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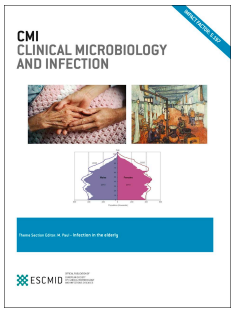

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Original article

Risk factors of community-onset extended-spectrum β-lactamase *Escherichia coli* and *Klebsiella pneumoniae* bacteraemia: An 11-year population-based case-control-control study in Denmark

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Abstract

Objectives: To investigate and explore temporal changes in risk factors of community-onset extended-spectrum β-lactamase (ESBL) *Escherichia coli* and *Klebsiella pneumoniae* bacteraemia in a region with low antibiotic resistance.

Methods: Population-based case-control study including 223 cases hospitalized with a first-time community-onset ESBL-producing *E. coli* and *K. pneumoniae* bacteraemia, 2,214 non-ESBL *E. coli* and *K. pneumoniae* bacteraemia controls, and 2,228 population controls in the North Denmark Region between, 2007 and 2017. We used conditional logistic regression to compute crude and adjusted (age, gender and comorbidity) odds ratios (aORs) and 95% confidence intervals (CIs) of risk factors and compared selected risk factors between 2007-2011 and 2016-2017.

Results: Several conventional risk factors of ESBL *E. coli* or *K. pneumoniae* were identified as compared with the population controls. Compared with the non-ESBL controls, use of fluoroquinolones (aOR 3.56 [CI; 2.52-5.05], ≥3 admissions within the recent year (aOR 2.18 [CI; 1.45-3.28]), ≥3 antibiotic prescriptions within 15-365 days prior to the admission (aOR 2.18 [CI; 1.53-3.10]), male sex (aOR 2.01 [CI; 1.50-2.69]), admission within 1-91 days (aOR 1.84 [CI; 1.37-2.48]), and antibiotic within 15-91 days (aOR 1.82 [CI; 1.37-2.42]) inferred the highest risk. Assessment of temporal dynamics between 2007-2011 and 2016-2017 revealed a slight reduction in risk factors associated with direct healthcare contact (e.g. hospital admission).

Conclusions: Recent and frequent hospitalization, and exposure to antibiotics, especially use of fluoroquinolones, appeared to be associated specifically with ESBL-production, and focus and interventions should be directed towards these areas. Our results indicated a dissemination of ESBLs into the community.

Introduction

Escherichia coli and *Klebsiella pneumoniae* remain the leading causes of gram negative community-onset bloodstream infections [1]. Since the millennium, an increasing proportion of strains capable of producing extended-spectrum β-lactamases (ESBL) has disseminated within the community, challenging empirical antibiotic treatment [2,3].

Several studies have reported risk factors associated with ESBL production [4], while fewer studies have focused strictly on community-onset risk factors. The most consistent community-onset risk factors include prior use of (specific) antibiotics [5–13], recent hospitalization [5,7,8], healthcare-associated infection [9,11,13] urological disease [6,8,9] and urinary catheter use [5,7,11]. Still, the majority of these studies have been from high prevalence areas, they were of limited size, and only one [6] was population-based. Also, adaptation of risk factors from different settings should be interpreted with caution, as risk factors are highly dependent on local epidemiology [14]. Lastly, no studies have ascertained potential temporal changes in risk factors of community-onset ESBL-producing bacteraemia. Theoretically, if ESBL-producing bacteria disseminated within the community, one would expect healthcare associated risk factors to diminish or even vanish with time.

Identification of patients at risk of infections with ESBL-producing bacteria upon admission is important to ensure early appropriate empirical antibiotic therapy while at the same time avoiding unnecessary use of broad-spectrum antibiotics. Moreover, knowledge about risk factors is essential to limit the spread of resistant bacteria by establishing optimized preventive measures and isolation strategies.

We therefore conducted a population-based study to 1) investigate potential risk factors of community-onset ESBL-producing *E. coli* and *K. pneumoniae* bacteraemia in our area with low

ESBL prevalence [15,16] and 2) to explore potential temporal changes in the distribution of risk factors during the study period.

Methods

Setting and data sources

We conducted this case-control-control study in the North Denmark Region (catchment population 580.000) between January 1, 2007 and December 31, 2017. The region has an 800-bed University Hospital, and eight regional hospitals in 2007 which dwindled down to five by 2017. In Denmark, the healthcare system is providing tax-funded free healthcare access to all residents.

