Predicting the potential impact of a cytotoxic T-lymphocyte HIV vaccine: How often should you vaccinate and how strong should the vaccine be?

Robert Smith?

The University of Ottawa

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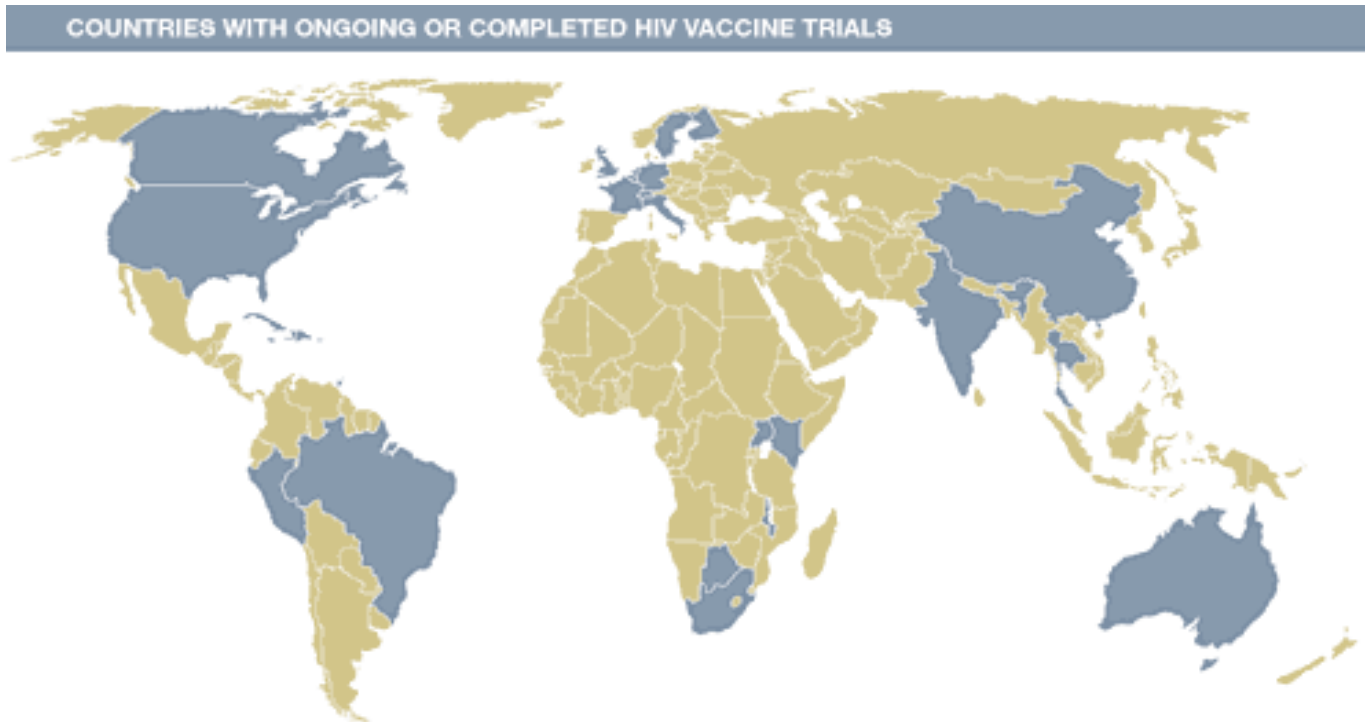
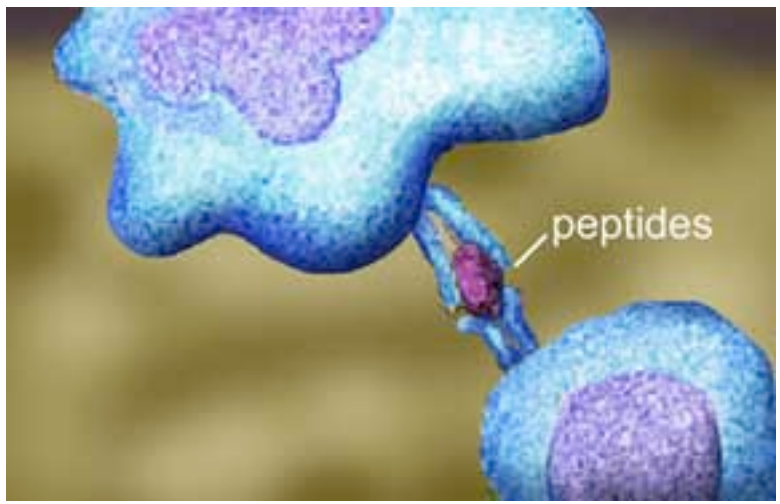
- $682 million is spent on HIV vaccine research annually.



Cytotoxic T Lymphocytes (CTLs)

- Cells with the ability to identify and destroy virally infected cells in the body



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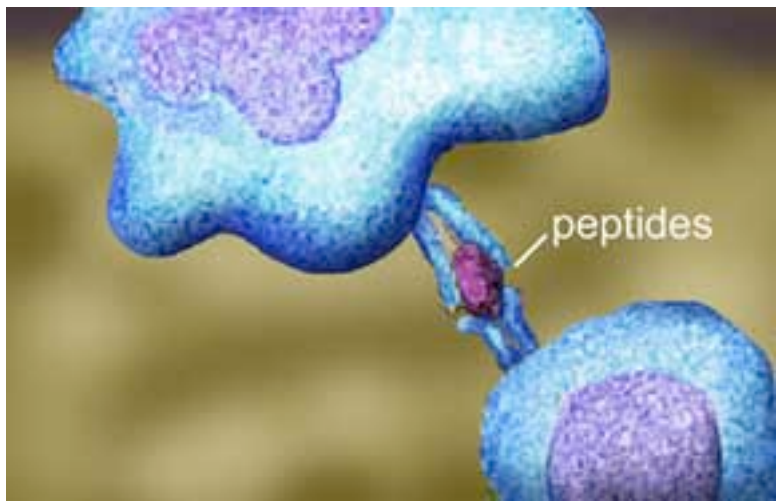

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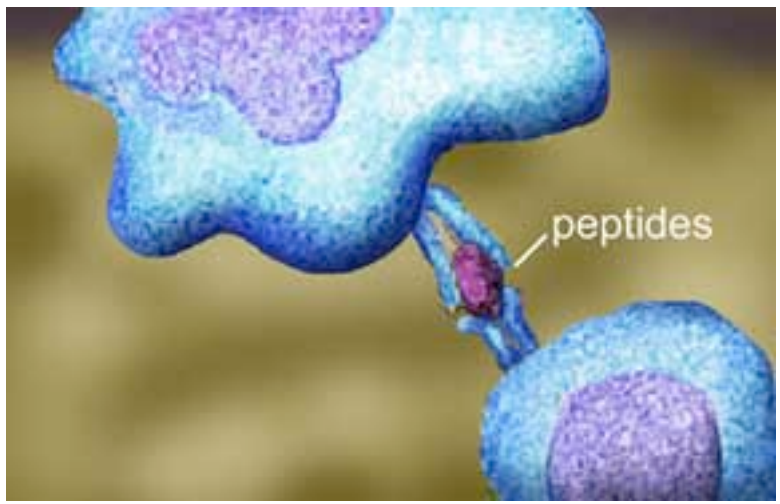
- One of the body's best natural defence mechanisms.



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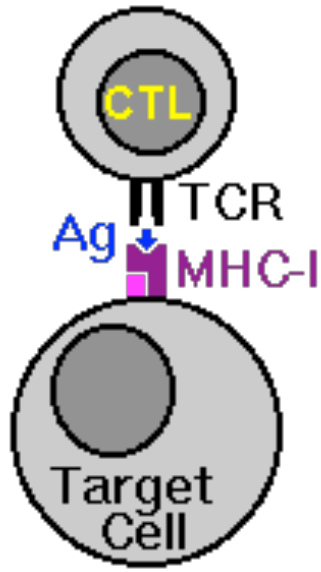
- Such a post-infection “vaccine” would be administered regularly and indefinitely.

Infected $CD4^+$ T cells

- Die at death rate *d*



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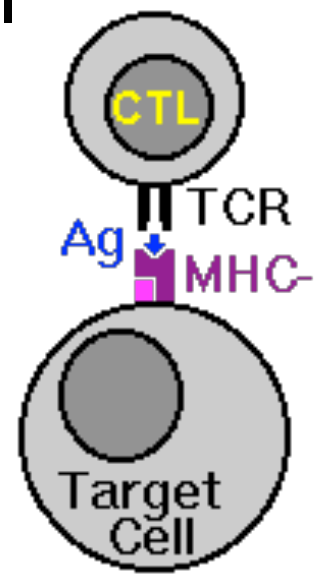

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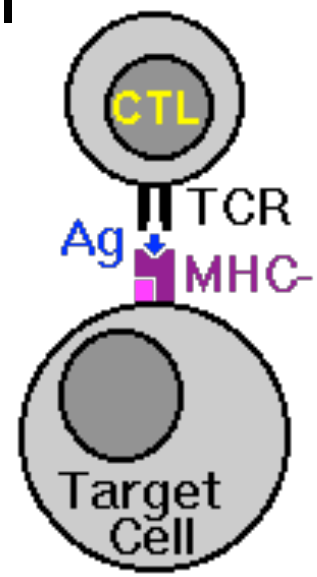

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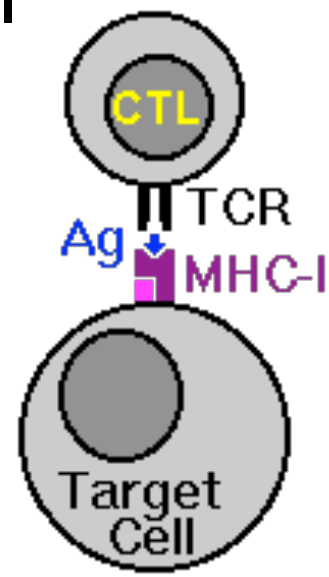

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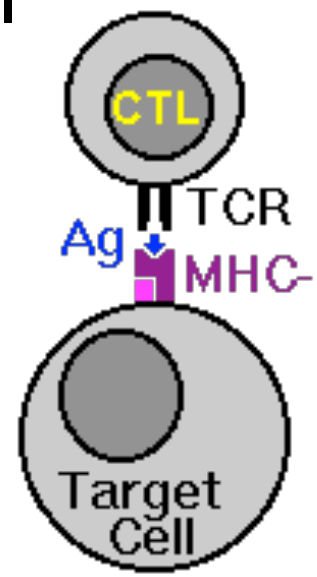
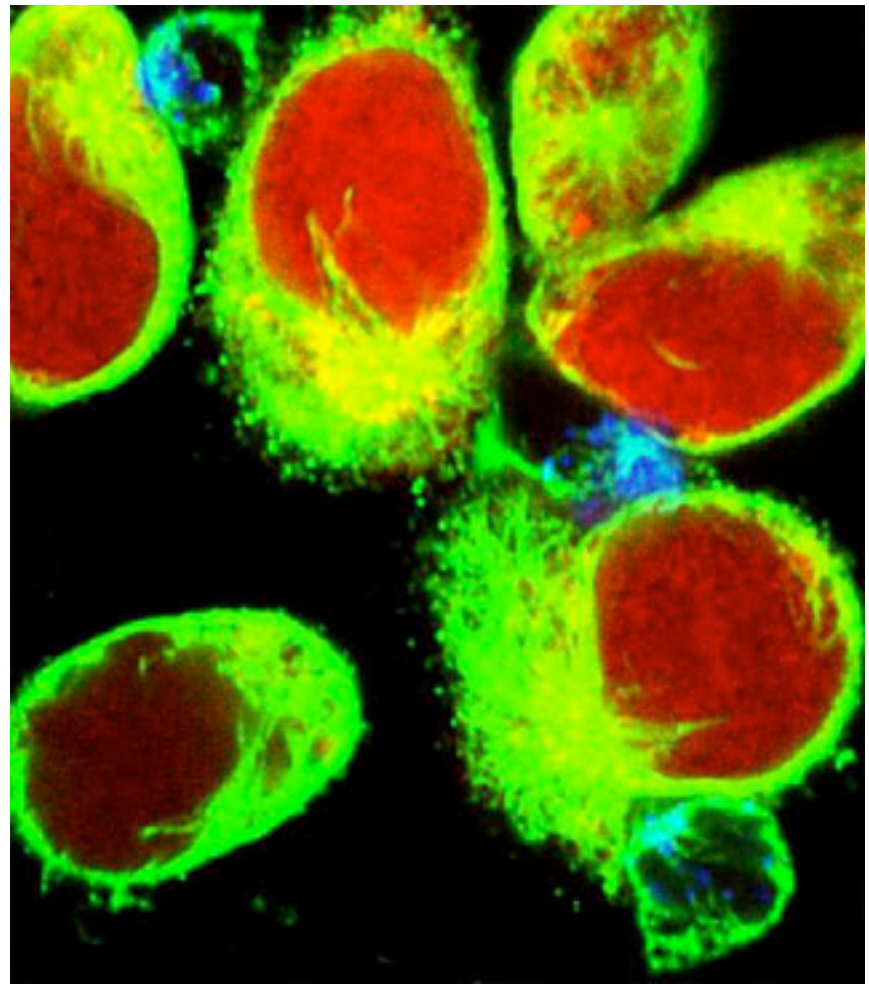
  (thus we use a steady-state viral load approximation when estimating parameters).



