**ABSTRACT**

The composition of the respiratory track microbiome is a notable predictor of infection-related morbidities and mortalities among both adults and children. Species of *Corynebacterium,* which are largely present as commensals in the upper airway and other body sites, are associated with lower colonization rates of opportunistic bacterial pathogens such as *Streptococcus pneumoniae* and *Staphylococcus aureus.* In this study, *Corynebacterium*-mediated protective effects against *S. pneumoniae* and *S. aureus* were directly compared using in vivo and in vitro models. Pre-exposure to *Corynebacterium pseudodiphtheriticum* reduced the ability of *S. aureus* and *S. pneumoniae* to infect the lungs of mice, indicating a broadly protective effect. Adherence of both pathogens to human respiratory tract epithelial cells was significantly impaired following pre-exposure to C. *pseudodiphtheriticum* or *Corynebacterium accolens*, and this effect was dependent on live *Corynebacterium* colonizing the epithelial cells. However, *Corynebacterium* secreted factors had distinct effects on each pathogen. *Corynebacterium* lipase activity was bactericidal against *S. pneumoniae*, but not *S. aureus*. Instead, the hemolytic activity of pore-forming toxins produced by *S. aureus* was directly blocked by a novel *Corynebacterium* secreted factor with protease activity. Taken together, these results suggest diverse mechanisms by which *Corynebacterium* contribute to the protective effect of the airway microbiome against opportunistic bacterial pathogens.