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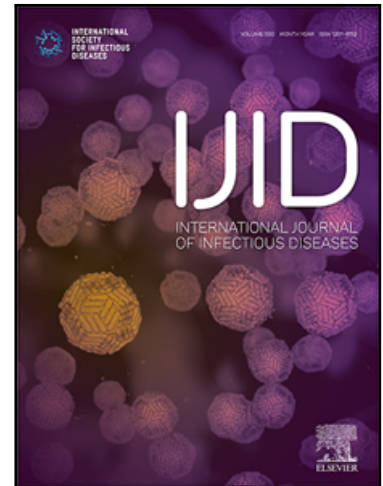
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Surging bloodstream infections and antimicrobial resistance during the first wave of COVID-19: a study in a large multihospital institution in the Paris region

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Highlights

COVID-19 first wave in 2020 had bacteriological collateral effects in French hospitals of Paris region :

- massive increase in blood culturing
- higher rates of positive blood culture and of blood stream infections
- concomitant increase in antimicrobial resistance (and in antibiotic use)

Keywords: COVID-19, blood culture, bloodstream infection incidence, antibiotic consumption, antimicrobial resistance

ABSTRACT 150 to 200 words

Objectives. We measured the impact of the first wave of COVID-19 (March-April 2020) on the incidence of bloodstream infections (BSIs) during at the Assistance Publique - Hôpitaux de Paris (APHP), the largest multisite public healthcare institution in France.

Methods. The number of patient admissions blood cultures (BCs) collected, positive BCs as well as antibiotic resistance and consumption was retrospectively analyzed for the first quarter of 2020, and of 2019 for comparison, in 25 APHP hospitals (ca. 14,000 beds).

Results. Up to a fourth on patients admitted in March-April 2020 in these hospitals had COVID-19. BSI rate per 100 admissions increased globally, by 24% in March and 115% in April 2020, and separately for the major pathogens (*Escherichia coli*, *Klebsiella pneumoniae*, enterococci, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, yeasts). A sharp increase in the rate of BSIs caused by microorganisms resistant to 3rd generation cephalosporins (3GC) was also observed in March-April 2020, particularly in *K.pneumoniae*, in enterobacterial species naturally producing inducible AmpC (*Enterobacter cloacae*...) and *P.aeruginosa*. A concomitant increase occurred in 3GC consumption.

Conclusions. COVID-19 pandemic had a strong impact on hospital management and also unfavorable effects on severe infections, antimicrobial resistance and laboratory work diagnostics.

Running title: Bloodstream infection surge during COVID-19 period

INTRODUCTION

Since the beginning of the coronavirus disease (COVID-19) pandemic in 2019, the world has been faced with an unprecedented surge of acute respiratory infections that often require intensive care and have a high case fatality rate. (Khalili et al., 2020) While the demographics, clinical characteristics and overall survival rate (Fried et al., 2020; Guan et al., 2020; Lippi et al., 2020) of hospitalized patients with COVID-19 have been already characterized in extensive reports from several parts of the world, little is known about the bacterial complications contributing to the morbidity or mortality of inpatients.

In general, it has been widely reported that patients receiving intensive care are at higher risk for hospital-acquired infections. This is due to invasive monitoring and support, exposure to multiple antibiotics and colonization with resistant microorganisms. (Maki et al., 2008) Among these nosocomial infections, bloodstream infections (BSIs) and respiratory tract infections are the most common and life threatening. (Prowle et al., 2011) Hence, we sought to analyze the impact of the first wave of the COVID-19 pandemic and the subsequent high demand for intensive care on the epidemiology of bloodstream infections in a large public multihospital institution in the Paris region.

