ORIGINAL ARTICLE

Seasonal Variation of *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* Bacteremia According to Acquisition and Patient Characteristics: A Population-Based Study

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OBJECTIVE. Seasonal variation is a characteristic of many infectious diseases, but relatively little is known about determinants thereof. We studied the impact of place of acquisition and patient characteristics on seasonal variation of bacteremia caused by the 3 most common pathogens.

DESIGN. Seasonal variation analysis.

METHODS. In 3 Danish health regions (2.3 million total inhabitants), patients with bacteremia were identified from 2000 through 2011 using information from laboratory information systems. Analyses were confined to *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. Additional data were obtained from the Danish National Hospital Registry for the construction of admission histories and calculation of the Charlson comorbidity index (CCI). Bacteremias were categorized as community acquired, healthcare associated (HCA), and hospital acquired. We defined multiple subgroups by combining the following characteristics: species, acquisition, age group, gender, CCI level, and location of infection. Assuming a sinusoidal model, seasonal variation was assessed by the peak-to-trough (PTT) ratio with a 95% confidence interval (CI).

RESULTS. In total, we included 16,006 *E. coli*, 6,924 *S. aureus*, and 4,884 *S. pneumoniae* bacteremia cases. For *E. coli*, the seasonal variation was highest for community-acquired cases (PTT ratio, 1.24; 95% CI, 1.17–1.32), was diminished for HCA (PTT ratio, 1.14; 95% CI, 1.04–1.25), and was missing for hospital-acquired cases. No seasonal variation was observed for *S. aureus*. *S. pneumoniae* showed high seasonal variation, which did not differ according to acquisition (overall PTT ratio, 3.42; 95% CI, 3.10–3.83).

CONCLUSIONS. Seasonal variation was mainly related to the species although the place of acquisition was important for *E. coli*.

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As early as 380 BC, Hippocrates observed annual seasonal variation of diseases that were later acknowledged as infectious.[1] Nonetheless, possible causes of seasonal variation are difficult to elucidate due to the complicated interactions between pathogens, hosts, and environment.[1]

Bacteremia, defined as bacteremia/fungemia associated with infection,[2] is a serious condition with a 30-day mortality of 15%–30%.[3] Bacteremia may be acquired in the community or the hospital setting.[4] Moreover, patients with community acquisition who receive home therapy, reside in a nursing home, or have had recent hospital contact are often characterized as having a healthcare-associated bacteremia (HCA).[5]

Among the many studies of seasonal variation of bacteremia,[6–17] only 2 have assessed whether seasonal variation is related to acquisition.[6,17] For *Escherichia coli* bacteremia in the United Kingdom[17] and Gram-negative bacteremia in

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PREVIOUS PRESENTATION. Gradel KO, Nielsen SL, Pedersen C, Knudsen JD, Østergaard C, Arpi M, Jensen TG, Kolmos HJ, Søgaard M, Lassen AT presented these data in part as Poster P0012, "Seasonal variation in blood stream infection in relation to bacterial agents and acquisition" at the 25th European Congress of Clinical Microbiology and Infectious Diseases, April 25–28, 2015, in Copenhagen, Denmark.

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Australia,[6] cases acquired outside the hospital showed a summer peak, whereas no peak was seen for hospital-acquired cases.

We previously reported that seasonal variation of non-typhoid *Salmonella* infections diminished with increasing severity of the infection.[18] In this study, we tested the hypothesis that seasonal variation of bacteremia decreases in frequency of acquisition origin from community acquired to HCA to hospital acquired. We investigated this hypothesis using 2 population-based bacteremia databases,[19,20] and we focused on the 3 most common bacteremia species (*E. coli*, *Staphylococcus aureus*, *Streptococcus pneumoniae*) as well as acquisition and patient characteristics (ie, gender, age, comorbidity, location of infection) to assess which factor was most closely associated with seasonal variation.

MATERIALS AND METHODS

Setting

The Danish healthcare system is tax financed and provides care free of charge for all residents. All acutely ill patients are admitted to the nearest public hospital in their area of residence, which prompts a population-based coverage. Our data covered 3 demographically well-defined areas (ie, the North Denmark Region, Capital Region, and Funen County) served by 4 Departments of Clinical Microbiology (DCMs) in hospitals in Aalborg, Herlev, Hvidovre, and Odense (2.3 million total inhabitants[20,21]).

