# Исследование влияния иммунного ответа на распространение респираторной вирусной инфекции

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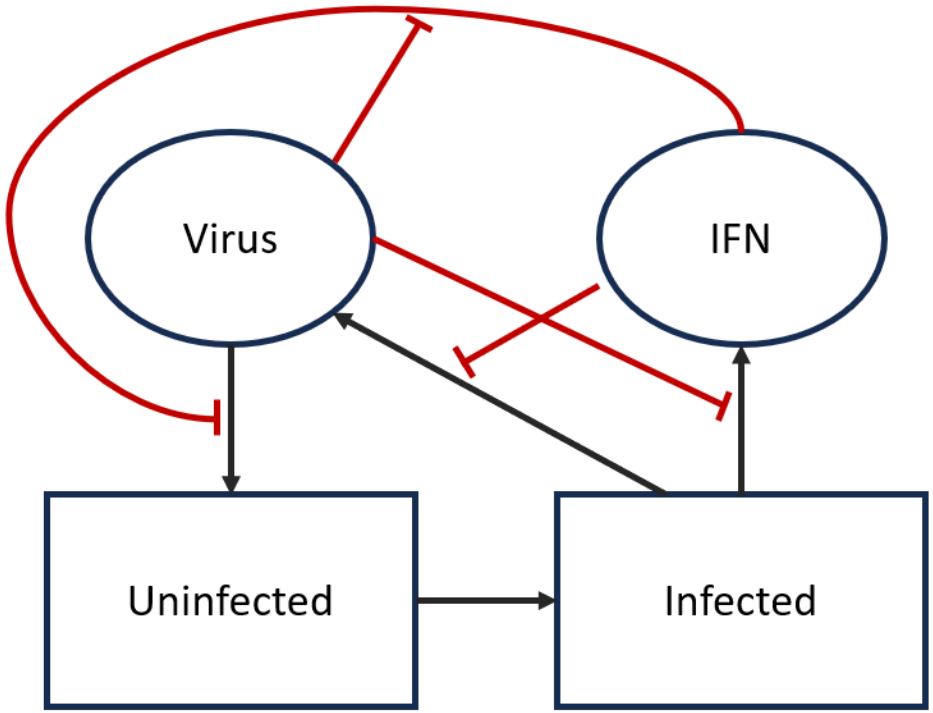
# Influence of the interferon (IFN) on infected and uninfected cells

- Virus enters the target cell and enfolds its genetic material. The cell become *infected*
- Infected cell starts to produce viral particles and IFNs
- IFNs has diverse effects though the production of different proteins by activated IFN-stimulated genes (ISG), in particular:
  - in infected cells: IFN reduces virus replication
  - in uninfected cells: "antiviral state"
- Viruses develop different mechanisms to overcome the IFN influence, in particular:
  - they reduce IFN production rate
  - they reduce IFN products influence on infected and uninfected cells

J.M. Shim et. al. Viruses. 2017 Aug 12;9(8):223. doi: 10.3390/v9080223.
M.G. Katze, Yu. He, M. Jr. Gale Nat Rev Immunol. 2002 Sep;2(9):675-87. doi: 10.1038/nri888.

# Scheme of virus–IFN interaction




Main characterisics:

- Virus replication number (if there an infection)
- Total viral load (virus infectivity)
- Speed of the wave propagation (virus virulence, i.e. disease severity)

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# Production of IFN by infected cells only

Consider the following model [1]:

$$\frac{\partial U}{\partial t} = -aUV, \tag{1}$$

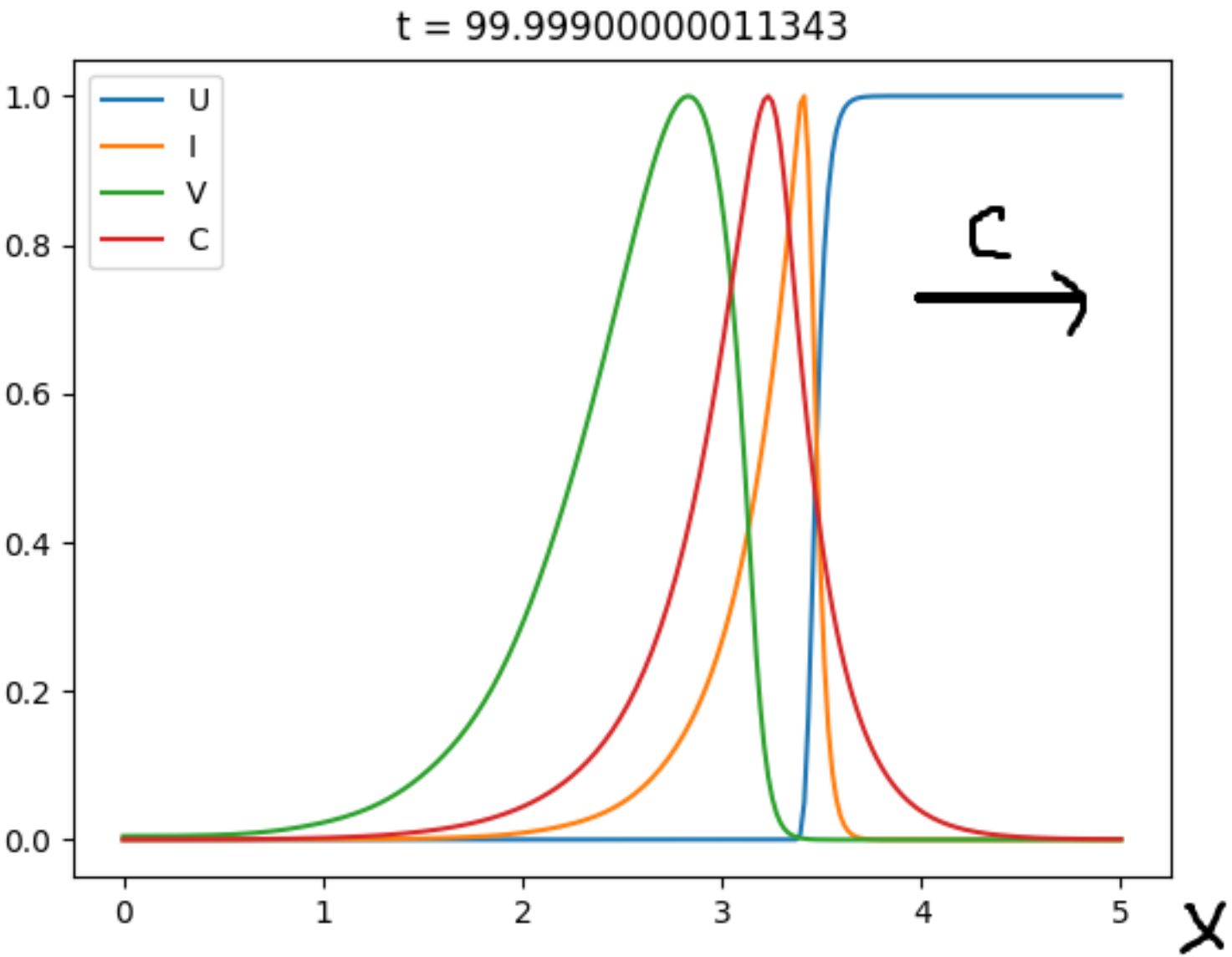
$$\frac{\partial I}{\partial t} = aUV - \beta I, \tag{2}$$

