In-host Models

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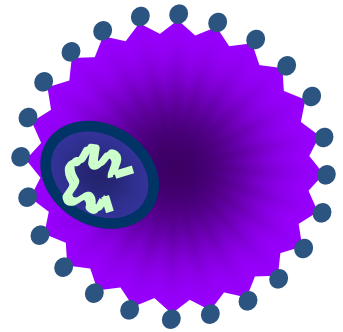
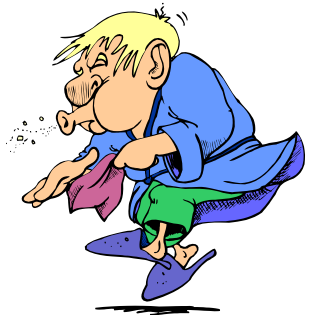


Immune System

- Works around the clock in thousands of different ways, largely unnoticed.
- When it fails, we notice
  - Get sick i.e. bacteria, viruses
- Also notice when it is at work
  - Splinter – inflammation and pain, puss
  - Mosquito bite - get a red, itchy bump
  - Infectious disease – fever, runny nose, cough - the immune system at work!!



Components of Immune system

- Skin - primary boundary between germs and your body
  - Epidermis contains special cells that are an important early-warning component in the immune system.
  - Skin also secretes antibacterial substances- most bacteria and spores that land on the skin die quickly.

- Nose, mouth and eyes - obvious entry points for germs
  - Tears and mucus contain an enzyme that breaks down the cell wall of many bacteria.
  - Saliva is also anti-bacterial.
  - Nasal passage and lungs are coated in mucus - many germs not killed immediately are trapped in the mucus and soon swallowed.
  - Mast cells also line the nasal passages, throat, lungs and skin

- Once inside the body, a germ deals with the immune system at a different level. The major components of the immune system are:
  - Thymus
  - Spleen
  - Lymph system
  - Bone marrow

  - White blood cells
  - Antibodies
  - Complement system
  - Hormones

Immune System

- Each day you
  - Inhale or eat thousands of germs (bacteria and viruses).
  - Your immune system deals with all of them without a problem – skin, mucous, saliva.
  - Occasionally a germ gets past the immune system and you get sick
    - Fever, runny nose, vomitting.
  - If you get better, your immune system was working.

- There are also human ailments that are caused by the immune system working in unexpected or incorrect ways that cause problems.
  - Examples:
  - Allergies - immune system overreacting to certain stimuli that other people don't react to at all.
  - Diabetes - caused by the immune system inappropriately attacking cells in the pancreas and destroying them.
  - Rheumatoid arthritis - caused by the immune system acting inappropriately in the joints

- Finally, immune system may somtimes prevent us from doing things that would be otherwise beneficial
  - i.e. Organ transplants - immune system often rejects the transplanted organ.

Bacteria and Viruses

- Your body
  - Multi-cellular organism made up of perhaps 100 trillion cells.
  - The cells in your body are fairly complicated machines - have a nucleus, energy production equipment, etc.

- Bacteria
  - Single-celled organisms that are much simpler (no nucleus)
  - About 1/100th the size of a human cell (1 micrometer long)
  - Can eat and reproduce
  - One bacterium divides into two separate bacteria perhaps once every 20-30 min
    - At that rate, one bacteria can become millions in just a few hours.

- Virus
  - Not really alive – virus particle is a fragment of DNA/RNA in a protective coat
  - Virus comes in contact with a cell, attaches itself to the cell wall and injects its DNA (and perhaps a few enzymes) into the cell
  - The DNA uses the machinery inside the living cell to reproduce new virus particles
  - Eventually the hijacked cell dies and bursts, freeing the new virus particles; or the viral particles may bud off of the cell so it remains alive

Immune System

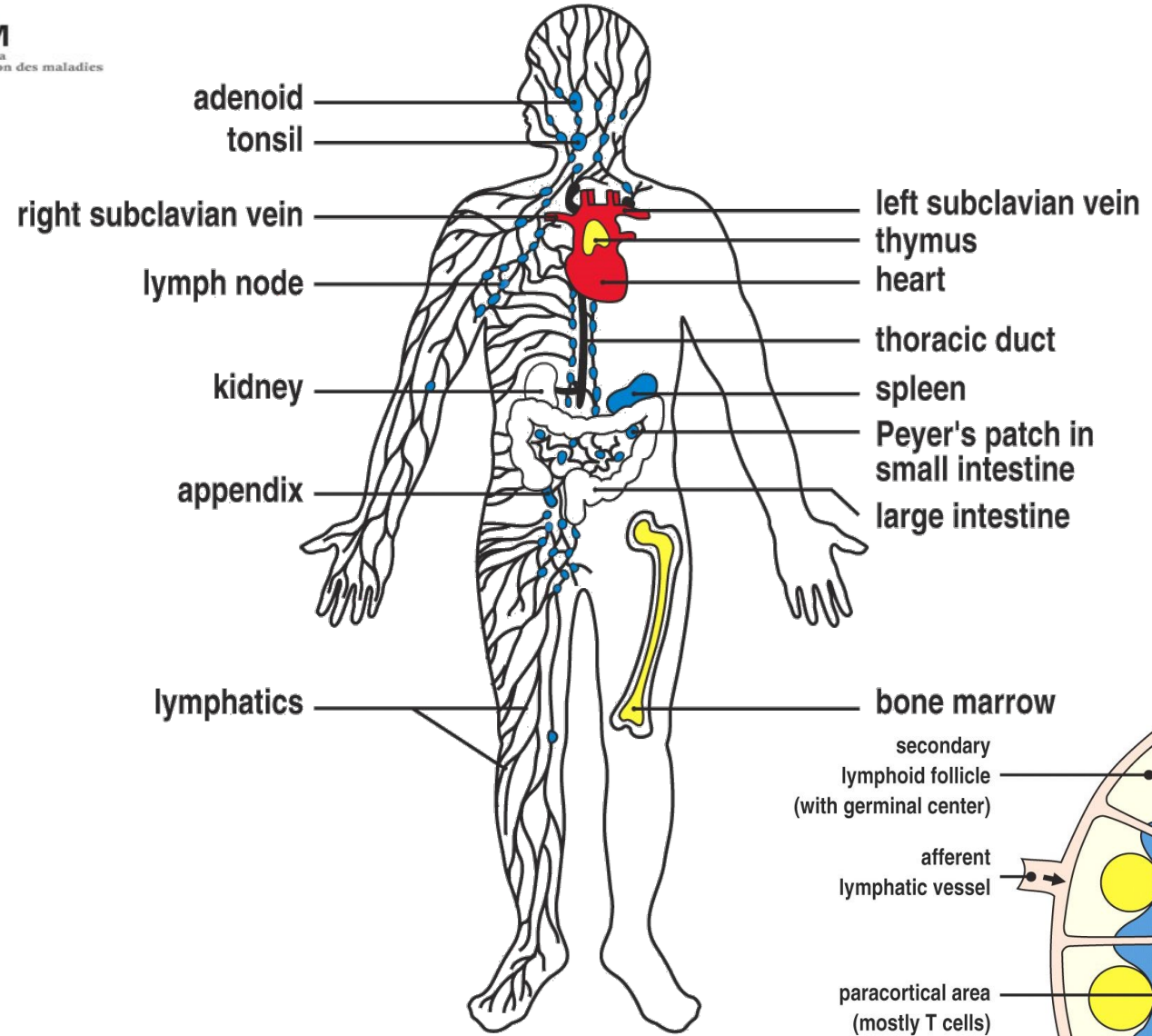
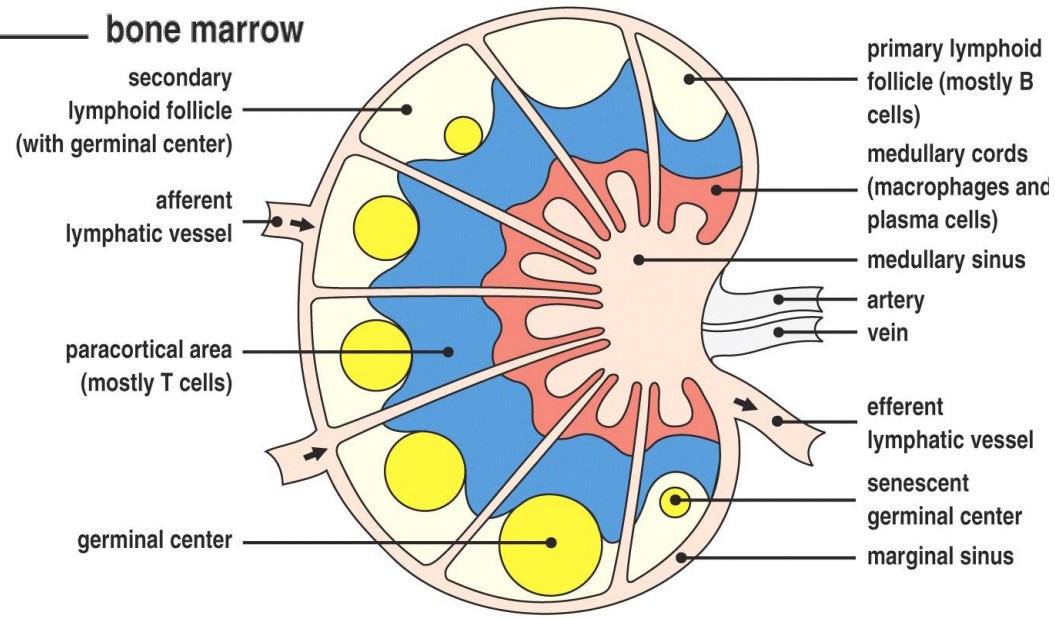


Figure 1-7 Immunobiology, 6/e. (© Garland Science 2005)



gure 1-8 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Immune System

- Like, the circulatory system, the lymphatic system is a network of vessels.
- Unlike the circulatory system, the lymphatic system has no "pump" located within the lymph vessels
  - Relies on bodily movement as well as nearby pulses from other vessels and organs in the body to facilitate the flow of the lymph fluid.
- I.e. if you do not move, the lymph does not move well.
- Very sedentary individuals – more prone to sickness

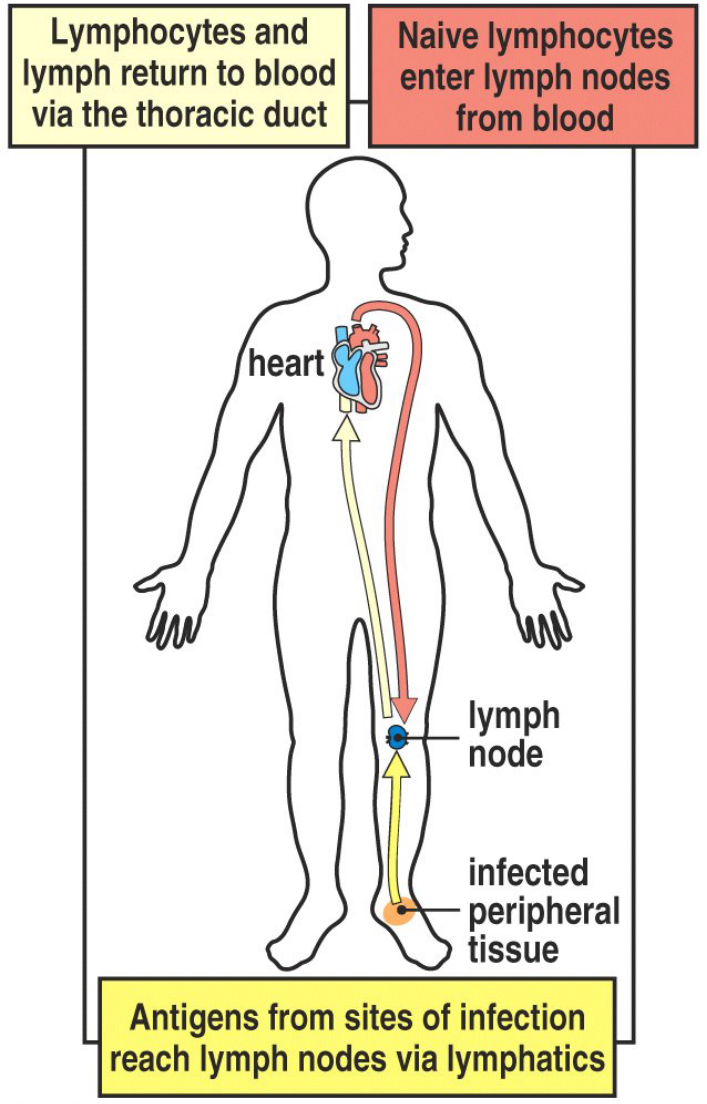


Figure 1-11 Immunobiology, 6/e. (© Garland Science 2005)

Figure 1-3 part 2 of 4

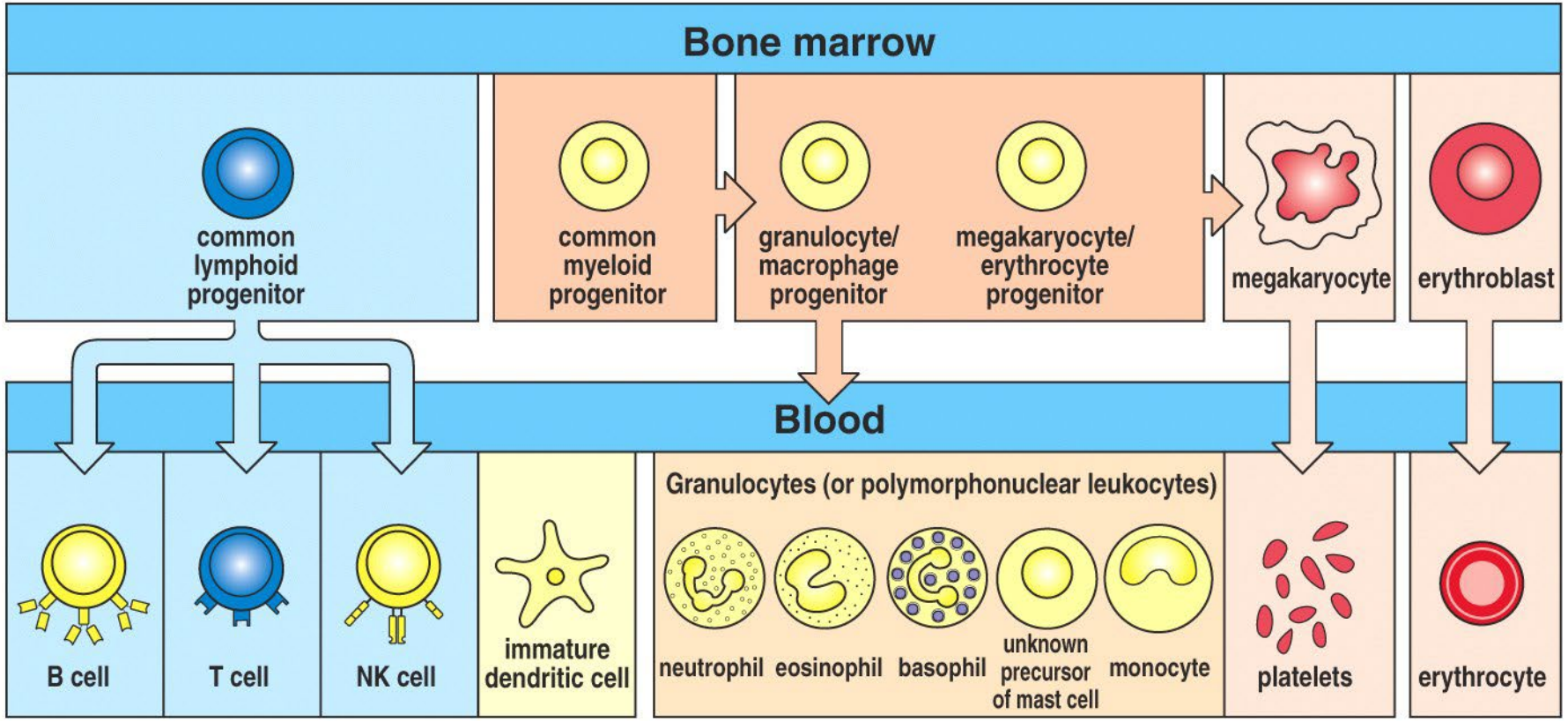


Figure 1-3 part 2 of 4 Immunobiology, 6/e. (© Garland Science 2005)

Figure 1-3 part 3 of 4

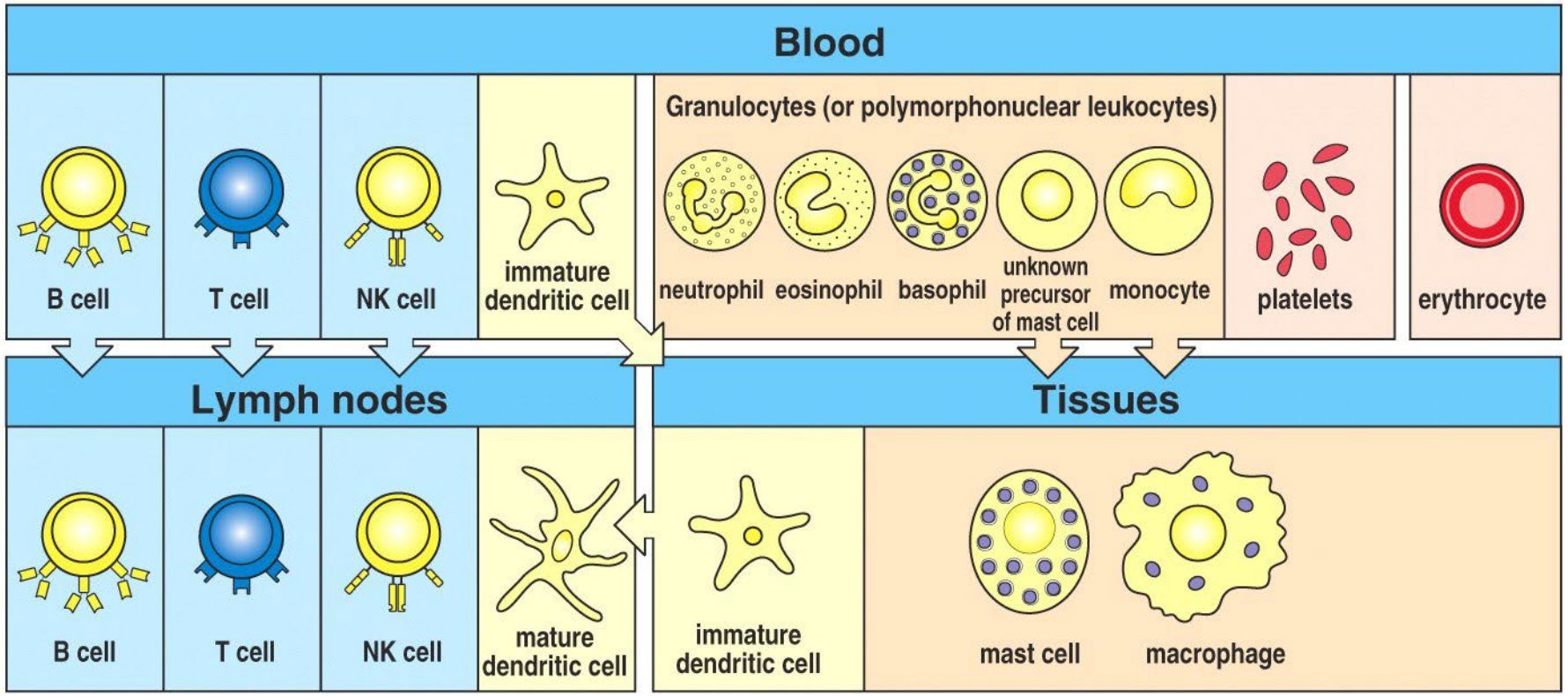


Figure 1-3 part 3 of 4 Immunobiology, 6/e. (© Garland Science 2005)

Figure 1-3 part 4 of 4

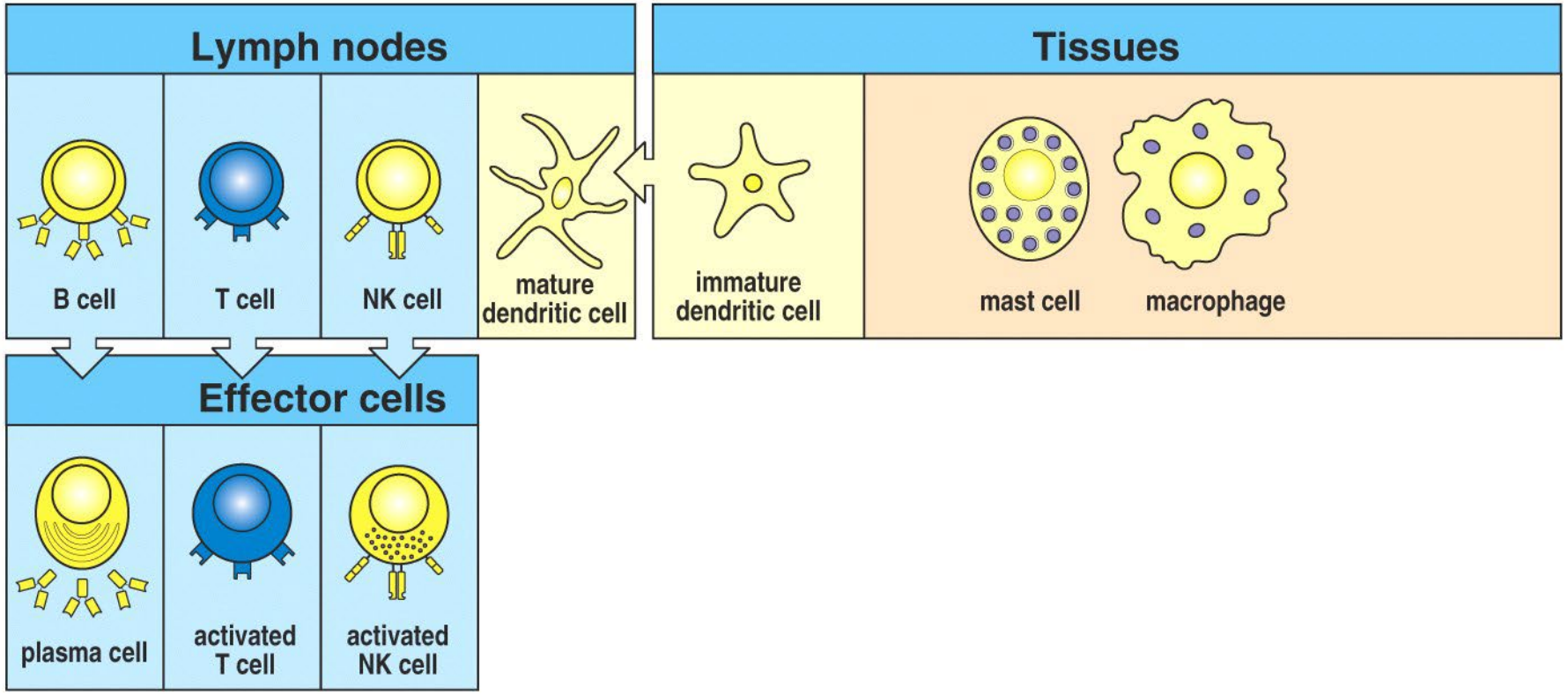
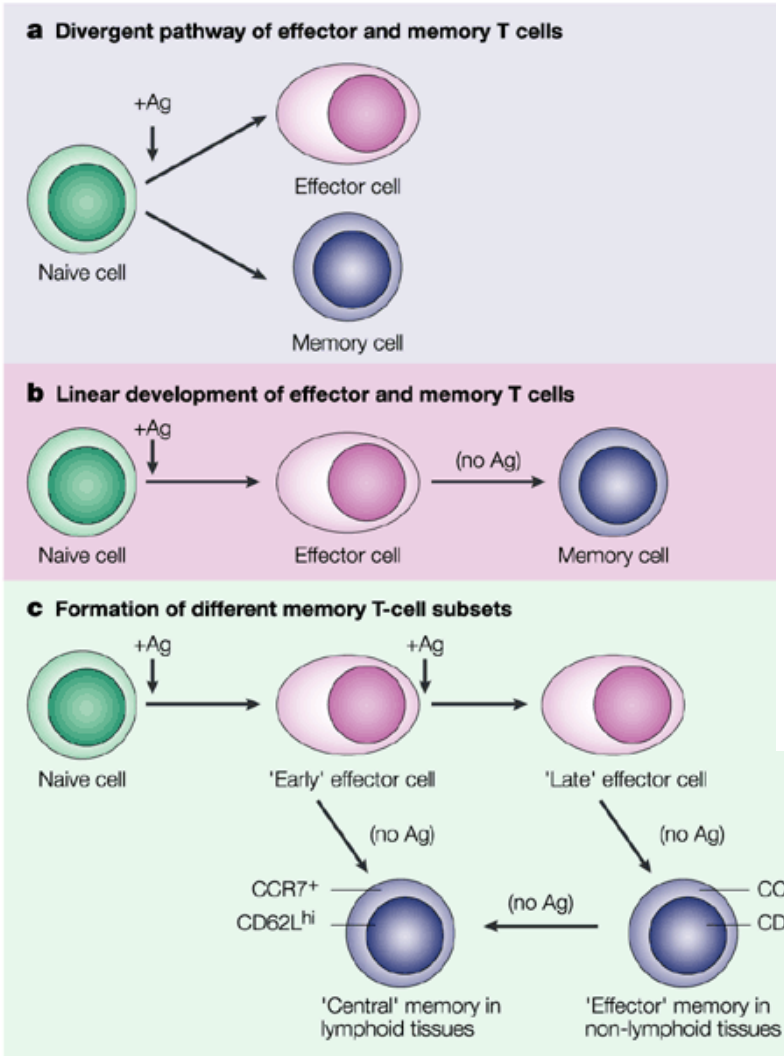
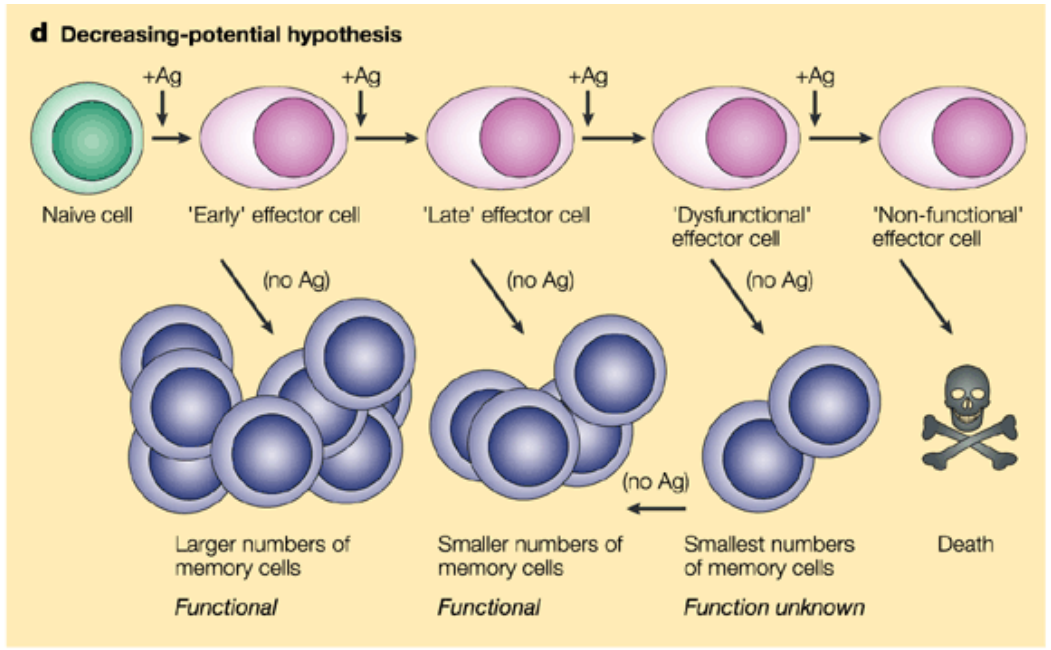


