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Severe influenza and *S. aureus* pneumonia
For whom the bell tolls?

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Influenza virus is a small virus with a negative stranded segmented RNA genome that causes infections of the respiratory tract in many species, commonly known as "the flu".[1] The clinical spectrum of influenza infection ranges from a self-limited febrile respiratory illness to severe outcomes, including respiratory failure and death.[2] On average from 1976 to 2009 in the US alone, approximately 66 000 deaths annually were attributed to combined categories of influenza and pneumonia.[3] Several lines of evidence emphasize the central role of bacterial coinfection in severe and fatal cases.[4,5] The 2009 pandemic influenza A (H1N1) virus resulted in an estimated 284 000 deaths worldwide.[3] Bacterial coinfections complicated up to one-third of pandemic influenza cases managed in the intensive care units and more than 50% of fatal cases.[4,6,7] Patients at highest risk for severe complications of influenza included children under the age of 5 years, adults 65 years of age or older, children and adults of any age with underlying chronic medical conditions, and pregnant women.[3] In a large series of critically ill children with the 2009 pandemic influenza strain,[8] 33% had evidence of bacterial confection within 72 h of admission. *S. aureus* was the most common pathogen accounting for 39% of isolates from respiratory cultures. Among *S. aureus* isolates 58% were methicillin-resistant (MRSA).

The 2009 pandemic of the new influenza A strain H1N1 highlighted several public health concerns: (1) While vaccination against influenza still remains the most effective means of preventing bacterial co-infections, the ever-changing nature of the circulating influenza viruses pose a major challenge in generating protective vaccines every year; (2) The number of immunocompromised individuals is increasing due to our aging society and improved survival of patients with underlying medical conditions: these individuals may not develop protective immunity in response to influenza vaccine; (3) The efficacy of antiviral therapy for the treatment of influenza infection is dependent on susceptibility of circulating influenza strain to available antiviral medication; and (4) *S. aureus* colonizes the nares of up to 30% of adult population.[9] Factors implicated in the increased prevalence of *S. aureus* colonization include but are not limited to pneumococcal vaccination, ecosystem degradation due to effects of widespread antibiotic use on the nasopharyngeal and cutaneous microbiota or a combination of these factors.[10,11] Over the past 10 years, methicillin-resistant *S. aureus* (MRSA) has become a major cause of pneumonia in the US particularly associated with influenza.[7,12] Necrotizing pneumonia due to community-acquired MRSA carries a mortality of up to 30%.[13]

In response to these public health concerns, efforts have been intensified to understand the factors contributing to severe influenza and *S. aureus* coinfection and develop strategies for prevention and treatment. Relevant clinical models are essential in expanding our understanding of the pathogenesis of coinfection.[14] Mouse models of coinfections were developed to parallel the severe influenza and MRSA co-infections observed in humans.[15-18] The majority of published studies have used high inocula with highly pathogenic mouse-adapted influenza strains with survival being a central endpoint. These models confirmed synergistic infection for influenza and *S. aureus* and contributed to our understanding of the pathogenesis of severe coinfection at the molecular level. Mice however share limited similarities with humans in terms of clinical presentation and course of monoinfection or dual infection with influenza and *S. aureus*.[14]

Nonhuman primates (NHP) have proven to be valuable models in studies of pathogenesis, prophylaxis, and therapy of seasonal and emerging influenza viruses.[19] Like humans, NHP infected with influenza virus exhibit fever, malaise, nasal discharge, and nonproductive cough; virus replication can be detected in the nasal passages and respiratory tract, and readily seroconvert after experimental inoculation with seasonal influenza virus.[20] Studies in macaques were instrumental in identifying the viral and immunologic basis for the severe disease caused by the 1918 virus pandemic.[21]

The work of Kobayashi et al.[22] in this issue represent a significant advance in the study of seasonal influenza A virus and *S. aureus* coinfection. Their study is the first to describe the natural history of non-severe coinfection in macaques. Starting from an established model of MRSA pneumonia in macaques,[23] the authors designed a coinfection model to parallel the natural history of typical influenza in humans. Timing of *S. aureus* inoculation relative to influenza infection as well as virologic,

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radiographic, and histologic assessments were based on the natural history of mild influenza and MRSA coinfection in humans. The authors tested the hypothesis that antecedent influenza A infection increases the severity of MRSA pneumonia. Their collective data indicate that antecedent mild influenza A H3N2 infection did not predispose the animals to subsequent severe infection with the prevalent community-associated MRSA clone USA300. Importantly, animals coinfected with the USA300 wild type and the isogenic strains lacking the encoding genes for the toxin Panton–Valentine leukocidin (PVL) had similar clinical course in agreement with their previous results of monoinfection with *S. aureus* in macaques.[23]

While the findings of Kobayashi et al.[22] diverge from majority of published studies of coinfection in mouse models,[15,16] they are not in contradiction with a large body of clinical evidence from humans.[3] It is estimated that bacterial coinfection complicates only a small fraction (approximately 0.5%) of all influenza cases in healthy young individuals and at least 2.5% of cases in older individuals and those with predisposing conditions.[24] Given the extent of the H1N1 pandemic[25-27] and current prevalence of MRSA in the community it is fair to assume that the majority of patients with influenza A and MRSA colonization did not develop severe coinfection. While *S. aureus* was the most frequent co-pathogen in severe cases of influenza, a number of co-existing conditions have been identified as risk factors for severe infection.[28]

Several factors may impact the broad applicability of the findings by Kobayashi et al in humans with the same or different influenza A strains: (1) Strains of influenza A are likely to vary in their capacity to cause disease in NHP; (2) Despite the close genetic similarities between humans and NHP there may be subtle interspecies differences in response to molecular products of *S. aureus*[29]; (3) The microbial community colonizing the human body is a complex ecosystem where commensals and pathogens co-exist in a dynamic state.[30] The outcome of host–pathogen interactions is likely a composite of the microbial ecology and the host immune response to colonization and infection. The status of the immune system at any given time is influenced by host genetics, age, and additional factors such as endogenous or exogenous immunosuppression.[31] Recent studies on bacterial–bacterial, viral–bacterial, and viral–viral associations in healthy children hint on the complexity and potential dynamics of microbial communities in the upper respiratory tract of children.[32]

The work of Kobayashi et al.[22] lays the foundation for further research to enhance our understanding of influenza and *S. aureus* pneumonia in humans. Such efforts must take advantage of the recent developments in functional genomics, bioinformatics, and other emerging technologies. Understanding the underlying immunological processes and host–pathogen interactions will enhance our ability to predict for whom the bell tolls and focus our efforts to protect the most vulnerable individuals.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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