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Original Article

Seasonal variation of hospital-acquired bloodstream infections: A national cohort study

Koen Blot MD[1,2], Naïma Hammami MD, MPH[3,4], Stijn Blot MSN, PhD[2,5], Dirk Vogelaers MD, PhD[2,6] and Marie-Laurence Lambert MD, PhD[1,7]

[1]Department of Epidemiology and Public Health, Sciensano, Brussels, Belgium, [2]Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium, [3]Healthcare-Associated Infections and Antimicrobial Resistance, Public Health and Surveillance Department, Sciensano, Brussels, Belgium, [4]Agentschap Zorg en Gezondheid, Vlaamse Overheid, Ghent, Belgium, [5]Burns, Trauma and Critical Care Research Centre, Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, Australia, [6]General Internal Medicine, Ghent University Hospital, Ghent, Belgium and [7]Institut National d'Assurance Maladie-Invalidité, Service des Soins de Santé, Brussels, Belgium

Abstract

Background: Hospital-acquired bloodstream infections (HABSIs) cause increased morbidity, mortality, and hospital costs that are partially preventable. HABSI seasonality has been described for gram-negative bacteria but has not been stratified per infection origin.

Objective: To assess seasonality among all types of HABSIs and their associations with climate.

Methods: Hospitals performing surveillance for at least 1 full calendar year between 2000 and 2014 were included. Mixed-effects negative binomial regression analysis calculated the peak-to-low monthly ratio as an adjusted HABSI incidence rate ratio (IRR) with 95% confidence intervals (CIs). Another regression model examined associations between HABSI rates and climate variables. These analyses were stratified by microorganism and infectious origin.

Results: The study population included 104 hospitals comprising 44,111 HABSIs. Regression analysis identified an incidence rate ratio (IRR) peak in August for gram-negative HABSIs (IRR, 1.59; 95% CI, 1.49–1.71), CLABSIs (IRR, 1.49; 95% CI, 1.30–1.70), and urinary tract HABSI (IRR, 1.52; 95% CI, 1.34–1.74). The gram-negative incidence increased by 13.1% (95% CI, 9.9%–16.4%) for every 5°C increase in temperature. Seasonality was most present among *E. coli*, *K. pneumoniae*, *E. cloacae*, and the nonfermenters. Gram-positive and pulmonary HABSIs did not demonstrate seasonal variation.

Conclusions: Seasonality with summer spikes occurred among gram-negative bacteria, CLABSIs, and urinary tract HABSIs. Higher ambient temperature was associated with gram-negative HABSI rates. The preventable causative factors for seasonality, such as the nurse-to-patient ratio, indoor room temperature or device-utilization, need to be examined to assess areas for improving patient safety.

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Hospitalized patients are susceptible to hospital-acquired bloodstream infections (HABSIs), which are an important cause of increased morbidity, mortality, length of stay, and hospital costs.[1,2] Due to their clinical and economic impact, the Belgian "Surveillance of Bloodstream Infections in Hospitals" program collects nationwide HABSI case-based data.[3]

Recent studies have recognized that hospital-acquired infections demonstrate seasonality, particularly gram-negative bacteria.[4] However, these studies focused on microorganisms and less on the infectious origin or the impact of climate. Seasonality is a multifactorial phenomenon associated with changes at the patient, pathogen, hospital and environmental levels.[5] Examples include seasonal changes in the nurse-to-patient ratio,[6] survival conditions of the pathogen, host immune status, antibiotic use,[7,8] postinfluenza bacterial or fungal superinfection,[9,10] and climate.[11] Unravelling the role of the underlying factors that drive infectious diseases seasonality will improve our understanding of host and pathogen ecology. This information can guide and inform infection prevention and surveillance studies.

In this study, we examined seasonal variation of monthly HABSI incidence rates based on nationally aggregated data from 2000 to 2014. A further analysis examined the influence of climate factors on HABSI incidence. To better characterize seasonality epidemiology, these analyses were stratified by HABSI and microorganism and infectious origin.

Methods

Study design and setting

A national cohort study of HABSI epidemiology was performed based on the Belgian "Surveillance data of BSI in Hospitals" program from January 2000 to December 2014. The full protocol,

Author for correspondence: Koen Blot, E-mail: koen.blot@ugent.be
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revised in 2013, is available online in Dutch and French (http://www.nsih.be).