Figure 1-3 part 4 of 4 Immunobiology, 6/e. (© Garland Science 2005)

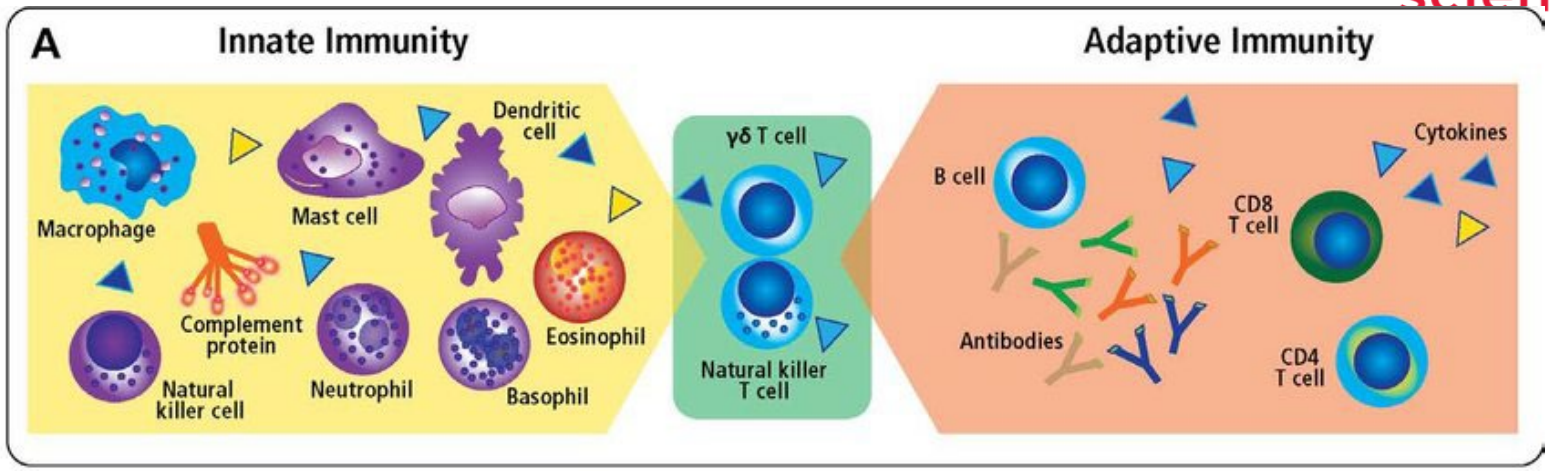
Memory Cells





Nature Reviews | Immunology

Effector and memory T-cell differentiation: implications for vaccine development
Susan M. Kaech, E. John Wherry & Rafi Ahmed
Nature Reviews Immunology **2**, 251-262 (April 2002)



Immunity
Ability to identify and eliminate harmful "non-self" microorganisms and substances (toxins)

Innate/natural/native immunity
(Early respone action within minutes)

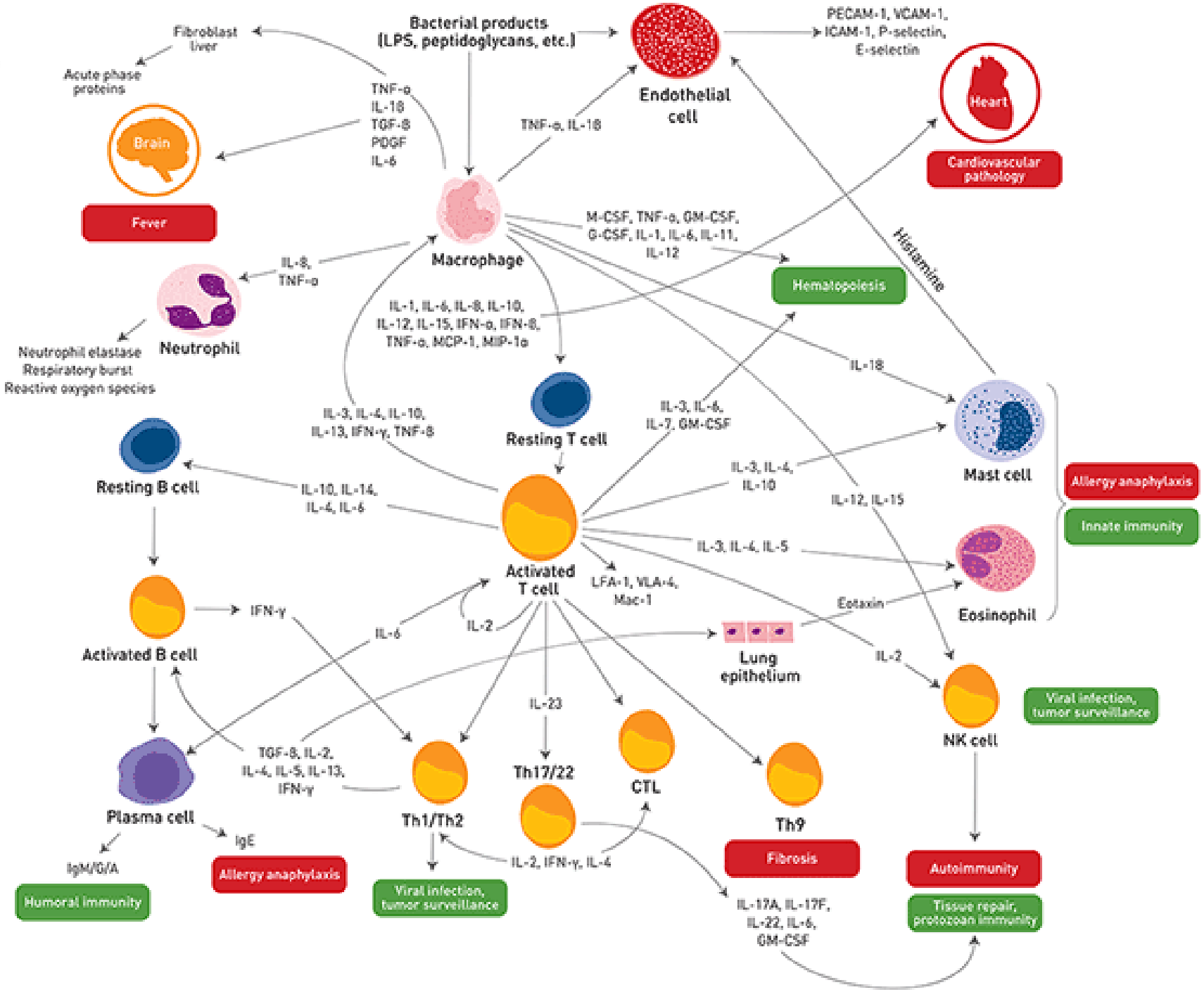
Adaptive/Acquired Immunity
(Later respone action in days)

Cells involved (Phagocytes)
- Neutrophils
- Macrophages
-Dendritic cells
- Eosinophils
- Basophils/mast cells
- Natural killer cells

Soluble factors involved
- Acute-phase proteins
- Cytokines
- Complement

Cells involved (Lymphocytes)
- T lymphocytes
- B lymphocytes
- Dendritic cells
-Antigen presenting cells(APC)

Soluble factors involved
- Antibodies


Fibroblast
liver
Acute phase proteins
Bacterial products (LPS, peptidoglycans, etc.)
Endothelial cell
PECAM-1, VCAM-1, ICAM-1, P-selectin, E-selectin
Heart
Cardiovascular pathology
TNF-α IL-1β TGF-β PDGF IL-6
TNF-α, IL-1β
Brain
Fever
Macrophage
M-CSF, TNF-α, GM-CSF, G-CSF, IL-1, IL-6, IL-11, IL-12
Hematopoiesis
Histamine
IL-8, TNF-α
Neutrophil
Neutrophil elastase
Respiratory burst
Reactive oxygen species
IL-1, IL-6, IL-8, IL-10, IL-12, IL-15, IFN-α, IFN-β, TNF-α, MCP-1, MIP-1α
IL-18
Resting T cell
IL-3, IL-4, IL-10, IL-13, IFN-γ, TNF-β
IL-3, IL-6, IL-7, GM-CSF
Resting B cell
IL-10, IL-14, IL-4, IL-6
Activated T cell
IL-3, IL-4, IL-10
Mast cell
Allergy anaphylaxis
Innate immunity
IL-12, IL-15
IL-3, IL-4, IL-5
LFA-1, VLA-4, Mac-1
Eotaxin
Eosinophil
Activated B cell
IFN-γ
IL-6
IL-2
Lung epithelium
IL-2
Viral infection, tumor surveillance
NK cell
IL-23
TGF-β, IL-2, IL-4, IL-5, IL-13, IFN-γ
Plasma cell
Th1/Th2
Th17/22
CTL
Th9
IgE
IgM/G/A
Humoral immunity
Allergy anaphylaxis
Viral infection, tumor surveillance
IL-2, IFN-γ, IL-4
Fibrosis
Autoimmunity
IL-17A, IL-17F, IL-22, IL-6, GM-CSF
Tissue repair, protozoan immunity

Immune System

- Innate Immunity
- Adaptive Immunity
  - Humoral immunity
    - B-cells and antibodies
  - Cell mediated immunity
    - T-cells
      - Helper and effector

- Lymphocytes
  - T – produced by thymus
    - CD4
      - Helper T-cells
      - Activated by antigen presenting cells
      - Activate the rest of the immune response
    - CD8
      - Killer/effector T-cells
  - B - produced in bone marrow
    - Mature in spleen
    - Plasma cells, antibodies
  - Naive, activated memory

Development of memory

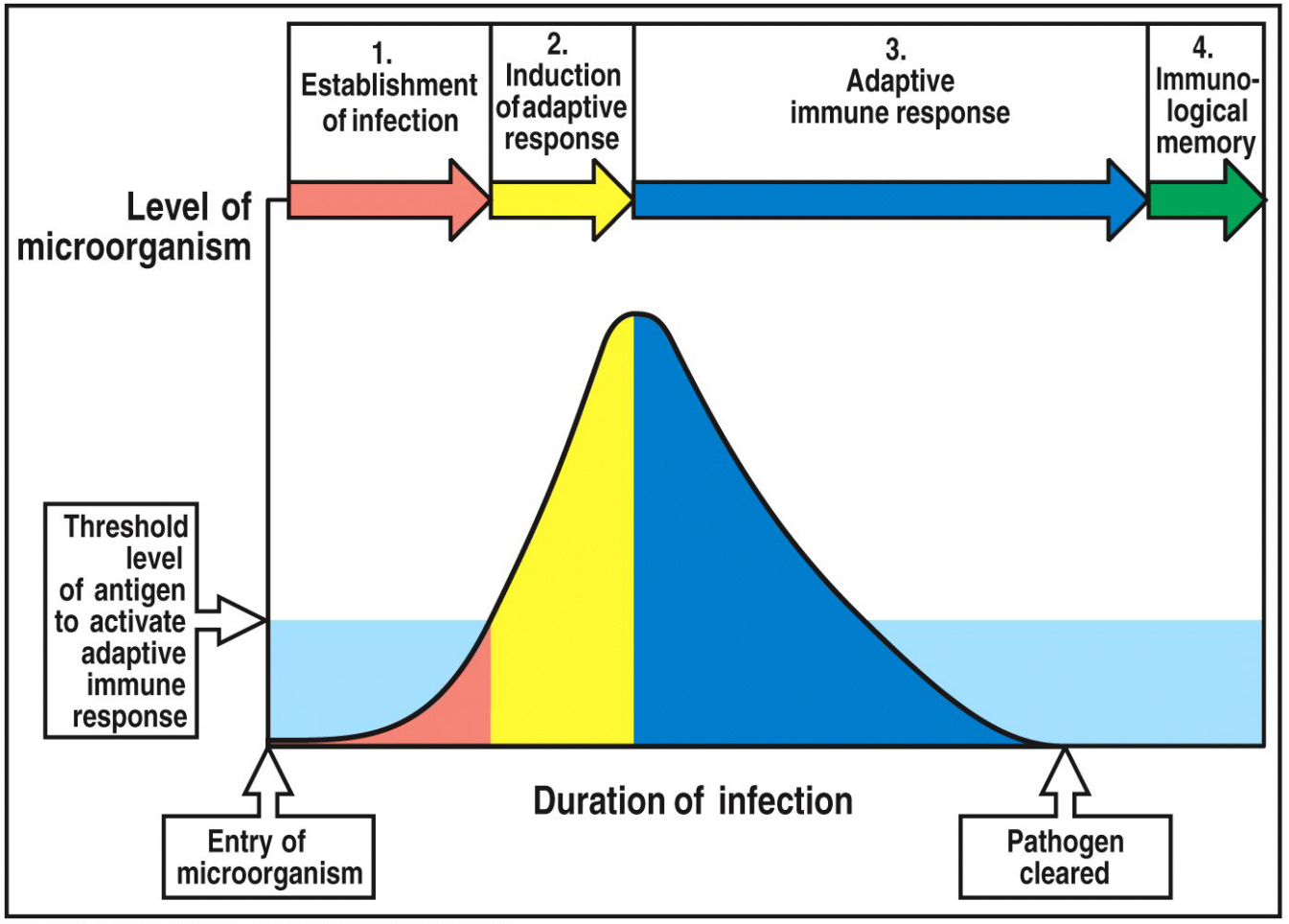
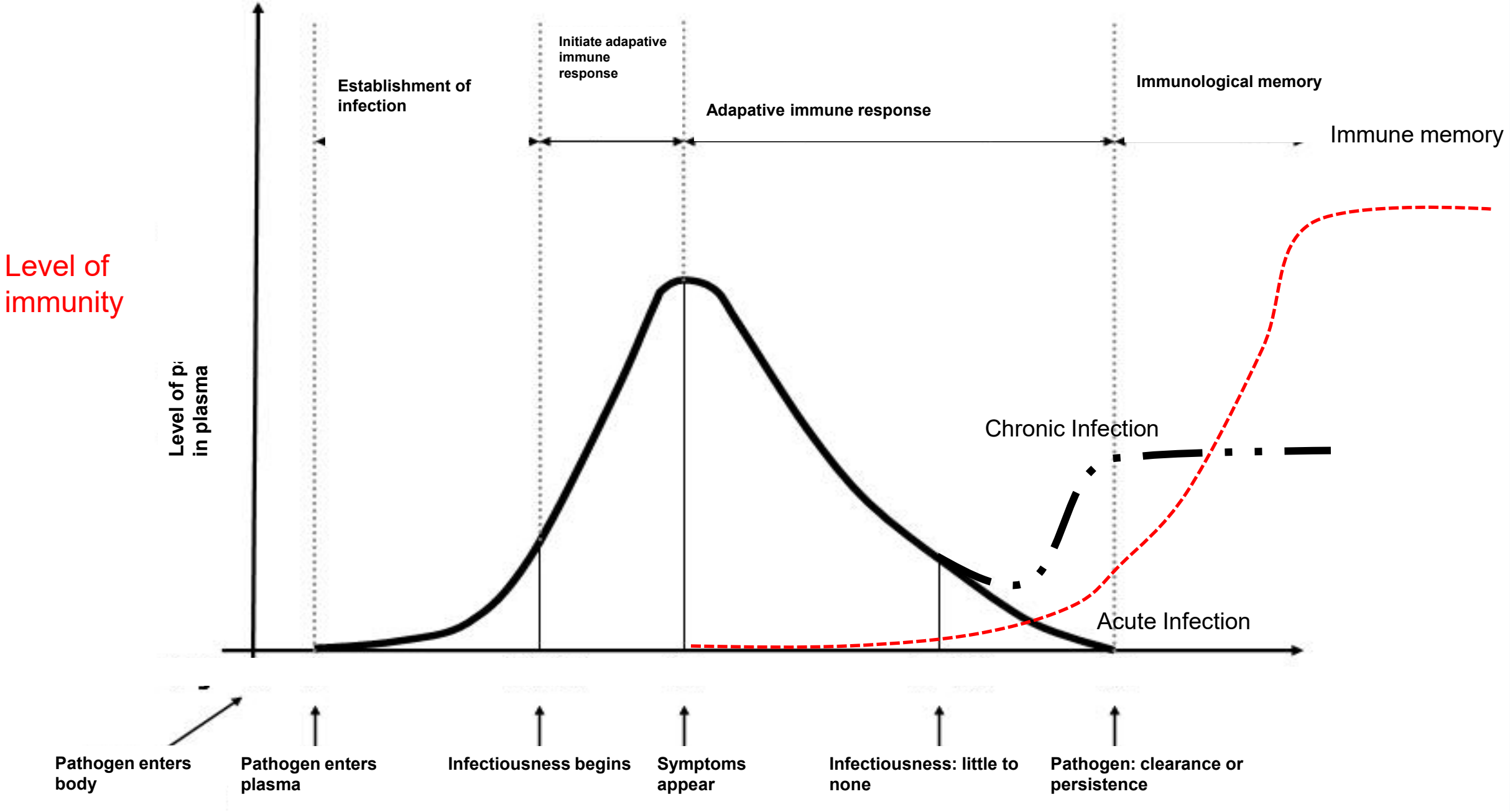
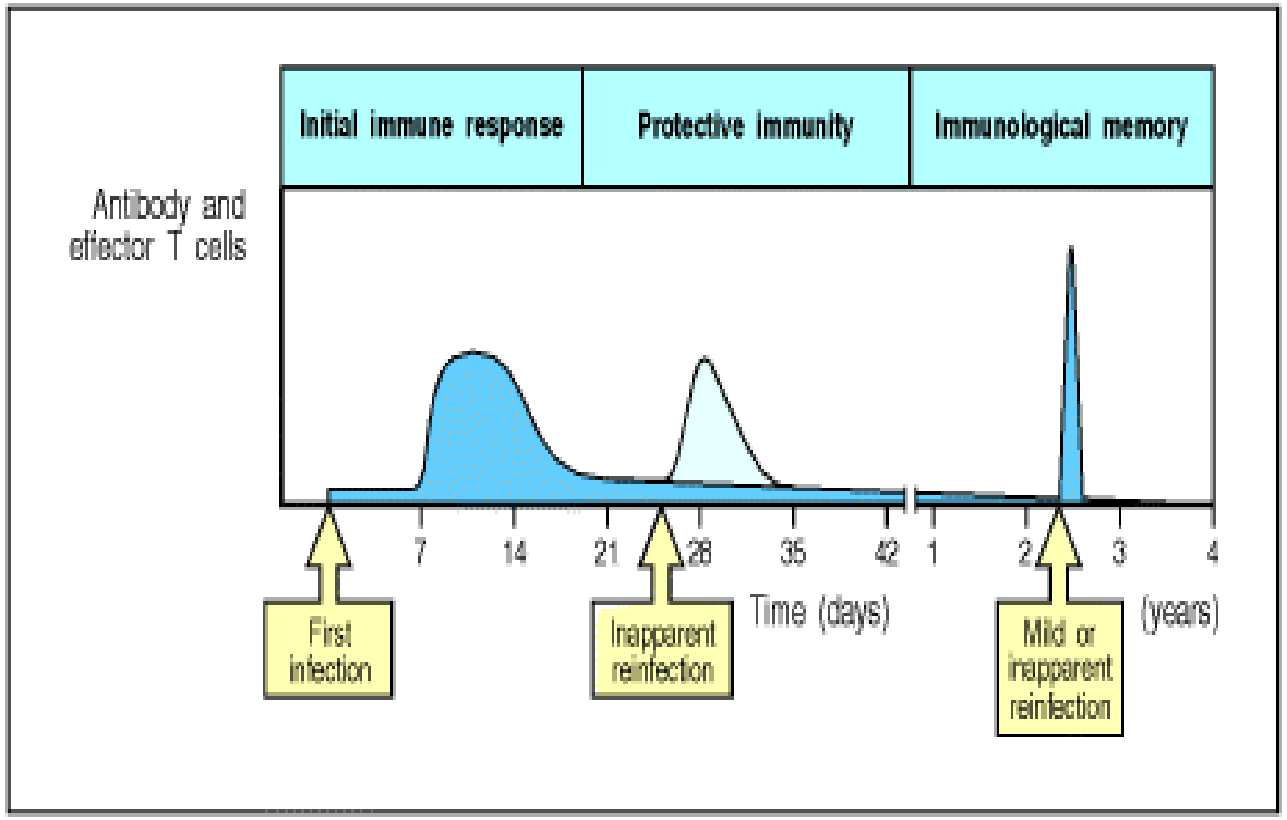


Figure 10-1 Immunobiology, 6/e. (© Garland Science 2005)

- The course of a typical acute infection


Level of immunity
Establishment of infection
Initiate adapative immune response
Adapative immune response
Immunological memory
Immune memory
Level of p
in plasma
Chronic Infection
Acute Infection
Pathogen enters body
Pathogen enters plasma
Infectiousness begins
Symptoms appear
Infectiousness: little to none
Pathogen: clearance or persistence

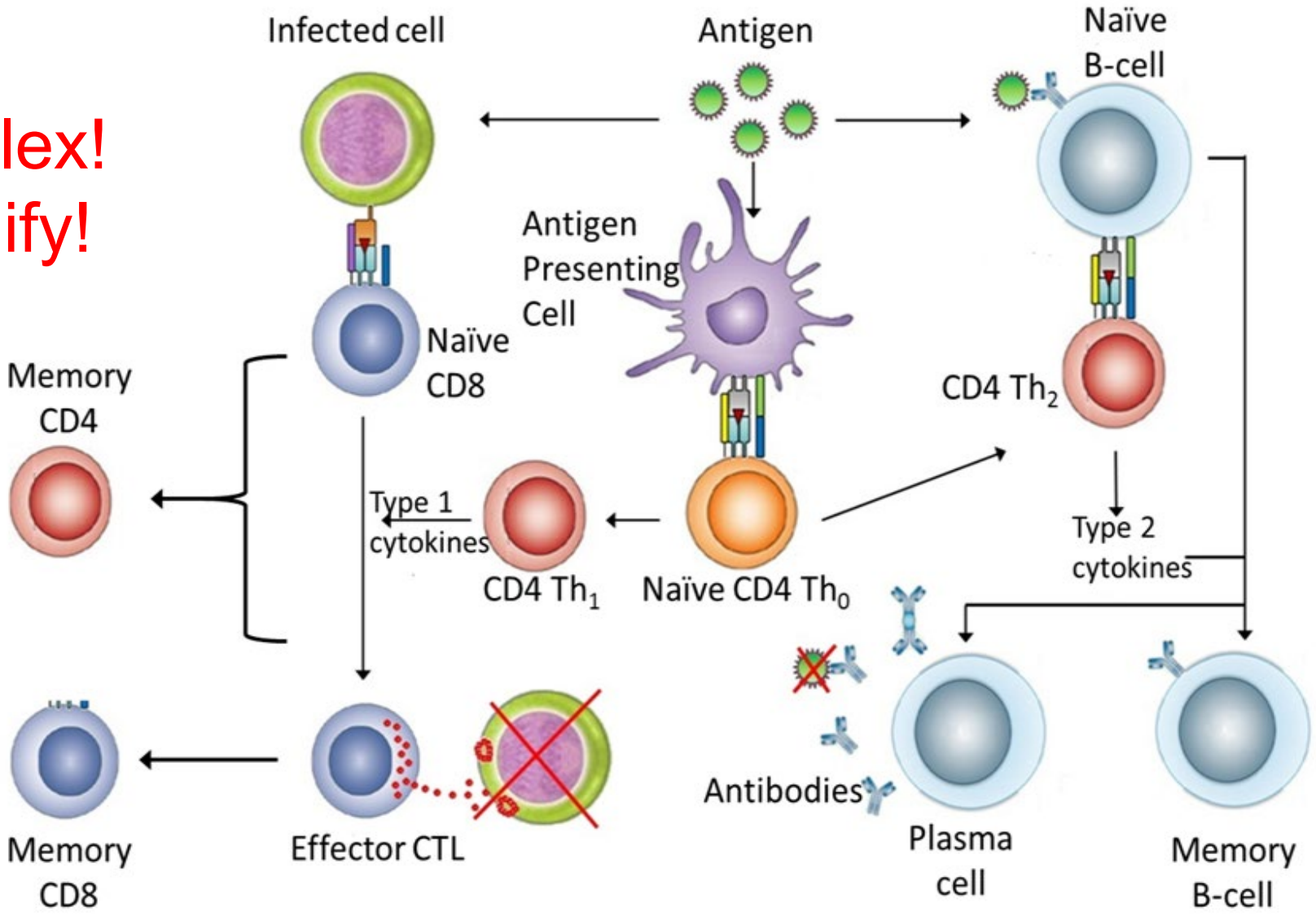
Immunological Memory



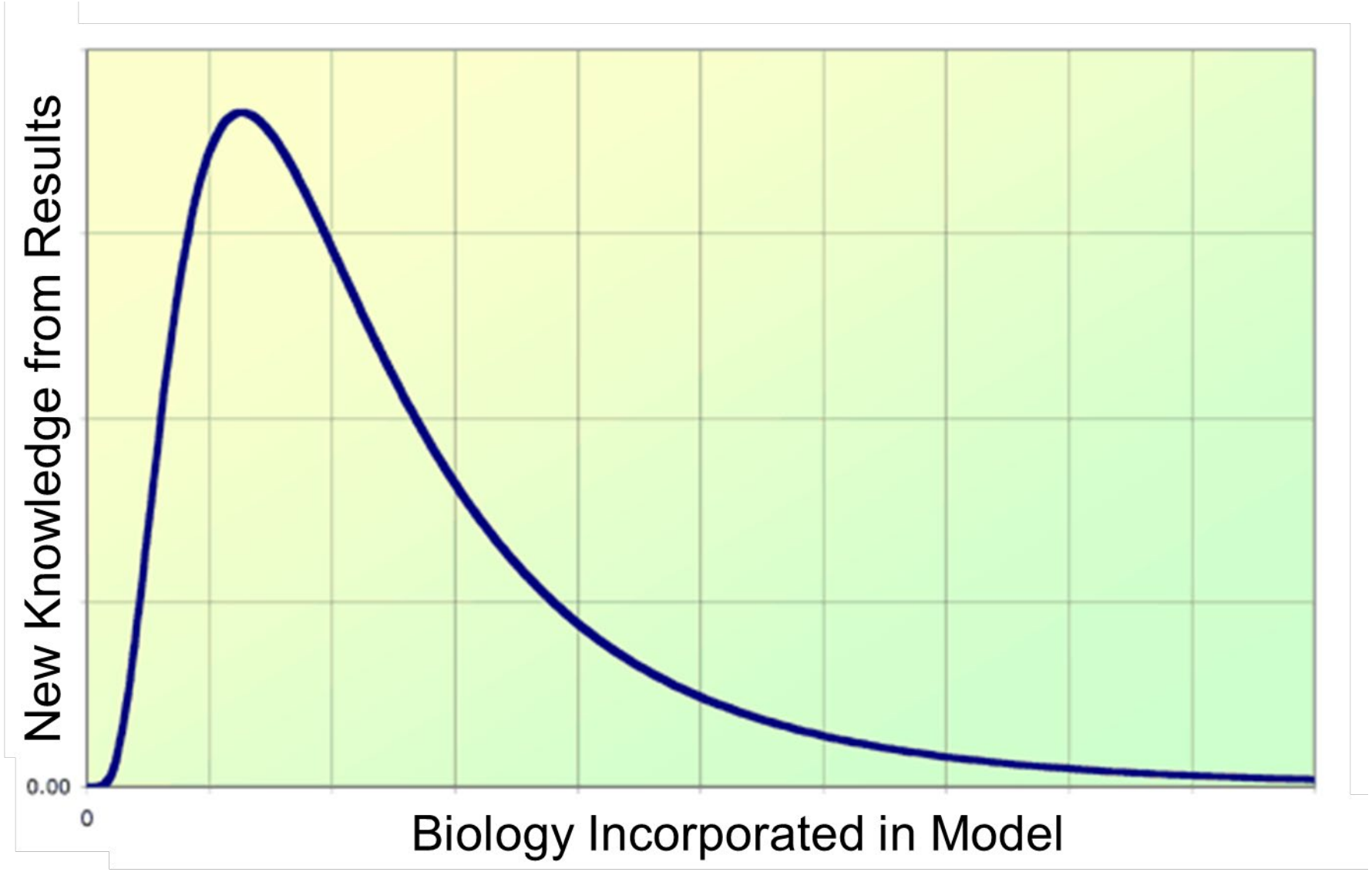
- Protective immunity consists of preformed immune reactants and immunological memory.

