis of levels of monocytes, neutrophils, lymphocytes, C-reactive protein (CRP), creatinine and urea at sample collection (continuous outcomes, closest value within [-2,+2] days), 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,[3] models adjusted for this change using a step-function. Out-of-hospital mortality was determined by routine updates from a national information system. 1% (82/5701) of patients could not be linked (for example due to incomplete identifiers particularly in older historical data where NHS numbers were not used consistently); again analyses were restricted to complete cases where out-of-hospital mortality was available. All analyses of laboratory parameters and 30-day mortality were adjusted for age and sex (which led to 5 community cases being dropped as sex was unknown). To investigate whether there was any evidence of differential severity in susceptible versus resistant cases, we extended these models for 30-day mortality following EC-BSI and neutrophils at presentation with EC-BSI to additionally include a binary

factor for whether the EC-BSI was co-amoxiclav-resistant versus co-amoxiclav-susceptible, and the interaction between this factor and calendar time (as represented by exact date of blood sample collection). The interaction term tests whether there is any evidence that these severity markers are changing differently in co-amoxiclav-resistant versus co-amoxiclav-susceptible EC-BSI. As there was no evidence of such heterogeneity, the interaction term was removed from the model and a main effect of co-amoxiclav-resistant versus co-amoxiclav-susceptible EC-BSI on 30-day mortality following EC-BSI and neutrophils at presentation with EC-BSI estimated.

In order to estimate a simple univariable association between hospital antimicrobial prescribing and nosocomial 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 and including the number of patients per primary-care facility per year as an offset. 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 from the community from 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 primary-care facility as explanatory variables, without primary-care facility.

Supplementary Results

(a) Further details of quasi-nosocomial BSIs
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 1**), with no major temporal variability (**Supplementary Figure 1A**).

There was no evidence that the antecedent admission was shorter in the 1132 quasi-nosocomial EC-BSI patients discharged in the preceding 30 days than the quasi-community EC-BSI patients discharged 31-365 days previously (median 2·0 (IQR:0·3-7·9) days vs 2·3 (0·3-8·2) respectively, ranksum p=0·15).

There was, however, 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 1B&C**), but these still comprised <25% of quasi-nosocomial EC-BSIs.

References

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Supplementary Table 1 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	1	2	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 2 Summary of current (2016) annual rate ratios

	Insert	Community aRR (95% CI)	Quasi-community aRR (95% CI)	Quasi-nosocomial aRR (95% CI)	Nosocomial 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<0.0001	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=0.0006	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<0.0001	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=0.0002	p=0.03
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<0.0001	p<0.0001	p<0.0001	p<0.0001
30-day mortality: all EC-BSI	Supp. Fig 7	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 7	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<0.0001	p<0.0001	p=0.99	p<0.0001
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)**
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<0.0001	p<0.0001	p<0.0001	p<0.0001

* 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 3 Relative contribution of recurrent EC-BSIs and EC-UTIs to total numbers in 2016 by recent hospital-exposure

	Community Recurrent/total (%)	Quasi-community Recurrent/total (%)	Quasi-nosocomial Recurrent/total (%)	Nosocomial 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 4 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 5 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 6 Yearly numerators/denominators (percentages) for 30-day mortality following EC-BSI, co-amoxiclav resistant EC-BSIs and 30-day mortality following EC-BSI in co-amoxiclav resistant versus sensitive cases

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
30-day mortality following EC-BSI																				
Community	11/65	9/67	9/79	10/68	7/72	16/80	13/73	10/80	21/81	10/81	12/84	17/88	10/84	13/107	14/112	18/129	18/141	17/133	19/160	254/1858
	(17%)	(13%)	(11%)	(15%)	(10%)	(20%)	(18%)	(12%)	(26%)	(12%)	(14%)	(19%)	(12%)	(12%)	(12%)	(14%)	(13%)	(13%)	(12%)	(14%)
Quasi-community	5/24	8/52	10/41	3/32	9/51	6/52	10/58	4/33	13/49	11/63	10/68	14/69	14/78	14/86	11/90	14/109	13/108	24/117	26/164	219/1346
	(21%)	(15%)	(24%)	(9%)	(18%)	(12%)	(17%)	(12%)	(27%)	(17%)	(15%)	(20%)	(18%)	(16%)	(12%)	(13%)	(12%)	(21%)	(16%)	(16%)
Quasi-nosocomial	5/34	7/36	8/37	5/27	9/38	8/32	10/48	5/32	16/53	15/54	9/62	23/82	16/83	11/82	12/89	14/85	8/76	17/87	19/91	217/1132
	(15%)	(19%)	(22%)	(19%)	(24%)	(25%)	(21%)	(16%)	(30%)	(28%)	(15%)	(28%)	(19%)	(13%)	(13%)	(16%)	(11%)	(20%)	(21%)	(19%)
Nosocomial	18/43	19/60	19/69	14/54	16/54	14/65	14/59	20/73	15/60	13/77	26/85	17/82	20/85	19/83	25/91	18/68	14/71	16/86	23/98	340/1365
	(42%)	(32%)	(28%)	(26%)	(30%)	(22%)	(24%)	(27%)	(25%)	(17%)	(31%)	(21%)	(24%)	(23%)	(27%)	(26%)	(20%)	(19%)	(23%)	(25%)
Numbers of co-amoxiclav resistant EC-BSIs																				
Community	8/72	3/70	9/87	7/70	6/74	8/85	9/78	7/82	19/86	15/81	16/87	21/93	20/88	22/110	17/113	48/135	44/144	42/136	46/162	367/1853
	(11%)	(4%)	(10%)	(10%)	(8%)	(9%)	(12%)	(9%)	(22%)	(19%)	(18%)	(23%)	(23%)	(20%)	(15%)	(36%)	(31%)	(31%)	(28%)	(20%)
Quasi-community	2/25	7/51	6/32	5/51	8/52	7/58	3/33	18/49	14/63	14/68	14/69	18/77	16/87	11/90	40/109	46/108	43/117	65/164	2/25	337/1343
	(8%)	(14%)	(19%)	(10%)	(15%)	(12%)	(9%)	(37%)	(22%)	(21%)	(20%)	(23%)	(18%)	(12%)	(37%)	(43%)	(37%)	(40%)	(8%)	(25%)
Quasi-nosocomial	5/35	2/36	3/37	1/27	1/38	3/32	8/48	3/32	11/53	18/54	11/63	20/84	36/83	19/81	23/89	41/85	27/76	34/87	47/91	313/1131
	(14%)	(6%)	(8%)	(4%)	(3%)	(9%)	(17%)	(9%)	(21%)	(33%)	(17%)	(24%)	(43%)	(23%)	(26%)	(48%)	(36%)	(39%)	(52%)	(28%)
Nosocomial	6/43	8/61	4/69	8/53	8/54	8/65	8/59	9/73	10/60	23/78	24/85	24/82	29/85	25/83	27/91	40/68	39/71	42/86	54/98	396/1364
	(14%)	(13%)	(6%)	(15%)	(15%)	(12%)	(14%)	(12%)	(17%)	(29%)	(28%)	(29%)	(34%)	(30%)	(30%)	(59%)	(55%)	(49%)	(55%)	(29%)
30-day mortality following EC-BSI: co-amoxiclav resistant versus sensitive																				
Community resistant	1/7	0/2	1/7	1/6	1/6	1/8	1/9	0/6	3/18	3/15	2/16	8/19	1/20	4/22	0/17	7/45	6/42	7/41	7/44	54/350
	(14%)	(0%)	(14%)	(17%)	(17%)	(12%)	(11%)	(0%)	(17%)	(20%)	(12%)	(42%)	(5%)	(18%)	(0%)	(16%)	(14%)	(17%)	(16%)	(15%)
Community sensitive	10/58	9/65	8/71	8/61	6/66	15/72	11/63	10/74	18/63	6/65	10/68	9/69	9/64	9/85	13/94	11/84	12/98	9/90	12/115	195/1425
	(17%)	(14%)	(11%)	(13%)	(9%)	(21%)	(17%)	(14%)	(29%)	(9%)	(15%)	(13%)	(14%)	(11%)	(14%)	(13%)	(12%)	(10%)	(10%)	(14%)
Quasi-community resistant	0/1	1/6	0/0	0/6	2/5	1/8	1/7	0/3	5/18	3/14	3/14	3/14	3/18	5/16	3/11	4/40	4/46	8/43	7/65	53/335
	(0%)	(17%)	(-)	(0%)	(40%)	(12%)	(14%)	(0%)	(28%)	(21%)	(21%)	(21%)	(17%)	(31%)	(27%)	(10%)	(9%)	(19%)	(11%)	(16%)
Quasi-community sensitive	5/23	7/45	10/40	3/26	7/46	5/44	9/51	4/30	8/31	8/49	7/54	11/55	11/59	9/70	8/79	10/69	9/62	16/74	19/99	166/1006
	(22%)	(16%)	(25%)	(12%)	(15%)	(11%)	(18%)	(13%)	(26%)	(16%)	(13%)	(20%)	(19%)	(13%)	(10%)	(14%)	(15%)	(22%)	(19%)	(17%)
Quasi-nosocomial resistant	1/5	1/2	0/3	0/1	1/1	2/3	0/8	0/3	3/11	4/18	0/11	5/20	6/36	4/19	3/23	10/41	4/27	5/34	13/47	62/313
	(20%)	(50%)	(0%)	(0%)	(100%)	(67%)	(0%)	(0%)	(27%)	(22%)	(0%)	(25%)	(17%)	(21%)	(13%)	(24%)	(15%)	(15%)	(28%)	(20%)
Quasi-nosocomial sensitive	4/29	6/34	8/34	5/26	8/37	6/29	10/40	5/29	13/42	11/36	9/51	18/62	10/47	6/62	9/66	4/44	4/49	12/53	6/44	154/814
	(14%)	(18%)	(24%)	(19%)	(22%)	(21%)	(25%)	(17%)	(31%)	(31%)	(18%)	(29%)	(21%)	(10%)	(14%)	(9%)	(8%)	(23%)	(14%)	(19%)
Nosocomial resistant	3/6	1/8	1/4	5/8	5/8	1/8	3/8	2/9	4/10	4/22	6/24	10/24	6/29	8/25	9/27	14/40	10/39	13/42	12/54	117/395
	(50%)	(12%)	(25%)	(62%)	(62%)	(12%)	(38%)	(22%)	(40%)	(18%)	(25%)	(42%)	(21%)	(32%)	(33%)	(35%)	(26%)	(31%)	(22%)	(30%)
Nosocomial sensitive	15/37	18/52	18/65	8/45	11/46	13/57	11/51	18/64	11/50	9/55	20/61	7/58	14/56	11/58	16/64	4/28	4/32	3/44	11/44	222/967
	(41%)	(35%)	(28%)	(18%)	(24%)	(23%)	(22%)	(28%)	(22%)	(16%)	(33%)	(12%)	(25%)	(19%)	(25%)	(14%)	(12%)	(7%)	(25%)	(23%)

