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Snapshot of COVID-19 superinfections in Marseille hospitals: where are the common pathogens?

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Abstract

Episodes of bacterial superinfections have been well identified for several respiratory viruses, notably influenza. In this retrospective study, we compared the frequency of superinfections in COVID-19 patients to those found in influenza-positive patients, and to controls without viral infection. We included 42 468 patients who had been diagnosed with COVID-19 and 266 261 subjects who had tested COVID-19 negative between 26 February 2020 and 1 May 2021. In addition, 4059 patients were included who had tested positive for the influenza virus between 1 January 2017 and 31 December 2019. Bacterial infections in COVID-19 patients were more frequently healthcare-associated, and acquired in ICUs, were associated with longer ICU stays, and occurred in older and male patients when compared to controls and to influenza patients ($P < 0.0001$ for all). The most common pathogens proved to be less frequent in COVID-19 patients, including fewer cases of bacteraemia involving *E. coli* ($P < 0.0001$) and *Klebsiella pneumoniae* ($P = 0.027$) when compared to controls. In respiratory specimens *Haemophilus influenzae* ($P < 0.0001$) was more frequent in controls, while *Streptococcus pneumoniae* ($P < 0.0001$) was more frequent in influenza patients. Likewise, species associated with nosocomial transmission, such as *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*, were more frequent among COVID-19 patients. Finally, we observed a high frequency of *Enterococcus faecalis* bacteraemia among COVID-19 patients, which were mainly ICU-acquired and associated with a longer timescale to acquisition.

Introduction

Among the factors that could contribute to COVID-19 mortality and morbidity, the role of bacterial superinfections remains unclear. The latter were common during pandemics such the Spanish flu pandemic in 1918 [1] and H1N1 influenza A in 2009 [2], in which invasive species such as *Staphylococcus aureus*, *Streptococcus pyogenes* or *S. pneumoniae* were identified. Comprehensive data regarding superinfections which complicate COVID-19 would allow rationalisation of the prescription of antimicrobial agents. In the literature, one meta-analysis covering 30 studies reported rates of bacterial superinfections of 7% in hospitalised patients and 14% of ICU patients; figures that appeared to be lower than those with influenza [3]. Surprisingly, in the latter study, *Mycoplasma pneumoniae* was the most frequent pathogen detected in COVID-19 patients followed by Gram-negative bacterial species. Moreover, a retrospective of patients hospitalised with COVID-19 reported acquisitions of superinfections to be both community-acquired and healthcare associated [4]. Interestingly, *S. pneumoniae* and *S. aureus* were the most frequent aetiological agents of community-acquired bacterial pneumonia, while enterobacteria and *Pseudomonas aeruginosa* were mostly found in healthcare-associated infections. Although a number of published studies have reported cases of co-infections with COVID-19 [5–10], they were conducted with a limited number of patients, often without a control group, thereby rendering it difficult to deduce whether such infections are actually associated with the acquisition of COVID-19 [11].

Since the beginning of the pandemic, we have diagnosed over 40 000 patients with COVID-19 and have access to microbiological results from patients admitted to public hospitals in Marseille. In this retrospective study, we aimed to provide a snapshot of bacterial superinfections in all COVID-19 patients for which microbiological investigations were conducted. To assess whether SARS-CoV-2 infection is associated with a specific epidemiology, we compared these results with those obtained from controls during the same period, as well as to a control group of influenza-positive patients between 2017 and 2019.

Methods

Study design and patients

This retrospective study was conducted at the IHU Méditerranée Infection in Marseille, France. We first extracted records of all patients with a positive diagnosis of COVID-19

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(cases) between 26 February 2020 and 1 May 2021. A COVID-19 diagnosis was confirmed by real-time reverse transcription PCR (RT-PCR) testing performed on nasopharyngeal throat swab specimens, as previously described [12]. Firstly, to compare infections among the cases with controls, we extracted the list of patients who had had at least one COVID-19 PCR test, and for whom all tests were negative (controls). Finally, we aimed to compare COVID-19 superinfections with influenza superinfections through extraction of all positive PCR results for influenza A, B or H1N1 [13] between 1 January 2017 and 31 December 2019. All microbiological tests results from cases, controls and influenza patients were analysed.

