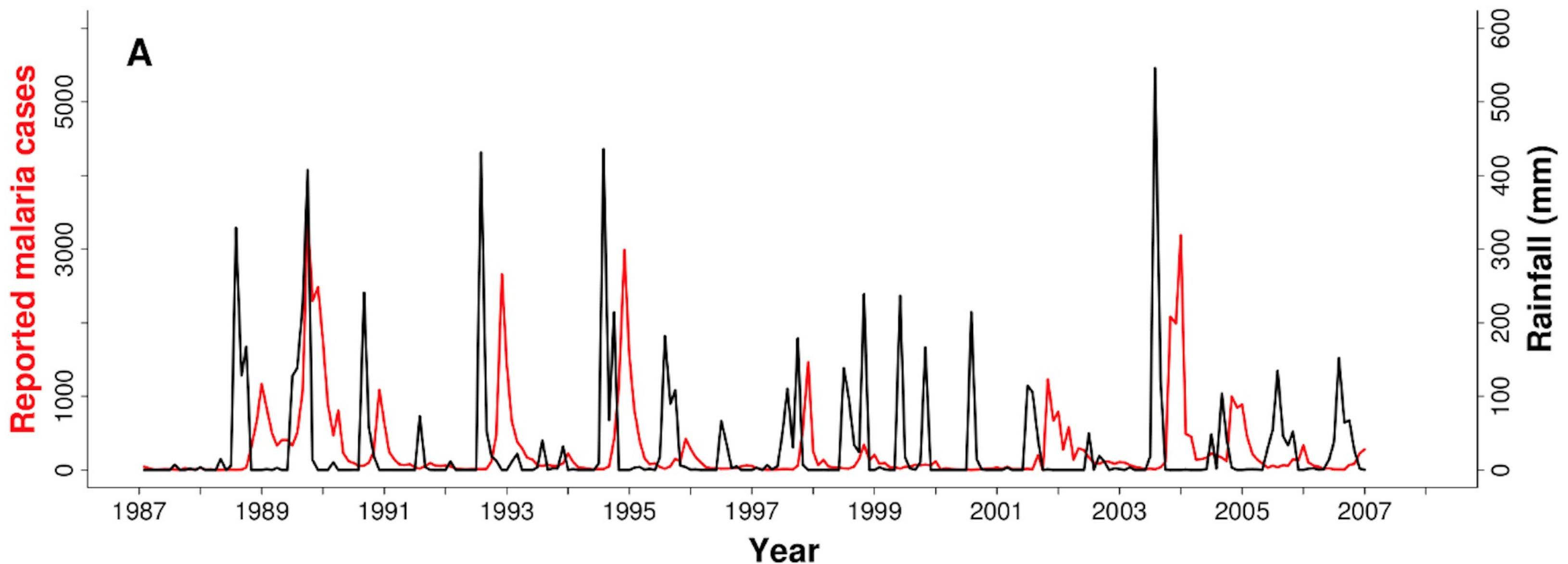


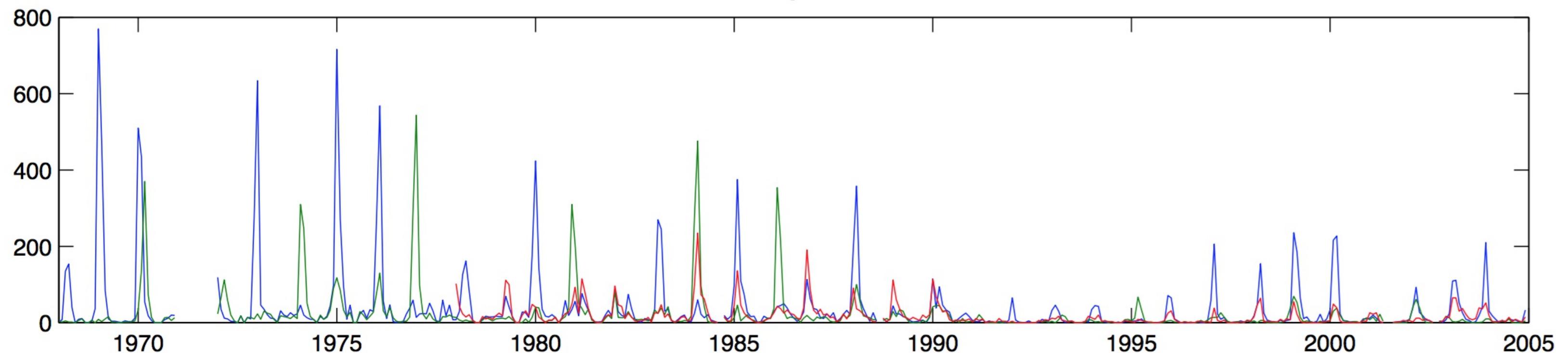
Immunity

Malaria and rain in India, 1987-2007

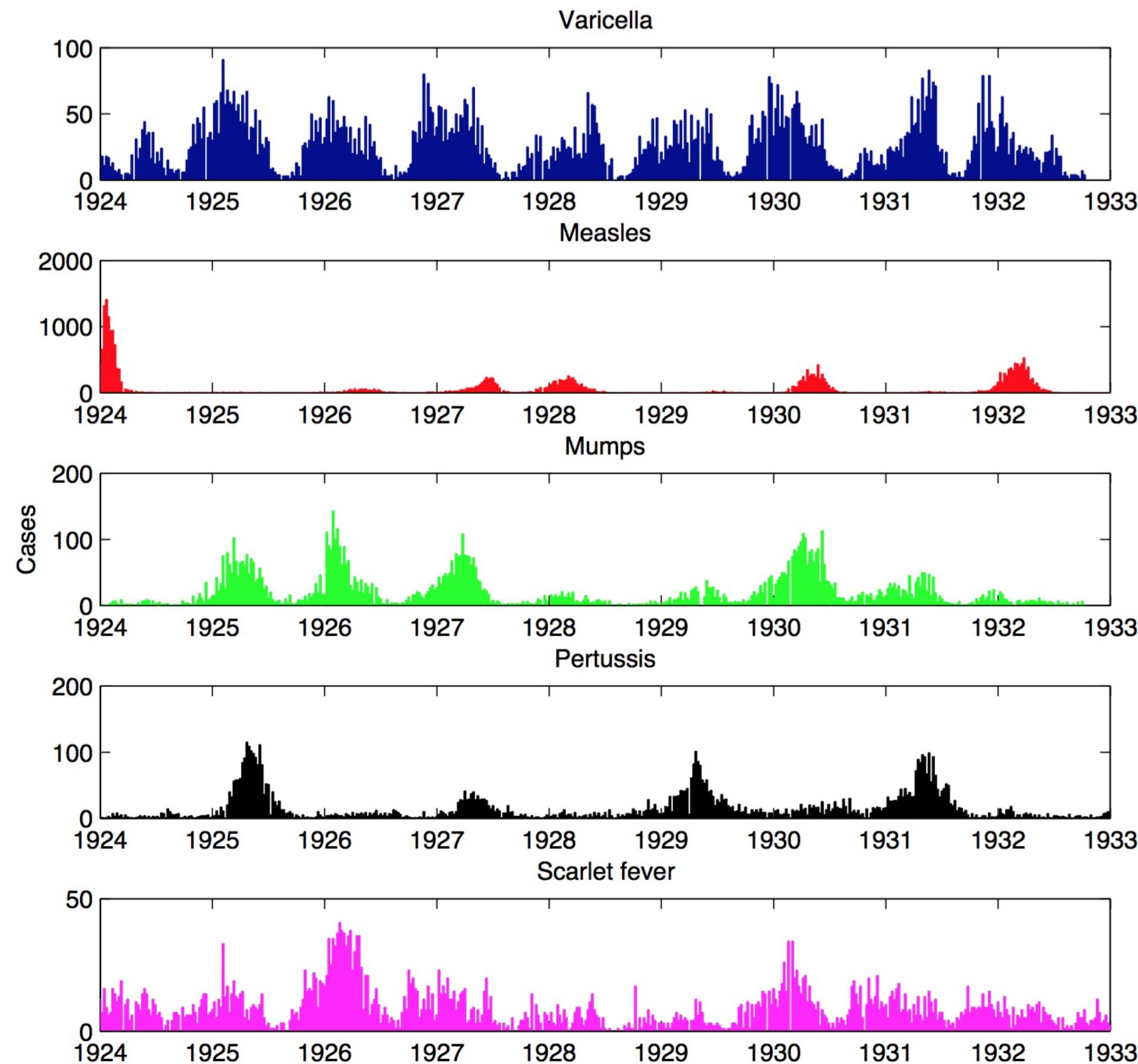


Laneri et al. 2010

Influenza in St. Petersburg, 1968-2005



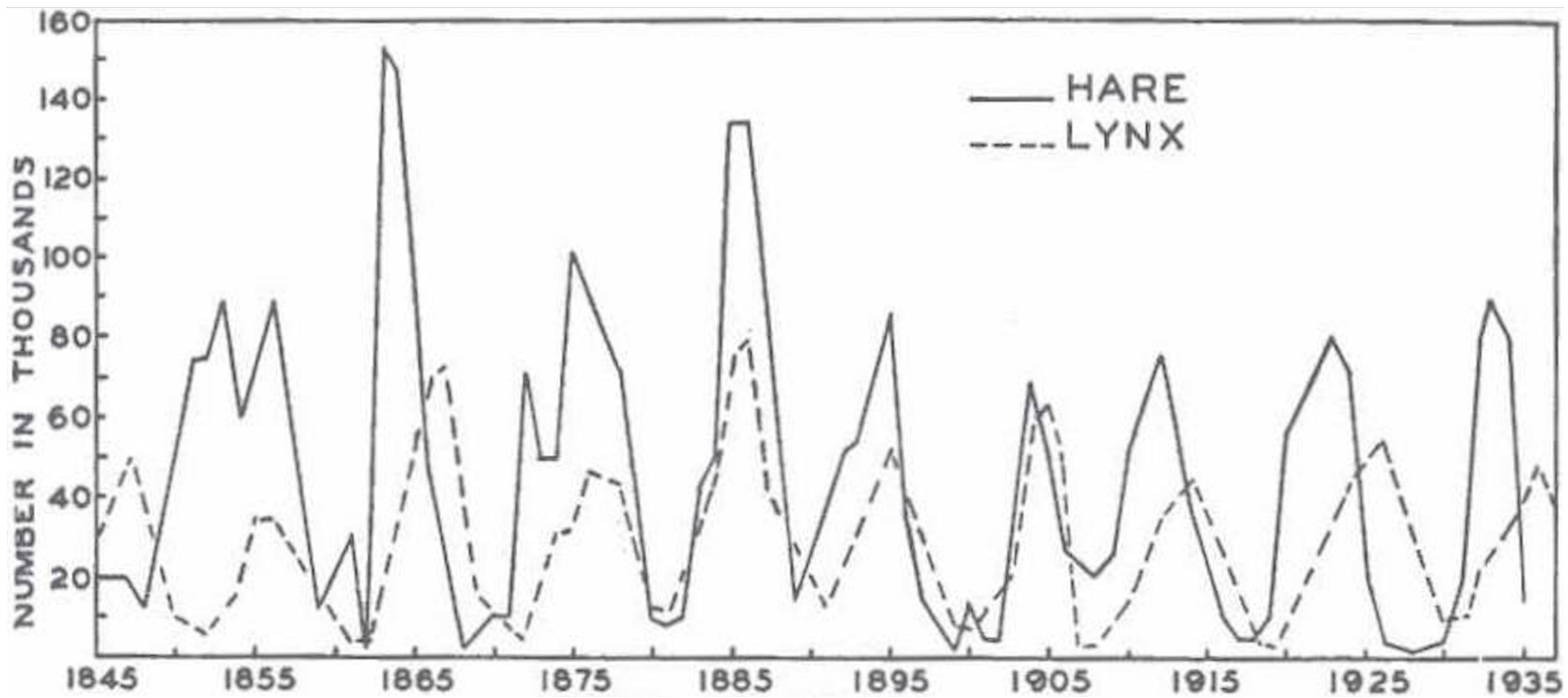
Infections in Seattle, 1924-1933





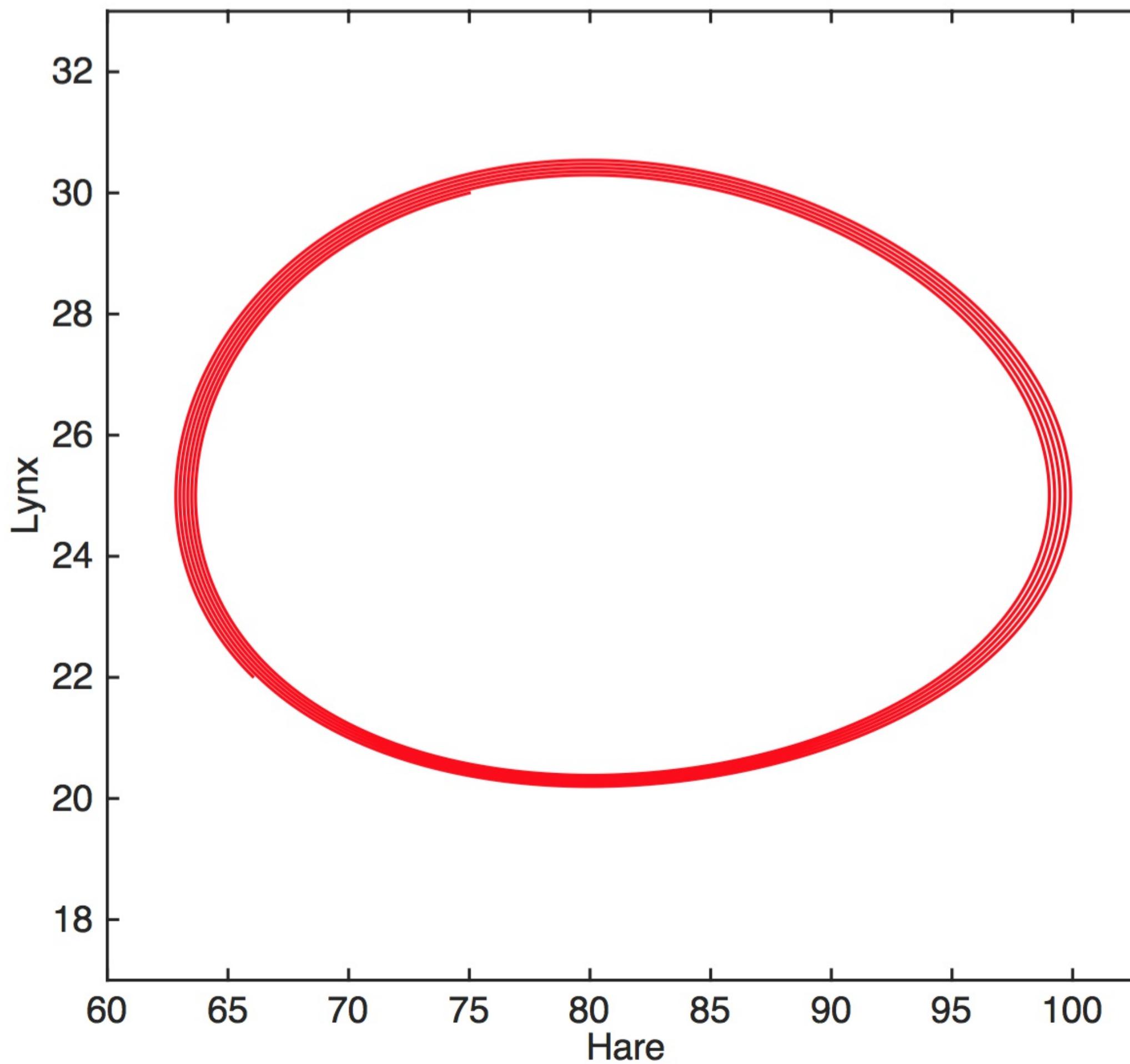
Ben Slack (Fort Frances Times, 2008)

Seemingly complex dynamics are common



MacLulich 1937

...and correlations can mislead



Partial solution: Mechanistic models

$$H' = aH - bHL$$

$$L' = cHL - dL$$

H hares, L lynxes

hare birth rate a , predation rate b ,
consumption rate c , death rate d

(working hypothesis)

Competition for susceptible hosts shapes
the ecological and evolutionary dynamics
of pathogens.

Implicit assumption of SIR model