We identified all *E. coli* and *K. pneumoniae* positive blood cultures submitted to the Department of Clinical Microbiology at Aalborg University Hospital, which has received samples from all hospitals for almost the entire study period [15]. Next, we obtained data from the following registries; (1) the Danish Civil Registration System (CRS) [17] holding information on sex and date of birth; (2) the Danish National Patient Registry (DNPR) [18] keeping data on date of admission and discharge, discharge diagnoses according to the International Classification of Diseases (ICD) and surgical procedures; (3) the Danish National Prescription Registry (DNPR*) [19] holding information of all redeemed prescription drugs dispensed in Danish community pharmacies, including date and Anatomical Therapeutic Chemical (ATC) classification codes. The unique identification number assigned to every Danish citizens upon birth or immigration was used for unambiguous individual-level record linkage among the registers [17].

Study population

Cases

Cases consisted of adult patients (≥16 years) with a first-time community-onset ESBL-producing *E. coli* or *K. pneumoniae* bacteraemia. The index date was defined as the day the sample was drawn. Community-onset bacteraemia was defined as a blood sample obtained ≤2 days of hospitalization [20,21].

Identification of ESBLs roughly corresponded to the $ESBL_A$ classification by Giske et al. [22], hereby excluding a minor proportion (<3%) of plasmid-mediated AmpC. A detailed description of identification of ESBL has previously been published [15].

Controls

To disentangle risk factors of bacteraemia from risk factors of bacteraemia *and* infection with an ESBL-producing bacterium we utilized two separate control groups. The first control group consisted of patients with a first-time community-onset non-ESBL-producing *E. coli* or *K. pneumoniae* bacteraemia, hereafter referred to as non-ESBL controls. For every case, ten non-ESBL controls were randomly included from the same laboratory information system, matched according to bacterium and time, i.e. controls were recruited within the following three months of the corresponding case.

The second control group consisted of persons residing in the North Denmark Region randomly selected from the CRS in a 10:1 ratio matched on age and sex. By matching on age and sex, we were not able to assess these as potential risk factors, however, not matching on these two factors would, in our opinion, hamper optimal comparisons. The population controls were assigned the same index date as the corresponding case.

We used risk set sampling for selection of both control groups, i.e. the control had to be alive and at risk of an ESBL-producing *E. coli* and *K. pneumoniae* infections at the index date. A control could only be included once for each case.

Potential risk factors and temporal dynamics

The potential risk factors investigated in our study were carefully selected *a priori* based first on the existing literature in prior studies and next on plausible biological mechanisms. Temporal dynamics in risk factors between 2007-2011 and 2016-2017 were also explored. These periods were chosen to obtain a similar number of patients in each period, while 2012-2015 comprised a "transition" period allowing for the risk factors "to-go-endemic". We *a priori* decided to restrict this analysis to common reported risk factors of community-onset ESBL-producing bacteraemia, i.e.; (1) any antibiotic exposure within 15-91 days, (2) hospital admission within 1-91 days, (3) ≥ 3 hospital admissions within a year (4) genitourinary tract surgery within a year, and (5) diabetes mellitus.

Demographics, comorbidity, and medication

Demographic characteristics (age and gender) were obtained from the CRS [17]. Data regarding comorbidities, genitourinary surgery procedures, and hospital admission was obtained from the DNPR [18]. We included all diagnoses within ten years and identified all comorbidities in the Charlson Comorbidity index (CCI) and constructed a modified CCI (m-CCI) of low (score=0), medium (score=1-2), and high (score≥3) according to the updated version by Quan et al [23]. Genitourinary surgery procedures and hospital admission within the recent year were assessed overall and subsequently categorized into time periods, i.e. 1-91 days, 92-182, and 183-365 days prior to index date.

From the DNPR* [19], we retrieved information about prescriptions of antibiotics, proton pump inhibitors (PPIs), and immunosuppressant drugs redeemed within one year of the index date. For antibiotics, we excluded prescriptions within 14 days prior to index date, to avoid introducing reverse causality into the study, as these antibiotics were considered likely to be consumed due to the infection leading to hospitalization. Inspired by Søgaard et al. [24], we categorized antibiotics as any antibiotics, narrow- spectrum antibiotics, broad-spectrum antibiotics, narrow- spectrum penicillin, broad-spectrum penicillin, fluoroquinolones, pivmecillinam, sulfamethizole, trimethoprim, macrolides, and nitrofurantoin (**Table S1**). To examine a potential temporal relation, we investigated antibiotics consumed 15-91 days, 92-182, and 183-365 days before the index date, and to examine a potential dose relation we divided into 0, 1, 2, and ≥3 antibiotic prescriptions within the previous year. In Denmark, antibiotics are only prescribed at the decision of a physician, and no antibiotics are available over-the-counter. Detailed information on the coding of these variables is available in **Table S1**.