Data collection and outcomes

For all cases, controls, and influenza patients for whom a bacterial infection had been identified, information was collected from electronic health records concerning demographics (age, gender), length of hospital stay, outcomes including death, and admission to the intensive care unit (ICU).

Microbiological procedures

Microbiological investigations included standard culture for urinary samples and blood cultures [14]. Respiratory specimens (i.e. sputa, pleural fluids, bronchoalveolar lavages (BALs), bronchial aspirates and pulmonary biopsies) were examined by standard cultures [15]; urine specimens were tested for pneumococcal antigen [16], and BAL by *S. aureus* (PCR) [17].

Definitions

We defined a superinfection by a positive sample to any bacteria and collected between two days before and 30 days after the diagnosis of the viral infection among COVID-19 and influenza patients. We did not consider the detection of *Candida albicans* and *Enterococcus* spp. from respiratory samples in this study. Bacteraemia was defined as the growth of a commensal non-skin flora in at least one blood culture vial, and involving a common skin coloniser (coagulase-negative staphylococci or *Corynebacterium* species) when at least two vials sampled within 48 h were positive for the same species. When the timescale between sampling the positive specimen exceeded 48 h after initial admission, these were defined as healthcare-associated infections. We removed duplicate data when a patient was positive to the same bacterial pathogen from the same anatomical site. The positivity rate for each category (i.e. respiratory infections and bacteraemia) was calculated by dividing the number of positive patients by the number of patients for which at least one blood or respiratory specimen was taken following their admission.

Statistical analysis

Statistical analyses were performed using Graphpad 6 (La Jolla, USA) and XLSTAT 2019 (Addinsoft, New York, USA). Continuous and categorical variables were presented as median (interquartile range) and absolute number (percentage) respectively. The Mann–Whitney *U* test, chi-square test and Fisher exact test were used when appropriate. Significance was set at $P < 0.05$.

Results

Patients included

In total, 42 468 subjects were positive according to a COVID-19 RT-PCR test during the study period and were considered as cases. Of these, 631 had at least one superinfection, accounting for 1321 episodes. During the same period, 266 261 subjects tested negative for COVID-19 amplification and were used as controls. A total of 4731 infections were identified among 2884 controls. Finally, from 2017 to 2019 we identified 4059 patients with at least one positive PCR for influenza virus; of these, 124 had at least one superinfection, as previously defined.

Patients' characteristics

The cases were older (68 years old *vs.* 58.9 years old and 56.6 years old; $P < 0.0001$) and were significantly more frequently male (sex ratio M/F: 2.9) compared to controls and influenza patients (sex ratio M/F: 1.6 and 1, respectively) ($P < 0.0001$) (Table 1). Among cases, the sex ratio of patients admitted to the ICU did not differ from that of patients hospitalised in other units. The proportion of ICU-acquired infections was significantly higher among cases (83.9%) compared to control and influenza groups (46.9% and 34.9%, respectively) ($P < 0.0001$) as well as to the proportion of hospital-acquired infections (82% *vs.* 61.1% and 44.1%, respectively) ($P < 0.0001$). The median length of stay in the ICU preceding the infection was longer among cases (9.63 days) compared to controls (6.71 days) and influenza patients (5.17 days).

Respiratory infections

We identified a total of 1069, 2697 and 87 respiratory infections among 535 cases, 1492 controls, and 68 influenza patients, respectively (Table 1). When compared to control and influenza groups, respiratory infections were more frequent among controls (41.1%) than among cases and influenza patients (35.6% and 10.7%, respectively) ($P < 0.001$). However, respiratory infections among cases were more frequently healthcare-associated (84.3% *vs.* 70.7% and 48.2%, respectively) ($P < 0.0001$) and more frequently ICU-acquired (88.7% *vs.* 60.9% and 40.6%, respectively) ($P < 0.0001$) compared to the control and influenza groups, respectively. Cases with respiratory infections were significantly more frequently male (sex ratio M/F: 3.7 *vs.* 2.1 and 1.1, respectively), and were older (mean age: 65.3 years old) than the controls only (55.4 years old) ($P < 0.0001$). The median length of stay in the ICU preceding the infection was higher among cases (9.2 days) when compared to that of controls (6.8 days) and influenza patients (3.9 days), while the mean timescale for acquiring respiratory superinfections was higher among cases (9.8 days) than influenza patients (5.95 days). Regarding the species identified, *S. epidermidis* ($P < 0.0001$), *K. aerogenes* ($P = 0.004$) and *Hafnia alvei* ($P = 0.001$) were more frequently recovered from respiratory specimens of cases, while *Haemophilus influenzae* ($P < 0.0001$), *Enterobacter cloacae* complex ($P = 0.003$) and *Escherichia coli* ($P = 0.001$) were more frequent among while *S. pneumoniae* ($P = <0.0001$) was more frequently detected from influenza patients (Fig. 1a). Regarding ICU-acquired infections, *H. alvei* ($P = 0.03$) and *S. epidermidis* ($P = 0.03$) were more predominant in cases, while *E. cloacae complex* ($P = 0.0001$), *E. coli* ($P = 0.0001$) *S. pneumoniae* ($P = 0.001$) and *H. influenzae* ($P < 0.0001$) were more frequent among controls (Fig. 1b). The only observed difference in non-ICU settings was the significantly higher detection of *S. pneumoniae* among influenza patients ($P < 0.0001$) (data not shown).