MATERIALS AND METHODS

Setting

The research was conducted at Assistance Publique - Hôpitaux de Paris (APHP), a multihospital institution covering the Paris region (the 12 million inhabitants of the city of Paris, its suburbs and the surrounding counties). APHP is the largest hospital institution in France. It provides a total of approximately 20,000 beds and admits around 1.4 million patients per year. Approximately 14,000 (70%) of these beds are distributed among 25

hospitals, including 18 acute care hospitals and seven rehabilitation/long-term care hospitals (see list in the supplementary material). These hospitals are served by laboratories of Bacteriology that all use the same laboratory information system (LIS), allowing standardized data extraction and combined analysis. The research was conducted in these 25 hospitals.

Study period

The study covers the four-month period from January to the end of April 2020 and, as control, the same four-month period in 2019. The March-April 2020 period that corresponds to the rise and the development of the first COVID-19 epidemic wave in the Paris region was referred as the 'COVID-19 period'.

Patient data

The number of patients admitted to the 25 hospitals during the two four-month periods (January-April), as well as the number of patients present each day in these hospitals in March and April 2020 with a virologically proven COVID-19 (based on a positive RT-PCR), were obtained from the central APHP administration.

Blood sample data processing

Data on blood cultures were extracted from the LIS of the laboratories serving these 25 hospitals and merged in a relational SQL-queryable database. A blood culture set (BC set) was defined as the combination of one aerobic and one anaerobic blood culture bottle drawn through the same puncture. A positive BC sets, defined as microbial growth in at least one of the two bottles.

A clinically significant episode of BSI was defined as a positive BC set growing a recognized pathogen.

(<https://www.ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/healthcare-associated-infections-HAI-ICU-protocol.pdf>) BC sets growing bacteria belonging to commensal skin microbiota (coagulase-negative staphylococci, corynebacteria and propionibacteria) are generally defined as contaminants, except in specific individual patient clinical situations. (Beekmann et al., 2005; <https://www.ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/healthcare-associated-infections-HAI-ICU-protocol.pdf>) These BC were not included in the study since clinical data were not available in the LIS. To remove duplicates, only one BSI episode was counted when several BC sets were positive with the same microorganism for a given patient. Antimicrobial resistance was extracted from the LIS, as explained above. All of the involved laboratories participate in the national accreditation process (COFRAC), including internal and external quality assessment programs, and use the EUCAST European quality standards for antimicrobial susceptibility testing (https://eucast.org/clinical_breakpoints/).

Antibiotic consumption

The consumption of third-generation cephalosporins (3GC, including cefotaxime, ceftriaxone and ceftazidime), a group of antibiotics largely used for treating serious bacterial infections in hospital settings, was recorded for the four-month periods of January-April 2019 and 2020 by the central APHP pharmacy and converted into defined daily doses (DDDs) using the WHO definitions. (https://www.whocc.no/ddd/definition_and_general_considera/)

Statistical analysis

Rate ratios and their confidence intervals were computed using Poisson models, with a linear time trend to account for possible changes in rate over time, independent of the COVID-19 pandemic. To account for multiple analyses, 99% confidence intervals were used.

RESULTS

Patients

The rise of the COVID-19 pandemic was observed at the beginning of March 2020 in the Paris region. It peaked at the beginning of April and declined until the end of that month (<https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-23-avril-2020>). Correspondingly, the number of COVID-19 inpatients present in APHP hospitals progressively increased in March, reached a plateau between April 4th and 14th, and decreased steadily during the second fortnight of that month. During the plateau period, between 4,700 and 4,800 COVID-19 inpatients were present at APHP, among which between 1,000 and 1,100 were in intensive care units (ICUs) (Figure 1). During this plateau period, COVID-19 patients represented as much as a quarter of all patients present at APHP. To deal with the massive influx of adult COVID-19 patients, the organization of the APHP hospitals was extensively modified. Some medical units were dedicated entirely to the admission of COVID-19 patients who did not require intensive care. The capacity of ICU beds for adults was multiplied by 2.6 by converting post-surgery recovery rooms, operating theaters and even some pediatric ICUs. Other beds were closed, particularly in surgery since non-urgent surgical procedures were largely postponed. In these cases, the corresponding personnel was redeployed to take care of the COVID-19 patients. Consequently, the overall number of patients admitted to the 25 hospitals decreased during the COVID-19 period (Table 1).

