Changing patterns of bloodstream infections in the community and in acute care across two COVID-19 epidemic waves: a retrospective analysis

Nina J Zhu (jiayue.zhu09@imperial.ac.uk)
National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London

Timothy M Rawson
National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London

Siddharth Mookerjee
Imperial College Healthcare NHS Trust

James R Price
National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London

Frances Davies
Imperial College Healthcare NHS Trust

Jonathan Otter
Imperial College Healthcare NHS Trust

Paul Aylin
Department of Primary Care and Public Health, School of Public Health, Imperial College London

Russell Hope
Public Health England

Mark Gilchrist
Imperial College Healthcare NHS Trust

Yeeshika Shersing
Imperial College Healthcare NHS Trust

Alison Holmes
National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London

Research Article

Keywords: healthcare associated infection, bacteraemia, SARS-CoV-2, hospital-acquired infection, community-acquired infection

Posted Date: July 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-690499/v1

Abstract

Introduction We examined the epidemiology of community- and hospital-acquired bloodstream infections (BSIs) in COVID-19 and non-COVID-19 patients across two epidemic waves.

Methods We analysed blood cultures, SARS-CoV-2 tests, and hospital episodes of patients presenting and admitted to a London hospital group between January 2020 and February 2021. We reported BSI incidence, as well as changes in sampling, case mix, bed and staff capacity, and COVID-19 variants.

Results 34,044 blood cultures were taken. We identified 1,047 BSIs; 653 (62.4%) defined epidemiologically as community-acquired and 394 (37.6%) as hospital-acquired. BSI rates and community / hospital ratio were similar to those pre-pandemic. However, important changes in patterns were seen. Among community-acquired BSIs, *Escherichia coli* BSIs remained lower than pre-pandemic level during the two COVID-19 waves, however peaked following lockdown easing in May 2020, deviating from the historical trend of peaking in August. The hospital-acquired BSI rate was 100.4 per 100,000 patient-days across the pandemic, increasing to 132.3 during the first COVID-19 wave and 190.9 during the second, with significant increase seen in elective non-COVID-19 inpatients. Patients who developed a hospital-acquired BSI, including those without COVID-19, experienced 20.2 excess days of hospital stay and 26.7% higher mortality, higher than reported in pre-pandemic literature. In intensive care units (ICUs), the overall BSI rate was 311.8 per 100,000 patient-ICU days, increasing to 421.0 during the second wave, compared to 101.3 pre-COVID. The BSI incidence in those infected with the SARS-CoV-2 Alpha variant was similar to that seen with earlier variants.

Conclusion The pandemic and national responses have had an impact on patterns of community- and hospital-acquired BSIs, in both COVID-19 and non-COVID-19 patients. Factors driving the observed BSI patterns are complex, including changed patient mix, deferred access to health care, and sub-optimal practice. Infection surveillance needs to consider key aspects of pandemic response and changes in healthcare access and practice.

Introduction

The pandemic caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is placing significant pressure on global health systems. As of February 2021, the UK has experienced two surges of COVID-19. Existing assessment of the impact of the pandemic on healthcare-associated infections (HCAIs) has largely been limited to bacterial and fungal co-infections and secondary infections in hospitalised COVID-19 patients [1,2], and based upon data which emerged from the first pandemic wave. These initial analyses did not consider the broader context of potentially shifting patterns of infections in non-COVID-19 patients, nor the changes in dominant COVID-19 variants, health capacity and practice across the pandemic waves.

Delivery of care, especially elective clinical services, was disrupted significantly during the first epidemic wave, whilst elective clinical services were partially sustained during the second wave. Within acute care, factors such as change in patient mix, including those who are critically ill, and prolonged duration of intensive care admission may have collectively influenced the incidence of HCAIs. Expanded use of antimicrobials, increased exposure to healthcare settings and invasive procedures such as mechanical ventilation, alongside disruption of routine infection prevention and control (IPC) activities including screening and isolation may have intensified the emergence and transmission of resistant pathogens [3–5]. Patients with COVID-19 have signs, symptoms, radiology and biomarkers that can mimic findings of bacterial and fungal infection. This, plus use of immune modulating drugs, has made it challenging to diagnose and monitor response to treatment of bacterial and fungal infection. Analysis of how the pandemic has affected the epidemiology of other HCAI in both COVID-19 and non-COVID-19 patients is urgently needed, and such analysis must take into account important variables such as changes in hospital and intensive care admission rates, capacity, culture sampling and screening practices. In addition, the impact of the Alpha (B117) variant, which dominated the second COVID-19 surge in the UK, and other variants on rates of bacterial and fungal infection also requires characterisation [4]. A clear understanding of HCAI in different patient groups enables understanding of the impact of the pandemic and the strengthening targeted IPC interventions to improve care for patients with and without COVID-19 patients.

In this study, we aimed to assess bloodstream infections (BSIs) identified in patients with and without COVID-19 presenting and admitted to a hospital group in North London across two COVID-19 epidemic waves, including both community- and hospital-acquired BSI, while taking into account the changes in healthcare access and practice, and the shifted dominant COVID-19 variants.

Methods

Data

In 2020, Imperial NIHR Biomedical Research Centre (BRC) developed the secure Clinical Analytics, Research and Evaluation (iCARE) high-performance analytics environment, which hosts secondary care data from a large teaching hospital group (Imperial College Healthcare NHS Trust (ICHNT)) in North West London. We used the de-identified individual-level hospital episode records, microbiology specimen results, and COVID-19 pathology data from ICHNT.

Descriptive and statistical analysis

We analysed blood culture results, SARS-CoV-2 test results, and prescribing records of hospital inpatients admitted to the hospital group during 01 January 2020 to 28 February 2021. We reported bloodstream infection incidence rates, susceptibility profiles, and antibiotic prescribing for different patient groups over time, alongside occupancy of hospital and intensive care. After adjusted for time to event, we compared average length of stay (LOS) and all-cause in-hospital mortality for patients with and without hospital-acquired BSI, and performed Mann–Whitney test and Pearson's $\chi 2$-test to determine whether the differences in LOS and mortality were significant. A P-value below 0.05 was considered statistically significant in this analysis.

Definition

Hospital admission: an admission is defined as the continued stay within one hospital as an inpatient (*i.e.,* multiple continued episodes). The methods of admission were elective, or non-elective (including emergency and maternity admission), as per NHS National Codes [6].

Patient characteristics: gender (female, male, other), age group (children: under 18 years old, adults: 18–64 years old, and elderly people: above 64 years old), ethnic group (Black, Asian and minority ethnic (BAME) and mixed background, white and unknown).

Bacterial and fungal bloodstream infection: in this analysis, a bloodstream infection was confirmed by bacterial or fungal isolates identified in blood cultures. If the organism is one of the common skin commensals, we followed the US Centers for Disease Control and Prevention (CDC) criteria [7] to define a true BSI by identifying at least two skin commensals of the same species isolated from blood cultures within 24 hours. Single cultures of skin commensals within 24 hours were considered as contaminants. An "episode" relates to the 14-day period following the initial specimen (or subsequent specimens more than 14 days apart from the previous sample). Positive blood cultures taken within 14 days of the first sample are considered to be indicative of the same episode of infection, unless a negative blood culture has been obtained in the interim. Positive blood cultures taken more than 14 days after the first sample of each episode were reported, as these are considered to be part of a new episode of infection. Repeated positives of the same species within a static 14-day window are considered to be indicative of a single episode of infection. If more than one pathogen was isolated from a blood culture, each was recorded individually at species level. A community-acquired (CA) infection episode is defined if the first positive blood culture was taken within 0-48 hours of an inpatient admission; a healthcare-acquired infection episode was defined if the first positive blood culture was taken after 48 hours of an inpatient admission [8], and prior to discharge; an infection episode is considered not relevant if all identified admissions (spells) of the same patient during the study period started after the last day of the infection episode, or ended before the first day of the infection episode. Sensitivity testing was performed by disc diffusion and Minimum Inhibitory Concentration (MIC) strips, and results were de-duplicated for each sample, the worst-case scenario was kept for each antimicrobial agent. A central-line associated bloodstream infection (CLABSI) case was defined following the US Centre of Disease Control (CDC) criteria [7], a patient with central line (including central venous cannula/catheter, haemodialysis cannula, extended dwell peripheral catheter, and peripherally inserted central catheter) in place between 2 to 7 days before BSI onset was considered a CLABSI.