CTLs

- Proliferate at rate α, proportional to density of both CTLs and infected T cells



Three CTLs (blue) annihilate target cells (red)

CTLs

- Proliferate at rate α, proportional to density of both CTLs and infected T cells
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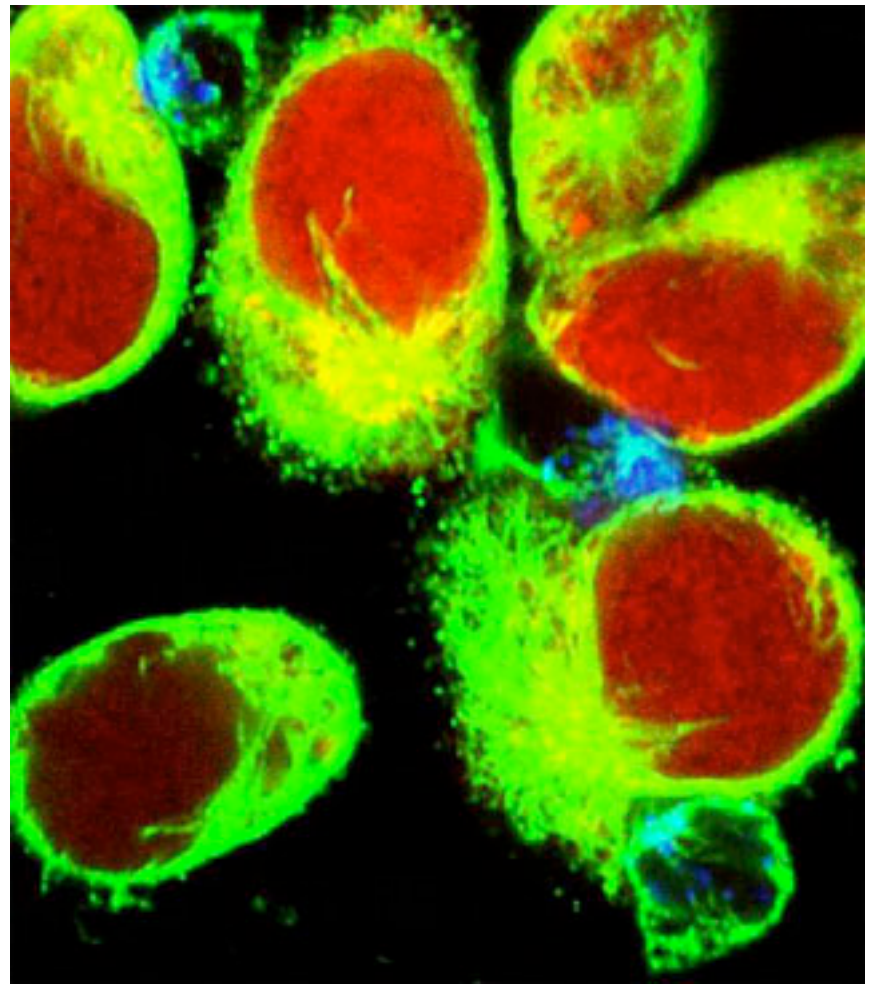

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The model without vaccination

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- trivial
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- nontrivial
  (coexistence)

$$(\bar{T}, \bar{C}) = \left(\frac{\delta}{\alpha}, \frac{\alpha\pi - \delta d}{p\delta}\right).$$

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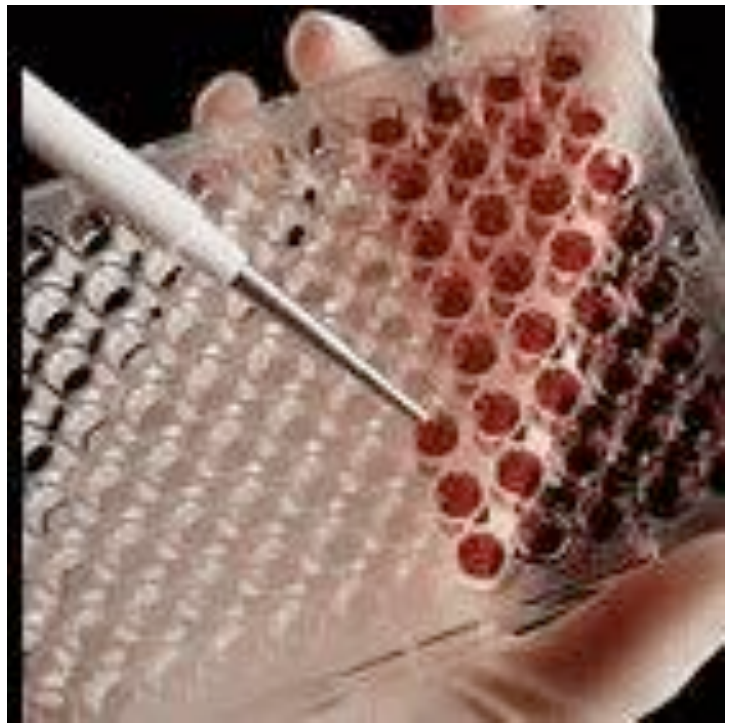
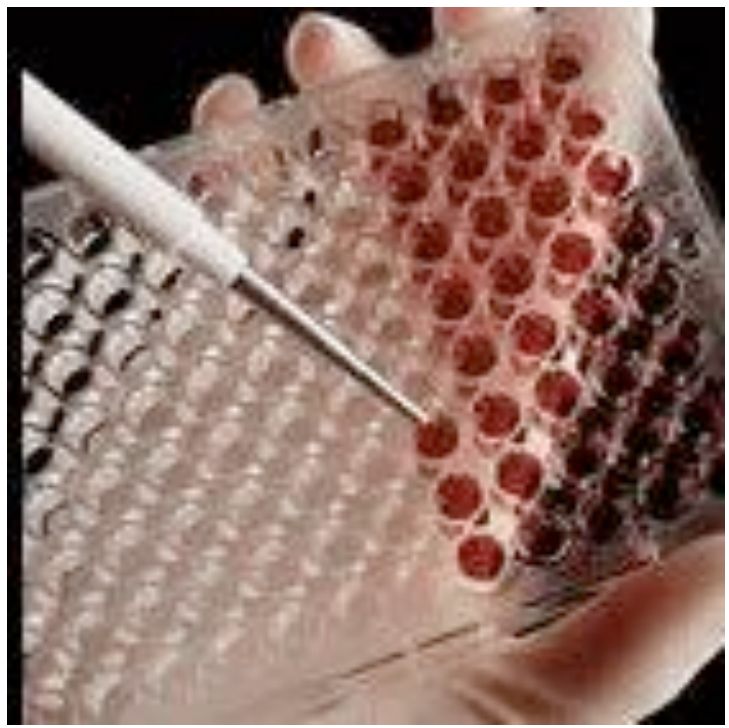
Hence:



Stability

Hence:

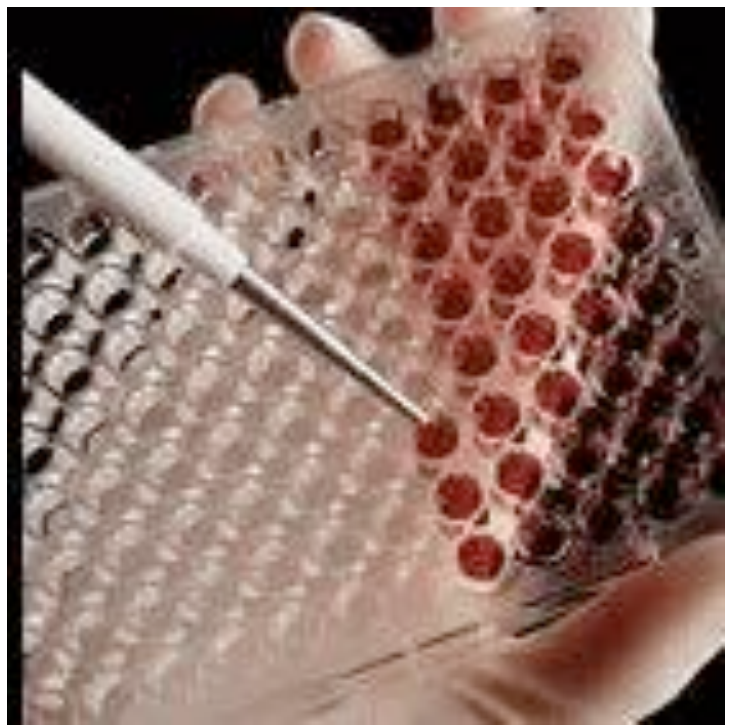
- the trivial steady state is unstable iff the nontrivial steady state exists in the positive plane



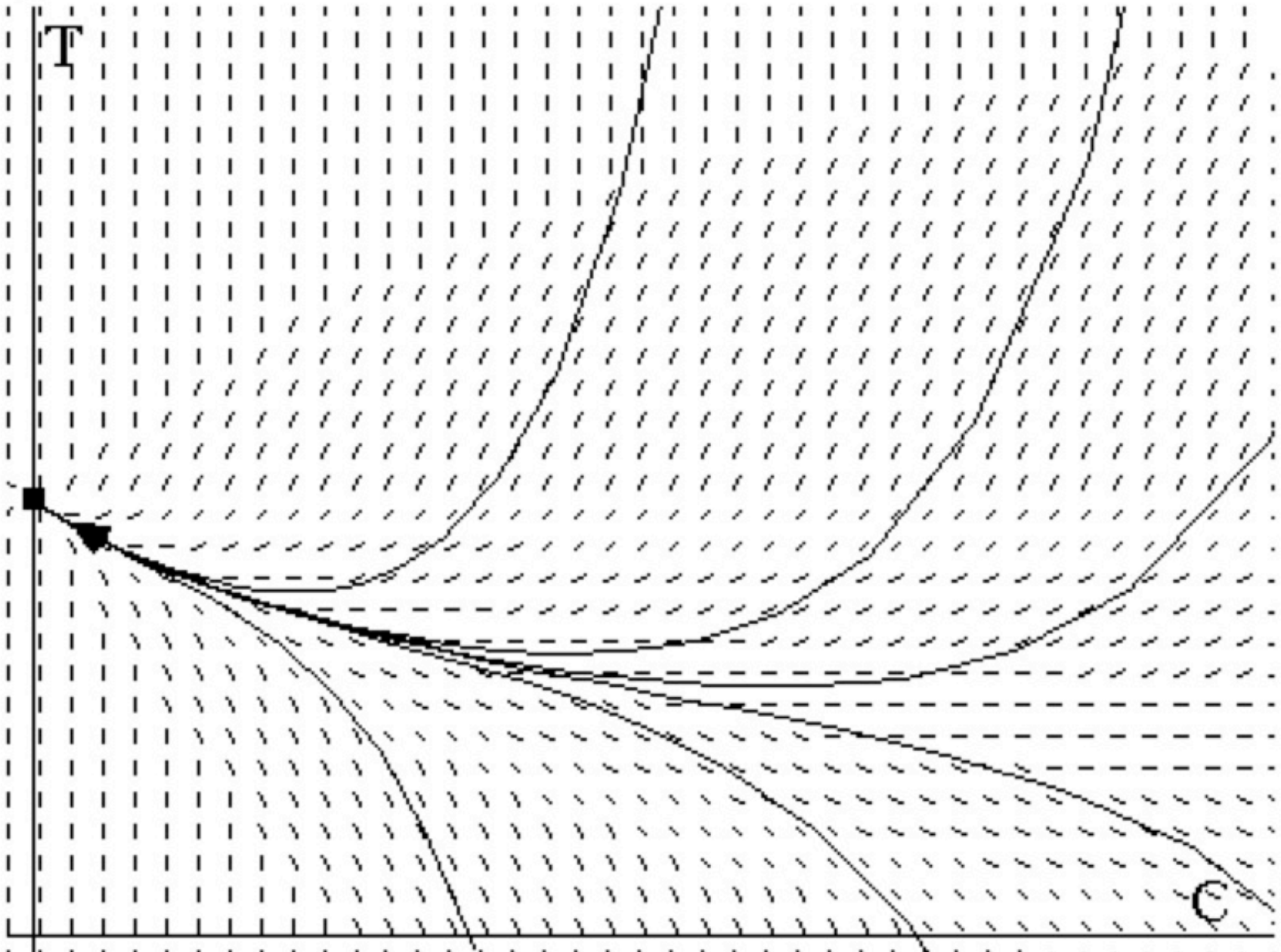
Stability

Hence:

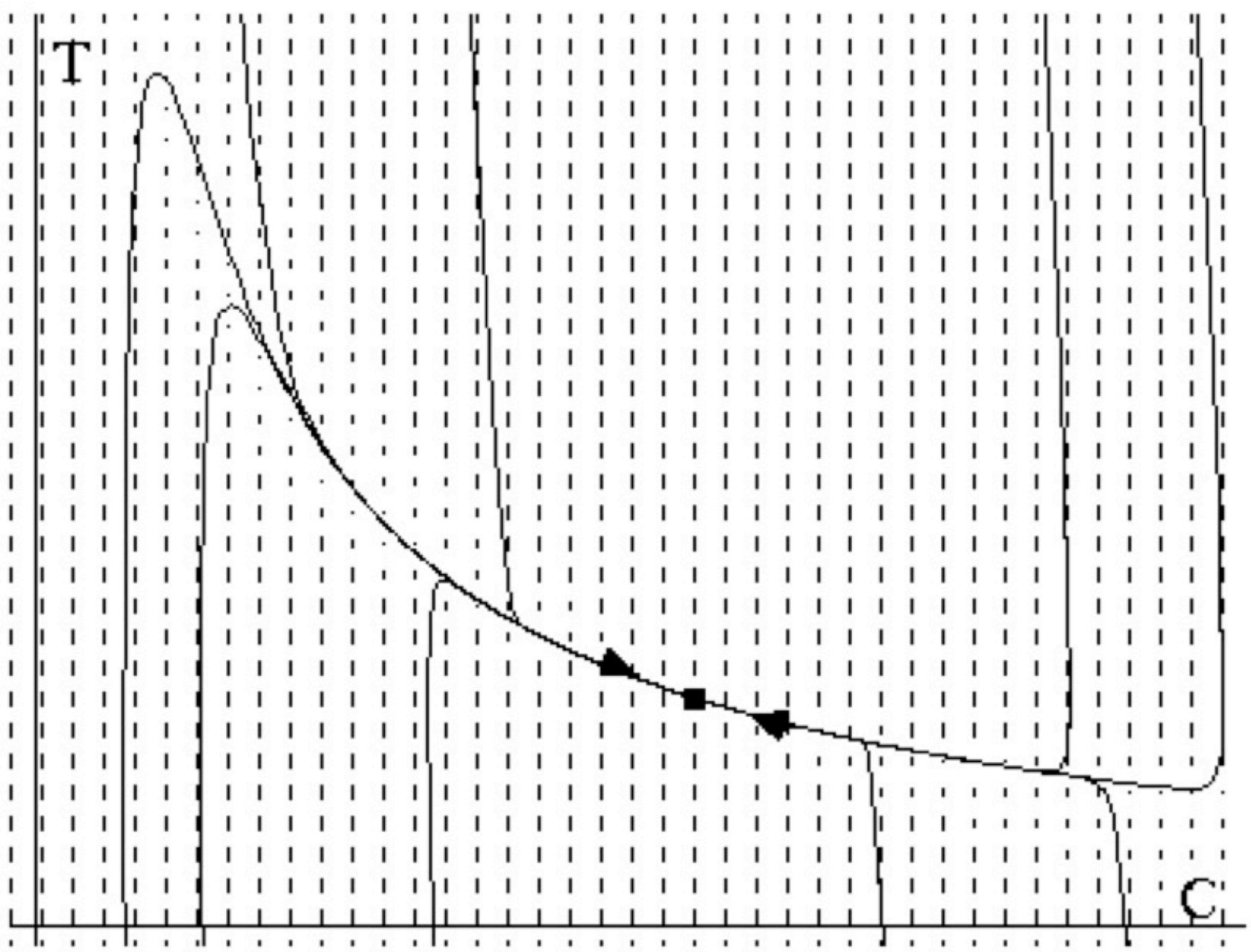
- the trivial steady state is unstable iff the nontrivial steady state exists in the positive plane
- the nontrivial steady state is asymptotically stable whenever it exists in the positive plane.