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Table 1. Characteristics of infections occurring in COVID-19 patients and those occurring in uninfected subjects between 26 February 2020 and 1 May 2021, and those occurring among influenza-positive patients between 1 January 2017 and 31 December 2019s (***$P < 0.001$)

	COVID-positive $N = 42\,468$	COVID-negative $N = 266\,261$	FLU-positive 4059
Overall coinfections			
Total number of coinfections (N)	1321	4731	166
Number of positive patients (N)	631	2884	124
Ratio M/F	**471/160 (2.9)*** **	1791/1093 (1.64)	63/61 (1.03)
Median hospital stay (days)	**8.69*** **	3.61	1.34
Healthcare-associated (N, %)	**1081/1318 (82)*** **	2862/4687 (61.1)	71/161 (44.1)
Median age (years)	**67.33*** **	64.5	60.73
Time to coinfection (days)	**9.7*** **	NA	5.53
Number of coinfections in ICU (n'/N, %)	**1108/1321 (83.9)*** **	2219/4728 (46.9)	58/166 (34.9)
Ratio M/F in ICU	**362/104 (3.48)*** **	665/358 (1.38)	19/14 (1.36)
Median ICU stay (days)	**9.63*** **	6709	5.17
Respiratory infections			
Number of coinfections (N)	1069	2697	87
Number of positive patients (N')	535	1492	68
Number of tested patients (N'')	1503	3632	638
Positivity rate (N'/N'', %)	535/1503 (35.6)	**1492/3632 (41.1)*** **	68/638 (10.7)
Ratio M/F	**842/227 (3.7)*** **	1812/885 (2.1)	46/41 (1.1)
Median hospital stay (days)	**8731*** **	4.64	1817
Healthcare-associated (n/N, %)	**899/1066 (84.3)*** **	1894/2680 (70.7)	41/85 (48.2)
Mean age (years)	**66.16**	61.6	64.3
Time to coinfection (days, mean)	9.8	–	5.95
Number of coinfections in ICU (n'/N, %)	**948/1069 (88.7)*** **	1640/2694 (60.9)	40/87 (46)
Median ICU stay (days)	**9.2*** **	6.8	3.9
Blood cultures			
Number of coinfections (N)	252	2034	79
Number of positive patients (N')	209	1686	67
Number of tested patients (N'')	5580	11 526	1864
Positivity rate (N'/N'', %)	209/5580 (3.75)	**1686/11 526 (14.6)*** **	67/1864 (3.6)
Ratio M/F	**160/49 (3.3)*** **	1028/658 (1.6)	44/35 (1.3)
Median hospital stay (days)	**8.632*** **	1.761	0.06111
Healthcare-associated (n/N, %)	**182/252 (72.2)*** **	968/2007 (48.2)	30/76 (39.5)
Median age (years)	66.9	66.9	**52.06*** **
Time to coinfection (days)	9.1	–	5.1
Number of coinfections in ICU (n'/N, %)	**160/252 (63.5)*** **	579/2034 (28.5)	18/79 (22.8)
Median ICU stay (days)	**12.95*** **	6.48	14.3

Values in bold indicate the group for which the difference is the most significant.

The latter species was also more common in community settings (i.e. 62.5%) out of the 10 most frequent species associated with COVID-19 respiratory superinfections.