COVID-19 infection: COVID-19 status is confirmed by at least one positive SARS-CoV-2 nasopharyngeal and oral swab PCR test during the study period. S-gene target failure is used as a proxy to indicate the infection caused by the Alpha (B117) variants. If multiple SARS-CoV-2 positive nasopharyngeal swabs were from the same patients, the patients were grouped to without SGTF if all specimens were tested without SGTF. Bacterial or fungal infection is defined by co-existence of at least one positive SARS-CoV-2 test and confirmed infection from blood or respiratory samples, with the positive SARS-CoV-2 sampled from the same day up to 21 days before the blood/respiratory sampling date, *i.e.,* we consider bacterial or fungal infections confirmed before a positive SARS-CoV-2, or more than 21 days after a positive SARS-CoV-2 not relevant to the COVID-19 infection.

Ethics

The iCARE system provides linked health records from ICNHT and NWL pathology, which have been de-identified and made available for approved research. This study was approved by the Imperial Academic Health Science Centre (AHSC) COVID Research Committee, the COVID-19 NWL Data Prioritisation Group, and the Discover Research Advisory Group (DRAG), which jointly provides a governance mechanism.

Results

Blood culture and patient characteristics

From 01 January 2020 to 28 February 2021, 34,044 blood culture results were identified from the hospital group. Overall, blood cultures were sampled from 19.9% (n = 15,077) patients admitted to the hospitals (compared to 16.8% pre-pandemic), and 59.9% (n = 2,311) patients admitted to intensive care. 64.6% (n = 9,743) of the admitted patients had blood cultures taken during the first 48 hours of admission. The average blood culture sampling rate was 86.8 sets per 1,000 patient-days during the study period, which increased to 150.7 sets per 1,000 patient-days during the two surges of COVID-19 (Figure 1).

From the 34,044 blood cultures included in the study, no pathogen was cultured in 93.2% (n = 31,727) samples. Growth was detected in 6.8% (n = 2,317) cultures, slightly below the pre-COVID figure of 7.3%. Blood cultures with growth detected were from 1,667 patients. In this cohort of patients, the mean age was 58.1 years (standard deviation (SD) = 24.1), most identified as male (949, 56.9%), tested negative for SARS-CoV-2 (954, 57.2%), and were not admitted to ICU (1,150, 69.0%) (Table 1).

Table 1 Characteristics of patients who had growth detected in blood cultures

Patient characteristics		n (%) (N = 1,667)	SARS-CoV-2 positive (N = 395)	SARS-CoV-2 negative (N = 1272)
Gender identity	Female	718 (43.1%)	154 (39.0%)	564 (44.3%)
	Male	949 (56.9%)	241 (61.0%)	708 (55.7%)
	Other	0	0	0
Age group, years	Children (<18)	139 (8.3%)	6 (1.5%)	133 (10.5%)
	Adult (18-64)	760 (45.6%)	211 (53.4%)	549 (43.2%)
	Elderly (>64)	768 (46.1%)	178 (45.1%)	590 (46.4%)
Ethnicity	BAME and mixed background	677 (40.6%)	204 (30.1%)	473 (69.9%)
	White	656 (39.4%)	110 (16.8%)	546 (83.2%)
	Unknown	334 (20.0%)	81 (20.5%)	253 (19.9%)
ICU admission	Admitted to ICU	517 (31.0%)	192 (48.6%)	325 (25.6%)
	Not admitted to ICU	1,150 (69.0%)	203 (51.4%)	947 (74.4%)
Infection status	Developed hospital-acquired BSI	553 (33.2%)	185 (46.8%)	368 (28.9%)
	Did not develop hospital-acquired BSI	1,114 (66.8%)	210 (53.2%)	904 (71.1%)
COVID-19 status	Had SARS-CoV-2 test, positive	395 (23.7%)		
	Had SARS-CoV-2 test, negative	954 (57.2%)		
	Had no SARS-CoV-2 test	318 (19.1%)		
In-hospital mortality	Deceased	449 (26.9%)	134 (33.9%)	315 (24.8%)
	Alive	1,218 (73.1%)	261 (66.1%)	957 (75.2%)

Causative organisms identified in blood cultures

The most common detected organisms in blood culture were Staphylococci (differentiated as *Staphylococcus aureus* and Coagulase-negative staphylococcus (CoNS)), Enterobacterales (including *Citrobacter*, *Enterobacter*, *Escherichia coli*, *Hafnia*, *Klebsiella*, *Morganella, Proteus*, and *Serratia species*), Enterococci, Streptococci, *Pseudomonas* sp., *Corynebacterium* sp. and *Candida* sp., which were isolated from 2,129 blood cultures (1,530 patients). CoNS was detected from 47.8% (n = 1,017) of the blood cultures with growth, which was an increase of 23.0% from 24.8% pre-COVID, followed by Enterococci (increased by 3.6%), and Streptococci (increased by 2.2%). *Escherichia coli* were detected in 15.5% of the blood cultures with growth, which has decreased by 0.9% from before-COVID. 41.3% (n = 879) of the blood cultures grew contaminants, compared to 31.5% pre-pandemic. The 1,250 non-contaminant blood cultures were grouped into 1,047 BSI episodes. 394 (37.6%) BSI episodes were hospital-acquired, and 653 (62.4%) were community-acquired (Table 2).

Table 2 Summary of positive blood cultures (January 2020 - February 2021)

Pathogen	Positive blood culture isolates (N = 2,129) (n, % positive blood cultures)	Positive blood culture isolates (pre-COVID) (% positive blood cultures)	Contaminants (N = 879) (n, % positive blood cultures with the pathogen)	Hospital-acquired BSI (N = 394) (n, % hospital-acquired BSI)	Community-acquired BSI (N = 653) (n, % community-acquired BSI)
Coagulase-negative staphylococcus	1,017 (47.8%)	24.8%	797 (90.7%)	48 (12.2%)	25 (3.8%)
Escherichia coli spp.	331 (15.5%)	16.4%	N/A	55 (14.0%)	246 (37.7%)
Staphylococcus aureus	212 (10.0%)	9.6%	N/A	34 (8.6%)	74 (11.3%)
Enterococci spp.	183 (8.6%)	5.0%	N/A	90 (22.8%)	48 (7.4%)
Streptococci spp.	147 (6.9%)	4.7%	56 (96.4%)	11 (2.8%)	68 (10.3%)
Klebsiella spp.	129 (6.1%)	5.5%	N/A	49 (12.4%)	60 (9.2%)
Pseudomonas spp.	119 (5.6)	3.9%	N/A	42 (10.7%)	49 (7.5%)
Corynebacterium spp.	41 (1.9%)	0.8%	41 (4.7%)	0	0
Candida spp.	40 (1.9%)	1.0%	N/A	30 (7.6%)	6 (0.9%)
Enterobacter spp.	40 (1.9%)	1.3%	N/A	14 (3.6%)	18 (2.8%)
Proteus spp.	38 (1.8%)	1.5%	N/A	4 (1.0%)	30 (4.6%)
Citrobacter spp.	21 (1.0%)	0.3%	N/A	8 (2.0%)	13 (2.0%)
Serratia spp.	21 (1.0%)	0.6%	N/A	6 1.5%)	11 (1.7%)
Morganella spp.	7 (0.3%)	0.2%	N/A	2 (0.5%)	5 (0.8%)
Hafnia spp.	2 (0.1%)	0.0%	N/A	1 (0.3%)	0

Community-acquired bloodstream infections

There were 653 (62.4%) community-acquired BSI episodes that presented during the study period (Figure 2). Monthly counts are shown in Figure 2, as well as the three national lockdowns imposed in March to May 2020, November to December 2020, and January to February 2021 [10].