Nontrivial eq^{m} absent $\Leftrightarrow$ trivial eq^{m} stable

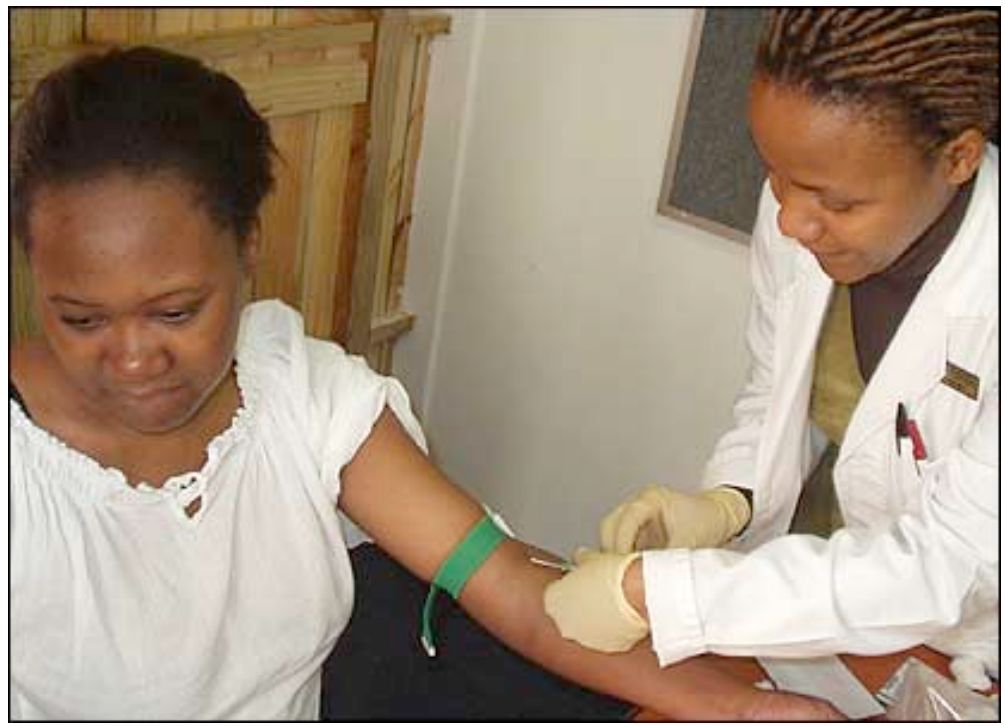


Nontrivial eq^{m} stable in the positive plane



Vaccination

- A fixed boost of CTLs, C^i



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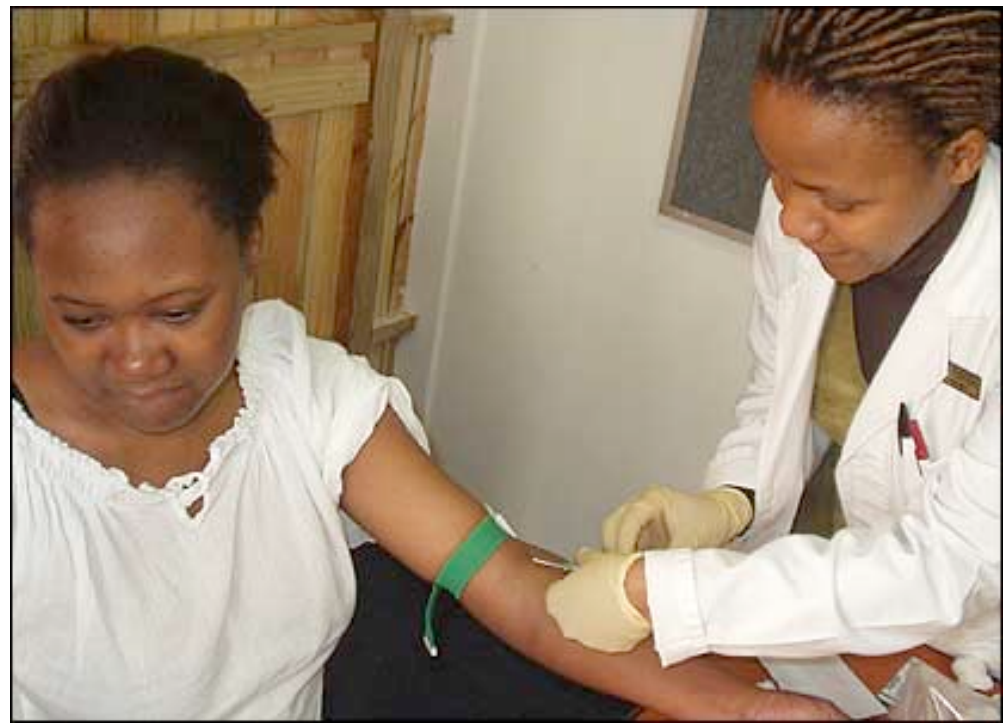

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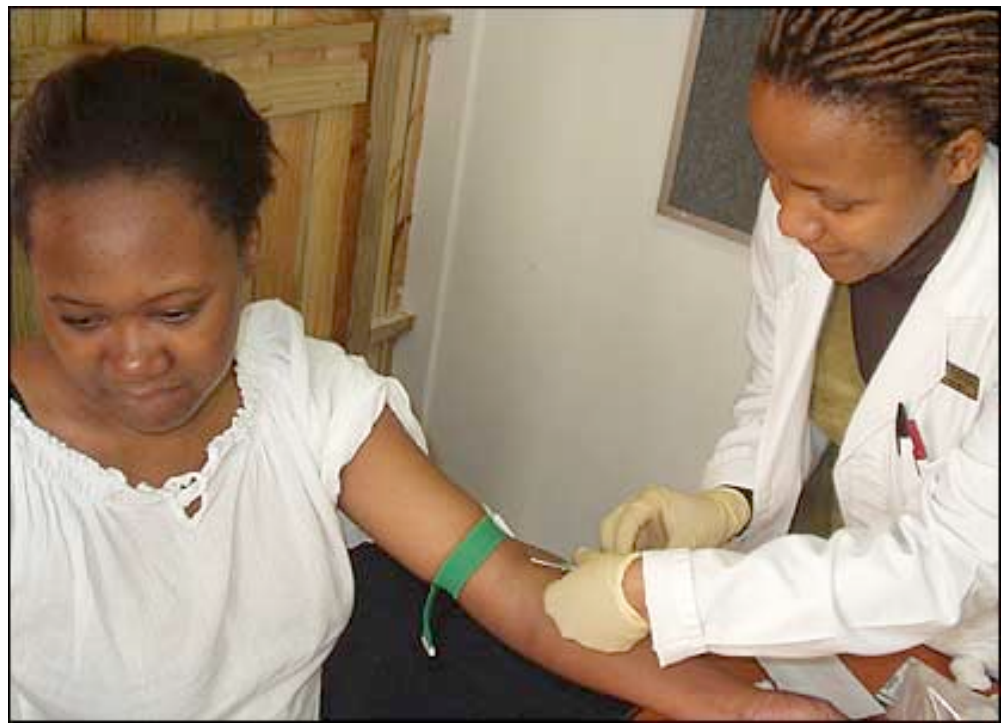

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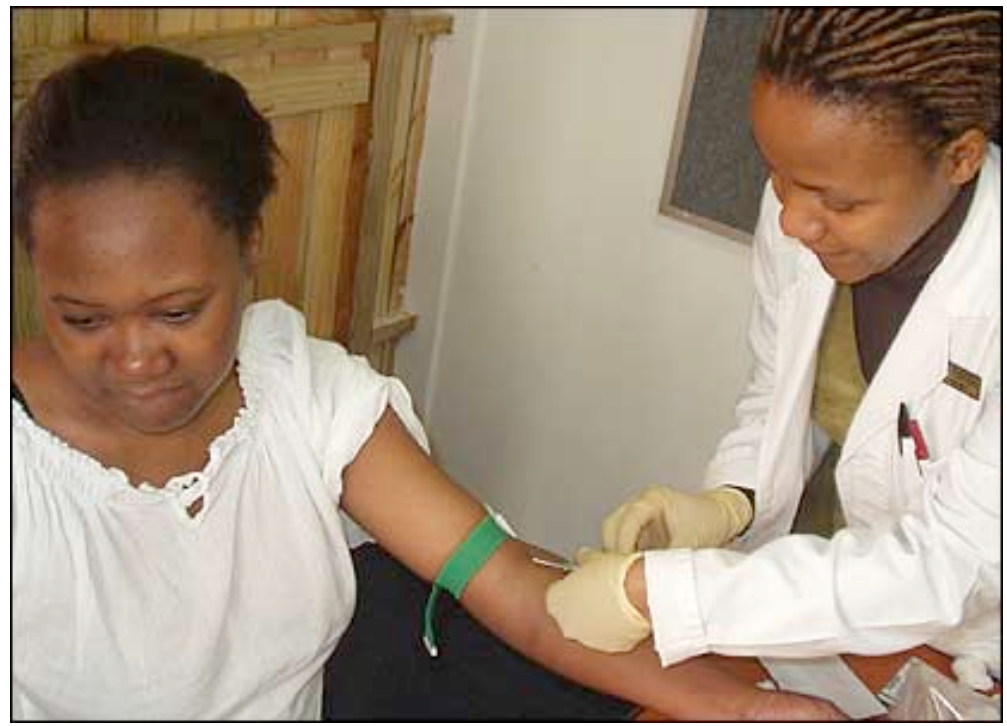
  ...this results in a series of *impulsive differential equations*.



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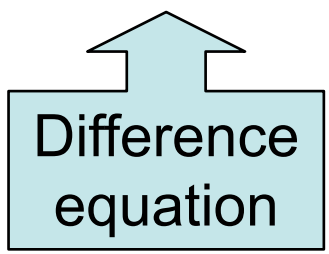

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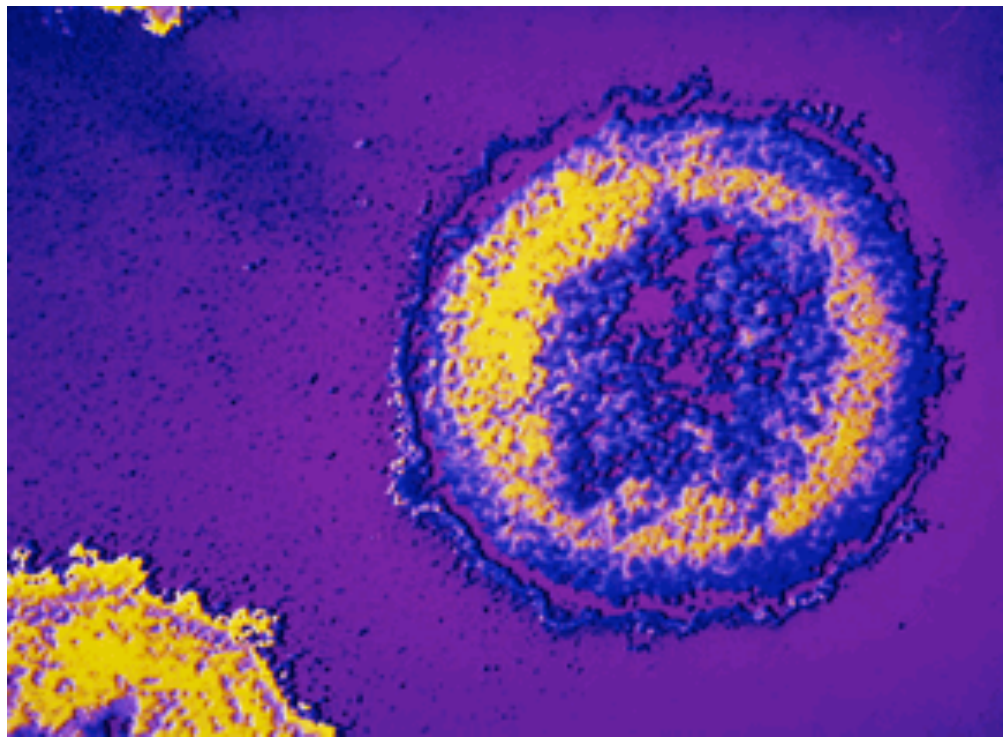
Difference equation

Depends on the time of impulse and the state immediately beforehand.

Impulsive DEs

- Solutions are continuous for $t \neq r_k$



Thousands of HIV particles emerging from an infected T-cell

r_k=*impulse time*

Impulsive DEs

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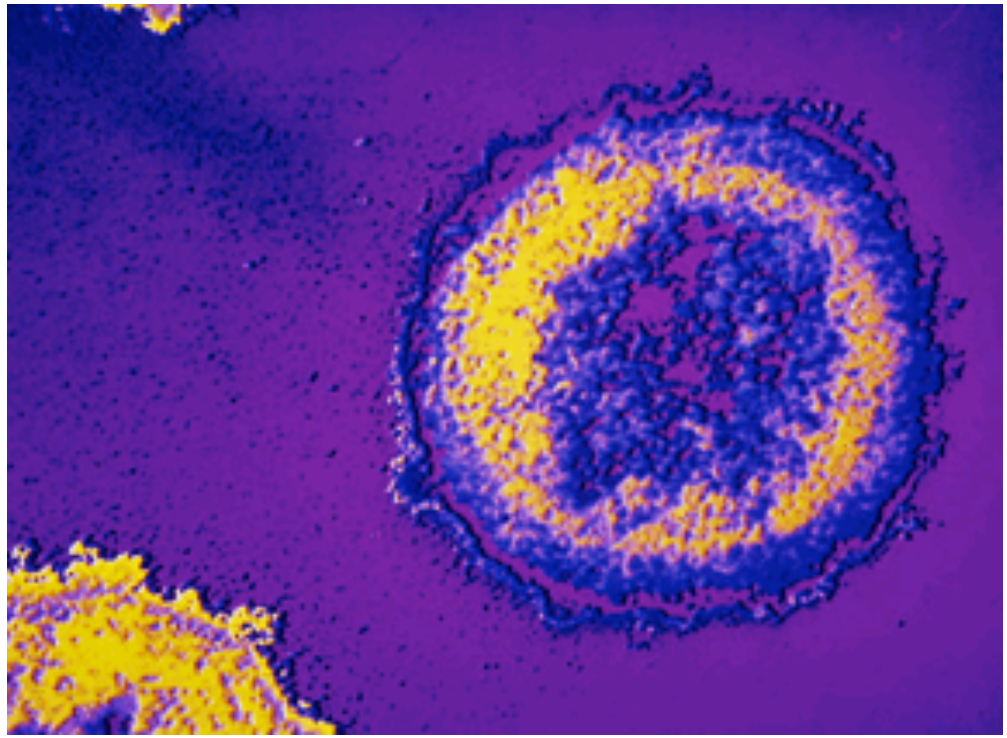