Note: not adjusted for age and sex, in contrast to model estimates. Mortality based on complete cases (those who could be routinely linked to national information systems, see Supplementary Methods).

Supplementary Table 7 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

Bacteraemias		Tested(%)	Resistant(%)	Tested in 2016(%)	Resistant in 2016(%)
	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 8 Cross-correlation between hospital antimicrobial prescribing and co-amoxiclav-resistant nosocomial EC-BSI

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

* bivariate cross-correlation between hospital antimicrobial prescribing and nosocomial co-amoxiclav resistant bacteremia incidence, see Supplementary Methods. 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, etc). The cross-correlation of largest absolute magnitude is shown.

Supplementary Figure 1. Annual quasi-nosocomial EC-BSIs according to the previous diagnostic code.
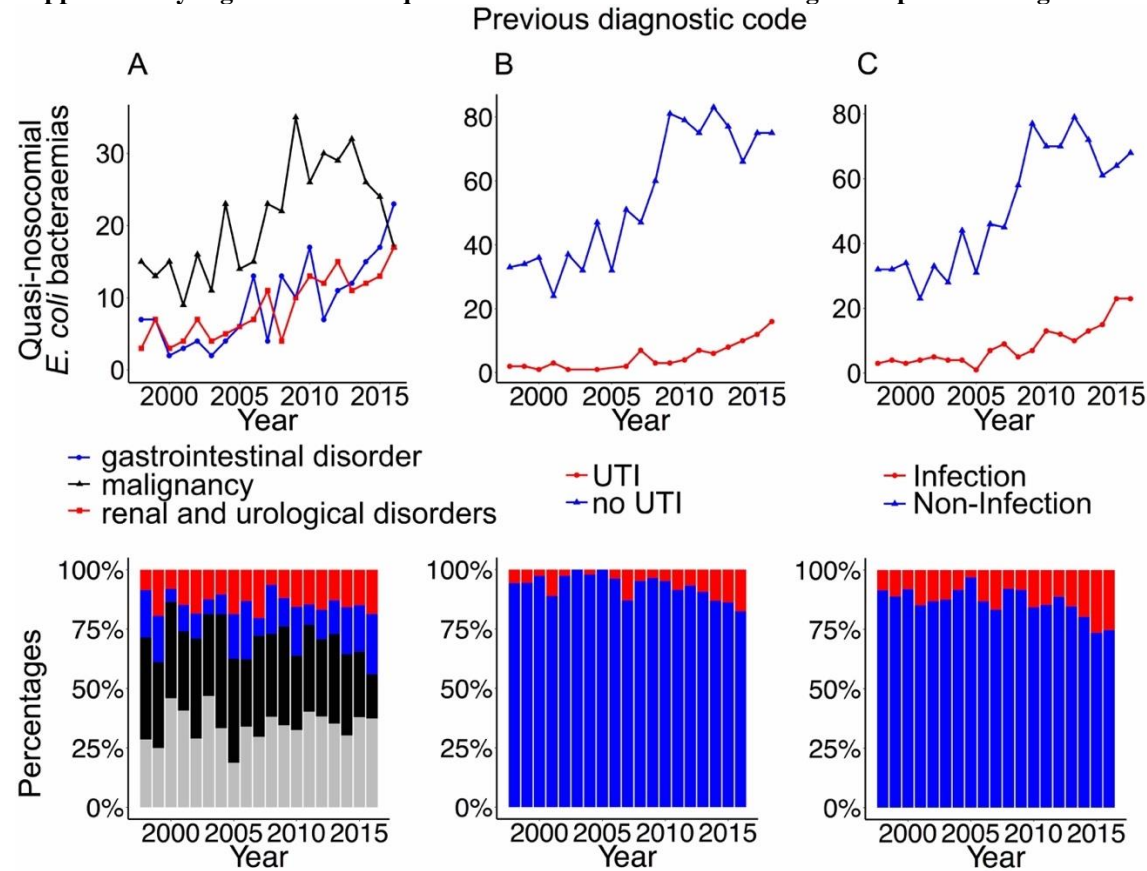
Footnote: (A) the three main categories of primary diagnostic codes for the antecedent admission, (B) having a UTI in any of the diagnostic codes of the previous admission to the EC-BSI, and (C) having the primary diagnostic code of the previous admission as an infection versus non-infection. See Supplementary Table 5 for all diagnostic code categories.

Supplementary Figure 2. Monthly EC-BSI according to recent hospital-exposure (A) first per patient only (B) recurrences within a patient only.
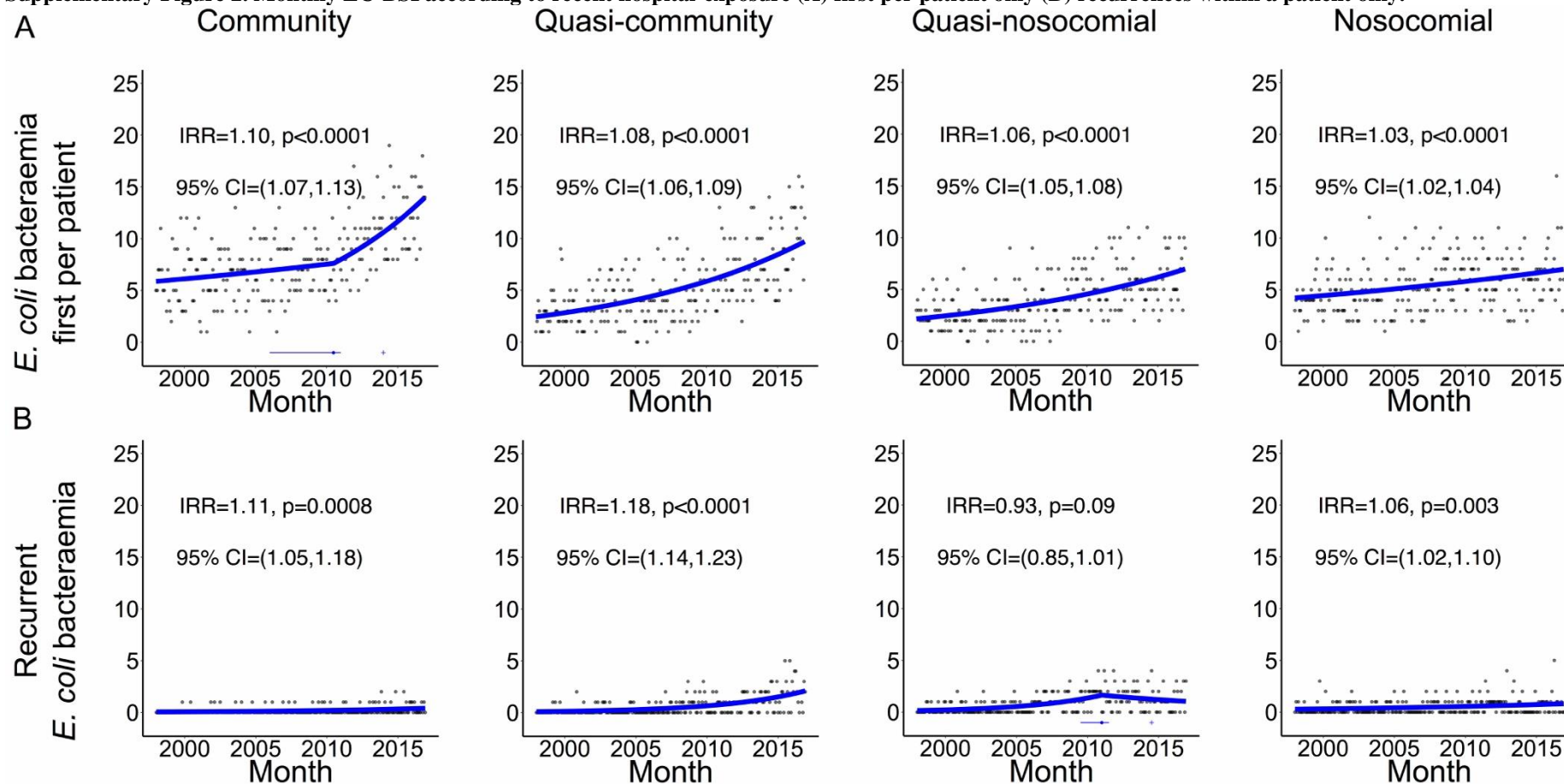
Footnote: IRR=annual incidence rate ratio in 2016, that is the relative increase in rate per year as estimated in 2016. See Table 1 for heterogeneity tests between first vs subsequent EC-BSIs.