The susceptible fraction determines a pathogen's growth rate

$$I' > 0 \Rightarrow \frac{\beta S}{N} > \gamma$$

If the SIR model fits poorly, what next?

Other possibilities

transient dynamics and noise

host population structure

...

more complex forms of immunity

multiple "immunophenotypes"

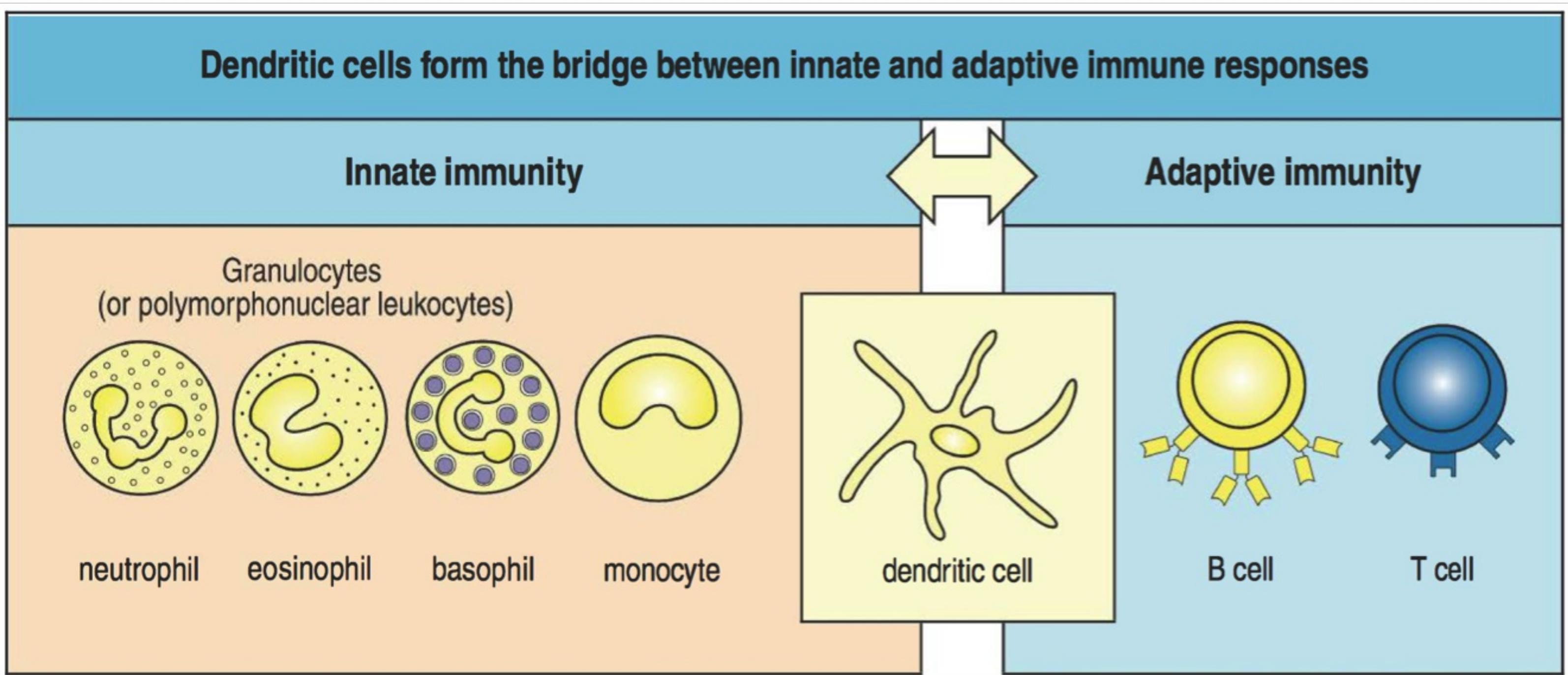
Antigenic variation

Formally, variation in surface proteins

Broader concepts may be more useful

Cobey 2014, Murphy 2011

Immunity: Coordinated innate and adaptive responses



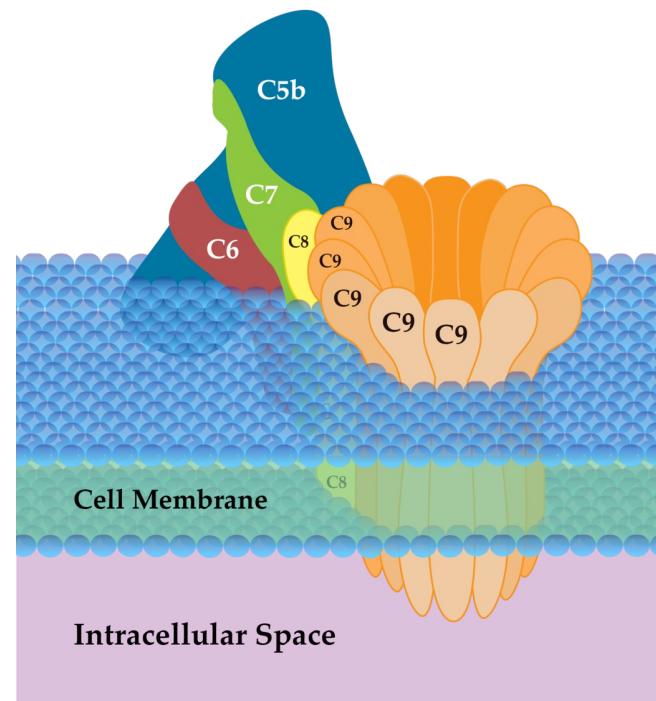
Innate immunity

Less specific

Nearly memoryless

The complement system

Extremely fast destruction, tagging, and signalling



Attacks via lectin, "alternative," and classical pathways

Effective against viruses, bacteria, parasites

Tags pathogens ("opsonization")