Understand immune system/in-host dynamics

Quite complex!
Simplify!



Adding in uncertainty



Memory Cells

- Long lived
- This can be a good thing (COVID-19, influenza, vaccination)
- This can be a bad thing (HIV…)

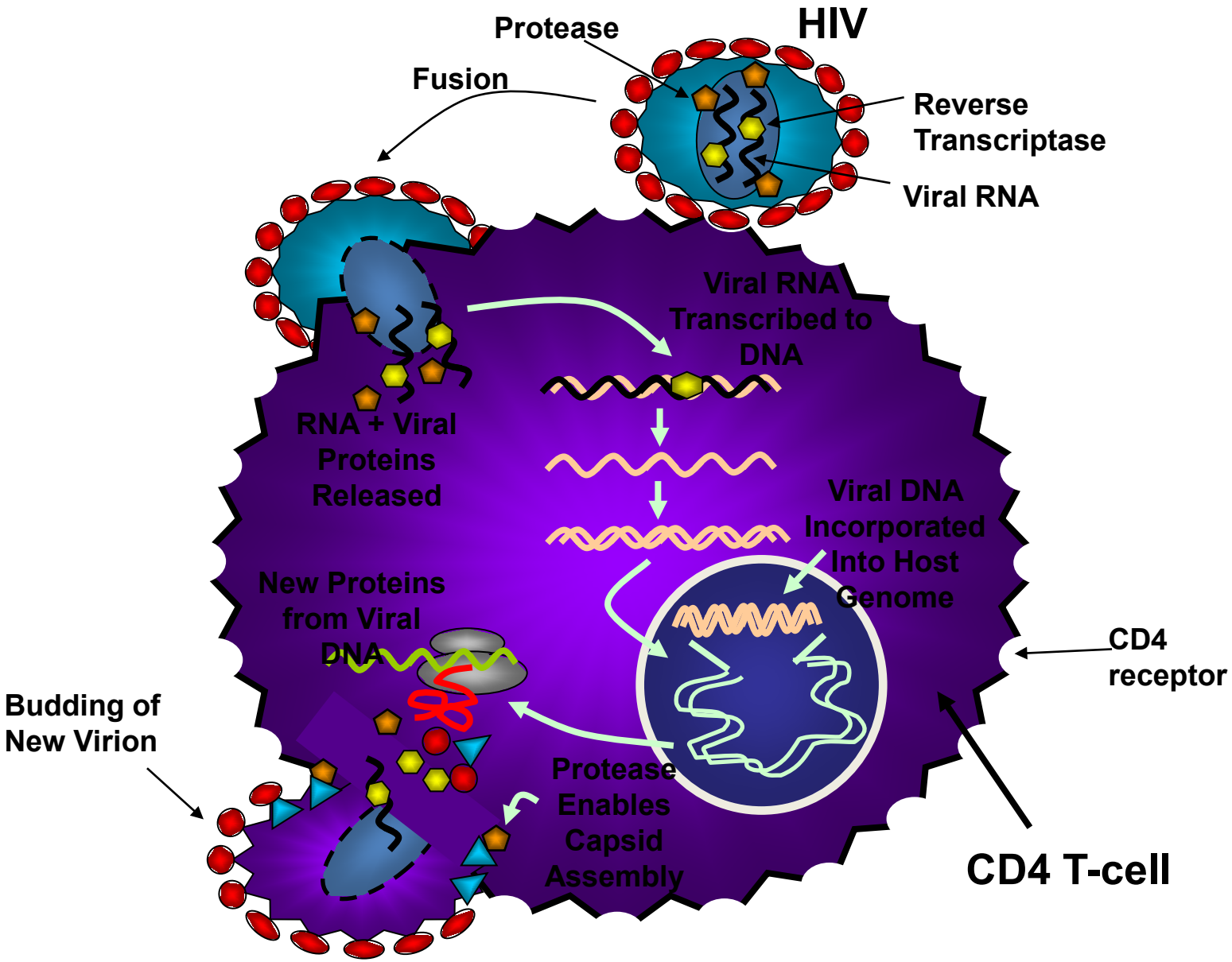
Virus Fitness

- Reproduction number
- Can define fitness for different virus variants
- We will also touch on this today

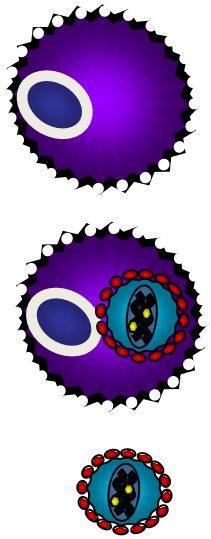
Basic Model

- Applicable to all studies of pathogen dynamics in-host
- Motivated by HIV
- Many extensions

Basic Model


HIV
Protease
Fusion
Reverse
Transcriptase
Viral RNA
Viral RNA
Transcribed to
DNA
RNA + Viral
Proteins
Released
Viral DNA
Incorporated
Into Host
Genome
New Proteins
from Viral
DNA
CD4
receptor
Budding of
New Virion
Protease
Enables
Capsid
Assembly
CD4 T-cell

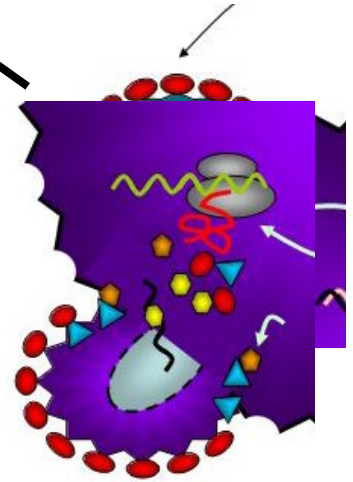
Basic Model



$$\frac{dx}{dt} = \lambda - d_x x - \beta x v$$

$$\frac{dy}{dt} = \beta x v - d_y y$$

$$\frac{dv}{dt} = k y - d_v v$$

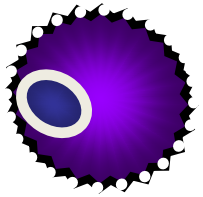


- x - uninfected cells
- y - infected cells
- v - free virus

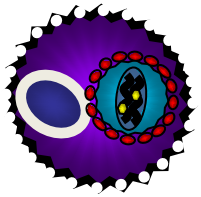
- λ, k - production rate
- β - efficacy of infection
- d_x, d_y, d_v - death rates/ clearance time

Nowak, M.A. and R.M. May, Virus Dynamics

Basic Model- with virus loss



$$\frac{dx}{dt} = \lambda - d_x x - \beta x v$$



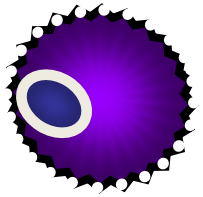
$$\frac{dy}{dt} = \beta x v - d_y y$$

$$\frac{dv}{dt} = k y - d_v v - \beta x v$$

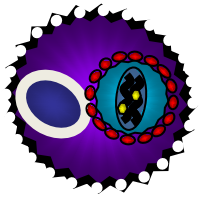
- x - uninfected cells
- y - infected cells
- v - free virus

- λ, k - production rate
- β - efficacy of infection
- d_x, d_y, d_v - death rates/ clearance time

Where is the immune system?



$$\frac{dx}{dt} = \lambda - d_x x - \beta x v$$



$$\frac{dy}{dt} = \beta x v - d_y y$$

$$\frac{dv}{dt} = k y - d_v v - \beta x v$$

- x - uninfected cells
- y - infected cells
- v - free virus

- λ, k - production rate
- β - efficacy of infection
- d_x, d_y, d_v - death rates/ clearance time

Intro Analysis

```
> restart :
> with(LinearAlgebra) :
> eq1 := lambda - dx·x - beta·x·v;
```

$$eq1 := \lambda - dx\,x - \beta\,x\,v$$

```
> eq2 := beta·x·v - dy·y;
```

$$eq2 := \beta\,x\,v - dy\,y$$

```
> eq3 := k·q·y - dv·v - beta·x·v;
```

$$eq3 := k\,q\,y - dv\,v - \beta\,x\,v$$

```
> eq4 := k·(1 - q)·y - dv·w;
```

$$eq4 := k\,(1 - q)\,y - dv\,w$$

```
> equil := solve( {eq1 = 0, eq2 = 0, eq3 = 0, eq4 = 0}, {x, y, v, w});
```

$$equil := \left\{ v = 0,\ w = 0,\ x = \frac{\lambda}{dx},\ y = 0 \right\},\ \left\{ v = -\frac{-\lambda\,\beta\,k\,q + \lambda\,\beta\,dy + dx\,dv\,dy}{dv\,dy\,\beta},\ w = -\frac{k\left(-\lambda\,\beta\,k\,q + \lambda\,\beta\,dy + dx\,dv\,dy\right)\left(-1+q\right)}{\beta\,dy\left(-k\,q + dy\right)dv},\ x = -\frac{dv\,dy}{\beta\left(-k\,q + dy\right)},\ y = \frac{-\lambda\,\beta\,k\,q + \lambda\,\beta\,dy + dx\,dv\,dy}{\beta\,dy\left(-k\,q + dy\right)} \right\}$$

```
> J := Matrix(4, 4, [ [diff(eq1, x), diff(eq1, y), diff(eq1, v), diff(eq1, w) ], [diff(eq2, x),
  diff(eq2, y), diff(eq2, v), diff(eq2, w) ], [diff(eq3, x), diff(eq3, y), diff(eq3, v), diff(eq3,
  w) ], [diff(eq4, x), diff(eq4, y), diff(eq4, v), diff(eq4, w) ]]);
```

$$J := \begin{bmatrix} -dx - \beta\,v & 0 & -\beta\,x & 0 \\ \beta\,v & -dy & \beta\,x & 0 \\ -\beta\,v & k\,q & -dv - \beta\,x & 0 \\ 0 & k\left(1-q\right) & 0 & -dv \end{bmatrix}$$

```
> equil := solve({eq1 = 0, eq2 = 0, eq3 = 0, eq4 = 0}, {x, y, v, w});
```

$$equil := \left\{ v = 0,\ w = 0,\ x = \frac{\lambda}{dx},\ y = 0 \right\},\ \left\{ v = -\frac{-\lambda\,\beta\,k\,q + \lambda\,\beta\,dy + dx\,dv\,dy}{dv\,dy\,\beta},\ w = -\frac{k\left(-\lambda\,\beta\,k\,q + \lambda\,\beta\,dy + dx\,dv\,dy\right)(-1+q)}{\beta\,dy\,(-k\,q + dy)\,dv},\ x = -\frac{dv\,dy}{\beta\,(-k\,q + dy)},\ y = \frac{-\lambda\,\beta\,k\,q + \lambda\,\beta\,dy + dx\,dv\,dy}{\beta\,dy\,(-k\,q + dy)} \right\}$$

```
> J := Matrix(4, 4, [[diff(eq1, x), diff(eq1, y), diff(eq1, v), diff(eq1, w)], [diff(eq2, x),
  diff(eq2, y), diff(eq2, v), diff(eq2, w)], [diff(eq3, x), diff(eq3, y), diff(eq3, v), diff(eq3,
  w)], [diff(eq4, x), diff(eq4, y), diff(eq4, v), diff(eq4, w)]]);
```

$$J := \begin{bmatrix} -dx - \beta\,v & 0 & -\beta\,x & 0 \\ \beta\,v & -dy & \beta\,x & 0 \\ -\beta\,v & k\,q & -dv - \beta\,x & 0 \\ 0 & k\,(1-q) & 0 & -dv \end{bmatrix}$$

> $eigvals := Eigenvalues(subs(\{x = x0, y = 0, v = 0, w = 0\}, J))$;

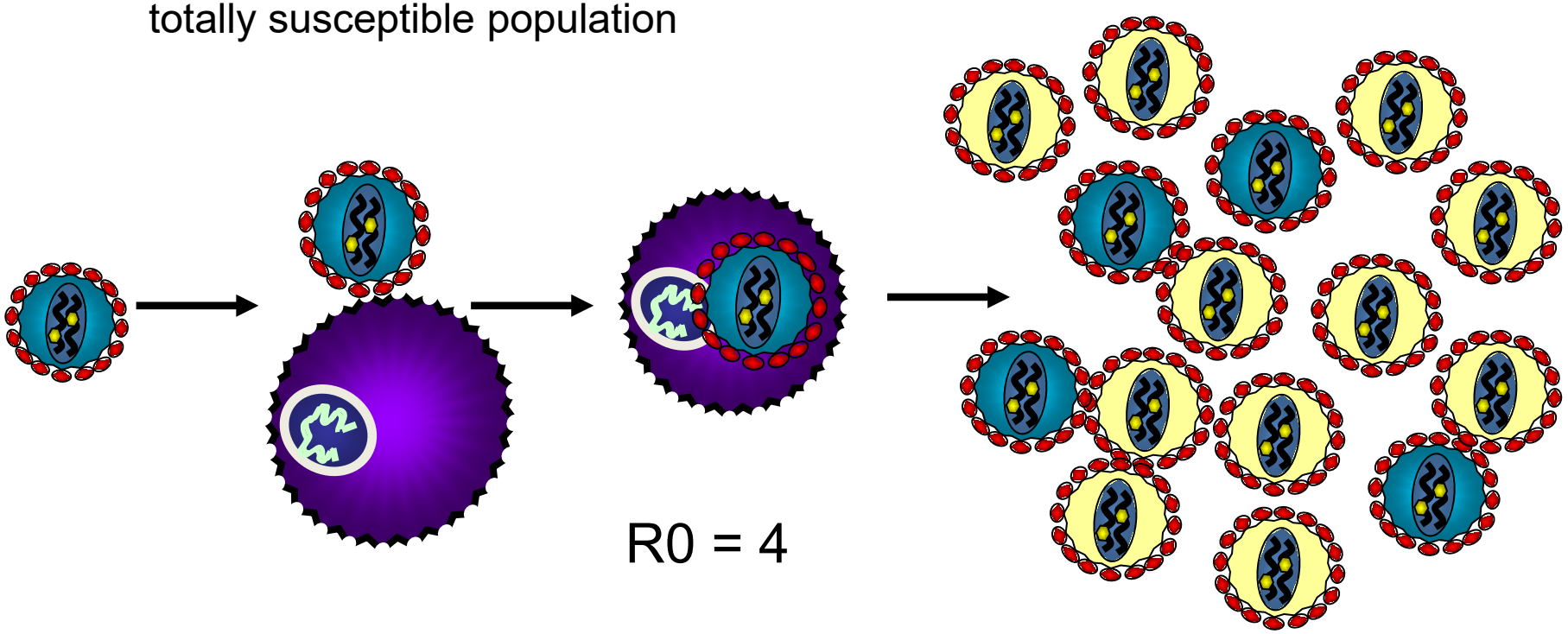
$$eigvals := \left[\left[-dx\right],\ \left[-dv\right],\ \left[-\frac{1}{2}\,dv - \frac{1}{2}\,dy - \frac{1}{2}\,\beta\,x0 + \frac{1}{2}\sqrt{dv^2 - 2\,dv\,dy + 2\,dv\,\beta\,x0 + dy^2 - 2\,dy\,\beta\,x0 + \beta^2\,x0^2 + 4\,k\,q\,\beta\,x0}\right],\ \left[-\frac{1}{2}\,dv - \frac{1}{2}\,dy - \frac{1}{2}\,\beta\,x0 - \frac{1}{2}\sqrt{dv^2 - 2\,dv\,dy + 2\,dv\,\beta\,x0 + dy^2 - 2\,dy\,\beta\,x0 + \beta^2\,x0^2 + 4\,k\,q\,\beta\,x0}\right]\right]$$

> $solve(eigvals[3] = 0, k) : R0 := \frac{k}{\%}$;

$$R0 := \frac{k\,q\,\beta\,x0}{dy\,(dv + \beta\,x0)}$$

In-host Model

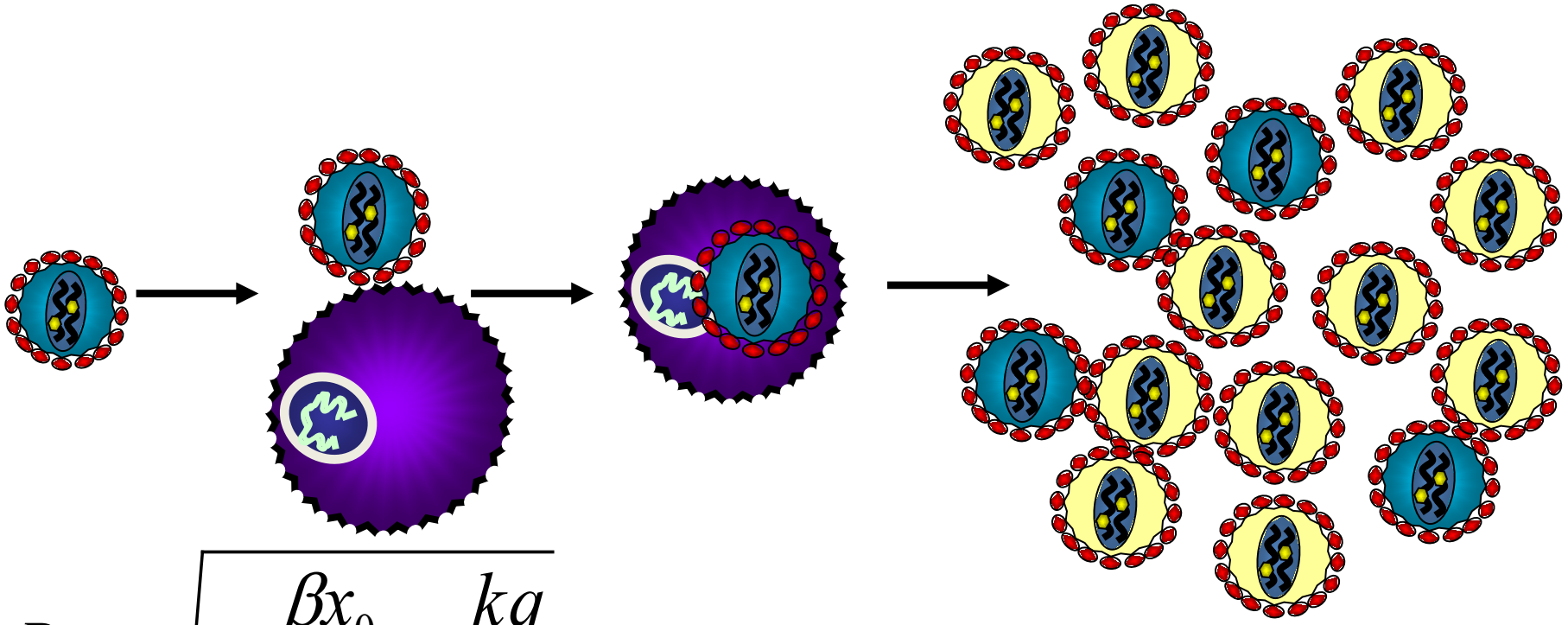
- Basic reproductive ratio
  - The number of secondary infections produced by an initial infective in a totally susceptible population



$$R_0 = \frac{\beta x_0}{u + \beta x_0} \frac{kq}{d_y}$$

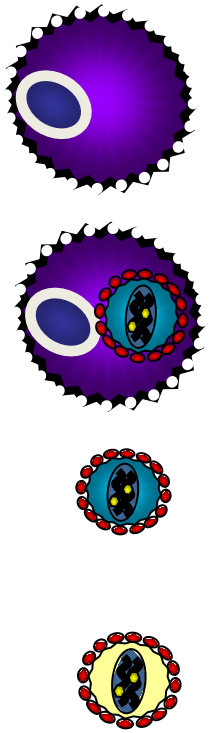
In-host Model

- Basic reproductive ratio
  - The number of secondary infections produced by an initial infective in a totally susceptible population



$$R_0 = \sqrt{\frac{\beta x_0}{d_v + \beta x_0} \frac{kq}{d_y}}$$

Basic Model- with drugs



$$\frac{dx}{dt} = \lambda - d_x x - \beta(1-\epsilon_{rt})xv$$

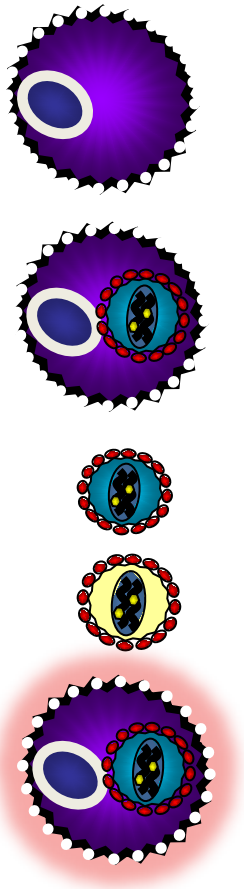
$$\frac{dy}{dt} = \beta(1-\epsilon_{rt})xv - d_y y$$

$$\frac{dv}{dt} = kq(1-\epsilon_p)y - d_v v - \beta x v$$

$$\frac{dw}{dt} = k(1-q(1-\epsilon_p))y - d_v w$$

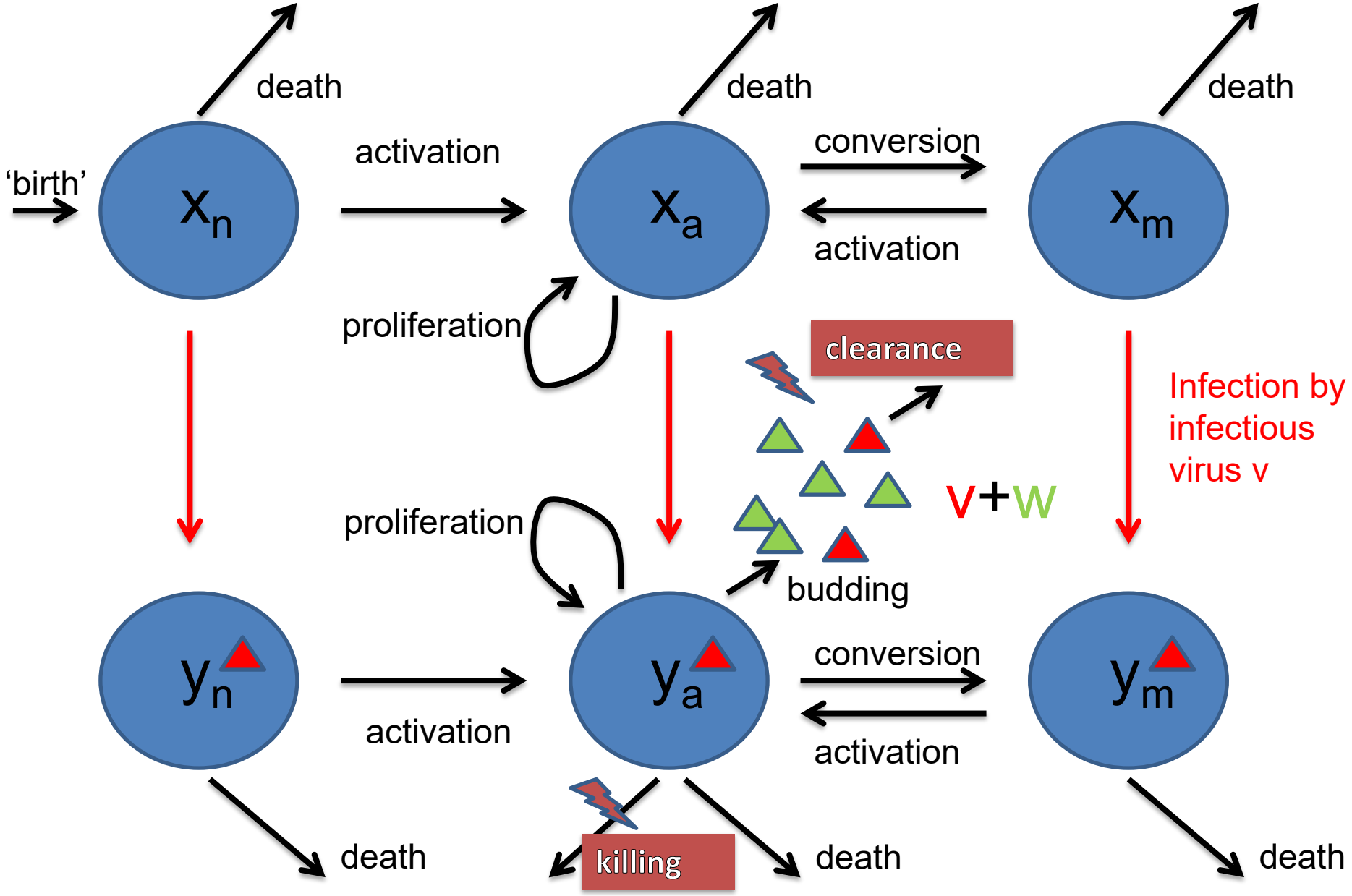
$$R_c = \frac{\beta(1-\epsilon_{rt})x_0}{\beta x_0 + d_v} \frac{kq(1-\epsilon_p)}{d_y}$$