$$\frac{\partial V}{\partial t} = D_1 \frac{\partial^2 V}{\partial x^2} + \frac{b_1}{1 + k_1 C} I(t - \tau_1) - \sigma_1 V, \tag{3}$$

$$\frac{\partial C}{\partial t} = D_2 \frac{\partial^2 C}{\partial x^2} + \frac{b_2}{1 + k_2 V} I(t - \tau_2) - \sigma_2 C. \tag{4}$$

Here $U(x,t)$ is the concentration of uninfected cells, $I(x,t)$ is the concentration of infected cells, $V(x,t)$ is the virus concentration in the extracellular space, and $C(x,t)$ is the IFN concentration.

# Example of simulations



# Basic replication number

In system (1)–(4) without diffusion:

- stationary points are $(U_0, 0, 0, 0)$
- for initial condition $U = U_0$, stationary point $(U_0, 0, 0, 0)$ is stable when

$$R_v = \frac{ab_1 U_0}{\beta\sigma_1} < 1, \tag{5}$$

  and it is unstable otherwise.
- $R_v$ is called *virus replication number*. It shows whether the infection progresses:
  - when $R_v < 1$, there is no infection,
  - when $R_v > 1$, there is an infection (can be wave solution in the case with diffusion).
- $R_v$ is independent from the parameters of IFN dynamics (it is the same as in the model without IFN from [2])

# Estimate of the wave speed

Consider system (1)–(4) with diffusion.
For this system the following proposition is proved [1]:

*Proposition 1. If there exists the travelling wave solution of system (1)–(4), then the minimal wave speed $c_0$ satisfies the inequality $c_0 \geq c$, where $c$ is given by*

$$c = \min_{\mu > \mu_0} \sqrt{\frac{D_1 \mu^2 (\mu + \beta)}{(\mu + \sigma_1)(\mu + \beta) - a u_0 b_1 e^{-\mu \tau_1}}} \tag{6}$$

- Under the travelling wave solution here and below we understand the continuous bounded solution of the form $\bar{u} = \bar{u}(x - ct)$, considered on the whole real axis with boundary conditions $w(\pm\infty) = 0$, $v(\pm\infty) = 0$, $u(+\infty) = u_0$, $u(-\infty) = u_f$, $0 < u_f < u_0$.
- The proposition is proved by the linearization method [2].
- The formula (6) does not depend on the parameters of the IFN dynamics, thus the production of the IFN by the infected cells does not influence the wave speed (i.e., the disease severity).