Blood cultures

Data on the 185,132 BC sets taken during the periods of January-April 2019 and 2020 in the 25 hospitals were reviewed. There was a dramatic increase in the number of blood cultures collected during the COVID-19 period, i.e. 42.9 BCs per 100 admissions during March-April 2020 vs 23.6 during January-April 2019 (Table 1). This increase was more precisely assessed by computing the rate ratios of BCs per 100 admissions, which was 1.6 in March 2020 and 2.37 in April 2020. This represents an increase of 60% (99% CI: 56 to 63) in March and 137% (99% CI: 131 to 142) in April 2020 in comparison to the rates recorded in the periods January-April 2019 and January-February 2020 (Figure 2). A similar increase in the rate ratio of positive BCs per 100 admissions occurred during the COVID-19 period (Figure 2). The proportion of positivity remained stable across all periods.

Microbial pathogens isolated from bloodstream infections

When considering only clinically significant microorganisms recovered from positive BCs, the rate ratios of BSIs per 100 admissions increased by 24% (99% CI: 11 to 38) in March and 115% (99% CI: 94 to 139) in April 2020 in comparison with the rates in January-April 2019 and January-February 2020 (Figure 2).

When computed according to bacterial species, the increase in the rate of BSIs per 100 admissions in April 2020 ranged between 46% (*Escherichia coli* and anaerobes) and 254% (enterococci) (Table 1).

The rates of clinically significant BSIs with an organism resistant to third-generation cephalosporins (3GC) per 100 admissions increased during the COVID-19 period, particularly in April 2020. That month saw an increase in *Klebsiella pneumoniae* producing extended-spectrum beta-lactamase (3.3 fold); cefotaxime-resistant isolates of enterobacteria naturally producing inducible AmpC (*Enterobacter cloacae*, *Klebsiella aerogenes*, *Serratia spp.*, etc.) (2.7 fold, likely through cephalosporinase overproduction); and ceftazidime-

resistant strains of *Pseudomonas aeruginosa* (2.4 fold), as well as for other non-fermenting gram-negative bacilli (1.5 fold) and methicillin-resistant *Staphylococcus aureus* (1.6 fold) (Table 1). This increase also concerned organisms that are naturally resistant to 3GC, e.g., enterococci (3.5 fold) and yeasts (3.3 fold).

Consumption of third-generation cephalosporins (3GC)

A sharp increase (DDDs per 100 admissions) in the consumption of 3GC, mostly of cefotaxime, occurred in the 25 hospitals during the COVID-19 period. In March, the increase was 131% and in April it was 148%, as compared with baseline consumption during the periods between January-April 2019 and January-February 2020 (Figure 3).

DISCUSSION

Our research showed a surge in blood culturing, BSIs, antibiotic resistance and antibiotic use during the first wave of COVID-19 pandemic (March-April 2020) in 25 hospitals in the Paris region, the region with the highest number of COVID-19 cases in France at that time. (<https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-23-avril-2020>) To our knowledge, this is the first study showing the global impact of the COVID-19 pandemic on such a broad scale (25 hospitals in a region of 12 million inhabitants).