Gram-negative bacteria (including *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*), and methicillin-susceptible *Staphylococcus aureus* (MSSA) were the most common causative pathogens, similar to pre-COVID. The overall incidence rates of community-acquired BSI caused by Gram-negative bacteria and MSSA were lower than pre-COVID level (Figure 3). During the study period, there were 87.7 Gram-negative BSIs and 18.5 MSSA BSIs per 100,000 patient-days. Pre-COVID rates were 107.0 and 24.6 per 100,000 patient days, respectively. However, between the two COVID-19 surges, during easing of the national lockdowns beginning on 10 May 2020, the BSIs caused by Gram-negative pathogens rose to 126.8 per 100,000 patient-days, in contrast to the pre-COVID annual trend of peaking in the quarter of July to September [11].

Hospital-acquired bloodstream infections in hospital patients with and without COVID-19

During the study period (01 January 2020 – 28 February 2021), 75,799 patients were admitted to the hospital group. 314 patients (0.4%) had at least one episode of hospital-acquired BSI. 288 hospital-acquired BSIs occurred outside intensive care (Figure 4), while 106 were ICU-onset.

During the first COVID-19 surge in April 2020, both elective and non-elective admissions reached their lowest levels (Figure 5). During this period admissions decreased by 53.6% from 15,178 admissions in January to 7,040 admissions in April, with a 65.0% reduction in elective admissions. The overall incidence rate of hospital-acquired BSI was 100.4 episodes per 100,000 patient-days during the study period across all levels of care, compared to 0.97 pre-COVID. Patients with COVID-19 had 170.2 episodes per 100,000 patient-days, while patients without COVID-19 had 90.1 episodes per 100,000 patient-days ($P < 0.05$). Hospital-acquired BSI incidence rate increased during both COVID-19 surges despite the reduced number of hospital admissions, the rate was 79.4 episodes per 100,000 patient-days during the first COVID-19 wave, and 132.8 during the second. More significant increases occurring among elective admissions.

Hospital-acquired BSI caused by MRSA had the largest increase among all causative pathogens in both COVID-19 and non-COVID-19 patients, compared to pre-COVID figures. The MRSA BSI incidence rose from 0.8 per 100,000 patient-days pre-COVID to 4.9 during the first COVID-19 wave and 6.0 during the second wave. After adjusted for time to event, the average LOS was 26.1 days (SD ±26.0) after BSI onset (27.4 days for COVID-19 patients, 25.6 days for non-COVID-19 patients). The crude excess LOS in patients with hospital-acquired BSI is 20.2 days (Mann–Whitney test, $P < 0.05$). 4,153 patients (5.5%) died during their stay in hospital. The all-cause in-hospital mortality was significantly increased in patients who developed a hospital-acquired BSI. In comparison, 101 (32.1%) of 315 patients with a hospital-acquired BSI died, whereas 4,052 (5.4%) of 75,483 patients who had not developed an hospital-acquired BSI died (Pearson's $\chi 2$-test, $P < 0.05$). Of those 314 patients who had healthcare associated BSI, 162 patients (51.6%) developed BSI during their ICU stay, and 89 were diagnosed with COVID-19 (28.3%).

Hospital-acquired bloodstream infections in intensive care

3,856 patients were admitted to ICU during the study period. 26.8% (1,035) of the ICU patients had documented central venous access. 43 episodes of central line associated blood stream infection (CLABSI) were identified during the 14-month study period. The overall incidence rate of CLABSI is 3.2 per 1000 line-days, and increased further to a highest rate of 8.4 during the second COVID-19 in January 2021, compared to 2.5 per 1000-line days pre-COVID. 106 hospital-acquired BSI episodes were onset in intensive care. The overall incidence rate of hospital-acquired BSI was 311.8 episodes per 100,000 patient-ICU days during the study period. Individuals with COVID-19 had 403.2 episodes per 100,000 patient-ICU days, while the patients without COVID-19 had 268.3 episodes per 100,000 patient-ICU days ($P = 0.051$). Outside ICU, the incidence rate of hospital-acquired BSI was 88.5 episodes per 100,000 patient-days, 92.7 in patients with COVID-19, and 66.7 in patients without COVID-19 ($P < 0.05$). The rate of hospital-acquired BSI in ICU remained stable during first COVID-19 wave (304.3 per 100,000 patient-ICU days), however increased to 421.0 during the second wave (Figure 6). A time lag of approximately a week between ICU admission and hospital-acquired BSI onset occurred throughout the study period (Figure 7).

In the study hospitals' ICUs, the average ICU bed occupancy was 95.1% across the study period compared to the pre-COVID level at 83.1% in 2019. Bed occupancy increased to 157.6% in the first surge, with 47.3% occupied by COVID-19 patients, and 182.8% in the second surge, with 64.0% occupied by COVID-19 patients. The number of ICU beds were expanded by 70.5%, from 88 before 2020 to 150 in December 2020. However, the monthly staff hours of registered ICU nurses only expanded by 27.5%, from 41,197.9 hours in July to 52,522.6 hours in December 2020, including the re-deployed non-ICU staff. Reporting of nurse and midwife staffing levels discontinued between March and May [12].

Bacterial and fungal infection in COVID-19 patients infected by the Alpha (B117) variants

A total of 1,171 SARS-CoV-2 positive nasopharyngeal and oral swabs from 850 patients were tested for S-gene target failure (SGTF) using Thermo Fisher assays. 398 (46.8%) patients were infected with SGTF isolate suggesting Alpha (B117) variants. 38 (4.5%) SARS-CoV-2 positive patients had infections caused other pathogens were confirmed within 21 days following a positive SARS-CoV-2 test. 17 (4.3%) patients with SGTF had cultures yielding at least one pathogen compared to 15 (3.3%) patients without SGTF. The difference in proportion of patients who developed bacterial and fungal infections in respiratory tract and blood stream and following a positive SARS-CoV-2 test was not significant in SGTF and non-SGTF groups ($p = 0.452$).

Discussion

The COVID-19 pandemic has exerted high pressure on health systems, with national lockdowns imposed, normal access to primary care disrupted, many elective medical services being suspended and hospital admissions being restricted to those who were critically ill [13]. [13]. The pandemic and the national response measures may have influenced the epidemiology of other infections, and their impact reflected by altered presentation of bacteraemia to healthcare and by altered patterns of bacteraemia seen within healthcare. Across the study period from January 2020 to February 2021, the average blood culture sampling rate and percentage of blood cultures with growth detected were lower than pre-pandemic. However, blood sampling rate increased during COVID-19 surges, as the incubation period for blood culture was reduced from 5 days to 2 days, to enable increased processing of samples in the serving laboratory. Blood cultures with contaminants and non-contaminant isolates (as percentage of all blood cultures) both increased compared to pre-COVID.