Attracts phagocytes

Macrophages

Long-lived sentinels and killers



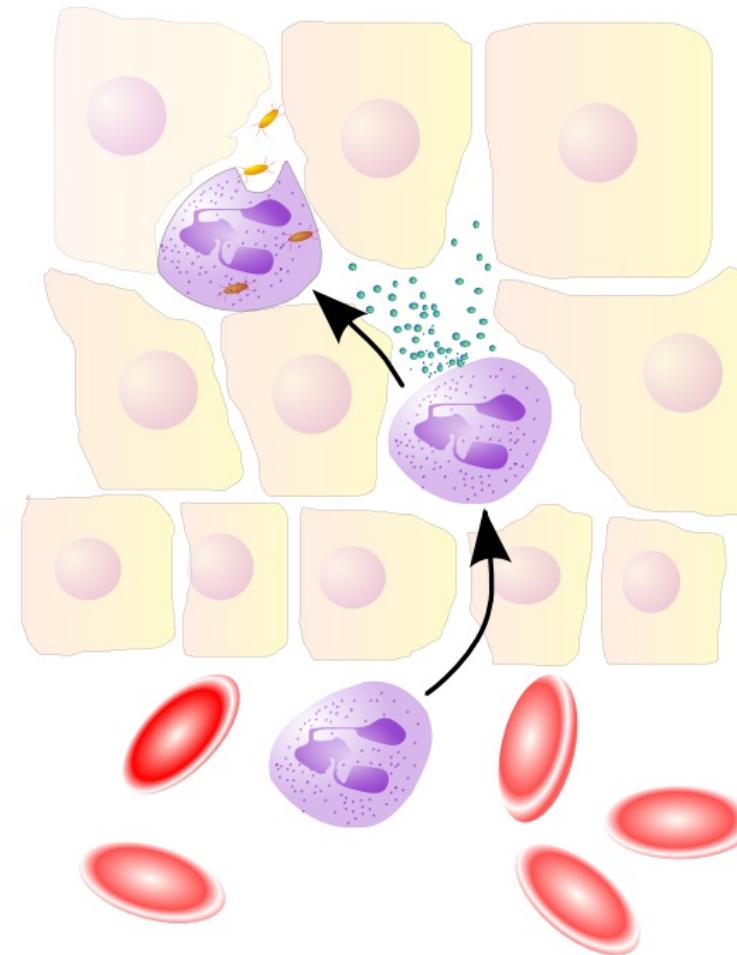
Resting, primed, or hyperactive

Display to T cells via MHC class II

Secret IL-1, TNF, complement proteins to kill and signal

Neutrophils

"On call," do most of the dirty work



70% of WBCs, 100 billion produced daily, live 5 days

Respond to IL-1, TNF, f-met peptides from macrophages

Just kill and signal (e.g., IL-2)

Natural killer (NK) cells

"On call" for some killing and signalling

Target tumor cells, virus-infected cells, bacteria, parasites, fungi

Kill cells not expressing MHC class I

Activated by LPS, interferons produced by dying cells

Major supplier of cytokines like IFN- γ and TNF

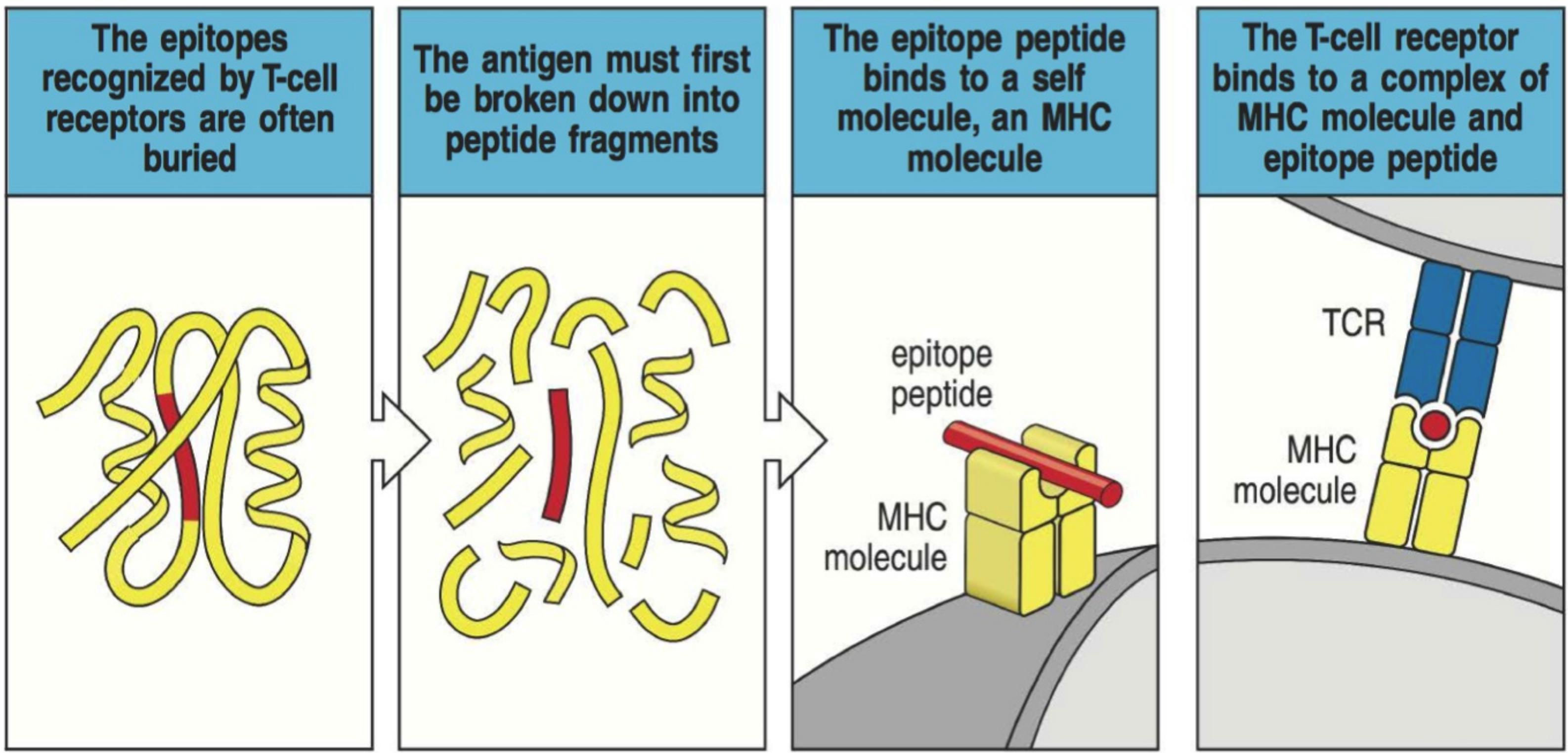
Where is there feedback?

