

# The Kinetics of Type 1 Interferons During Influenza Virus Infection

Maggie Myers

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## Abstract

Influenza A virus (IAV) infections pose a considerable public health threat and are a leading cause of death. The host immune response works to limit virus growth and quickly resolve the infection. Type 1 interferons (IFN- $\alpha$ ,  $\beta$ ), in particular, aid viral control by inhibiting the infection of epithelial cells and by stimulating and regulating the activity of immune cells. To investigate the role of type 1 IFNs during IAV infection, we infected groups of mice with influenza A/Puerto Rico/8/34 (PR8) and measured their viral load, IFN concentration, and immune cell populations daily. The data indicated a two-phase decline in virus titers and a double peak in IFN. Because published kinetic models of IFN dynamics fail to reproduce these data, we developed two new models: a two-source immune model and a refractory-state reversion model. In both models, the first wave of IFN is produced from infected epithelial cells. The second wave of IFN in the two-source model is from an immunological source, such as macrophages or dendritic cells. In contrast, the refractory reversion model suggests that the second wave of IFN is produced by epithelial cells that have exited the IFN-induced antiviral state and became infected. Although each model is biologically reasonable, the two-source immune model reproduced more features of our data. The models also provide support for enhanced activity of CD8<sup>+</sup> T cells in the presence of IFN. Taken together, these results provide insight into the regulation of host immune responses during IAV infection.