Reported spread of communicable pathogens in the community have decreased, potentially associated with physical distancing and emphasised IPC measures [14]. However, an alternative explanation for the reported fall in community-acquired infections identified in acute care was due to reduced elective procedures [15]. There was a concern that patients with symptoms of infection were not seeking medical attention, leading to missed episodes of bacterial infection such as urinary tract associated sepsis [16]. The National Office for Statistics reported one-third excess mortality in private homes during the first pandemic wave [17], of which, 25.6% were due to non-COVID causes [18], including untreated sepsis which [16]. In our analysis, though the average incidence

of community-acquired BSI across the pandemic was below the pre-COVID level, we saw a rise in Gram-negative bacteraemia occurring between COVID-19 surges, suggesting potentially suppressed or delayed presentation or management during the pandemic waves.

In April 2020, elective admissions reduced by 65.0% in the hospital group. During the second surge between December 2020 and January 2021, clinical services were partially suspended with 27.0% reduction in elective admission. Despite the reduced number of admissions, hospital-acquired BSI incidence increased in both surges. The overall incidence rate of hospital-acquired BSI was 100.4 episodes per 100,000 patient-days during the study period, with a more significant rise occurring in the non-COVID-19 elective admissions.

Patients who developed hospital-acquired BSI stayed in the hospital for 20.2 days longer and had 26.7% higher all-cause mortality. The crude excess LOS and all-cause mortality in patients with hospital-acquired BSI were higher than what has been reported in previous literature, of which the excess LOS in patients with hospital-acquired BSI was estimated to be 16.9 days [19]. One explanation could be that the case mix was skewed during the COVID-19 surges as elective admission has been restricted to those who were critically ill, and more likely to acquire infections and had longer hospital stay.

The most significant increase occurred in MRSA BSI, of which the incidence rate increased from 0.8 per 100,000 patient-days pre-COVID-19 to 4.9 during the first COVID-19 wave and 6.0 during the second wave. In intensive care, the incidence rate of hospital-acquired BSI was 311.8 episodes per 100,000 patient-ICU days. High hospital-acquired BSI incidence rate was observed in both COVID-19 (403.2 per 100,000 patient-ICU days) and non-COVID-19 patients (268.3 per 100,000 patient ICU-days). CLABSI rates increased from 2.5 per 1000 line-days pre-COVID to an average rate of 3.2 during the study period, and 8.4 during the second COVID-19 wave.

In our analysis, no significant difference in the prevalence of bacterial and fungal infections was detected in bloodstream or respiratory tract after a positive SARS-CoV-2 test of Alpha and other variants, suggesting the Alpha variant, which dominated UK's second COVID-19 surge, is not likely to directly contribute to the increased incidence of hospital-acquired BSI.

Factors driving reported variation in bacteraemia incidence appear to be highly complex. Earlier concerns have been raised over disrupted routine screening, laboratories having less capacity to process samples, and infections directly attributable to SARS-CoV-2. In this hospital group, blood culture sampling practice was maintained during the pandemic, although the capacity to collect accurate data on vascular line days was compromised. The variation in epidemiology occurring during the pandemic waves is associated with changes in patient case mix and adjustments in healthcare access and practice. The rise in hospital-acquired bacteraemia in intensive suggested that change in staffing pattern (widening of staff to patient ratios), proning patients, excess or sub-optimal use of PPE (double gloving, gelling gloves, not changing single-use PPE between patients) might have had a negative impact on IPC practices and subsequently on HCAIs. During the pandemic, the hospital group rapidly expanded the ICU capacity from 88 to 150 beds, however, without additional trained staff and without new facilities built to the same Health Technical Memorandum standards. In April 2020, acute trusts in England changed their critical care staffing model from a nurse-to-patient ratio from 1:1 to 6:1, and consultant-to-patient ratio to 30:1 from no more than 15:1, as the NHS sought to rapidly expand its capacity [20]. As winter approached and a second wave arrived in November 2020, NHS hospitals temporarily suspended the recommended 1:1 nurse-to-patient ratio again and each ICU nurse needed to take care of two patients [21]. Since the COVID-19 pandemic, the hospital group reported excess skin organisms yielded from clinical samples with over-representations in critical are. We observed a bimodal excess of CoNS identified from 3.0% all blood cultures during the pandemic with peaks occurring during the first and second wave, compared to the 2.4% in 2019. In addition, blood cultures yielding Corynebacterium species, in particular *C. striatum,* were identified at higher rates than previous observed within the institutes. Increased rates of contaminants detected in blood cultures suggested a breakdown of IPC practices, and pointed a direction for future intervention [15].

During the pandemic, elective admission was suspended, and microbiology laboratories had less capacity to process samples as COVID-19 testing has taken the priority. Analysis of microbiology data needs to be contextualised to ensure robust interpretation of the observed infection incidence. Existing HCAI surveillance systems rarely included metrics to monitor pressure on health systems. However, without understanding the context, surveillance data might be misinterpreted. In our analysis, we captured infection epidemiology and prescribing pattern, as well as institutional characteristics such as routine screening for MRSA and carbapenemase-producing organisms (CPO), blood culture sampling, bed occupancy and staffing level, which allows cross-centre and cross-country comparison. Standardised metrics, which could improve the external validity of studies in infection epidemiology, enable comparison across locations and settings, and widen the evidence base of IPC intervention design, are yet to be developed and tested [22].

Our study has some limitations. First, identical datasets prior to 2020 were not available to provide a baseline. We compared our results with aggregated data from the same hospitals from multiple secondary sources. Second, monitoring of device associated BSI was not available between January to March 2020 due to operational challenges in capturing accurate data on indwelling device days. Third, the time lag between reporting from hospital laboratories to the central data registry might cause missed identification of blood cultures towards the end of the study period.

To conclude, our study provides a comprehensive analysis of the impact of the pandemic on bloodstream infections arising from the community and from acute care in both COVID-19 and non-COVID-19 patients, and across two COVID-19 waves in the UK. Existing infection surveillance needs to consider key aspects of the pandemic response and changes in healthcare access and practice to ensure learning and introduction of appropriate interventions to minimise unintended direct and indirect consequences to care and clinical outcomes.

Notes

Author Contributions: NZ, TMR, and AH developed the concept and methodology for this research. NZ undertook data extraction and analysis. TMR, MG, and FD supported with additional data. NZ drafted the initial manuscript. TMR, SM, JRP, MG, FD, JO, PA, YS and AH contributed significantly to data interpretation, revision of the manuscript and finalisation for submission. AH is the guarantor of the study. The corresponding author attests that all listed authors meet the ICMJE criteria for authorship and that no other meeting the criteria have been omitted.

Transparency statement: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Disclaimer: The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, the Department of Health and Social Care, or Public Health England.

Financial support: This research was funded by 1) the World Health Organization (WHO), 2) National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at Imperial College London in partnership with Public Health England (PHE), in collaboration with Imperial Healthcare Partners, University of Cambridge and University of Warwick, 3) the Department for Health and Social Care, who funded Centre for Antimicrobial Optimisation (CAMO) at Imperial College London, and 4) the NIHR Imperial Biomedical Research Centre (BRC), who developed and funded the iCARE high performance analytics environment to provide data used in this research. AH is a NIHR Senior Investigator. PA is supported by the NIHR Applied Research Collaboration Northwest London. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Acknowledgement: The authors thank Damien Ming and Isa Ahmad for the support in data, and Paul Randell for the assistance in interpreting SARS-CoV-2 virology test results. The authors thank Dimitri Papadimitriou from the Imperial Colleague Healthcare NHS Trust for the assistance in conducting analysis within the iCARE environment.