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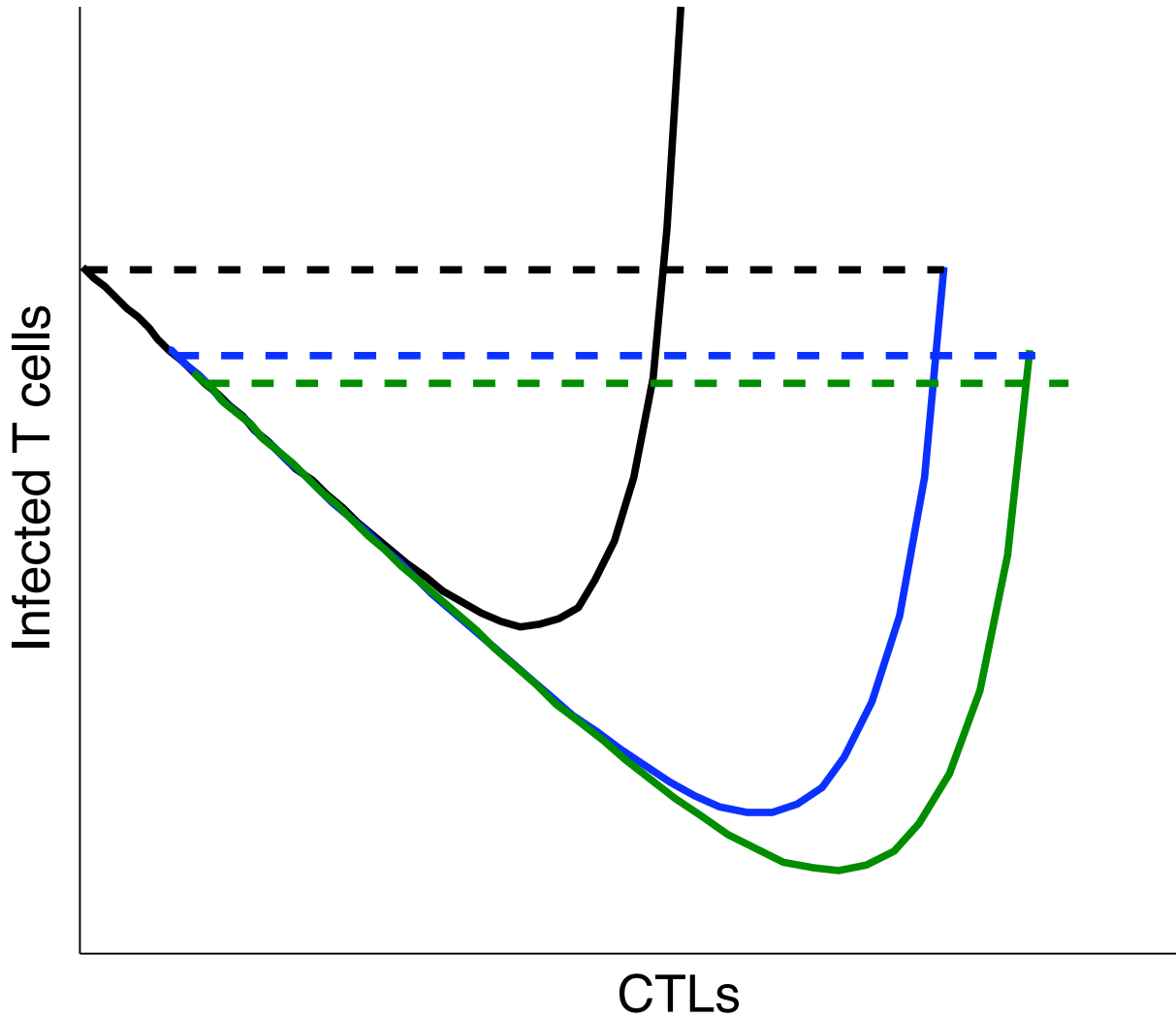
Putting it together

- The model thus consists of a system of ODEs (infected T cells and CTLs) together with a difference equation (CTL boost).

Impulsive interruption

- The impulsive effect “interrupts” the continuous trajectories



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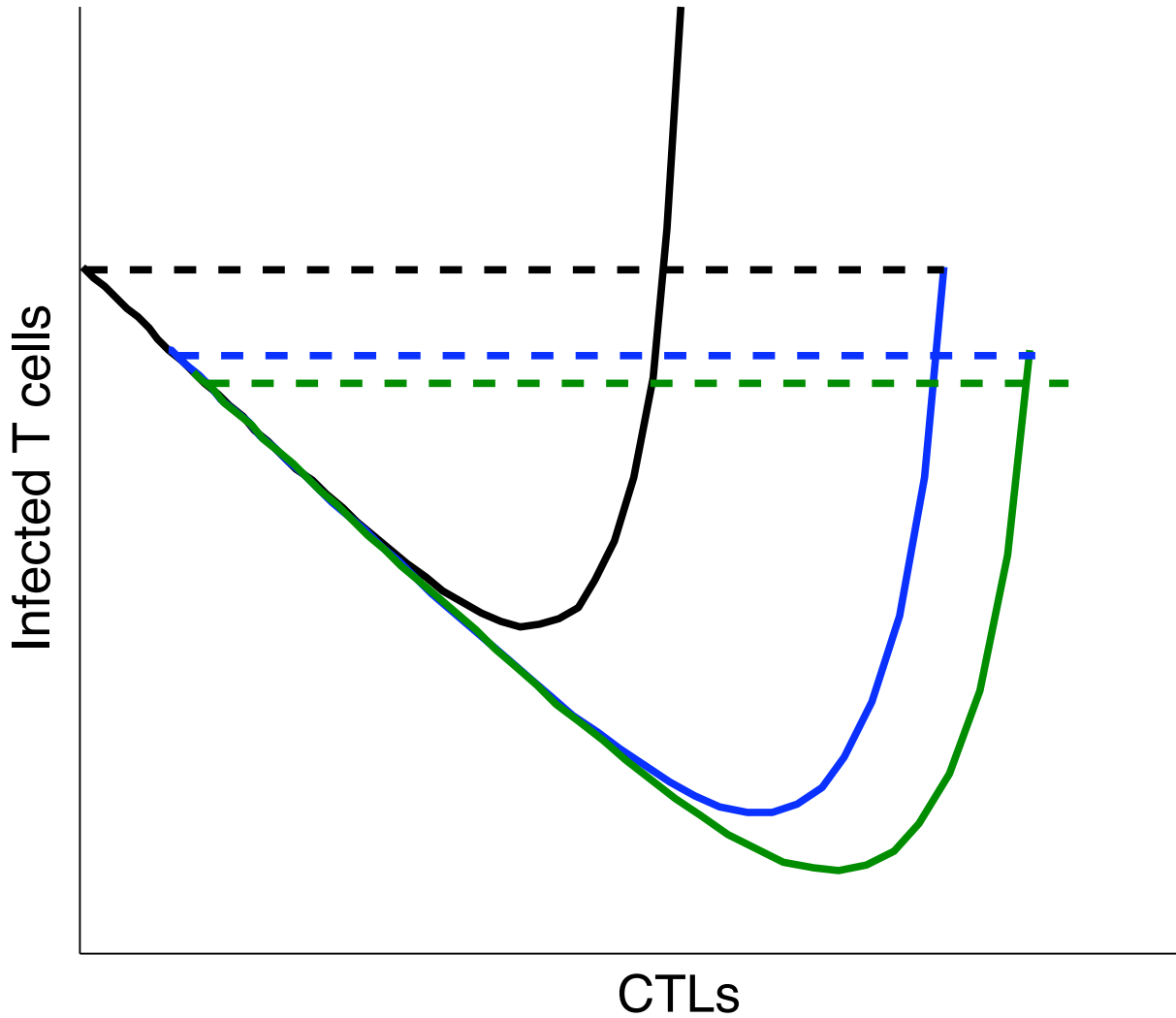

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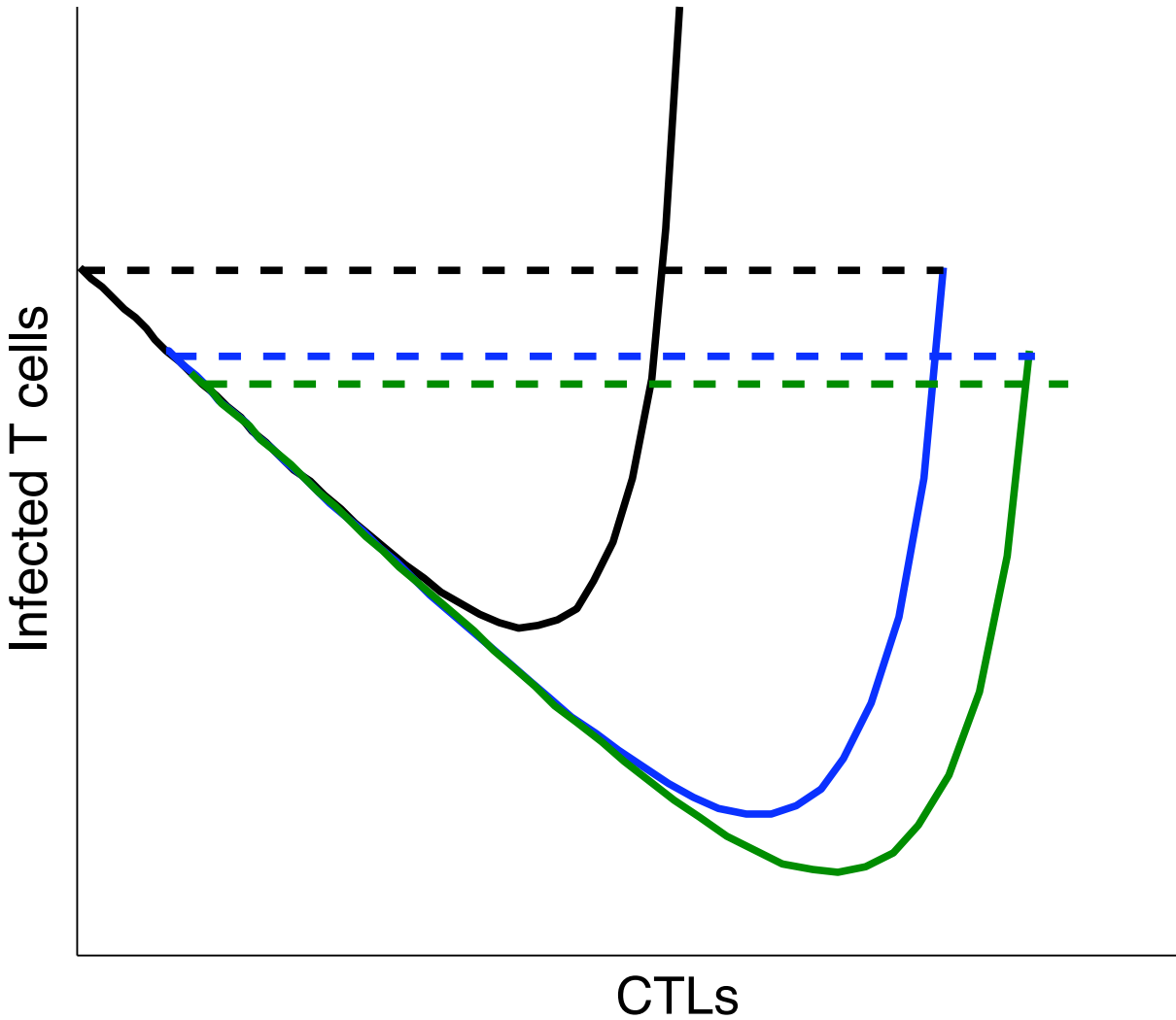

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$$\therefore \quad C(t) = C(0) e^{\int_0^t (\alpha T(u) - \delta) du}.$$

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Defining T_{int}

- Define

  where $\tau = t_{k+1} - t_k$ is the vaccine administration interval (assumed constant)
- T_{int} is a measure of the ratio of the number of CTLs at the end of an impulsive cycle to those at the beginning

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- T_{int} is a measure of the ratio of the number of CTLs at the end of an impulsive cycle to those at the beginning
- Thus, $T_{\text{int}}<1$ is necessary for an impulsive orbit to exist.

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An impulsive periodic orbit

- In particular, if $C(0^+) = \frac{C^i}{1-T_{\text{int}}}$

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- Thus we have an impulsive periodic orbit

$$C(t) = \frac{C^i e^{\int_0^t (\alpha T(u) - \delta) du}}{1 - T_{\text{int}}}$$

for $0 < t < \tau$

- Endpoints of the impulsive orbit are

$$C(0^+) = \frac{C^i}{1 - T_{\text{int}}} \quad \text{and} \quad C(\tau^-) = \frac{C^i T_{\text{int}}}{1 - T_{\text{int}}} .$$

T_{int}=cell ratio measure C=CTLs C^i=vaccine strength
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Impulsive Floquet Theory

- From the impulsive DEs, define

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Reworks impulse times as a smooth function.

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Nontrivial 2D Floquet multiplier

- The nontrivial Floquet multiplier is

(ξ , η)=(T,C) periodic orbit t_k=impulse times
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$$\mu_2 = \Delta_1 \exp\left[\int_0^\tau \left(\frac{\partial P}{\partial T}(\xi(t),\eta(t)) + \frac{\partial Q}{\partial C}(\xi(t),\eta(t))\right) dt\right]$$

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Calculating the nontrivial Floquet multiplier

$$\mu_2 \quad < \quad \frac{1}{T_{\text{int}}} \exp \int_0^{\tau} \left(\frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) dt$$

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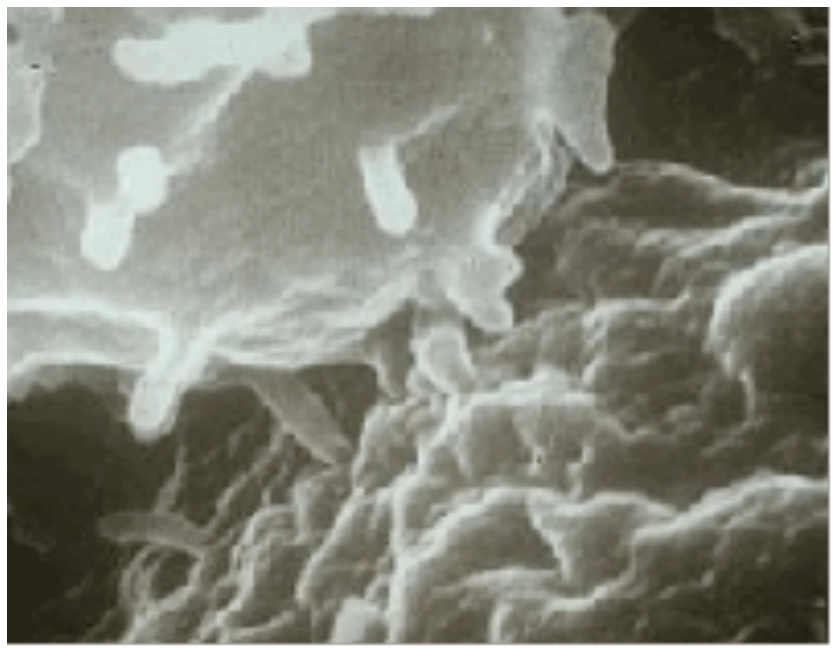
- In particular, there might be impulsive orbits with more than one impulse per period
- However, this does not appear to be the case, for the parameter ranges under consideration.