Participants

Participation in the surveillance program entails case-based recording of all HABSIs for a minimum of 1 trimester per year. Participation was voluntary but became mandatory from 2014 onward. Eligible hospitals were all hospitals with >150 beds. To analyze seasonal variation, hospitals included in this cohort study performed surveillance for HABSIs (numerator) with patient day (denominator) data for a full year, that is, 4 trimesters within a calendar year, during at least 1 year.

Case definitions and variables

A laboratory-confirmed BSI requires at least 2 separate samples if the causal microorganism is a skin commensal and at least 1 sample if the causal microorganism is a recognized pathogen (Appendix 1 online). HABSIs were those not present or incubating at the time of admission to the acute-care setting (≥48 hours). An episode in the same patient caused by the same microorganism was considered a novel occurrence if 14 days elapsed between the 2 episodes. HABSI origins were classified as central-line associated; unknown origin; secondary to pulmonary, urinary, skin and soft-tissue, abdominal infection; or surgical sites. HABSI diagnosis could be classified as confirmed instead of probable when the same microorganism was cultured from the probable infectious focus. Catheter-related BSI diagnosis required a concomitant positive central venous catheter (CVC) tip and blood culture with identification of the same microorganism (Appendix 2 online). Central-line–associated BSI consisted of a BSI without microbiological confirmation but with a CVC in place within 48 hours, unrelated to an infection from another site, and considered by the clinician to originate from the CVC.

Collected data included infection onset date, infectious origin, causal microorganism(s), and university-affiliated hospital status. Denominator data included number of hospitalwide patient days and admissions per trimester. HABSI incidence was reported as a rate per 10,000 patient days.

Statistical methods

Mixed-effects negative binomial distribution regression model calculated the adjusted incidence rate ratio (IRR) with 95% confidence interval (CI) for both monthly HABSI rates. This method allowed the identification of a peak-to-low ratio between 2 months, which describes the amplitude of the seasonal pattern by comparing the month with the lowest incidence rate to the month with the highest incidence rate.[12] Further stratification analyzed incidence rate ratios for gram-positive, gram-negative, and fungal infections. The least common *Enterobacter* spp (*E. proteus*, *E. serratia*, *E. morganella*, and *E. citrobacter* spp) were grouped together for regression analysis. The analysis was performed hospitalwide and includes the intensive care unit. Fixed effects included year, acute versus chronic care hospitals, university hospital status, and infection risk exposure expressed as monthly patient days. Varying hospital participation and heterogeneity were accounted for by applying individual hospital units as random effects. Although denominator patient-day data were reported per trimester, it was averaged between the 3 months to allow for monthly patient-day exposure and incidence rate analysis.

Statistical significance depends on both the strength of the association and the amount of data and thus does not measure the strength of seasonal occurrence. Instead, measures that compare estimates of rates should be used.[12] To graph and describe the seasonal changes, composite monthly HABSI rates were estimated based on the regression analysis results. In this way, both the relative (incidence rate ratio) and absolute changes (mean incidence rate per patient days) could be presented. Because the regression analysis may identify a single statistically significant peak incidence within 1 month, a peak-to-low ratio comparing the seasonal peak-to-low incidence rate ratio (ie, winter to summer period) was calculated to determine whether significant variation occurred between seasons. In this manner, we were able to distinguish between a monthly outlier versus a relevant, continued, absolute incidence rate change within an entire season.

To assess the influence of climate on the infection incidence, monthly average temperature (°C), humidity (%), and precipitation (mm) from 2000 through 2014 were collected from an online data system.[13] A separate mixed-effects negative binomial regression model applied climate variables to identify associations with HABSI. A second model examined temperature and humidity per season with weather-by-season interaction terms (Appendix 3 online). Thus, we were able to distinguish between a warm versus a cold season.[14] Seasons were defined as winter (December–February), spring (March–May), summer (June–August), and autumn (September–November).

All statistical analyses were performed using Stata version 14 software (StataCorp, College Station, TX). The mixed-effects negative binomial regression analysis was performed with the *menbreg* function. Interquartile ranges (IQR) were reported as the 25^{th}–75^{th} percentile. Statistical significance was set at $P \leq .05$; however, considering the number of analytical computations and the large data set, a $P \leq .01$ should be considered more relevant to indicate statistical significance.

Results

In total, 49,021 cultured microorganisms from 44,111 HABSIs were reported by 104 hospital sites (Table 1). Selection of hospitals performing surveillance for an entire calendar year led to the exclusion of 20,034 HABSIs (31.2%). Only 63 HABSIs (0.1%) were excluded due to missing patient-day data.