Statistical analysis

The study population was characterized by descriptive statistics. Conditional logistic regression was used to compute the crude and adjusted (age, gender and comorbidity) odds ratios (ORs) with 95% confidence intervals (CIs). When assessing a specific comorbidity, this comorbidity was excluded from the m-CCI. Finally, we examined for potential temporal dynamics in risk factors between 2007-2011 and 2016-2017. In a sensitivity analysis of antibiotic exposure, we excluded patients with a positive ESBL *E. coli* or *K. pneumoniae* urine culture collected within one year prior to index date. Statistical analyses were performed using Stata 15 (Stata Corp, College Station, TX).

Ethics

In Denmark, register studies do not require ethical approval. The study was approved by the Danish Patient Safety Authority (reference no: 3-3013-2298/1).

Results

We identified 223 cases, 2,214 non-ESBL controls and 2,228 population controls. The median age of cases was 73 years (interquartile range [IQR], 64-82), 66.8% were males, and *E. coli* accounted for the vast majority of bacteraemias (n=189 (84.8%)). Characteristics of the cases and the matched control groups are presented in **Table 1** and **Table 2**. The proportion of community-onset *E. coli* and *K. pneumoniae* bacteraemia with an ESBL-producing strain increased from 2.7% in 2007 to 7.7% in 2016, with an average of 5.6% (data not shown).

Risk factors

Compared with the non-ESBL controls, the highest risk of ESBL *E. coli* or *K. pneumoniae* bacteraemia was conferred by ≥3 admissions within the recent year (adjusted OR (aOR) 2.18 [CI; 1.45-3.28]), male sex (aOR 2.01 [CI; 1.50-2.69]), admission within 1-91 days (aOR 1.84 [CI; 1.37-2.48]) (**Table 3**), fluoroquinolone-treatment (aOR 3.56 [CI; 2.52-5.05]), and ≥3 antibiotic prescriptions within 15-365 days (aOR 2.18 [CI; 1.53-3.10]) (**Table 4**). Additional risk factors included a high m-CCI score, use of broad- and -narrow-spectrum antibiotics/penicillins and trimethoprim within 15-365 days.

Compared with the population controls, the highest aORs comprised ≥3 admissions within the recent year (OR 22.48 [CI; 13.35-37.87]), urological procedures within 1-91 days (OR 15.55 [CI; 6.46-37.43]), high m-CCI score (OR 15.37 [CI; 10.18-23.19]), and ≥3 antibiotic prescriptions (OR 7.11 [4.79-10.57]). Additional risk factors included several comorbidities and treatment with PPIs, immunosuppressant drugs and antibiotics. Time since antibiotic prescription, admission, and urological surgical procedures were associated with considerable risk of ESBL bacteraemia, and a "dose-response" relationship regarding number of antibiotic prescriptions/admission and ESBL bacteraemia was apparent.

In the sensitivity analysis, in which patients with a prior positive ESBL-producing urine culture (n=52, 23.3% of patients with ESBL-bacteraemia) were excluded, the association with antibiotic exposure as a risk factor was slightly altered, thus the association with trimethoprim seemed to disappear, while macrolides now appeared to be associated with ESBL-production (OR 1.76 [1.13-2.73]) (**Table S2**).

Temporal dynamics in risk factors

Fifty-nine and 61 ESBL cases were included in the time periods 2007-2011 and 2016-2017, respectively. Recent hospital contact (admission and genitourinary surgery) as a risk factor of ESBL-producing bacteraemia seemed to diminish with time when compared with both non-ESBL and population controls (**Figure 1**). Recent prescription of antibiotics as a risk factor seemed to increase, whereas diabetes mellitus remained unchanged.