Data Linkage

Each Danish resident has a unique personal identification number used for all health contacts, which permits unambiguous linkage between health administrative registries.[22]

Core Dataset

The study period comprised 2000–2011 (the North Denmark and Capital regions) or 2000–2008 (Funen County).

All microbiological results were recorded in the following electronic laboratory information systems: Aalborg, Herlev, and Hvidovre use ADBakt (Autonik, Sköldinge, Sweden) and Odense used the local Patient Administrative System in 2000–2005 and have used the MADS system (www.madsonline.dk) thereafter. Blood culture procedures were described previously.[23,24]

Key data included dates of blood draw and receipt of the blood culture in the DCM as well as isolate identification data. For all positive blood cultures, we used previously published computer algorithms to derive bacteremia cases.[25] For each case, we defined the bacteremia date as reported previously[20] and retrieved all mono-microbial bacteremia cases with the 3 most common bacteria (*E. coli, S. aureus,* or *S. pneumoniae*), which constituted ~50% of all bacteremia cases.[20]

Linkage to the Danish National Hospital Registry

We linked the core dataset to the Danish National Hospital Registry (DNPR)[26] inpatient data and retrieved the records for hospital admissions that included the bacteremia date. We further retrieved hospital contacts up to 30 days before the bacteremia admission. For bacteremia cases, we used previously reported computer algorithms to derive acquisition of bacteremia (community acquired, HCA, hospital acquired).[24] A case was considered to be community acquired if the bacteremia date was on the admission date or the day after, without any hospital contact in the preceding 30 days. A case was considered HCA if the bacteremia date occurred in the same time span, with hospital contact in the preceding 30 days, and a case was considered hospital acquired if the bacteremia date was ≥2 days after the admission date.

We linked the core dataset to the DNPR to retrieve all first-time diagnoses included in the Charlson comorbidity index[27] within a 6-year period prior to the bacteremia date. In this index, 19 major disease categories (eg, malignancy, cardiovascular diseases, diabetes mellitus) are assigned a score; higher scores are given to prognostically more severe diseases. For each patient, a Charlson score is computed from the summation of scores for each individual disease category.

Linkage to the North Denmark Bacteremia Research Database

Bacteremia cases from North Denmark, 2000–2011, were linked to the North Denmark Bacteraemia Research Database, which comprises prospectively recorded data on the location of infection.[28]

Statistical Analyses

We categorized the bacteremia cases according to the following 6 subcategories: (1) bacteria (*E. coli*, *S. aureus*, or *S. pneumoniae*), (2) combination of bacteria and acquisition, (3) combination of bacteria and gender, (4) combination of bacteria, acquisition, and gender, (5) combination of bacteria, age group (0–64, 65–79, +80 years), and Charlson score group (0, 1–2, ≥3), and (6) combination of bacteria and location of infection. Data related to (6) were from bacteremia cases in North Denmark and were limited to 3 major categories: *E. coli* (intra-abdominal, urinary tract, unknown), *S. aureus* (skin/connective tissue/muscles, intravascular catheters, bones/joints, unknown), and *S. pneumoniae* (respiratory tract, unknown). For all unique combinations (n = 72), we computed the number of bacteremia cases in each calendar month, cumulatively over the study period after assessing graphically that the differences between years were minor.

For each unique subcategory, we then assessed the seasonal variation by computing the peak-to-trough (PTT) ratio with 95% confidence intervals (CIs) and the peak date, based on smoothed monthly numbers of bacteremia cases adjusted for variable month lengths.[29] The model assumes that the

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monthly incidence rates perform a single annual cycle that can be modeled using a sinusoidal curve, confirmed by visual inspection of all relevant graphs. The PTT ratio is the ratio between the peak and trough of the sinusoidal curve.

We repeated all of the above analyses for the patients' first cases considered to be independent of each other.

For subcategory 2, we further depicted curves with monthly ratios, computed by dividing the smoothed number of monthly observations by the mean monthly smoothed number, which was computed from the annual number of bacteremia cases divided by 12, adjusting for different month lengths.