Adaptive immunity

More specific

Some memory

Cellular immunity: Recognition of presented peptides



MHC class I

Bind peptides 8-11 amino acids long

Expressed on almost every cell

In humans, six genes encoded by HLA-A, HLA-B, HLA-C

Recognized by CTLs

MHC class II

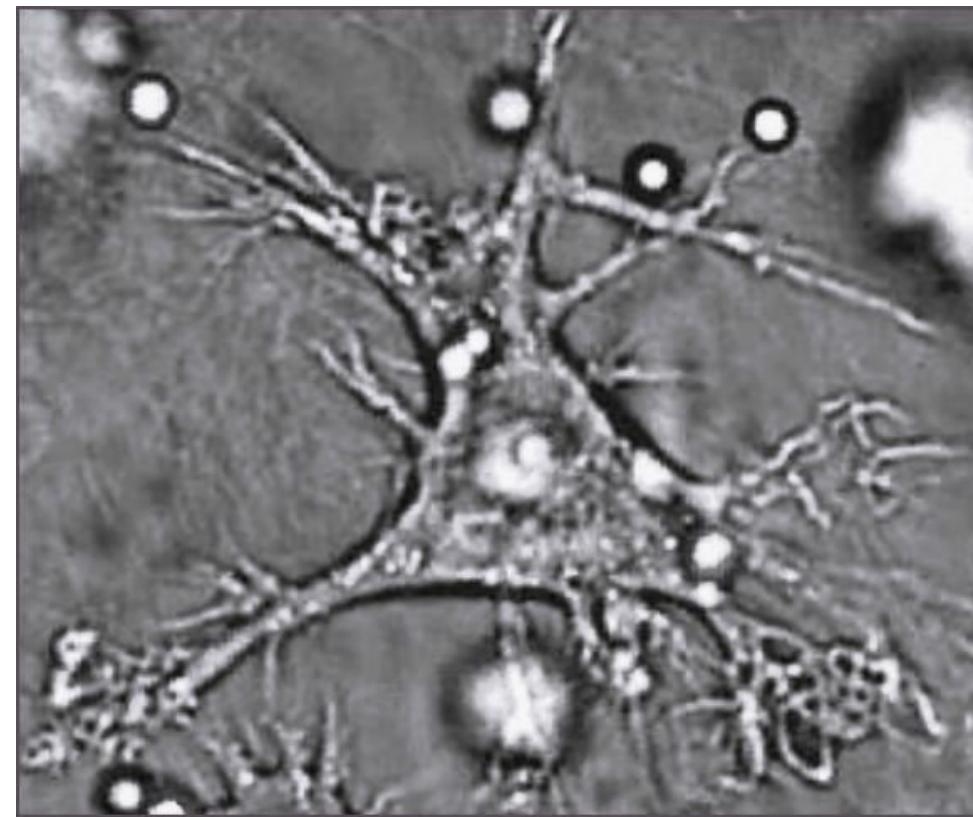
Bind peptides 13-25 amino acids long

Expressed only by immune cells

In humans, encoded by HLA-D

Recognized by helper T cells

Dendritic cells: Master intelligence



Use TLRs and other receptors to detect pathogens

Sensitive to local cytokine profiles

Once in lymph nodes, use diverse costimulatory molecules to
activate T cells

T cells: Activated by antigen presentation

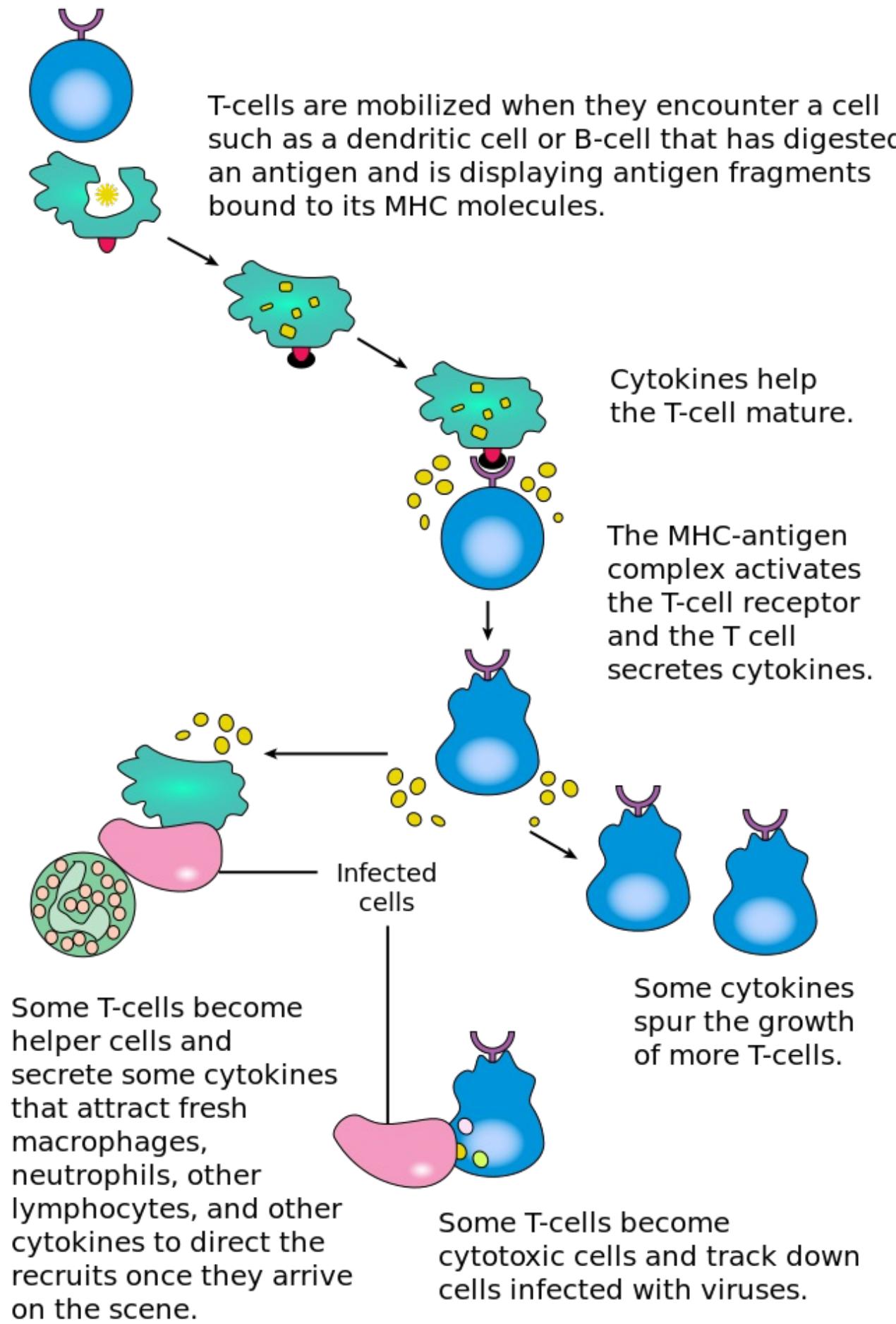
Antigens presented by dendritic cells, macrophages, B cells

Co-stimulation required (B7 binds to CD28)

Dendritic cells provide "snapshot"

Macrophages provide sustained support

B cells can concentrate rare and familiar antigen



So... what are Th cells?

Produced by rearrangement, educated in thymus

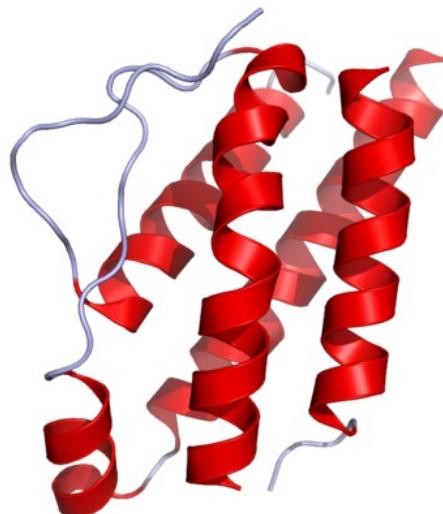
If stimulated by DCs, proliferate (6-h doubling time)

After several days, become "effector cells", which

- (1) remain in blood, helping B cells and CTLs, or
- (2) help innate and adaptive cells in infected tissue.

Th cells secrete specific cytokine profiles!

General profiles of Th cells



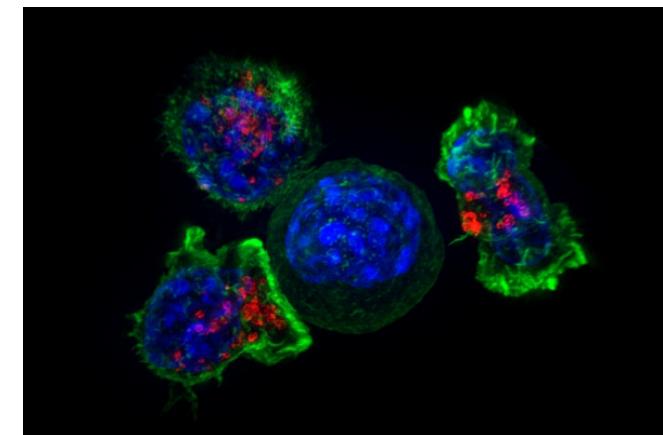
Th1: IL-2, IFN- γ , TNF (viruses and bacteria)

Th2: IL-4, IL-5, IL-10 (parasite and mucosal infections)

Th17: IL-17A, IL-17F, IL-21, IL-22 (mucosal infections)

Signalling is local!

CTLs: Kill infected cells



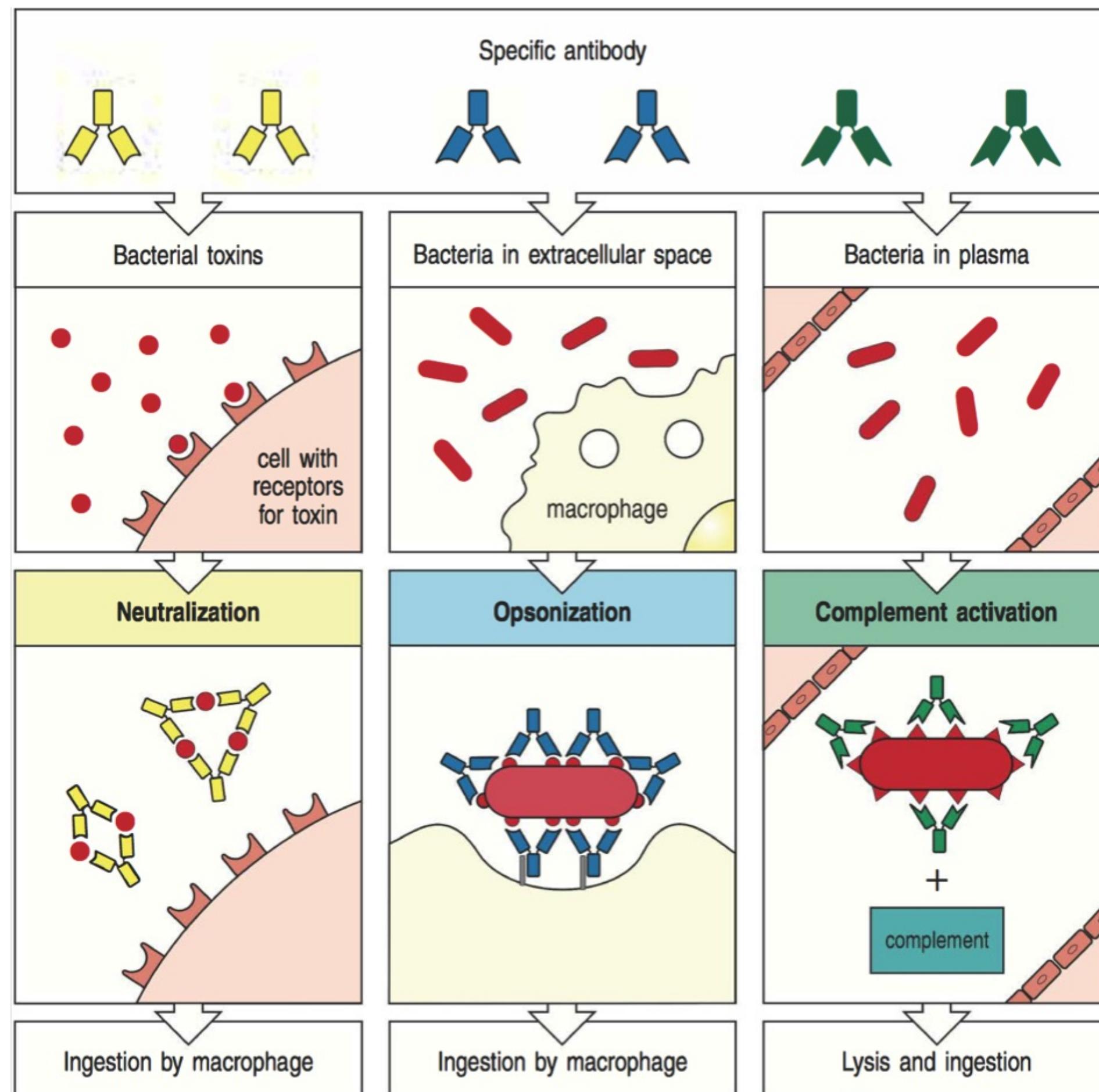
Activated in lymph node, requires Th

Proliferates following activation, enters tissue

Carefully kills infected cells via MHC I

Requires IL-2 (often from Th) to keep proliferating

B cells recognize protein structure



Two sources of B cell diversity

Rearrangement of variable gene segments

Somatic hypermutation during affinity maturation

Adaptive immune memory

Unclear how memory B and T cells selected

Location of activation affects trafficking

(some circulate, some resident)

Tolerance by T cells

Central tolerance: positive and negative selection

Peripheral tolerance: lack of co-stimulation, activation-induced cell death, regulatory T cells