Average # of infected T cells

- The average number of infected T cells during a single cycle of the impulsive periodic orbit is

$$T_{av} \equiv \frac{1}{\tau} \int_0^{\tau} T(u) du \,.$$

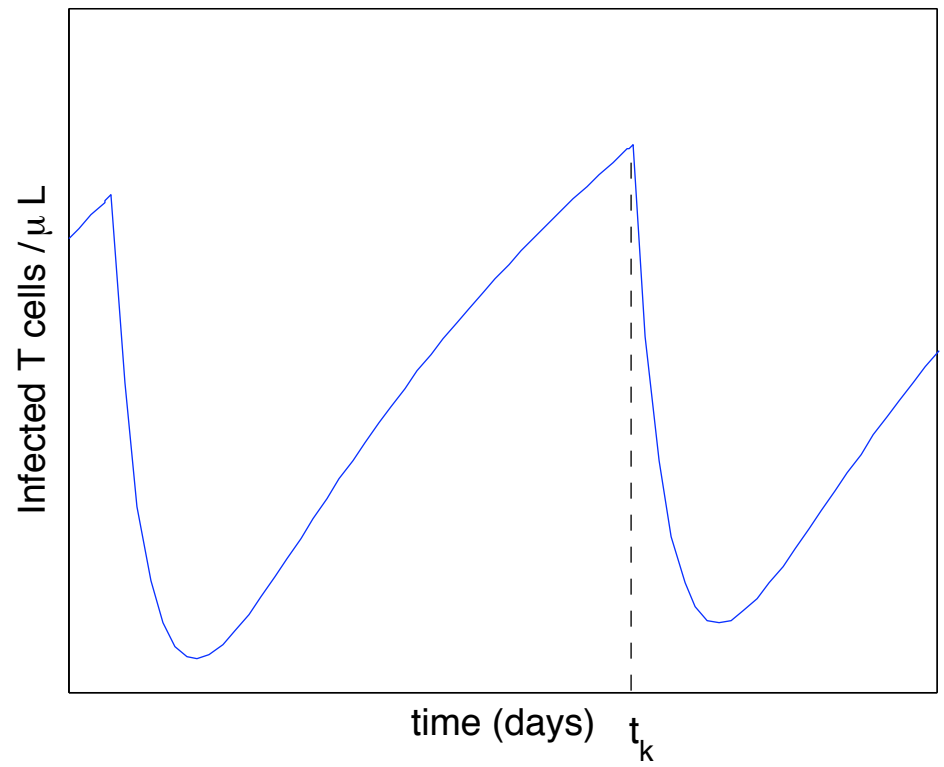


A CTL recognising a tumour

T=infected cells τ=vaccination period

Infected T cell minimum

- Easy to show:



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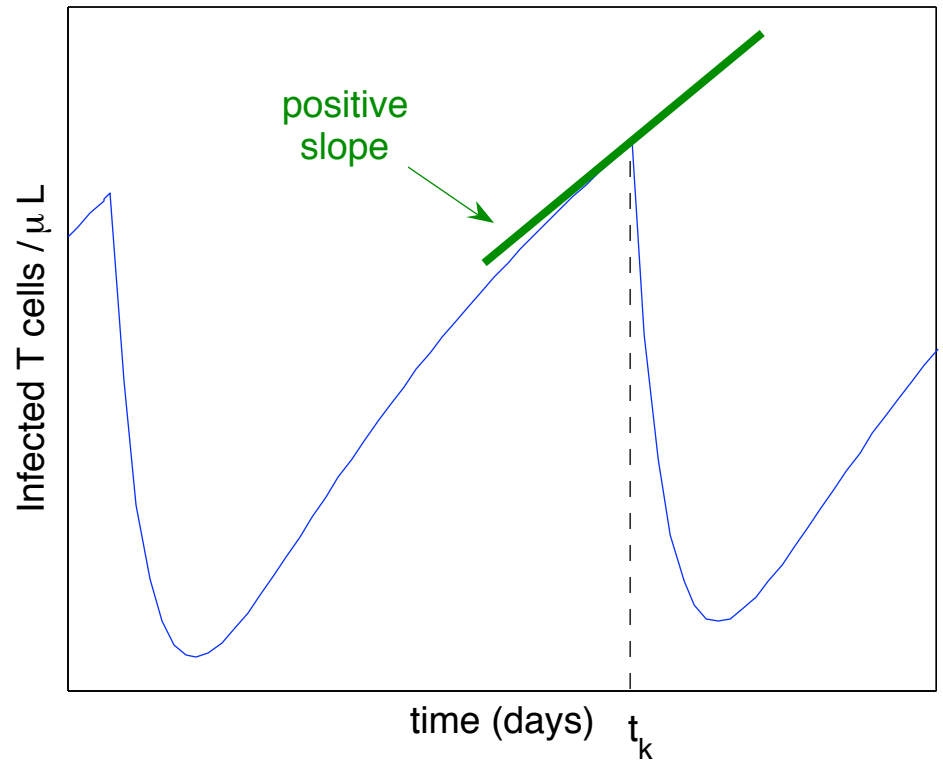

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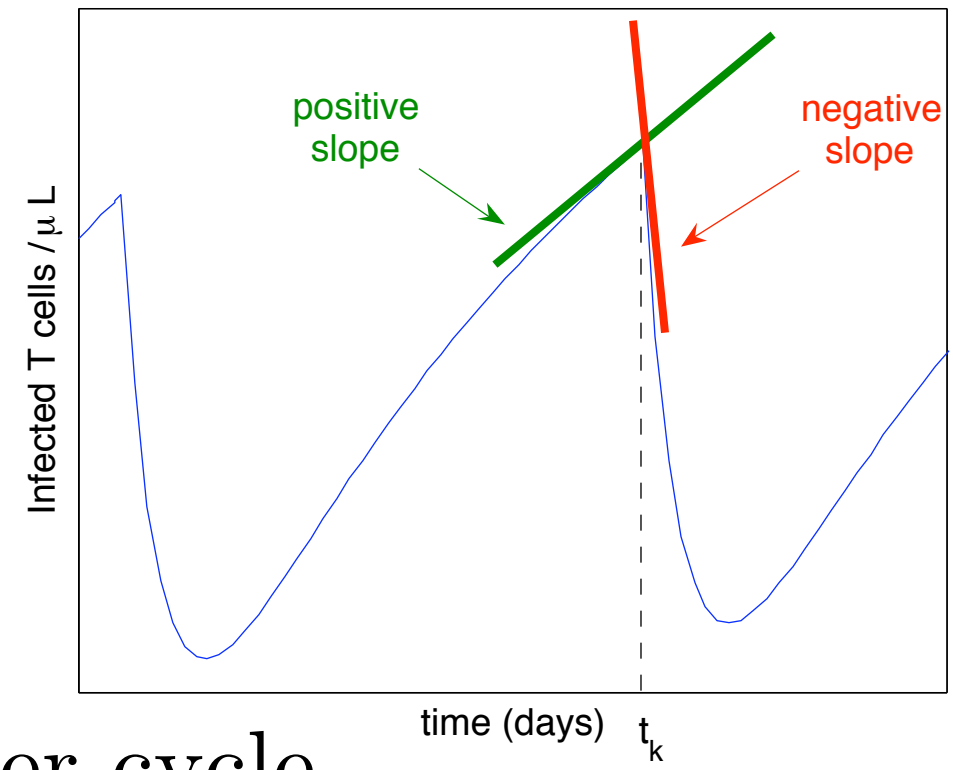

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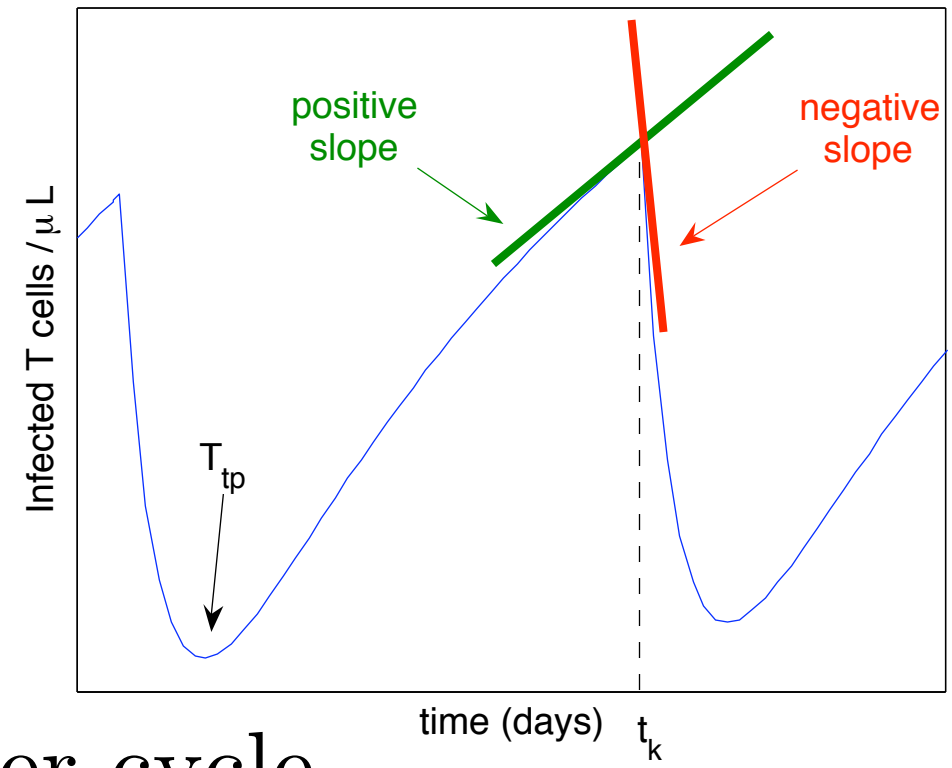

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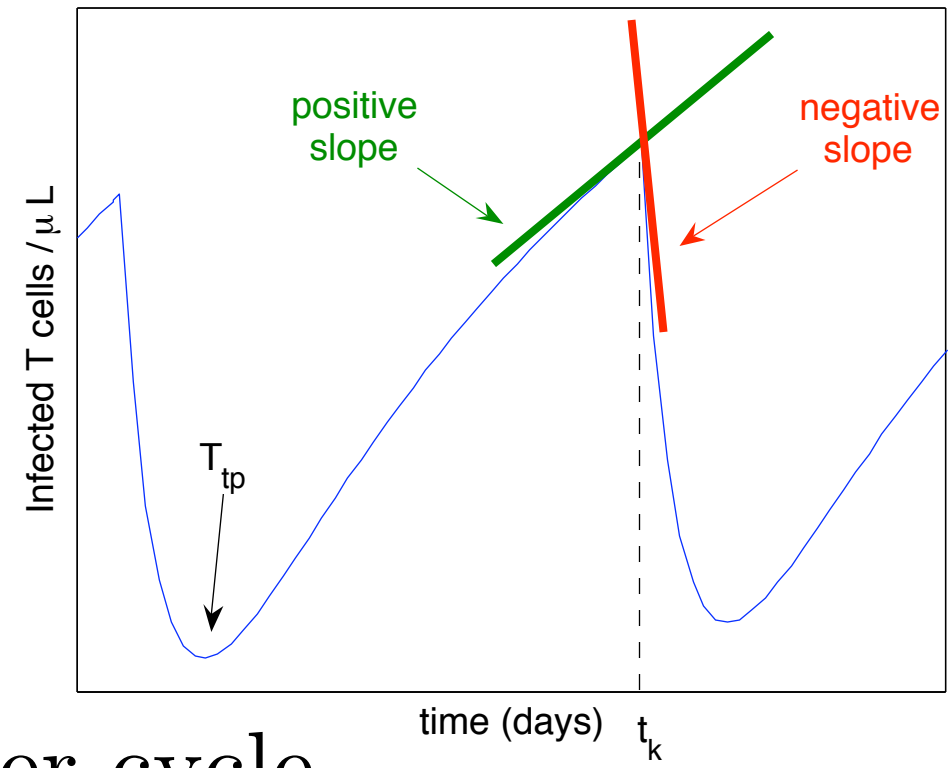

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Estimating the vaccination period

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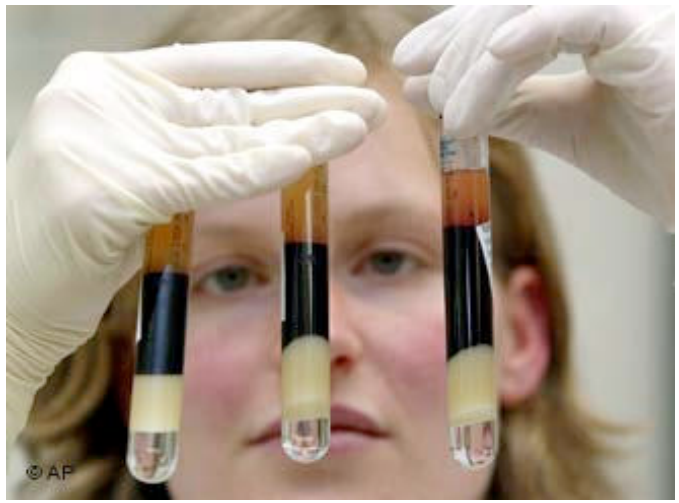

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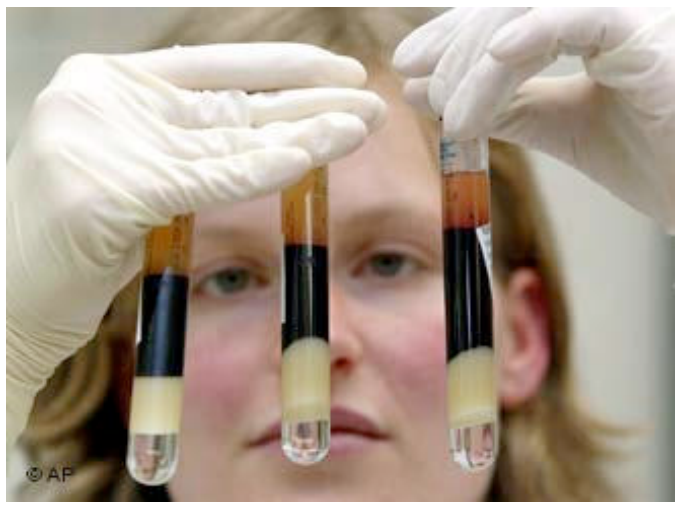

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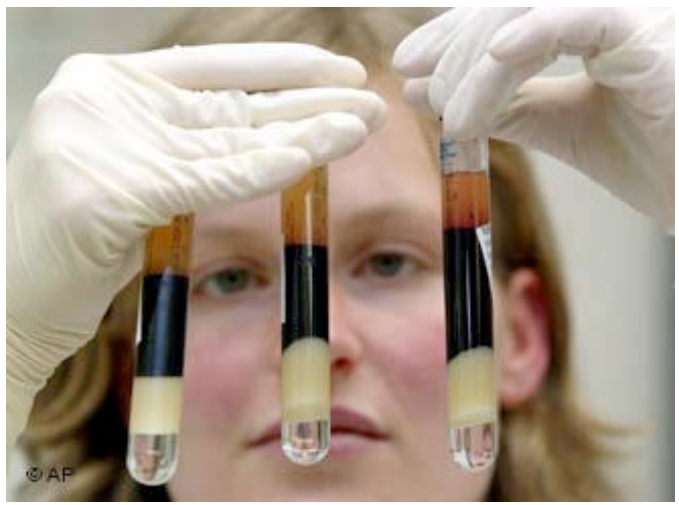