Bacteraemia

We identified a total of 252, 2034 and 79 bacteraemia among 209 cases, 1686 controls, and 67 influenza patients, respectively (Table 1). Bacteraemia was significantly more frequent among controls (14.6%) than cases (3.75%) and influenza patients (3.6%) ($P < 0.0001$). However, bacteraemia among cases were predominantly healthcare-associated (72.2% *vs.* 48.2% and 39.5%, respectively), more frequently ICU-acquired (63.5% *vs.* 28.5% and 22.8%, respectively, $P < 0.0001$), with an over-representation of male subjects (sex ratio M/F = 3.3 *vs.* 1.6 and

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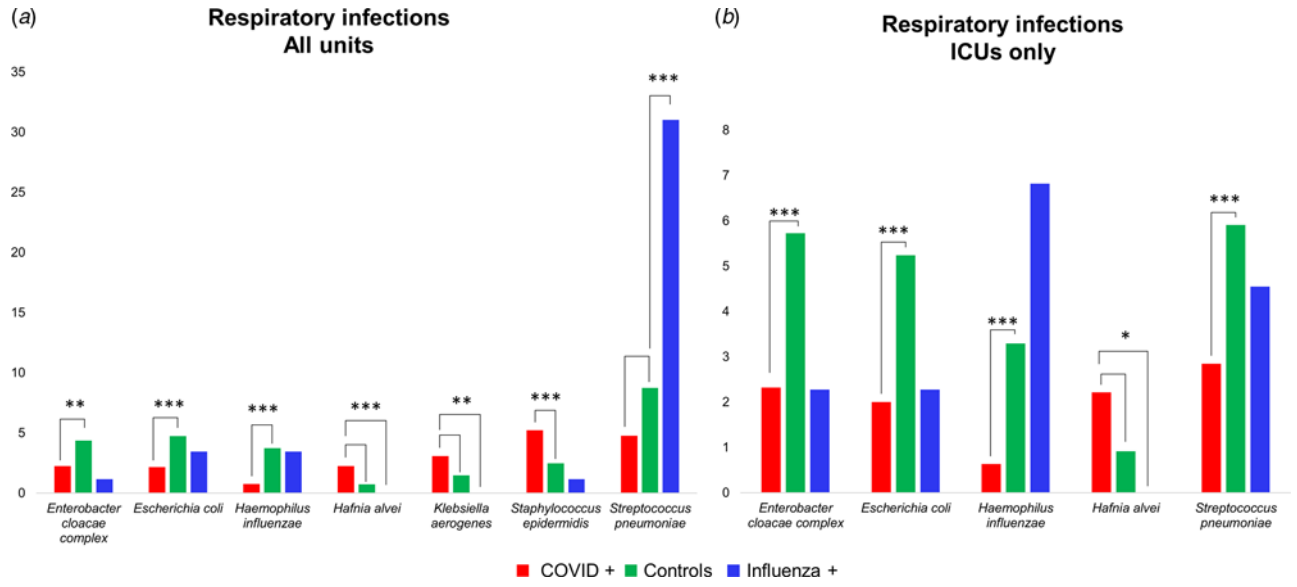

Fig. 1. Microorganisms detected in respiratory specimens, the frequency of which is significantly different among COVID-19 patients, controls and influenza-positive subjects (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). (a) All units and (b) ICU only.