Discussion

We identified several risk factors of bacteraemia with ESBL-producing pathogens, however, the majority were related merely to the risk of bacteraemia in general, and only male sex, a high comorbidity score, recent and frequent hospitalization, and antibiotic exposures were associated with risk of ESBL *E. coli* or *K. pneumoniae* bacteraemia specifically. However, risk factors associated with direct healthcare contact (e.g. recent and frequent hospital admission) decreased during the study period, which might indicate a dissemination of ESBL-positive pathogens into the community.

A recent nationwide Swedish study [6] demonstrated multiple co-morbidities, urological procedures, hospitalization, and recent exposure to antibiotics to be risk factors of ESBL-producing Enterobacteriaceae bacteraemia as compared with matched population controls [6]. We confirmed most of these findings in our study. However, in the Swedish study, no non-ESBL comparison group was included, rendering it difficult to disentangle the specific influence of ESBL-production on risk factors. Of notice, the magnitude of the association in general was markedly reduced when compared to the non-ESBL controls, indicating that the associations observed were primarily driven by the risk of bacteraemia. Our study thus extends the Swedish study by identifying risk factors that might be specific mediators of ESBL-production.

Other studies have identified prior use of (specific) antibiotics [5–13,25], as risk factors of community-onset ESBL bacteraemia. Most of these studies have utilized a case-control design with the susceptible (non-ESBL-producing) strain as control group. However, the use of a control group with susceptible bacteria has some obvious pitfalls, that may lead to falsely overestimated ORs of antibiotic exposure as a risk factor [26,27]. In our study, both broad -and narrow-spectrum antibiotics and penicillins, and especially fluoroquinolones, were associated with ESBL-production compared with the non-ESBL controls. These remained risk factors when compared with the

population controls, indicating that they were indeed associated with ESBL-producing bacteraemia. We were not able to demonstrate nitrofurantoin as a risk factor of ESBL-producing bacteraemia which has previously been associated with ESBL-producing *E. coli* urinary tract infection from primary care in our region [24]. In the sensitivity analysis excluding patients with a prior ESBL-positive urine culture (**Table S2**) any association with nitrofurantoin was further diminished, indicating that the finding by Søgaard et al., might partly reflect a reverse causation, i.e. nitrofurantoin is prescribed to patients with confirmed (or at high risk of) ESBL-producing infections rather than mediate resistance [24]. Recent (within 15-91 days) antibiotic exposure and in particular fluoroquinolones conferred the highest ORs, strengthening the findings by Isendahl et al [6].

We investigated temporal dynamics in risk factors between 2007-2011 and 2016-2017, where the proportion of ESBL-producing *E. coli* and *K. pneumoniae* bacteraemia increased from 4.8% to 7.2% (data not shown). Interestingly, the finding that indicators of direct healthcare contact slightly decreased with time, while risk factors not directly related to hospital contact (e.g. diabetes mellitus and outpatient antibiotic consumption) remained unchanged or even increased, could indicate ESBL *E. coli* or *K. pneumoniae* disseminating in the community (**Figure 1**). Nonetheless, recent and frequent hospital admissions remained risk factors of ESBL production also in 2016-2017. To our knowledge, this is the first study to examine temporal dynamics in risk factors of community-onset ESBL-producing bacteraemia. This information may be of considerable value in identifying targets and modifiable risk factors to influence the effect of preventive measures.

Strengths of the present study include the population-based design in a setting of tax-supported healthcare access, hereby limiting diagnostic and referral bias. The use of pre-existing national registers limits selection and recall bias, and most bias would tend to be non-differential

with respect to the study groups. Finally, the use of two control groups allowed for separate interpretation of risk factors associated with "ESBL-production" or/and "bacteraemia".

The study also has some limitations besides its observational nature, which cannot rule out unmeasured or residual confounding. We lacked information not available through our registers, especially on use of in-hospital antibiotics (which might have resulted in a falsely low level of exposure impacting our results), residency in nursing homes, catheter use and data on international travel which was previously shown to be risk factors of ESBL production [11,28,29]. We decided to include both *E. coli* and *K. pneumoniae* into the analyses, as we believe this resembles the clinical situation, where it is often difficult to distinguish the two pathogens before clinical microbiology results are available. However, we acknowledge that *E. coli* and *K. pneumoniae* bacteraemia constitutes quite different epidemiological entities [30]. Sensitivity analyses of risk factors restricting to individual pathogens are available in supplementary material (**Table S3-Table S6)**. Interestingly, when compared with non-ESBL controls, both β-lactam antibiotics and most non-β-lactam antibiotics (fluoroquinolones, trimethoprim, macrolides) were associated with ESBL production in *E. coli* (**Table S6**), whereas only pivmecillinam appeared to be a risk factor of ESBL production in *K. pneumoniae* (**Table S4**).

