Rift Valley fever virus (RVFV) is a major human and animal pathogen associated with severe disease including hemorrhagic fever or encephalitis. RVFV is endemic to parts of Africa and the Arabian Peninsula, but there is significant concern regarding its introduction into non-endemic regions and the potentially devastating effect to livestock populations with concurrent infections of humans. To date, there is little detailed data directly comparing the host response to infection with RVFV and correlation with viral pathogenesis. We characterized clinical and systemic immune responses to infection with wild-type strain ZH501 or vaccine strain MP-12 in the C57BL/6 mouse. Animals infected with live-attenuated MP-12 survived productive viral infection with little evidence of clinical disease and minimal cytokine response in evaluated tissues. In contrast, ZH501 infection was lethal, caused depletion of lymphocytes and platelets and elicited a strong, systemic cytokine response which correlated with high virus titers and significant tissue pathology. Lymphopenia and platelet depletion were indicators of disease onset with indications of lymphocyte recovery correlating with increases in G-CSF production. RVFV is hepatotrophic and in these studies significant clinical and histological data supported these findings, however significant evidence of a pro-inflammatory response in the liver was not apparent. Rather, viral infection resulted in a chemokine response indicating infiltration of immunoreactive cells, such as neutrophils, which was supported by histological data. In brains of ZH501 infected mice, a significant chemokine and pro-inflammatory cytokine response was evident, but with little pathology indicating meningoencephalitis. These data suggest that RVFV pathogenesis in mice is associated with a loss of liver function due to liver necrosis and hepatitis. Funded by NIAID Fellowship: F31AI030162-02