Latently Infected Cells

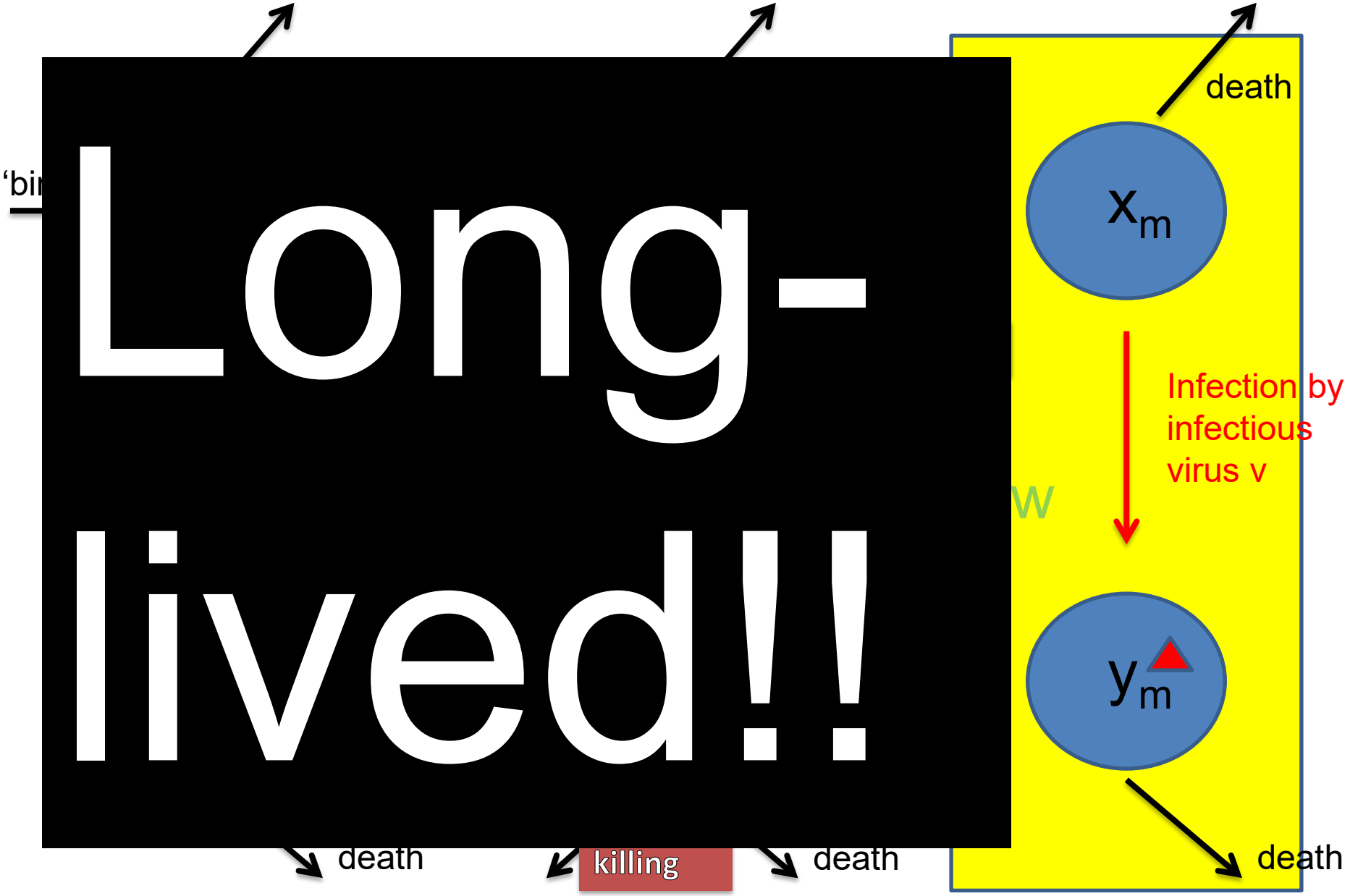


$$
\begin{aligned}
x' &= \lambda - d_x x - \beta x v \\
y' &= (1-f)\beta x v - d_y y + \psi l \\
v' &= kqy - d_v v - \beta x v \\
w' &= k(1-q)y - d_v w \\
l' &= f\beta x v - d_l l - \psi l
\end{aligned}
$$

CD4 T-cell immunity & Latently Infected Cells



CD4 T-cell immunity



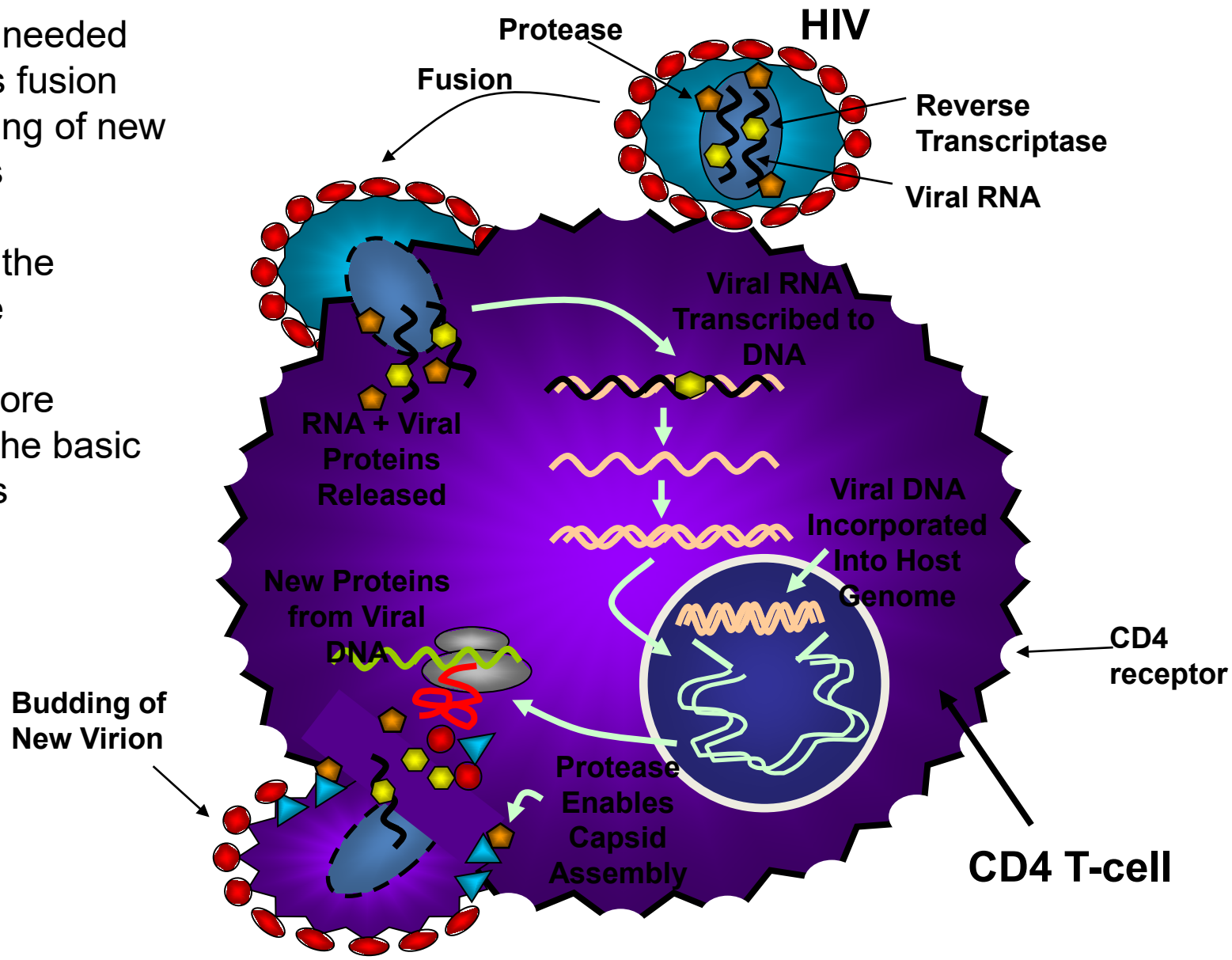
Long-lived!!

Eclipse Stage

Some time is needed between virus fusion and the budding of new virus particles

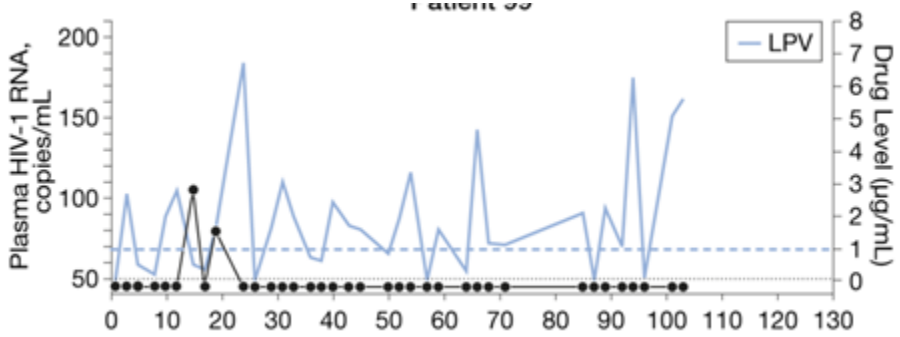
This is called the Eclipse Stage

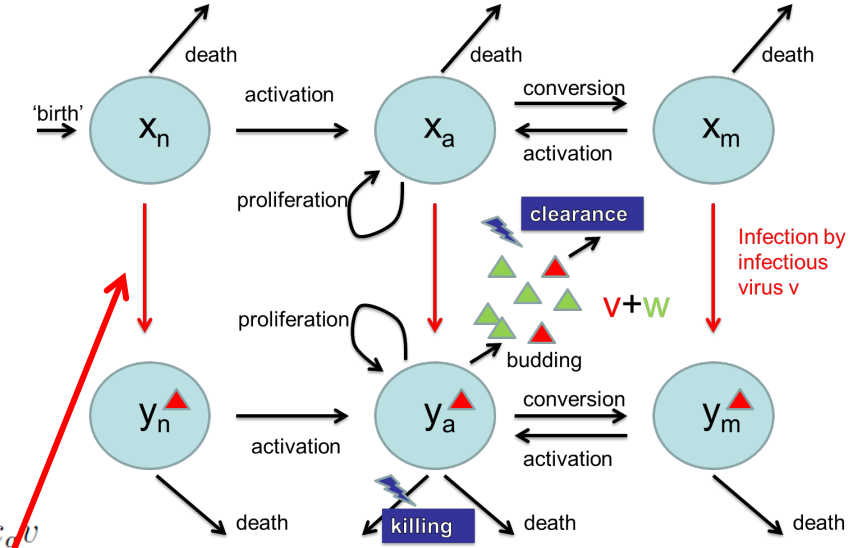
Add one or more equations to the basic model of virus dynamics



Viral Blips

- ODEs, include long lived memory cells





$$\frac{dx_n}{dt} = \lambda - d_{x_n} x_n - \beta x_n v - \gamma x_n (v + \delta)$$

$$\frac{dx_a}{dt} = \gamma x_n (v + \delta) + c x_m v + \rho x_a \frac{v}{v+C} - d_{x_a} x_a - p x_a - \beta x_a v$$

$$\frac{dx_m}{dt} = p x_a - c x_m v - d_{x_m} x_m - \beta x_m v$$

$$\frac{dy_a}{dt} = \gamma y_n v + \beta x_a v + \rho y_a \frac{v}{v+C} + c y_m v - d_{y_a} y_a - p y_a - \xi y_a f(v, x_a, y_a)$$

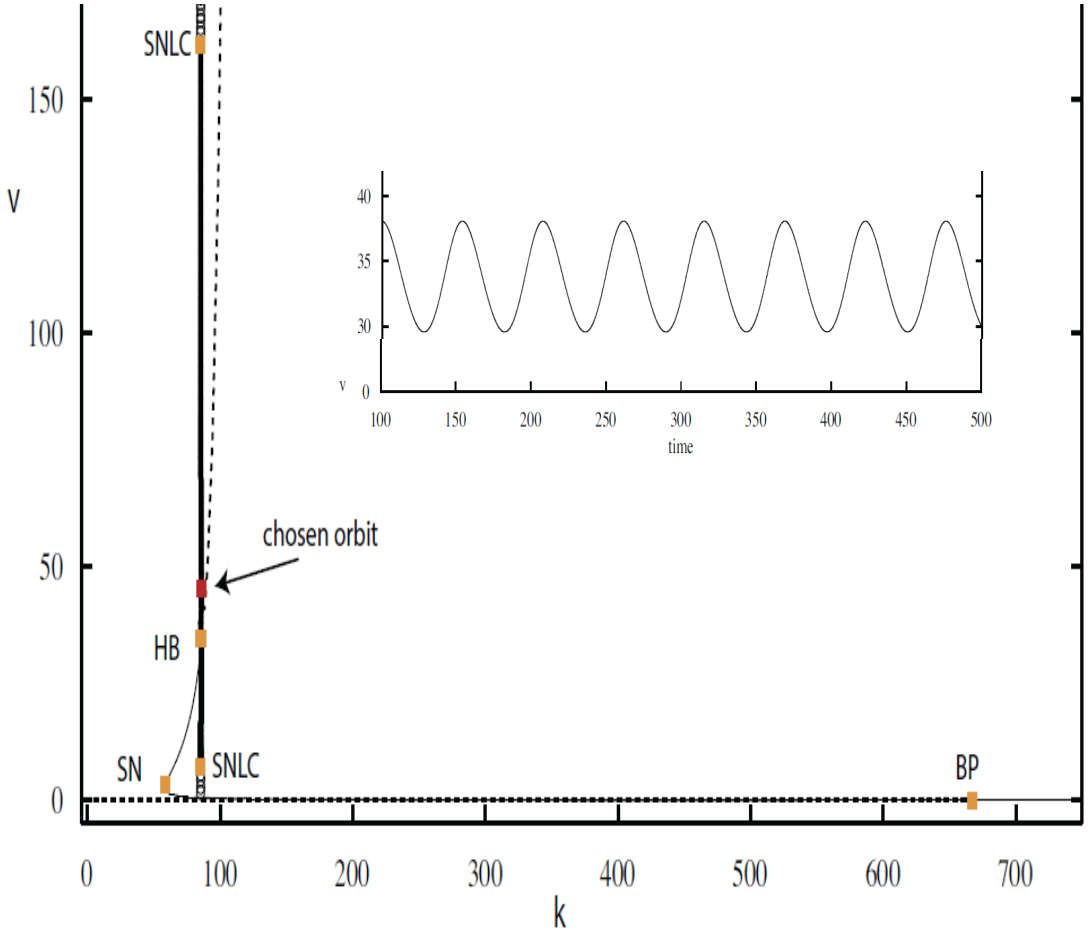
$$\frac{dy_m}{dt} = p y_a + \beta x_m v - c y_m v - d_{y_m} y_m$$

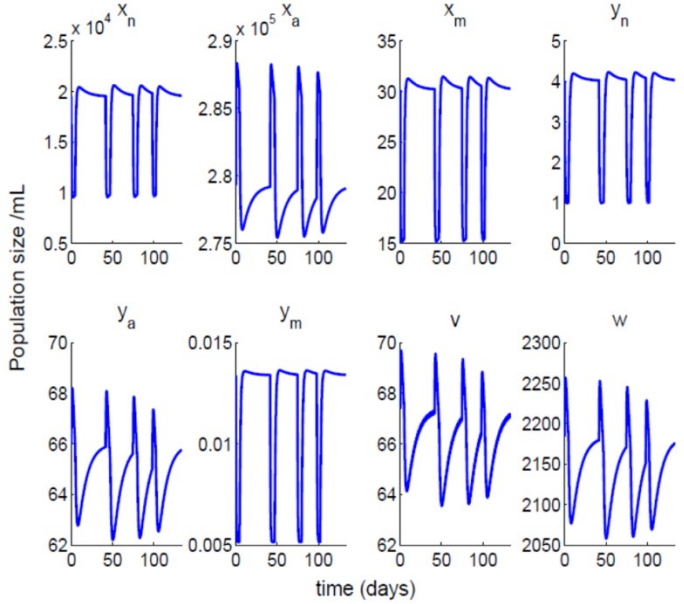
$$\frac{dv}{dt} = k q y_a - u v - s \beta v (x_n + x_a + x_m)$$

Frascoli F, Wang Y, et al. (2014). *CAMQ*, in press.

Viral Blips

- ODEs, include long lived memory cells





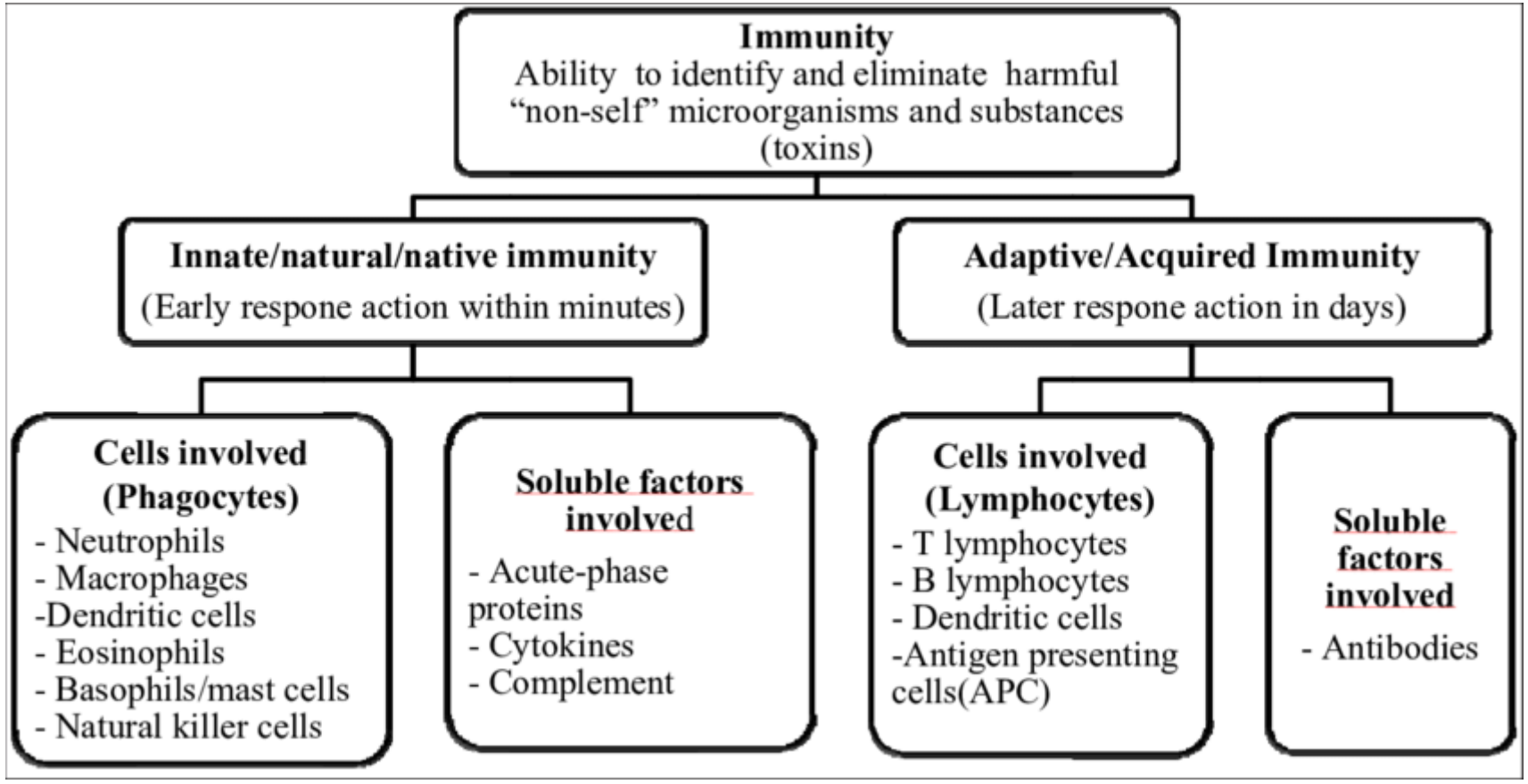
Tat ‘on-off’ switch

Bifurcations: Backward (1 or 2), Hopf (1 or 2), depend on s anf f(x,y,v)Tat ‘on-off’ switch

<u>On-going MI2 work</u>

Frascoli F, Wang Y, et al. (2014). *CAMQ*, in press.

More to consider…



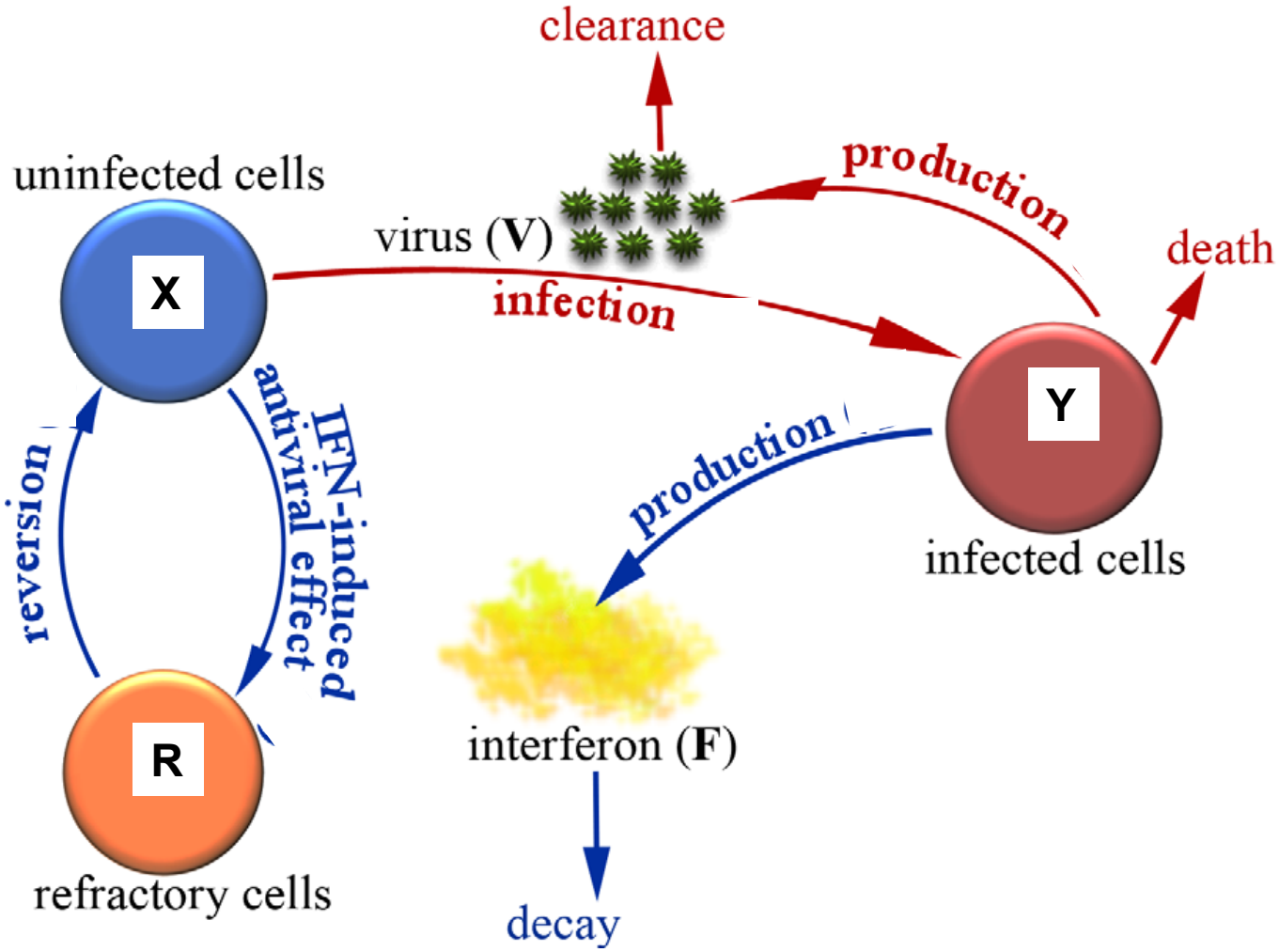
Basic Model
with killer cells and antibodies

$$
\begin{aligned}
x' &= \lambda - d_x x - \beta x v \\
y' &= \beta x v - d_y y - \xi y z \\
v' &= kqy - d_v v - \beta x v - \phi a v \\
z' &= F(x, y, v, z, a) - d_z z \\
a' &= G(x, y, v, z, a) - d_a a
\end{aligned}
$$

$$
R_0 = \frac{\beta x_0}{\beta x_0 + d_v + a_0} \frac{kq}{d_y + z_0}
$$

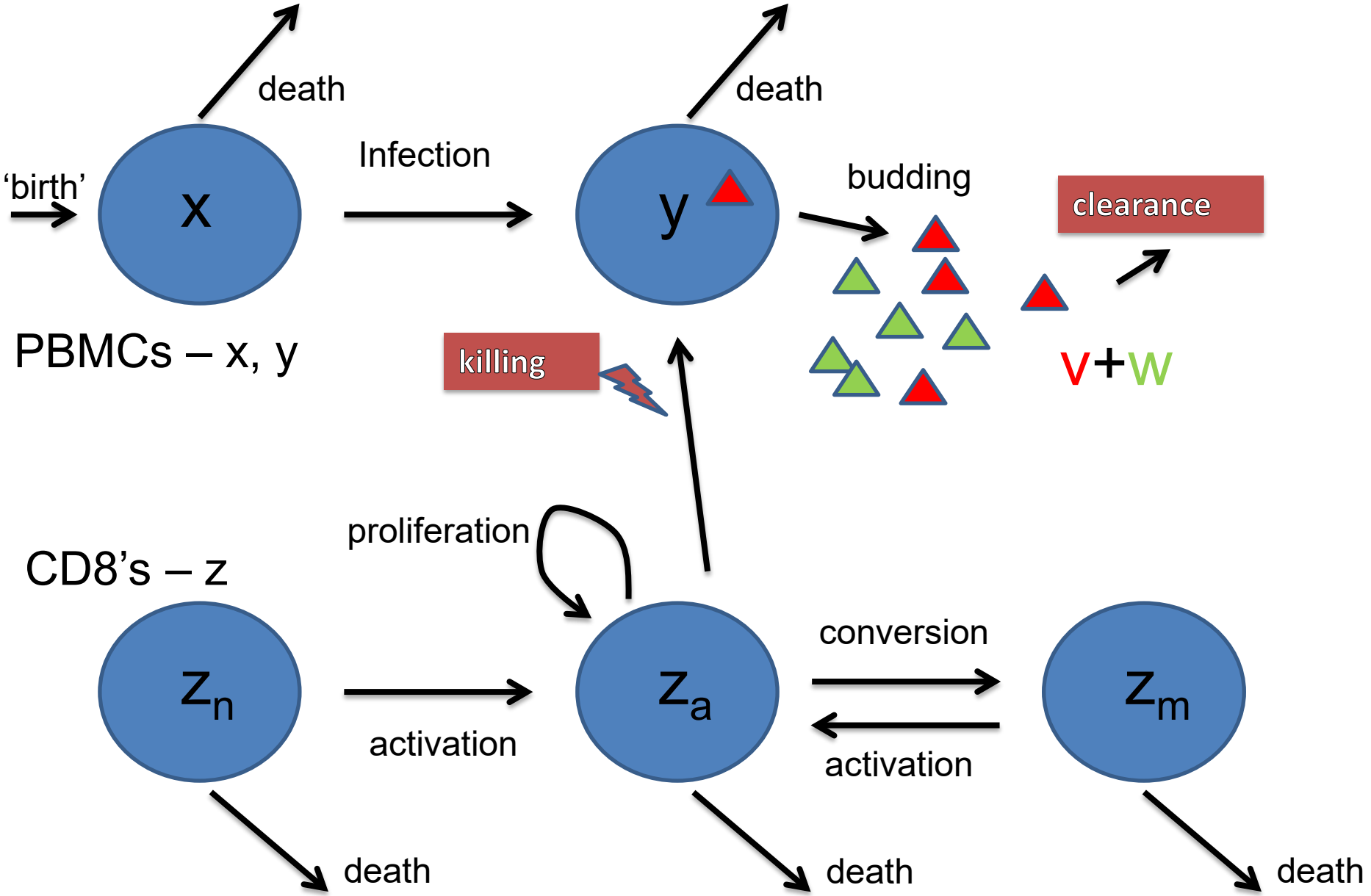
Can add in drug therapies that may excite the immune system too….