In conclusion, recent and frequent hospitalization and antibiotic exposure, specifically fluoroquinolones appeared to be associated with risk of ESBL-producing bacteraemia, highlighting targets for focus and interventions. We demonstrated temporal dynamics in risk factors indicating a possible dissemination of ESBL *E. coli* or *K. pneumoniae* into the community.

Transparency declaration

None of the authors reports any conflict of interest, and no funding was received for this study.

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None.

Authors´ contributions

RR: study concept and design, data management, analysis and interpretation, and manuscript preparation. PLA: data management, analysis and interpretation, and manuscript review. JS, HCS, HN: study concept and design, interpretation of the data, manuscript review, and study supervision. All the authors have read and approved the final draft submitted.

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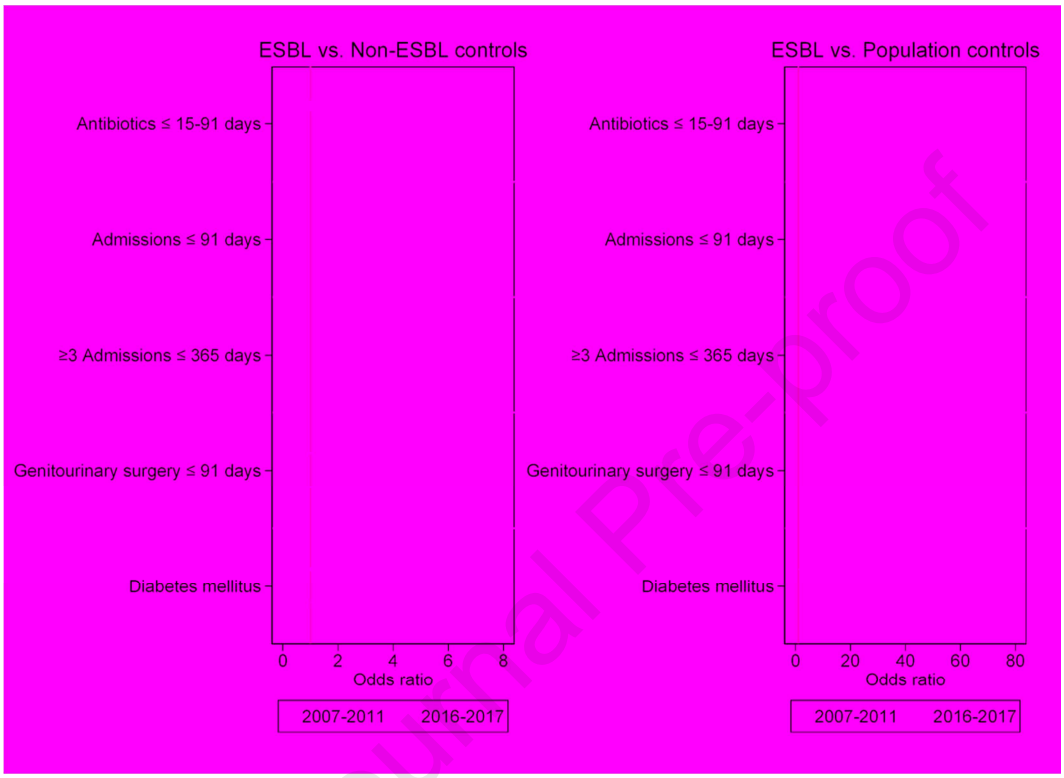
405

406 **Figures**

407 **Figure 1.** Temporal dynamics in crude risk factors of ESBL-producing *E. coli* and *K. pneumoniae*
408 bacteraemia compared to non-ESBL controls (left) and population controls (right), between 2007-
409 2011 and 2016-2017.