Potential conflicts of interest: All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no authors received personal fees in the past three years outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

References

1 Gerver SM, Guy R, Wilson K, *et al.* National surveillance of bacterial and fungal co- and secondary infection in COVID-19 patients in England – Lessons from the first wave. *Clin Microbiol Infect* 2021.

2 Russell CD, Fairfield CJ, Drake TM, *et al.* Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. *The Lancet Microbe* 2021;**5247**:1–12. doi:10.1016/s2666-5247(21)00090-2

3 Hsu J. How covid-19 is accelerating the threat of antimicrobial resistance. BMJ. 2020. doi:10.1136/bmj.m1983

4 Rawson TM, Wilson RC, Holmes A. Understanding the role of bacterial and fungal infection in COVID-19. Clin. Microbiol. Infect. 2021. doi:10.1016/j.cmi.2020.09.025

5 Patel A, Emerick M, Cabunoc MK, *et al.* Rapid Spread and Control of Multidrug-Resistant Gram-Negative Bacteria in COVID-19 Patient Care Units. *Emerg Infect Dis* 2021;**27**. doi:10.3201/eid2704.204036

6 NHS England. Admission method. NHS Data Model Dict. 2020.https://datadictionary.nhs.uk/attributes/admission_method.html?hl=admission%2Cmethod (accessed 20 Feb 2020).

7 Centers for Disease Control and Prevention. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection). 2021.https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf (accessed 20 Apr 2021).

8 NHS England and NHS Improvement. Surveillance, management and reporting of infections. 2015.http://www.doncasterccg.nhs.uk/wp-content/uploads/2015/09/Surveillance-management-and-reporting-of-infections-June-2014.pdf (accessed 20 Mar 2021).

9 Public Health England. AMR local indicators. Fingertips. 2020.

10 UK Government. Prime Minister's statement on coronavirus (COVID-19): 23 March 2020. 2020.https://www.gov.uk/government/speeches/pm-address-to-the-nation-on-coronavirus-23-march-2020 (accessed 20 Sep 2020).

11 Public Health England. Annual epidemiological commentary: Gram-negative bacteraemia, MRSA bacteraemia, MSSA bacteraemia and C. difficile infections, up to and including financial year April 2019 to March 2020.

2020.https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/940716/Annual_epidemiology_commentary_April_ (accessed 20 May 2021).

12 Imperial College Healthcare NHS Trust. Nurse and midwife staffing levels. Safe Nurse Midwife Staff. 2020.

13 Willan J, King AJ, Jeffery K, *et al.* Challenges for NHS hospitals during covid-19 epidemic. BMJ. 2020. doi:10.1136/bmj.m1117

14 Rawson TM, Moore LSP, Castro-Sanchez E, *et al.* COVID-19 and the potential long-term impact on antimicrobial resistance. *J Antimicrob Chemother* 2020;**75**:1681–4. doi:10.1093/jac/dkaa194

15 Denny S, Rawson TM, Satta G, *et al.* Bacteraemia variation during the COVID-19 pandemic: a multi-centre UK secondary care ecological analysis. *BMC Infect Dis*

16 British Society for Antimicrobial Chemotherapy. Plummeting number of UTI diagnoses since the advent of COVID brings huge uncertainty to the management of serious infections in vulnerable patients. 2020.https://bsac.org.uk/plummeting-number-of-uti-diagnoses-since-the-advent-of-covid-brings-huge-uncertainty-to-the-management-of-serious-infections-in-vulnerable-patients/ (accessed 20 Feb 2021).

17 Office for National Statistics. Analysis of death registrations not involving coronavirus (COVID-19), England and Wales: 28 December 2019 to 10 July 2020. Anal. death Regist. not Involv. coronavirus (COVID-19), Engl. Wales. 2020.https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/analysisofdeathregistrationsnotinvolvingcoronavir (accessed 20 Feb 2021).

18 Kontopantelis E, Mamas MA, Webb RT, *et al.* Excess deaths from COVID-19 and other causes by region , neighbourhood deprivation level and place of death during the first 30 weeks of the pandemic in England and Wales: A retrospective registry study. *Lancet Reg Heal - Eur* 2021;**000**:100144. doi:10.1016/j.lanepe.2021.100144

19 Karagiannidou S, Triantafyllou C, Zaoutis TE, *et al.* Length of stay, cost, and mortality of healthcare-acquired bloodstream infections in children and neonates: A systematic review and meta-analysis. Infect. Control Hosp. Epidemiol. 2020. doi:10.1017/ice.2019.353

20 Hill B. Changes to nurse-to-patient ratios in intensive care during the pandemic. *Br J Nurs* 2020;**29**:1238–40.

21 Dunhill L. Intensive care staffing ratios dramatically diluted. HSJ. 2020.https://tinyurl.com/y34pf53y ((accessed 20 Jan 2021).

22 Tacconelli E, Cataldo MA, Paul M, *et al.* STROBE-AMS: recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship. *BMJ Open* 2016;**6:e010134**.