During the first wave of the COVID-19 pandemic, the rate ratios of blood culture collection per 100 admissions increased in the 25 hospitals by 60% in March and 137% in April 2020. The same trend was observed when using rates of 1,000 patient days as an indicator (data not shown). A sharp increase in blood culturing during the COVID-19 pandemic was also reported in January through March 2020 in five hospitals in New York city, overwhelming

local laboratory capacity and leading to a decrease in the duration of bottle incubation in order to free space in the automated systems. (Sepulveda et al., 2020) In contrast, no variation in BCs was observed during the first wave of COVID-19 in five London hospitals. (Denny et al., 2021)

Concomitantly to the increase of clinical samples, there have been an increase in the number of infections. Indeed, the rate ratio of BSIs per 100 admissions increased by 24% in March and 115% in April 2020. Such an increase was also observed during a separate analysis of the major pathogens (*E. coli*, *K. pneumoniae*, enterococci, *S. aureus*, *P. aeruginosa*, yeasts, etc.). These findings are in line with the results of research of several monocentric works in China, Italy and Switzerland that found that COVID-19 ICU patients are at a high risk of developing BSI. (Cataldo et al., 2020; Søggaard et al., 2021; Zhang et al., 2020) Conversely, a study conducted in six tertiary care hospitals in Sweden and the London study did not find a high proportion of positive BCs with clinically relevant organisms during the COVID-19 epidemics, but the incidences of BSIs were not reported. (Denny et al., 2021; Søggaard et al., 2021) In fact, an increase in BSIs associated with an influx of COVID-19 patients is not surprising, since serious bacterial and fungal infections, including BSIs, frequently occur during the hospital stays of severely ill patients. (Bassetti et al., 2016; <https://www.health.org.uk/news-and-comment/blogs/covid-19-five-dimensions-of-impact>) In the 25 hospitals from the present study, the number of ICU beds used to treat severely ill COVID-19 patients increased by 260%. This accounts for up to a quarter of the COVID-19 inpatients present in AHP hospitals, clearly indicating the severity of their status. The more severe the condition of the patients, the more often invasive procedures are carried out, therefore leading to more infections and more diagnostic tests. It should be noted that at least

2/3 of the BSIs diagnosed in March and April 2020 in this study can be considered as hospital-acquired based on the time interval between patient admission and BCs.

Moreover, we report not only an increase in the rate of BSIs, but also in the rate of BSIs caused by microorganisms resistant to 3GC, as compared to a reference period. Several authors have warned of the possible negative impact of the COVID-19 pandemic on antimicrobial resistance. (Cantón et al., 2020; Monnet and Harbarth, 2020) Taking resistance to 3GC as an indicator of antibiotic resistance is justified for several reasons. Indeed, 3GC are a major class of injectable antibiotics widely used for severely ill patients in a hospital setting and recommended in the Surviving Sepsis Campaign guidelines for the management of critically ill adults with COVID-19. (Alhazzani et al., 2020) These drugs are among the main indicators in use both at the European level as well as worldwide to assess antibiotic consumption and resistance. (<https://apps.who.int/iris/bitstream/handle/10665/279656/9789241515061-eng.pdf>; <https://www.ecdc.europa.eu/sites/default/files/documents/surveillance-antimicrobial-resistance-Europe-2018.pdf>) The observed increase concerned mainly gram-negative species resistant via ESBL production and cephalosporinase overproduction (*Klebsiella*, *Enterobacter*, *Pseudomonas*), species known to cause hospital-acquired infections. We confirm on a large scale the findings of other reports in smaller settings showing an increase in multiresistant gram-negative species during the COVID-19 epidemic. (Arcari et al., 2021; Belvisi et al., 2021) In addition, we also report an increase in the rate of BSIs caused by *Staphylococcus aureus* with acquired resistance to methicillin and cephalosporins (MRSA), as well as enterococci and yeast, two types of microorganisms characterized by their natural resistance to 3GC.