The program Stata (release 13; StataCorp) was used for all analyses, except for computing PTT ratios, CIs, and peak dates using Episheet.[30]

Ethical Considerations

The study was approved by the Danish Data Protection Agency (record nos. 2007-41-0627, 2013-41-2579, and 2008-58-0028). Approval by an ethics committee or consent from participants (including next of kin/caregiver for children or deceased) is not required for registry-based research in Denmark.

RESULTS

In total, 16,006 *E. coli*, 6,924 *S. aureus*, and 4,884 *S. pneumoniae* bacteremia cases were recorded in 25,487 patients: 23,598 patients (92.6%) had 1 case, 1,583 (6.2%) had 2, and the remaining 306 (1.2%) had 3–12 cases (data not shown). Table 1 shows characteristics of the bacteremia cases. We were able to access data on the location of infection for 6,832 cases (Table 2).

Acquisition varied considerably according to bacterial species (Table 1). *S. aureus* had the lowest proportion of community acquisition (33.3%), but the highest proportion of hospital acquisition (41.3%). The reverse was seen for *S. pneumoniae* (74.8% vs 8.4%), whereas the respective proportions of *E. coli* were intermediate (54.8% vs 23.2%). HCA was more equally distributed between the 3 bacterial species.

Seasonal Variation and Peak Dates for *E. coli* and Subgroups

Overall, the diagnosis of *E. coli* bacteremia showed seasonal variation (PTT ratio, 1.17; 95% CI, 1.12–1.22) with August 24 as the peak date (Table 3). The seasonal variation was highest for community-acquired cases, was diminished for HCA, and was missing for hospital-acquired cases, both overall and for males and females (Table 3, Fig. 1). Little difference in seasonal variation was observed in relation to gender or location of infection, and no general trend of higher or lower seasonal variation was observed for higher age and/or Charlson comorbidity. Most peak dates for subgroups with seasonal variation occurred in August or September.

Seasonal Variation and Peak Dates for *S. aureus* and Subgroups

No seasonal variation was encountered for *S. aureus*, either overall or for any of the subgroups, except for some locations of infection (ie, intravascular catheters and unknown) (Table 3 and Fig. 2). Peak dates varied throughout the year, thus corroborating the lack of seasonal variation.

Seasonal Variation and Peak Dates for *S. pneumoniae* and Subgroups

With a PTT ratio of 3.42 (95% CI, 3.10–3.83), *S. pneumoniae* showed high seasonal variation (Table 3). Seasonal variation

TABLE 1. Characteristics of Bacteremia Cases

Characteristic	All Bacteremia Cases, No. (%) (N = 27,814)	*Escherichia coli*, No. (%) (N = 16,006)	*Staphylococcus aureus*, No. (%) (N = 6,924)	*Streptococcus pneumoniae*, No. (%) (N = 4,884)
Acquisition				
Community	14,736 (53.0)	8,778 (54.8)	2,303 (33.3)	3,655 (74.8)
Healthcare-associated	6,106 (22.0)	3,519 (22.0)	1,765 (25.5)	822 (16.8)
Hospital	6,972 (25.1)	3,709 (23.2)	2,856 (41.3)	407 (8.3)
Gender				
Males	13,680 (49.2)	7,162 (44.8)	4,175 (60.3)	2,343 (48.0)
Females	14,134 (50.8)	8,844 (55.3)	2,749 (39.7)	2,541 (52.0)
Age group/Charlson score group				
0–64 y/0	4,505 (16.2)	2,076 (13.0)	1,068 (15.4)	1,361 (27.9)
0–64 y/1–2	2,856 (10.3)	1,409 (8.8)	927 (13.4)	520 (10.7)
0–64 y/>2	2,185 (7.9)	984 (6.2)	907 (13.1)	294 (6.0)
65–79 y/0	2,621 (9.4)	1,585 (9.9)	503 (7.3)	533 (10.9)
65–79 y/1–2	3,981 (14.3)	2,483 (15.5)	900 (13.0)	598 (12.2)
65–79 y/>2	2,989 (10.7)	1,748 (10.9)	888 (12.8)	353 (7.2)
+80 y/0	2,792 (10.0)	1,824 (11.4)	501 (7.2)	467 (9.6)
+80 y/1–2	3,699 (13.3)	2,496 (15.6)	716 (10.3)	487 (10.0)
+80 y/>2	2,186 (7.9)	1,401 (8.8)	514 (7.4)	271 (5.6)

