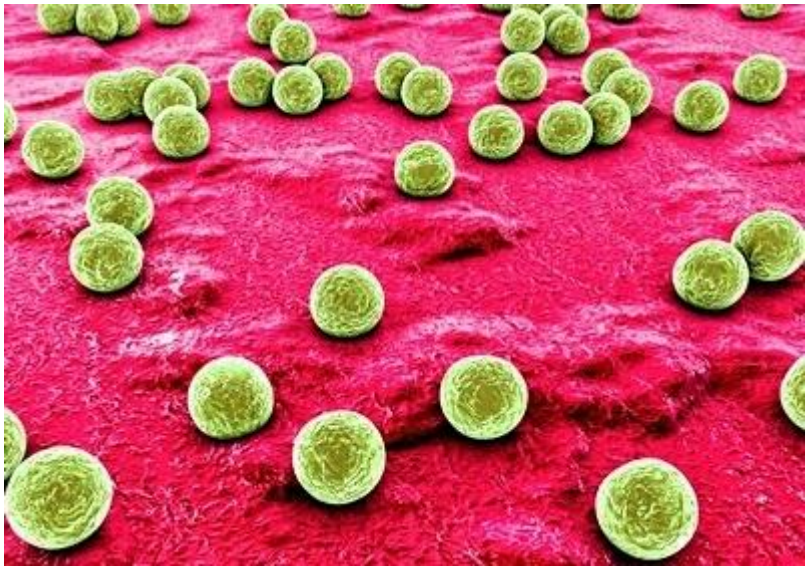
Staphylococcus aureus (S. aureus) bacteremia is a life-threatening condition with high morbidity and mortality rates. Several studies have addressed the incidence, prevalence, and clinical outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and *S. aureus* coinfection, but the genomic differences between pandemic and pre-pandemic strains have not been explored. In this study, the Spanish authors used *S. aureus* isolates to investigate the clinical aspects and genomic characteristics of bacterial strains isolated from patients with bacteremia before and during the COVID-19 pandemic (2014–2022). Comparative genomics analysis of 339 isolates showed adaptation of *Staphylococcus aureus* to COVID-19 selective pressure.

Understanding the interplay between viral and bacterial infections, including the prevalence and impact of *S. aureus* in COVID-19 cases, is important for effective patient care and public health measures. *S. aureus* has been described as a leading cause of secondary infection during the COVID-19 pandemic, significantly increasing patient mortality rates. Interestingly, a previous study employing a computational integrative approach for epitope prediction and identification revealed the molecular similarity between antigenic sites in the SARS-CoV-2 receptor binding domain (RBD) and 54 antigenic determinants of fifteen pathogenic bacteria, parasites, and viruses. The antigenic determinant predicted from *Staphylococcus aureus* with molecular similarity with SARS-CoV-2 RBD antigens was Enterotoxin A. The author stated that these findings are seriously alarming, as the presence of antigenic determinants that are similar to those found in highly pathogenic microorganisms explains numerous pathophysiological complications in COVID-19, including a deregulated immune response, unleashed or dysregulated cytokine secretion (cytokine storm), and multiple organ failure.
https://discovermednews.com/molecular-similarities-between-sars-cov-2-rbd-and-pathogens/



Staphylococcus aureus

About the Study and Results

The study included 339 adult patients diagnosed with *S. aureus* bloodstream infection between 2014 and 2022. Persistent bacteremia was defined as the presence of positive blood cultures after 72 h of appropriate antibiotic therapy. Only the first episode of *S. aureus* bacteremia was included in the analysis for each patient. Most patients were male (69.3%), and the mean age was 63.7 ± 19.9 years. 93 patients died (27.4%), and the median time to the patient's death was 20 days.

The most frequent clinical diagnoses were diabetes (31.6%), the presence of a foreign device (25.4%), ischemic heart disease (17.7%), congestive heart failure (16.5%), solid neoplasm (15.3%), peripheral arteriopathy (12.7%), and chronic obstructive pulmonary disease (10.0%). Most *S.aureus* infections were nosocomial (56.6%), while 27.4% were community-acquired and 16.0% were healthcare-related. The predominant primary sources of infection were vascular catheters (31.8%), skin infections (18.0%), and pneumonia (9.4%), whereas 30.7% of episodes were of unknown origin.

Antibiotic tests identified resistance to penicillin (86.1%), erythromycin (30.4%), clindamycin (20.9%), ciprofloxacin (16.8%), levofloxacin (15.3%), oxacillin (13.9%), amoxicillin/clavulanic acid (13.6%), gentamicin (10.0%), tetracycline (2.9%), cotrimoxazole (1.5%), linezolid (0.3%), and rifampicin (0.3%).

The multilocus sequence typing software classified *S.aureus* isolates in 24 different lineages. The major identified lineages were CC30 (19.5%), CC5 (17.1%), CC45 (12.1%),

ST398 (8.8%), CC8 (8.8%), CC22 (8.0%), and CC15 (5.9%). 18 isolates could not be classified into a known sequence type. The distribution of lineages remained relatively stable over the years of study.

Methicillin-resistant S. aureus

Changes in molecular characteristics of pandemic S.aureus isolates

200 adult patients were diagnosed with *S. aureus* bloodstream infection after March 14th, 2020, and 32% tested positive for SARS-CoV-2. Strains isolated from March 14th, 2020 onwards were considered as pandemic clones.