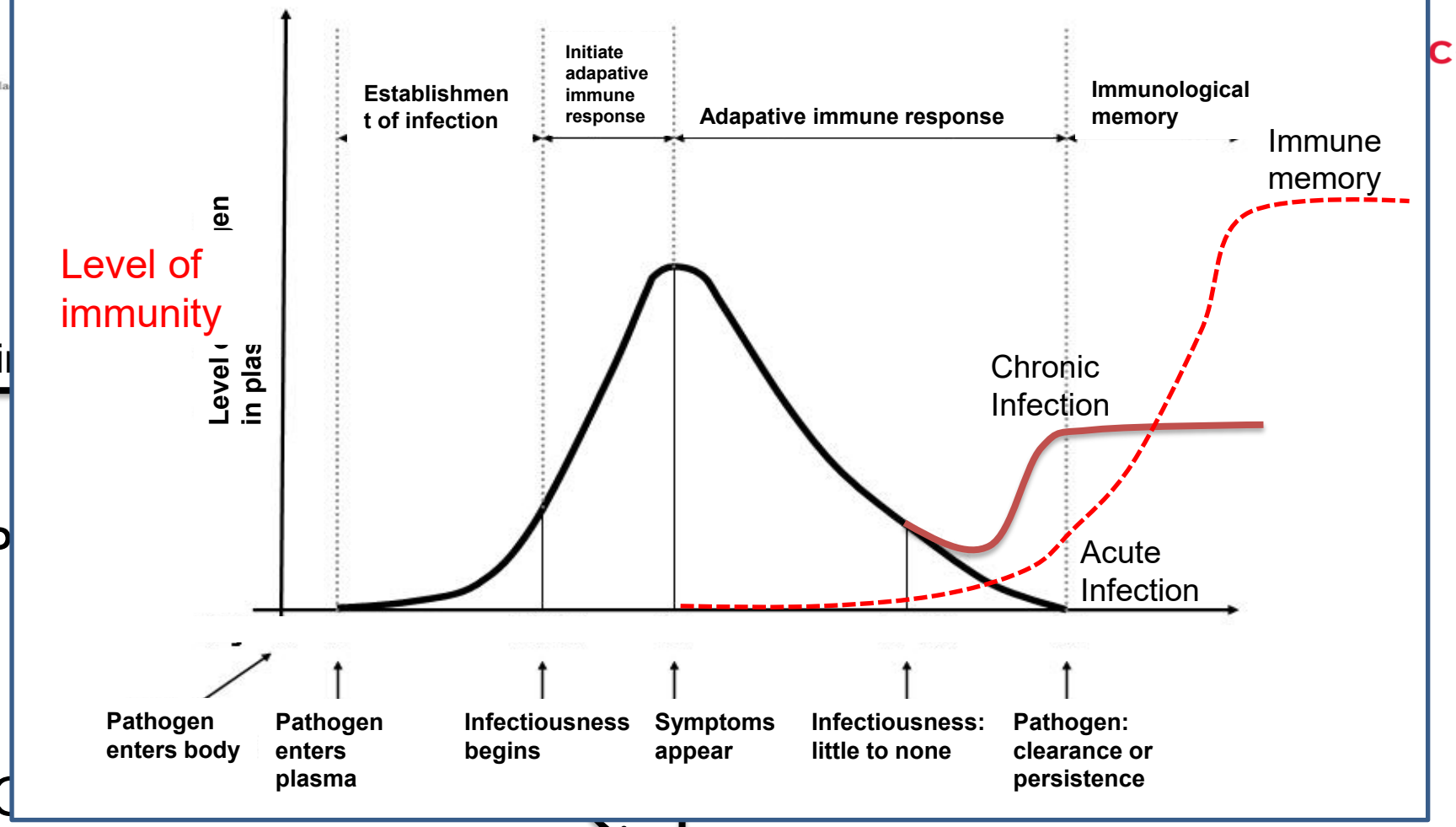
An extension

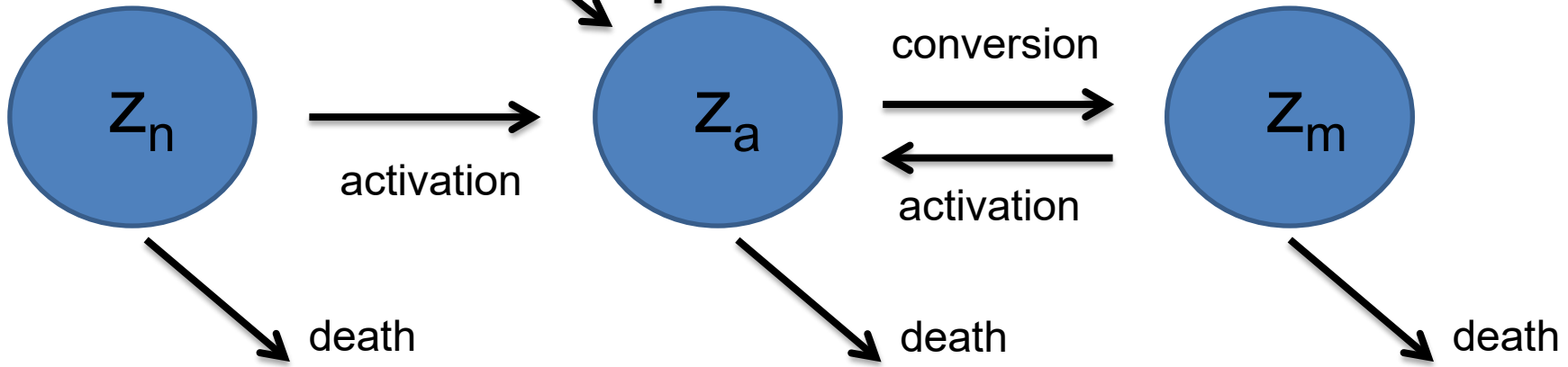


Pawelek et al (2012), Heffernan & Ciupe (2017)

Immunity/memory cells




Establishmen
t of infection
Initiate
adapative
immune
response
Adapative immune response
Immunological
memory
Immune
memory
Level of
immunity
Chronic
Infection
Acute
Infection
Pathogen
enters body
Pathogen
enters
plasma
Infectiousness
begins
Symptoms
appear
Infectiousness:
little to none
Pathogen:
clearance or
persistence


z_n
activation
z_a
conversion
activation
z_m
death
death
death

Model-Bacteria

- Tuberculosis
- Macrophages

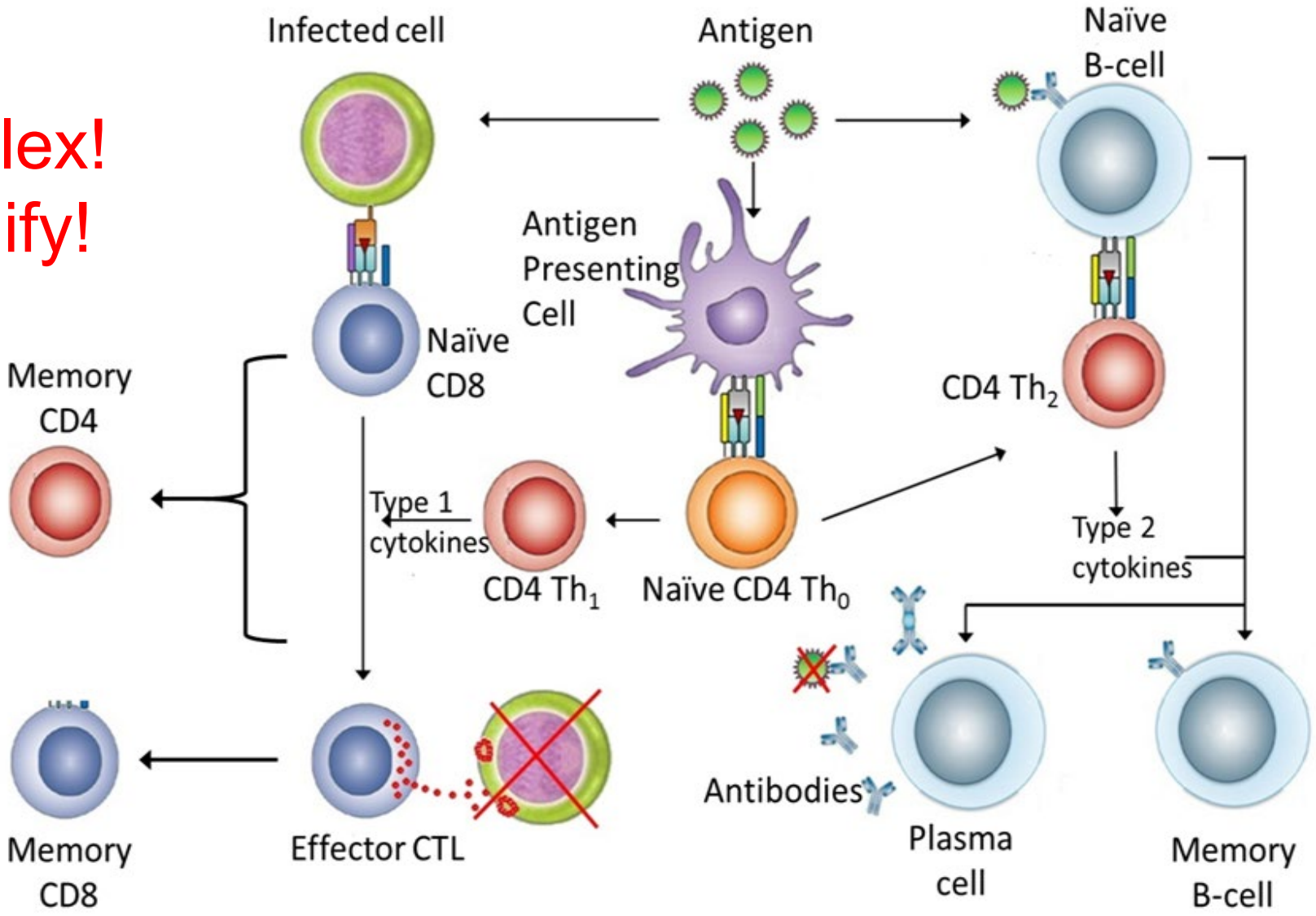
$$\begin{cases} \dfrac{dM_u}{dt} = s_M - \mu_M M_u - \beta M_u B, \\ \dfrac{dM_i}{dt} = \beta M_u B - bM_i - \gamma M_i \dfrac{(T/M_i)}{(T/M_i)+c}, \\ \dfrac{dB}{dt} = \delta B\left(1 - \dfrac{B}{K}\right) + N_1 bM_i + N_2 \gamma M_i \dfrac{(T/M_i)}{(T/M_i)+c} - \eta M_u B - N_3 \beta M_u B, \\ \dfrac{dT}{dt} = s_T + \dfrac{c_M M_i T}{e_M T + 1} + \dfrac{c_B B T}{e_B T + 1} - \mu_T T. \end{cases}$$

- Bacteria can replicate on their own

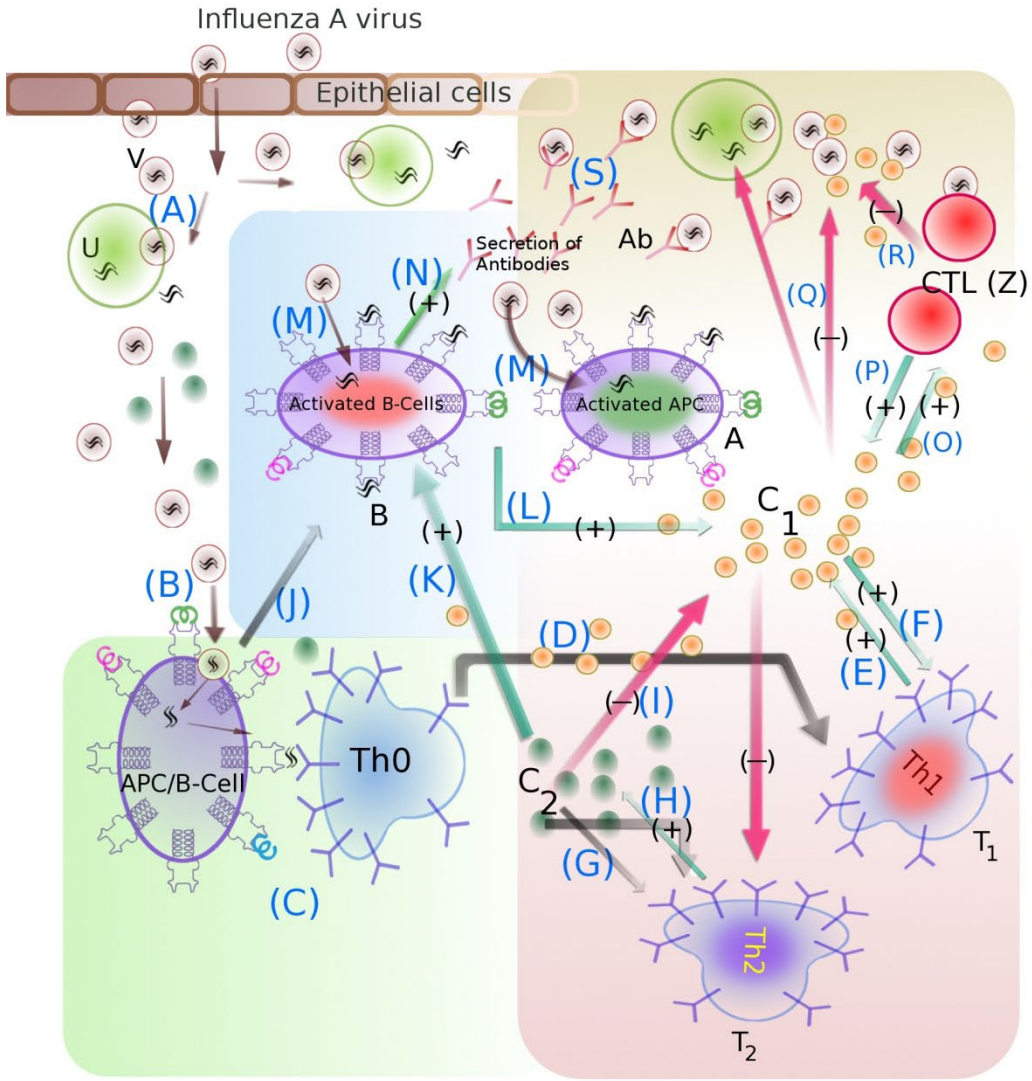
$$\mathcal{R}_0 = \frac{\delta}{(\eta + N_3\beta)M_u^0} + \frac{N_1 b + N_2 \gamma}{b+\gamma}\frac{\beta}{\eta + N_3\beta}$$

Understand immune system/in-host dynamics

Quite complex!
Simplify!



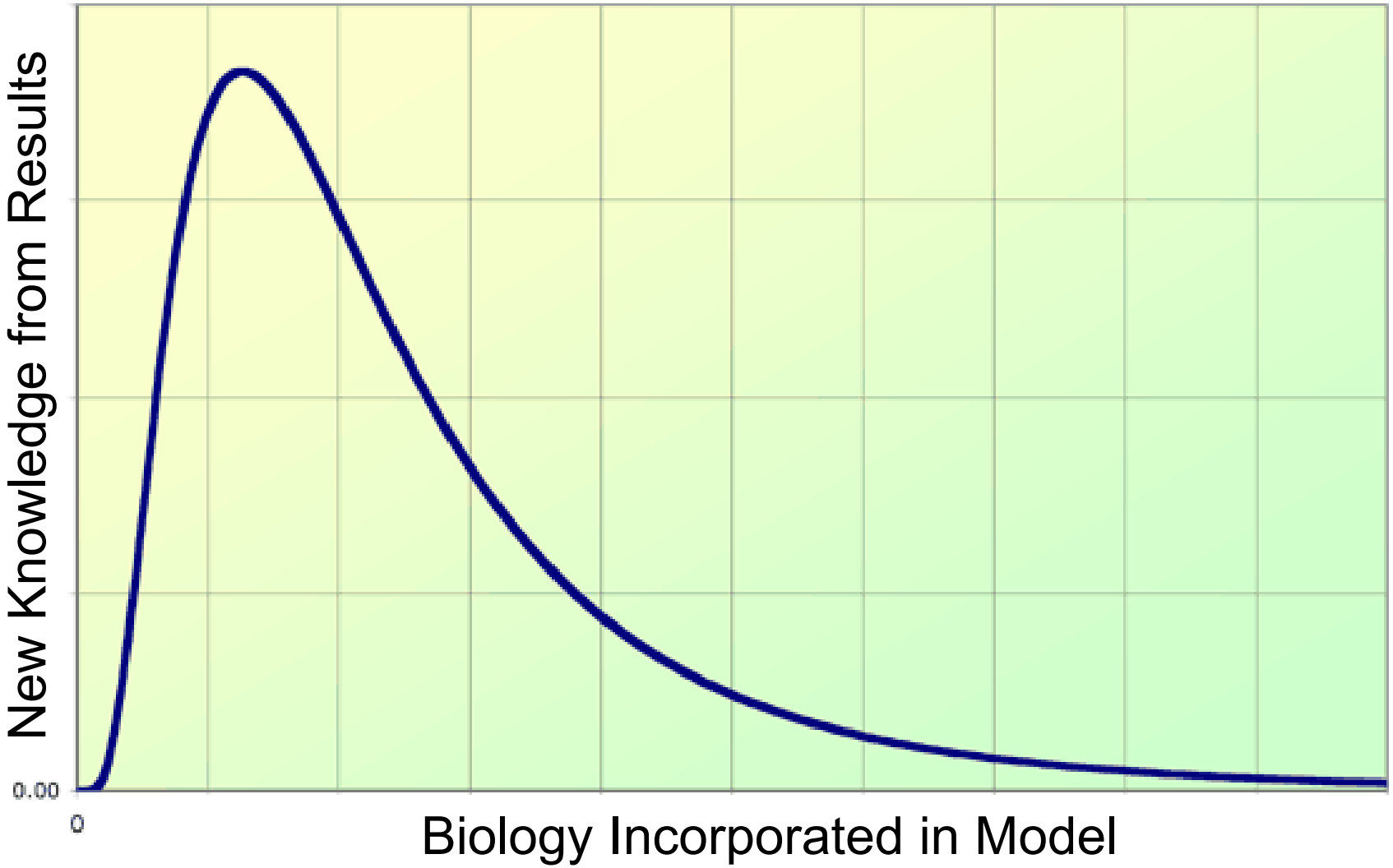
In-host model: Influenza



(A): virions infect healthy cells (U).
(B): virions are engulfed by Antigen Processing Cells (APC) and B-Cells, are processes and a derived peptide-antigens are expressed on MHC-II surface molecule.
(C): Naive T-cells (Th0) interact with APC/B-cell to recognize the peptide-antigens.
(D): Class-I cytokines (Cy1) (IL-12, IFN-g, IL-18) promote Th0 differentiate into activated Th1.
(E): Th1 up-regualtes further production of Cy1 - specially IL-2, IFN-g and TFN-b.
(F); Positive feedback loop that enhances growth of activated Th1 by Cy1.
(G): Class-II cytokines (Cy2) promote Th0 differentiate into activated Th2.
(H): Activated Th2 upregulates production of Cy2.
(I): Cy2 inhibition of growth of Cy1.
(J): APC and B-cells gets activated upon Th0 activation.
(K): Cy2 upregulates growth and activation of B-cells.
(L): Activated APC/B-cells up-regulate production of Cy1 (IFN-g).
(M): Activaated APC/B-cells recruite more virions for expression.
(N): Activated B-cells secrete influenza-A specific antibodies.
(O): Cy1 promotes activation of Cytotoxic T Lymphocytes (CTL*).
(P): CTL* up-regulates production of Cy1.
(Q): Cy1 inhibition of viral mRNA (editing).
(R): CTL* mediated direct lysis of infected cells and virions.
(S): B-cell secreted antibody mediated lysis of infected cells and virions.

MANY EQUATIONS, ASSUMPTIONS – PARAMETER IDENTIFIABILITY!!

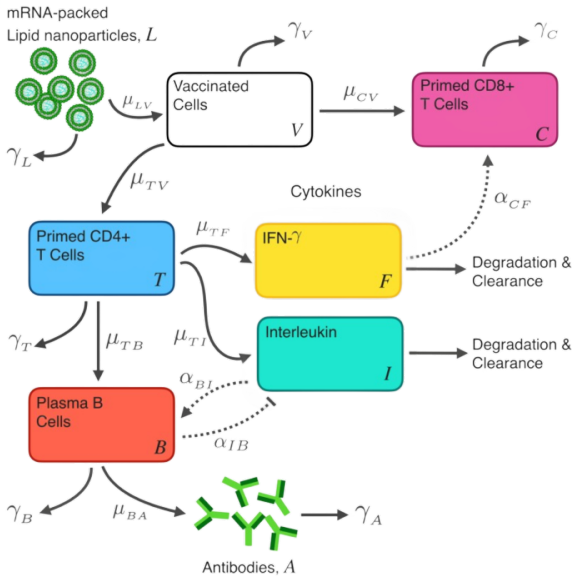
More vs. More

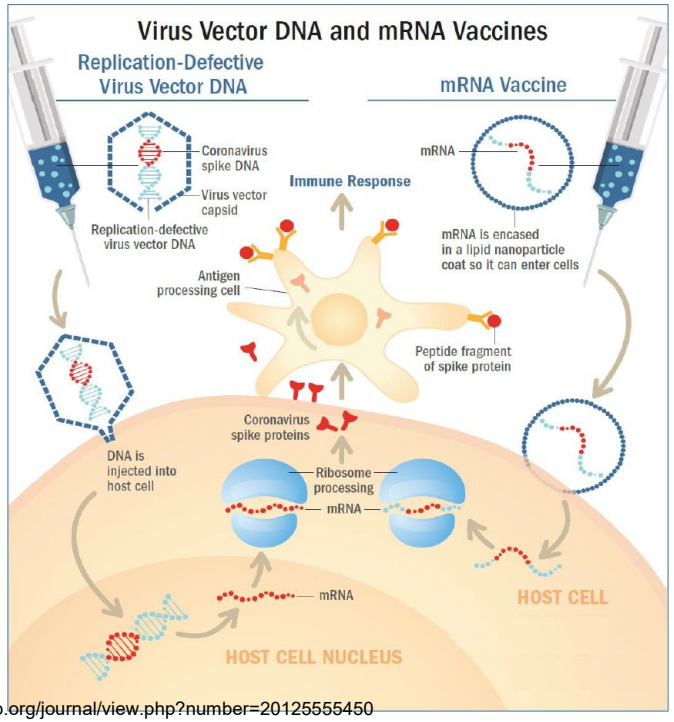

New Knowledge from Results
0.00
0
Biology Incorporated in Model

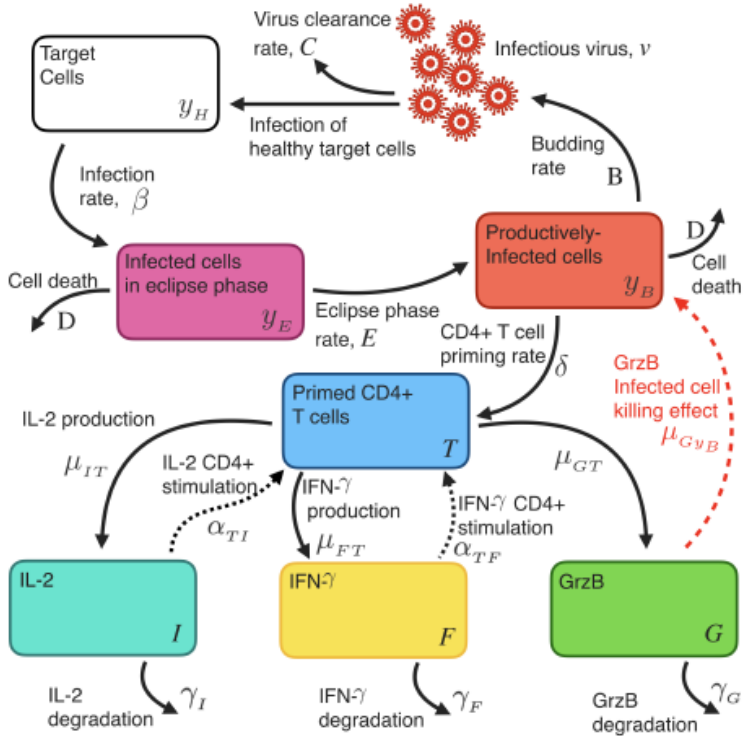
CDM Centre for Disease Modelling | CMM Centre de la modélisation des maladies

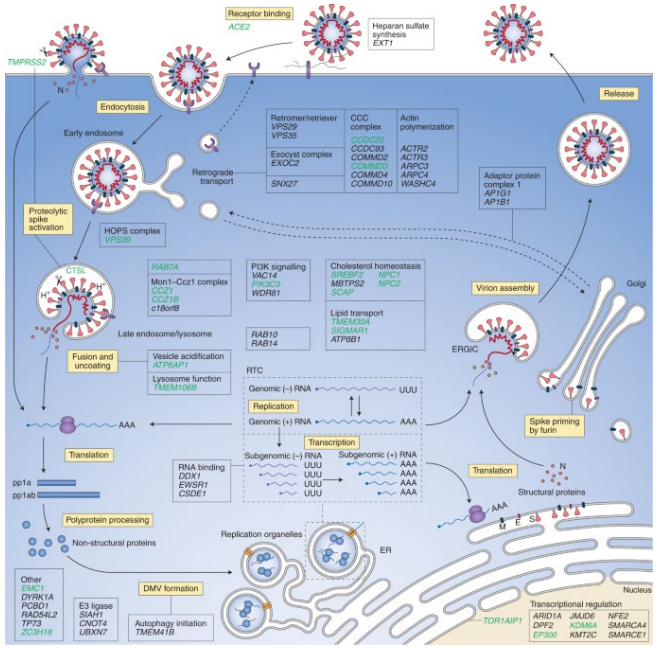
In-host model

Farhang-Sardroodi et al., (2021) Vaccines
Korosec et al., (2022) Scientific Reports
Gholami et al., (2022) Math Biosci
Lin, Korosec, et al., (2022) J Am Soc Microbiol