The hospitalwide median HABSI incidence rate was 7.0 per 10,000 patient days (IQR, 4.93–9.47), with a CLABSI rate of 1.14 per 10,000 patient days (IQR, 0.64–2.14). Monthly average ambient temperature ranged from a minimum of −0.7 to a maximum of 23°C with higher temperature during June–August. Relative humidity showed a range between 62% and to 92%, with higher percentages during December–February.

The most common pathogens consisted of coagulase-negative staphylococci (CNS), *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Klebsiella pneumoniae*. The most frequent HABSI foci were of central-line, urinary tract, pulmonary, or intra-abdominal origin (Appendix 4 online). Polymicrobial infection occurred among 4,317 (9.8%) of 44,111 HABSIs. A definite diagnosis of the infectious origin (ie, culture of the same microorganism from blood and primary infectious site) was reported among 13,636 (27.8%) of 49,021 HABSI microorganisms. Approximately one-third of HABSI cases were classified as being of unknown origin (34.1%). Appendix 5 (online) displays the distribution of microorganisms per HABSI origin. CLABSI consisted primarily of CNS, followed by gram-

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Table 1. Hospitalwide Hospital-Acquired Bloodstream Infection (HABSI) Incidence by Season[a]

Variable	Season				Total
	Winter	Spring	Summer	Autumn	
HABSI	10,689	10,474	11,675	11,273	44,111
Patient days	13,130,543	12,755,878	12,091,905	12,546,358	50,524,684
Patient admissions	5,275 204	5,164,098	4,887,702	5,053,537	20,380,541
Mean HABSI rate	8.14	8.21	9.65	8.98	8.73
Temperature, median °C (IQR)	4 (3–6)	11 (8–14)	18 (17–19)	11 (9–15)	11 (6–16)
Relative humidity, median % (IQR)	87 (83–89)	73 (70–76)	74 (71–77)	84 (80–88)	79 (74–90)

Note. IQR, interquartile range.
[a]Seasonal data on hospitalwide mean HABSI rates per 10,000 patient days.

negative bacteria, *S. aureus* and *Candida* spp. Nearly all urinary-tract HABSIs were caused by gram-negative pathogens.

Mixed-effects regression analysis identified significant seasonal (IRR, 1.22; 95% confidence interval [CI], 1.18–1.26 CI; $P < .001$) and monthly peak-to-low relative rate changes (IRR, 1.42; 95% CI, 1.34–1.50; $P < .001$) for total HABSIs. When stratified, this seasonality was present for most microorganisms and HABSIs per infectious origin but at varying levels of magnitude. Table 2 lists the HABSIs peak-to-low seasonal (summer-to-winter) and monthly IRRs, stratified ny microorganism and infectious origin. Gram-negative HABSIs demonstrated a larger seasonal peak-to-low ratio during the summer (IRR, 1.37; 95% CI, 1.32–1.43; $P < .001$) compared to gram-positive pathogens (IRR, 1.07; 95% CI, 1.03–1.12; $P = .002$).

Based on monthly peak-to-low IRRs, HABSI estimates were plotted to quantify absolute incidence rate seasonality (Fig. 1). Figure 1a displays the monthly incidence of all pathogens with significant monthly peak-to-low IRRs. Figure 1b illustrates monthly variation among pathogens with lower incidence rates. They display a seasonal pattern, with a trough incidence rate during February that peaks 5–6 months later in July or August. Some HABSI rates only displayed significant IRR during 1 peak month and not the entire summer, which statistically appears as a discrepancy between the seasonal and monthly peak-to-low IRR, as in the cases of *S. aureus*, CNS, and *P. aeruginosa*.

When examining Figure 1a, pathogens that displayed the clearest seasonality with a spike during July–August were CNS, *E. coli*, *K. pneumoniae*, *E. cloacae*, and a group of less common Enterobacterales. Despite their relatively lower peak-to-low seasonal and monthly IRRs, CNS and *E. coli* demonstrated important absolute rate changes (Fig. 1a). Although *S. aureus* demonstrated significant peak-to-low IRR increases during the summer, seasonality was less clear when examining absolute rate changes. *P. aeruginosa*, *Acinetobacter* spp, *K. oxytoca*, and *Stenotrophomonas* spp (bacteria with lower incidence rates) also demonstrated summer seasonality (Fig. 1b). *S. pneumoniae* displayed the opposite trend, with peaks during the winter.

