Influenza Virus Primes Mice for Pneumonia From Staphylococcus aureus

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Superinfections from Staphylococcus aureus following influenza are an increasing concern. We assessed several laboratory and clinical strains in a mouse coinfection model with influenza virus. A methicillin-resistant USA300 clone and several recent clinical strains from patients with necrotizing pneumonia caused high mortality following influenza virus infection in mice. Both viral and bacterial lung titers were enhanced during coinfections compared with single infections. However, differences in titers did not correspond with differences in disease outcomes in a comparison of superinfections from a highly pathogenic strain with those from a poorly pathogenic strain. These strains did differ, however, in expression of Panton-Valentine leukocidin and in the degree of inflammatory lung damage each engendered. The viral cytotoxin PB1-F2 contributed to the negative outcomes. These data suggest that additional study of specific bacterial virulence factors involved in the pathogenesis of inflammation and lung damage during coinfections is needed.

Bacterial superinfections are a common cause of excess mortality following influenza, particularly in pandemic years [1]. It has been estimated that >95% of all fatal influenza cases during the 1918–1919 pandemic were complicated by to secondary bacterial pneumonia [2]. Pneumococci were the most frequently recovered etiologic agents in these cases [1–3] and were the typical agents of disease in recent decades during seasonal influenza outbreaks [4] and during the 1968–1969 pandemic [5]. During the 1957–1958 pandemic, however, staphylococci assumed a novel prominence as the leading etiologic agent of secondary bacterial disease [6, 7]. Secondary staphylococcal disease continued to be seen through the second wave of the “Asian flu” in 1960–1961 [8], but for the following several decades staphylococci once again became uncommon as a cause of either primary or secondary pneumonia. The epidemiological characteristics of S. aureus pneumonia have changed during the past decade with the emergence of the USA300 and USA400 clones of methicillin-resistant S. aureus [9]. These strains are now frequently being identified as agents of bacterial pneumonia, particularly in children with influenza [10, 11].

Because it is difficult to define the etiological characteristics of secondary bacterial pneumonia, there is a dearth of information regarding the true incidence and clinical features of mild disease. In studies examining severe or fatal cases, however, the pathogenesis of influenza-associated S. aureus pneumonia seems to be distinct from that of typical community-acquired pneumonia. The disease is characterized as fulminant, with short intervals between onset of illness and diagnosis of pneumonia (<7 days) and rapid (often within <24 h) progression to severe disease with multilobar involvement [6, 7, 9, 11, 12]. Death in fatal cases
follows rapidly after the diagnosis of severe pneumonia, with the clinical course seemingly unaffected by the appropriateness and timing of antibiotic administration [6–9]. Louria et al [13] proposed during the 1957–1958 pandemic that 3 groups of patients could be recognized: those with primary influenza virus pneumonia, those with late bacterial pneumonia presenting after resolution of primary influenza, and those with concomitant viral-bacterial pneumonia. Cases in the concomitant viral-bacterial pneumonia group tended to be more fulminant and more often fatal than cases of late bacterial pneumonia, and S. aureus was more commonly found in the combined group than in the late group, in which Streptococcus pneumoniae was the predominant secondary pathogen.

The emergence of the novel pandemic H1N1 influenza virus in 2009 [14] has added urgency to understanding interactions between S. aureus and influenza viruses. Although few data are available, it seems that bacterial pneumonia is complicating around 30% of fatal cases, with S. aureus the most commonly recognized pathogen [12, 15, 16]. We undertook the present study to better understand the pathogenesis of S. aureus superinfections following influenza. This interaction has been studied previously in animal models including mice, ferrets, and monkeys, with results suggesting that animal coinfections can reliably model many aspects of the disease [17–22]. Our goals were to thoroughly characterize the mouse model of influenza-staphylococcal coinfection and to compare it with our well-described model of influenza-pneumococcal coinfection [22–25]. In particular, we were interested in determining whether there were strain-dependent differences in the pathogenesis of secondary lung infections following influenza with use of clinically relevant S. aureus isolates, including the recently emerged USA300 and USA400 clones.