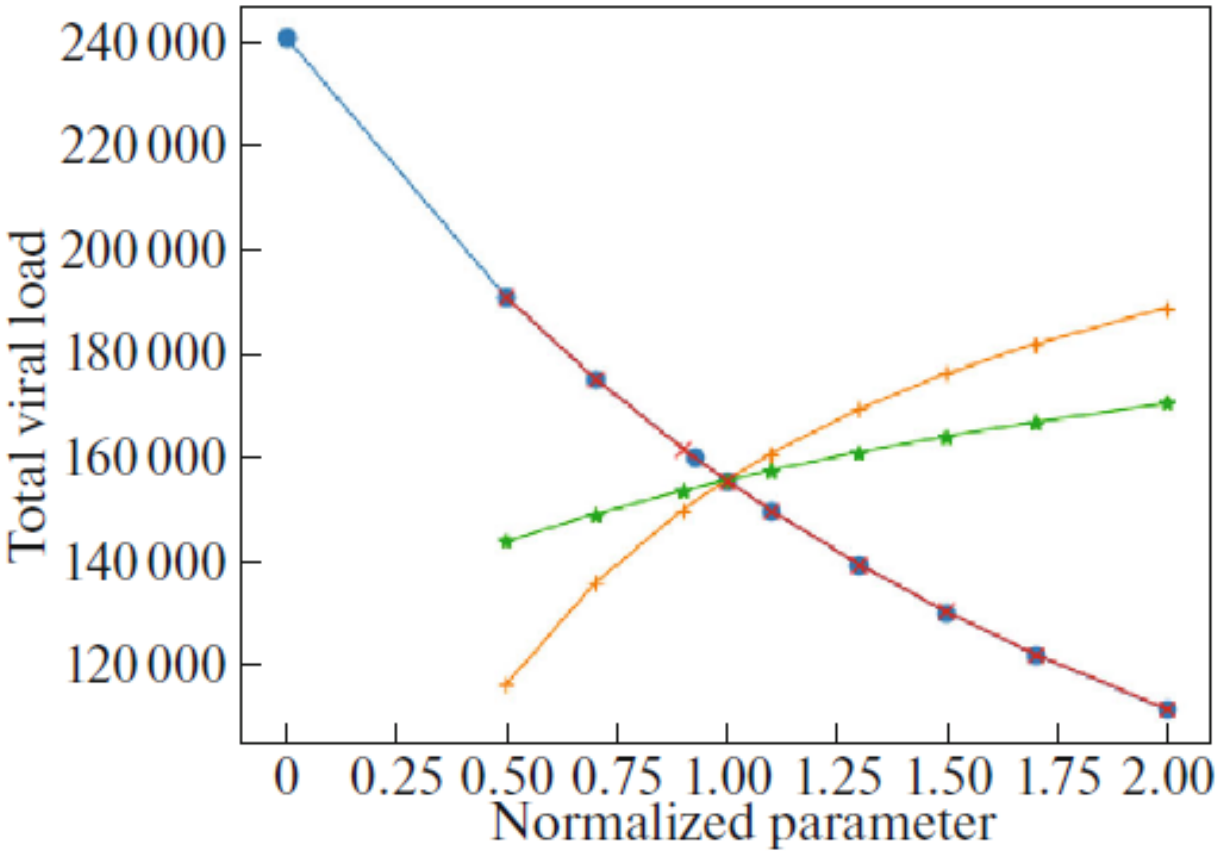
# Wave speed

Let $F(\mu)$ be

$$F(\mu) = \frac{D_1\mu^2(\mu+\beta)}{(\mu+\sigma_1)(\mu+\beta) - au_0 b_1 e^{-\mu\tau_1}}. \tag{7}$$

The denominator has the positive root $\mu_0$ if and only if $R_v > 1$.

# Viral load




- blue — $b_2$ (IFN production rate)
- red — $k_1$ (IFN down regulation of virus production)
- yellow — $\sigma_2$ (IFN degradation rate)
- green — $k_2$ (virus down regulation of IFN production)

# IFN influence on uninfected cells

In uninfected cells, IFN leads to the developing of the "antiviral state" which results in reduced penetration of the virus into the uninfected cells. The model with this effect is the following [3]:

$$\frac{\partial U}{\partial t} = -\frac{a}{1 + k_3 C} UV, \tag{8}$$

$$\frac{\partial I}{\partial t} = \frac{a}{1 + k_3 C} UV - \beta I, \tag{9}$$

$$\frac{\partial V}{\partial t} = D_1 \frac{\partial^2 V}{\partial x^2} + \frac{b_1}{1 + k_1 C} I(t - \tau_1) - \sigma_1 V, \tag{10}$$

$$\frac{\partial C}{\partial t} = D_2 \frac{\partial^2 C}{\partial x^2} + \frac{b_2}{1 + k_2 V} I(t - \tau_2) - \sigma_2 C. \tag{11}$$

It can be shown, that these changes in the model do not influence the virus replication number, nor the estimate for the wave speed. The same is true also for the rate of replication equals $\frac{a}{a + \frac{k_3}{1+k_4} C} = \frac{a + k_5 V}{1 + k_3 C + k_4 V}$ (with respect to virus counteraction to the IFN).

# Production of IFN by infected and immune cells

IFN can be produced not only by infected cells, but also by immune cells. In this case, we can assume that the distribution of the IFN in the infection region does not depend on space variable:

$$\frac{\partial U}{\partial t} = -aUV, \tag{12}$$

$$\frac{\partial I}{\partial t} = aUV - \beta I, \tag{13}$$

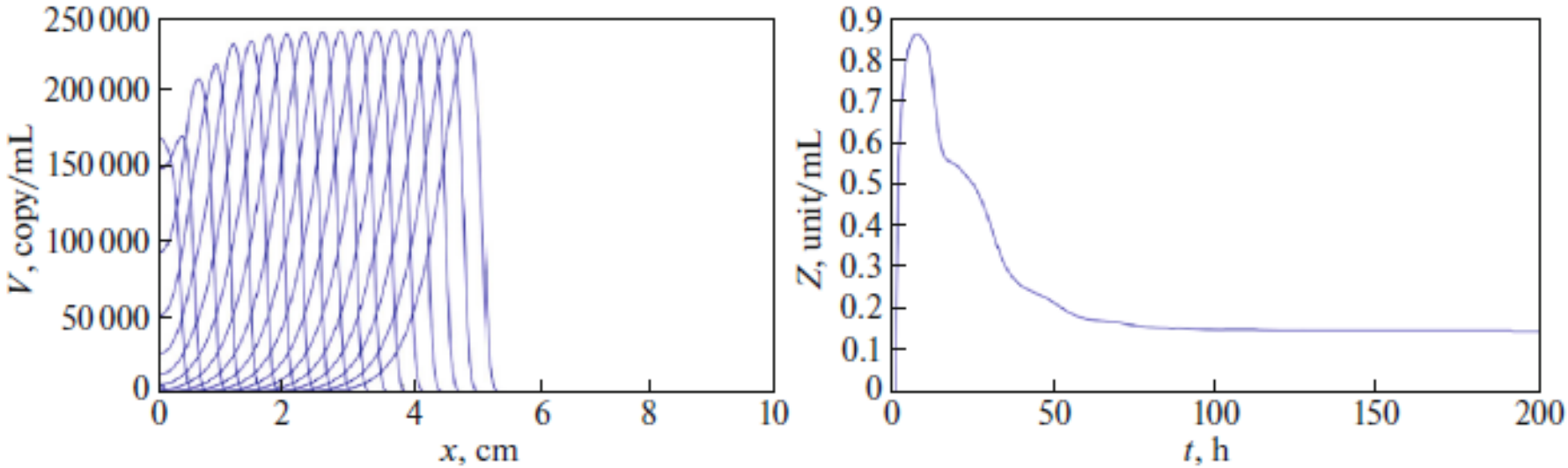
$$\frac{\partial V}{\partial t} = D_1 \frac{\partial^2 V}{\partial x^2} + \frac{b_1}{1 + k_1 Z} I(t - \tau_1) - \sigma_1 V, \tag{14}$$

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = b_2 J(I) e^{-k_2 J(V)} - \sigma_2 Z, \tag{15}$$

where

$$J(I) = \int_{-\infty}^{+\infty} I(x,t)\,\mathrm{d}x, \; J(V) = \int_{-\infty}^{+\infty} V(x,t)\,\mathrm{d}x. \tag{16}$$

# Example of simulations




Concentrations $U(x,t)$, $V(x,t)$, and $I(x,t)$ have travelling wave profile, and the concentration $Z(t)$ tends to some constant value.

# Basic replication number

Consider system (12)–(15) without diffusion, and assume that $J(I) = LI$, $J(V) = LV$, where $L$ is a length of the considered space interval. As before, the following statements are true for this system:

- The stationary points are $(U_0, 0, 0, 0)$
- For initial condition $U = U_0$ stationary point $(U_0, 0, 0, 0)$ is stable when condition (5) is satisfied, and unstable otherwise.

# Travelling wave solution

In system (12)–(16), we move to the wave variable $\xi = x - ct$, and obtain the following system:

$$cu' - auv = 0, \tag{17}$$

$$cw' + auv - \beta w = 0, \tag{18}$$

$$D_1 v'' + cv' + \frac{b_1}{1 + k_1 z} w(\xi + c\tau_1) - \sigma_1 v = 0, \tag{19}$$

$$b_1 J(w) e^{-k_2 J(v)} - \sigma_2 z = 0. \tag{20}$$

Assume that we know constant $c$, then from this system we can obtain the algebraic equation for the total viral load $J(v) = \int_{-\infty}^{+\infty} v(\xi)\,\mathrm{d}\xi$, which corresponds to the virus infectivity.

# Total viral load

Doing some calculus on equations of the system (17)–(20) and integrating on the whole real axis with the following boundary conditions

$$u(+\infty) = u_0,\ u(-\infty) = u_f,\ v(\pm\infty) = 0,\ w(\pm\infty) = 0, \tag{21}$$

we can obtain the following algebraic equation:

$$J(v) = A\left(1 - e^{-\frac{a}{c}J(v)}\right)\left(b_1 - PJ(v)e^{-k_2 J(v)}\right), \tag{22}$$

where $A = \frac{cu_0}{\beta\sigma_1}$ , $P = \frac{k_1 b_2 \sigma_1}{\sigma_2}$, or rewriting it for $\mu = u_f/u_0$, $0 < \mu < 1$:

$$\ln\mu = R_v(\mu - 1)\left(1 + B\mu^\gamma \ln\mu\right), \tag{23}$$

$$B = \frac{ck_1 b_2 \sigma_1}{ab_1\sigma_2},\ \gamma = \frac{ck_2}{a}$$

which has biologically justified solutions $\mu \in (0, 1)$ only if $R_v > 1$.

# Total viral load and wave speed

*Proposition 2. If there exists a travelling wave solution of system (12)–(16), then the wave speed and the total viral load satisfy the equality:*

$$J(v) = A\left(1 - e^{-\frac{a}{c}J(v)}\right)\left(b_1 - PJ(v)e^{-k_2 J(v)}\right),$$

*where* $A = \frac{cu_0}{\beta\sigma_1}$ , $P = \frac{k_1 b_2 \sigma_1}{\sigma_2}$.
*The minimal wave speed* $c_0$ *satisfies the inequality* $c_0 \geq c$, *where* $c$ *is given by*

$$c^2 = \min_{\mu>\mu_0} \frac{D\mu^2(\mu+\beta)}{(\mu+\beta)(\mu+\sigma_1) - ab(J)u_0 e^{-\tau\mu}}, \tag{24}$$

*where*

$$b(J) = b_1 - \alpha J(v)e^{-k_2 J(v)},\ \alpha = \frac{k_1 b_2 \sigma_1}{\sigma_2}. \tag{25}$$