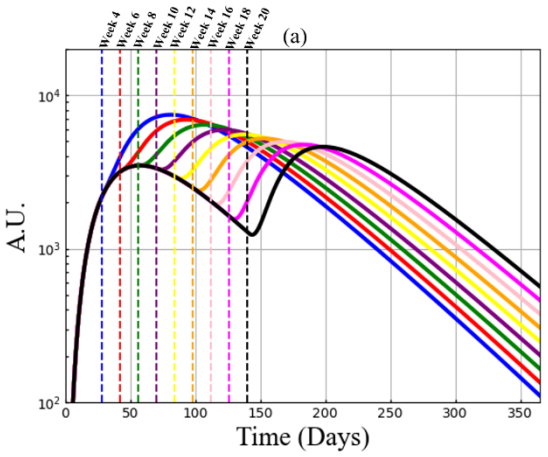


https://www.e-cep.org/journal/view.php?number=20125555450

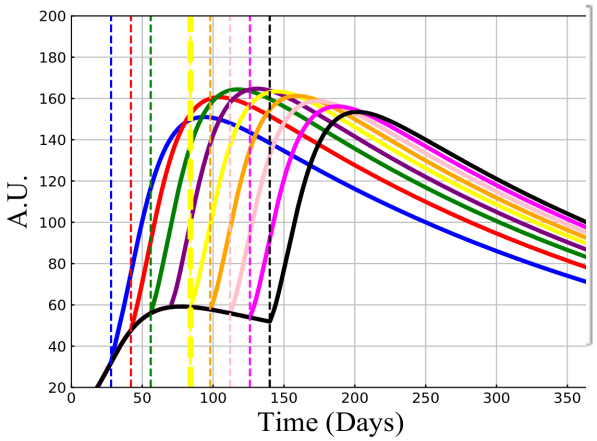
https://www.nature.com/articles/s41564-021-00958-0

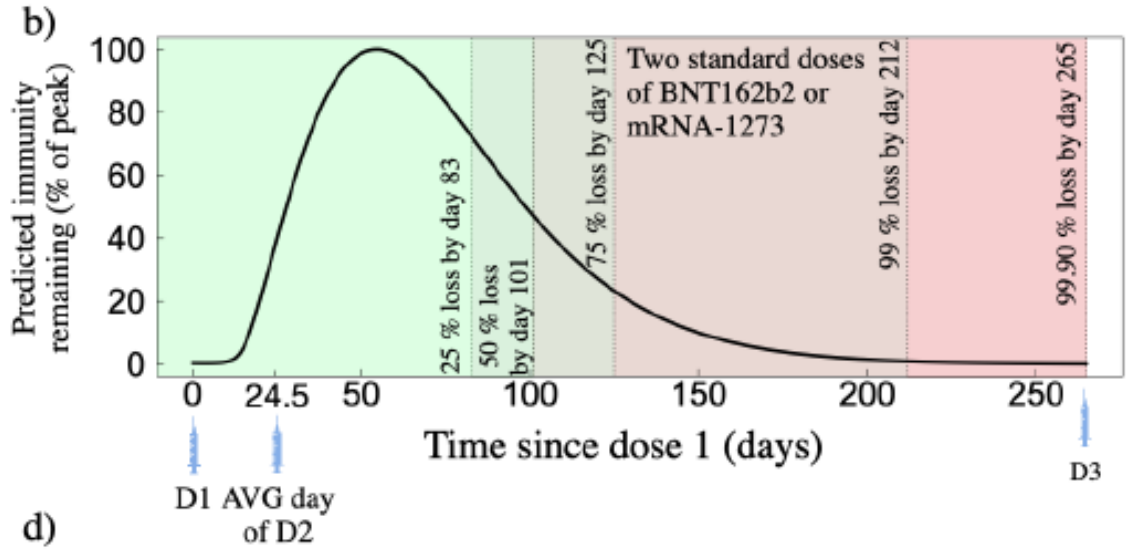
Modelling Vaccination In-Host

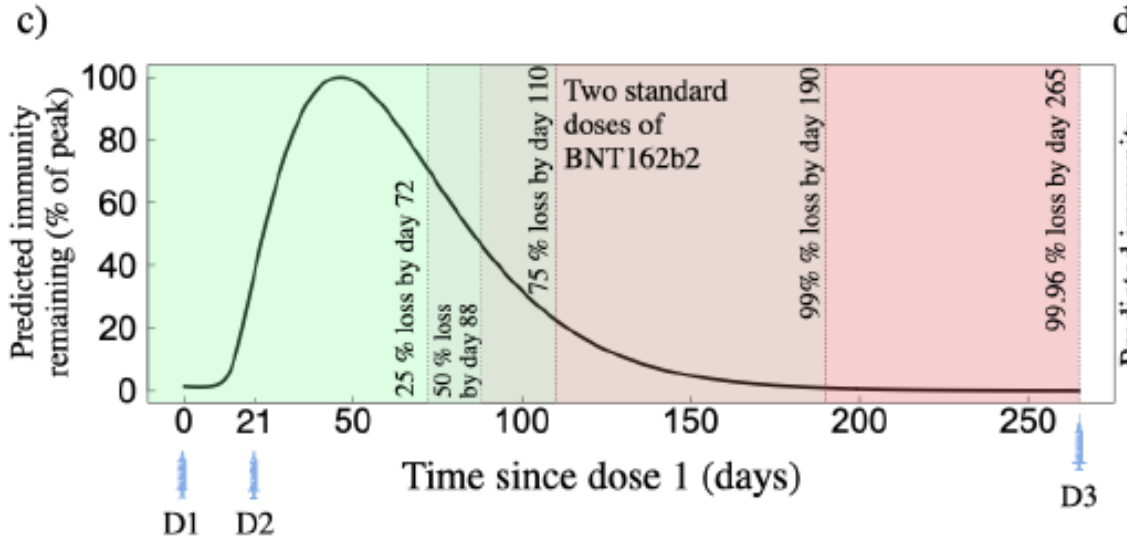
Antibodies

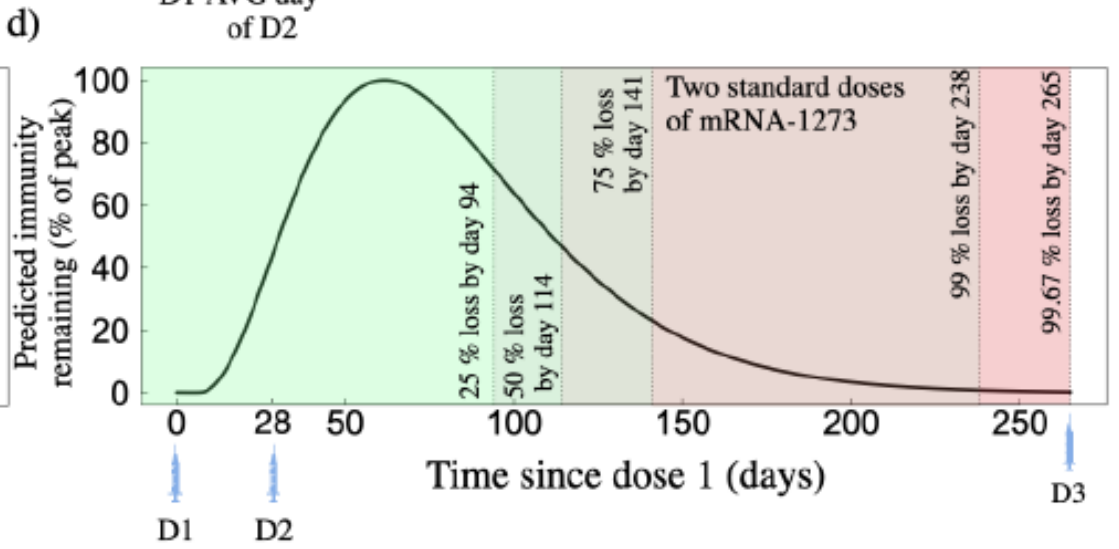


T-cells

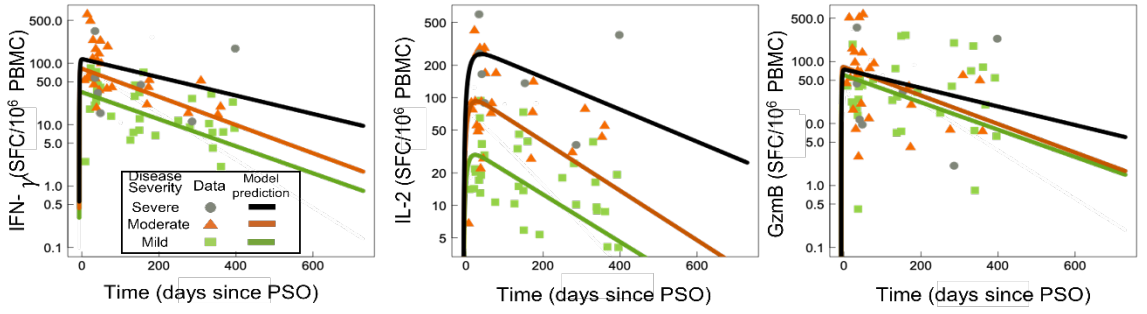


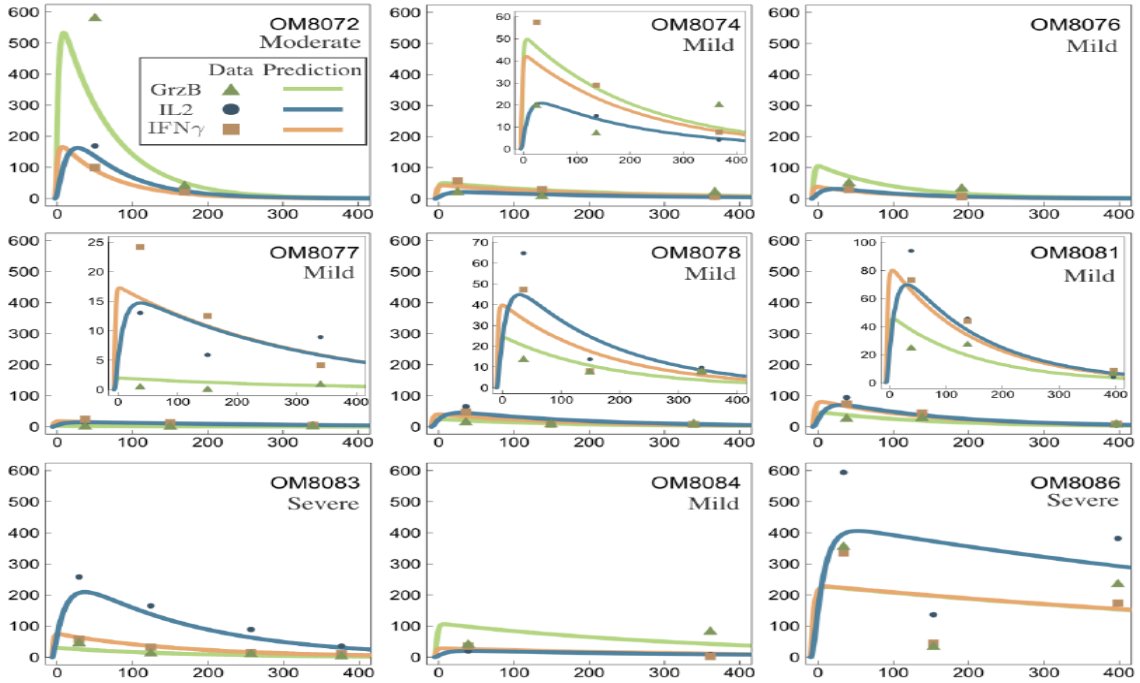


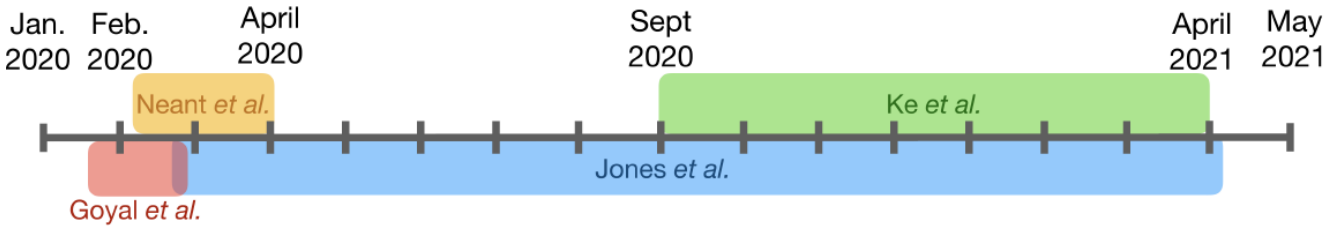


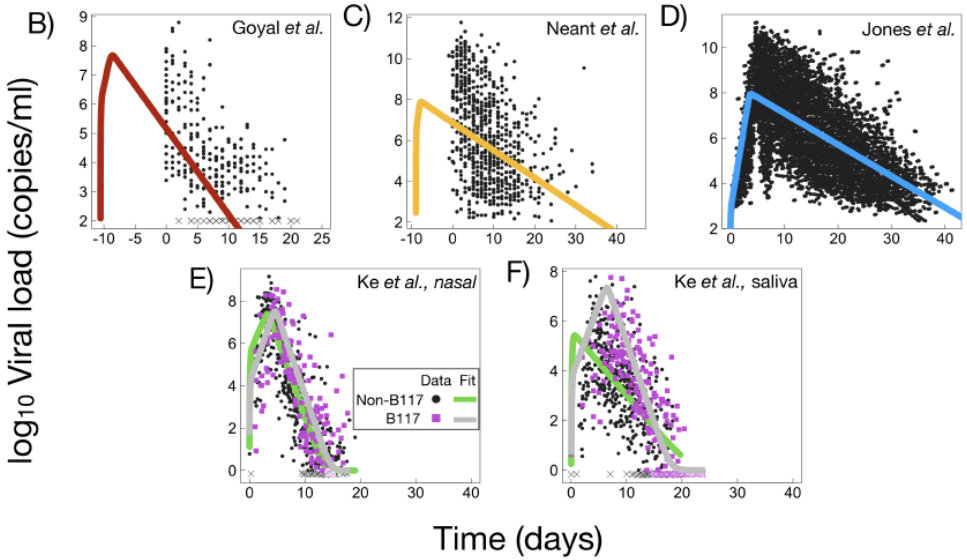


Modelling Infection In-Host



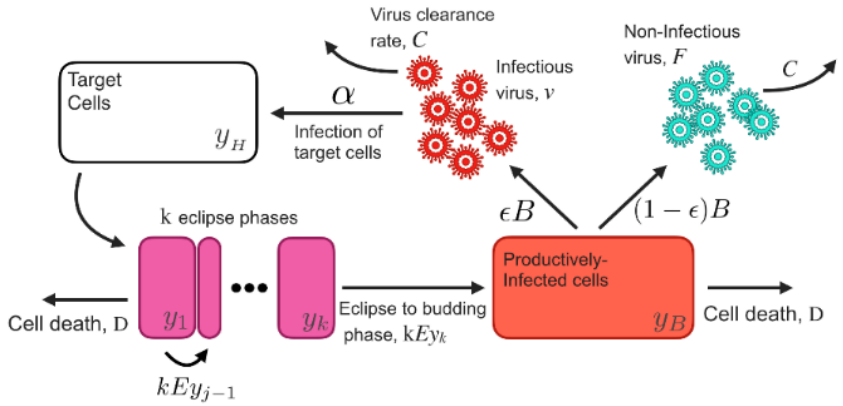




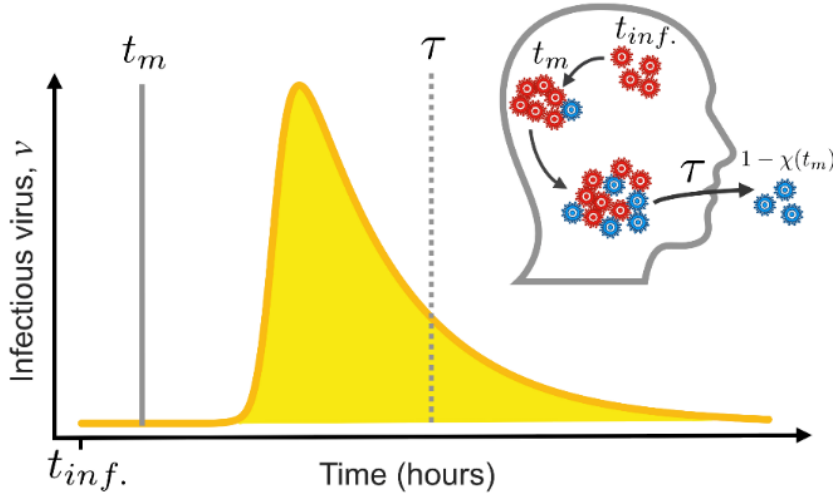


Severity of Infection, Mutation

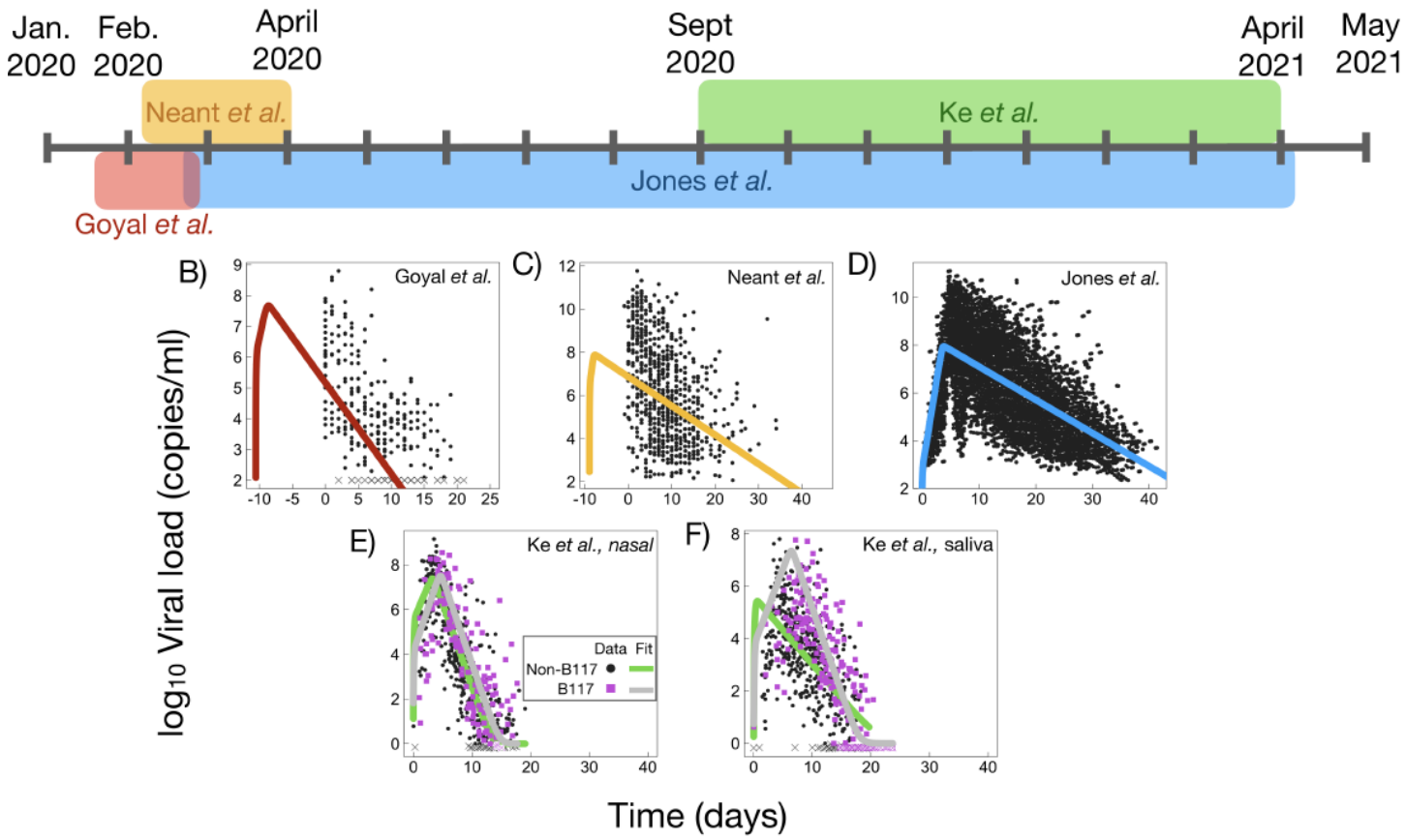
A) Schematic of target-cell limited model (Eq.1)



B) Schematic of transmission bottleneck model (Eq.2)



$t_{inf.}$: Time of infection
t_m : Time of virus mutation, $0 < t_m < \tau$
τ : Time of disease transmission
$1-\chi(t_m)$: Survival probability of mutated strain



Korosec et al., in prep

Infection & Immunity Observations

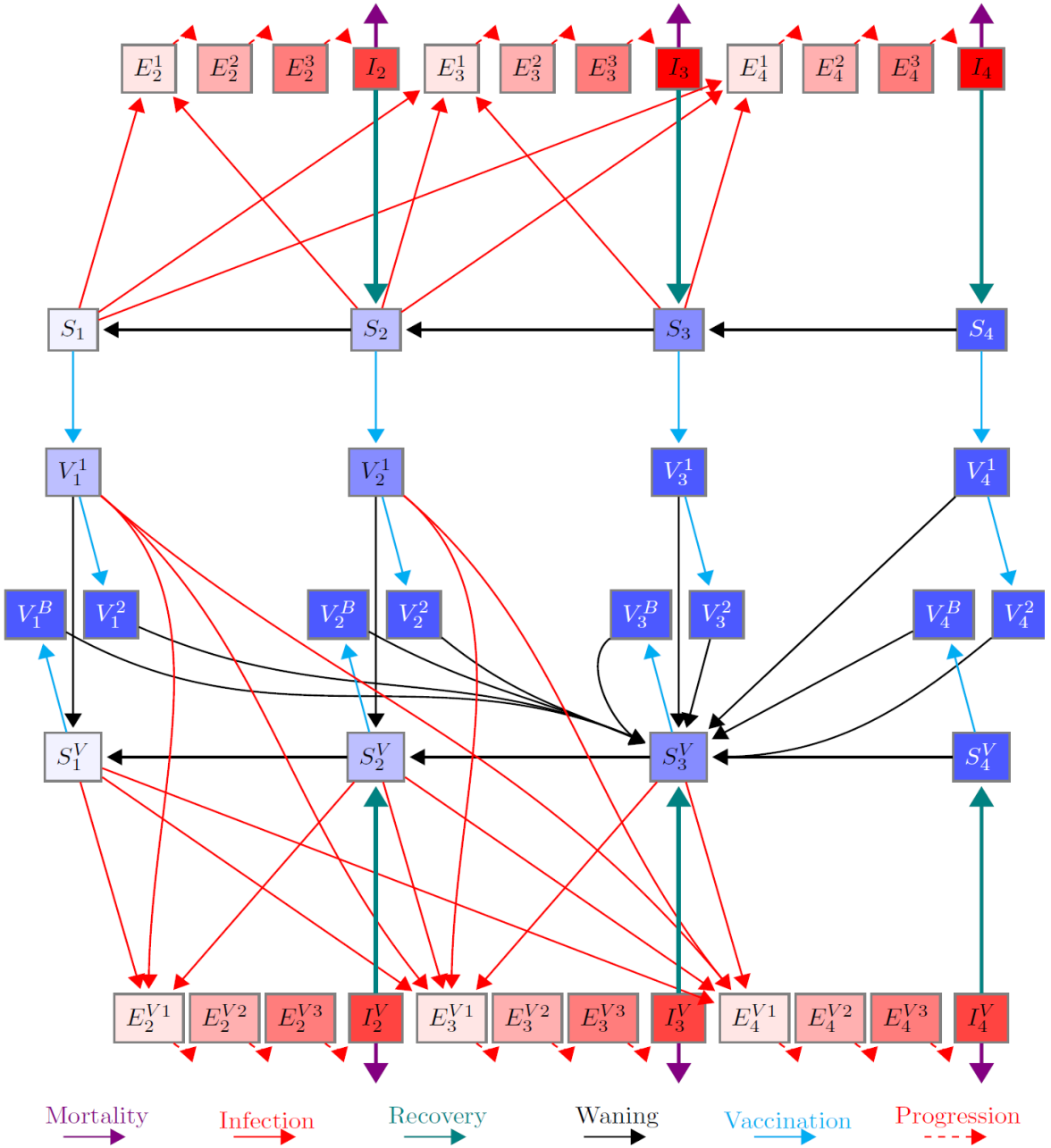
Model Fitting

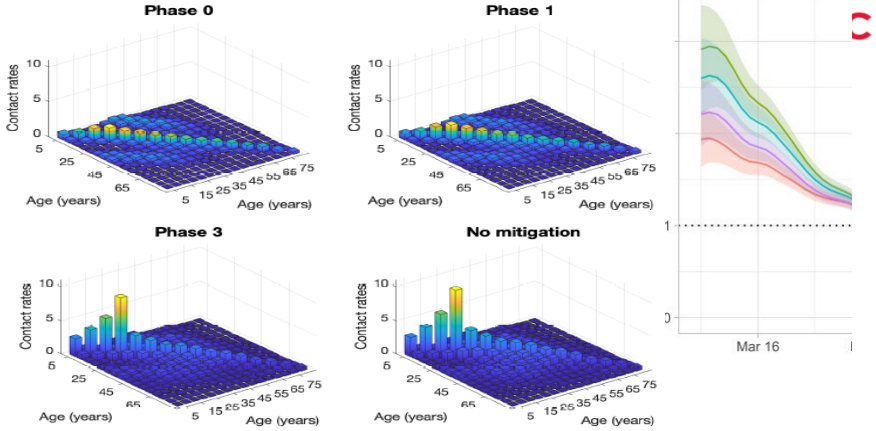
- Immunity gained after infection correlates with the severity of the infection
- Immunity gained from infection and vaccination can wane over similar periods of time

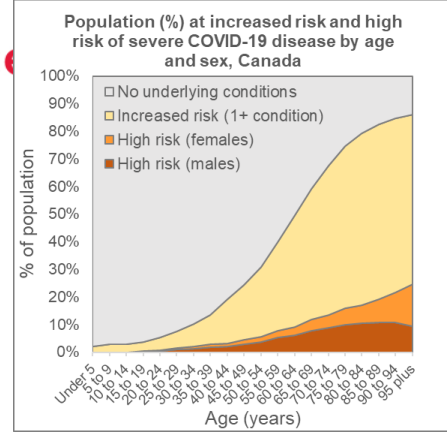
- Mild infections are shorter in duration than moderate infections
- Moderate infections are shorter than severe infections
- Viral load correlates with severity of infection, and thus will affect transmissibility