Finally, concomitantly to the rise of BSI and resistance, a sharp increase in 3GC consumption was observed. Similar increases of broad spectrum beta-lactams, and particularly 3GC, have been reported during the COVID-19 pandemic in different countries but always in a single facility that may not be representative. (Abelenda-Alonso et al., 2020; Bork et al., 2020; Giacomelli et al., 2021; Nestler et al., 2020) Intensive use of 3GC is known to exert a selective pressure on enterobacteria with acquired resistance to these antibiotics, either through ESBL production or cephalosporinase overproduction (Mizrahi et al., 2020; Padmini et al., 2017) as well as on naturally resistant organisms such as yeasts (Arendrup, 2010) and enterococci. (García-Solache and Rice, 2019) This dual impact is not surprising since a strong correlation between the rates of natural and acquired resistance in BSIs has been established in recent research in European countries. (Jarlier et al., 2019)

Despite the strengths of this study, which covers a large set of regional hospitals, we should acknowledge several limitations. First, the scale of the study that dealt with the approximately 120,000 patients admitted in March and April 2020 made an analysis at the individual level (invasive procedures, antibiotics prescriptions...) impossible. The research therefore captured the overall impact of COVID-19 pandemic, without patient stratification, on four indicators in the 25 hospitals. More specifically, stratification of BCs and BSIs by COVID-19 status was not performed because of lack of a unified comprehensive clinical, and microbiological database. Second, our study focused on BSIs because bacteriological results of blood cultures are relatively simple to interpret. Other major types of infections, such as lower respiratory tract infections (LRTIs), would have been of interest in the context of COVID-19 pulmonary involvement. However, these infections are difficult to assess based simply on bacteriological results without an analysis of clinical data that are not available in LIS (cf supra). Similarly, the lack of individual data on indwelling catheters or other invasive procedures made the

identification of ‘true’ BSIs due to skin commensal species (coagulase negative staphylococci, etc.) impossible. Third, we did not evaluate other factors such as nursing staff ratios or staff expertise that could have affected BSIs rates in a more complex context. (Amarsy et al., 2020; Robert et al., 2000)

Upheaval in hospital organization has been reported in many countries where the health system has been overwhelmed by the spread of the COVID-19. (Grasselli et al., 2020; <https://www.health.org.uk/news-and-comment/blogs/covid-19-five-dimensions-of-impact>)

Health care systems can be rapidly compromised in cases of explosive outbreaks of emerging infections (Crawford et al., 2016; Elston et al., 2017; Nuzzo et al., 2019) or in the case of conflicts and natural disasters. (López Tagle and Santana Nazari, 2011; Roberts et al., 2003)

The collateral effects of the COVID-19 crisis on BSIs, antimicrobial resistance (AMR) and antibiotic consumption have not been reported simultaneously and at the scale of a large region. Comprehensive studies in more focused populations will be needed to assess the respective contributions of risk factors to BSIs and increases in antibiotic resistance during the pandemic. A combination of responsible use of antimicrobials and adequate hygiene measures should be used in order to minimize the risk of unfavorable outcomes following another sudden crisis of a similar magnitude.

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None.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

This study did not require any specific ethical approval, as it uses data that were extracted anonymously according to current French regulations. All patients admitted to APHP hospitals are informed about the potential use of their data for research purposes.

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None to declare

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Figure 1. Evolution of the number of patients with COVID-19 present daily during March and April 2020 at Assistance Publique - Hôpitaux de Paris (APHP)