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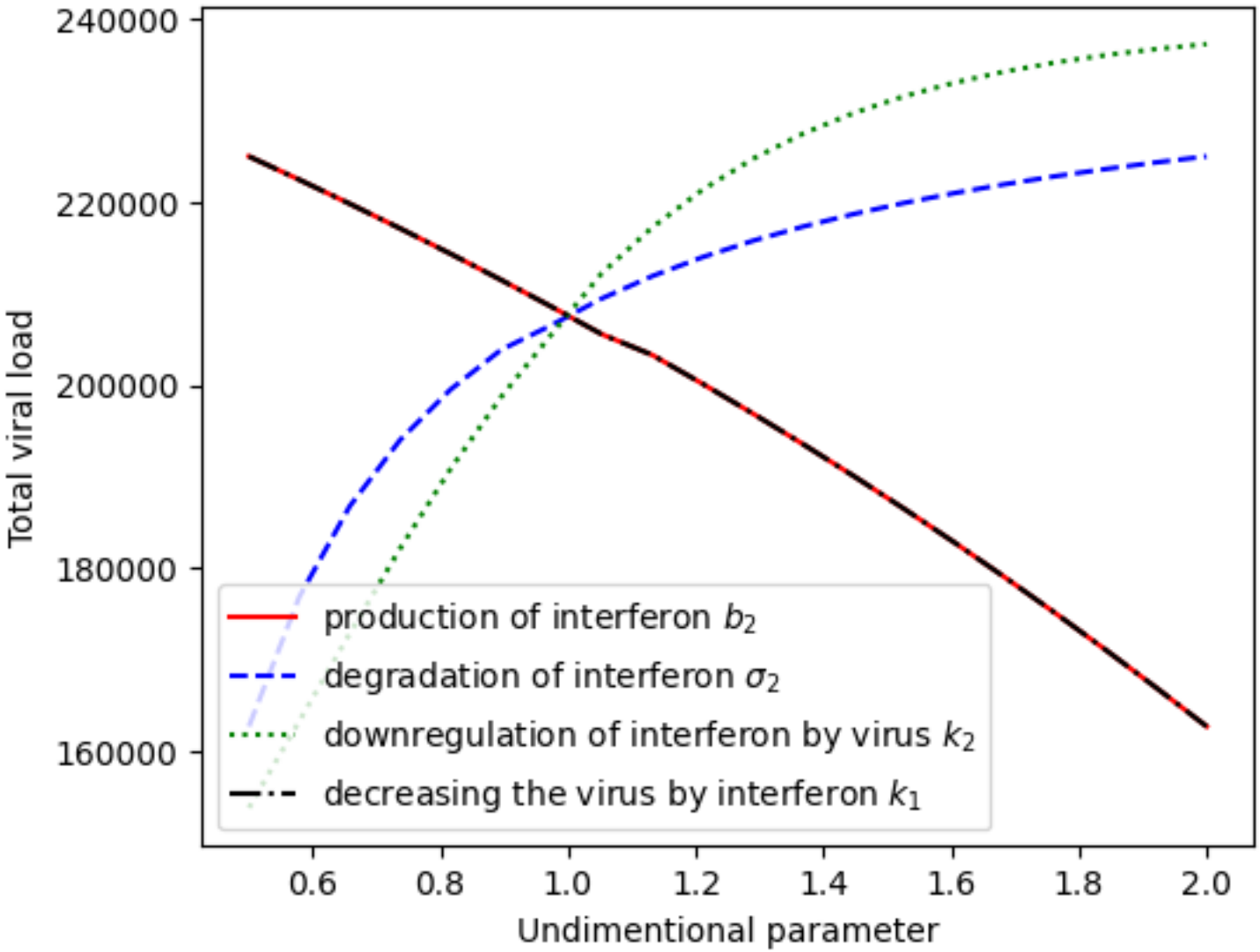