Supplementary Figure 3. Monthly EC-UTIs according to recent hospital-exposure (A) first per patient only (B) recurrences within a patient only.
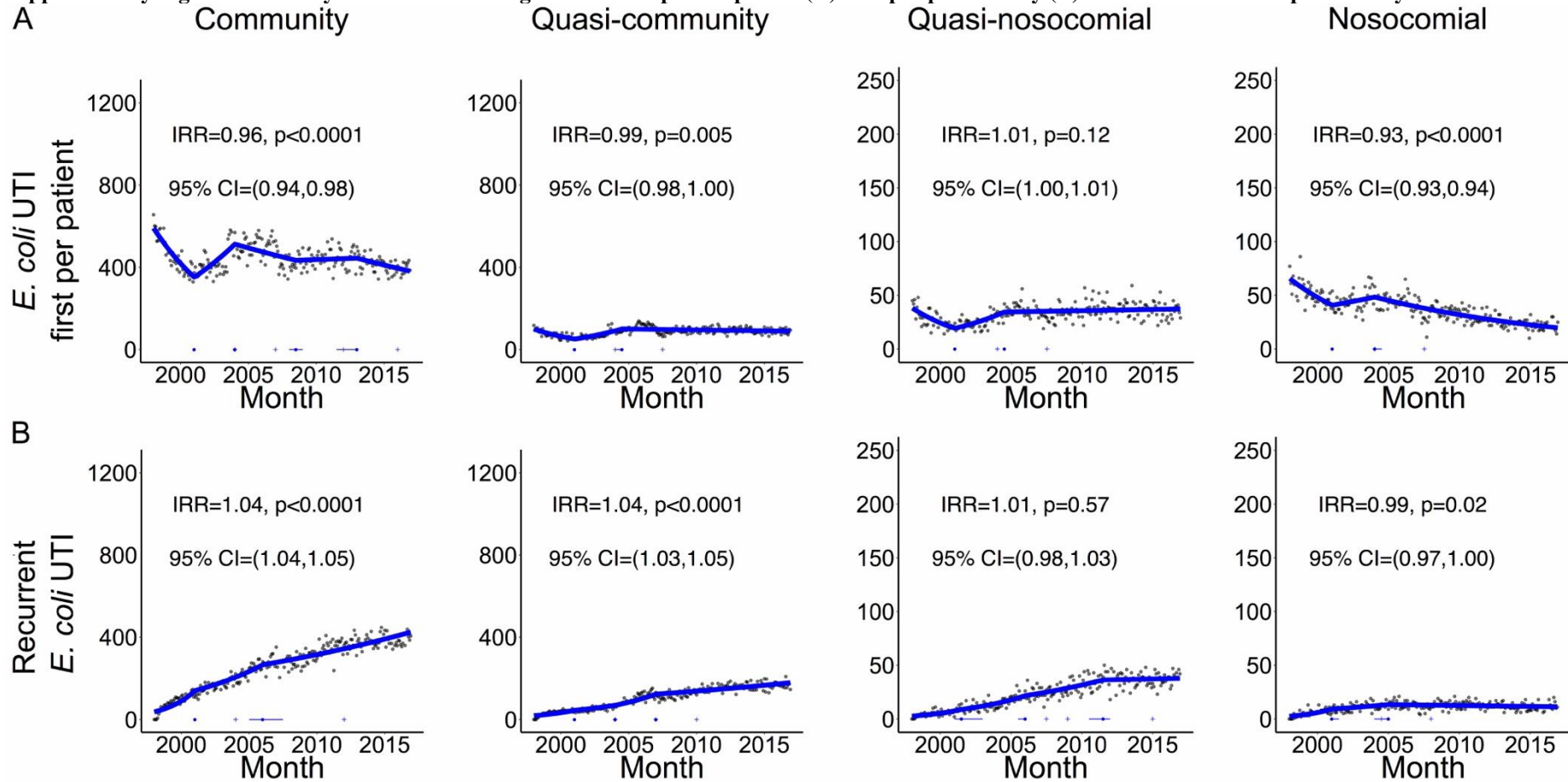
Footnote: IRR=annual incidence rate ratio in 2016, that is the relative increase in rate per year as estimated in 2016. See Table1 for heterogeneity tests between first vs subsequent EC-UTIs.