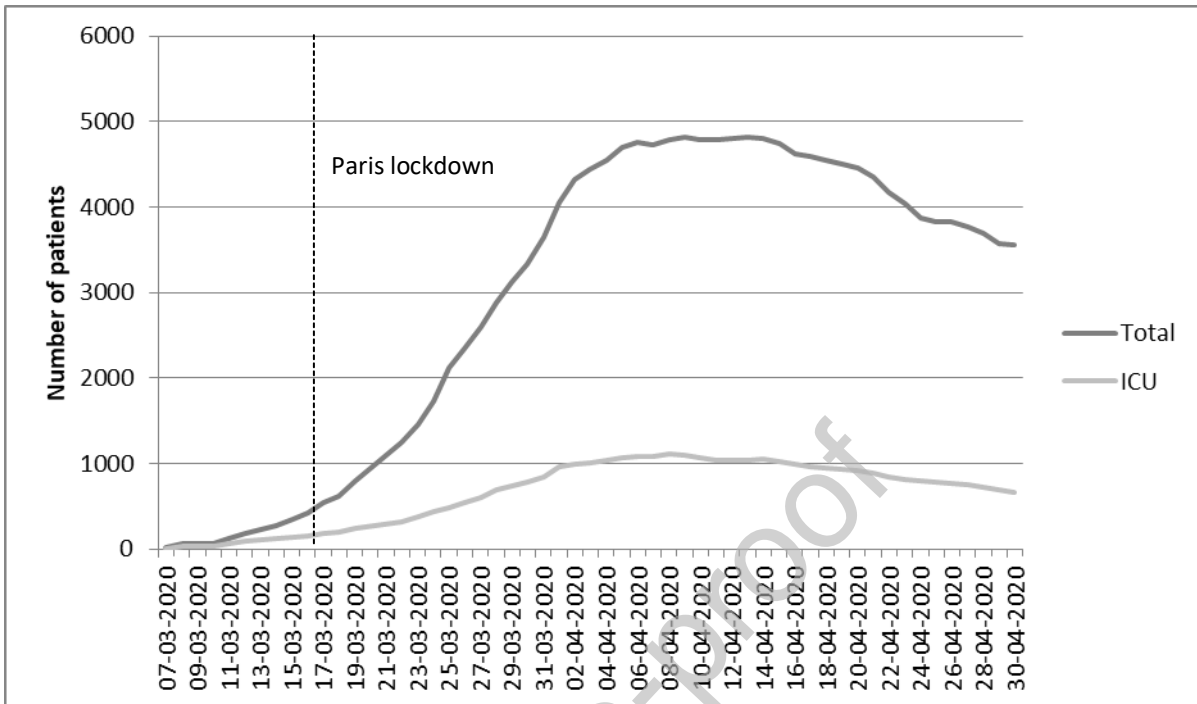


Figure 2. Rate ratios of blood cultures collected (BC), positive blood cultures (BC+) and bloodstream infections (BSI) per 100 admissions in March and April 2020 compared to expected values. 99% confidence intervals are provided.