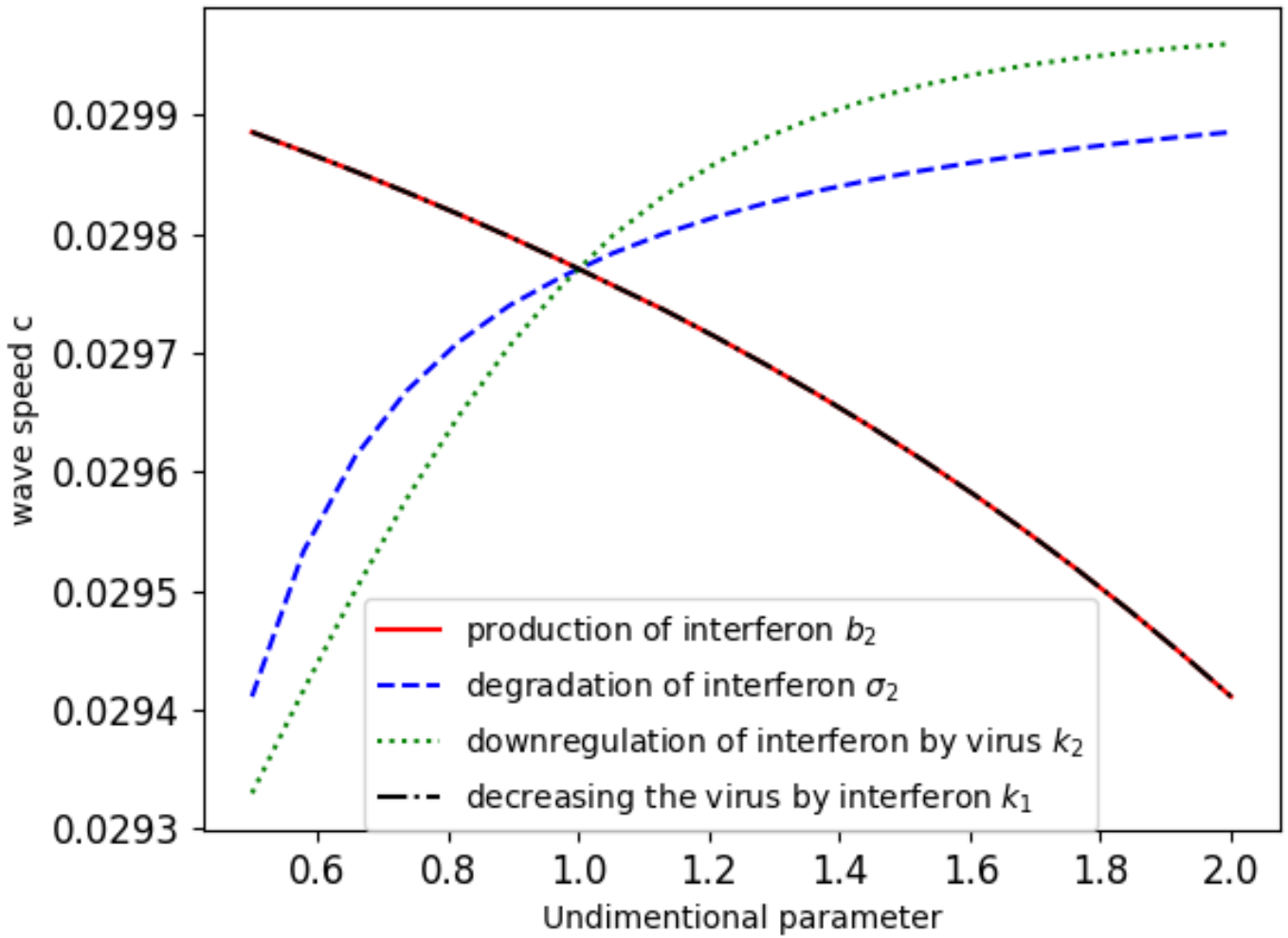
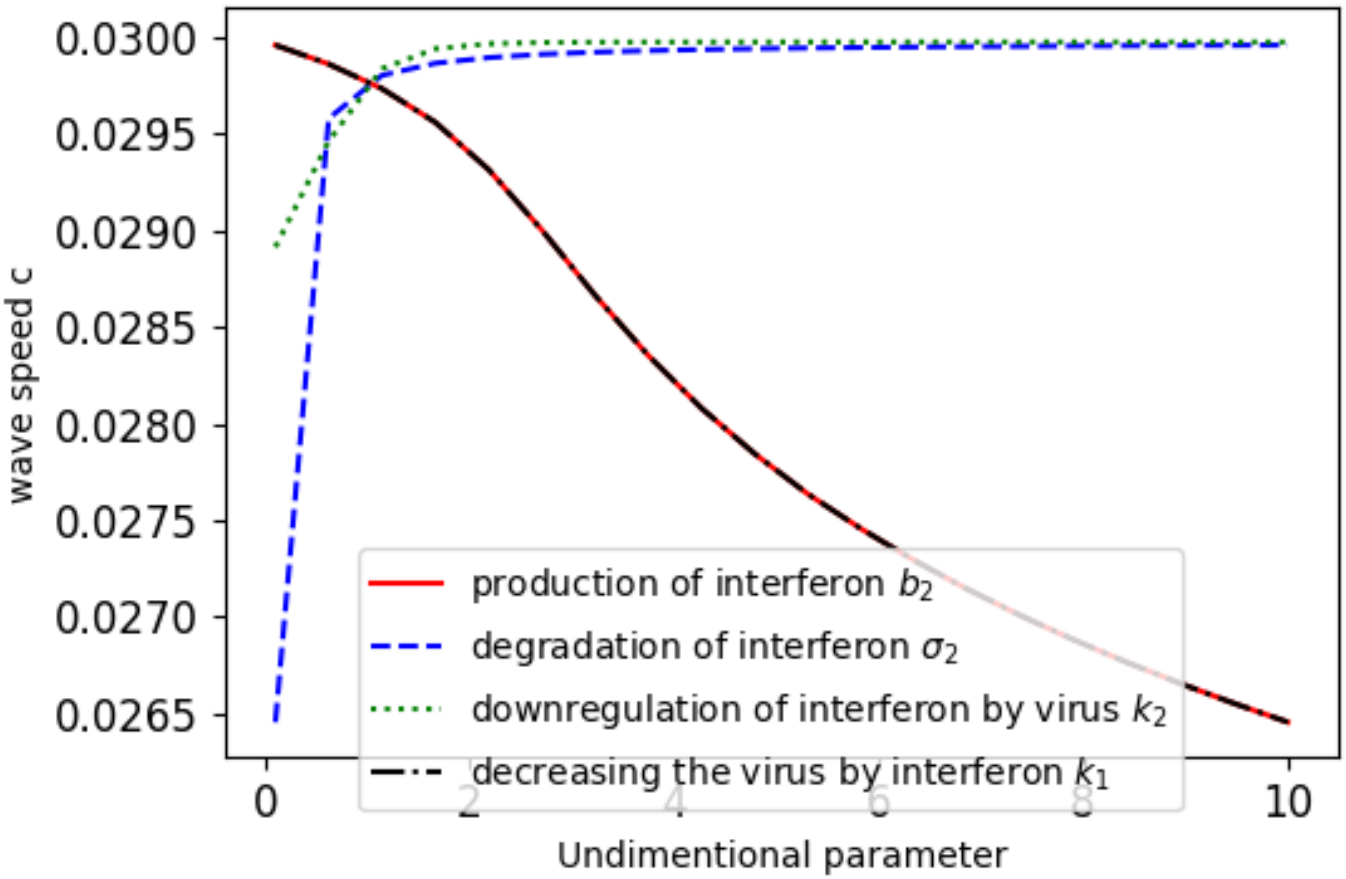
# IFN influence on $J(V)$