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TABLE 2. Location of Infection for 6,832 Bacteremia Cases, North Denmark

Location of infection	*Escherichia coli*, No. (%)	*Staphylococcus aureus*, No. (%)	*Streptococcus pneumoniae*, No. (%)
Urinary tract	2,297 (56.6)	99 (6.3)	0 (0)
Respiratory tract	38 (0.9)	93 (5.9)	911 (76.1)
Intra-abdominal	622 (15.3)	37 (2.4)	11 (0.7)
Intravascular catheters	5 (0.1)	286 (18.2)	1 (0.1)
Bones/joints	21 (0.5)	166 (10.5)	7 (0.6)
Skin/connective tissue/muscles	19 (0.5)	146 (9.3)	0 (0)
Heart	1 (0)	100 (6.4)	8 (0.7)
Neuro infections	13 (0.3)	11 (0.7)	74 (6.2)
Female genitals	14 (0.3)	1 (0.1)	2 (0.2)
Blood vessels	1 (0)	16 (1.0)	0 (0)
Miscellaneous	15 (0.4)	3 (0.2)	0 (0)
Unknown	1,014 (25.0)	617 (39.2)	183 (15.3)
Total	4,060 (100.0)	1,575 (100.0)	1,197 (100.0)

TABLE 3. Seasonal Variation and Peak Date for Bacteremia Cases and Subgroups

		Eschericia coli		*Staphylococcus aureus*		*Streptococcus pneumoniae*	
Group	Category	PTT ratio (95% CI)	Peak date	PTT ratio (95% CI)	Peak date	PTT ratio (95% CI)	Peak date
All		**1.17 (1.12–1.22)**[1]	24 Aug	1.05 (1.00–1.13)	6 Sep	**3.42 (3.10–3.83)**	8 Feb
Acquisition	Community	**1.24 (1.17–1.32)**	16 Aug	1.03 (1.00–1.16)	21 Jul	**3.62 (3.16–4.14)**	7 Feb
	HCA	**1.14 (1.04–1.25)**	17 Aug	1.14 (1.00–1.31)	18 Sep	**2.85 (2.22–3.67)**	14 Feb
	Hospital	1.07 (1.00–1.17)	31 Oct	1.07 (1.00–1.18)	14 Oct	**2.93 (2.04–4.20)**	14 Feb
Gender	Males	**1.16 (1.08–1.23)**	10 Sep	1.07 (1.00–1.17)	11 Sep	**3.19 (2.73–3.73)**	12 Feb
	Females	**1.19 (1.12–1.26)**	13 Aug	1.07 (1.00–1.19)	17 Aug	**3.66 (3.11–4.30)**	5 Feb
Acquisition/Gender	Community/males	**1.20 (1.09–1.32)**	13 Sep	1.15 (1.00–1.33)	27 Jul	**3.43 (2.83–4.16)**	10 Feb
	Community/females	**1.29 (1.19–1.39)**	4 Aug	1.11 (1.00–1.34)	10 Feb	**3.79 (3.13–4.58)**	4 Feb
	HCA/males	**1.16 (1.01–1.33)**	20 Aug	1.10 (1.00–1.30)	13 Sep	**2.56 (1.83–3.58)**	13 Feb
	HCA/females	1.08 (1.00–1.22)	14 Aug	1.11 (1.00–1.37)	24 Sep	**3.13 (2.15–4.55)**	15 Feb
	Hospital/males	1.04 (1.00–1.18)	10 Oct	1.04 (1.00–1.19)	23 Nov	**2.75 (1.71–4.43)**	2 Mar
	Hospital/females	1.08 (1.00–1.23)	15 Nov	1.06 (1.00–1.25)	29 Jun	**3.45 (1.92–6.19)**	27 Jan
Age group/Charlson score group	0–64 y/0	**1.27 (1.12–1.43)**	17 Aug	1.08 (1.00–1.28)	18 Jul	**3.59 (2.88–4.48)**	15 Feb
	0–64 y/1–2	1.07 (1.00–1.24)	14 Aug	1.12 (1.00–1.35)	16 Oct	**2.22 (1.67–2.95)**	5 Feb
	0–64 y/>2	**1.24 (1.04–1.49)**	4 Nov	1.19 (1.00–1.43)	23 Aug	**2.54 (1.71–3.79)**	9 Feb
	65–79 y/0	1.11 (1.00–1.28)	31 Aug	1.15 (1.00–1.48)	3 Jan	**4.40 (2.96–6.55)**	2 Feb
	65–79 y/1–2	1.03 (1.00–1.15)	15 Oct	1.13 (1.00–1.36)	19 Dec	**3.21 (2.35–4.39)**	8 Feb
	65–79 y/>2	**1.18 (1.03–1.35)**	13 Aug	1.15 (1.00–1.39)	15 Aug	**2.86 (1.95–4.20)**	10 Feb
	80+ y/0	**1.20 (1.05–1.37)**	4 Aug	1.17 (1.00–1.50)	28 Apr	**5.32 (3.29–8.62)**	28 Jan
	80+ y/1–2	1.07 (1.00–1.20)	18 Aug	1.16 (1.00–1.43)	6 Oct	**4.31 (2.86–6.51)**	30 Jan
	80+ y/>2	**1.49 (1.28–1.74)**	15 Aug	1.17 (1.00–1.49)	12 Feb	**3.05 (1.94–4.80)**	7 Mar
Location of infection[2]	Urinary tract	**1.17 (1.04–1.31)**	5 Jul	...	...	...	...
	Respiratory tract	...	...	...	...	**3.55 (2.72–4.64)**	9 Feb
	Intra-abdominal	1.21 (1.00–1.51)	20 Aug	...	...	...	...
	Intravasc. catheters	...	...	**1.60 (1.13–2.26)**	1 Oct	...	...
	Bones/joints	...	...	1.30 (1.00–2.02)	19 Aug	...	...
	S/CT/M	...	...	1.42 (1.00–2.29)	13 Jun	...	...
	Unknown	**1.23 (1.03–1.46)**	29 Sep	**1.36 (1.08–1.71)**	28 Aug	**1.72 (1.11–2.68)**	20 Feb

