Viral Coinfection Interaction through Interferon

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Background Information

Severity of Coinfections

- Respiratory viral infections cause many deaths worldwide every year.
- In the past decade, researchers have investigated the possibility that co-circulating respiratory viruses could simultaneously infect and be detected in a single host, finding that respiratory coinfections are not uncommon.
- Sometimes simultaneous viral infections exhibit viral interference, when one virus blocks growth of another. In other cases, both viruses can effectively replicate without interference in the host.
- While some studies suggest that viral coinfections are similar in severity with single virus infections others show that coinfections cause more significant and chronic problems than single infections.
- There has been evidence that respiratory coinfections increase disease severity and create a longer hospital stay for patients, especially for those who have pulmonary diseases such as asthma and bronchiolitis or who are immunocompromised

Role of Immune Response

- The impact of the innate immune response on viral coinfection has not been determined, although it is hypothesized to be a mechanism of interaction between viruses.
- For example, the innate immune response can vary when two viruses infect the host at the same time causing a coinfection that results in higher viral loads versus when a primary virus infects the cell before a secondary virus.

Mathematical modeling

- Mathematical modeling can help us develop an understanding of coinfections.
- By creating and utilizing a mathematical model that examines the effects of interferons on two viruses coinfected, we can obtain a stronger understanding of the innate immune system's role and response to coinfection. We will also be able to observe under what conditions coinfection duration is the shortest and in which both viruses are effectively suppressed.
- This can be used to develop treatments and drugs that aid the immune system and work along with the interferons produced by the innate immune system.

Objective

We will use a mathematical model to examine the interaction via interferons between respiratory syncytial virus (RSV) and influenza A virus (IAV) during coinfections. This model will measure viral titer, duration of the viral infection, and interferon production allowing us to understand how interferon production of one virus helps or hinders the secondary virus.

Methodology

We extended a mathematical model of viral coinfections that allows viruses to interact through competition for target cells.

$$
\begin{aligned}
\text{Target cells}: \quad & \frac{dT}{dt} = -\beta_1 T V_1 - \beta_2 T V_2 \\
\text{Eclipse cells}: \quad & \frac{dE_1}{dt} = \beta_1 T V_1 - k_1 E_1 \qquad \frac{dE_2}{dt} = \beta_2 T V_2 - k_2 E_2 \\
\text{Infected cells}: \quad & \frac{dI_1}{dt} = k_1 E_1 - \delta_1 I_1 \qquad \frac{dI_2}{dt} = k_2 E_2 - \delta_2 I_2 \\
\text{Virus}: \quad & \frac{dV_1}{dt} = p_1 I_1 - c_1 V_1 \qquad \frac{dV_2}{dt} = p_2 I_2 - c_2 V_2.
\end{aligned}
$$

We assume that it either affects the production rates p1(F) and p2(F) or infection rates **β**1(F) and **β**2(F) of the viruses. The functions of **β**(F) and p(F) are represented in the functions below:

$$
\begin{aligned}
\beta(F) &= \frac{\beta}{1+\epsilon F} \\
p(F) &= \frac{p}{1+\eta F},
\end{aligned}
$$

For simulations, we used parameter values describing influenza (virus 1) and respiratory syncytial virus (virus 2), whose parameters were determined from fits to data. The parameter values are given in Table below.

Table 1: Definition of model variables and parameters.

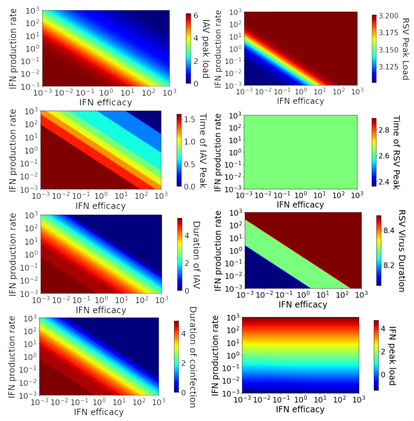
Variable	Definition	Units
T	number of uninfected target cells	relative cell counts
E	number of cells in eclipse phase	relative cell counts
I	number of infectious cells	relative cell counts
V	infectious viral titer	PFU/mL

Parameter	Definition	IAV	RSV	Units
T_0	initial target cells	1.0	1.0	relative cell counts
V_0	initial viral titer	1.0	1.0	PFU/mL
β	viral infection rate	82.73×10^{-7}	0.03	$(\text{PFU/mL})^{-1}\cdot\text{d}^{-1}$
k	transition rate from E to I	4.20	1.27	d
δ	death rate of infectious cells	4.20	1.27	d
p	viral production rate	0.12×10^{9}	76.45×10^{2}	$(\text{PFU/mL})\cdot\text{d}^{-1}$
c	viral clearance rate	4.03	1.27	d^{-1}

Simulations were performed in Python using the scipy odeint function to integrate the differential equations. We set the initial values of both RSV and IAV (E1, E2, I1, I2, V1, V2, F) to 0, except for target cells, which was set to 1.0.