MATERIALS AND METHODS

Infectious Agents
The pandemic strain A/California/7/09 (H1N1), the St. Jude strain of mouse-adapted influenza virus A/Puerto Rico/8/34 (H1N1; PR8), and otherwise isogenic viruses engineered either not to express the PB1-F2 protein (PR8/ΔPB1-F2) or to express the A/Brevig Mission/1/18 (H1N1) PB1-F2 (PR8/1918 PB1-F2) [25] were grown in Madin-Darby canine kidney cells as described elsewhere [23]. S. aureus strains were grown for stocks on tryptic soy agar and frozen in brain-heart infusion medium with 50% glycerol. UAMS-1 is an osteomyelitis isolate obtained from M. Smeltzer, PhD, at the University of Arkansas for Medical Sciences. ATCC-49755 and ATCC-27733 are laboratory strains obtained from the American Type Culture Collection (ATCC). NRS-157, NRS-193 (USA400), NRS-194 (USA400), and NRS-261 are clinical strains from patients with necrotizing pneumonia and were obtained from the Network for Antimicrobial Resistant S. aureus. LAC is a USA300 clinical strain and was obtained from M. Otto, PhD, at the National Institutes of Health.

Animal Infection Model
Eight-week-old female BALB/c mice (Jackson Laboratory) were maintained in a Biosafety Level 2 facility in the Animal Resource Center at St. Jude Children’s Research Hospital (SJCRH). All experimental procedures were approved by the Animal Care and Use Committee at SJCRH. Influenza virus was administered intranasally in sterile phosphate-buffered saline (PBS) in a volume of 100 μL. S. aureus stocks were grown overnight in tryptic soy broth at 37°C and resuspended in sterile PBS in a volume of 100 μL for intranasal, intratracheal, or intravenous (in the tail vein after suspension in agar as described elsewhere [26]) administration. Intravenous administration in agar allows targeted delivery of bacteria to the lungs and prevents the rapid clearance seen when the organisms are suspended in saline [26]. Viability of the inocula was confirmed by means of plate counts with each experiment. Heat-killed bacteria were generated by means of incubation at 100°C for 15 minutes, and loss of viability was confirmed by means of plating. Spent media from overnight cultures were harvested by means of centrifugation and filter sterilized using 0.45 μM filters. Infected mice were weighed and assessed daily for illness and mortality for 21 days. The virus infectious dose for most experiments was 30 times the median tissue culture infective dose (TCID₅₀), which caused 10%–15% weight loss and no mortality when given alone. For the comparison of wild-type PR8 with ΔPB1-F2, these viruses were dosed at 100 TCID₅₀.

Cultures and Histopathology
Bacterial and viral titers were determined from blood, lung, or spleen homogenates as previously described [24, 25, 27]. Microscopic evaluation of lungs was performed by an experienced veterinary pathologist (K.L.B.) blinded to study purpose and design and to group composition. A semiquantitative grading scheme was used to score the overall character of the pneumatic process and the pathology specifically observed in the interstitium and terminal airways as previously described [25].

Cellular Depletion
Mice were depleted of either neutrophils, CD4⁺ T cells, or macrophages on days 4, 6, and 8 after viral infection with a 100 μL intraperitoneal administration in sterile PBS of either Ly-6G antibodies (0.005 mg; BD Pharmagen #55149), anti-CD4⁺ antibodies (P. Thomas, PhD, SJCRH), or clodronate-loaded liposomes (25 mg; Roche Diagnostics GmbH), respectively.

Real-Time Polymerase Chain Reaction
Real-time polymerase chain reaction (RT-PCR) analyses were performed on bacterial isolates to determine the presence
or absence of selected virulence or control genes as described elsewhere [28]. Oligonucleotides and RT-PCR conditions designed for the detection of additional genes of interest not previously described (\textit{sak}, \textit{clfA}, \textit{hlb}, \textit{hlg} ABC, \textit{hlg} B, and \textit{hlg} C) are available on request.

Statistical Analysis

The survival rates of the groups of mice were compared with the log-rank \(\chi^2\) test using the Kaplan-Meier survival data. Weight loss and bacterial or viral titers were compared between groups by means of analysis of variance using SigmaStat for Windows, version 3.11 (SysStat Software). A \(P\) value of <.05 was considered to reveal a significant difference.