Supplementary Figure 4. Monthly blood samples submitted for culture regardless of result according to recent hospital-exposure (first and repeat samples per patient).
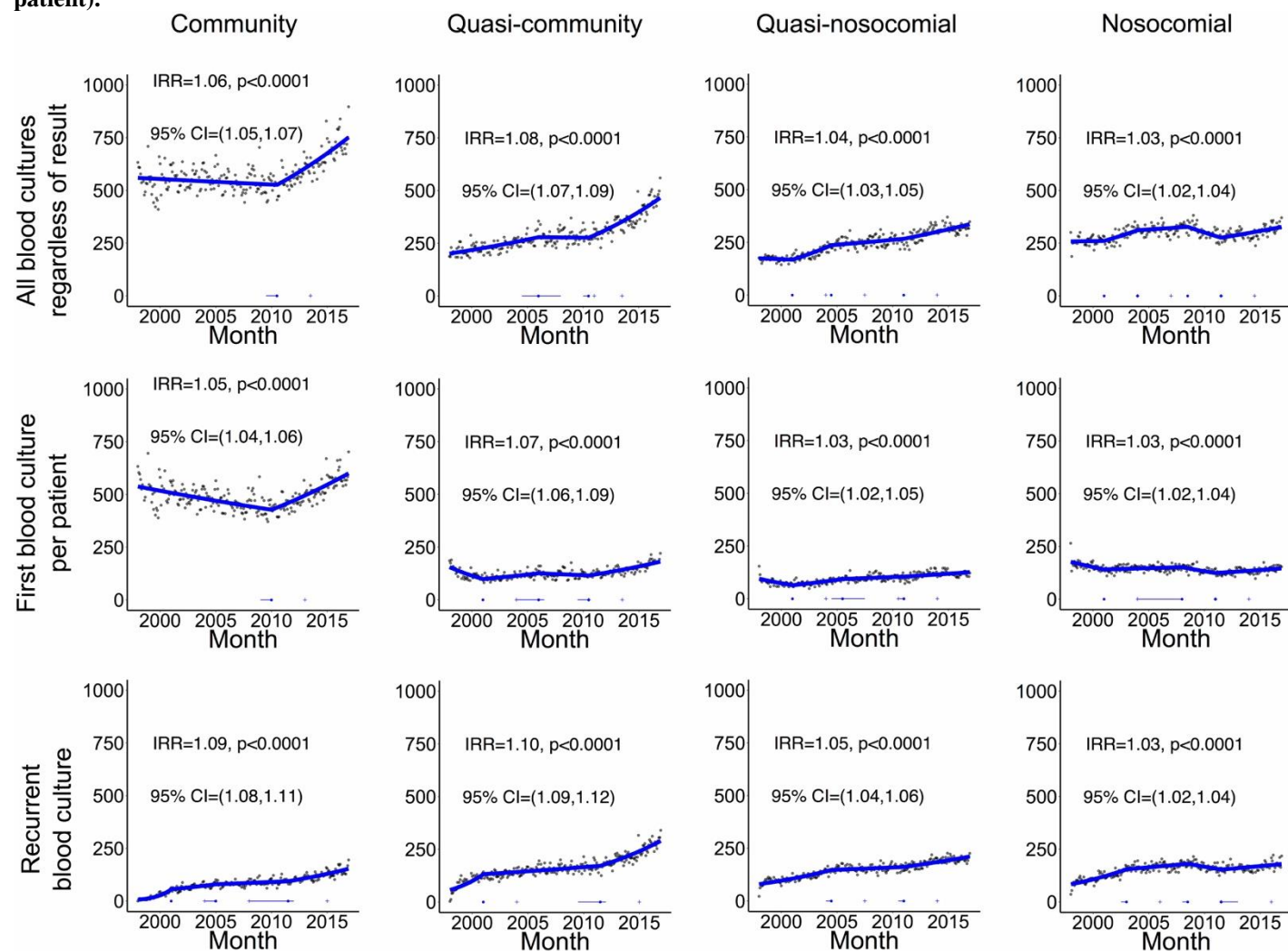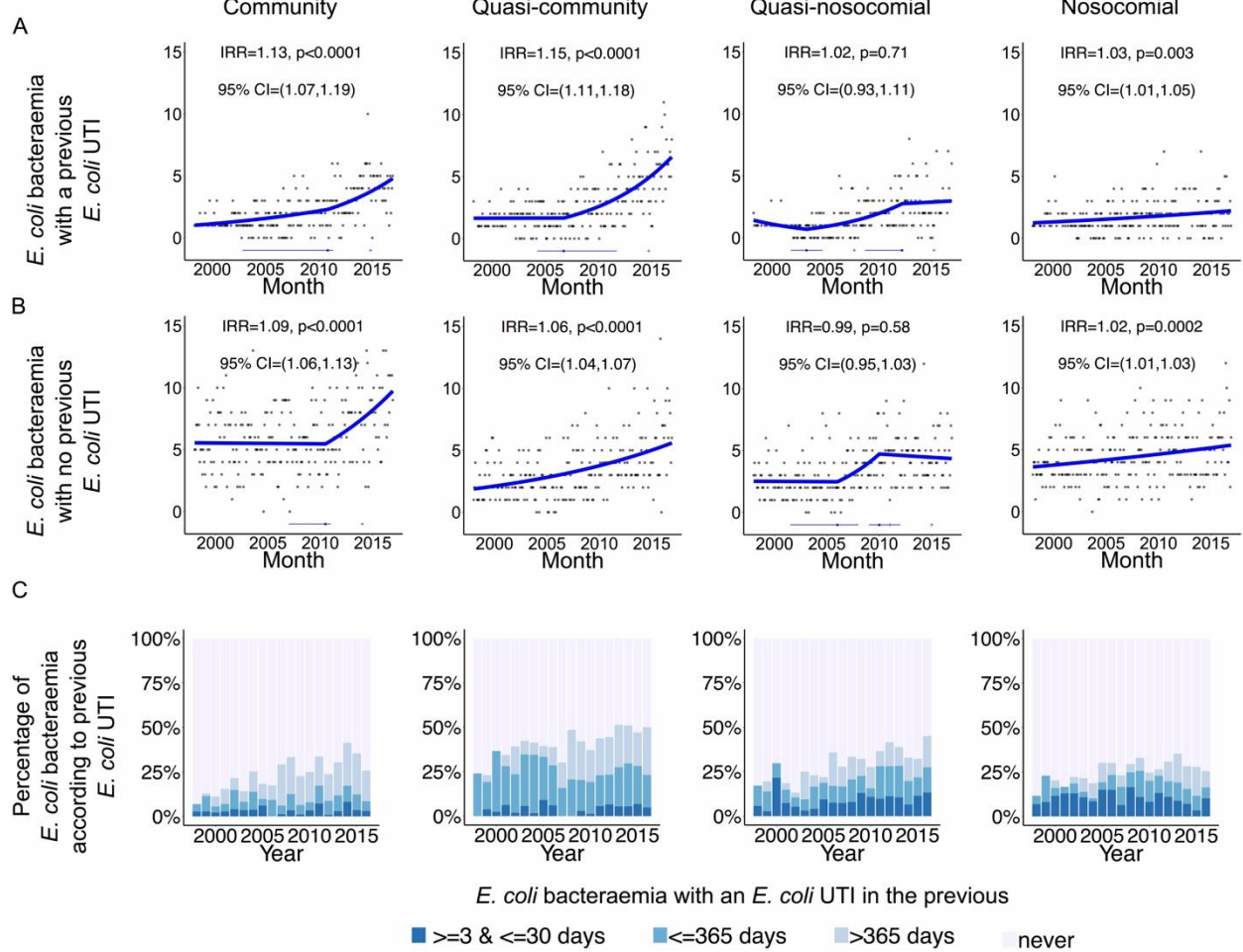

Footnote: including repeat samples submitted >14 days after an index sample. IRR=annual incidence rate ratio in 2016, that is the relative increase in rate per year as estimated in 2016.

Supplementary Figure 5. 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).
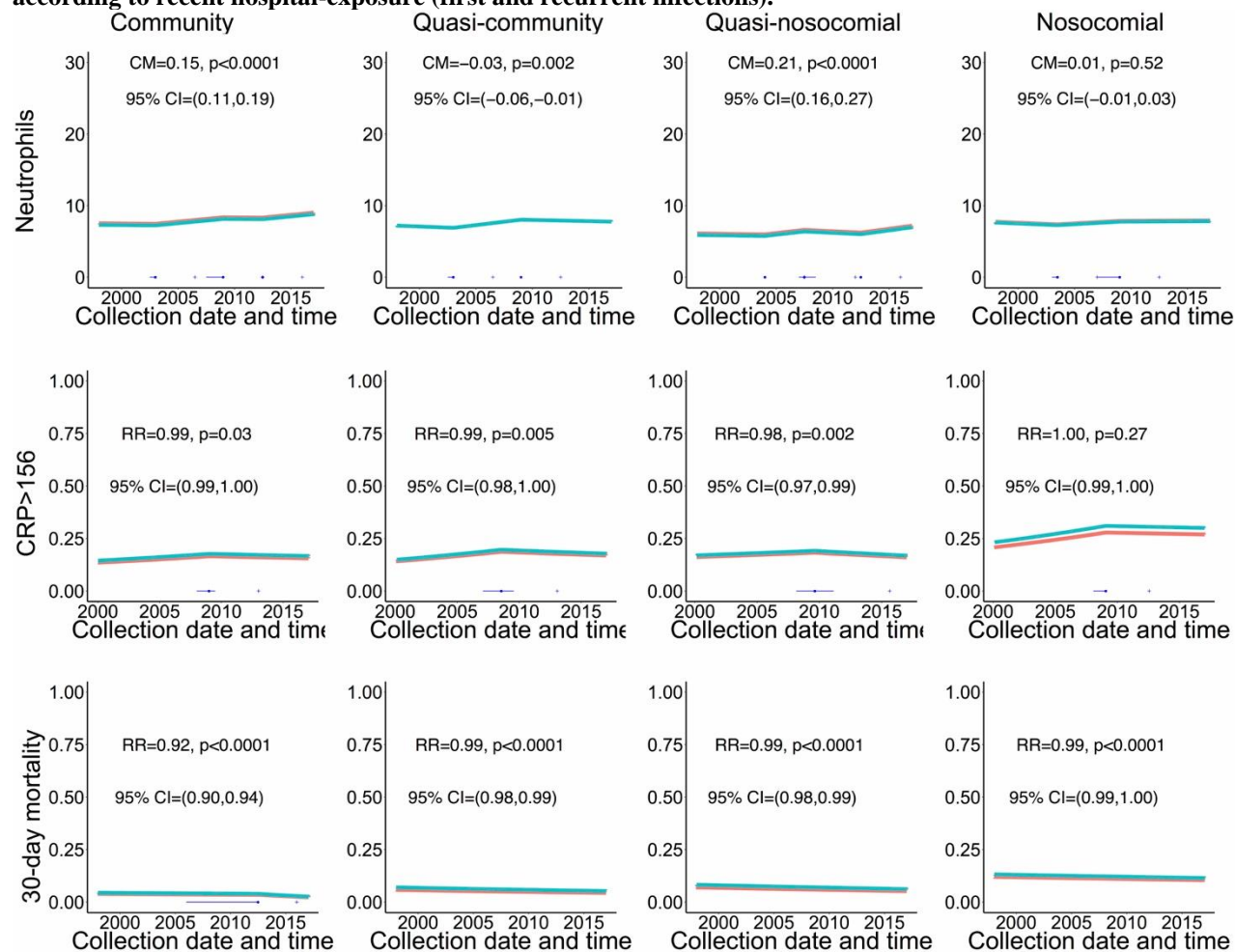
Footnote: including repeat samples submitted >14 days after an index sample. Fitted lines are for men (blue) and women (red) at mean age, IRR=annual rate ratio in 2016, that is the relative increase in rate per year as estimated in 2016. CM=change in median in 2016