NOTE. PTT, peak-to-trough; CI, confidence interval; HCA, healthcare associated; S/CT/M, skin/connective tissues/muscles.
[1]Bold type indicates seasonal variation (lower 95% CI > 1).
[2]Only for North Jutland cases (cf, Table 2).

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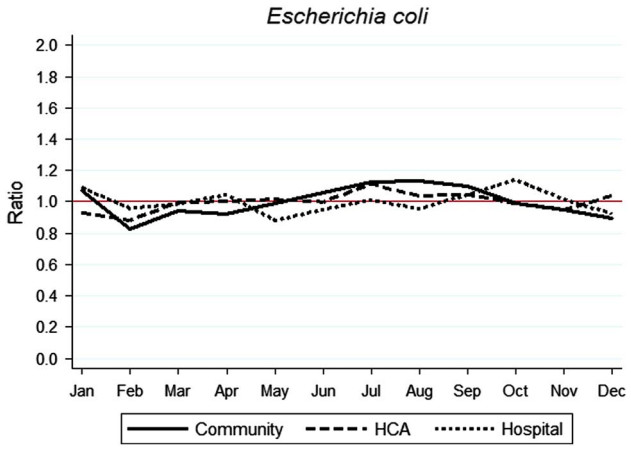

FIGURE 1. Monthly ratios (smoothed number of monthly observations divided by the mean monthly smoothed number) for *Escherichia coli* bacteremia, according to acquisition. HCA, health-care associated.

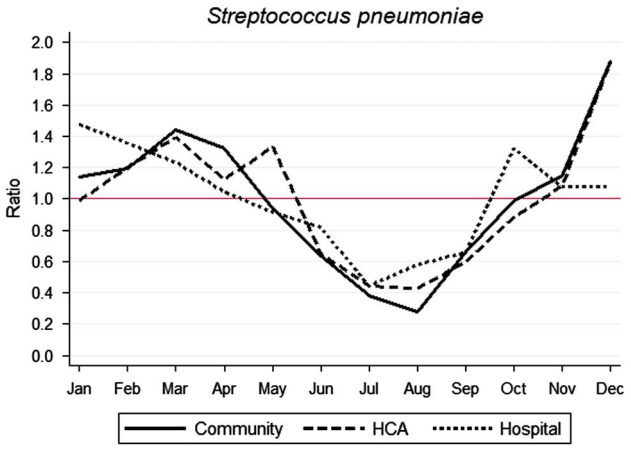

FIGURE 3. Monthly ratios (smoothed number of monthly observations divided by the mean monthly smoothed number) for *Streptococcus pneumoniae* bacteremia, according to acquisition. HCA, health-care associated.