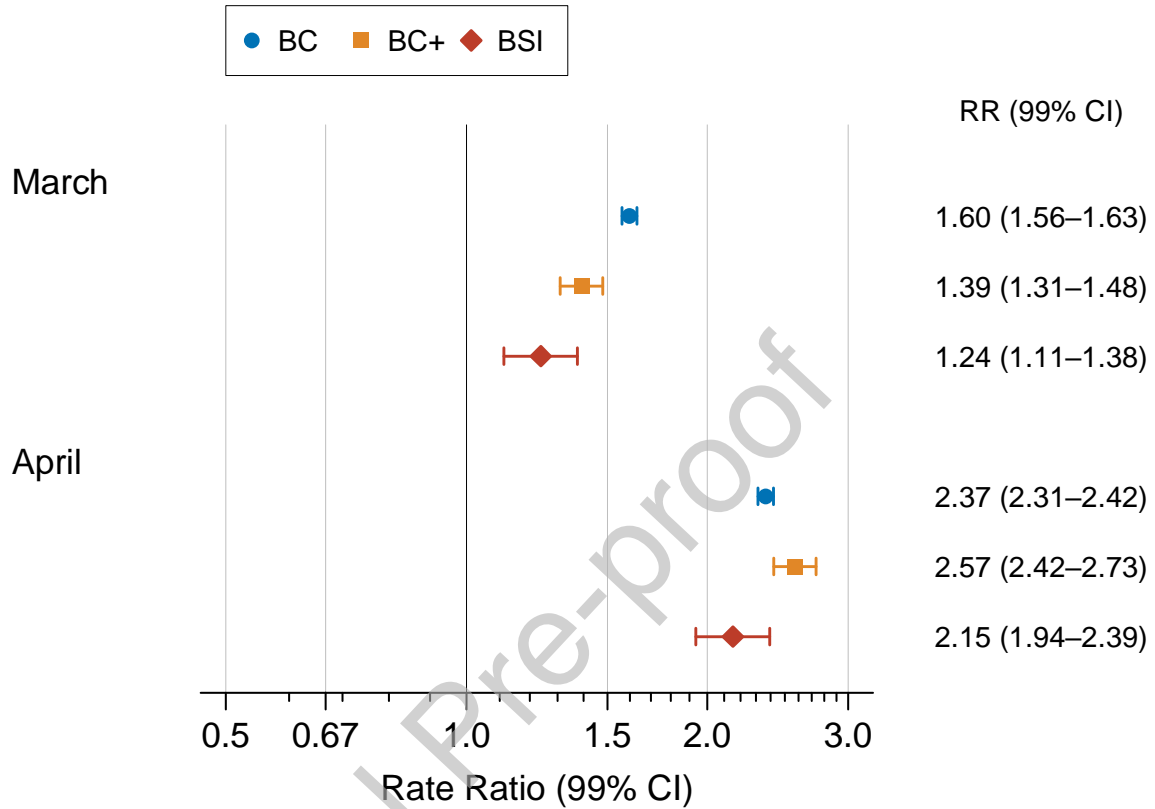


Figure 3. Monthly consumption of third-generation cephalosporins, expressed as defined daily doses (DDDs) per 100 admissions, during the first four months of years 2019 and 2020 in the 25 hospitals of Assistance Publique - Hôpitaux de Paris (APHP)