Supplementary Figure 6. Monthly urine samples submitted for culture regardless of result according to recent hospital-exposure (first and repeat samples per patient).
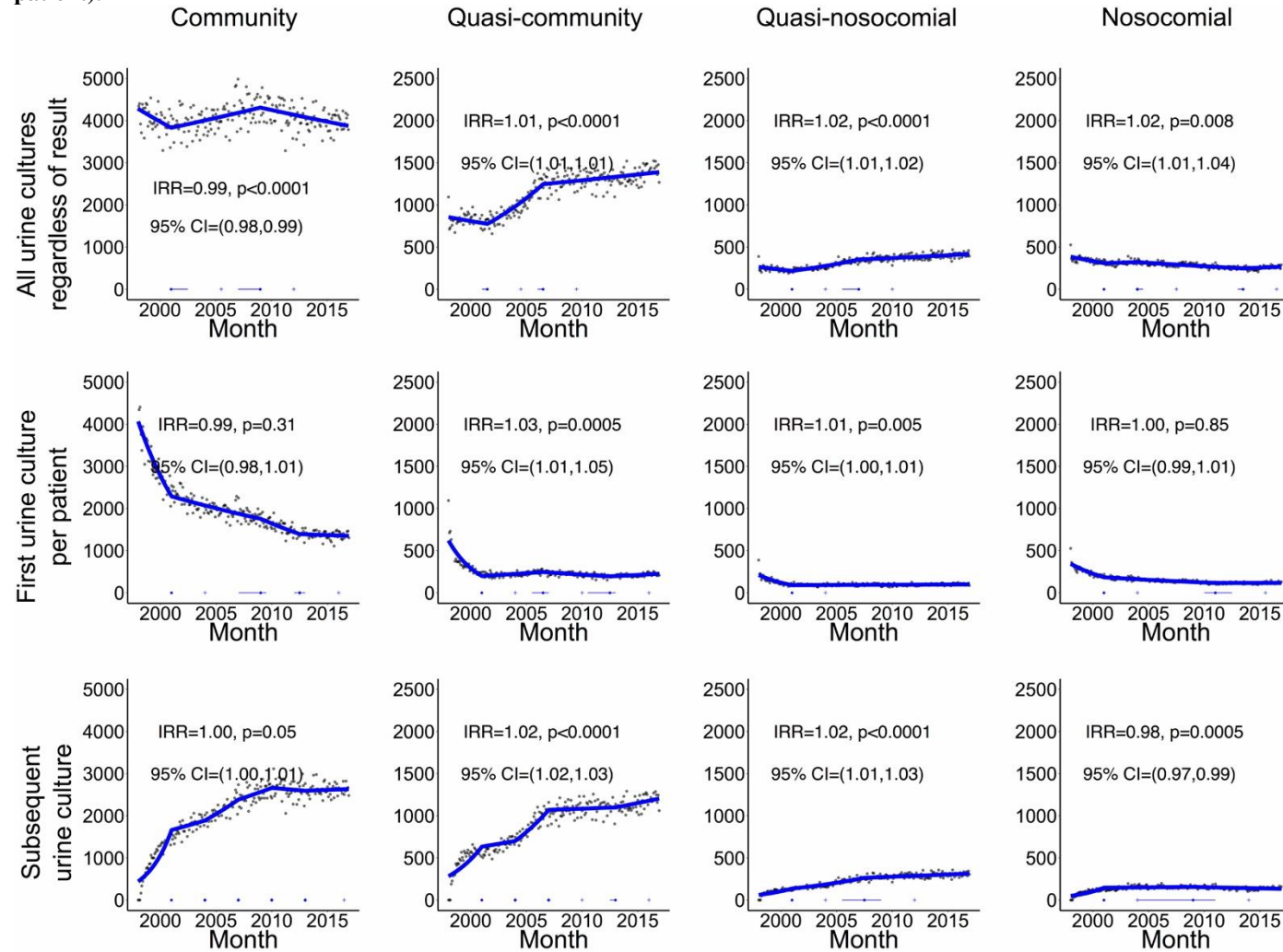
Footnote: including repeat samples submitted >90 days after an index sample. IRR=annual incidence rate ratio in 2016, that is the relative increase in rate per year as estimated in 2016.

Supplementary Figure 7. Trends in haematology/biochemistry test results and 30-day mortality following EC-BSI according to recent hospital-exposure (first and recurrent infections).
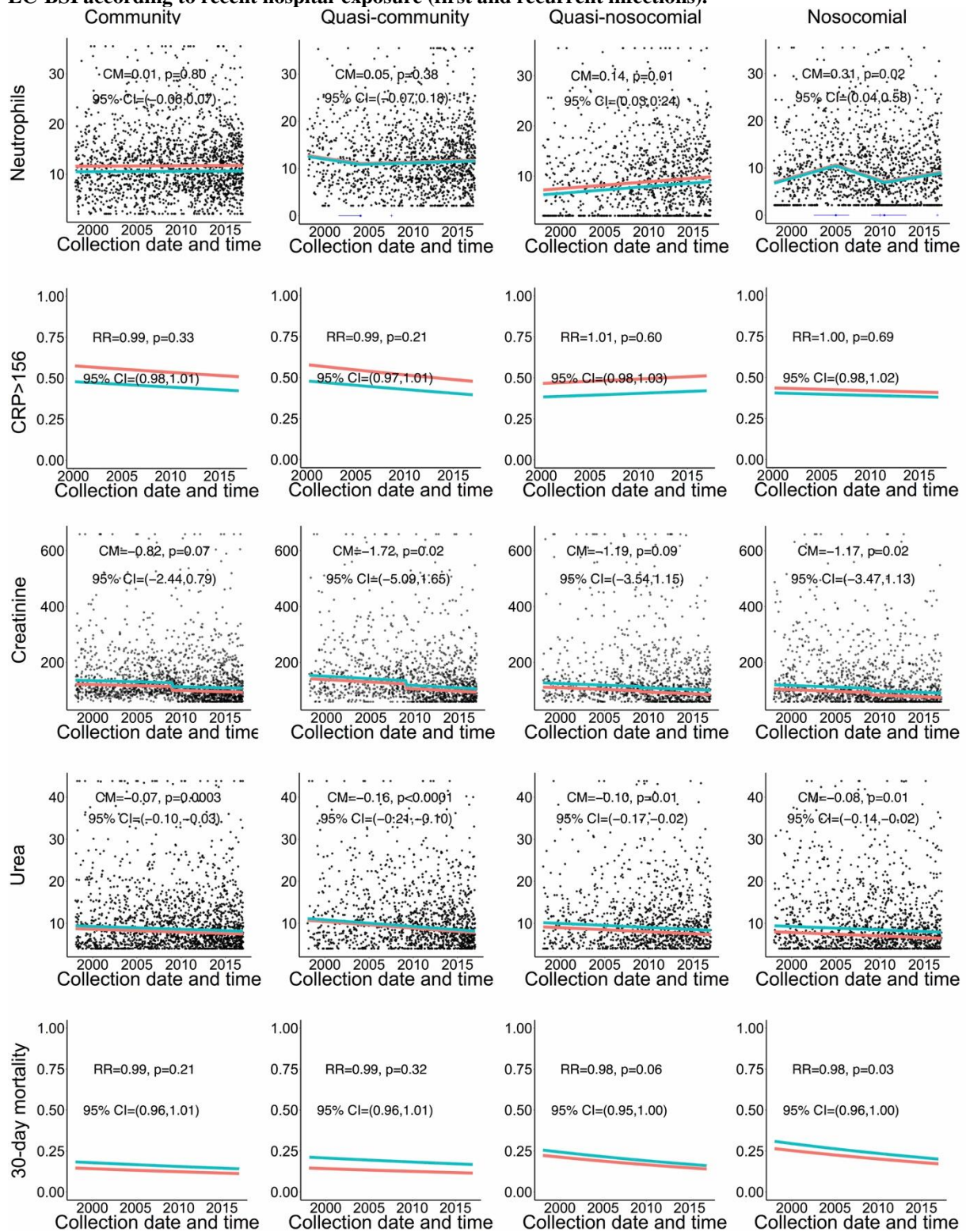
Footnote: CM=change per year in median value in 2016, that is the relative increase in rate per year as estimated in 2016. Adjusted for age and gender. Fitted lines are for men (blue) and women (red) at mean age, IRR=annual rate ratio in 2016.

Supplementary Figure 8. EC-BSIs: whether (A) patient had had an EC-UTI ≥3 days previously (B) patient had not had an EC-UTI ≥3 days previously (C) EC-BSIs according to time from previous EC-UTI.