HABSIs from different infectious origins also exhibited seasonal variation showing summer spikes (Table 2). The clearest examples were central-line– and urinary tract–associated HABSIs (Fig. 2). Subgroup analysis of catheter-related bloodstream infections (ie, with concomitant positive catheter tip or catheter blood culture) confirmed this seasonality. The seasonal peak-to-low IRR was statistically significant among intra-abdominal, skin and soft-tissue, and surgical site infections; however, the effect size was smaller as evidenced by the smaller absolute rate changes. HABSIs of pulmonary origin exhibited no seasonal variation. Subgroup analysis of gram-negative pulmonary HABSI showed subtle increases during the summer months (Appendix 6 online).

Table 3 describes the associations between ambient climate variables and HABSI incidence rates per microorganism or per infectious focus. Gram-negative bacteria displayed significant associations between climate and IRR both year-long and within all seasons. Those that demonstrated the highest correlation with temperature were *Stenotrophomonas*, *Acinetobacter*, and *Klebsiella* spp. Although *P. aeruginosa* displayed seasonality with summer peaks, a period that is paired with lower relative humidity, there was no positive association with ambient temperature but rather with humidity. *Stenotrophomonas* spp and *Bacteroides* spp also displayed positive associations with higher relative humidity (Table 3). *Streptococcus pneumoniae* incidence was negatively associated with temperature. The only type of HABSI that demonstrated clear associations with climate was CLABSI, with increased incidence at higher temperatures. Urinary tract HABSI also showed an association with temperature but with a very small effect size. Precipitation was not associated with any HABSI microorganism nor type of infection.

Discussion

This national surveillance program identified seasonal variation in HABSI incidence rates. Summer incidence spikes occurred among *Enterobacterales* (*E. coli*, *K. pneumoniae*, and *E. cloacae*), nonfermenters (*P. aeruginosa*, *Acinetobacter*, and *Stenotrophomonas* spp), CLABSIs, and urinary tract HABSIs. Higher monthly ambient temperature was associated with increased gram-negative HABSI and CLABSI incidences. There was no association between HABSI and precipitation because precipitation has a confounding effect that influences temperature and humidity.

Previous reports have also identified summer increases in gram-negative infections and associations with ambient temperature.[4,11,14,15] One tertiary-care center also identified CLABSI seasonal variation but was limited by the single-center design, short-term surveillance of 24 months, and lack of microorganism data.[16] There was no clear hospital-acquired *S. aureus* seasonality, which is in line with a previous literature review.[5]

The strengths of this study include nationwide long-term surveillance over multiple hospitals, detailed microorganism and infectious origin identification, and mixed-effects regression analysis with correction for confounding factors such as hospital heterogeneity, patient days, years, and seasons.[12] This is the first

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Table 2. Peak-to-Low Hospital-Acquired Bloodstream Infection (HABSI) Seasonal and Monthly Incidence Rate Ratios (IRRs) per Microorganism and Origin of Infection[a]