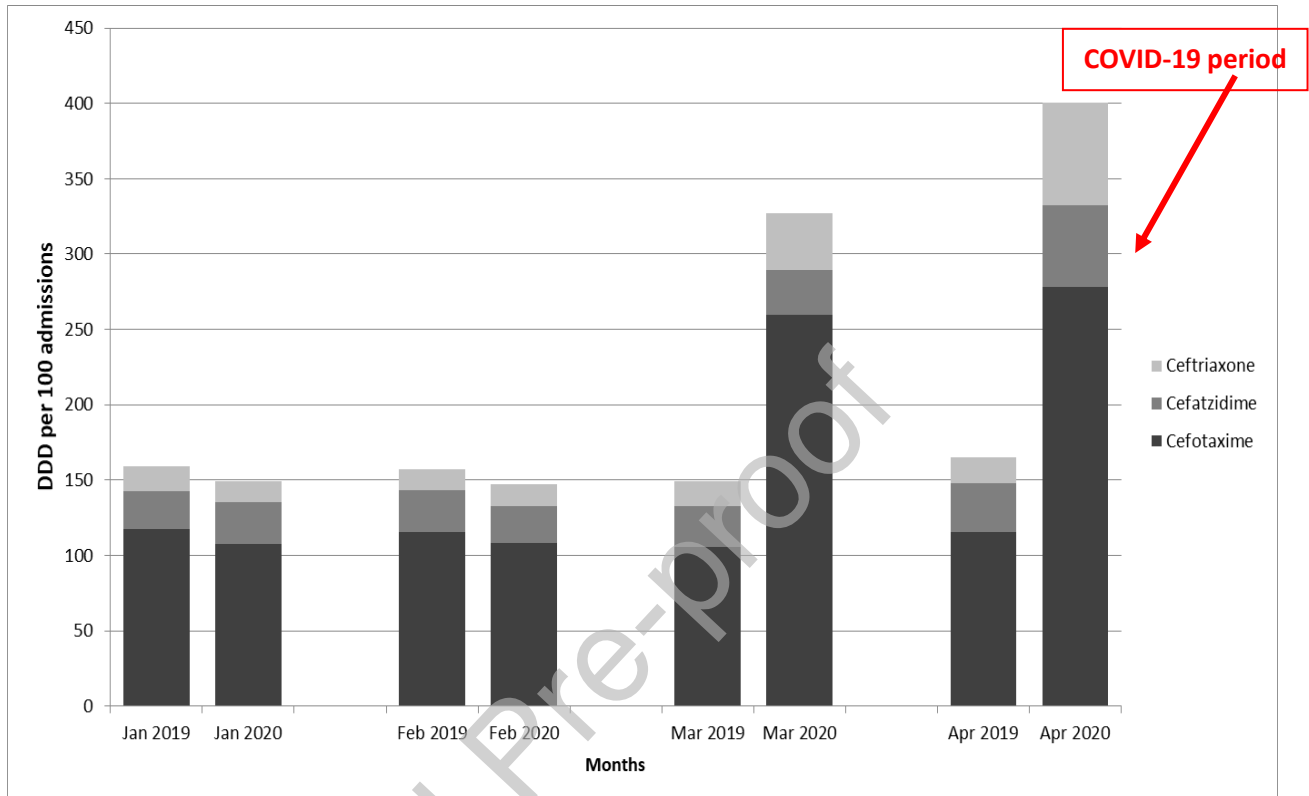


Table 1. Blood cultures and bloodstream infections (BSIs) during the four-month period of 2019 and 2020 in the 25 hospitals of Assistance Publique - Hôpitaux de Paris (APHP)

	January		February		March		April	
	2019	2020	2019	2020	2019	2020*	2019	2020*
Number of admitted patients	99467	97873	90417	88369	93711	74633	95414	48086
Collected Blood culture sets /100 admitted patients	24,7	22,7	25,2	23,4	23,7	36,2	20,9	53,3
Positive Blood cultures sets/100 admitted patients	3,1	2,9	3	3	2,9	4	2,6	7,5
BSIs /100 admitted patients	1,08	1,09	1,01	1,01	1,05	1,29	1,01	2,25
<i>Escherichia coli</i>	0,25	0,25	0,25	0,24	0,28	0,30	0,25	0,37
Enterococci	0,12	0,10	0,10	0,09	0,12	0,16	0,11	0,38
Streptococci	0,16	0,15	0,12	0,14	0,14	0,16	0,14	0,26
<i>S. aureus</i>	0,13	0,13	0,14	0,12	0,12	0,14	0,11	0,28
<i>Klebsiella spp.</i>	0,10	0,10	0,10	0,10	0,10	0,12	0,11	0,25
Enterobacteriaceae naturally producing inducible AmpC‡	0,08	0,09	0,09	0,10	0,07	0,12	0,07	0,22
Non fermentative gram-negative bacilli including <i>Pseudomonas aeruginosa</i>	0,11	0,11	0,13	0,11	0,11	0,12	0,11	0,27
Yeasts	0,04	0,02	0,04	0,03	0,03	0,06	0,04	0,11
BSIs with 3CG[§]-resistant microorganisms /100 admitted patients								
ESBL [¶] -producing <i>Klebsiella spp.</i>	0,04	0,03	0,03	0,02	0,02	0,04	0,03	0,09
Cefotaxime resistant Enterobacteriaceae naturally producing inducible AmpC‡	0,01	0,02	0,02	0,02	0,02	0,02	0,01	0,05
Ceftazidime resistant non-fermentative gram-negative bacilli including <i>P. aeruginosa</i>	0,02	0,02	0,02	0,01	0,02	0,01	0,02	0,03
Methicillin-resistant <i>Staphylococcus aureus</i>	0,02	0,02	0,02	0,02	0,01	0,02	0,01	0,03
Enterococci (intrinsic resistance)	0,12	0,10	0,10	0,09	0,12	0,16	0,11	0,38
Yeasts (intrinsic resistance)	0,04	0,02	0,04	0,03	0,03	0,06	0,04	0,11

*: COVID-19 period

‡: *Enterobacter cloacae*, *Enterobacter aerogenes*, *Serratia spp*

§: Third-generation cephalosporins

¶: Extended-spectrum-β-lactamase