Footnote: C: had had an EC-UTI 3-30 days previously, 31 to 365 days previously, more than 365 days previously, or never. IRR=annual incidence rate ratio in 2016, that is the relative increase in rate per year as estimated 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 9. EC-BSIs: whether (A) patient had had a catheter urine specimen (CSU) previously (B) patient had not had a CSU previously (C) EC-BSIs according to time from previous CSU.
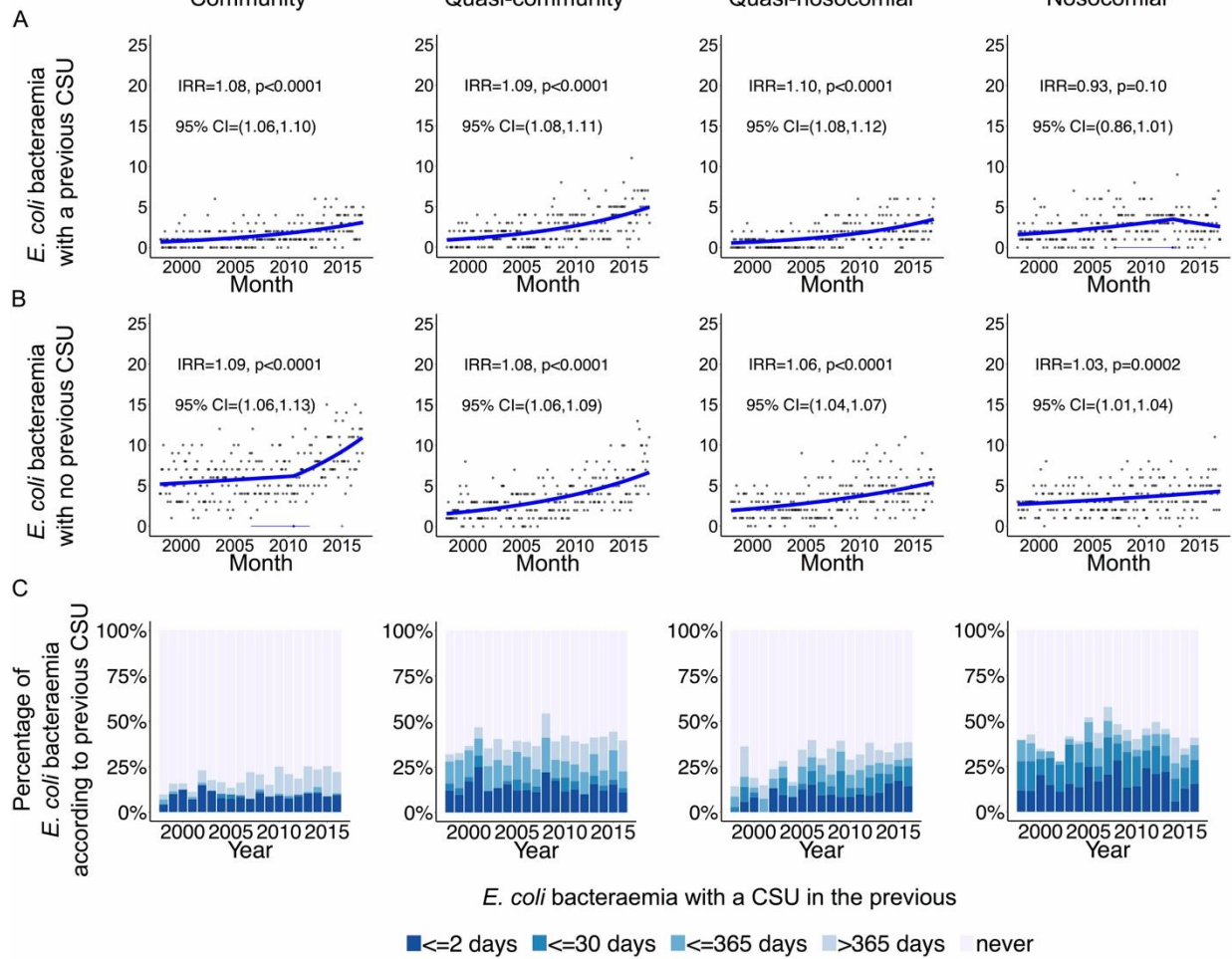

Footnote: C: had had a CSU in the previous 2 days, 3-30 days previously, 31 to 365 days previously, more than 365 days previously, or never. IRR=annual incidence rate ratio in 2016, that is the relative increase in rate per year as estimated in 2016. See Supplementary Table 1 for heterogeneity tests between patients with and without a CSU previously.

