

Although respiratory pathogens are a leading cause of death worldwide, we know very little about how invading bacterial pathogens directly overcome resident microbiota to colonize a host. Recently, we observed displacement of both culturable and unculturable bacteria from the upper respiratory tract upon murine infection with a common murine respiratory pathogen, *Bordetella bronchiseptica*. We examine the mechanistic basis for *B. bronchiseptica* displacement of other respiratory microbiota during infection. In parallel, we have demonstrated that resident microorganisms can prevent *B. pertussis* colonization and influence (apparent) host specificity, and provide rationale for manipulating microbiomes to create more-accurate animal models of infectious diseases. These results reveal complex intra-host competition between invading pathogen and resident microbiota and demonstrate novel effects of bacterial secretion systems and host immune functions in this in vivo competition. They also provide a striking example of displacement of chronic colonizers of the mammalian respiratory tract, potentially revealing novel pathways to disrupt the carrier state of a variety of common opportunistic respiratory pathogens.