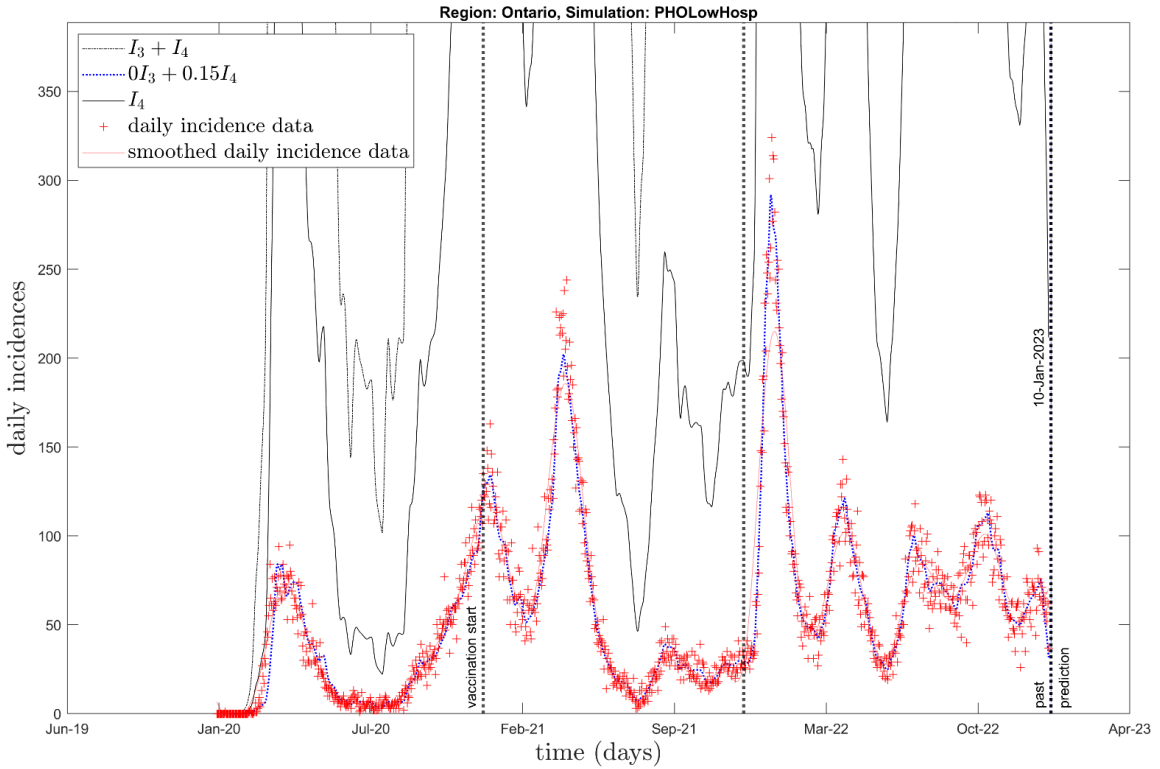
Extra

- Literature
- Assumptions
- Sensitivity analysis

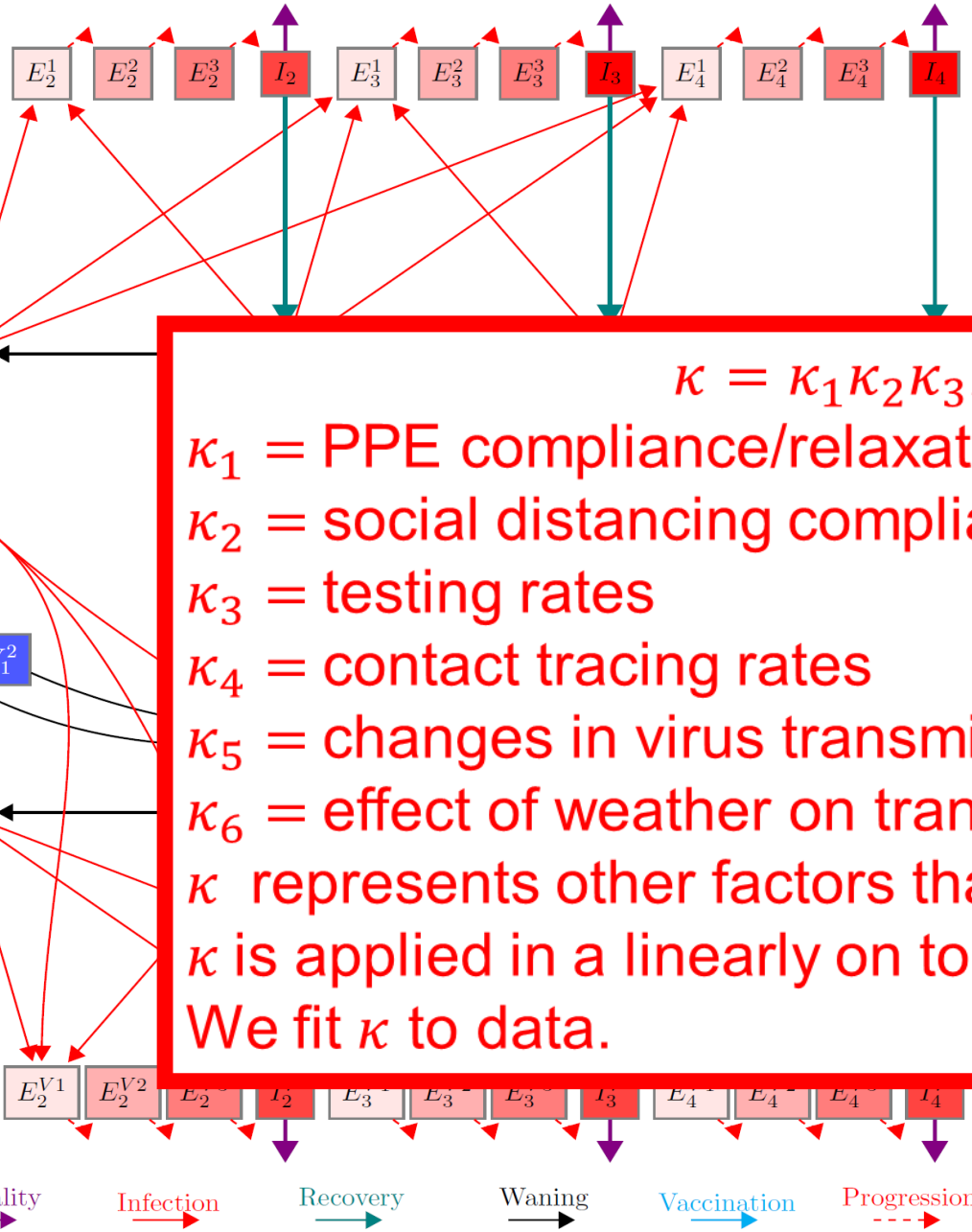


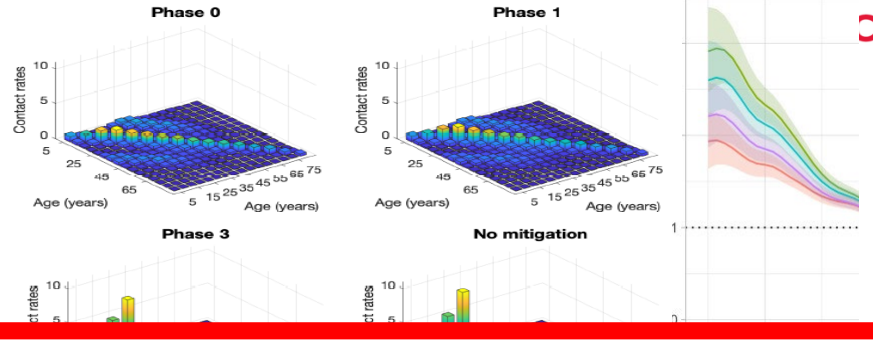


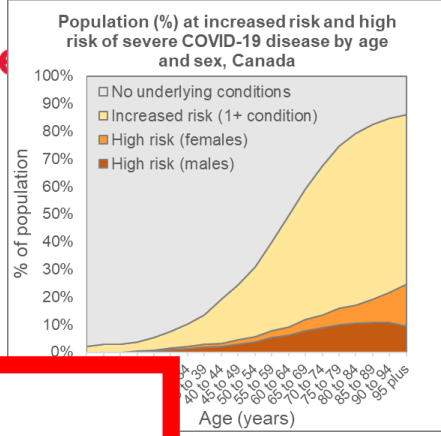




S – susceptible E- infected, no symptoms, not infectious
V – vaccinated I – infected, infectious, symptoms – mild (asymp), moderate, severe)







$$\kappa = \kappa_1\kappa_2\kappa_3\kappa_4\kappa_5\kappa_6 \qquad (kappa)$$

κ_1 = PPE compliance/relaxation

κ_2 = social distancing compliance/relaxation

κ_3 = testing rates

κ_4 = contact tracing rates

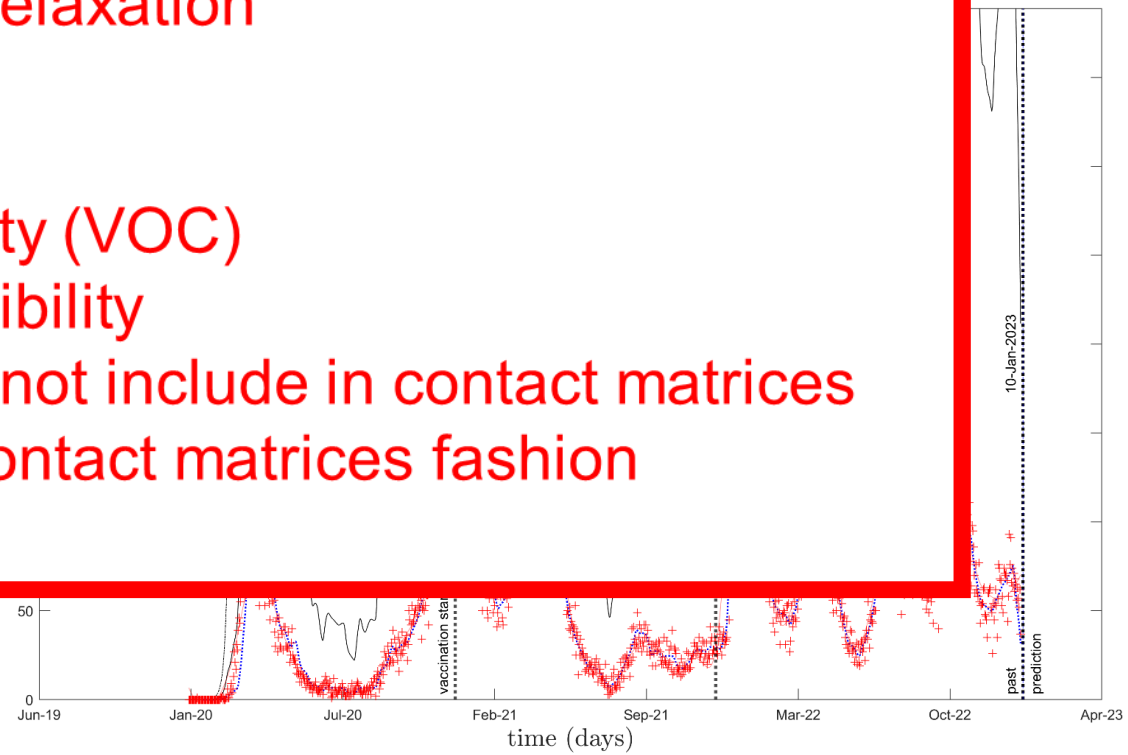
κ_5 = changes in virus transmissibility (VOC)

κ_6 = effect of weather on transmissibility

κ represents other factors that are not include in contact matrices

κ is applied in a linearly on top of contact matrices fashion

We fit κ to data.



S – susceptible

V – vaccinated

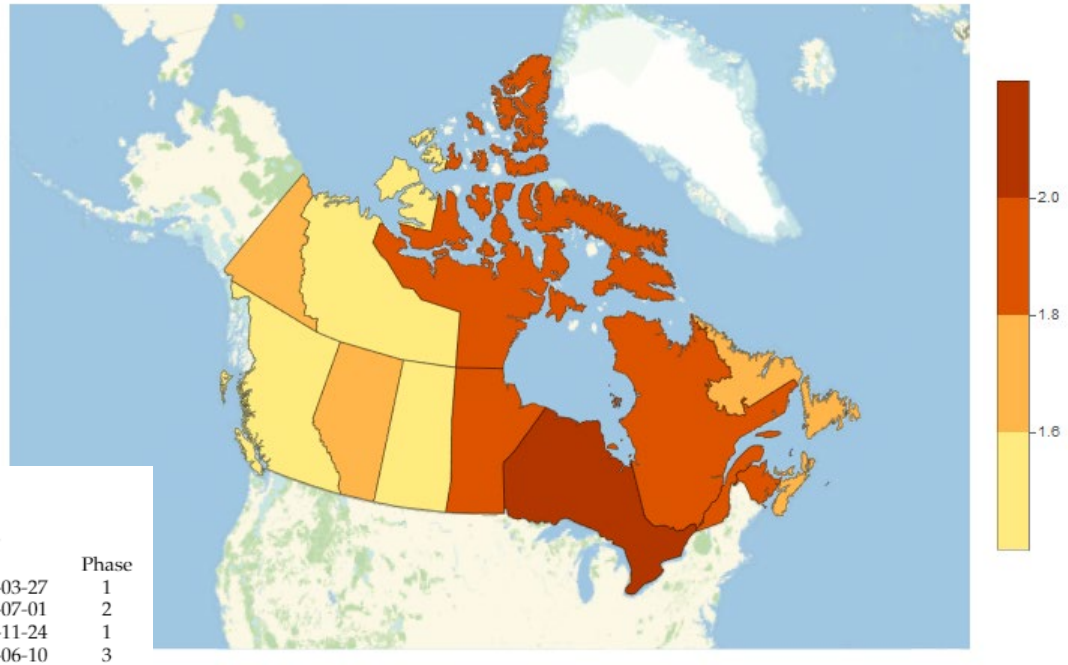
E- infected, no symptoms, not infectious

I – infected, infectious, symptoms – mild (asymp), moderate, severe)

Analysis: Public Health Mitigation

Scale	School	Work
0	no restrictions	no restrictions
1	open with restrictions	open with restrictions
2	blended learning	most businesses closed except for some sectors
3	closed	only essential services operating

Scale	Other
0	no restrictions
1	minor restrictions on gatherings, travelling, activities
2	moderate restrictions on gatherings, travelling, activities
3	strict restrictions on gatherings, travelling, activities



Alberta-Schools

Start	End	Phase
2020-03-05	2020-05-14	3
2020-05-14	2020-09-01	2
2020-09-01	2020-11-30	1
2020-11-30	2020-12-18	2
2020-12-18	2021-01-11	3
2021-01-11	2021-03-27	1
2021-03-27	2021-04-06	3
2021-04-06	2021-05-07	1
2021-05-07	2021-05-25	3
2021-05-25	2021-06-30	1
2021-06-30	2021-07-28	3

Manitoba-Schools

Start	End	Phase
2020-03-23	2020-09-08	3

Alberta-Work

Start	End	Phase
2020-03-17	2020-03-28	1
2020-03-28	2020-05-04	3
2020-05-04	2020-12-13	2
2020-12-13	2021-02-08	3
2020-02-08	2021-05-04	2
2021-05-04	2021-06-10	3
2021-06-10	2021-07-01	1
2021-07-01	2021-07-28	0

Manitoba-Work

Start	End	Phase
2020-03-20	2020-04-01	1
2020-04-01	2020-05-04	3
2020-05-04	2020-06-01	2
2020-06-01	2021-11-02	1

Alberta-Other

Start	End	Phase
2020-03-12	2020-03-27	1
2020-03-27	2020-07-01	2
2020-07-01	2020-11-24	1
2020-11-24	2021-06-10	3
2020-06-10	2021-07-01	2
2021-07-01	2021-07-28	0

Manitoba-Other

Start	End	Phase
2020-03-17	2020-03-20	1
2020-03-20	2020-04-01	2
2020-04-01	2020-06-01	3
2020-06-01	2021-09-28	2

Dick, Heffernan, submitted.

CDM CMM
Centre for Disease Modelling
Centre de la modélisation des maladies

ONTARIO

March 12, 2020
Public schools close.

March 17, 2020
Ontario declares state of emergency.

March 24, 2020
All non-essential businesses close.

May 4, 2020
Ontario starts to ease restrictions. Seasonal business: garden centers & nurseries reopen.

May 19, 2020
Workplaces, retail stores, pet stores, recreational facilities reopen and constructions resume.

June 12, 2020
Hair saloons, restaurant patios, swimming pools and all child-care centres reopen. Social circles expand to 10 people.

July 2, 2020
Face coverings required for TTC passengers.

July 17, 2020
Restaurants resume indoor service. Movie theatres, gyms, casinos reopen with restrictions. Gathering limits increase to 50 indoor and 100 outdoors.

September 8, 2020
Schools reopen across the province.

September 18, 2020
Private gatherings limit reduced to 10 indoors and 25 outdoors.

October 9, 2020
Indoor dining, gyms, casinos, movie theatres close.

December 26, 2020
Indoor private gatherings prohibited. Shopping malls close (curb-side pickup only).

January 4, 2021
Schools move to remote learning.

January 14, 2021
Ontario declares stay-at-home order. Outdoor gatherings reduced to 5 people.

February 16, 2021
Stay-at-home order lifted in most regions. Partial reopening of non-essential businesses begins. Schools reopen to in-person learning.

April 8, 2021
Ontario declares stay-at-home order. Non-essential businesses ordered to close.

April 12, 2021
Schools close, students move to remote learning.

June 11, 2021
Ontario moves to Step 1 of reopening plan. Non-essential retail opens at 15% capacity. Outdoor dining & fitness permitted. Day camps for children open.

June 30, 2021
Ontario moves to Step 2 of reopening plan. Child care centres reopen. Outdoor social gatherings increase to 25 people & indoor gatherings limit to 5 people.

July 16, 2021
Ontario moves to Step 3 of reopening plan. Outdoor social gatherings limit increase to 100, indoor gatherings to 25 people. Museums, cinemas, amusement parks reopen at 50% capacity.

September 7, 2021
Schools reopen to in person learning with restrictions.

September 22, 2021
Proof of Covid-19 vaccine required to access non-essential services.

October 25, 2021
Capacity limits in non-essential business are lifted: in restaurants, gyms, casinos.

December 19, 2021
Indoor gathering limit decrease to 10 people, outdoor gathering limit to 25.

January 5, 2022
Indoor gathering limit decrease to 5 people, outdoor gathering limit to 10. Retail stores, personal care services open at 50% capacity. Restaurants, gyms, casinos, cinemas close. Schools implement remote learning.

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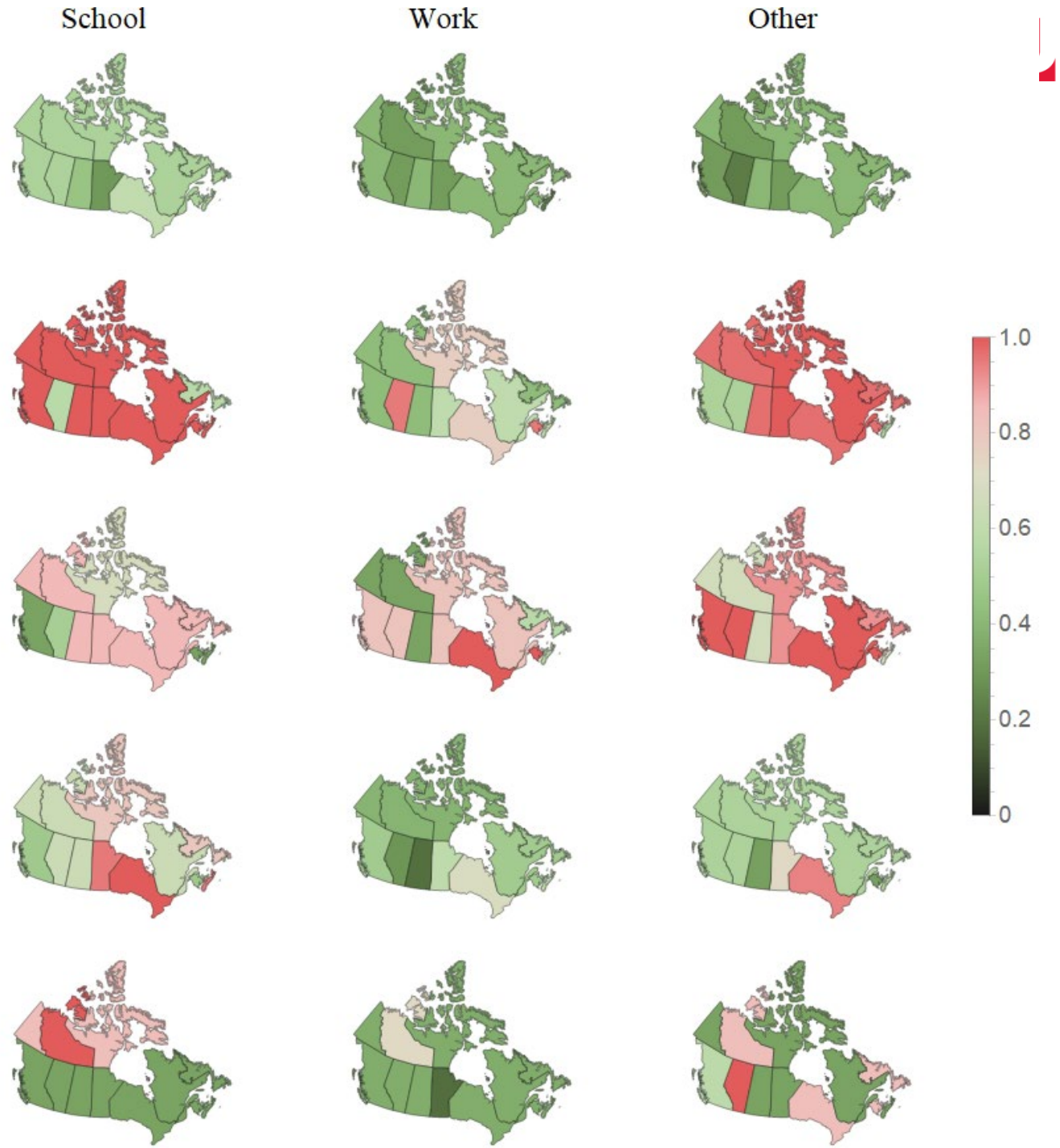
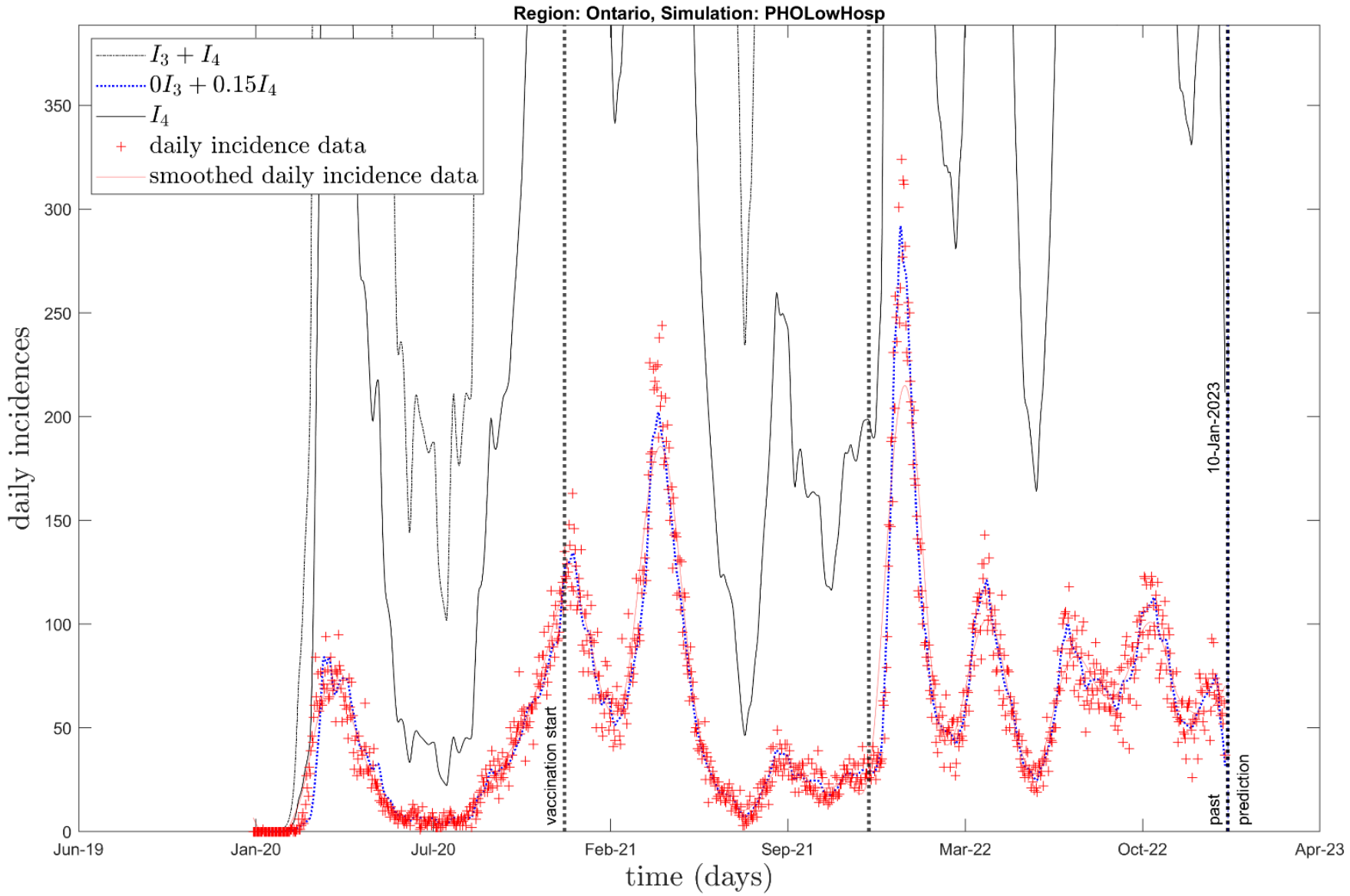
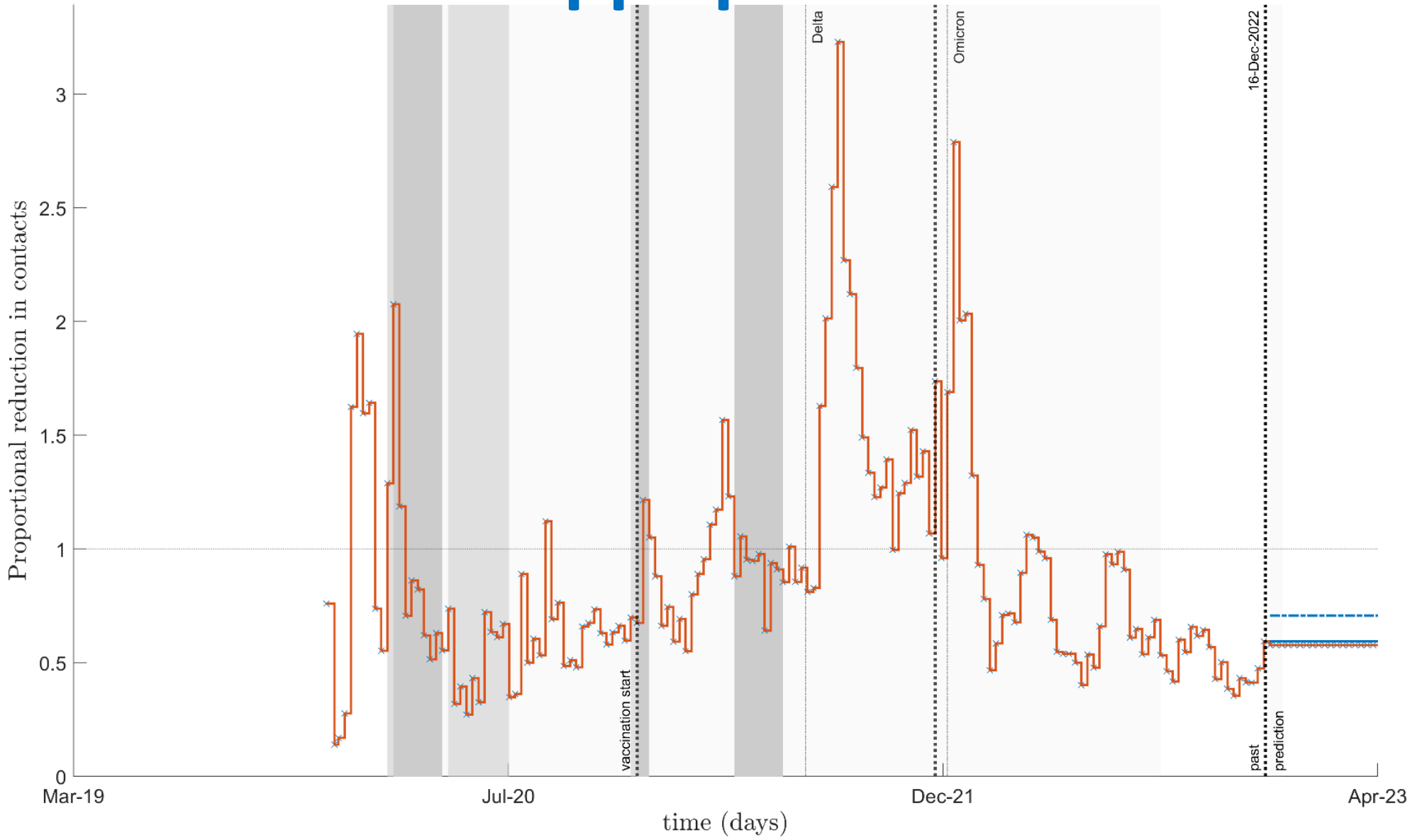