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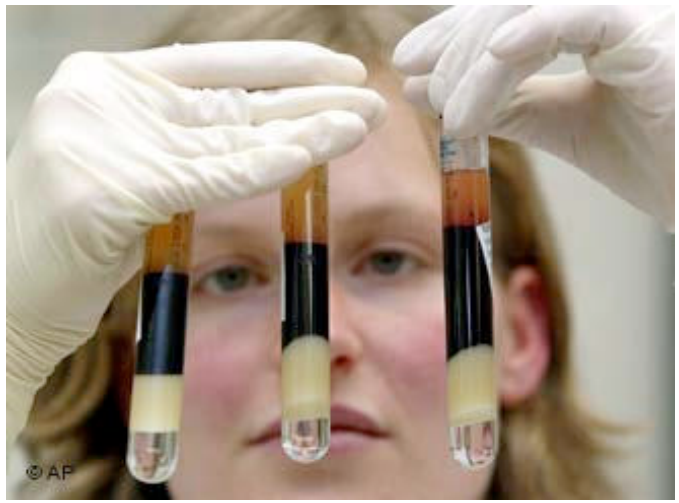

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Parameter	Value	Units	Reference
π	1.5	cells day^{-1} μL^{-1}	de Boer & Perelson (1998)
d	0.5	day^{-1}	Essunger & Perelson (1994)
p	0.05	μL cells^{-1}day^{-1}	Bonhoeffer *et al.* (2000)
α	0.067	μL cells^{-1}day^{-1}	de Boer & Perelson (1998)
δ	0.2	day^{-1}	de Boer & Perelson (1998)

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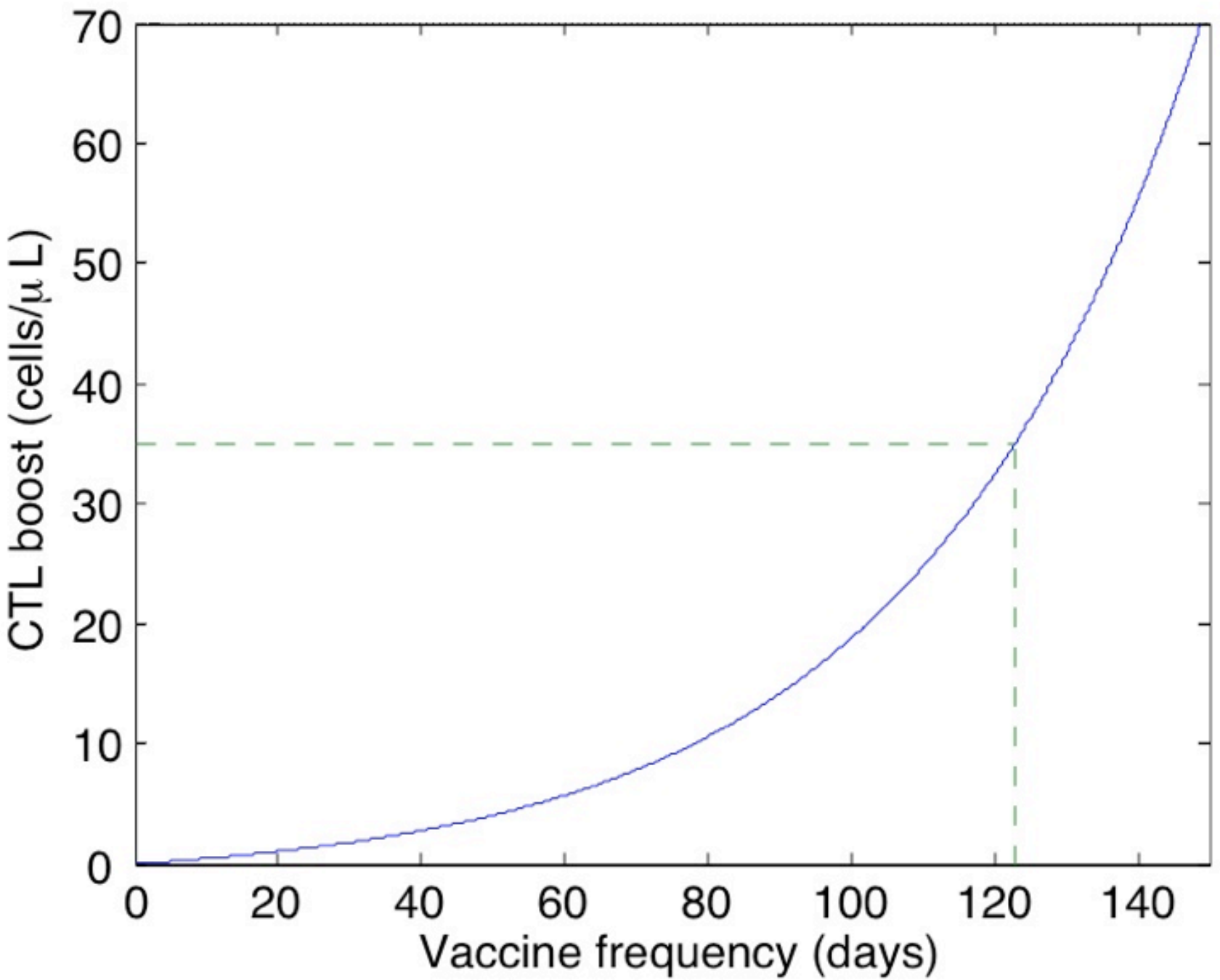
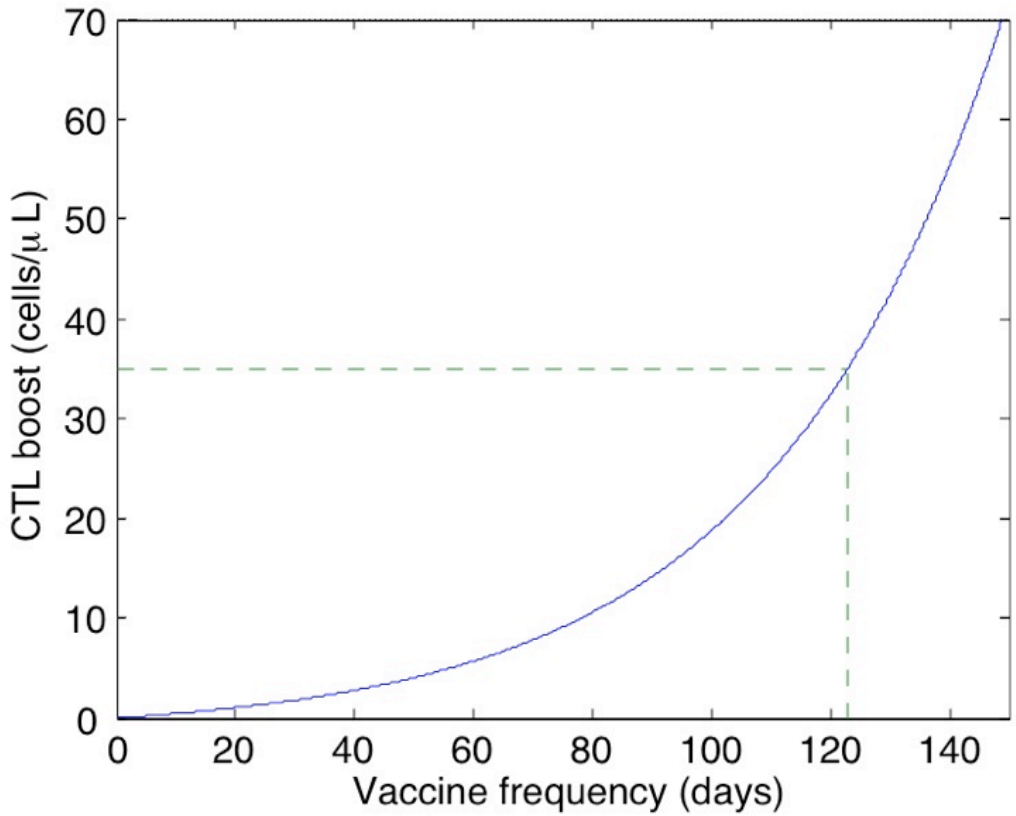


How strong and how often?

A CTL boost of 35 cells μL^{-1} that was applied every 122 days or fewer would ensure the average infected T cell count remained below 2.6 cells μL^{-1}.



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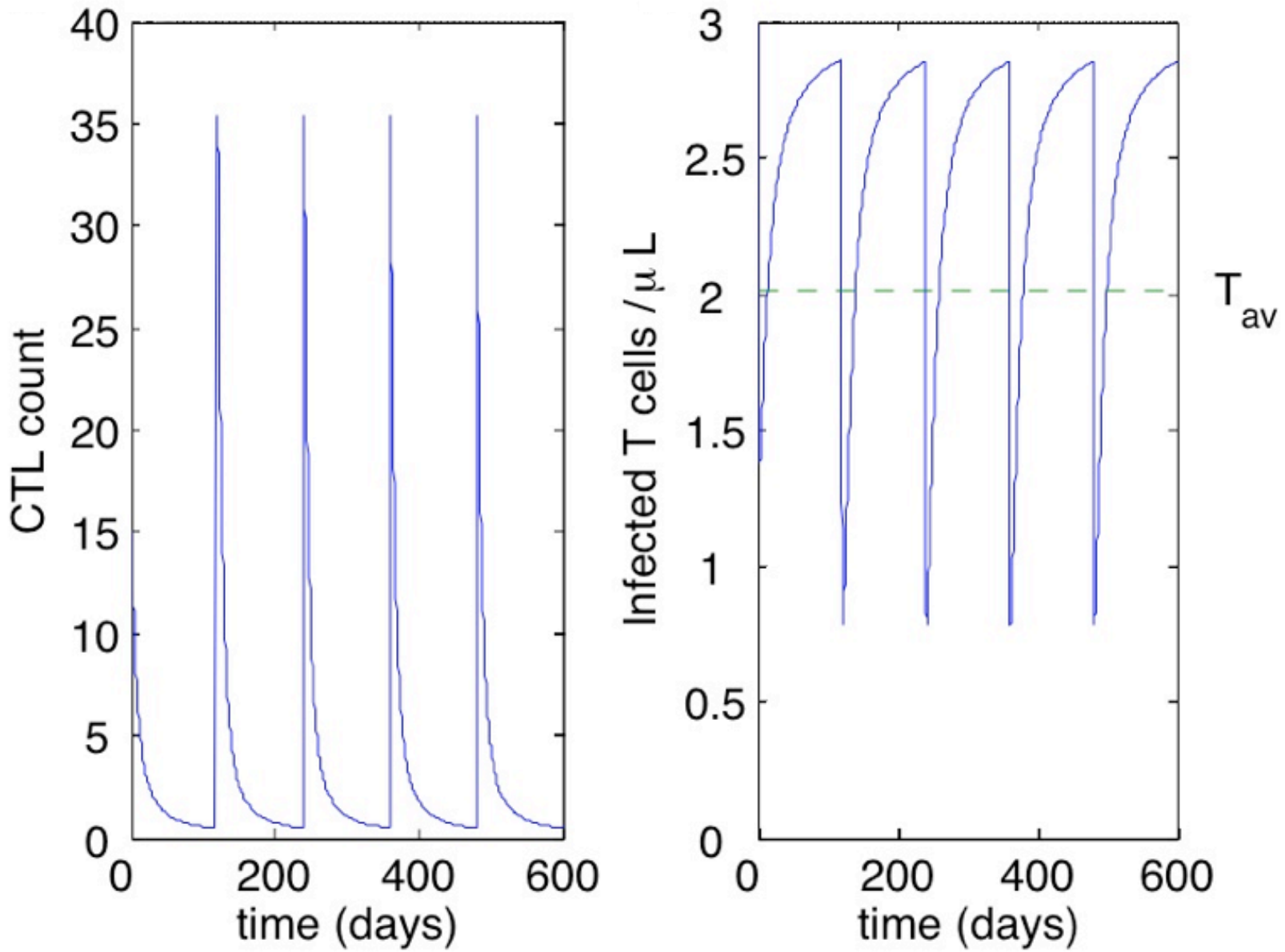

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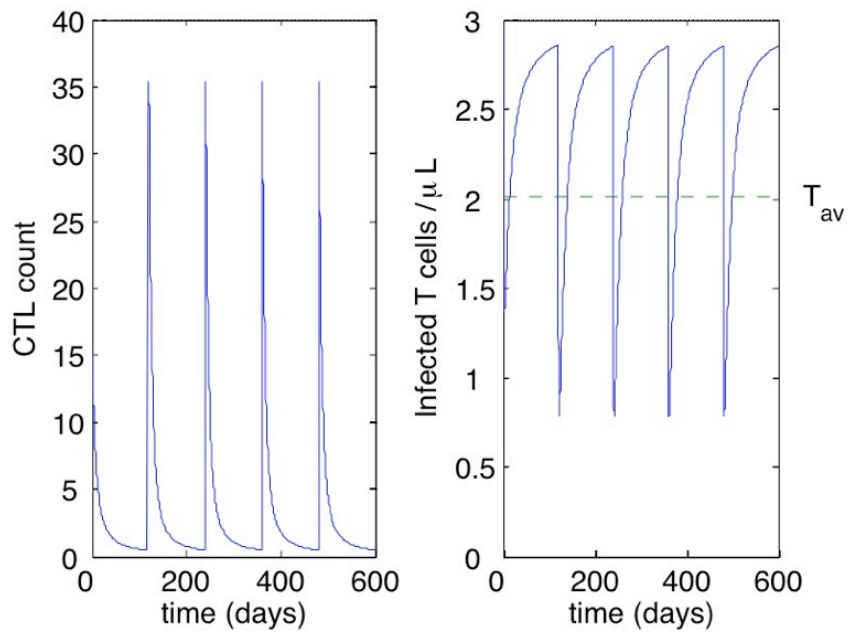

