The effect of cell-to-cell transmission on viral coinfections

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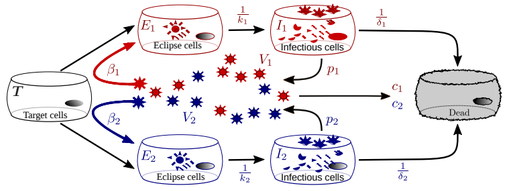
Background

- Studies have shown that anywhere from 30%-70% of patients in hospitals with influenza-like illness are actually infected with more than one respiratory virus.
- It's not clear whether coinfections are clinically more severe than single infections.
- Mathematical models can help us understand when coinfections might be more severe than single infections.
- Mathematical models studying coinfection have assumed that virus infects cells by being released from one cell and moving through extracellular space to infect another cell.
- Some viruses can tunnel directly from one cell to another, which could alter how they interact with a coinfecting virus.
- This project will look at how coinfecting viruses compete if they transmit through cell-to-cell transmission.

Dual transmission model



We extend a model of coinfection to include cell-to-cell transmission,

$$\begin{aligned}
\frac{dT}{dt} &= -\beta_1 V_1 T - \beta_2 V_2 T + k_1 I_1 + k_2 I_2 \\
\frac{dI_1}{dt} &= \beta_1 V_1 T - k_1 I_1 - \beta_2 V_2 I_1 \\
\frac{dI_2}{dt} &= \beta_2 V_2 T - k_2 I_2 - \beta_1 V_1 I_2 \\
\frac{dI}{dt} &= \beta_2 V_2 I_1 + \beta_1 V_1 I_2 - \delta I \\
\frac{dV_1}{dt} &= p_1 I - c_1 V_1 \\
\frac{dV_2}{dt} &= p_2 I - c_2 V_2
\end{aligned}$$

To incorporate cell-to-cell transmission, we allow infected cells I_1 and I_2 to infect the susceptible uninfected target cells, T, at rates γ_1 and γ_2. Free virus (V_1 and V_2) can also infect target cells at rates β_1 and β_2. The newly infected cells enter an eclipse phase, E_1 or E_2, where infected cells take some time to produce viral components. After an average time $\frac{1}{k_1}$ or $\frac{1}{k_2}$, the cells produce viruses at rates p_1 and p_2. The lengths of time over which infectious cells produce viruses are $\frac{1}{\delta_1}$ and $\frac{1}{\delta_2}$ after which the infectious cells die. Virus is cleared at rates c_1 or c_2.

Model parameters

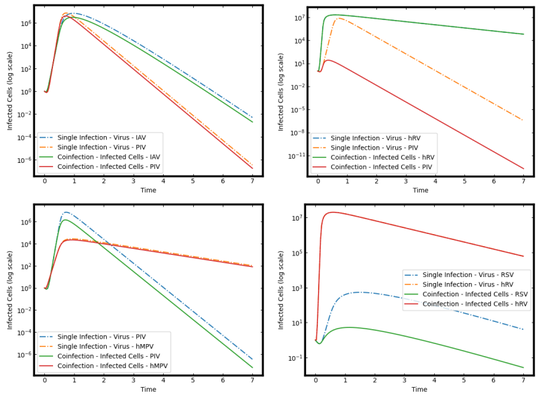
We simulated coinfections of five common respiratory viruses, influenza (IAV), respiratory syncytial virus (RSV), human rhinovirus (hRV), parainfluenza virus (PIV), and human metapneumovirus (hMPV). Parameters for simulating these viruses were found by fitting to single virus infections (Pinky and Dobrovolny, Plos One (2016)).

Table 1: Model parameter values used in simulations.