	Seasonal Peak-to-Low Ratio			Monthly Peak-to-Low Ratio		
Variable	IRR[b]	95% CI	*P* Value	IRR[b]	95% CI	*P* Value
Total HABSI	1.22	1.18–1.26	<.001	1.42	1.34–1.50	<.001
Microorganism						
Gram-positive bacteria	1.07	1.03–1.12	.002	1.26	1.17–1.36	<.001
CNS	1.10	1.03–1.18	.006	1.37	1.22–1.54	<.001
S. aureus	1.09	1.01–1.18	.03	1.36	1.19–1.55	<.001
S. pneumoniae	0.47	0.38–0.60	<.001	0.29	0.19–0.46	<.001
Enterococcus spp	1.10	1.01–1.21	.03			NS
Viridans streptococci	1.25	1.03–1.52	.03			NS
Gram-negative bacteria	1.37	1.32–1.43	<.001	1.59	1.49–1.71	<.001
Stenotrophomonas spp	2.22	1.57–3.14	<.001	3.02	1.67–5.45	<.001
E. cloacae	2.06	1.79–2.38	<.001	2.70	2.11–3.46	<.001
Acinetobacter spp	1.77	1.47–2.14	<.001	2.74	1.97–3.81	<.001
K. pneumoniae	1.69	1.50–1.89	<.001	2.00	1.64–2.45	<.001
K. oxytoca	1.39	1.17–1.65	<.001	1.71	1.26–2.32	<.001
P. aeruginosa	1.29	1.15–1.43	<.001	1.77	1.47–2.14	<.001
Other *Enterobacterales*	1.29	1.16–1.44	<.001	1.61	1.33–1.95	<.001
E. coli	1.24	1.17–1.32	<.001	1.41	1.27–1.56	<.001
K. aerogenes	1.15	0.97–1.35	.10	1.66	1.24–2.23	<.001
Bacteroides spp			NS			NS
Candida spp	1.12	1.01–1.26	.04	1.36	1.13–1.66	.002
Infectious origin						
Central-line–associated	1.26	1.17–1.36	<.001	1.48	1.30–1.67	<.001
Catheter-related	1.31	1.21–1.41	<.001	1.49	1.30–1.70	<.001
Urinary tract	1.30	1.21–1.40	<.001	1.52	1.34–1.74	<.001
Pulmonary			NS			NS
Intra-abdominal	1.30	1.16–1.46	<.001	1.46	1.20–1.78	<.001
Deep surgical site	1.32	1.10–1.59	.003	1.79	1.29–2.48	<.001
Skin and soft tissue	1.41	1.19–1.68	<.001	2.09	1.54–2.85	<.001

Note. NS, non-significance; CNS, coagulase-negative staphylococci; HABSI, hospital-acquired bloodstream infections. Group of other *Enterobacterales* includes *Proteus*, *Serratia*, *Morganella* and *Citrobacter* spp.

[a]Estimates of the mixed-effects negative binomial regression model adjusted for year, acute vs chronic care hospitals, university-affiliated status, and infection risk exposure expressed as monthly patient days. Peak-to-low monthly incidence rates vary per HABSI, but the trough levels are usually in February with a peak during July–August, with the exception of *S. pneumoniae*. Figures 1 and 2 display these monthly peak and trough incidence rates.

[b]IRRs are expressed as a peak-to-low ratio between the lowest and highest incidence rate between seasons (seasonal peak-to-low ratio between winter and summer) and between months (monthly peak-to-low ratio).

national study to analyze both seasonality of microorganism and infections per origin. Seasonality is a phenomenon that manifests due to interconnected changes in patient, pathogen, hospital, and environmental variables. For example, the number of available hospital beds decreases during the summer, which leads to lower patient admissions and possibly a selection bias of hospitalized patients with relatively higher comorbidities, which increases the risk of HABSI.

This study had several limitations. Insufficient information was available for confounding factors such as in-hospital temperature and humidity, patient comorbidities, nurse-to-patient ratio, and invasive device use (eg, central lines, endotracheal intubation, and urinary catheterization).

Notably, CLABSIs and urinary-tract HABSIs, infections associated with invasive device use, demonstrated seasonal variation. Although most CLABSIs are caused by gram-positive skin commensals, there was an association between higher ambient temperature and CLABSI rates. Catheter dressing disruption due to increasing skin perspiration or a changing nurse-to-patient ratio during the summer could be responsible.[17] A lower nurse-to-patient ratio has been shown to lead to worse patient outcomes such as mortality and HABSI.[18-20] However, studies that analyzed seasonal variation in nurse staffing have found both lower nursing hours per patient days and worse patient outcomes during the winter.[6,21,22] This nurse-to-patient ratio decrease is secondary to increased patient admissions during the influenza season. Another study in an acute-care hospital could not identify clear seasonal nurse-staffing patterns.[23] Belgian national hospital registry data on nurse staffing is available for the months of March, June, September, and December.[24] Unfortunately, these reports did not collect nurse staffing data during July–August,