RESULTS

Influenza Infection Enhances Disease from \textit{S. aureus}

We have previously demonstrated that influenza virus infection in mice enhances secondary bacterial pneumonia from \textit{S. pneumoniae} [23–25, 27]. To determine whether a similar phenomenon occurs when \textit{S. aureus} is the secondary agent, we infected mice with a sublethal dose of influenza virus or mock-infected them with PBS and challenged both groups 7 days later with \(10^7\), \(10^8\), or \(10^9\) colony-forming units (CFUs) of \textit{S. aureus} strain NRS-193, recovered from a child with necrotizing pneumonia [29]. More weight loss was observed in mice preinfected with influenza virus than in mock-infected mice, and priming with virus significantly enhances disease from \textit{S. aureus}.

Figure 1. Influenza-staphylococcal superinfection. Groups of 6–10 mice were infected with influenza virus or mock infected with phosphate-buffered saline (PBS) and then 7 days later challenged with \textit{Staphylococcus aureus} \textit{A}, Weight loss, and \textit{B}, Survival at 3 different bacterial challenge doses are plotted using \textit{S. aureus} strain NRS-193 (USA400). An asterisk indicates that the log-rank test on the Kaplan-Meier survival data revealed a significant difference between the influenza-infected mice and the corresponding mock-infected controls \((P < .05)\). \textit{C}, Survival is plotted using 8 different \textit{S. aureus} strains as the secondary challenge following influenza. An asterisk indicates a significant difference compared with all other groups; a double asterisk indicates a significant difference compared with the 5 groups indicated by filled symbols.

Figure 2. State, route, and timing of superinfection. Groups of 6 mice were infected with influenza virus and then challenged \((\textit{A})\) 7 days later with \(10^8\) colony-forming units (CFUs) of \textit{Staphylococcus aureus} strain NRS-193 (live), \(10^8\) CFUs of heat-killed NRS-193, or spent media from \(10^9\) CFUs of NRS-193; \((\textit{B})\) 7 days later with \(10^8\) CFUs of \textit{S. aureus} strain NRS-193 intranasally (I.N.), intratracheally (I.T.), or intravenously (I.V.); or \((\textit{C})\) at intervals corresponding to 3 days prior to influenza virus infection (day −3), simultaneously with influenza virus infection (day 0), or 3, 7, 14, or 21 days after influenza virus infection. An asterisk indicates a significant difference revealed by the log-rank test on the Kaplan-Meier survival data \((P < .05)\) compared with \((\textit{A})\) the other 2 groups or \((\textit{B})\) groups with intervals of <3 days or >7 days.
enhanced mortality at all 3 doses, resulting in 100% mortality at the highest dose used (Figure 1A, B). Strain specificity was examined by repeating this challenge with several laboratory and clinical strains at the 10^8-CFU dose. Most of the clinical strains and 1 ATCC strain (49775) killed the majority of the mice (Figure 1C). The osteomyelitis isolate UAMS-1 killed only 3 (50%) of 6 mice following influenza, and the ATCC strain 27733 killed only 1 of 6 mice. We conclude from this that strain-specific differences in the ability of *S. aureus* to cause secondary bacterial pneumonia exist and that the recently emerged USA300 and USA400 clones that have been linked to a surge in necrotizing pneumonia in patients with influenza [9–11, 15, 29–31] act synergistically with influenza virus.

We next sought to characterize the parameters of the model in depth. Because large amounts of bacteria were required for expression of disease and mortality in this model, in contrast to the pneumococcal model [23], we first examined whether the effect was mediated by exposure to cell wall components from heat-killed bacteria and extracellular toxins secreted into spent media or required growth of living organisms. Although an intranasal administration of 10^9 CFUs of heat-killed bacteria did result in modest disease and some deaths following influenza, 10^8 CFUs of live bacteria caused significantly more mortality than the heat-killed preparation or the spent media from 10^9 CFUs of bacteria (Figure 2A). Second, we examined whether the route of administration mattered. No differences were seen when bacteria were given intranasally, intratracheally, or intravenously (suspended in agar beads) following influenza (Figure 2B). Finally, we studied the role that the relative timing between exposure to the virus and exposure to the bacteria played in outcomes. Reversing the order or giving the virus and the bacteria together resulted in no excess weight loss or

### Table 1. Detection of Virulence Factors by Real-Time Polymerase Chain Reaction in 2 Strains of *Staphylococcus aureus*