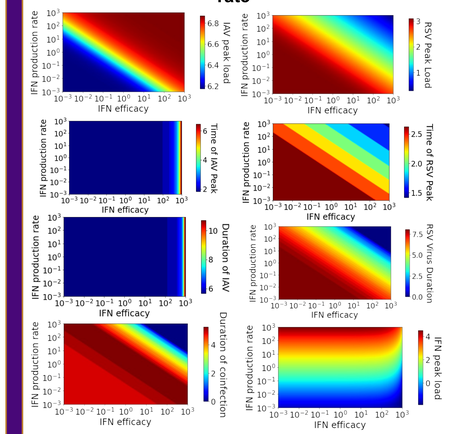
Interferon affecting Production Rate

RSV Producing Interferon affecting IAV Infection rate



- The interferon productions suppresses IAV causing IAV Peak load and Duration of IAV to decrease and RSV Peak Load and Virus Duration to increase.
- While the time of IAV peak decreases throughout the graph, the time of RSV peak remains constant.
- However, the duration of coinfection of both viruses decrease with RSV interferon production increasing.

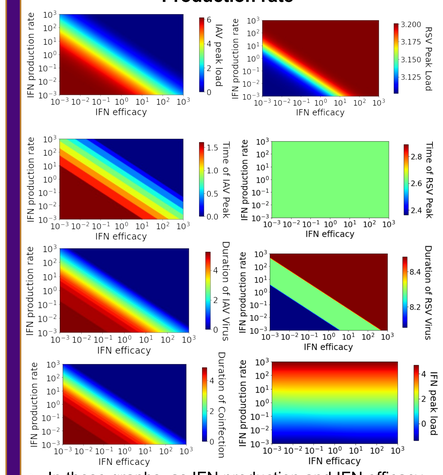
IAV Producing Interferon affecting RSV infection rate



- IFN's effects on RSV causing it to suppress, reduces competition and allows IAV duration to increase.
- IAV peak load, however, increase throughout the graph equally dependent on both interferon production and RSV production rates.
- Coinfection duration decreases as interferon production and RSV production increases.

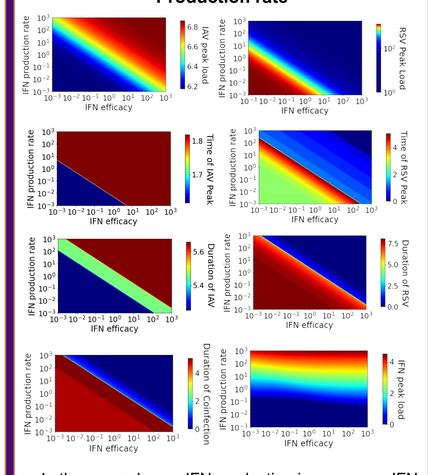
Interferon affecting Infection Rate

RSV Producing Interferon affecting IAV Production rate



- In these graphs, as IFN production and IFN efficacy rise, IAV production rate is suppressed causing IAV Peak load and Duration of IAV decrease.
- The decrease in IAV production leads to a higher peak RSV viral load and longer viral duration.
- Coinfection decreases throughout the graph as IAV production rate and interferon production rate rises however it seems to be more dependent on the IAV production rate changes.

IAV Producing Interferon affecting RSV Production rate



- In these graphs, as IFN production increases or IFN efficacy RSV infection rate is suppressed, causing a lower and earlier peak in RSV.
- IAV peak viral load increases with increasing IFN production or efficacy.
- Coinfection duration follows the duration of the RSV infection since there is no detectable coinfection when RSV does not rise above the threshold of detection.

Conclusions

These results suggest a variety of aspects about coinfection and their durations.

- Coinfection appears to be most severe when IAV produces interferon that affects RSV infection rate.
- Coinfection appears to be the least severe when RSV produces interferon that affects IAV production rate.
- The coinfection severity when RSV produces interferon that affects IAV infection or production rate is almost the same.
- IAV producing interferon that affects RSV production rate has a greater effect on RSV than when RSV is producing interferon that is affecting IAV production rate and affects IAV. The opposite pattern is seen in interferon production rate affecting infection rate where RSV interferon production has a greater effect on IAV than IAV interferon production on RSV.

Investigation of the role of Adaptive Immune Response and Superinfection

- One limitation of this model is that it only focuses on the innate immune system and does not consider the adaptive immune system. Through measuring the interferon interaction via coinfection of the two viruses, the model focuses on how the innate immune system impacts and influences the severity of coinfection. However, the adaptive immune system also plays a key role in coinfections.
- Another limitation that this model presents is that it does not measure superinfection. Superinfection is simultaneous infection of two different viruses in the same cell.