Tolerance by B cells

"Receptor editing" occurs in bone marrow

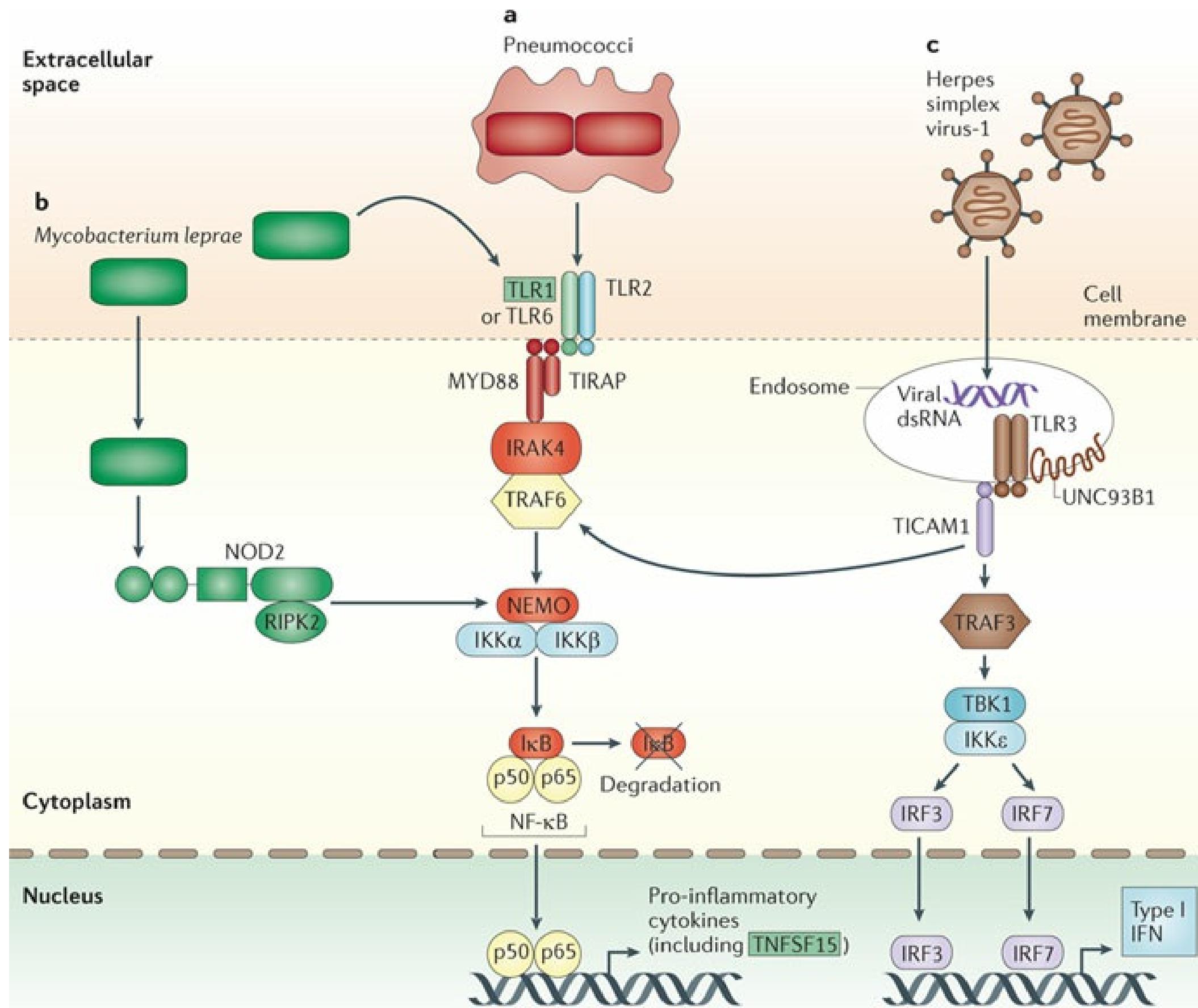
T cells prevent some binding to self

Self-antigens rarely opsonized

Heterogeneity in immune responses

Arises in innate and adaptive immunity

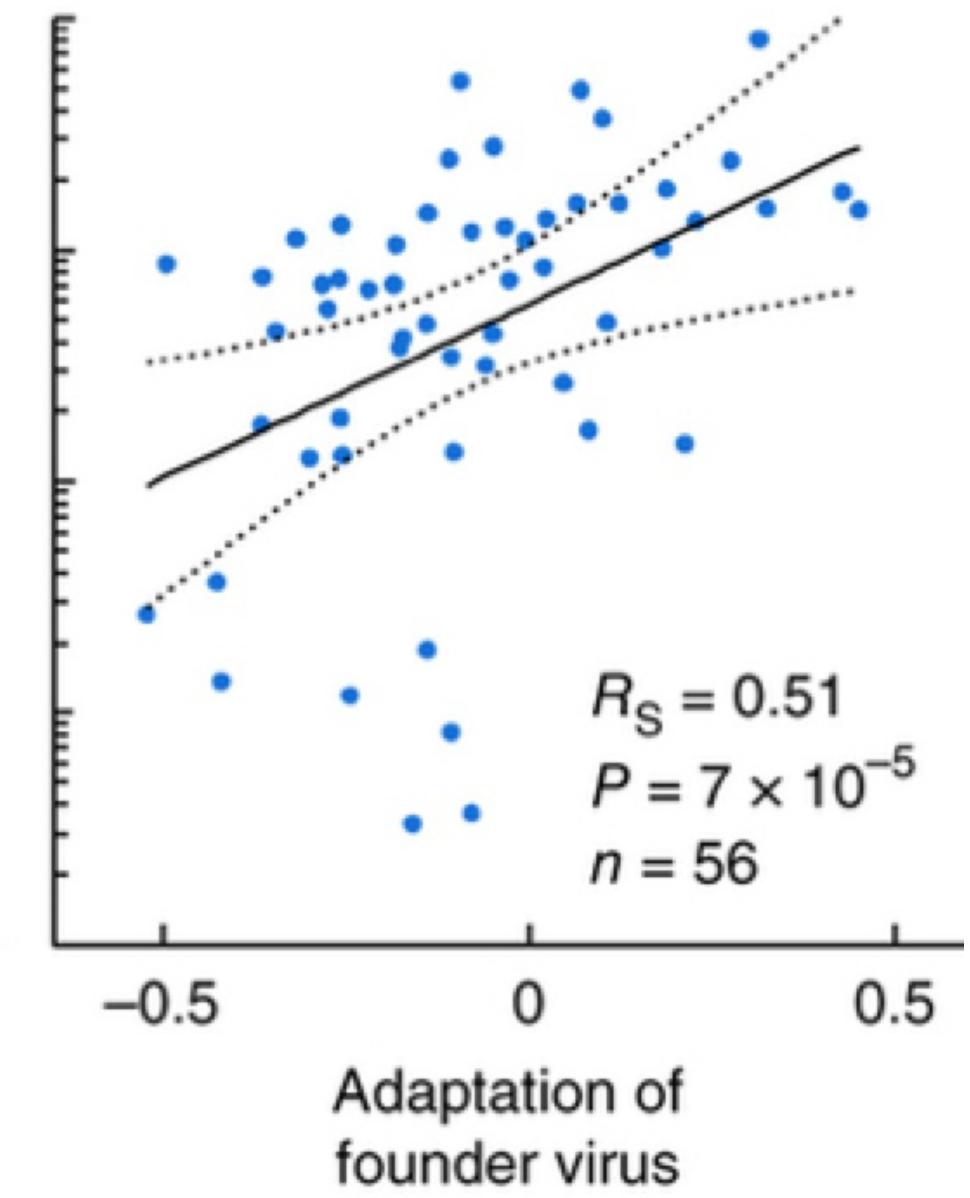
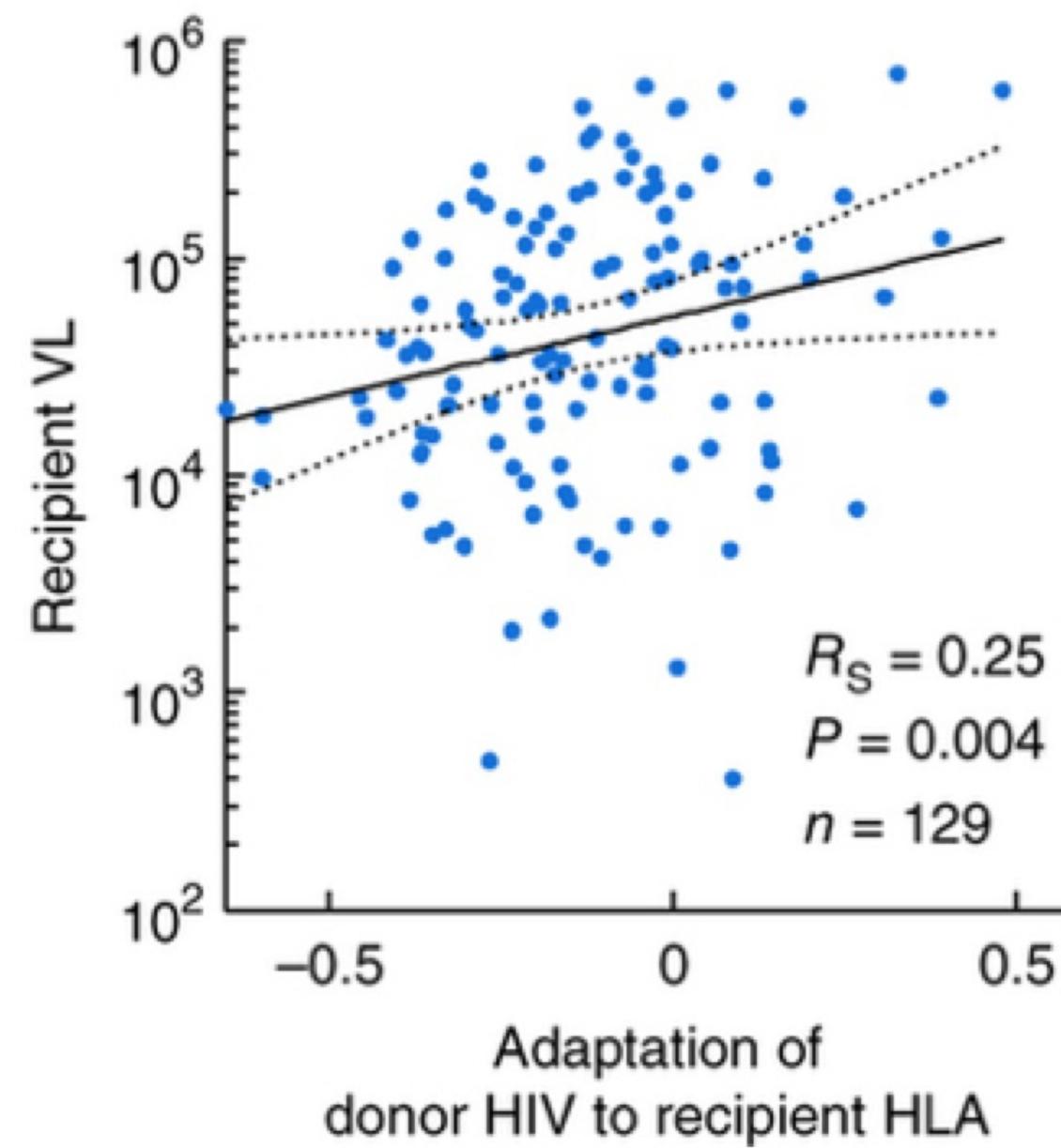
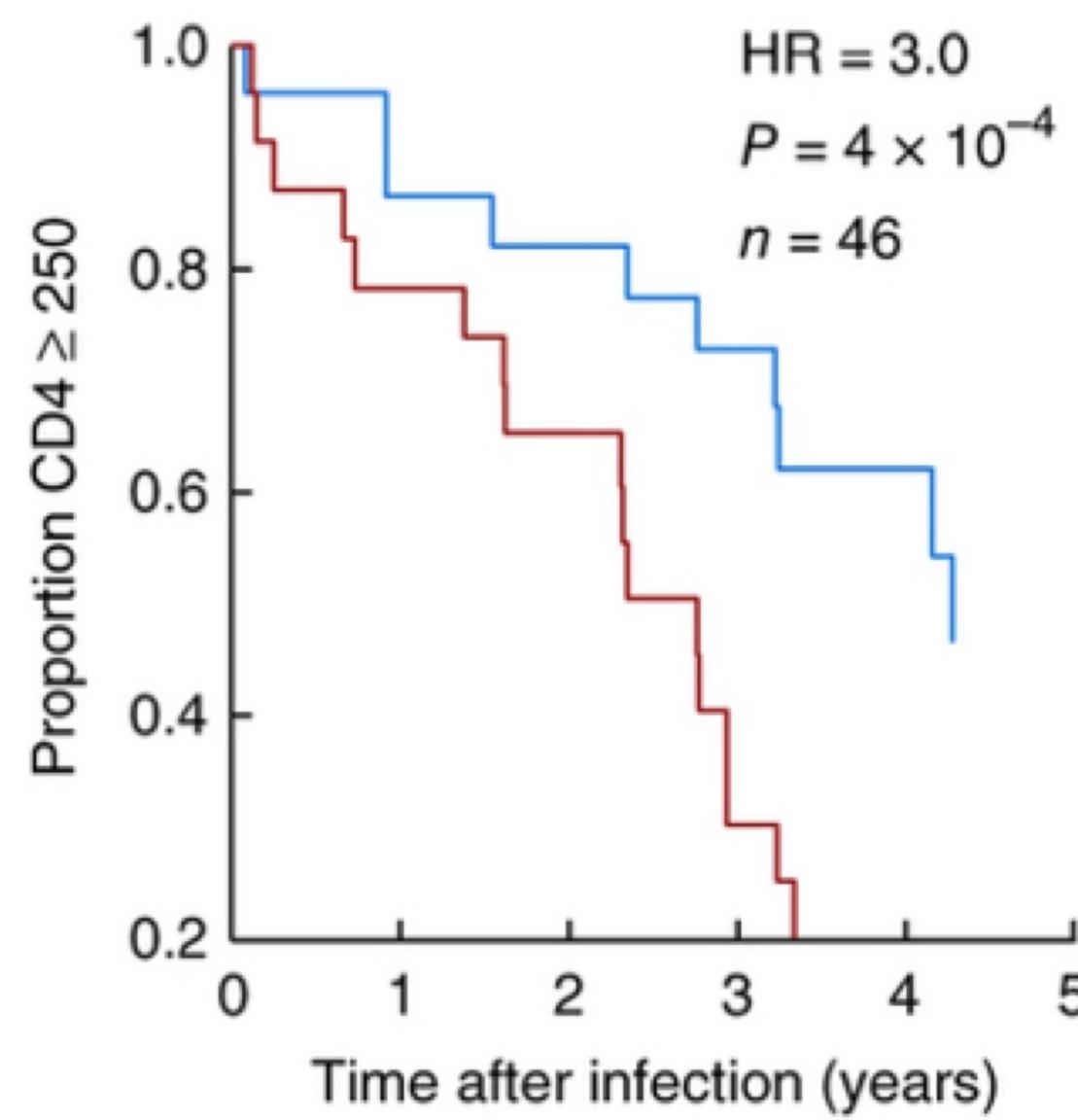
Polymorphism in TLRs affects susceptibility