<table>
<thead>
<tr>
<th>Virulence factor</th>
<th>hla</th>
<th>hlb</th>
<th>hlgABC</th>
<th>hlgB</th>
<th>hlgC</th>
<th>SEA</th>
<th>SEB</th>
<th>TSST</th>
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<tbody>
<tr>
<td>ATCC 27733</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
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<tr>
<td>NRS-193</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Virulence factor</td>
<td>gyra</td>
<td>sak</td>
<td>ETA</td>
<td>ETB</td>
<td>mecA</td>
<td>PVL</td>
<td>clfA</td>
<td>LukD/E</td>
</tr>
<tr>
<td>ATCC 27733</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
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**NOTE.** *gyra* is not considered a virulence factor but is included as a control for the assay.
mortality over separate administration of the virus or the bacteria (Figure 2C). Administering *S. aureus* 3 or 7 days after influenza virus resulted in 100% mortality, an effect that was no longer evident when *S. aureus* was administered 14 days after virus infection. We conclude from these data that influenza is altering the innate host defenses in a manner that enhances disease from subsequent challenge with live *S. aureus* and that the route by which the bacteria gain access to the lung is unimportant in the model.

**Increased Bacterial Growth Is Not Responsible for Strain-Specific Differences in Outcomes**

In the pneumococcal secondary infection model, influenza virus enhances the bacterial load of *S. pneumoniae* recovered from the lungs and blood of mice, and strain-specific differences between outcomes are directly related to the total bacterial lung load [23, 32, 33]. To determine whether this held true for *S. aureus* superinfections, we challenged mice previously infected with influenza virus or mock infected with PBS with either the NRS-193 strain, which caused substantial mortality following influenza, or the ATCC 27733 strain, which caused little disease or death. Although significant differences in NRS-193 lung titers could be seen between mock-infected mice and mice preinfected with influenza virus, there was no significant difference between NRS-193 lung titers and ATCC 27733 lung titers for infected mice, nor was there a significant difference for mock-infected mice (Figure 3A). Surprisingly, blood and spleen titers were significantly higher at early time points following ATCC 27733 infection than following NRS-193 infection (Figure 3B,C). Both staphylococcal strains enhanced the total viral lung load in the mice (Figure 3D), but the virus was not found outside the lungs. We conclude from these data that, although coinfection with virus and either *S. aureus* strain enhances the growth of each strain in clinically relevant organs, strain-specific differences in the degree of these increases do not account for differences in outcomes between strains.

![Figure 4](image-url)
Figure 5. Contribution of PB1-F2 to mortality. Groups of 6 mice were either mock infected with phosphate-buffered saline or infected with influenza viruses at the doses indicated in the legends and then challenged 7 days later with $10^6$ CFU of *Staphylococcus aureus* strain NRS-193. A) Viruses included wild-type PR8 and an isogenic virus that cannot express the viral cytotoxin PB1-F2 (PR8/ΔPB1-F2). B) Viruses included wild-type PR8, an isogenic version of PR8 expressing the 1918 PB1-F2 protein (PR8/1918 PB1-F2) and the 2009 pandemic H1N1 strain (pH1N1). An asterisk indicates a significant difference revealed by the log-rank test on the Kaplan-Meier survival data ($P < .05$) compared with the other 2 groups.

To assess other potential differences between the strains that may be related to different outcomes, we probed the 2 strains using RT-PCR to determine whether each encoded a selection of proteins that are traditionally regarded as virulence factors of *S. aureus* (Table 1). Both strains have genes for the α- and β-hemolysins (*hla, hlb*), staphylokinase (*sak*), the fibrinogen-binding protein clumping factor A (*clfA*), and both genes of the bicomponent toxin *LukD/E*. Both strains lack the genes for the F component of the γ-toxin (*hlgB*), the staphylococcal toxic shock syndrome superantigen *TSST-1*, and exfoliative toxins A and B (*ETA, ETB*). Only 1 gene was present in ATCC 27733 and absent in NRS-193, *SEA*, which codes for the superantigenic enterotoxin A. However, NRS-193 has genes that code for the closely related gene *SEB*, which is absent in ATCC 27733. Interestingly, NRS-193 alone has both components of the leukotoxin Panton-Valentine leukocidin (PVL), which has been proposed as a marker for the enhanced virulence of USA300 and USA400 clones, particularly when their ability to cause necrotizing pneumonia in humans has been considered [30, 31].