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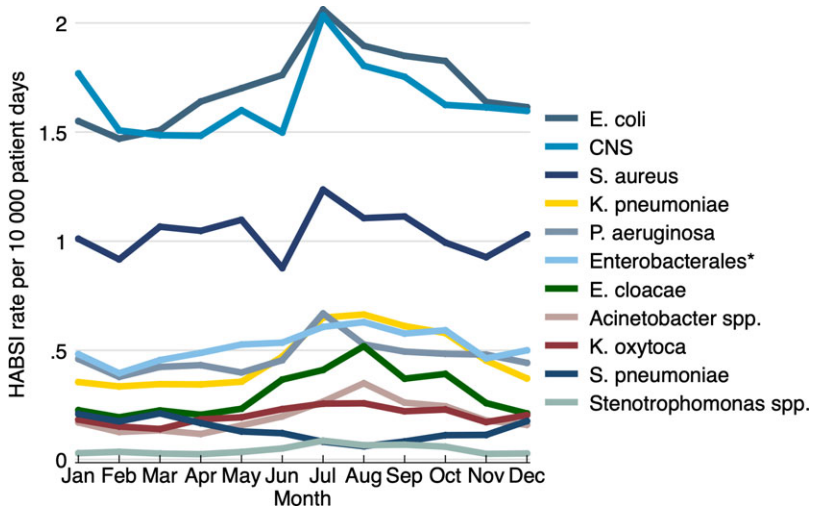

Fig. 1a. Seasonal variation of hospital-acquired bloodstream infections (HABSIs), all pathogens. Composite monthly HABSI incidence rates of microorganisms with significant seasonal and monthly variation based on the mixed-effects regression analysis with peak-to-low monthly incidence rate ratios (see Table 2). *Grouped combination of the other less common *Enterobacterales* spp (*E. proteus*, *E. serratia*, *E. morganella*, and *E. citrobacter*). Note. CNS, coagulase-negative staphylococci.

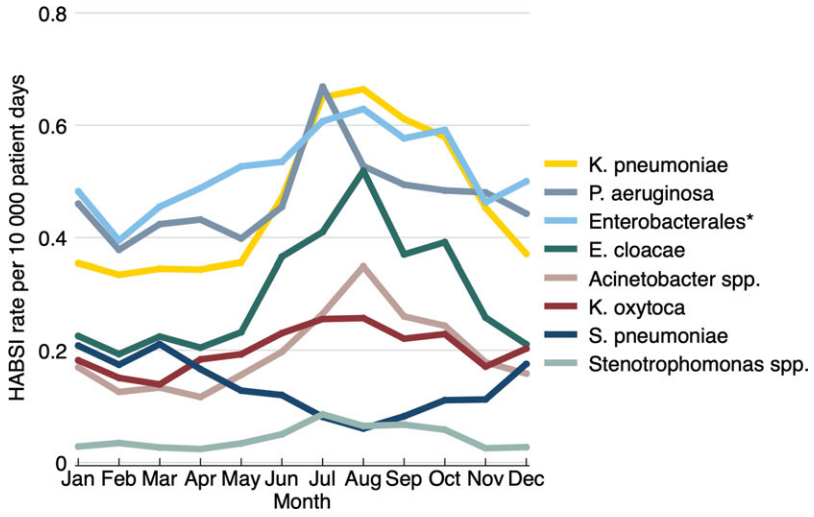

Fig. 1b. Seasonal variation of hospital-acquired bloodstream infections (HABSIs), focus on pathogens with low incidence rates. Composite monthly HABSI incidence rates of microorganisms with significant seasonal and monthly variation based on the mixed-effects regression analysis (see Table 2). This figure focuses on pathogens with lower incidence rates to properly display the large rate increases relative to their baseline incidence. *Group of least common *Enterobacterales* spp (*E. proteus*, *E. serratia*, *E. morganella*, and *E. citrobacter*).

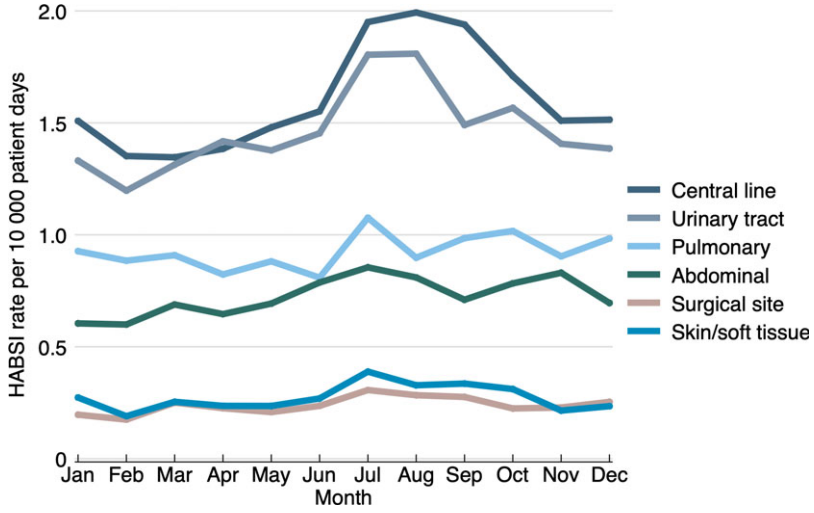

Fig. 2. Seasonal variation of hospital-acquired bloodstream infections (HABSIs), per infectious origin. Composite monthly HABSI incidence rates based on the mixed-effects multivariable regression (see Table 2). HABSIs from central-line and urinary tract infections demonstrate the clearest seasonal incidence peaks during the summer.

