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Investigating the mechanisms of influenza viral interference using within-host models based on a ferret re-exposure experiment

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Viral interference, whereby infection with one type of virus may temporarily "protect" the host from subsequent infection with another virus has been described for a number of influenza strains and in a number of different host species. In particular, experiments performed in ferrets with influenza A(H1N1)pdm09, A(H3N2) and B have demonstrated strong levels of interference dependent upon the particular virus pair, order of infection and precise timing of re-exposure. Mathematical modelling, which aims to capture the viral time course of the re-exposure behaviour based on plausible immunological mechanisms, is a particularly useful tool to study viral interference, opening up a new approach to advancing our understanding of viral dynamics and the host immune response.

In this talk, I will first briefly describe the ferret re-exposure experiments performed by our collaborators. In the experiments, naïve ferrets were inoculated with one virus (i.e. primary infection) and subsequently exposed to another (to induce the secondary infection) after a certain time interval (1 – 14 days). Viral interference was observed when the inter-exposure interval was less than a week. Furthermore, viruses differed in their ability to induce a protective immune response against subsequent exposure.

I will then introduce the model-based approaches that we have used to investigate immune-mediated viral interference. We begin with a qualitative approach by introducing and analysing a family of within-host models of re-exposure viral kinetics which differ in their hypothesised mechanisms of action for the non-specific innate immune response. We assumed that different viruses stimulate the innate immune response to different degrees and demonstrate the models' ability to qualitatively reproduce the observed viral shedding profile in the secondary infection for short inter-exposure intervals (less than 5 days). We then extend the models by incorporating cross-reactive adaptive immunity (in particular CD8+ T cells), which provides an explanation of the viral shedding profile of the secondary infection for longer inter-exposure intervals (5-14 days).

Finally, I will briefly describe our most recent efforts to calibrate the proposed models to the re-exposure data in a Bayesian framework, providing quantitative insight. Through this approach, we have shown that models fitted to the re-exposure data are able to predict the outcome of viral interference more accurately than models fitted only to the data from a single infection.

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