**Inflammatory Lung Damage Contributes to Secondary Staphylococcal Pneumonia**

Lungs, liver, and spleens from mice mock infected with PBS or infected with influenza virus, followed by challenge with either the NRS-193 strain or the ATCC 27733 strain, were compared by means of histopathologic examination. The lungs of mice mock infected with PBS and then challenged with either bacterial strain were indistinguishable; a mild, purulent perivascular inflammatory process consisting of macrophages and neutrophils admixed with fibrinous exudates was seen in a perivascular distribution and increased in severity between the 24- and 48-h time points (Figure 4C–E). A mild inflammatory infiltrate could be seen in the airways without necrosis or hyperplasia. In mice preinfected with influenza, the inflammatory infiltrate was more severe, extending into the interstitium and the pleura, and focal areas of airway necrosis were observed, together with significant hyperplasia (Figure 4F,G). These processes progressed from 24 to 48 h (Figure 4E). The degree of inflammatory involvement, the severity of airway necrosis, and the extent of fibrinous exudate were clearly worse in the lungs of mice superinfected with NRS-193 than in mice superinfected with ATCC 27733 (Figure 4E–G). Massive alveolar and bronchial necrosis with interstitial consolidation and copious protein-rich exudates into both alveoli and the interstitium were prominent in NRS-193–superinfected mice. The livers from both groups of virus-primed mice showed perivascular infiltrates and scattered inflammatory foci, whereas the corresponding spleens showed mild lymphoid follicular hyperplasia. Spleens and livers from PBS-primed mice were normal.

We next sought to determine the mechanism underlying the inflammatory damage observed in the lungs of superinfected mice. We had previously revealed, with use of the pneumococcal secondary infection model, that the increased inflammatory responses caused by expression of the influenza virus cytotoxin PB1-F2 contributed to morbidity and mortality [25]. Similarly, in the staphylococcal superinfection model, lack of PB1-F2 significantly decreased mortality either using an isogenic virus (Figure 5A) or using the novel pandemic H1N1 strain that does not code for full-length PB1-F2 (Figure 5B) [34], whereas expression of the more inflammatory PB1-F2 [25] from the 1918 pandemic strain increased mortality.

To determine whether a specific cell type was responsible for the inflammatory pathology, we depleted groups of virus- or mock-infected mice of either neutrophils, CD4$^+$ T cells, or macrophages followed by challenge with *S. aureus* using a sublethal dose, $5 \times 10^6$ CFUs. Depletion of any single cell type had no effect on weight loss (data not shown) or bacterial lung titers (Figure 6A–C). We then repeated the macrophage depletion and challenged with a higher dose ($10^8$ CFUs) of *S. aureus*. Although bacterial titers were significantly higher in the nondepleted group (data not shown), weight loss and histopathology scores did not differ (Figure 6D). We conclude from these data that virus-induced inflammatory responses contribute to poor outcomes during combined influenza-staphylococcal pneumonia but that no single cell type is responsible for the observed lung injury.
DISCUSSION

Influenza-staphylococcal coinfections have increased following the emergence of the USA300 and USA400 lineages [9, 11, 30, 31], and S. aureus has been identified as a common cause of death during the recent H1N1 influenza pandemic [12, 15]. To study this interaction, we have thoroughly characterized a mouse model of staphylococcal superinfection that is in many ways analogous to the well-characterized influenza-pneumococcal model with which we have been working for the past decade [23, 25, 35]. As in the pneumococcal model [23], morbidity and mortality are increased when influenza precedes live bacterial challenge, the lung titers of both the virus and the bacteria increase during coinfection, and strain-specific differences in outcomes are apparent. In both models, enhanced inflammatory responses seem to be important in potentiating disease when the virus and the superinfecting bacteria are present together [25]. However, the models differ in some respects as well. Significantly larger amounts of bacteria are required for expression of lung disease with S. aureus than with S. pneumoniae, bacterial strain–dependent differences in outcomes following influenza appear to be more dependent on inflammatory potential than on lung titer with S. aureus, and no synergistic enhancement of disease was seen 2 weeks after influenza when S. aureus was the secondary pathogen.