when a lower level may have been expected due to personnel vacation. In a similar vein, varying skill mix as inexperienced nurses and physician residents begin during the summer period could also have influenced the HABSI risk. Unfortunately, available data were insufficient to perform a subgroup analysis on urinary tract HABSIs associated with catheterization.

Nonetheless, the regression model identified associations between temperature, humidity, and gram-negative HABSI incidence

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Table 3. Associations Between Hospital-Acquired Bloodstream Infection (HABSI) Microorganisms and Climate, Year-Long and by Season[a]

	Adjusted IRR (95% CI) for HABSI, per Microorganism				
HABSI	All seasons[b]	Winter[c]	Spring[c]	Summer[c]	Autumn[c]
Temperature					
Gram-positive bacteria	3.7 (0.3–7.2)*	−0.5 (−8.3 to 7.5)	1.9 (−3.0 to 6.7)	13.6 (5.4–21.8)***	5.1 (0.8–9.5)*
S. pneumoniae	−36.6 (−51.2 to 21.5)***	−24.6 (−55.1 to 8.1)	−43.7 (−62.9 to −23.9)***	−25.9 (−68.9 to 21.3)	−30.0 (−51.3 to −7.8)**
CNS	9.3 (3.9–14.7)***	−1.2 (−13.5 to 11.4)	10.0 (2.2–17.9)*	26.2 (13.5–39.2)***	9.5 (2.8–16.3)**
S. aureus	7.9 (2.0–13.9)**	−4.9 (−18.2 to 8.7)	5.1 (−3.1 to 13.4)	13.0 (−0.9 to 27.2)	12.8 (5.1 to 20.6)***
Gram-negative bacteria	13.1 (9.9–16.4)***	9.7 (2.1–17.4)*	10.1 (5.4–14.8)***	22.3 (15.1–29.7)***	15.3 (11.2–19.4)***
Stenotrophomonas spp	60.7 (29.7–93.6)***	37.7 (−34.4 to 121.0)	45.9 (−2.4 to 98.9)	40.4 (−16.6 to 104.3)	72.4 (35.0–112.5)***
K. aerogenes	23.4 (10.0–37.2)***	34.8 (2.3–69.4)*	20.1 (0.2–40.8)*	22.3 (−8.1 to 54.6)	23.3 (6.9–40.3)**
Acinetobacter spp	20.0 (4.7–35.8)**	2.5 (−33.2 to 40.8)	12.4 (−11.3 to 37.1)	18.6 (−12.8 to 51.9)	27.2 (8.8–46.2)**
K. pneumoniae	16.6 (7.3–26.0)***	15.5 (−6.8 to 38.9)	9.8 (−4.2 to 24.2)	24.4 (4.9–44.8)*	19.9 (8.8–31.2)***
Other Enterobacterales[d]	16.2 (7.8–24.7)***	4.6 (−15.2 to 24.7)	16.1 (4.0–28.5)**	24.0 (5.1–43.5)*	18.1 (7.6–28.8)***
E. cloacae	15.4 (4.1–27.0)**	−10.7 (−37.9 to 18.1)	4.6 (−12.4 to 22.3)	36.1 (12.6–60.7)**	24.6 (10.7–38.8)***
K. oxytoca	13.6 (0.01–27.6)*	−0.5 (−31.3–32.3)	20.6 (0.1–41.9)*	18.7 (−10.7 to 49.9)	14.0 (−3.0 to 31.5)
E. coli	8.9 (4.3–13.6)***	13.9 (2.9–25.2)*	6.3 (−0.4 to 13.1)	19.5 (8.8–30.4)***	9.1 (3.2–15.0)**
Central line	12.2 (6.0–18.5)***	−13.9 (−28.2 to 0.9)	9.0 (0.1–17.9)*	18.7 (4.7–33.2)**	19.1 (11.4–27.0)***
Urinary tract	6.4 (0.4–12.5)*	3.1 (−11.0 to 17.6)	5.3 (−3.1 to 13.9)	17.4 (3.8–31.3)*	6.3 (−1.2 to 14.0)
Humidity					
Gram-negative bacteria	6.8 (3.0–10.7)***	8.8 (4.7–12.9)***	8.8 (4.3–13.3)***	5.0 (0.8–9.2)*	8.1 (4.3–12.0)***
Stenotrophomonas spp	35.1 (1.5–69.8)*	36.3 (−0.2 to 74.0)	32.9 (−7.8 to 75.3)	38.4 (3.7–74.3)*	26.9 (−7.4 to 62.3)
Bacteroides spp	22.3 (4.2–40.7)*	19.8 (1.1–38.9)*	21.6 (0.9–42.6)*	23.0 (2.5–43.9)*	19.2 (1.4–37.3)*
P. aeruginosa	11.9 (1.6–22.3)*	14.4 (3.3–25.1)*	14.8 (2.8–26.9)*	9.4 (−1.9 to 20.8)	12.8 (2.5–23.2)*