# IFN influence on $c$

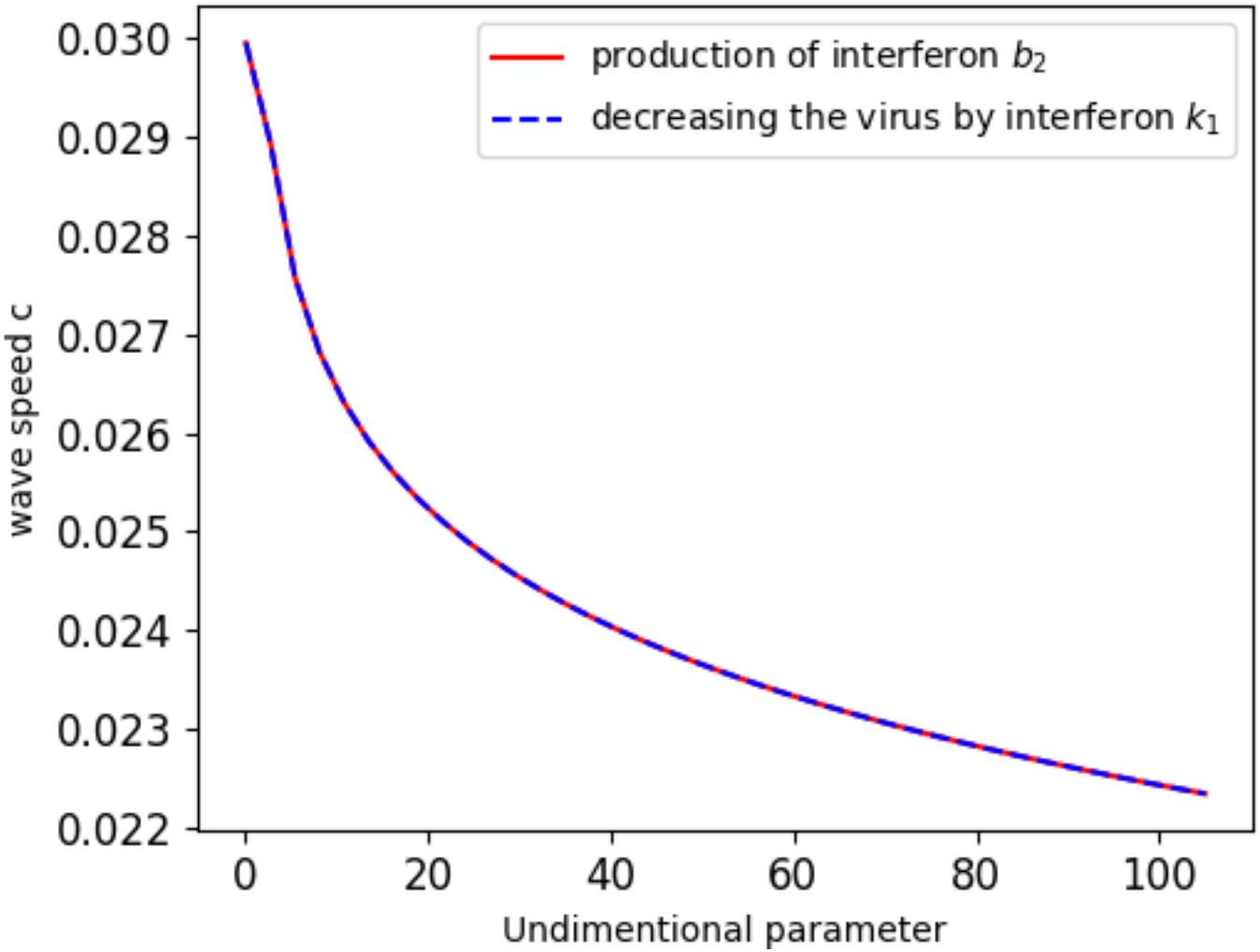


# IFN influence on wave speed — limits



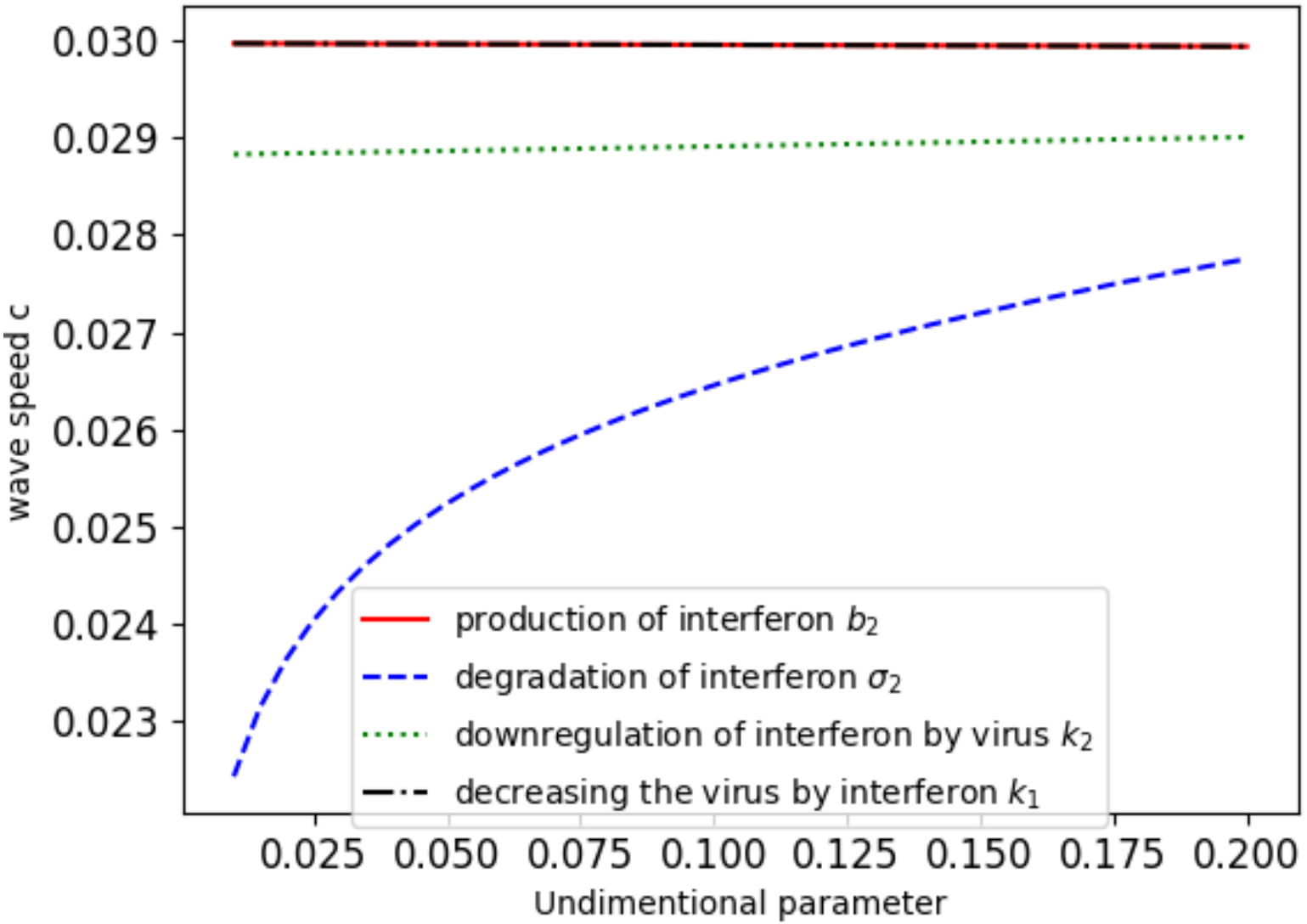

The value of the wave speed is bounded from above by the value of wave speed in system without IFN

# Influence of effective IFN production




Is the value of wave speed is bounded from below?

# Influence of IFN



# Limiting values of the wave speed and total viral load

Consider limits of $c$ and $J(v)$ for $b_2 \to 0$ and $b_2 \to +\infty$.

$$J(v) = A\left(1 - e^{-\frac{a}{c}J(v)}\right)\left(b_1 - PJ(v)e^{-k_2 J(v)}\right),\ A = \frac{cu_0}{\beta\sigma_1},\ P = \frac{k_1 b_2 \sigma_1}{\sigma_2},$$

$$c^2 = \min_{\mu>\mu_0} \frac{D\mu^2(\mu+\beta)}{(\mu+\beta)(\mu+\sigma_1) - ab(J)u_0 e^{-\tau\mu}},$$

$$b(J) = b_1 - \alpha J(v)e^{-k_2 J(v)},\ \alpha = \frac{k_1 b_2 \sigma_1}{\sigma_2}.$$

- for $b_2 \to 0$: $P \to 0$, $\alpha \to 0$, equations for $J(v)$ and $c$ take the same forms as for the system without IFN
- the denominator of the function $F(\mu)$ has the positive root if

$$\beta\sigma_1 < a\left(b_1 - \varkappa b_2 J(v)e^{-k_2 J(v)}\right)u_0, \tag{26}$$

and thus the value of $b_2$ cannot exceed some value

$$b_2 < \frac{\beta\sigma_2(R_v - 1)}{au_0 k_1 J(v)}e^{k_2 J(v)}.$$

# Immunity effectiveness number

The denominator of $F(\mu)$ has a positive root if