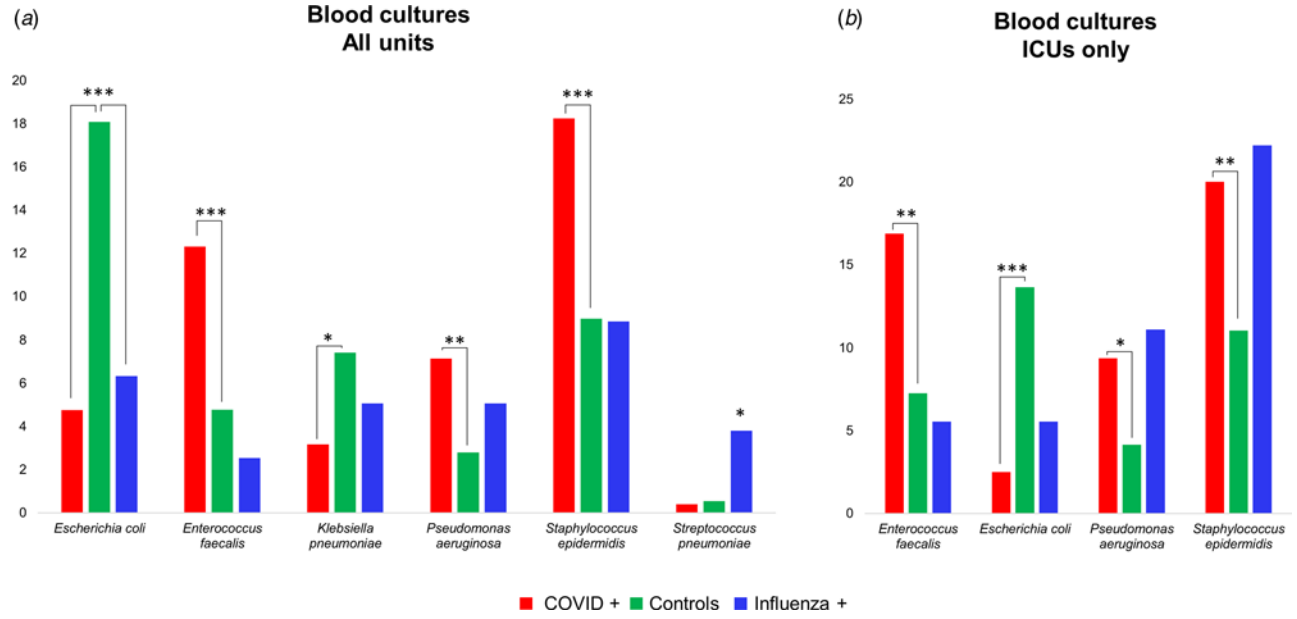

Fig. 2. Microorganisms detected from blood cultures, the frequency of which is significantly different among COVID-19 patients, controls, and influenza-positive subjects between 1 January 2017 and 31 December 2019 (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). (a) All units and (b) ICU only.

1.3, respectively, $P < 0.0001$) (Table 1). The median length of stay in the ICU preceding the infection was longer among cases (13 days) compared to controls (6.5 days) but not for influenza patients (14.3 days), while the mean timescale between viral diagnosis and acquisition of bacteraemia was longer among cases (9.1 days) than influenza patients (5.1 days). Regarding the species identified, *S. epidermidis* ($P < 0.0001$), *E. faecalis* ($P < 0.0001$) and *P. aeruginosa* ($P = 0.002$), were more frequently isolated from blood cultures of cases while *E. coli* ($P \ll 0.0001$) and *K. pneumoniae* ($P = 0.03$) were more frequent among controls, and *S. pneumoniae* among influenza patients ($P = 0.02$) (Fig. 2a). Similar findings were apparent with ICU-acquired infections for *S. epidermidis* ($P = 0.005$), *E. faecalis* ($P = 0.002$), *P. aeruginosa* ($P = 0.016$), and *E. coli* ($P < 0.0001$), but not for *K. pneumoniae* and *S. pneumoniae* (Fig. 2b). In non-ICU settings, *S. pneumoniae* was, however, more frequent among influenza patients ($P = 0.014$), as well as *E. coli* among controls ($P < 0.001$). Of the 10 species most frequent among cases, only *E. coli and S. hominis* were more associated with community settings. Among COVID-19 patients, bacteraemia due to *E. faecalis* generally occurred later when compared to those due to other pathogens (13.7 days *vs.* 8.5 days, respectively) ($P < 0.0001$), and more frequently in ICU settings (87% *vs.* 52.8%, respectively, $P < 0.0001$), but were not associated with more deaths.

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Discussion

In this study, we provide a snapshot of the superinfections (associated with COVID-19 over a 13-month period). Our data rely on microbiologic investigations that were assessed by microbiologists and validated by two study operators. First, we found that bacterial infections in COVID-19 patients were more frequently healthcare-associated, often acquired in ICUs, associated with a longer ICU stay, and occurred in older male patients, compared to controls and influenza subjects (Table 1). The usual main pathogens were less frequent in COVID-19 patients as illustrated by fewer bacteraemias involving *E. coli* and *K. pneumoniae* than among controls (Fig. 2a). Most importantly, the respiratory pathogens such as *H. influenzae* and *S. pneumoniae*, commonly involved in viral superinfections, were under-represented in COVID-19 patients compared with controls and influenza patients (Fig. 1a and b). These findings are in line with other studies agreeing that community-acquired superinfections are more common in COVID-19 positive subjects [18]. The present work showed that infections in COVID-19 patients are generally dominated by nosocomial-transmitted microorganisms, such as Gram-negative bacteria in respiratory infections, and coagulase negative staphylococci and *P. aeruginosa* in bacteraemia.