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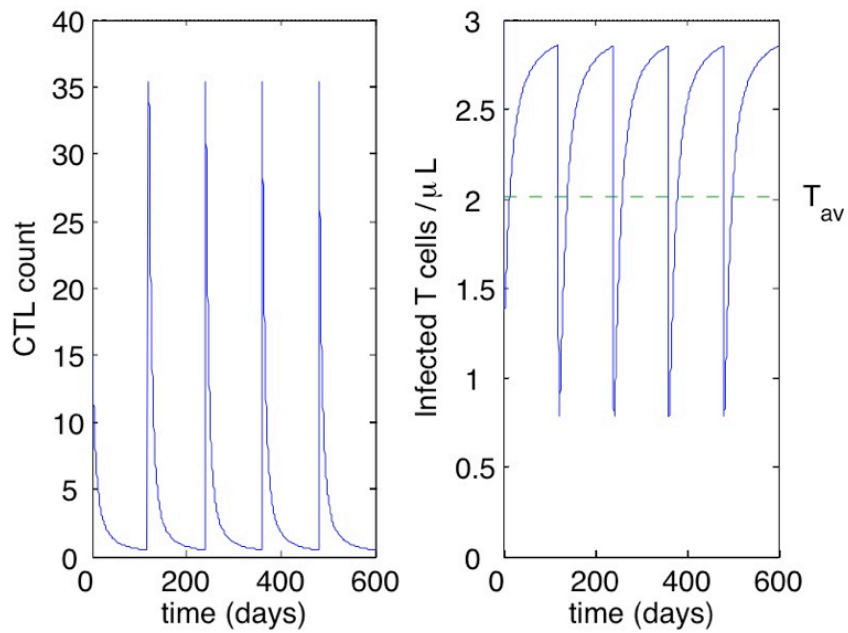
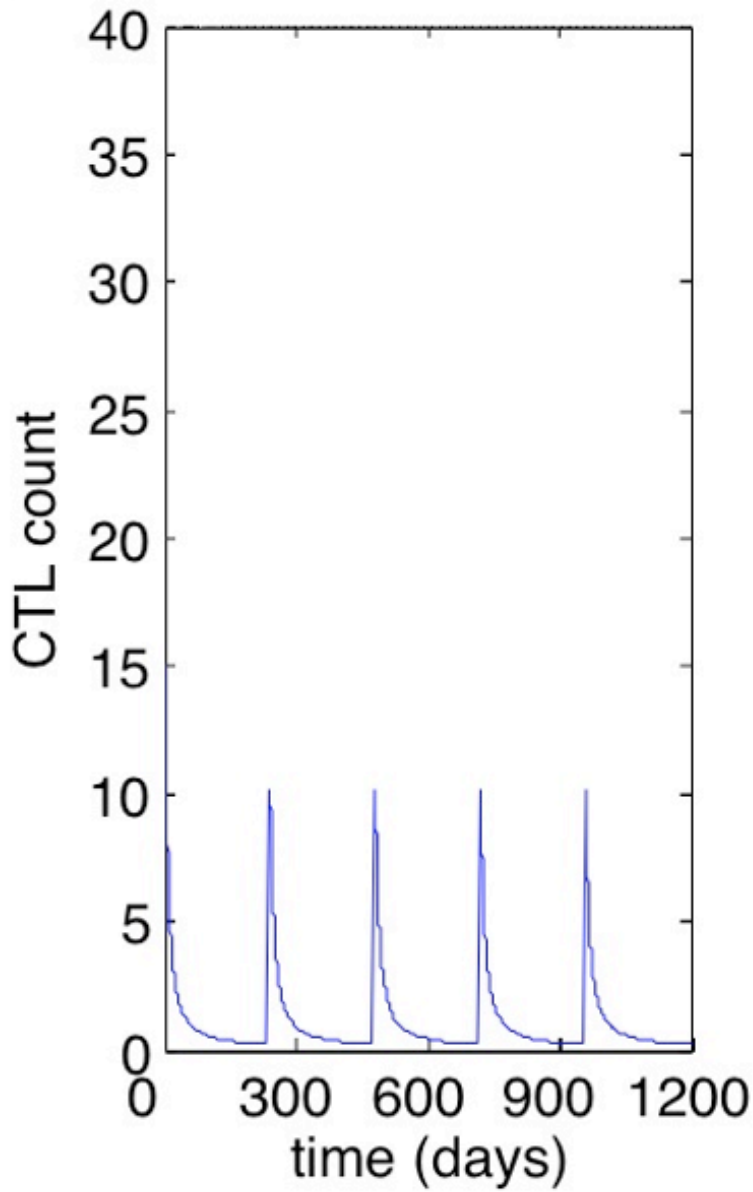
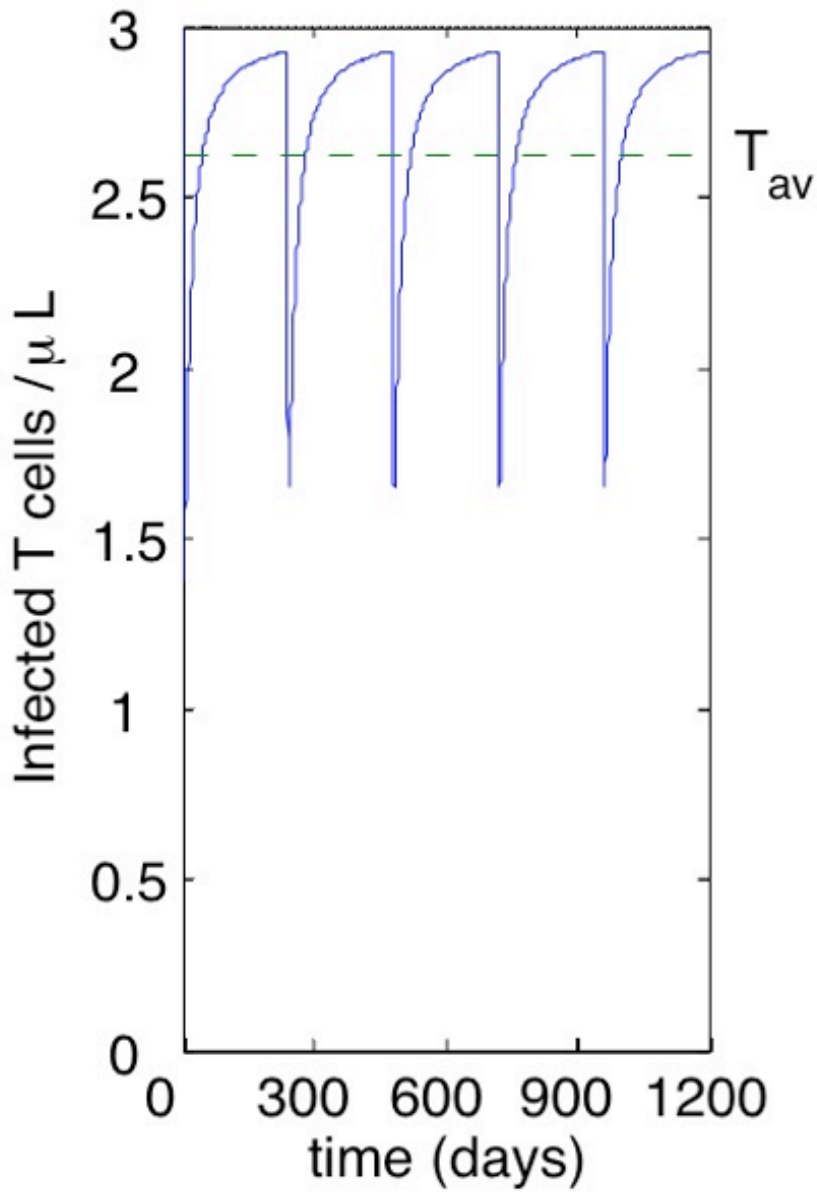
  (better than the desired 2.6 cells μL^{-1}).



C^i = 10 cells μL^{-1}, τ = 240 days





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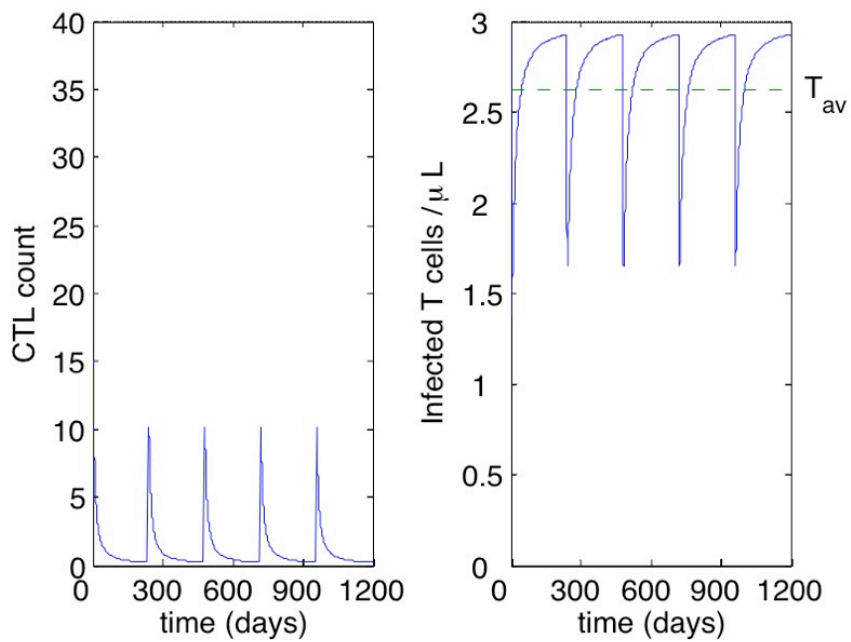

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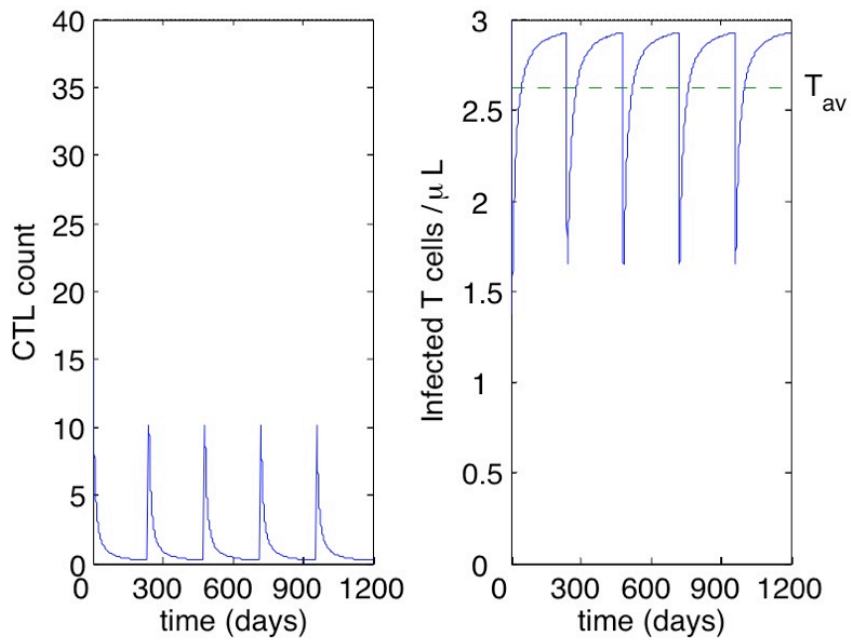

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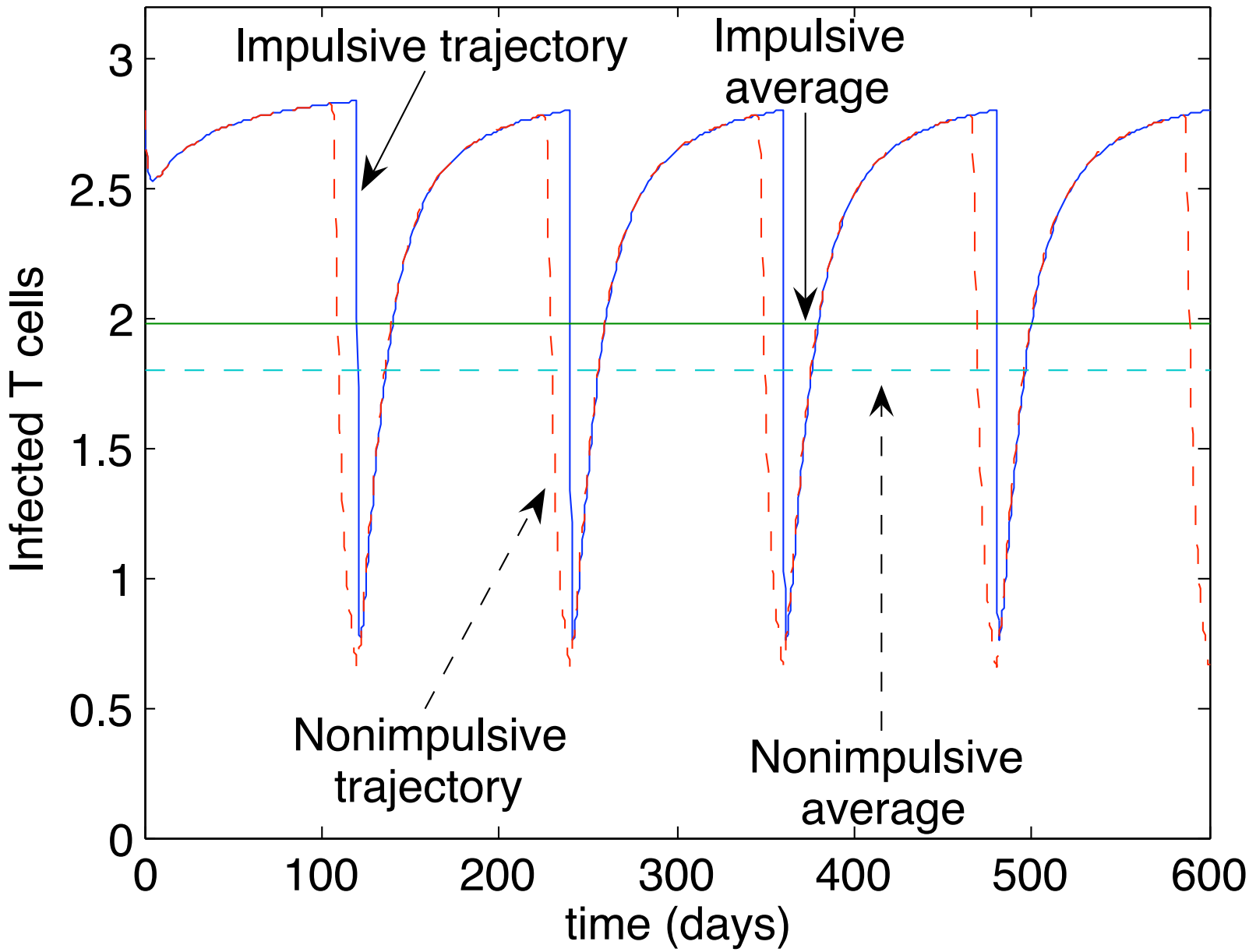
- This might be too coarse for an impulsive approximation...
- ...so we ran numerical simulations to test the accuracy of the results.

A reasonable approximation



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- It follows that the actual average will be lower if our recommendations are implemented.

