We reported previously that early-life exposure to particulate matter containing environmentally persistent free radicals (EPFRs) damages lung epithelium and suppresses immune responses to influenza virus (Flu) infection thereby enhancing Flu severity. Interleukin 22 (IL22) is important in resolving lung injury following Flu infection. In the current study, we determined the effects of EPFR exposure on pulmonary IL22 responses using our neonatal mouse model of Flu infection. Exposure to EPFRs resulted in an immediate increase in pulmonary IL22 expression; however, IL22 expression was not maintained and failed to increase with continued exposure to EPFRs or subsequent Flu infection of EPFR exposed mice. The microbiome plays a major role in maintaining epithelial integrity and directing immune responses. Exposure to EPFRs induced lung microbiota dysbiosis and altered the levels of microbial metabolite, indole. Treatment with recombinant IL22 or indole-3-carboxaldehyde prevented EPFR-associated lung injury and protected against mortality in Flu infected mice exposed to EPFRs. Together, these data suggest that insufficient levels of IL22 may be responsible for aberrant epithelial repair and immune responses, leading to increased Flu severity.