Nevertheless, it was surprising to observe the high frequency of *E. faecalis* bacteraemia among COVID-19 patients that were mainly ICU-acquired (87%) with a longer timescale of acquisition when compared to the other microorganisms. We wondered whether empirical antimicrobial therapy could have contributed to selecting enterococcal species, but fewer than the half of the patients with a positive blood culture for *E. faecalis* had received either cephalosporins or carbapenems prior to sampling (data not shown). Nevertheless, gut microbiota enrichment with *E. faecalis* has been associated with an abnormal immune response in COVID-19 patients [19].

We did not find increased mortality in patients with bloodstream infections involving *E. faecalis* although other studies have also noted an unexpected frequency of bacteraemia involving enterococci [20], particularly in ICU settings with often equal distribution between *E. faecalis* and *E. faecium* [21, 22], One of the hypotheses raised is the possible increased permeability of the gut barrier induced by the virus when replicating in enterocytes. However, patients developed *E. faecalis* bacteraemia within a mean timescale of 13.7 days in our series, when the virus replicates little, rendering this hypothesis less probable.

The rate of superinfection during COVID-19 has been reported to be usually low, ranging from 6% to 8% depending on the studies [3, 4, 23, 24]. Our study shows that COVID-19 patients experience more respiratory superinfections than individuals with influenza, due to a high proportion of pathogens with nosocomial transmission, whereas the rate of bloodstream infections is similar. Discrepant results were also reported which found similar rates of superinfection between COVID-19 patients and influenza-positive individuals, but it remains difficult to extract how many infections were ICU-acquired [24].

We acknowledge that the clinical application of our findings could be limited by the fact that the study was conducted primarily from a microbiological viewpoint, and that patients were not classified according to the severity of their illness. However, stringent inclusion criteria were used for the definition of bacteraemia to avoid inclusion of contaminants when collecting our data, and interpreted the results according to relevant parameters, including the proportion of ICU admissions, and the length of stay in the ICU. It is also acknowledged that only standard cultures and two rapid assays (i.e. pneumococcal antigen detection in urine and molecular detection of MRSA) were utilised and possibly may have missed pathogens detected by other approaches such as serological testing or other specific PCRs. Finally, we did not analyse the antibiotic treatments administered during the patient's stay. Indeed, antimicrobial agents were largely prescribed for COVID-19 patients, which could have thereby reduced the incidence.

Overall, this study shows that the superinfections occurring with COVID-19 are more frequent than with influenza primarily due to prolonged stays in the ICU. Pathogens that are commonly isolated from patients presenting with routine clinical infections are under-represented, while those most often associated with nosocomial transmission were predominant. Notably, there was an unexpectedly high frequency of *Enterococcus faecalis* bacteraemia among COVID-19 patients, a finding which warrants further investigation.

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Author contributions. Conceptualisation: G. D., D. R.; Methodology: D. R., G. D., E. L. G.; Validation: G. D., D. R.; Formal analysis: E. L. G., G. D.; Investigation: E. L. G., G. D.; Writing: E. L. G., G. D., D. R.; Visualisation: E. L. G., G. D.; Supervision: G. D., D. R.

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Conflict of interest. Didier Raoult has been a consultant for Hitachi High-Technologies Corporation, Tokyo, Japan, from 2018 to 2020. He is a scientific board member of Eurofins company and a founder of a microbial culture company (Culture Top). Other authors declare no conflicts of interest.

Ethical standards. All data were generated as part of routine work at the Assistance Publique-Hôpitaux de Marseille (APHM) (Marseille university hospitals), and this study results from routine standard clinical management. Access to the patients' biological and registry data issued from the hospital information system was approved by the data protection committee of the APHM and was recorded in the European General Data Protection Regulation registry under number RGPD/APHM 2021-131.

Consent to participate. Not applicable.

Consent for publication. All authors have approved the manuscript and gave their consent for submission and publication.

Data availability statement. The data that support the findings of this study are not openly available, as requested by the data protection committee of APHM.

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