Supplementary Figure 10. Annual EC-BSIs according to recent hospital-exposure and antibiotic susceptibility (A) by antibiotic, (B) summary.
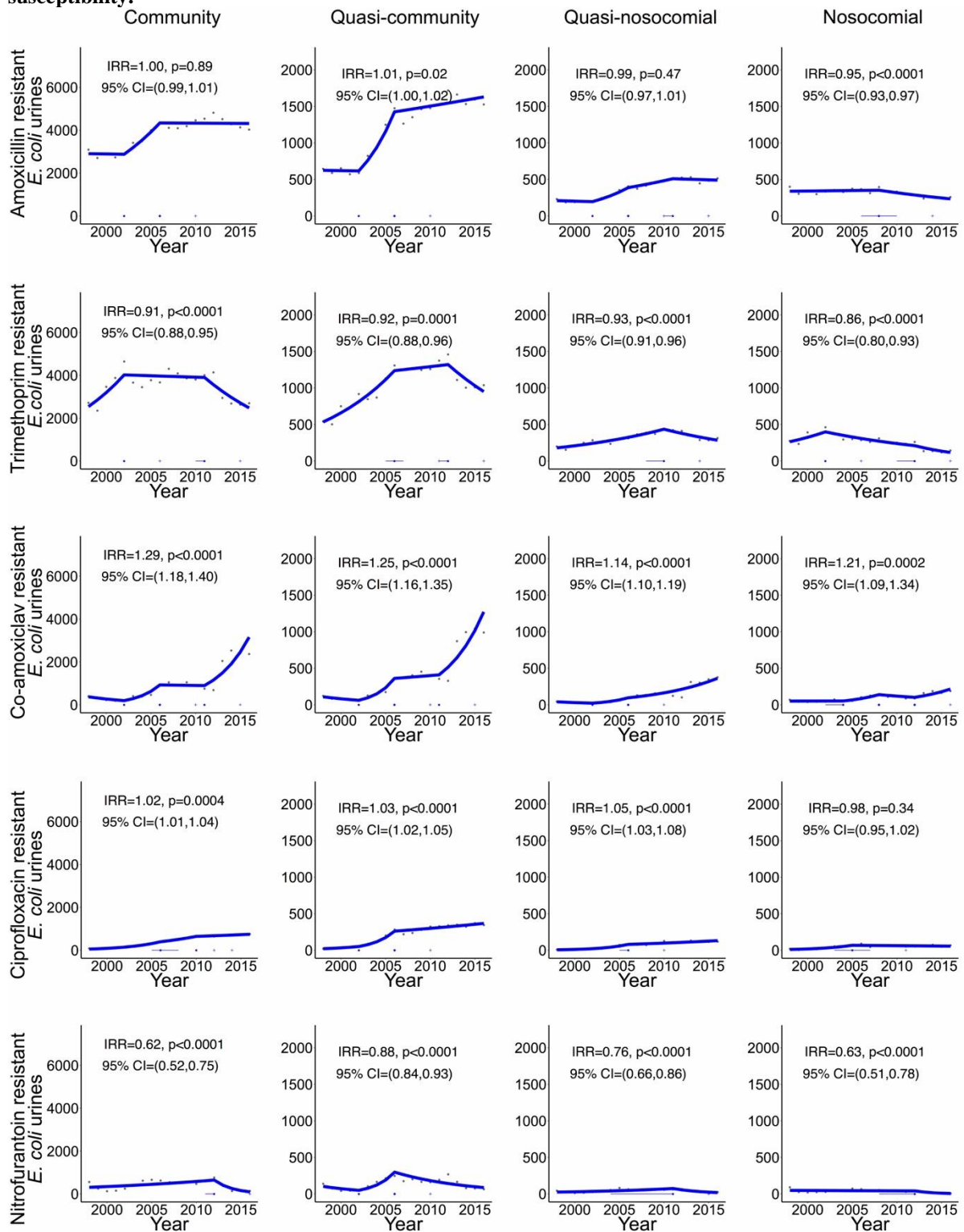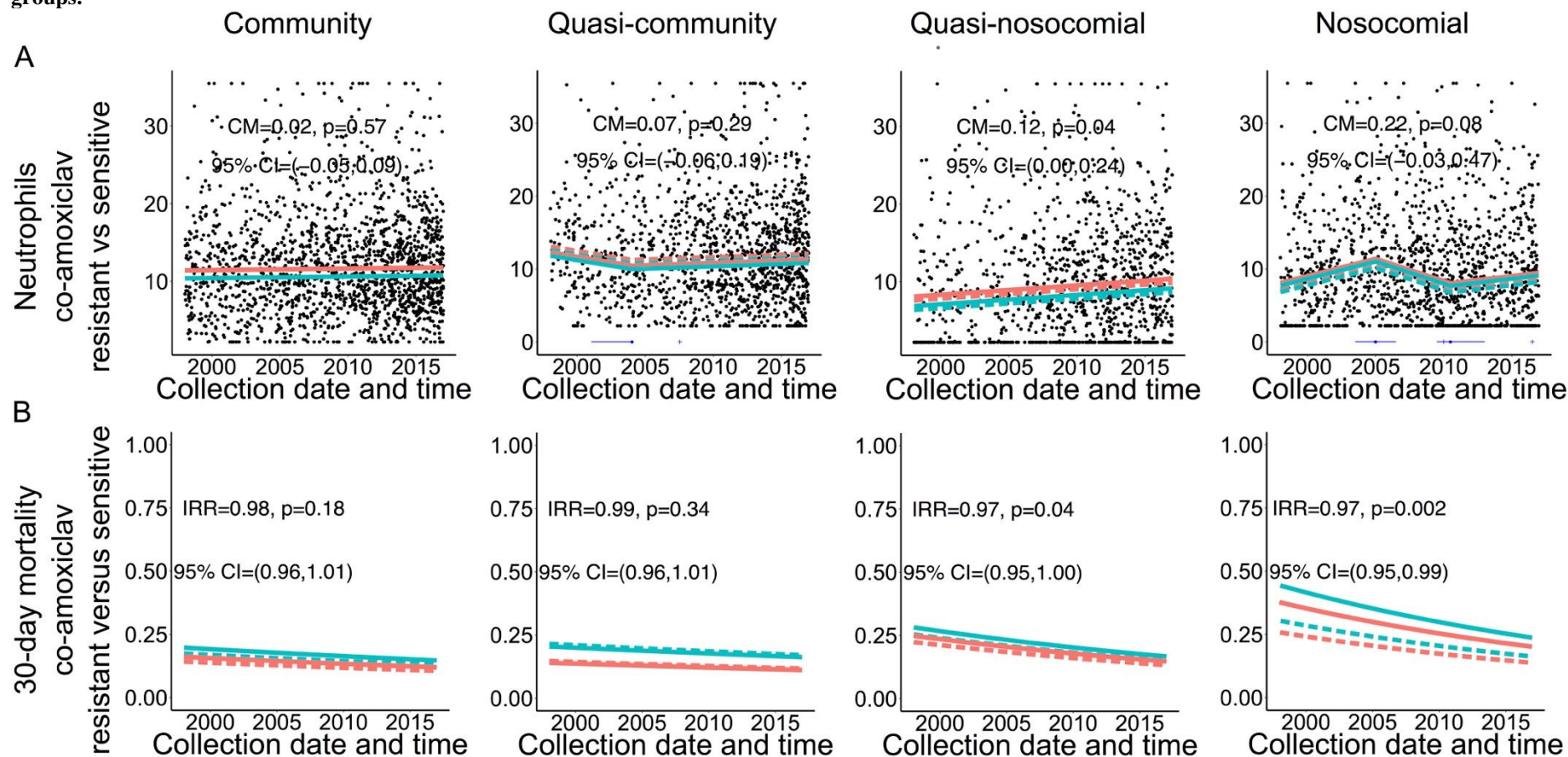
(A) by antibiotic
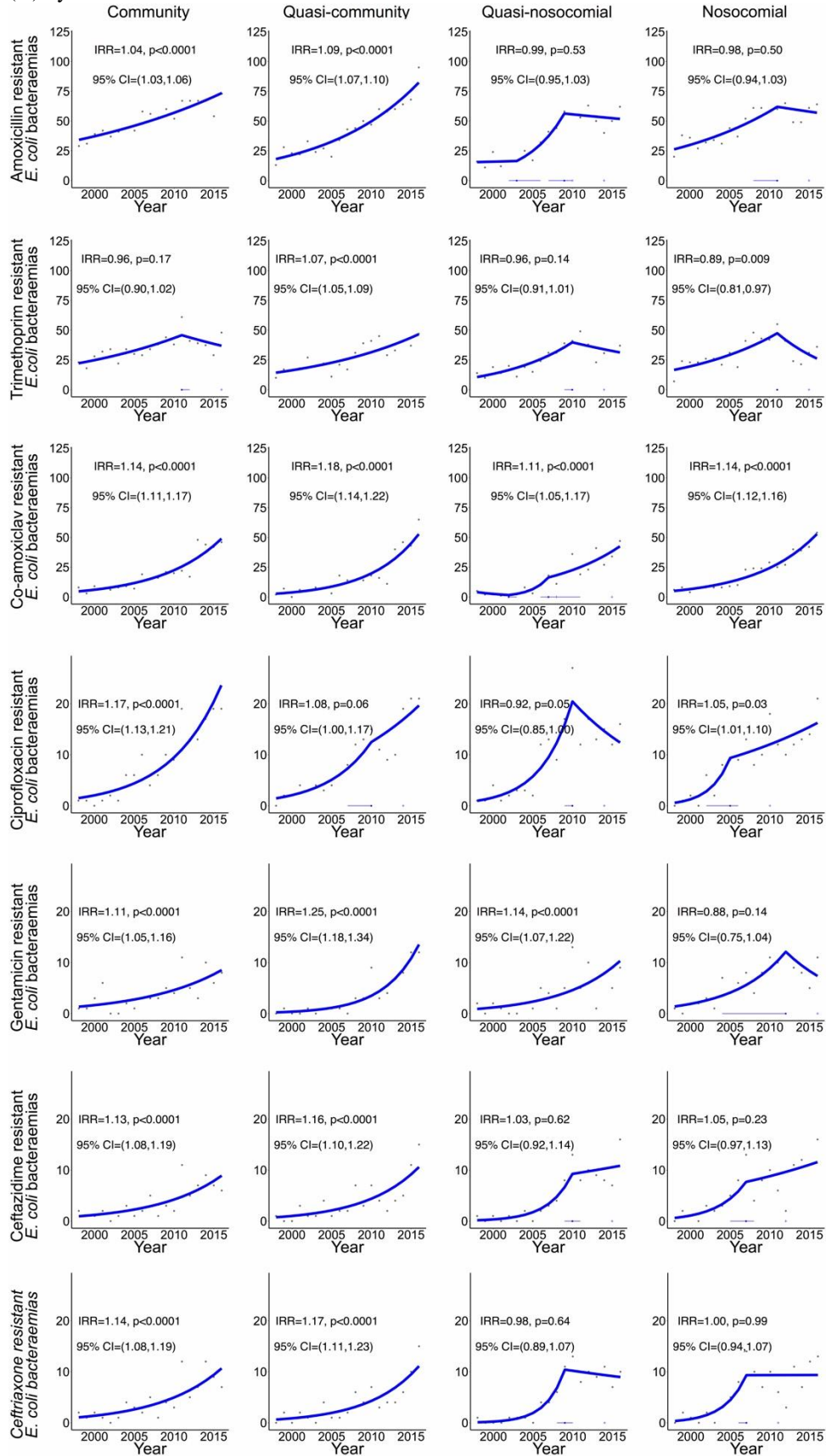
(B) summary
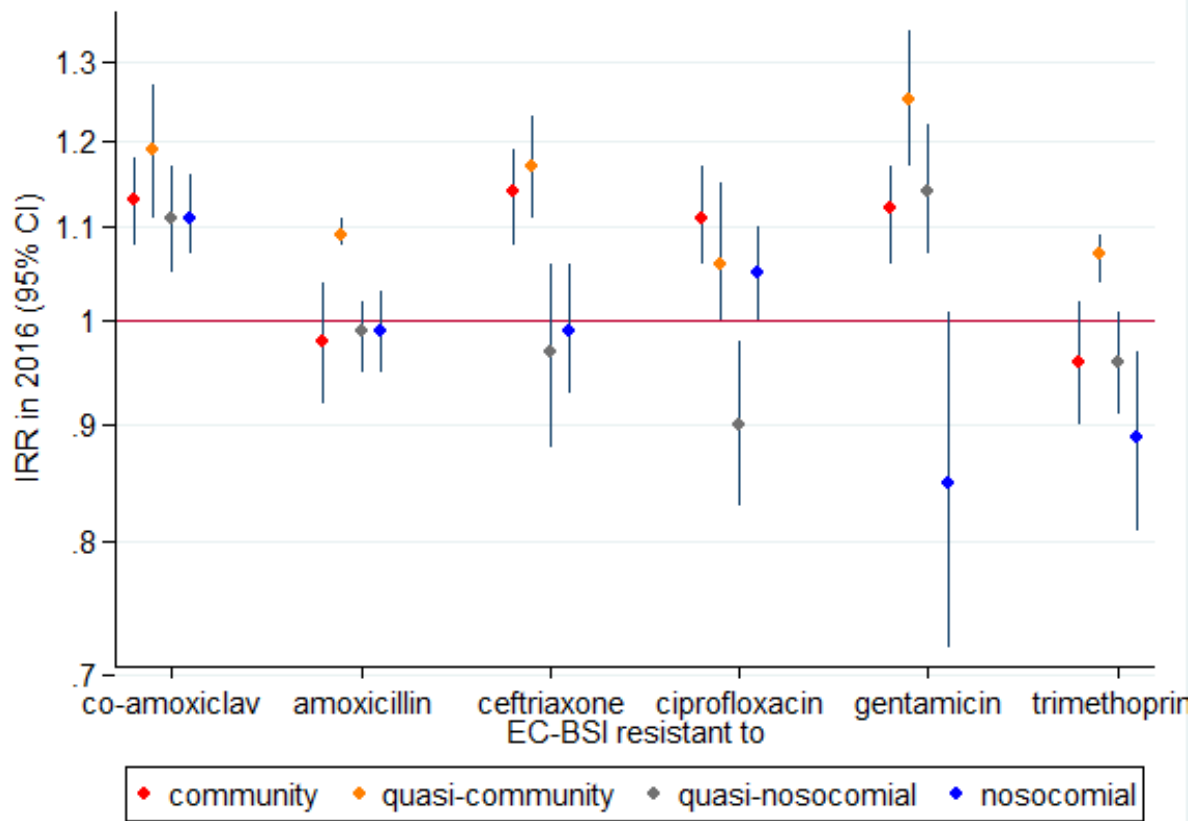
Footnote: IRR=annual incidence rate ratio in 2016, that is the relative increase in rate per year as estimated in 2016.