$$\beta\sigma_1 < a\left(b_1 - \varkappa b_2 J(v)e^{-k_2 J(v)}\right)u_0. \tag{27}$$

Rewrite it in the form

$$R_v > 1 + \bar{P}J(v)e^{-k_2 J(v)},\ \bar{P} = \frac{au_0 k_1 b_2}{\beta\sigma_2}. \tag{28}$$

This inequality can be reinforced in the following way:

$$R_v > 1 + P, \tag{29}$$

$$R_v = \frac{ab_1 u_0}{\beta\sigma_1},\ P = \bar{P}e^{-k_2} = \frac{au_0 k_1 b_2}{\beta\sigma_2 e^{k_2}}.$$

Let us call the number $P$ as *immunity effectiveness number*. It shows if the infection can propagate in the tissue with the innate immune response

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# Results

- IFN production by infected cells only
  - does not change the conditions of infection progression $R_v$,
  - decreases total viral load (infectivity),
  - does not influence the wave speed (severity).
- IFN production by infected cells and immune cells
  - decreases both total viral load (infectivity) and wave speed (severity).
  - Values of the total viral load and the wave speed are bounded from above with values in the system without IFN.
  - The virus replication number should exceed some threshold value (immunity effectiveness number) for that the virus can develop an infection in tissue with the innate immune response.

# References


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Thank you for your attention!