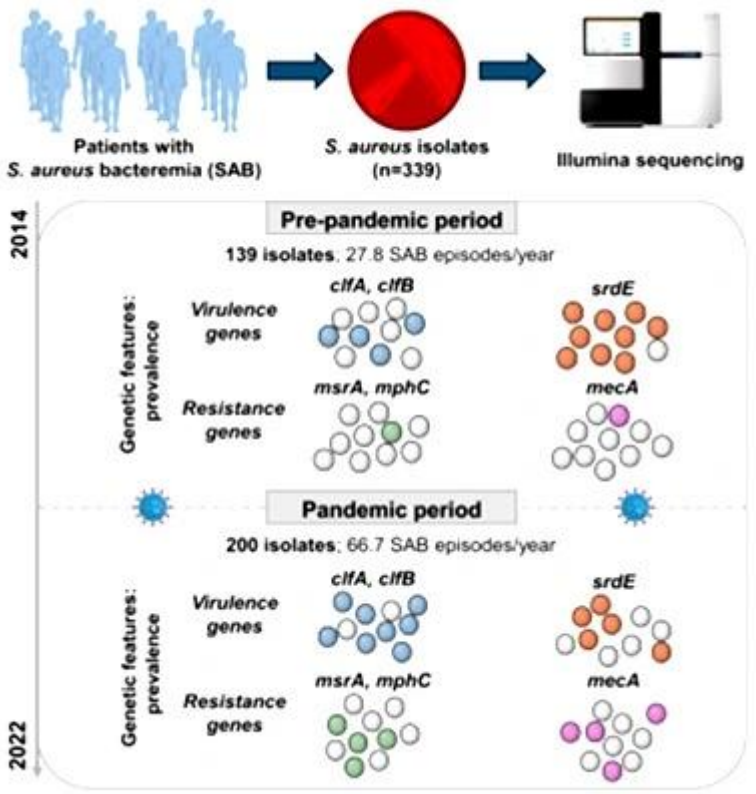
During the COVID-19 pandemic, the number of episodes of *S. aureus* bacteremia *per* year increased by 140% (from 28 in the pre-pandemic years to 67 in the pandemic years). Nosocomial infections rose from 69 episodes in the pre-pandemic years to 119 during the pandemic. Specifically, there was an increase in the prevalence of *S. aureus* bacteremia originating from catheters and surgical sites, methicillin-resistant *S. aureus* (MRSA) strain infections, and endocarditis cases. The number of community-acquired *S. aureus* bacteremia was significantly reduced.

During the pandemic, the researchers did not detect emerging *S. aureus* clones, and the prevalence of lineages throughout the pandemic period was indistinguishable from those before the pandemic. Similarly, core genome phylogenetic analysis did not reveal the

presence of emerging sub-lineages within the major lineages during the pandemic years.

However, the genetic differences between pre-pandemic and pandemic strains of *S. aureus* were significant. The prevalence of strains carrying the *clfA* and *clfB* genes, which are MSCRAMMs encoding fibrinogen-binding clumping factors A and B, increased. ClfA is the major virulence factor responsible for *S. aureus* clumping in blood plasma, and ClfB interacts with cytokeratin 10 and loricrin and facilitates *S. aureus* infection of the skin. ClfA and ClfB are involved in the aggregation of bacteria and platelets. In contrast, the prevalence of the *sdrE* gene, which encodes an MSCRAMM that prevents phagocytosis of *S. aureus* by sequestering human complement factor H (CFH) on the bacterial cell surface, was reduced. The SARS-CoV-2 spike protein has been shown to block CFH, leading to dysregulation of complement on the human cell surface. The presence of *clfA*, *clfB*, and *sdrE* genes in *S. aureus* co-infecting COVID-19 patients had no impact on the clinical outcome of bacteremia.

Genetic features in pandemic isolates also revealed a higher prevalence of methicillin (*mecA*) and macrolide (*msrA* and *mphC*) resistance genes. It should be noted that macrolides were extensively used as accessory therapy for COVID-19.



Original illustration from study by Sánchez-Osuna M et al. iScience 27, 110402, 2024

According to the authors, these results imply that the prevalence of these genes is increasing across diverse lineages, suggesting a genetic enrichment process rather than the emergence of dominant lineages during the pandemic. This reflects an evolutionary scenario in which specific genes are convergently selected among diverse isolates, regardless of lineage, likely due to selective pressure during the COVID-19 infection.

Conclusion

Comparative genomic analysis of 339 *S. aureus* isolates from patients with bacteremia highlighted the adaptation of *Staphylococcus aureus* to COVID-19 selective pressure. Some virulence factors and antibiotic resistance genes were enriched in pandemic *S. aureus* isolates. The presence of the *clfA* and *clfB* genes gave *S. aureus* an advantage in the context of SARS-CoV-2 coinfection by enhancing fibrinogen binding. As macrolides were extensively used as accessory therapy for COVID-19 patients, the higher prevalence of macrolide

resistance genes (*msrA* and *mphC*) indicates the evolving nature of *S. aureus* infections in the COVID-19 pandemic.

According to the authors, these results suggest convergent selection for the presence of these genes in multiple lineages, a widespread phenomenon rather than the emergence of particular lineages.

This study shows that genomics enables the tracking of specific strains and the identification of emerging threats, contributing to infection surveillance and control.

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