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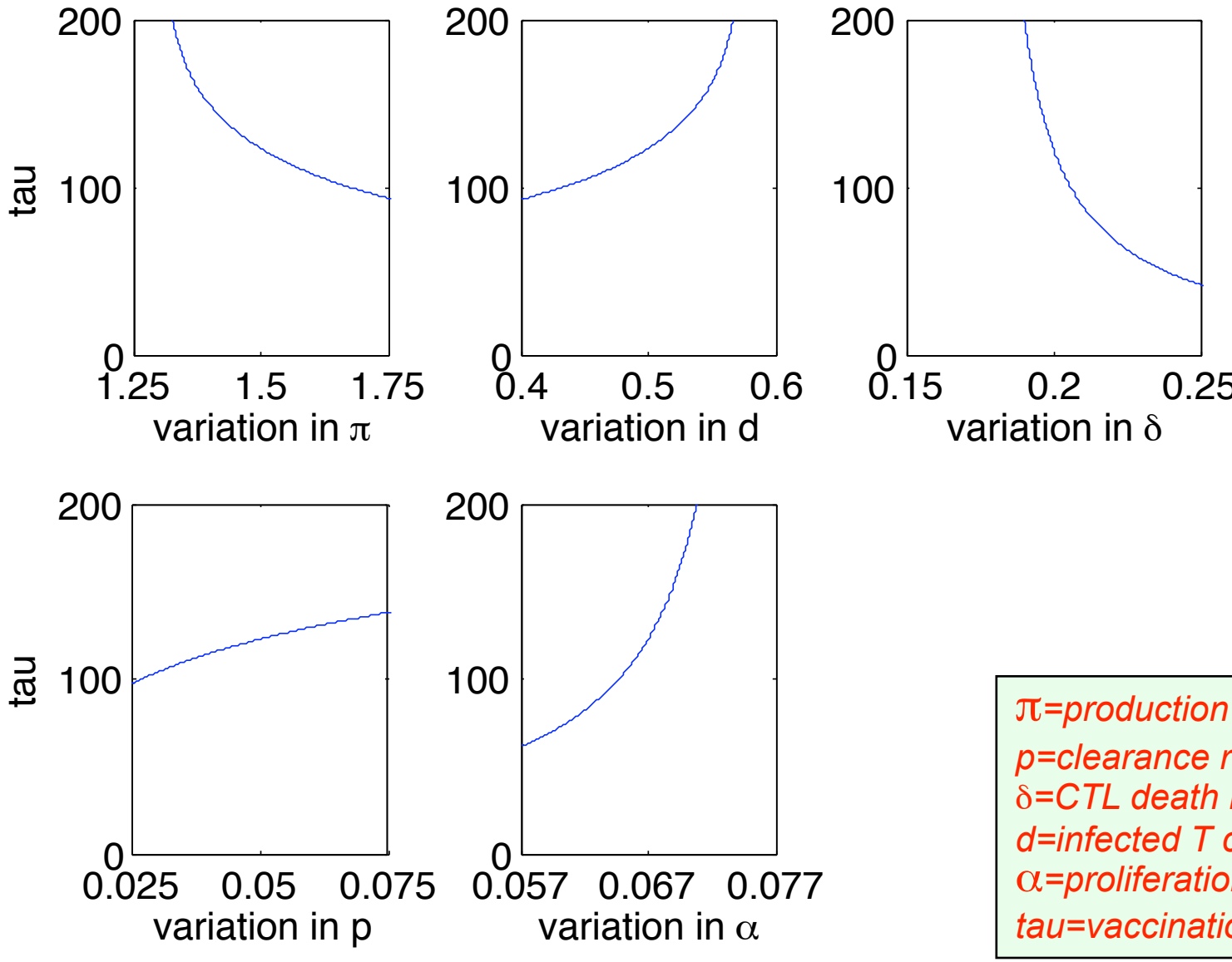
Sensitivity of parameters



π=production rate
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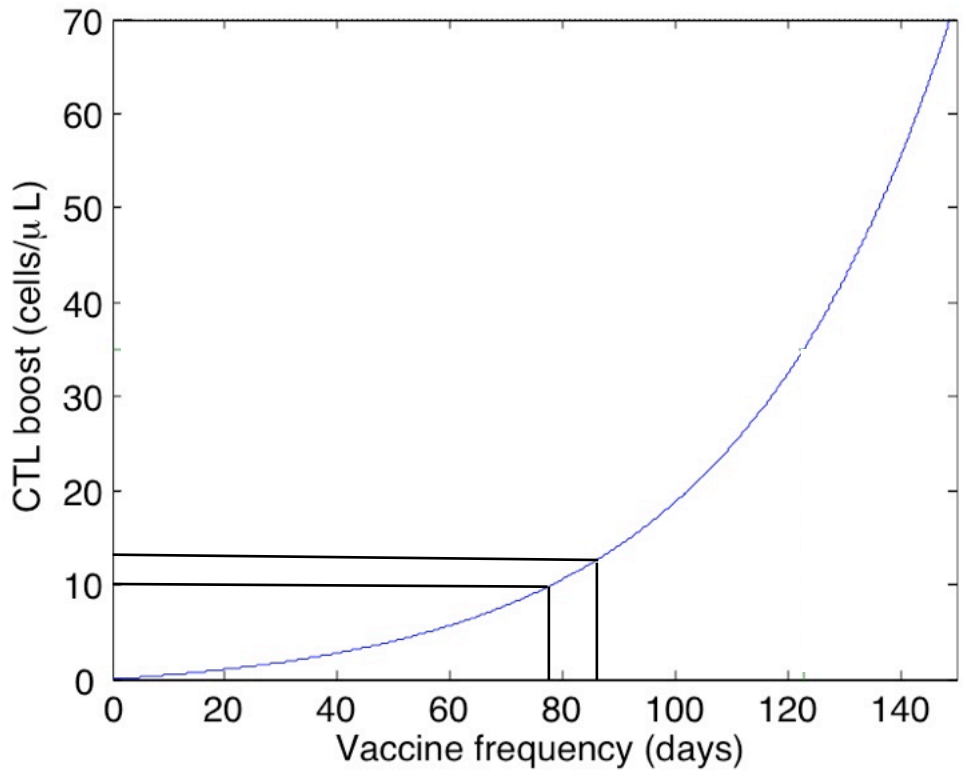
- Impulsive Floquet theory is not easily extendable to higher-order models.

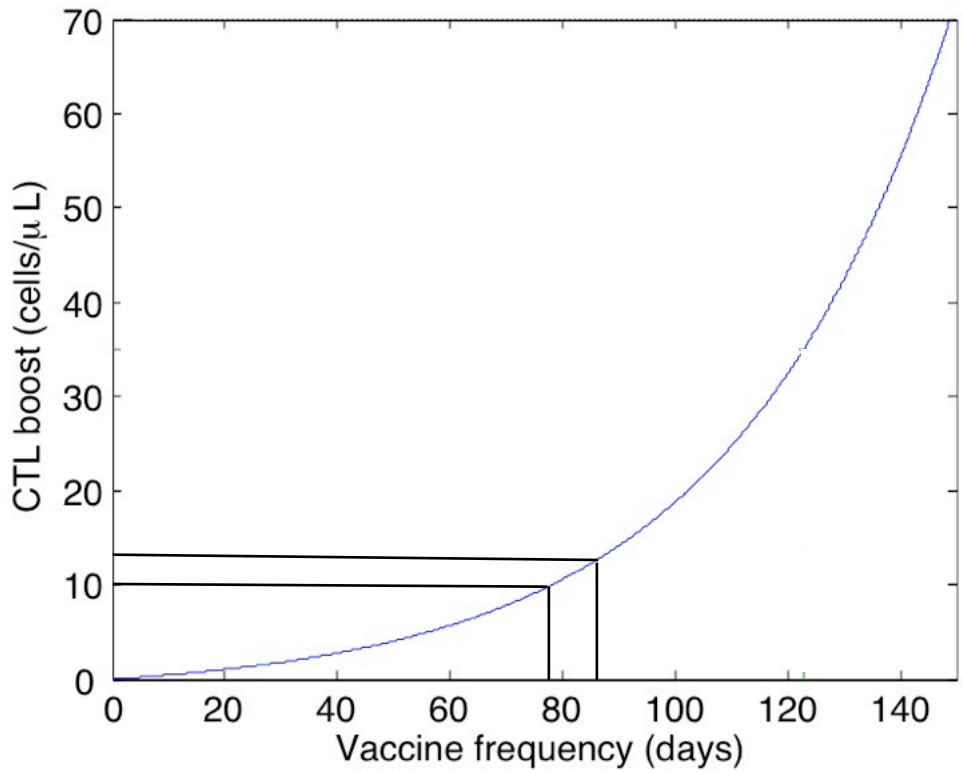
Implications for weak vaccines

- A small increase in the vaccine strength may result in a significantly larger range of possible vaccination intervals when the boost is low



Implications for weak vaccines

- A small increase in the vaccine strength may result in a significantly larger range of possible vaccination intervals when the boost is low
- Thus, CTL vaccines whose strength is too low would be less desirable, even if the frequency could be tolerated.



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- The consequences of missing a single vaccination are more severe than missing a single drug dose.

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- The effects of fluctuations in the vaccination time, even if administered quasi-regularly

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- Consequences of vaccine “resistance”.

Summary

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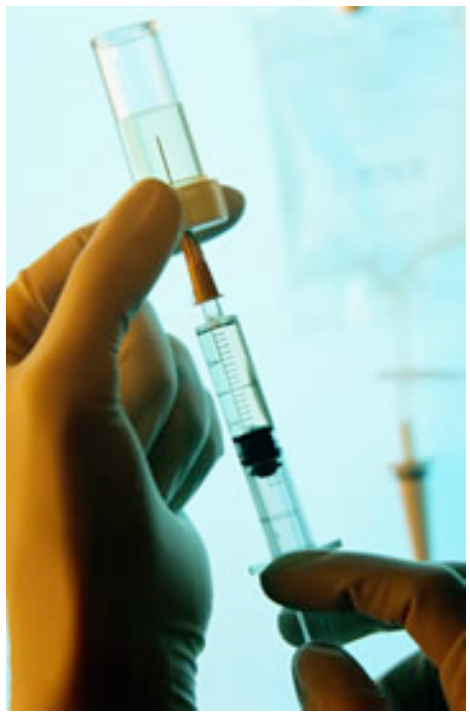

Summary

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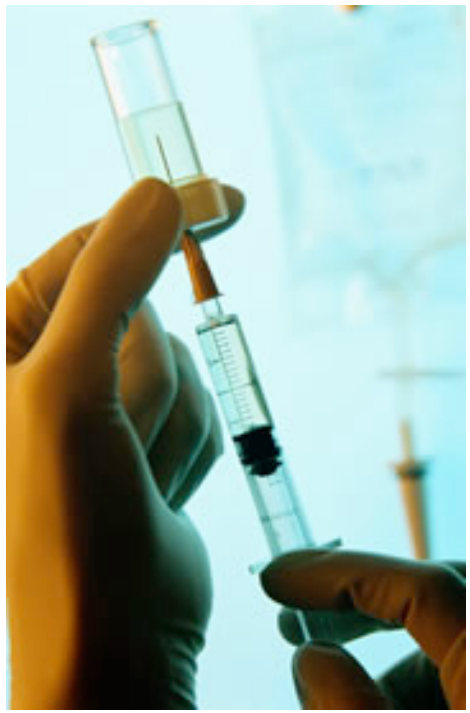
- The estimate is overconservative, so this will actually result in a lower average number of infected T cells than theoretically predicted.



Conclusions

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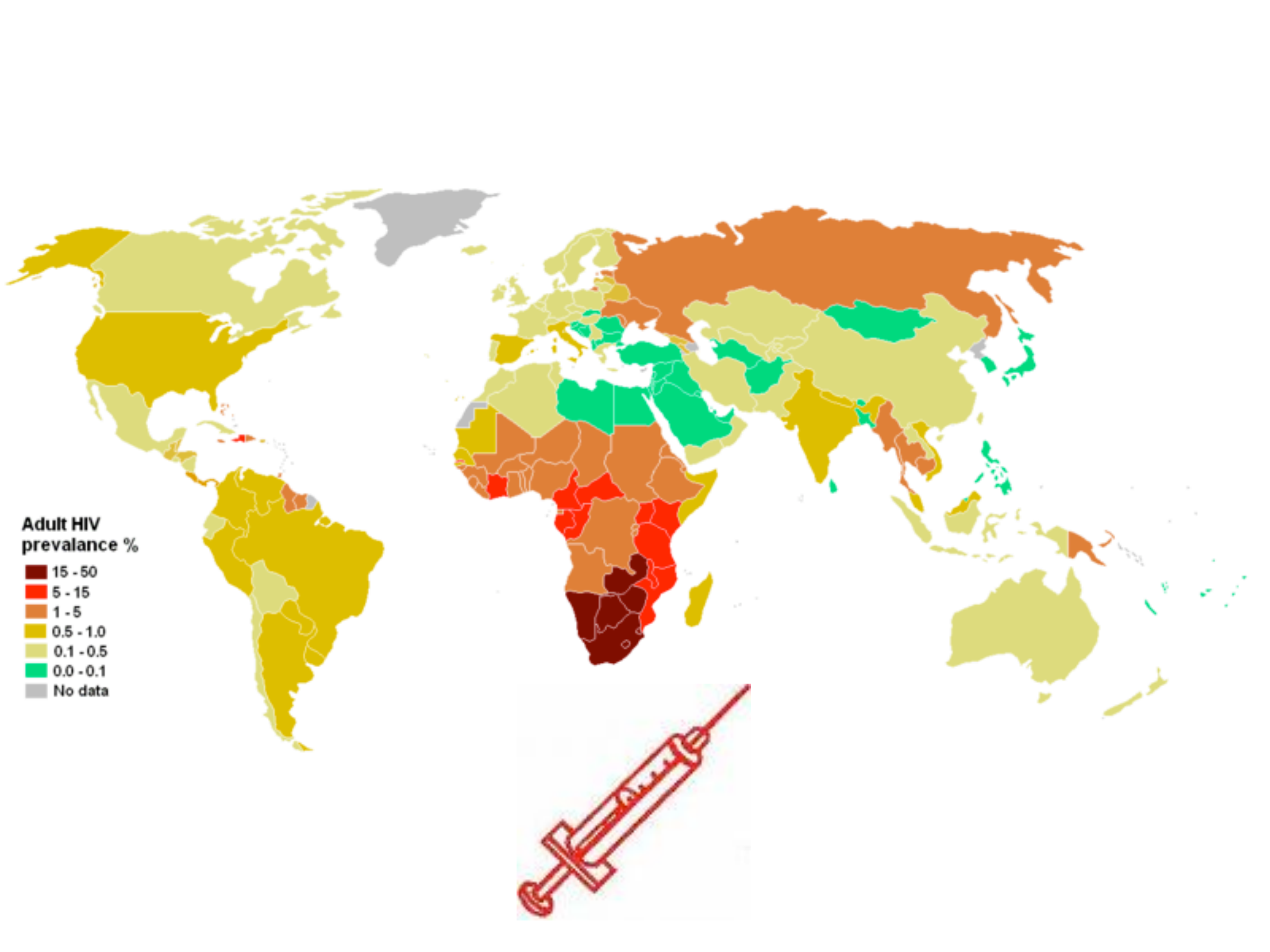
- Such a vaccine would offer a realistic alternative to the daily pill burden of antiretroviral drug therapy

Conclusions

- A post-infection CTL vaccine would be highly desirable, assuming perfect patient adherence
- Such a vaccine would offer a realistic alternative to the daily pill burden of antiretroviral drug therapy
- We recommend that such a vaccine should be available for self-administration by patients.

Key reference

- R.J. Smith? and E.J. Schwartz, Predicting the potential impact of a cytotoxic T-lymphocyte HIV vaccine: how often should you vaccinate and how strong should the vaccine be? (*Mathematical Biosciences 2008, 212:180-187*)


Adult HIV
prevalance %
15 - 50
5 - 15
1 - 5
0.5 - 1.0
0.1 - 0.5
0.0 - 0.1
No data