Figures

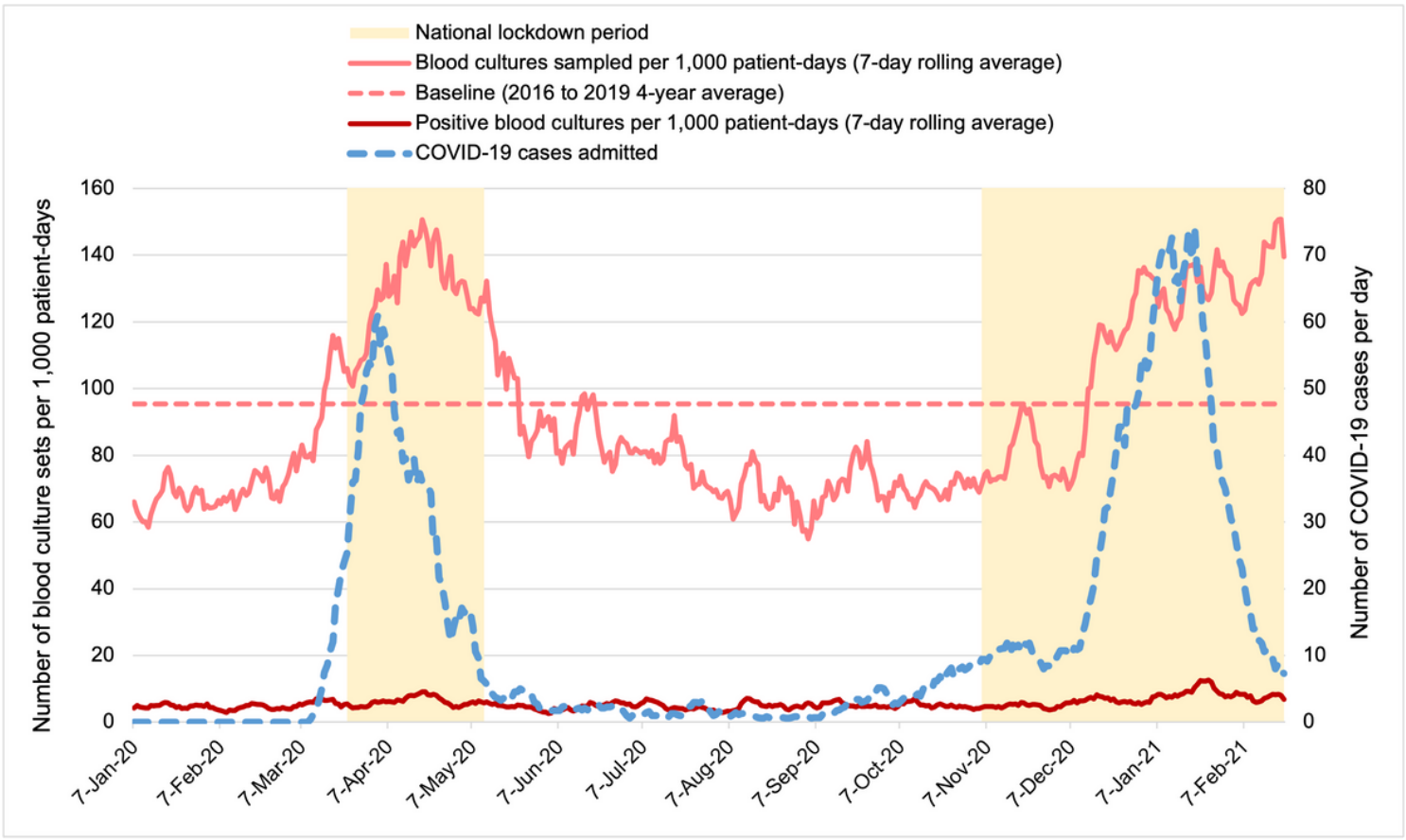

Figure 1

Blood culture sets per 1,000 patient-days (January 2020 - February 2021)

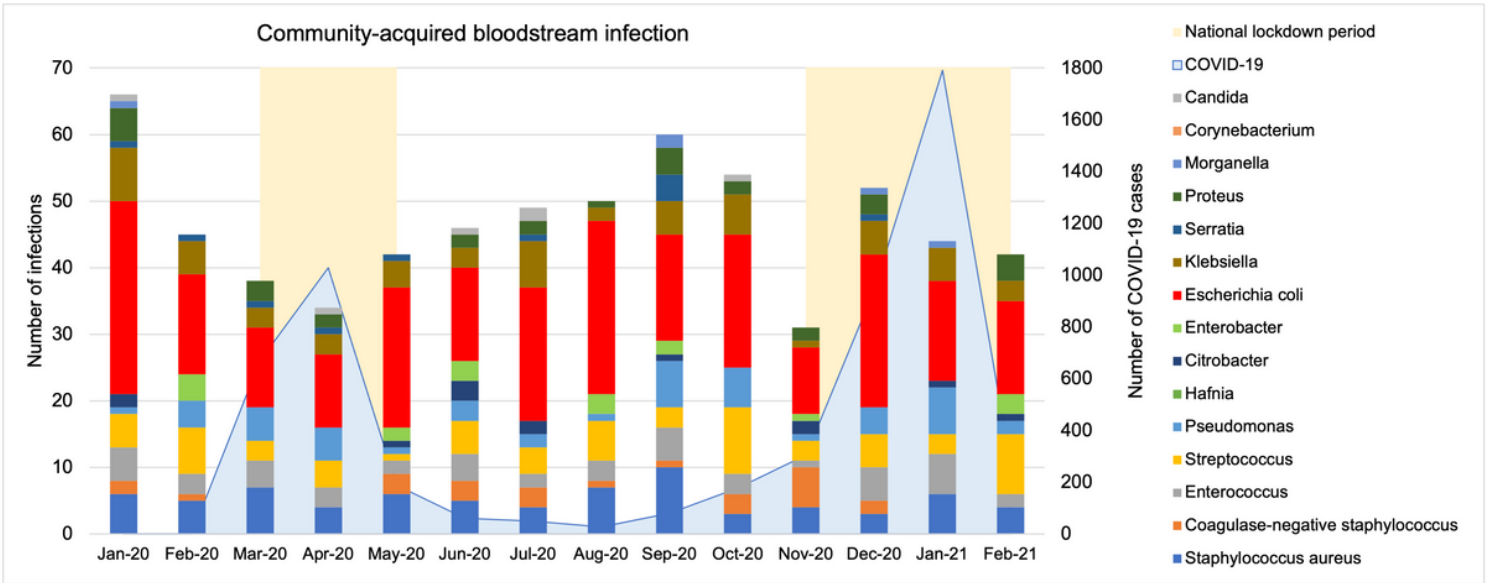

Figure 2

Monthly counts of community-acquired bloodstream infections

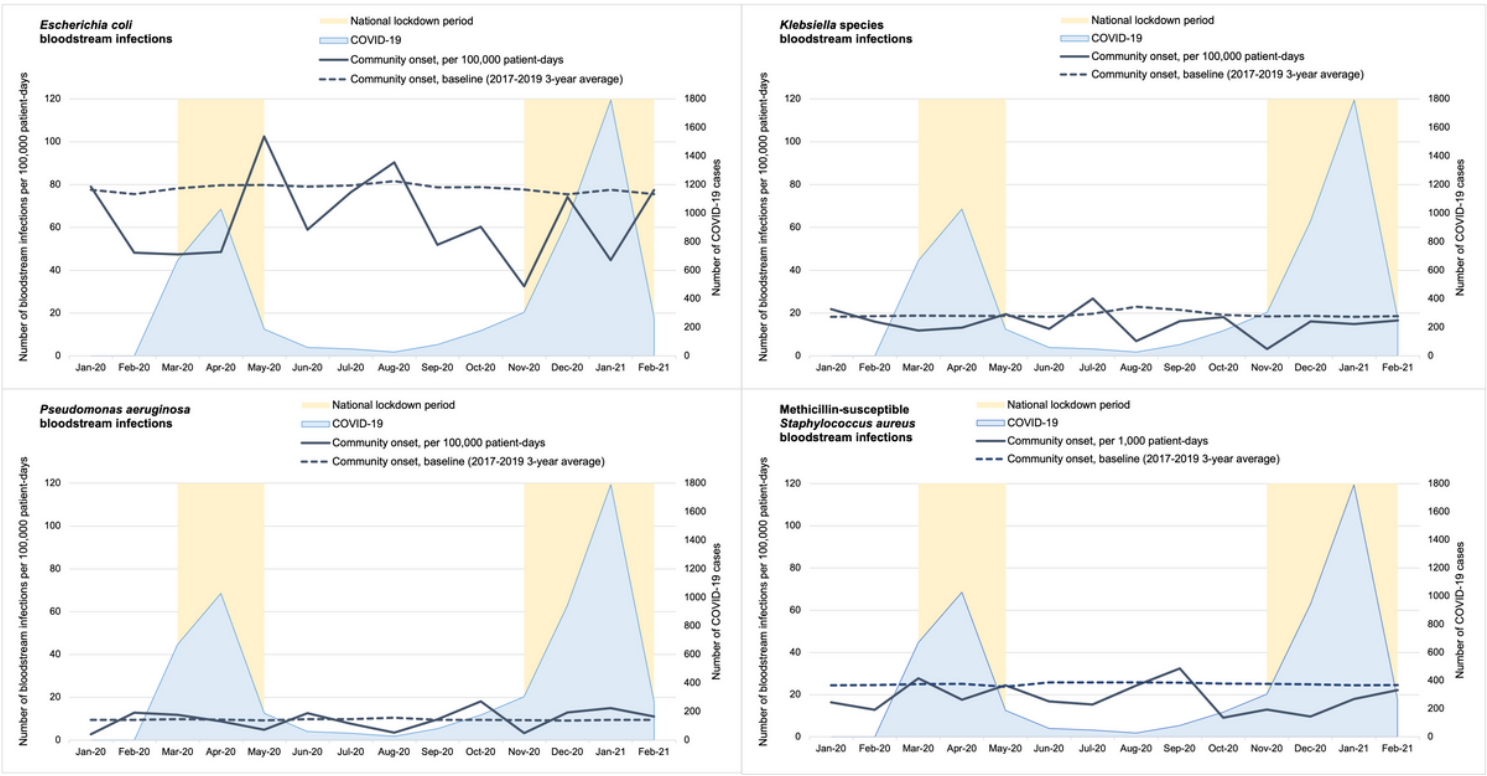

Figure 3

Community onset bloodstream infections caused by a) Escherichia coli, Klebsiella species, Pseudomonas aeruginosa, and d) methicillin-susceptible Staphylococcus aureus (January 2020 - February 2021)