Nature Reviews | Genetics

Chapman and Hill 2012

MHC shapes HIV dynamics



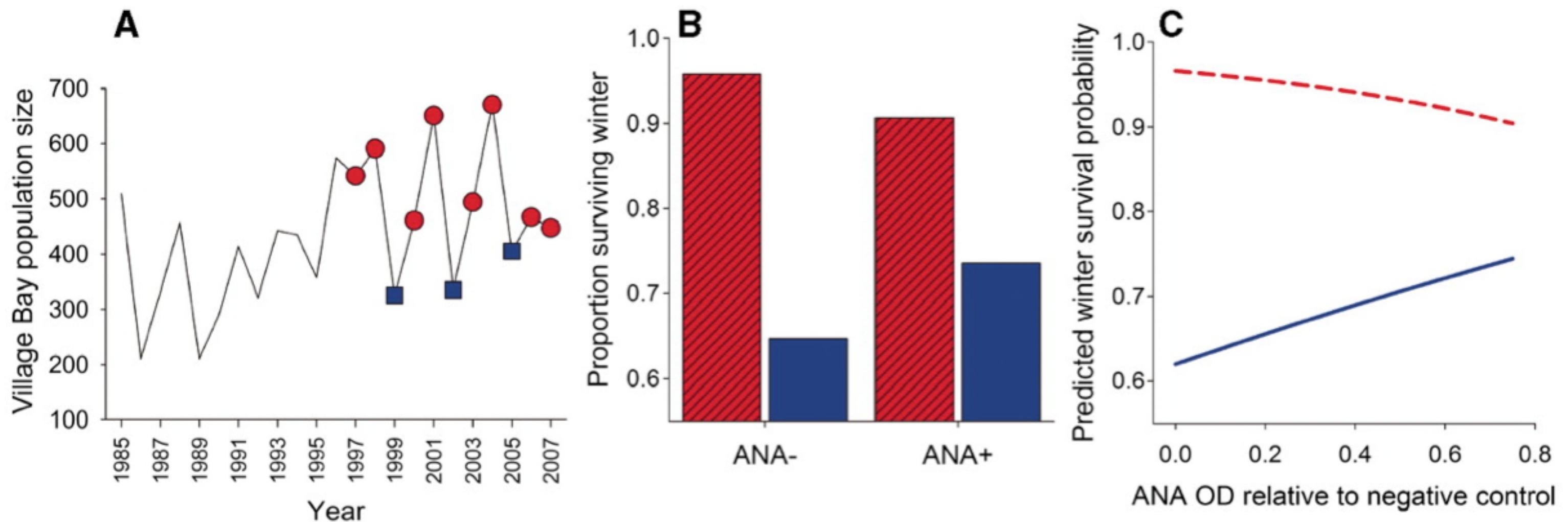
Carlson et al. 2016



Discover/Arpat Ozgul

Balancing selection

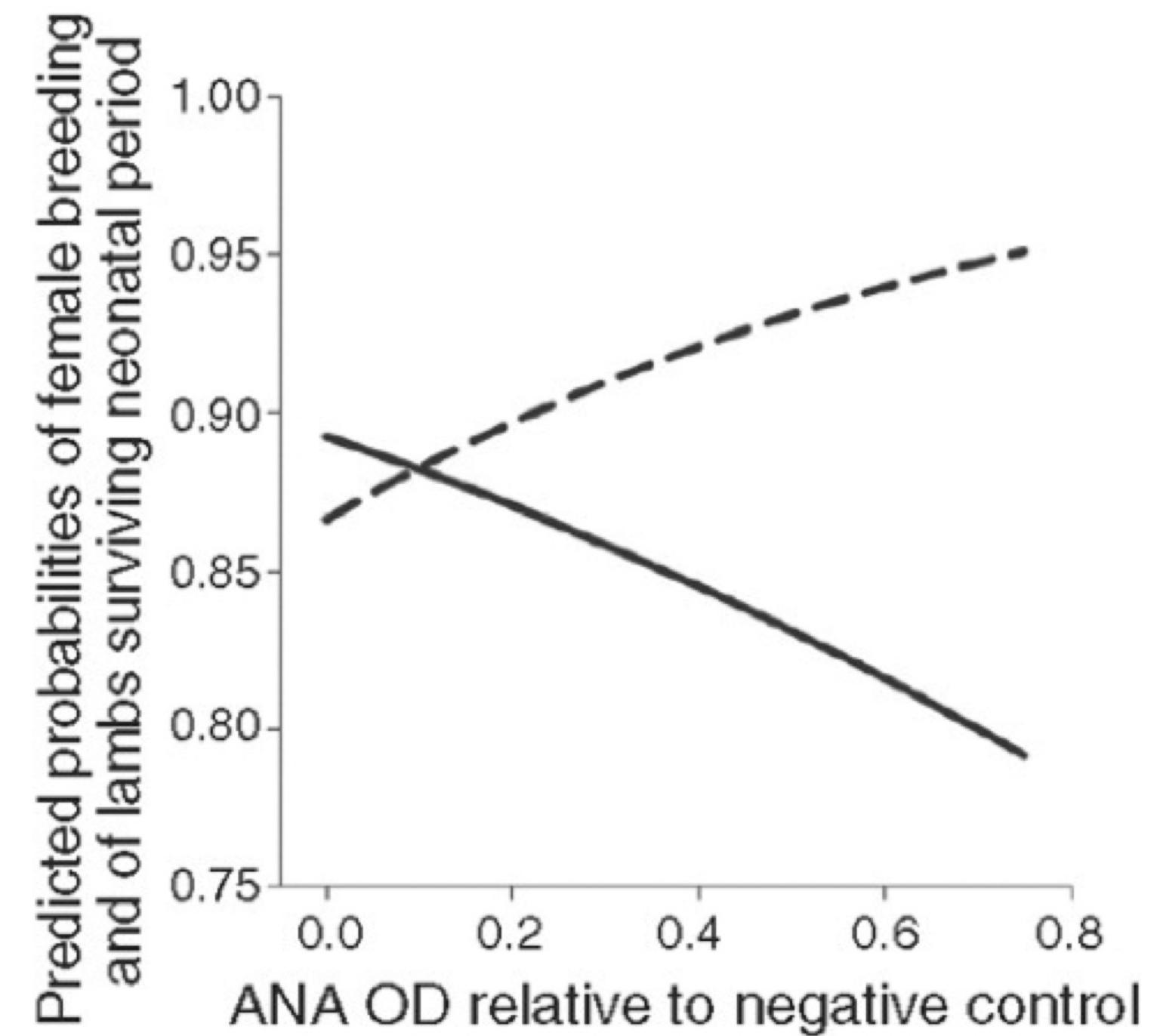
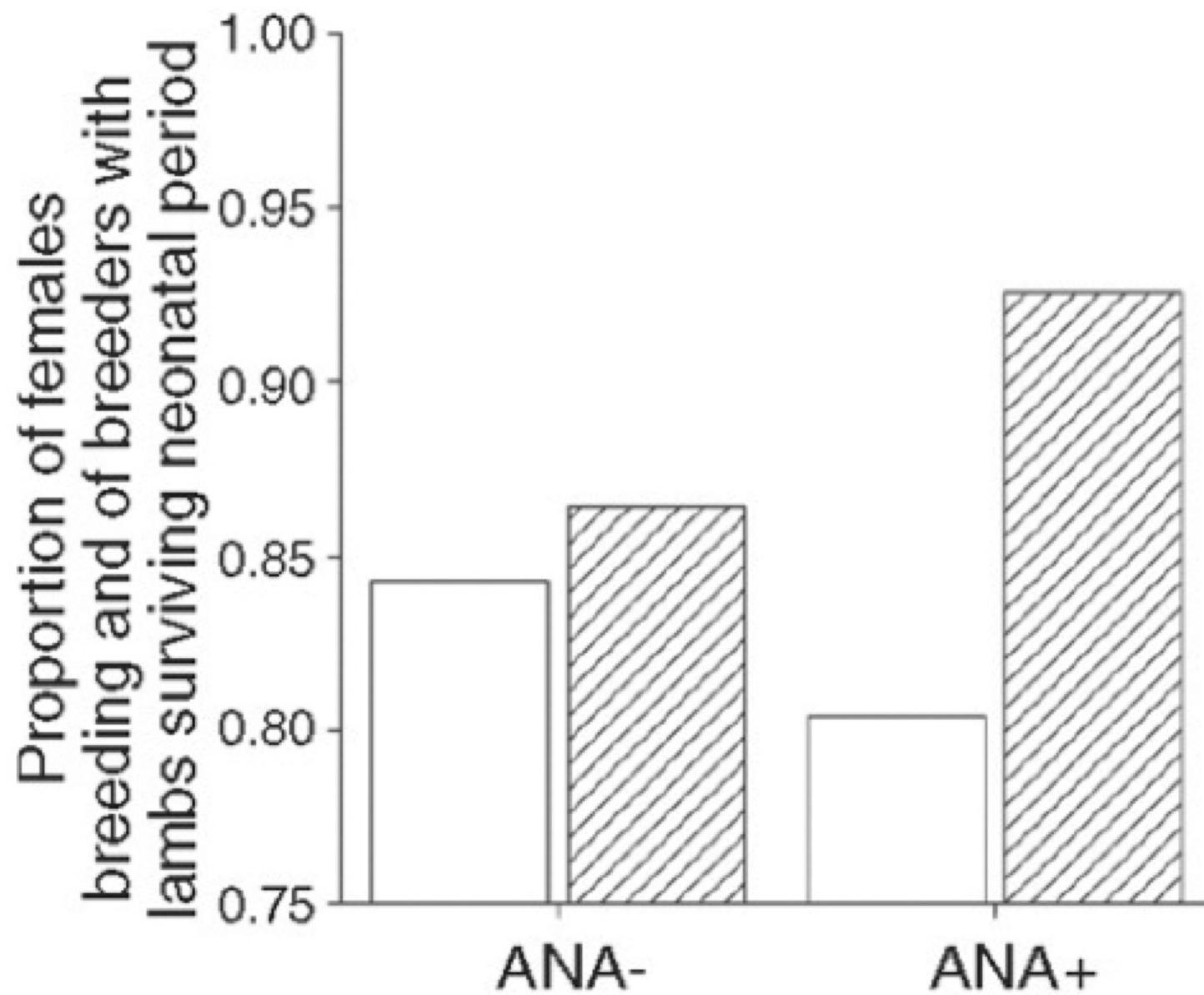
Autoimmunity costly but increases winter survival