Note. CI, confidence interval; IRR, incidence rate ratio; CNS, coagulase-negative staphylococci.
[a]The mixed-effects negative binomial regression model adjusts for year, university-affiliated status and infection risk exposure expressed as monthly patient days. IRRs are expressed as a % change with 95% confidence intervals per increase in monthly average of ambient temperature by 5°C or 10% relative humidity. Only microorganisms with significant associations with climate variables year-round are reported.
[b]Regression analysis model included season, temperature, humidity and precipitation as fixed effects.
[c]Regression analysis model was performed with climate-by-season interaction terms as fixed effects.
[d]Group of other *Enterobacterales* includes *E. proteus*, *E. serratia*, *E. morganella*, and *E. citrobacter*.
* $P \leq .05$; ** $P \leq .01$; and *** $P \leq .001$.

after adjustment for different seasons. This model partially corrects for possible seasonal nurse-to-patient ratio variations. The association with temperature and gram-negative HABSI remained significant within the summer season, indicating a difference in gram-negative incidence between warmer and colder summers. Gram-negative incidence was also associated with higher relative humidity, which is actually lower during the summer period. Although the landmass of Belgium is relatively small (30,700 km^2), the climate variables in the country's center may not represent all geographic regions of the country. Climate factors were limited to ambient measurements, and although not all hospitals in Belgium are climate controlled, this method acts as a proxy for in-hospital climate. Heating, ventilation, and air-conditioning systems may maintain a relatively constant indoor temperature. However, not all hospitals use hospitalwide air-conditioning systems, and changes in ambient temperature and humidity may affect water reservoirs or moisture in the hospital environment.[25] Another explanation is that the changes in ambient temperature influence human activities and subsequently the risk of infection. Higher incidence of severe trauma during the summer may introduce certain pathogens into the hospital environment.

Gram-negative bacteria grow more readily in aquatic milieus and show optimal growth at warmer temperatures of 32–36°C.[26-28] Increases in gram-negative bacterial loads have been observed during the warm months in pond water and city water reservoirs.[29,30] Multidrug-resistant gram-negative bacteria have been described as waterborne pathogens causing healthcare-associated infections, commonly linked to contaminated sinks as a reservoir.[31] Biological studies have demonstrated that closer distance to the equator (ie, higher ambient temperature) is associated with higher proportions of anaerobic gram-negative bacteria and lower gram-positive bacteria in the human gut microbiome.[32] However, in this study, we did not focus on aerobic bacteria such as Enterobacterales. It has been suggested that the influx of patients or personnel into the hospital could carry microorganisms over onto the inanimate hospital environment and subsequently the hospitalized patient.[33] In this way the increased ambient environmental gram-negative load during the summer could influence the hospital environment, patient microbiome, and risk of infection. These considerations fall under the Centers for Disease Control and Prevention "One Health" concept, which recognizes that health is connected to the environment.

Seasonal variation among hospital-acquired infections has been clearly documented. The presence of CLABSI seasonality should be considered when interpreting infection prevention interventions. Future research should assess whether influenceable factors such

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as nurse-to-patient ratio, indoor climate, and device-utilization practices influence HABSI seasonality. In general, quality improvement and infection prevention interventions should be continuously applied. Depending on the underlying cause of seasonality, targeted preventive measures could be implemented during the summer, when HABSI risk is highest.

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