Several broad mechanisms for viral-bacterial synergism have been explored in animal models [1]. First, functional or physical alterations to the airways that favor bacterial growth can be caused by viral-induced cell death and/or uncovering and up-regulation of ligands for bacterial adherence [23, 24, 36, 37]. Second, viral-induced defects in immune responses may prevent bacterial clearance [33, 38–40]. Third, the inflammatory response during coinfection may be enhanced, leading to worse outcomes mediated by the immune response [25, 41]. Fourth, the bacterial infection may contribute to the pathogenesis of the primary viral infection [42]. In this S. aureus superinfection model, we demonstrate increased bacterial titers in the lungs, blood, and secondary organs, accompanied by inflammatory lung damage. Together, these resulted in significantly greater morbidity and mortality from combined infection than was seen with either pathogen alone. In addition, S. aureus significantly increased viral lung titers during the coinfection by means of an unclear mechanism, although the importance of this for pathogenesis is questionable, since the low-virulence S. aureus strain enhanced viral titers to the same extent as the high-virulence strain. The viral cytotoxin PB1-F2 contributed to mortality in this model in a manner similar to that seen with pneumococcus [25], and expression of the pandemic 1918 PB1-F2 enhanced mortality. However, the 2009 H1N1 strain, which lacks a functional PB1-F2, did not appreciably enhance disease at the doses used in this study. This absence of the proinflammatory activity
of PB1-F2 may explain why this pandemic has been milder and has featured many fewer secondary bacterial infections than the 1918 H1N1 pandemic [2].

The timing of infection with the 2 organisms in coinfection models affects outcomes. There seems to be biphasic response to the virus that alters innate responses to the secondary bacterial pathogen. Little to no enhancement of disease is seen if the bacterial infection precedes exposure to the virus or the organisms are encountered together [23]. Roughly 3–10 days after viral infection, a proinflammatory state characterized by granulocyte and monocyte influx into the lungs amplifies host responses to bacteria, resulting in poor outcomes [23, 25, 43]. Late after infection, when virus has cleared (>12 days), desensitization of pattern recognition receptors to stimuli reverses this effect, preventing beneficial inflammatory responses from contributing to bacterial clearance [40]. In both scenarios, function of the effector cells is impaired by influenza virus infection, so only the harmful effects of the inflammatory response are realized [33, 44–46]. In the staphylococcal superinfection model presented here, the broad, early, effector cell–mediated inflammatory response seems to be more important than functional alteration of bacterial killing according to specific cell types, since depletion of T cells, macrophages, or neutrophils had no effect on outcomes. This, coupled with the lack of a synergistic response when the 2 infections were separated by ≥14 days, and the decoupling of lung and blood titers from strain-dependent differences in outcomes, implies that inflammatory responses may be more important for secondary staphylococcal disease than for pneumococcal disease. In the context of the Louria classification scheme [13], S. aureus is likely to be a secondary invader primarily during concomitant viral-bacterial pneumonia, whereas pneumococcus is equally well suited as a late secondary pathogen following the clearance of the virus. We did not assess the function of natural killer cells as did Small et al in a similar model [46], but our results suggest that alteration of macrophage function alone through a natural killer cell–mediated mechanism is not sufficient to explain increased susceptibility to S. aureus.

Our data reveal that strain-dependent differences exist in the ability of staphylococci to cause pneumonia following influenza. Of note, the USA300 and USA400 strains that have recently emerged and now cause most serious clinical disease attributed to S. aureus are among those that are more pathogenic following viral infection. This likely explains the changed epidemiological character that has been observed during the past decade, as S. aureus coinfections with influenza have become more common [10, 11, 47]. An immediate concern for additional study is what virulence factors account for this characteristic. It has been suggested that expression of the leukotoxin PVL is either responsible for or a marker for the unique virulence characteristics of the USA300 and USA400 clones, including necrotizing pneumonia in humans [30, 31, 48]. It is interesting that, of the virulence factors surveyed for this study, only PVL is present in the strain that expressed high virulence following influenza, NRS-193, but is absent in the strains that did not, ATCC 27733 (Table 1) and UAMS-1 [49]. Since PVL seems to have few effects on virulence in both primary and secondary mouse pneumonia models [22, 50], other virulence factors that are common in these clones are likely responsible for the mouse phenotype. Nevertheless, the pathogenesis of fulminant S. aureus superinfection following influenza is likely to be mediated at least in part by viral and bacterial toxin expression and the resulting ineffectual yet damaging inflammatory response.

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References