410

411 **Tables**

412 **Table 1.** Baseline characteristics of ESBL-producing *E. coli* or *K. pneumoniae* bacteraemia, non-

413 ESBL controls, and population controls in the period 2007-2017.

	ESBL	Non-ESBL	Population
	n (%)	n (%)	n (%)
Numbers	223	2,214	2,228
Species			
E. coli	189 (84.8)	1,887 (85.3)	-[1]
K. pneumoniae	34 (15.3)	327 (14.8)	-[1]
Demographic			
Age, median [IQR]	73 [64-82]	74 [63-82]	73 [64-82][1]
Age, years			
≤65	62 (27.8)	646 (29.2)	624 (28.0)
66-80	102 (45.7)	924 (41.7)	991 (44.5)
≥81	59 (26.5)	644 (29.9)	611 (27.5)
Sex, male	149 (66.8)	1,085 (49.0)	1,488 (66.8)[1]
Comorbidities			
Myocardial infarction	16 (7.2)	147 (6.6)	132 (5.9)
Congestive heart failure	29 (13.0)	220 (9.9)	114 (5.1)
Dementia	10 (4.5)	78 (3.5)	31 (1.4)
Chronic pulmonary disease	45 (20.2)	370 (16.7)	171 (7.7)
Ulcer disease	11 (4.9)	143 (6.5)	53 (2.4)
Diabetes[2]	45 (20.2)	347 (15.7)	151 (6.8)
Moderate or severe renal disease	25 (11.2)	184 (8.3)	38 (1.7)

Any malignancy (including leukemia and lymphoma)	75 (33.6)	640 (28.9)	204 (9.2)
Moderate to severe liver disease	6 (2.7)	30 (1.4)	5 (0.2)
Metastatic solid tumor	17 (7.6)	141 (6.4)	12 (0.5)
m-CCI			
Low (CCI=0)	70 (31.4)	913 (41.2)	1,684 (75.6)
Medium (CCI=1-2)	91 (40.8)	821 (37.1)	438 (19.7)
High (CCI≥3)	62 (27.8)	480 (21.7)	106 (4.8)
Medication[3]			
Proton-pump-inhibitors	113 (50.7)	982 (44.4)	488 (21.9)
Immunosuppressant treatments	49 (22.0)	439 (19.8)	169 (7.6)
Hospitalization			
Admission within			
1 -91 days	119 (53.4)	797 (36.0)	127 (5.7)
92-182 days	67 (30.0)	513 (23.2)	136 (6.1)
183-365 days	85 (38.1)	642 (29.0)	228 (10.2)
Number of admissions within 1 year			
0	61 (27.4)	938 (42.4)	1,832 (82.2)
1	63 (28.3)	536 (24.2)	258 (11.6)
2	28 (12.6)	296 (13.4)	86 (3.9)
≥3	71 (31.8)	444 (20.1)	52 (2.3)
Urological procedures within			
1-91 days	21 (9.4)	144 (6.5)	12 (0.5)
92-182 days	8 (3.6)	56 (2.5)	11 (0.5)

183-365 days	6 (2.7)	61 (2.8)	21 (0.9)

[1] Population controls matched according to age, gender and residence.

[2] Diabetes with – and without organ complications.

[3] Within 1-365 days of index date.

417 **Table 2.** Antibiotic exposure for community-onset ESBL-producing *E. coli* or *K. pneumoniae*

418 bacteraemia**,** non-ESBL controls, and population controls in the period 2007-2017.

	ESBL n (%)	Non-ESBL n (%)	Population n (%)
Any Antibiotics[1]	160 (71.7)	1327 (59.9)	707 (31.7)
Broad-spectrum antibiotics	120 (53.8)	891 (40.2)	342 (15.4)
Narrow-spectrum antibiotics	122 (54.7)	960 (43.4)	519 (23.3)
Broad-spectrum penicillin	58 (26.0)	420 (19.0)	183 (8.2)
Narrow-spectrum penicillin	82 (36.8)	622 (28.1)	344 (15.4)
Fluoroquinolones	58 (26.0)	420 (19.0)	60 (2.7)
Pivmecillinam	56 (25.1)	572 (25.8)	149 (6.7)
Sulfamethizole	22 (9.9)	194 (8.8)	67 (3.0)
Trimethoprim	21 (9.4)	133 (6.0)	32 (1.4)
Macrolides	32 (14.3)	235 (10.6)	126 (5.7)
Nitrofurantoin	11 (4.9)	87 (3.9)	21 (0.9)
Any antibiotics within			
15-91 days	105 (47.1)	743 (33.6)	233 (10.5)
92-182 days	87 (39.0)	654 (29.5)	288 (12.9)
183-365 days	102 (45.7)	819 (37.0)	466 (20.9)
Number of AB prescriptions[1]			
0	63 (28.3)	887 (40.1)	1,521 (68.3)
1	37 (16.6)	438 (19.8)	354 (15.9)
2	32 (14.4)	279 (12.6)	162 (7.3)
≥3	91 (40.8)	610 (27.6)	191 (8.6)

[1] Redeemed prescription(s) within 15-365 days of index date. In-hospital dispensed antibiotics are not included.