Graham et al. 2010

Balancing selection

Autoimmunity also increases offspring survival



Escaping immunity

Hide (human papillomavirus, HIV, EBV)

Suppress (cytomegalovirus)

Distract (hepatitis B virus)

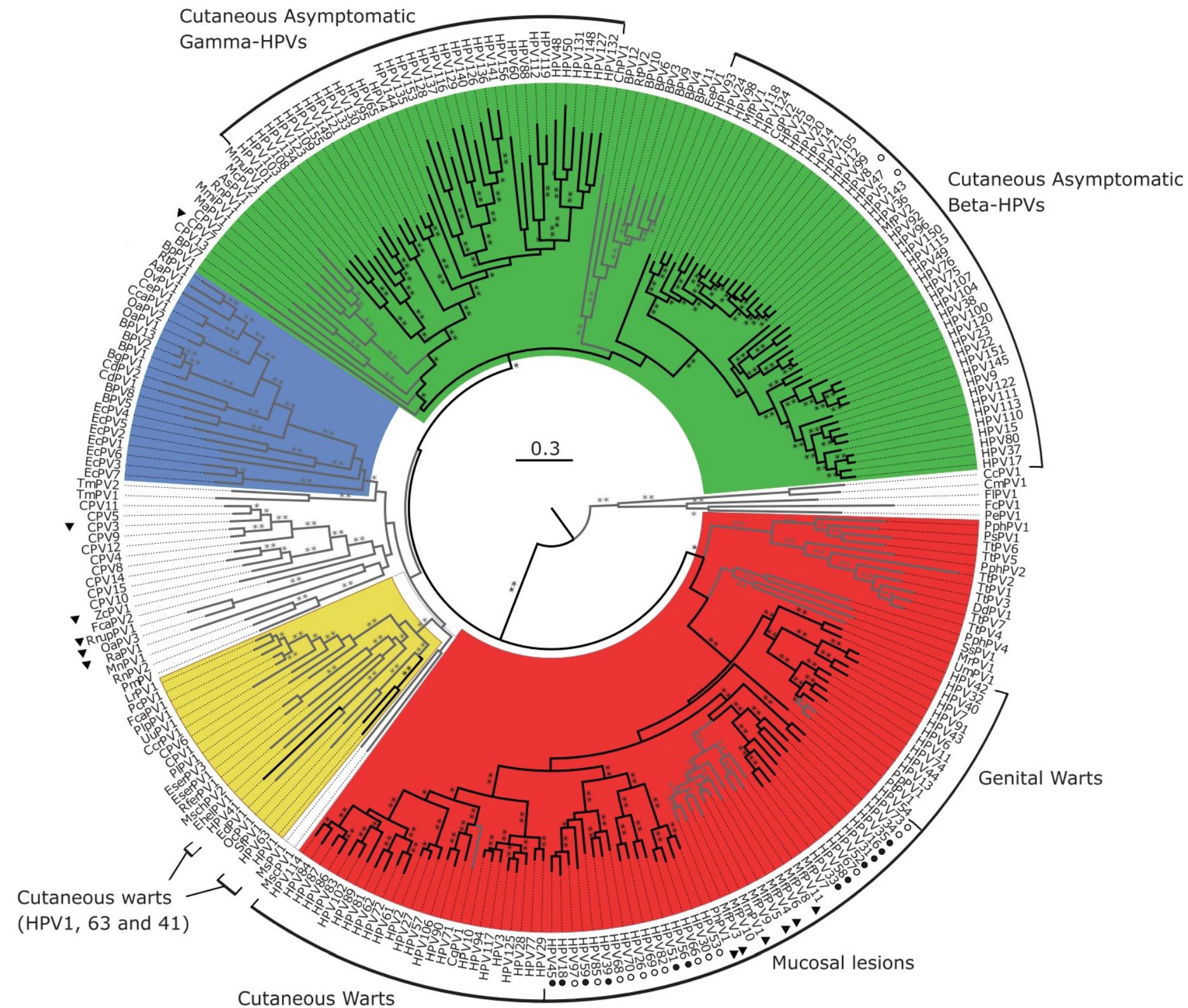
Disguise (HIV)

Outrun (influenza A)

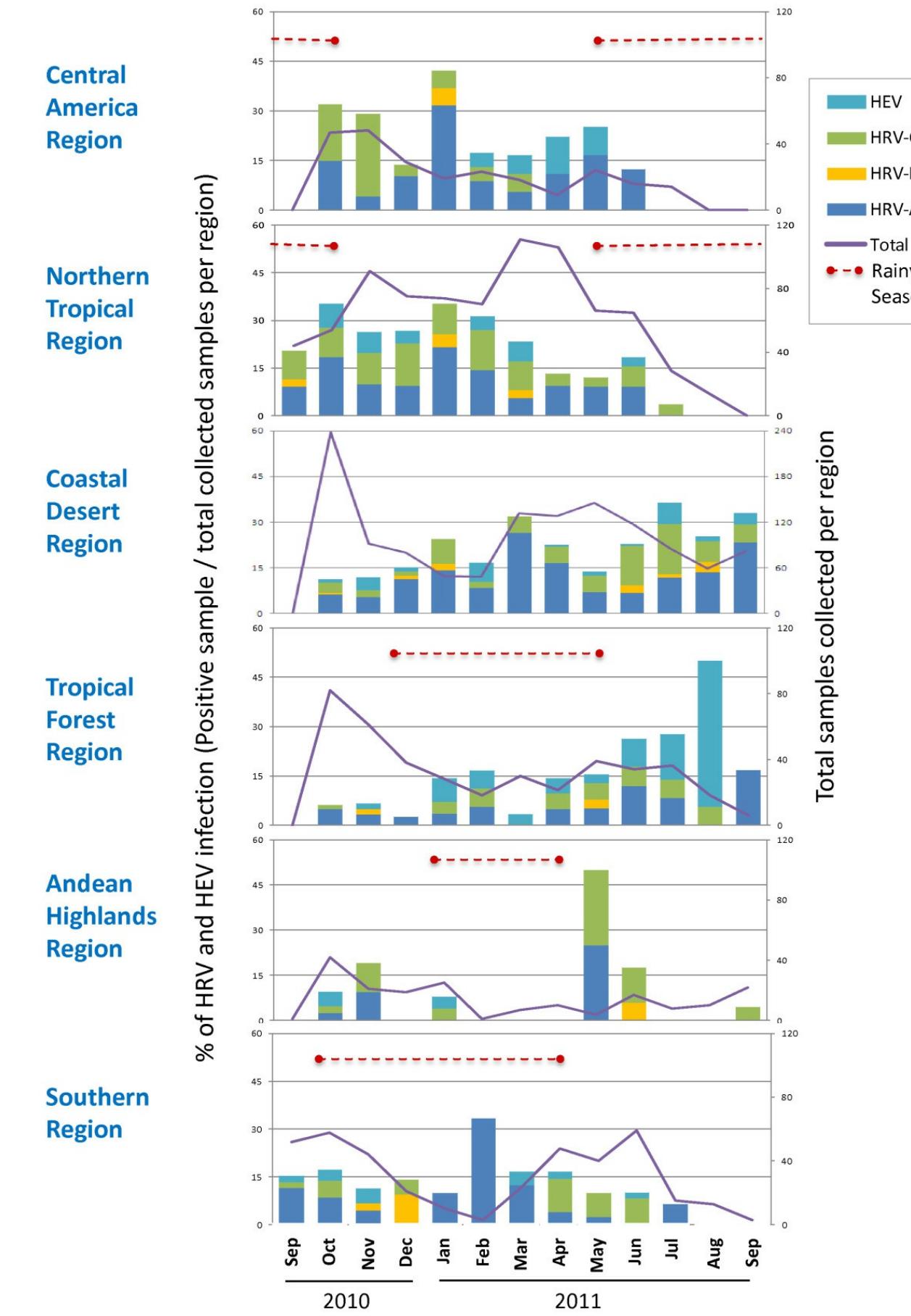
What are the most common pathogens in humans?
What does their abundance have to do with their immune interactions?