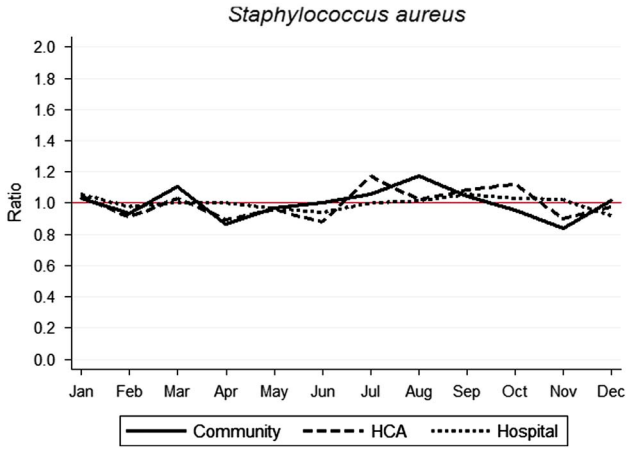

FIGURE 2. Monthly ratios (smoothed number of monthly observations divided by the mean monthly smoothed number) for *Staphylococcus aureus* bacteremia, according to acquisition. HCA, health-care associated.

did not differ according to acquisition (Table 3, Fig. 3), gender, or combinations of these, whereas seasonal variation was smaller for cases with an unknown location of infection. Seasonal variation tended to increase with higher age and decrease with higher Charlson comorbidity; however, these results should be interpreted with caution due to the wide CIs. All peak dates occurred in or adjacent to February.

First-Time Bacteremia Cases

Restrictions to the 25,487 first-time cases (including 6,163 with location data) yielded no material differences in any of the above analyses (data not shown).

DISCUSSION

For the 3 most common bacteremia species (*E. coli*, *S. aureus*, *S. pneumoniae*), seasonal variation or lack thereof occurred irrespectively of acquisition (community, HCA, hospital) or patient characteristics (gender, age, Charlson comorbidity, location of infection), thus refuting our hypothesis of decreasing seasonal variation with increasing severity of infection. An exception was a weak seasonal variation of community-acquired *E. coli* bacteremia that tended to diminish over HCA to hospital-acquired bacteremia cases.

In accord with our overall results, seasonal variation of bacteremia has been reported for *S. pneumoniae* to peak in the winter,[7,10,12,14] *E. coli* to peak in the summer,[8,9,11,15,17,31] and to lack seasonal variation for *S. aureus*.[11,12,31,32]

While numerous studies have assessed seasonal variation in relation to climatic factors[7,8,11,13,15,31,33,34] or viral respiratory infections[7,10,32,35] fewer studies have assessed seasonal variation of host susceptibility, as reviewed by Dowell.[36] Previously, we reported that seasonal variation of non-typhoid *Salmonella* infections diminished with increasing severity of infection. This may, in part, be explained by the higher impact of exogenous factors (eg, climate and behavioral factors, which exert seasonal variation) on the acquisition of less severe infections, whereas endogenous host characteristics (eg, age and chronic diseases, with no seasonal variation) are more important in more severe infections.

To our knowledge, only 2 studies have related the seasonal variation of bacteremia to acquisition.[6,17] In agreement with our results, a recent study from the United Kingdom, with an impressive number of 79,155 *E. coli* bacteremia cases, reported seasonal variation with a summer peak for the 75% community-acquired cases, but no seasonal variation for the 25% hospital-acquired cases.[17] The same was reported for

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Gram-negative bacteremia in Australia, although the low number of 181 community-acquired (34 *E. coli*) and 259 (62 *E. coli*) hospital-acquired cases makes comparisons to our study difficult.[6] The Australian authors mainly explained the seasonal variation for outpatients by the influence of climate. Inpatients, on the other hand, were under climate control in the hospital, and the UK study group suggested that climatic factors had little impact on the seasonal variation of community-acquired bacteremia cases.