420 **Table 3.** Risk factors of community-onset ESBL-producing *E. coli* or *K. pneumoniae* bacteraemia
421 compared with non-ESBL controls and population controls.

	OR for ESBL vs. non-ESBL (95% CI)		OR for ESBL vs. population controls (95% CI)	
	Crude	**Adjusted[1]**	**Crude**	**Adjusted[1]**
Demographics				
Age				
≤65	1.00 (ref)	1.00 (ref)	-[2]	-[2]
66-80	1.16 (0.83-1.61)	0.98 (0.70-1.38)	-	-
≥81	0.95 (0.66-1.38)	0.86 (0.59-1.26)	-	-
Sex, male	2.08 (1.56-2.78)	2.01 (1.50-2.69)*	-	-
Comorbidities				
Myocardial infarction	1.09 (0.64-1.87)	0.94 (0.54-1.62)	1.24 (0.71-2.15)	0.65 (0.36-1.17)
Congestive heart failure	1.36 (0.90-2.06)	1.34 (0.87-2.06)	2.79 (1.80-4.31)	1.82 (1.13-2.93)*
Dementia	1.29 (0.66-2.53)	1.31 (0.66-2.61)	3.47 (1.64-7.32)	3.85 (1.68-8.80)*
Chronic pulmonary disease	1.28 (0.90-1.81)	1.23 (0.86-1.76)	3.11 (2.15-4.51)	2.56 (1.72-3.82)*
Ulcer disease	0.76 (0.40-1.42)	0.75 (0.40-1.42)	2.14 (1.01-4.17)	1.46 (0.70-3.04)
Diabetes[3]	1.36 (0.96-1.92)	1.29 (0.91-1.83)	3.51 (2.43-5.09)	2.22 (1.47-3.34)*
Moderate or severe renal disease	1.39 (0.89-2.17)	1.25 (0.79-1.96)	7.10 (4.20-12.00)	3.61 (1.99-6.54)*
Any malignancy (including leukemia and lymphoma)	1.24 (0.93-1.67)	1.11 (0.82-1.50)	5.16 (3.74-7.13)	4.30 (3.02-6.12)*
Moderate to severe liver disease	2.01 (0.83-4.88)	1.56 (0.63-3.86)	12.00 (3.67-39.32)	6.48 (1.72-24.43)*
Metastatic solid tumor	1.20 (0.71-2.09)	1.05 (0.61-1.79)	14.17 (6.77-29.66)	5.48 (2.51-11.96)*
m-CCI				
Low (CCI=0)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Medium (CCI=1-2)	1.46 (1.05-2.02)	1.38 (0.99-1.92)	5.71 (4.04-8.08)	5.74 (4.05-8.11)*

High (CCI≥3)	1.69 (1.18-2.42)	1.55 (1.08-2.24)*	15.39 (10.20-23.22)	15.37 (10.18-23.19)*
Medication[4]				
PPI	1.28 (0.97-1.68)	1.23 (0.92-1.62)	3.81 (2.85-5.09)	2.80 (2.05-3.82)*
Immunosuppressant treatments	1.14 (0.82-1.59)	1.05 (0.74-1.49)	3.50 (2.44-5.01)	1.85 (1.24-2.75)*
Hospitalization				
Admission within				
1-91 days	2.06 (1.56-2.73)	1.84 (1.37-2.48)*	20.89 (14.54-29.99)	12.78 (8.67-18.82)*
92-182 days	1.43 (1.05-1.93)	1.26 (0.91-1.73)	6.62 (4.70-9.31)	3.34 (2.29-4.87)*
183-365 days	1.51 (1.13-2.01)	1.37 (1.01-1.86)*	5.74 (4.19-7.86)	3.05 (2.15-4.33)*
Number of admissions within 1 year				
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.82 (1.26-2.64)	1.70 (1.15-2.49)*	8.38 (5.63-12.47)	5.76 (3.79-8.74)*
2	1.47 (0.92-2.36)	1.36 (0.84-2.23)	9.84 (5.86-16.52)	6.10 (3.53-10.53)*
≥3	2.51 (1.74-3.62)	2.18 (1.45-3.28)*	42.62 (26.42-68.77)	22.48 (13.35-37.87)*
Urological procedures within				
1-91 days	1.50 (0.92-2.43)	1.40 (0.86-2.28)	20.03 (9.41-42.64)	15.55 (6.46-37.43)*
92-182 days	1.43 (0.68-3.04)	1.27 (0.59-2.72)	8.10 (3.10-21.16)	4.53 (1.57-13.03)*
183-365 days	0.98 (0.42-2.29)	0.96 (0.40-2.26)	3.04 (1.18-7.82)	2.70 (0.96-7.61)

Note: Asterisks (*) indicate a possible association in the adjusted analysis.

