Body: Smoking promotes enhanced colonization of the upper and the lower respiratory tract with potential pathogens, which increases the susceptibility to pulmonary infections. Here, we examined whether smoke exposure favors colonization of the upper-respiratory tract with bacterial pathogens such as Streptococcus pneumoniae and translocation of bacteria into the lung. To investigate this, mice were exposed to cigarette smoke in a long-term-smoke model for 8 months and afterwards colonized with S. pneumoniae in the upper-respiratory tract. Smoked mice showed higher colonization levels of the upper-respiratory tract compared to non-smoke controls and were more susceptible to bacterial translocation into the lung. Furthermore, smoke exposure suppressed innate immune functions of the upper-respiratory tract and the lung. Release of inflammatory mediators in the upper-respiratory tract and in the lung, such as KC and IL-1β, in response to bacterial colonization was reduced in smoked mice compared to non-smoked controls. Our results show that smoke impacts innate immunity of the airways rendering the host susceptible for bacterial colonization and infection. Colonization of the upper airways after Sp D39 colonization.