Non-climatic factors may also contribute to the diminishing seasonal variation of *E. coli* parallel to closer hospital contact. Different risk factors are probably related to acquisition outside or inside the hospital. In our study, 60.5% of community acquired, 51.4% of HCA, and 46.6% of hospital-acquired *E. coli* bacteremia was encountered in women, whereas there were no notable differences in age distribution between males and females within any of the 3 acquisition modes (data not shown). Likewise, no conspicuous differences in seasonal variation were found in relation to gender or age/Charlson comorbidity groups. A US study also reported a summer peak for 6,035 *E. coli* isolates, of which 74% were isolated from urine and only 9% were isolated from blood.[31] Although that study did not report separate seasonal variation analyses according to acquisition, 56% of the *E. coli* infections were community acquired, which is comparable to the 54.8% in our study. The pathogenesis of *E. coli* bacteremia probably also differs in relation to location of infection; the urinary tract or intra-abdominal locations were the most common.[37–39] A higher prevalence of urinary tract locations was reported in community acquired than in hospital-acquired bacteremia[37,38] and in more females than males.[37,39] A recent study reported seasonal variation with a summer peak for urinary tract infections.[40] For 6,832 cases, we had data on the location of infection determined prospectively and based on all microbiological and clinical evidence during admission.[28] The 2,297 *E. coli* cases located in the urinary tract exhibited seasonal variation with a PTT ratio of 1.17 (95% CI, 1.04–1.31) and a peak date on July 5, whereas the 622 cases located intra-abdominally showed no seasonal variation. The location of infection also varied according to acquisition, most notably in the intra-abdominal area (13.2% community-acquired and 22.4% hospital-acquired, respectively) and the urinary tract (64.3% vs 43.3%) (data not shown).

The aforementioned Australian study found no seasonal variation for Gram-positive bacteremia for the 149 cases acquired outside or for the 252 acquired inside the hospital. Unfortunately, the frequency of Gram-positive bacterial species was not reported.[6] These results agree with our findings for *S. aureus*, but not for *S. pneumoniae*. The minor impact of acquisition on seasonal variation, both overall and in subgroup analyses, for *S. aureus* and *S. pneumoniae* in our study, may indicate that the risk factors for bacteremic infection were the same regardless of whether it was acquired outside or inside the hospital. Interestingly, seasonal variation was observed for 286 *S. aureus* cases with intravascular catheters as the location of infection and for 617 cases with an unknown location of infection. For *S. pneumoniae*, there was less seasonal variation in the 183 cases with an unknown location of infection. Although definite conclusions are precluded due to relatively low numbers of cases, we have not encountered other such findings in the literature.

Most other studies on the seasonal variation of bacteremia comprising specific bacteria incorporated far fewer bacteremia cases than our study, with 79,155 *E. coli*[17] and 7,266 and 4,147 *S. pneumoniae* cases[10,35] as notable exceptions. High numbers of cases are especially important when observations are distributed over 12 months and various subgroups and our relatively narrow 95% CIs in most analyses indicated high statistical precision. Moreover, our study was population based, and valid data on bacterial species and hospital admissions enabled us to define acquisition, including HCA as an intermediate entity between community and hospital acquisition. Finally, for part of our study cohort, we had valid data on the location of infection.[28]

However, our study also had limitations that warrant further discussion. First, the study was mainly based on administrative registries without clinical data, of which information on location would especially be beneficial. Second, we had no data on behavioral factors, which could strengthen or weaken our hypothesis on seasonal behavioral factors (eg, traveling) being more predominant in less severe infections. Third, exact acquisition criteria may vary, as shown in a review of 23 studies of pediatric bacteremia patients.[41] However, we have recently reported that time windows do not necessarily represent sharp transitions pertaining to acquisition,[19] and we believe such discrepancies are of minor importance in this study. Finally, some subgroups had a low number of cases, which could preclude the detection of seasonal variation.

In conclusion, for mono-microbial *E. coli*, *S. aureus*, and *S. pneumoniae* bacteremia, seasonal variation was mainly related to the bacterial species, regardless of acquisition or patient characteristics such as gender, age, comorbidity, or location of infection.

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