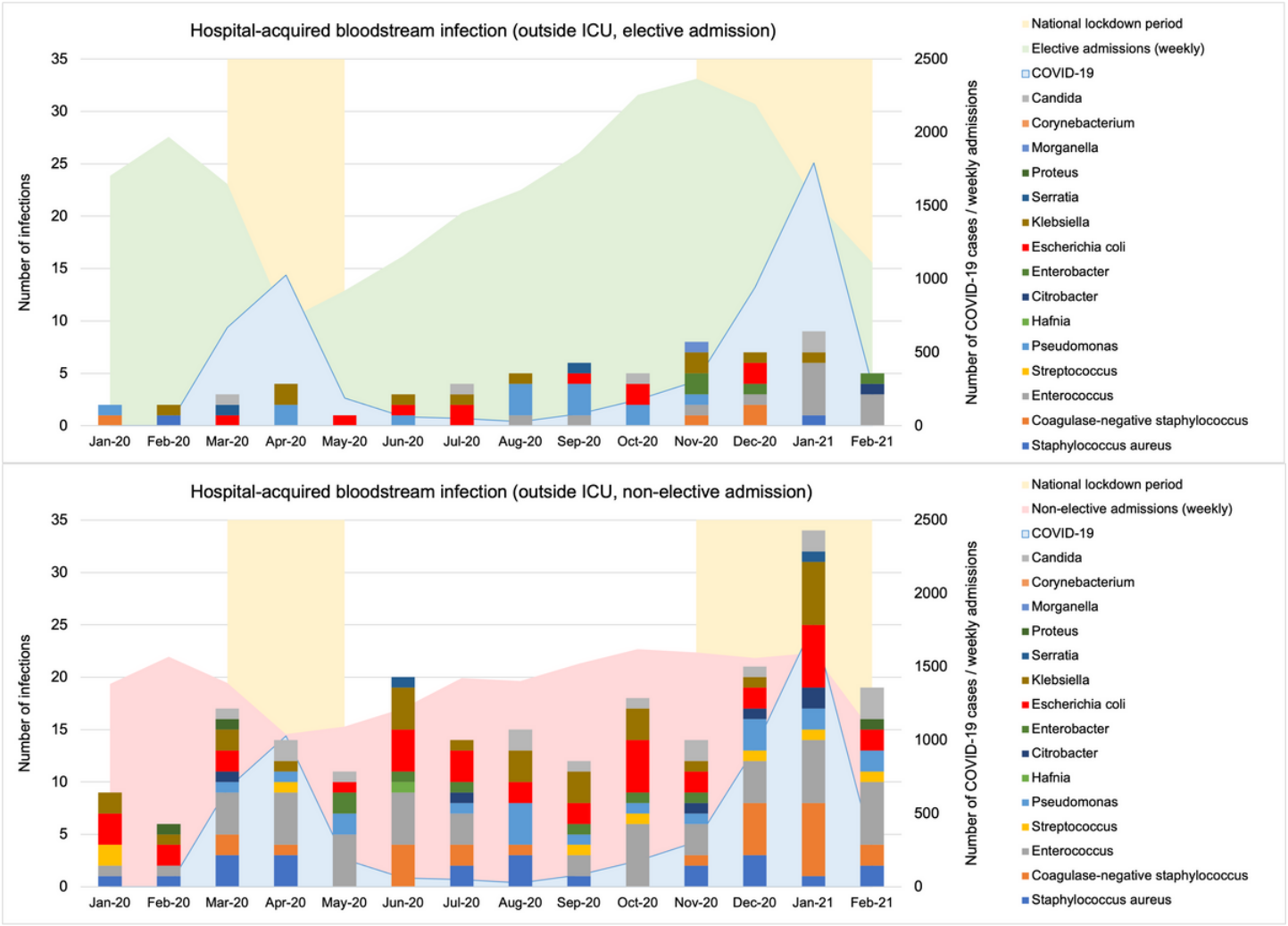

Figure 4

Hospital-acquired bloodstream infections in patients (with and without COVID-19) outside ICU, a) elective, b) non-elective (January 2020 - February 2021)

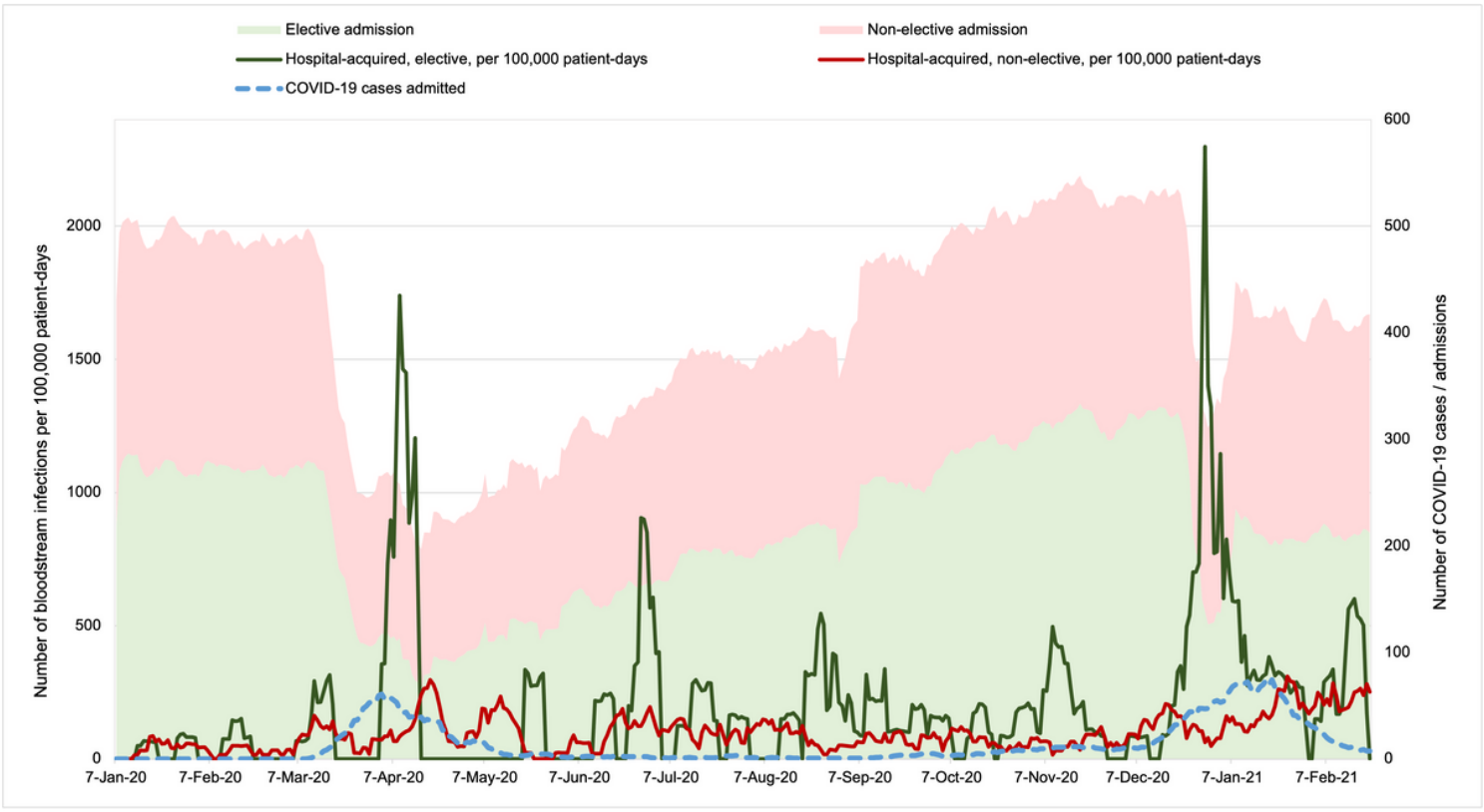

Figure 5

Hospital admissions, COVID-19 cases, and hospital-acquired bloodstream infection incidence rates across all levels of care (January 2020 - February 2021)