Human papillomaviruses

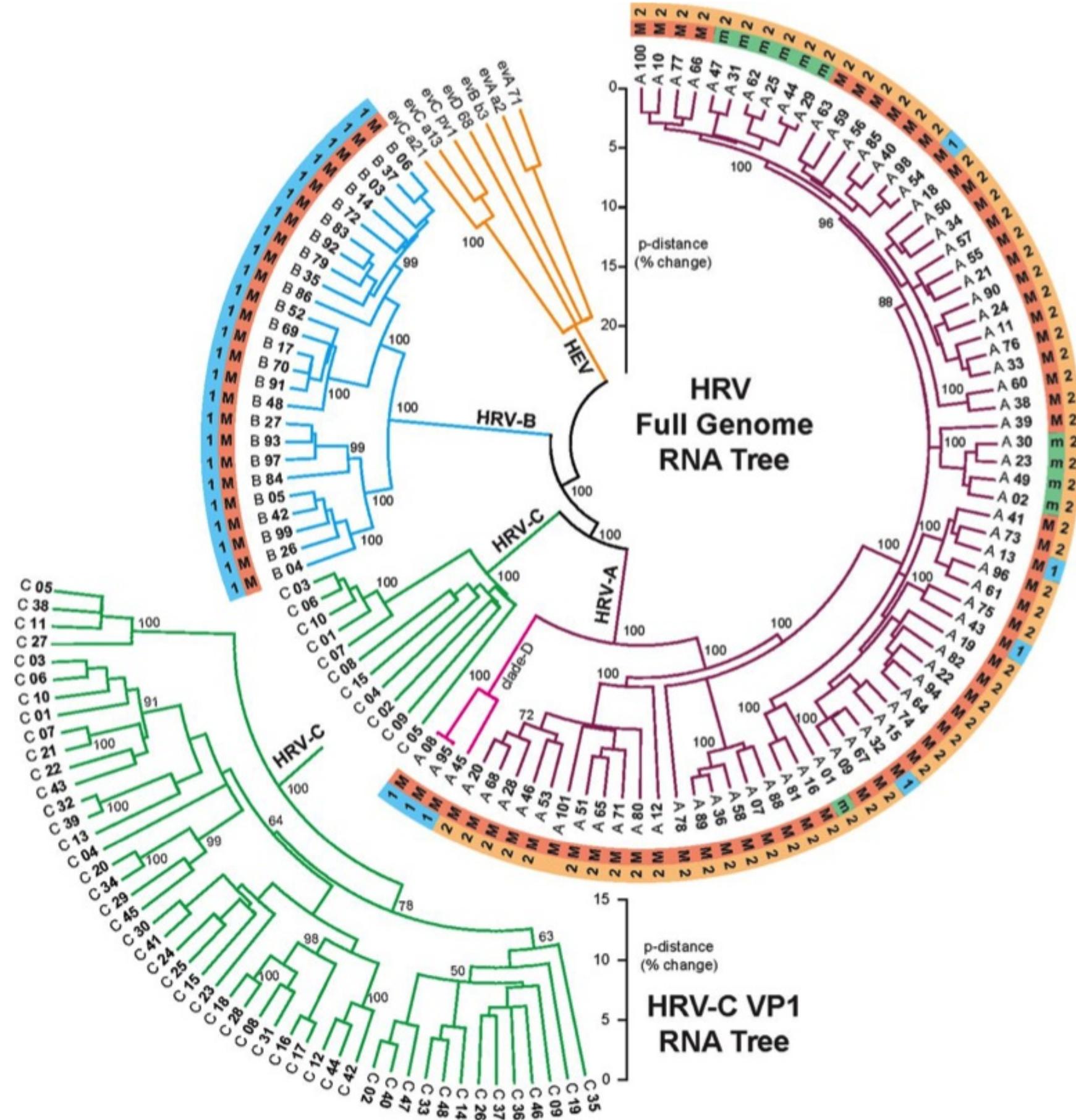
Nearly 100% prevalence, but slow evolution



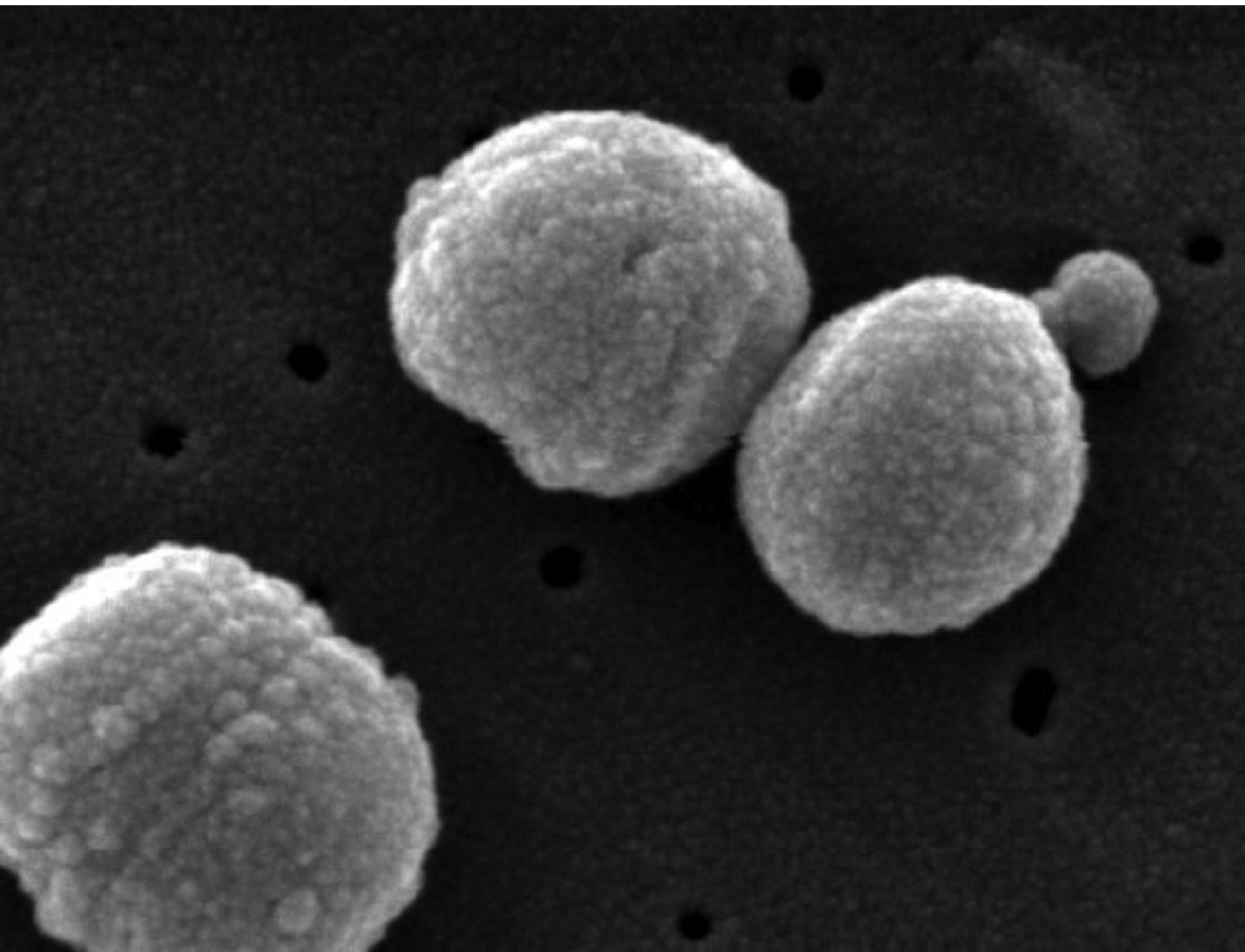
Enteroviruses: Common colds



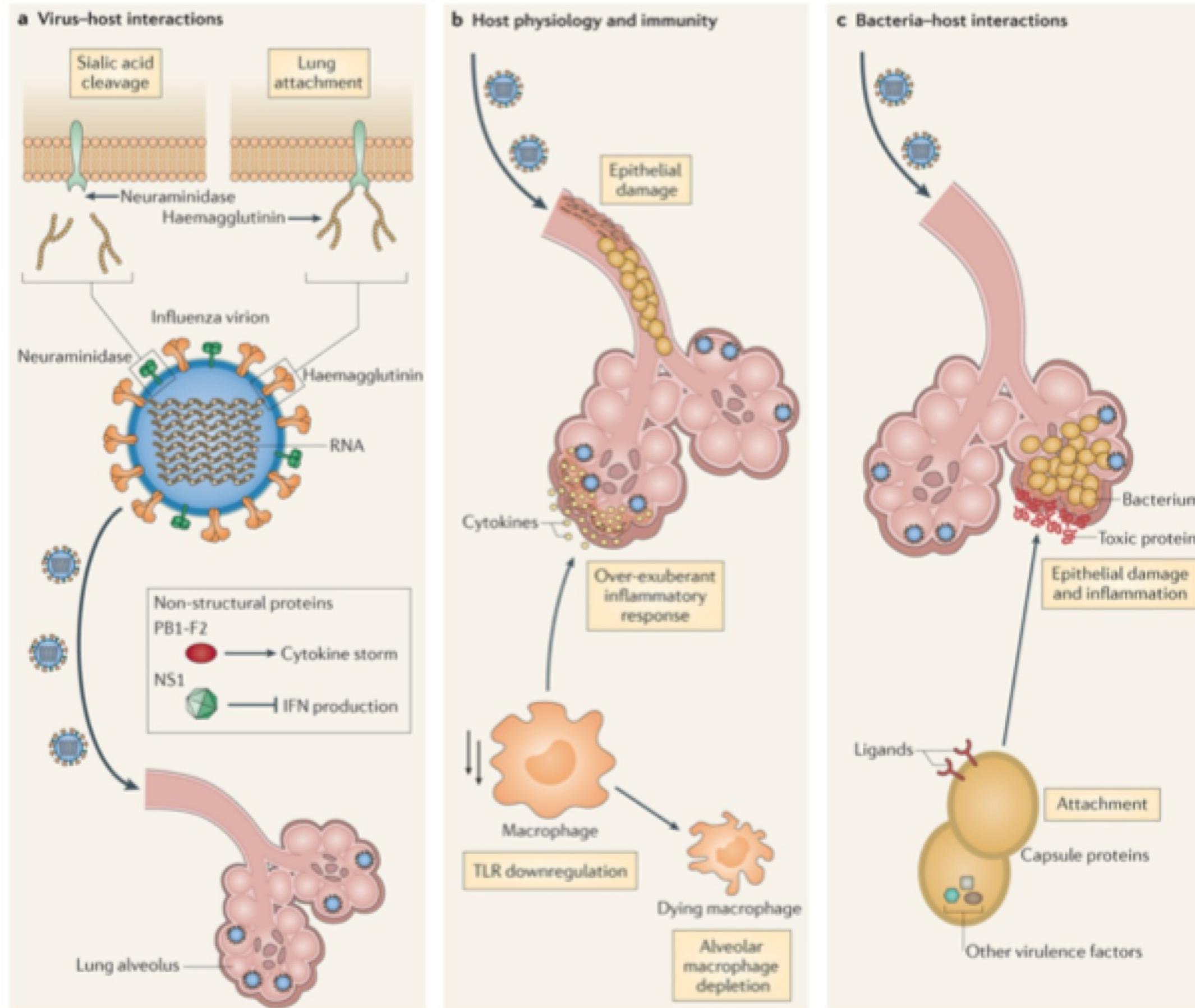
Rhinoviruses include >100 serotypes



>90 serotypes of *Streptococcus pneumoniae*



Flu facilitates pneumococcus



Competition for susceptible hosts generates complex dynamics

Mechanistic models beat intuition

Pathogens interact with multiple immune populations

Pathogens interact with very different hosts

Pathogens show extensive diversity, not only antigenic

Pathogens can compete with and facilitate one another