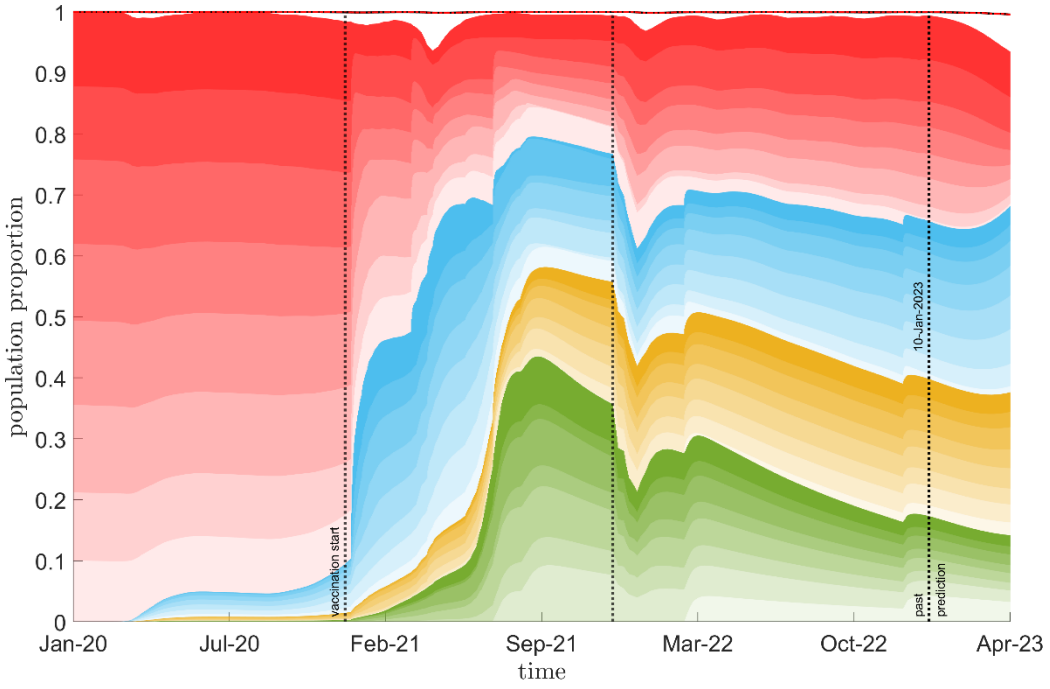
Calibration to Hosp Data

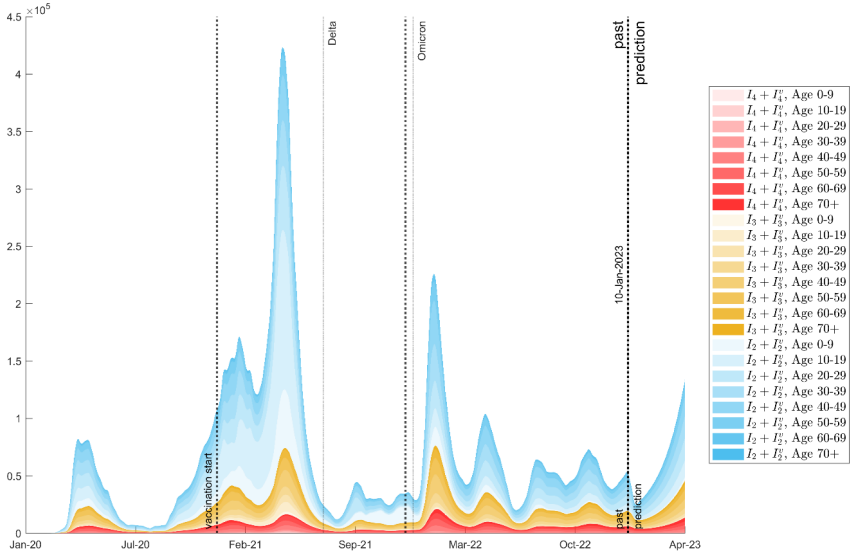


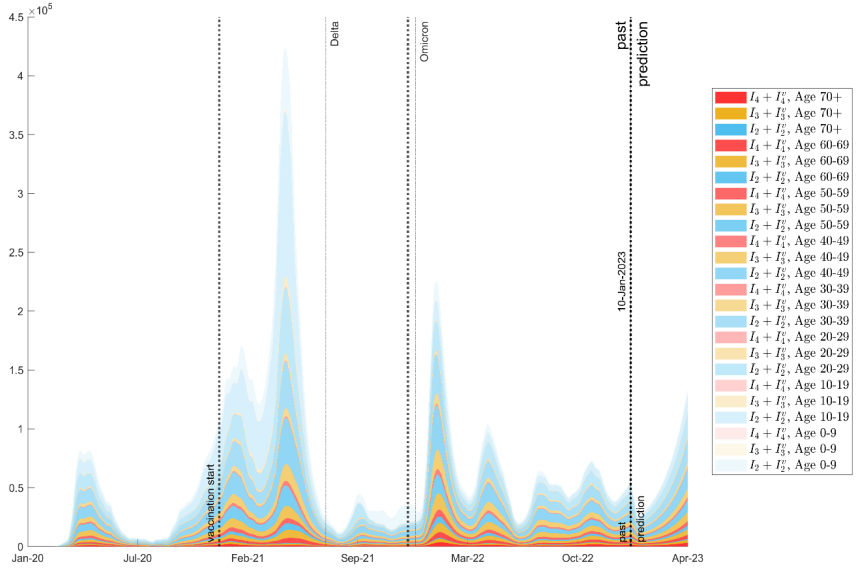
Kappa parameter



Immunity & Infection Distn



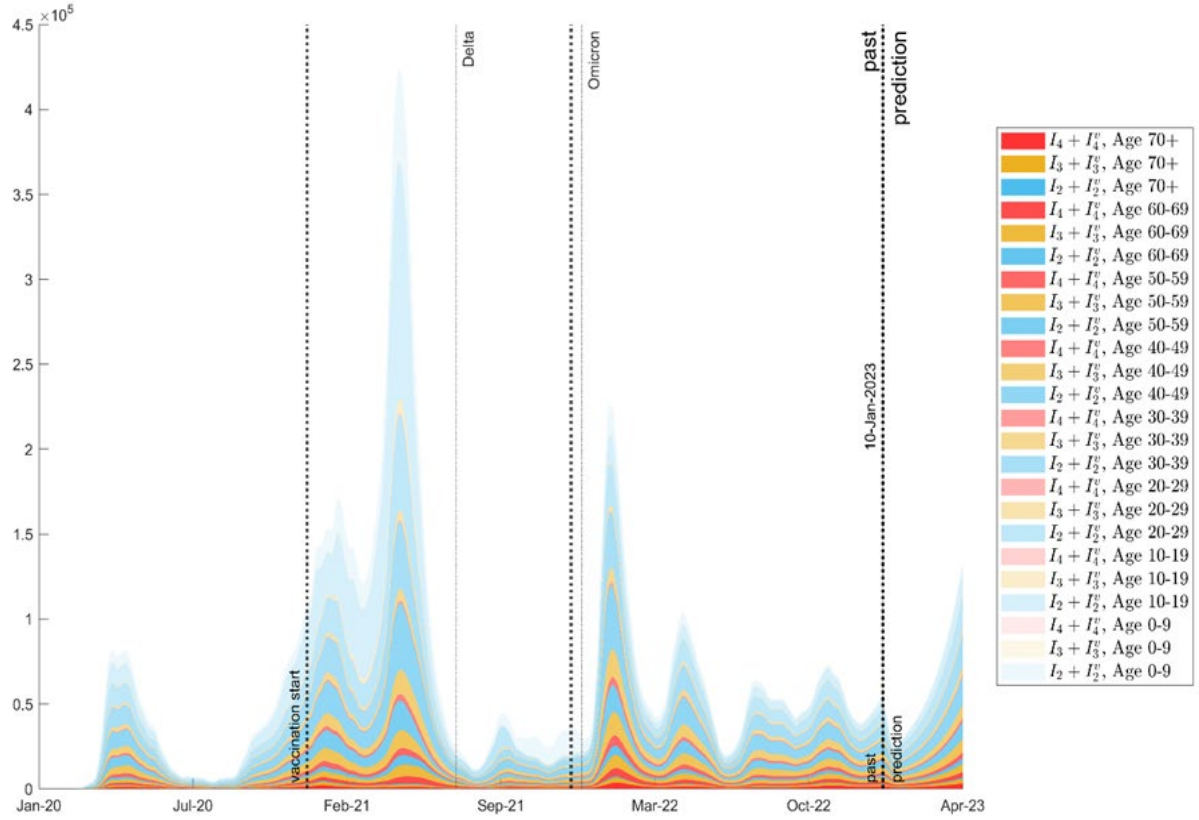


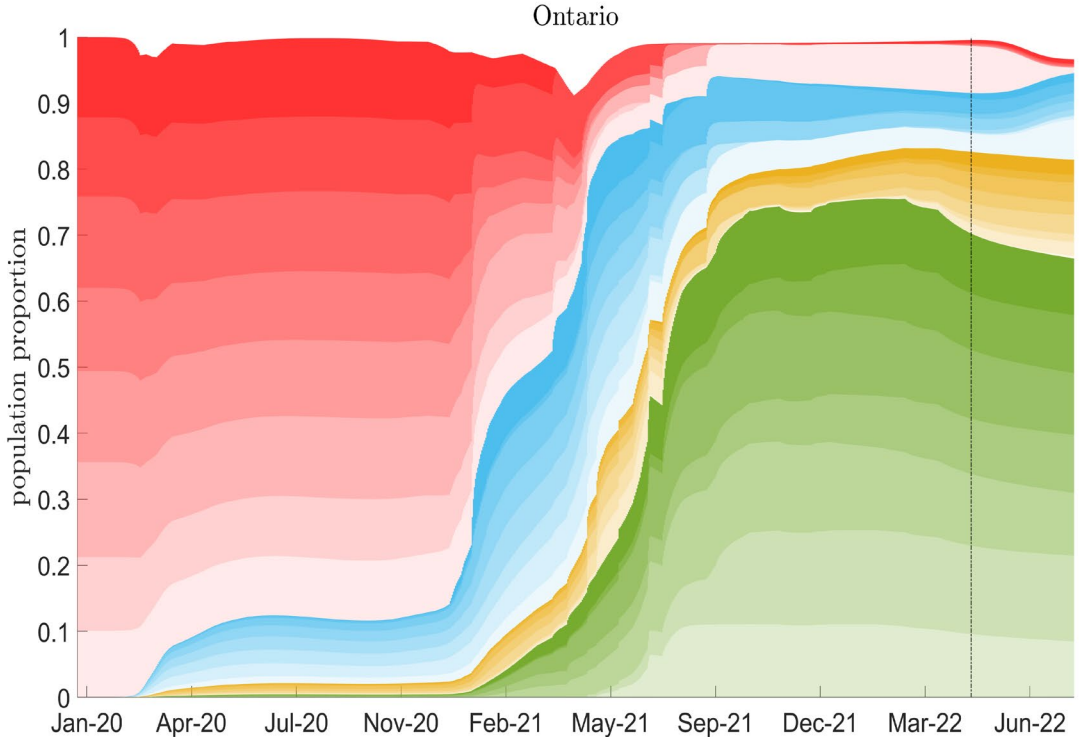


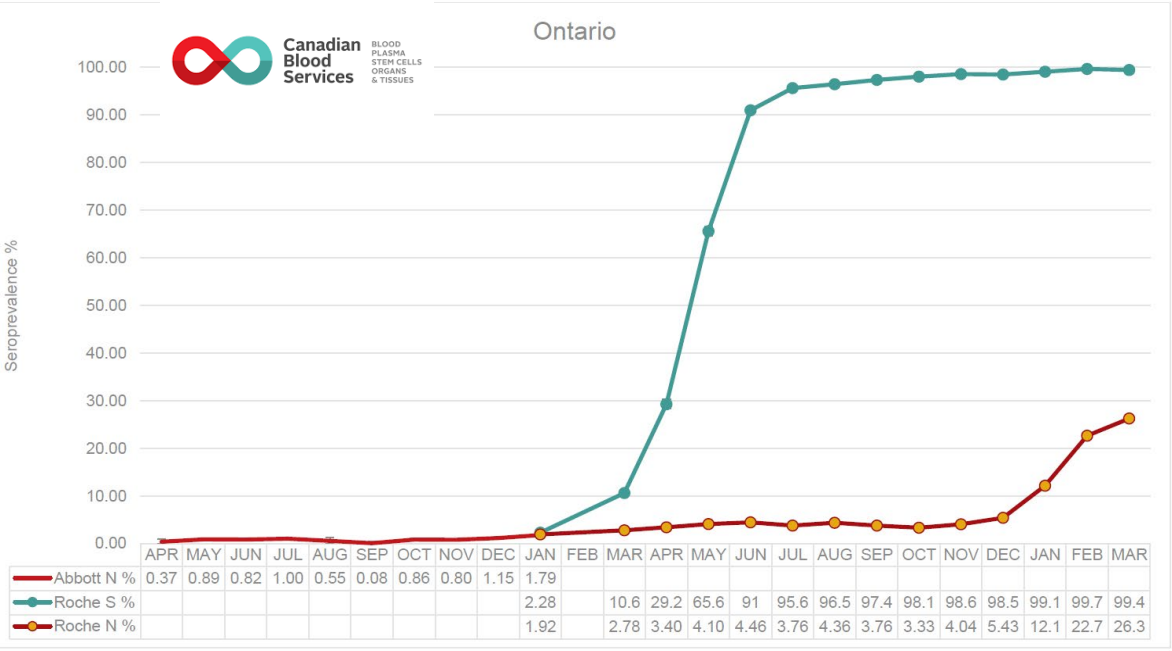
$S_4 + S_4^V + \sum_{i=3}^4 V_i^1 + \sum_{i=1}^4 V_i^2 + \sum_{i=1}^4 V_i^B$, Age 0-9
$S_4 + S_4^V + \sum_{i=3}^4 V_i^1 + \sum_{i=1}^4 V_i^2 + \sum_{i=1}^4 V_i^B$, Age 10-19
$S_4 + S_4^V + \sum_{i=3}^4 V_i^1 + \sum_{i=1}^4 V_i^2 + \sum_{i=1}^4 V_i^B$, Age 20-29
$S_4 + S_4^V + \sum_{i=3}^4 V_i^1 + \sum_{i=1}^4 V_i^2 + \sum_{i=1}^4 V_i^B$, Age 30-39
$S_4 + S_4^V + \sum_{i=3}^4 V_i^1 + \sum_{i=1}^4 V_i^2 + \sum_{i=1}^4 V_i^B$, Age 40-49
$S_4 + S_4^V + \sum_{i=3}^4 V_i^1 + \sum_{i=1}^4 V_i^2 + \sum_{i=1}^4 V_i^B$, Age 50-59
$S_4 + S_4^V + \sum_{i=3}^4 V_i^1 + \sum_{i=1}^4 V_i^2 + \sum_{i=1}^4 V_i^B$, Age 60-69
$S_4 + S_4^V + \sum_{i=3}^4 V_i^1 + \sum_{i=1}^4 V_i^2 + \sum_{i=1}^4 V_i^B$, Age 70+
$S_3 + S_3^V + V_2^1$, Age 0-9
$S_3 + S_3^V + V_2^1$, Age 10-19
$S_3 + S_3^V + V_2^1$, Age 20-29
$S_3 + S_3^V + V_2^1$, Age 30-39
$S_3 + S_3^V + V_2^1$, Age 40-49
$S_3 + S_3^V + V_2^1$, Age 50-59
$S_3 + S_3^V + V_2^1$, Age 60-69
$S_3 + S_3^V + V_2^1$, Age 70+
$S_2 + S_2^V + V_1^1$, Age 0-9
$S_2 + S_2^V + V_1^1$, Age 10-19
$S_2 + S_2^V + V_1^1$, Age 20-29
$S_2 + S_2^V + V_1^1$, Age 30-39
$S_2 + S_2^V + V_1^1$, Age 40-49
$S_2 + S_2^V + V_1^1$, Age 50-59
$S_2 + S_2^V + V_1^1$, Age 60-69
$S_2 + S_2^V + V_1^1$, Age 70+
$S_1 + S_1^V$, Age 0-9
$S_1 + S_1^V$, Age 10-19
$S_1 + S_1^V$, Age 20-29
$S_1 + S_1^V$, Age 30-39
$S_1 + S_1^V$, Age 40-49
$S_1 + S_1^V$, Age 50-59
$S_1 + S_1^V$, Age 60-69
$S_1 + S_1^V$, Age 70+
vaccination start
booster vaccination start
past/prediction

Age

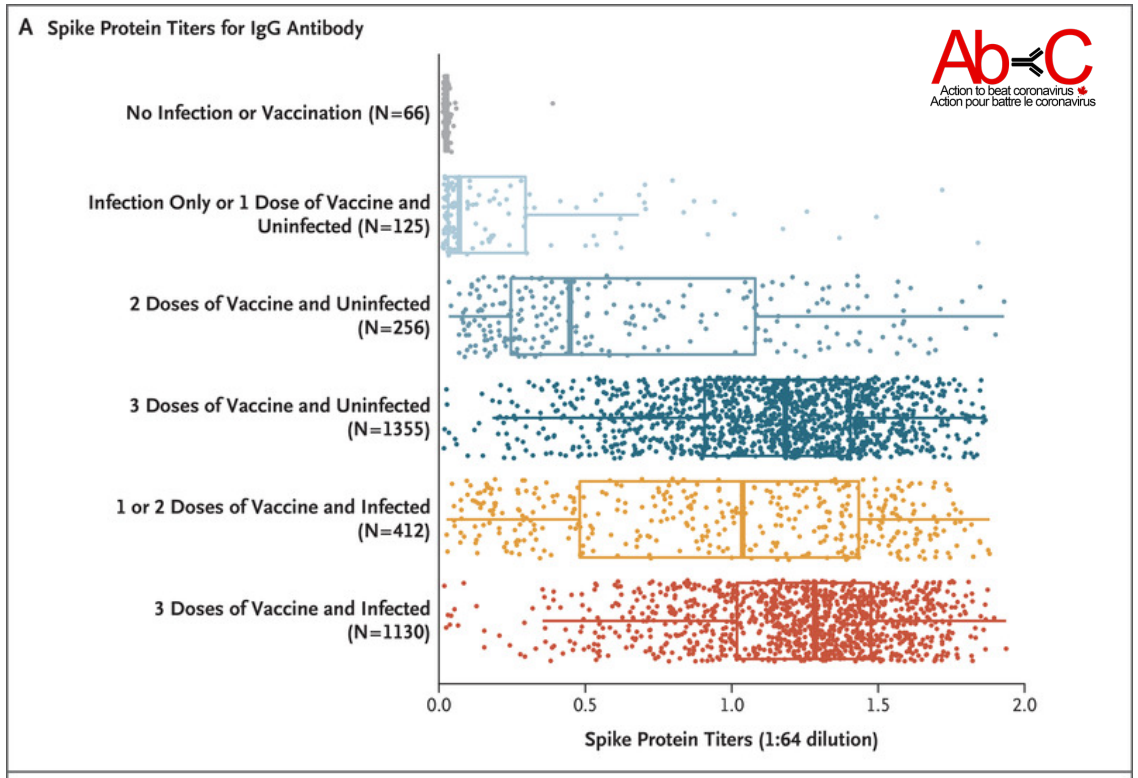

Pre-vaccine
Vaccine
Omicron waves
Seroprevalence (%)
Median Age
Apr 2020
Jul 2020
Oct 2020
Jan 2021
Apr 2021
Jul 2021
Oct 2021
Jan 2022
Apr 2022
Jul 2022
Oct 2022
Jan 2023

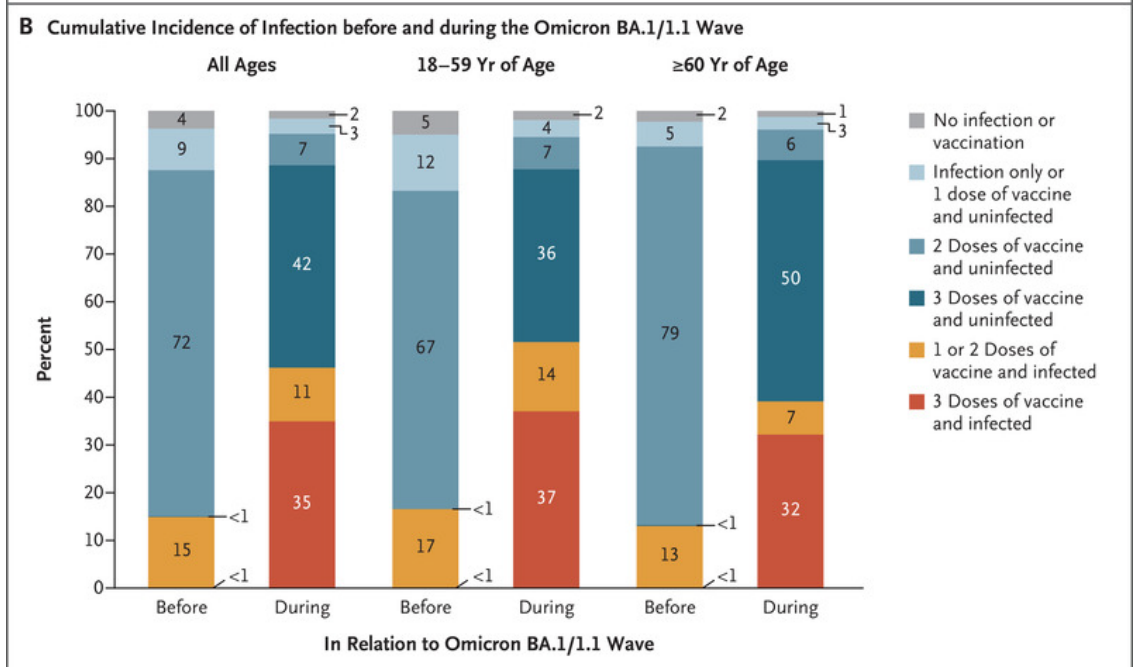

Delta
Omicron
past
prediction
10-Jan-2023
vaccination start
Jan-20
Jul-20
Feb-21
Sep-21
Mar-22
Oct-22
Apr-23





	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR
Abbott N %	0.37	0.89	0.82	1.00	0.55	0.08	0.86	0.80	1.15	1.79														
Roche S %										2.28		10.6	29.2	65.6	91	95.6	96.5	97.4	98.1	98.6	98.5	99.1	99.7	99.4
Roche N %										1.92		2.78	3.40	4.10	4.46	3.76	4.36	3.76	3.33	4.04	5.43	12.1	22.7	26.3





Reading

- Heffernan and Ciupe
- Wodarz and Nowak
- Perelson and Nelson

Homework Problem 1 – 10 points

- Consider the basic model of in-host infection with the virus loss term AND an eclipse stage split into 2 parts
- Draw a flow diagram
- Describe model variables and parameters
- Derive the basic reproduction number
- Find the model equilibria (fixed points)
- Show that the infected equilibrium can only exist if the basic reproduction number is greater than 1

$$\frac{dx}{dt} = \lambda - d_x x - \beta x v$$

$$\frac{de_1}{dt} = \beta x v - d_e e_1 - \alpha e_1, \qquad \frac{de_2}{dt} = \alpha e_1 - d_e e_2 - \alpha e_2$$

$$\frac{dy}{dt} = \alpha e_2 - d_y y$$

$$\frac{dv}{dt} = k y - \beta x v - d_v v$$

Homework Problem 2 – 8 points

- Again, consider the basic model of in-host infection with the virus loss term AND an eclipse stage split into 2 parts (see Homework Problem 1)
- Rewrite the model to take into consideration infectious and non-infectious virus particles. Justify the structure that you chose.
- Add an equation for antibodies. Add in the neutralization for virus particles by antibodies. Justify why you added antibodies in the structure that you chose.
- Add an equation for cytotoxic T-cells. Add in the killing of infected cells. Justify why you added CTL in the format that you chose.
- Add an equation for Interferon and add in terms that represent the effects of interferon into the model. Justify your choices.

Homework Problem 3 – 4 points

- Read
  - Heffernan, J. M., and M. J. Keeling. "An in-host model of acute infection: Measles as a case study." *Theoretical population biology* 73.1 (2008): 134-147.
  - Heffernan, J. M., and M. J. Keeling. "Implications of vaccination and waning immunity." *Proceedings of the Royal Society B: Biological Sciences* 276.1664 (2009): 2071-2080
- Comment on the utility of embedding in-host information into epidemiological models (1 page)