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


Footnote: IRR=annual incidence rate ratio in 2016, that is the relative increase in rate per year as estimated 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, that is the relative increase in rate per year as estimated 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. Co-amoxiclav-resistant EC-UTIs (A), EC-UTIs (B) and urine samples submitted regardless of result (C), per 1000 patients per primary-care facility 2012-2016 compared with co-amoxiclav usage.
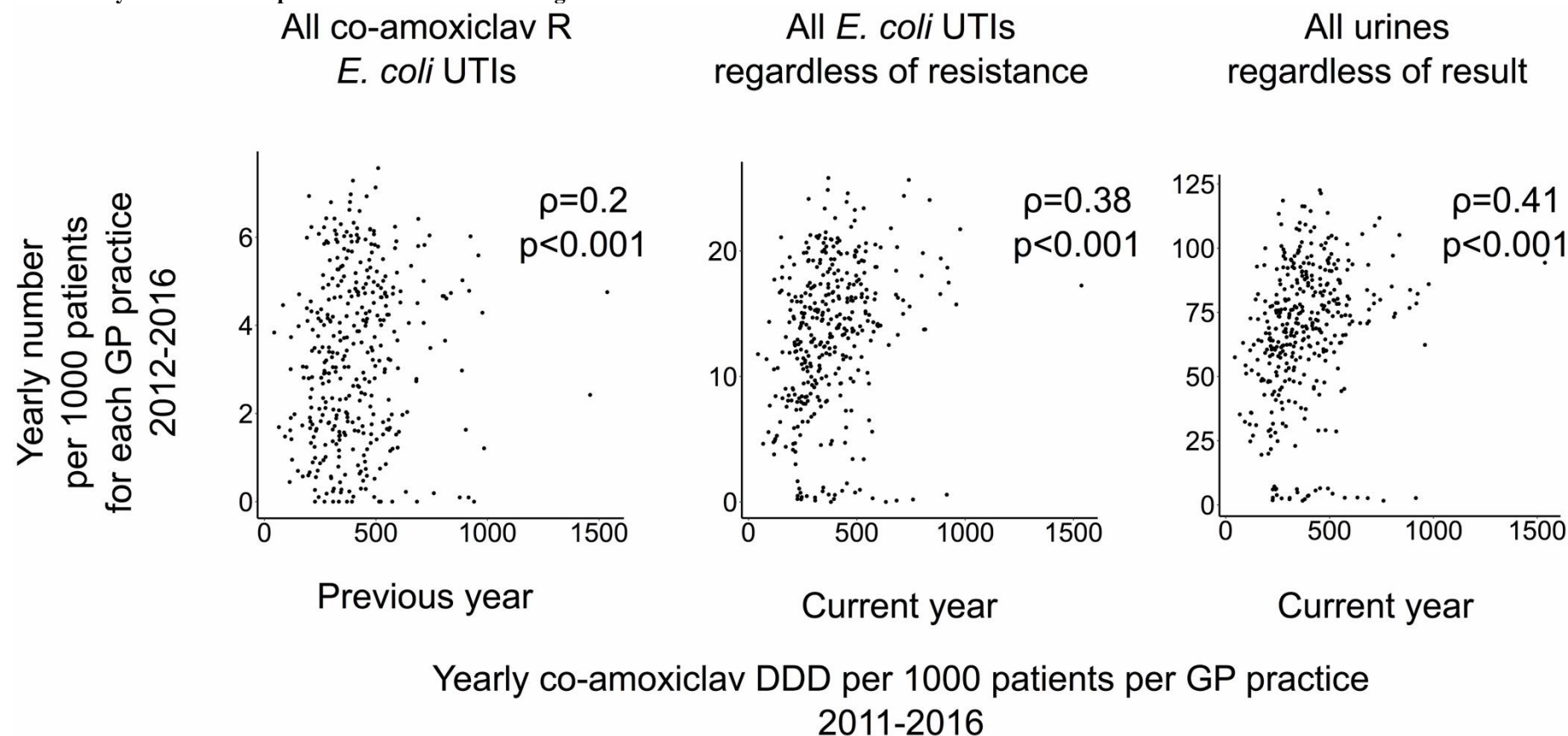
Footnote: showing one record per year per primary-care facility. For (A) the strongest predictor was co-amoxiclav DDD per 1000 patients per general practice in the previous year; for (B) and (C) the strongest predictor was co-amoxiclav DDD per 1000 patients per general practice in the current year. Spearman rho (and models) for each panel excludes 5 facilities which submitted less than 151 samples over 2011-2016 (all others submitted over 300). Spearman rho univariable associations with previous vs current co-amoxiclav usage for the 3 outcomes left to right $\rho=0.2$ vs $\rho=0.05$, $\rho=0.36$ vs $\rho=0.38$, $\rho=0.38$ vs $\rho=0.41$ respectively.

Supplementary Figure 14: Co-amoxiclav resistance in EC-BSIs according to different testing methods
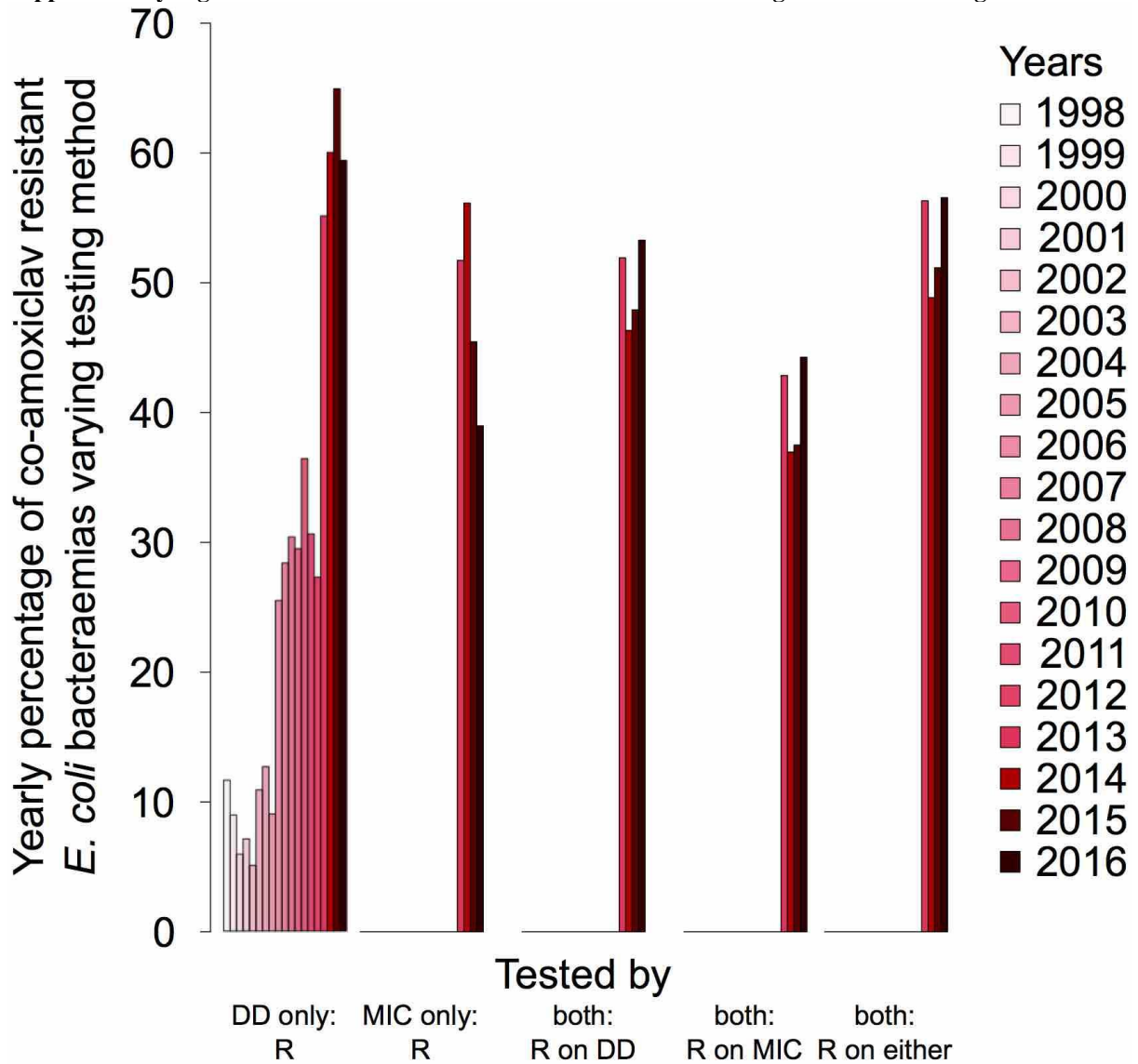
Footnote: DD=disc diffusion. MIC=median inhibitory concentration by microbroth dilution (Phoenix)