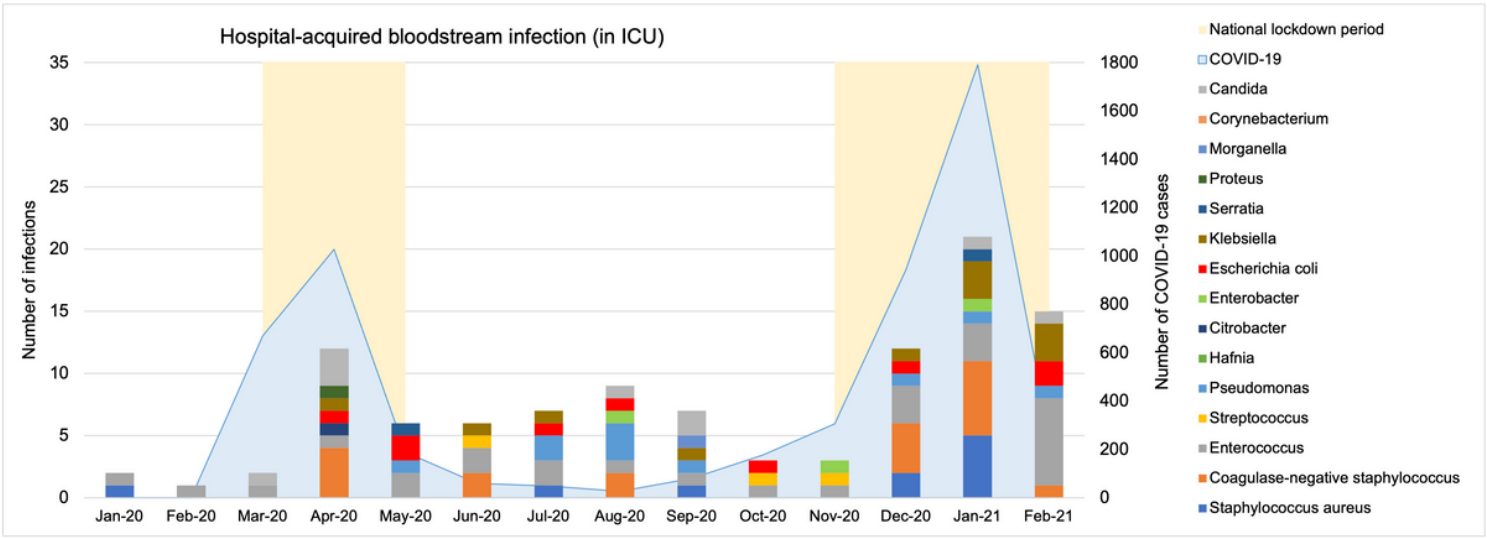

Figure 6

Hospital-acquired bloodstream infections in patients (with and without COVID-19) in ICU (January 2020 - February 2021)

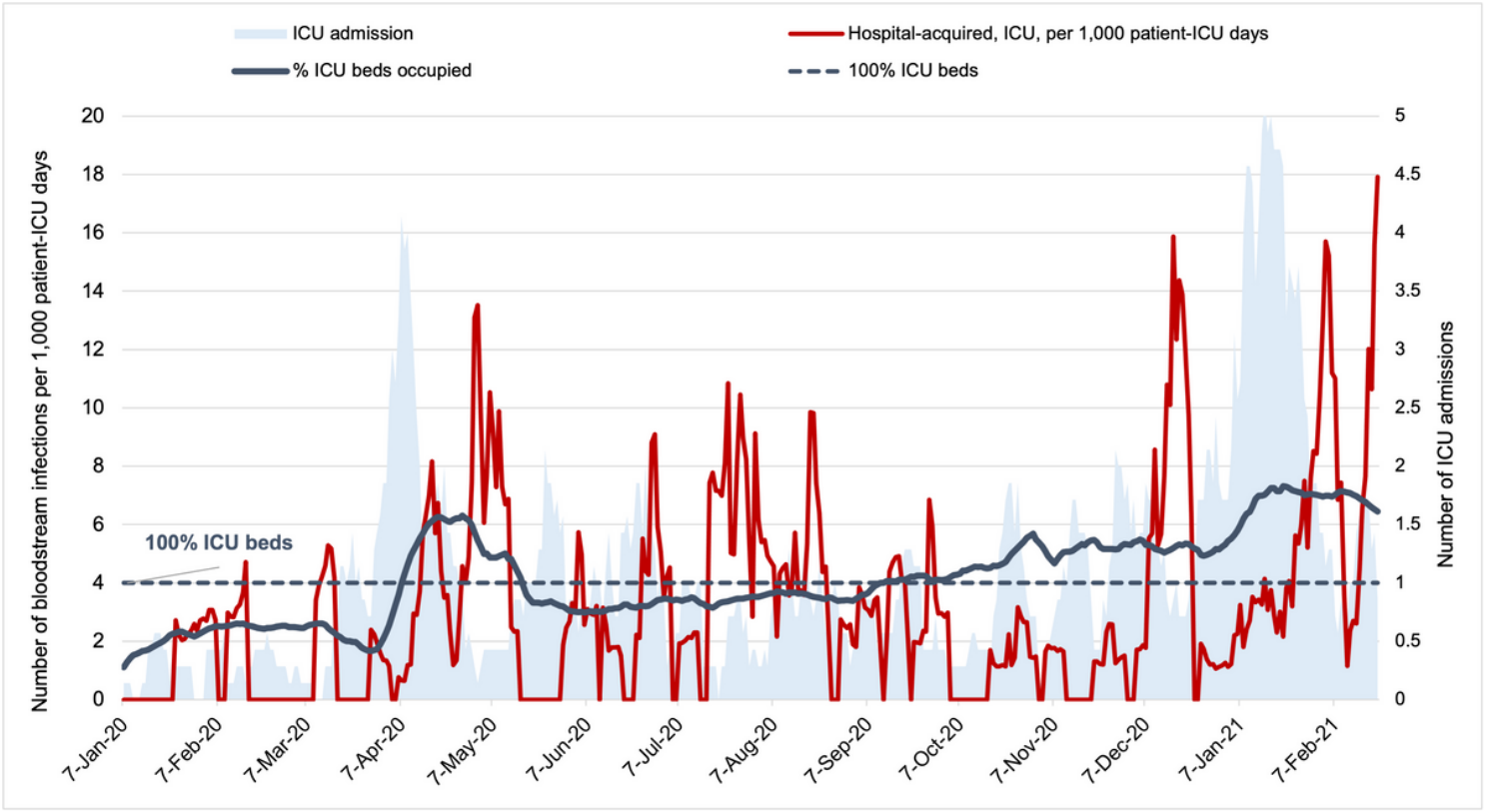

Figure 7

ICU admissions, bed occupancy, and hospital-acquired bloodstream infection incidence rates in intensive care unit (January 2020 - February 2021)