Virus	β [V^{-1} d^{-1}]	γ [I^{-1} d^{-1}]	k [d^{-1}]	δ [d^{-1}]	p [V d^{-1}]	c [d^{-1}]
IAV	8.265×10^{-6}	246	4.20	1.2×10^{8}	4.20	4.03
RSV	0.0308	185	1.27	7.64×10^{3}	1.27	1.27
hRV	2.06×10^{-6}	18136	0.937	8.1×10^{9}	50.5	0.92
PIV	4.82×10^{-7}	180	13.2	2.12×10^{8}	13.2	0.567
hMPV	2.19×10^{-3}	542	0.957	6.49×10^{6}	29.4	26.2

Coinfection with cell-to-cell transmission

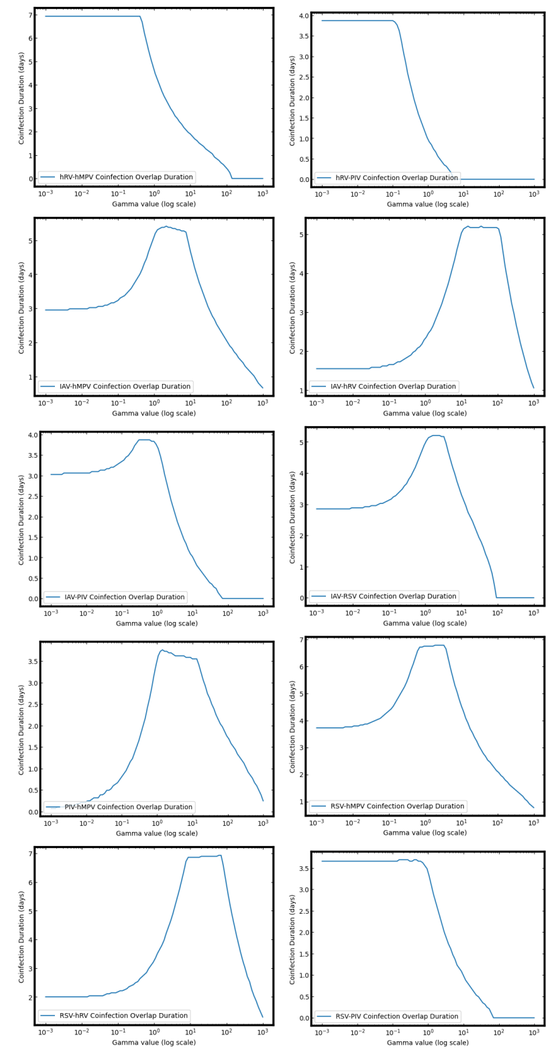
Coinfection simulations were conducted through the combination of two viruses that share the common target cell population.



The trajectories were calculated for all virus combinations on graphs that contained a single infection line (for each virus pair) and a coinfection line.

Coinfection duration

The coinfection duration is defined as the time during which both viruses are above a threshold of 1 [V]. We use coinfection duration as a measure of the severity of the infection.



Conclusions

- Viral production p increases the viral load in coinfection, while the clearance rate c, infected cell death δ, and antibody production l significantly reduced infection duration and overlap.
- Coinfection outcomes depend on the transmission pathway used, with the cell-to-cell transmission strength γ producing three distinct qualitative patterns.
- Coexistence between coinfecting viruses is primarily determined by competition for a limited target cell pool, where small differences between viruses can lead to suppression or dominance.

Future directions

- There needs to be more biological factors included to create a more accurate simulation of virus growth. An example of this could be interferon production, which would allow for an immune response.
- To determine when the overlap between the two viruses is too strong to the extent that comment antiviral medications will be ineffective.
- We can use real target cell counts to accurately simulate how many cells are susceptible to infection.

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When patients are hospitalized with respiratory illness, they are often infected with more than one virus at the same time. It is unclear whether these "coinfections" make patients sicker than a single infection would. We used mathematical models to study how two viruses compete inside the body. Importantly, we included a mechanism where viruses can spread by passing directly between cells, rather than traveling through bodily fluids. We simulated five common respiratory viruses and found that this direct cell-to-cell transmission significantly changes how viruses interact.