[1] Adjusted for age, gender and comorbidity.

[2] Population controls matched according to age, gender and residence.

[3] Diabetes with – and without organ complications.

[4] Within 1-365 days of index date.

427 **Table 4.** Antibiotic exposure as risk factor of community-onset ESBL-producing *E. coli* or *K.*

428 *pneumoniae* bacteraemia compared with non-ESBL controls and population controls.

	OR for ESBL vs. non-ESBL (95% CI)		OR for ESBL vs. population controls (95% CI)	
	Crude	**Adjusted[1]**	**Crude**	**Adjusted[1]**
Antibiotics[2]				
Any antibiotics vs. none	1.70 (1.25-2.30)	1.72 (1.26-2.35)*	5.78 (4.23-7.90)	3.99 (2.86-5.56)*
Broad-spectrum antibiotics	1.73 (1.31-2.28)	1.77 (1.33-2.36)*	6.80 (5.05-9.15)	4.34 (3.14-6.01)*
Narrow-spectrum antibiotics	1.59 (1.20-2.11)	1.59 (1.20-2.12)*	4.15 (3.11-5.54)	3.24 (2.37-4.44)*
Broad-spectrum penicillin	1.50 (1.09-2.06)	1.45 (1.04-2.00)*	3.96 (2.82-5.55)	2.28 (1.57-3.31)*
Narrow-spectrum penicillin	1.49 (1.12-1.99)	1.43 (1.07-1.91)*	3.24 (2.40-4.37)	2.43 (1.75-3.38)*
Fluoroquinolones	3.78 (2.69-5.31)	3.56 (2.52-5.05)*	12.58 (8.39-18.87)	9.96 (6.23-15.95)*
Pivmecillinam	0.95 (0.70-1.31)	1.01 (0.73-1.40)	5.23 (3.62-7.56)	3.44 (2.30-5.16)*
Sulfamethizole	1.14 (0.71-1.82)	1.29 (0.80-2.09)	3.86 (2.27-6.56)	3.04 (1.70-5.45)*
Trimethoprim	1.62 (1.00-2.62)	1.74 (1.06-2.84)*	7.93 (4.33-14.51)	7.61 (3.81-15.22)*
Macrolides	1.41 (0.95-2.11)	1.47 (0.98-2.20)	2.80 (1.85-4.25)	2.29 (1.44-3.64)*
Nitrofurantoin	1.27 (0.67-2.41)	1.32 (0.69-2.53)	5.81 (2.70-12.52)	4.64 (1.96-10.98)*
Any antibiotics within				
15-91 days	1.78 (1.34-2.35)	1.82 (1.37-2.42)*	8.19 (6.00-11.19)	6.03 (4.29-8.47)*
92-182 days	1.53 (1.15-2.04)	1.53 (1.14-2.06)*	4.47 (3.30-6.06)	2.89 (2.08-4.01)*
183-365 days	1.43 (1.09-1.89)	1.41 (1.06-1.88)*	3.21 (2.41-4.26)	2.25 (1.64-3.07)*
Number of AB prescriptions[2]				
0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1	1.19 (0.78-1.81)	1.21 (0.79-1.84)	2.65 (1.72-4.07)	2.01 (1.27-3.17)*

2	1.63 (1.04-2.55)	1.69 (1.07-2.66)*	5.12 (3.22-8.15)	3.97 (2.42-6.50)*
≥3	2.10 (1.50-2.95)	2.18 (1.53-3.10)*	12.01 (8.33-17.31)	7.11 (4.79-10.57)*

Note: Asterisks (*) indicate a possible association in the adjusted analysis.

[1] Adjusted for age, gender and comorbidity.

[2] Redeemed prescriptions within 15-365 days of index date. In-hospital dispensed antibiotics are not included.