Chronic Viral Infections vs. Our Immune System:

Revisiting our view of viruses as pathogens

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Challenge your idea of classic viral infection and disease

- Define the microbiome and the virome
- Brief background on persistent viruses
- Illustrate how viruses change disease susceptibility
  - mutualistic symbiosis
  - gene + virus = disease phenotype
  - virome in immune responses

Bacteria-centric view of the microbiome

The microbiome defined

Definition of microbiome – Merriam-Webster
1 :a community of microorganisms (such as bacteria, fungi, and viruses) that inhabit a particular environment and especially the collection of microorganisms living in or on the human body

2 :the collective genomes of microorganisms inhabiting a particular environment and especially the human body

Virome
- Viral component of the microbiome
- Includes both commensal and pathogenic viruses
- Viruses that infect host cells
- Virus-derived elements in host chromosomes
- Viruses that infect other organisms in the body e.g. phage/bacteria

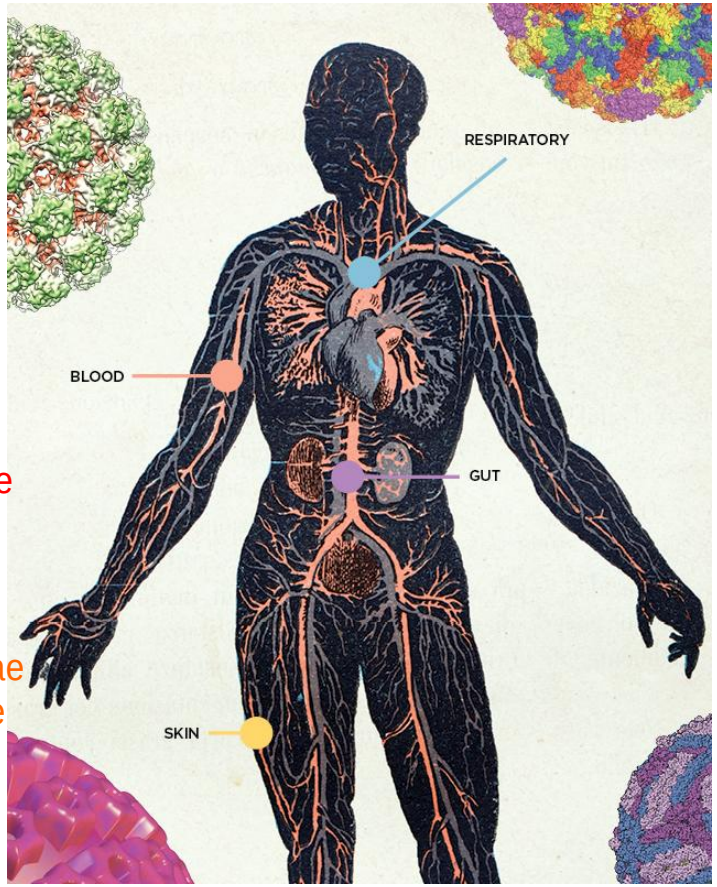
Viruses are everywhere!

- “intracellular parasites with nucleic acids that are capable of directing their own replication and are not cells” – Roossinck, Nature Reviews Microbiology 2011.
- Viruses infect all living things.
- We are constantly eating and breathing viruses from our environment
- Only a small subset of viruses cause disease.
- We even carry viral genomes as part of our own genetic material!

Diverse viruses all over the body

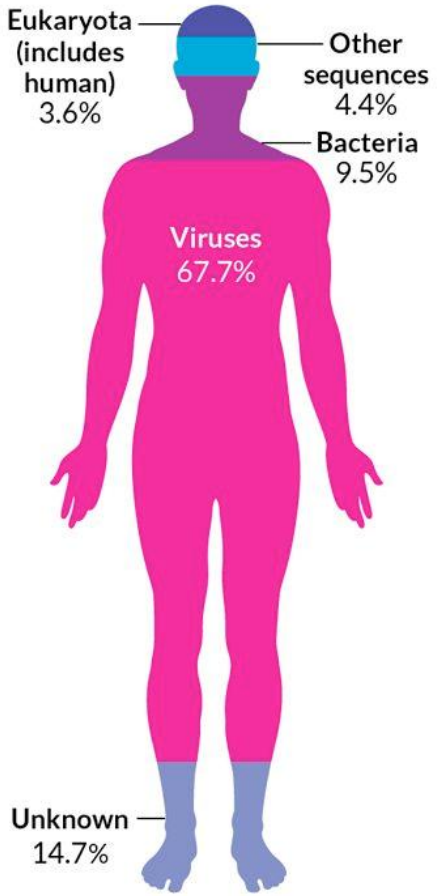
Anelloviridae
Astroviridae
Flaviviridae
Herpesviridae
Parvoviridae
Picornaviridae
Polyomaviridae

Papillomaviridae
Polyomaviridae



Adenoviridae
Picornaviridae
Polyomaviridae

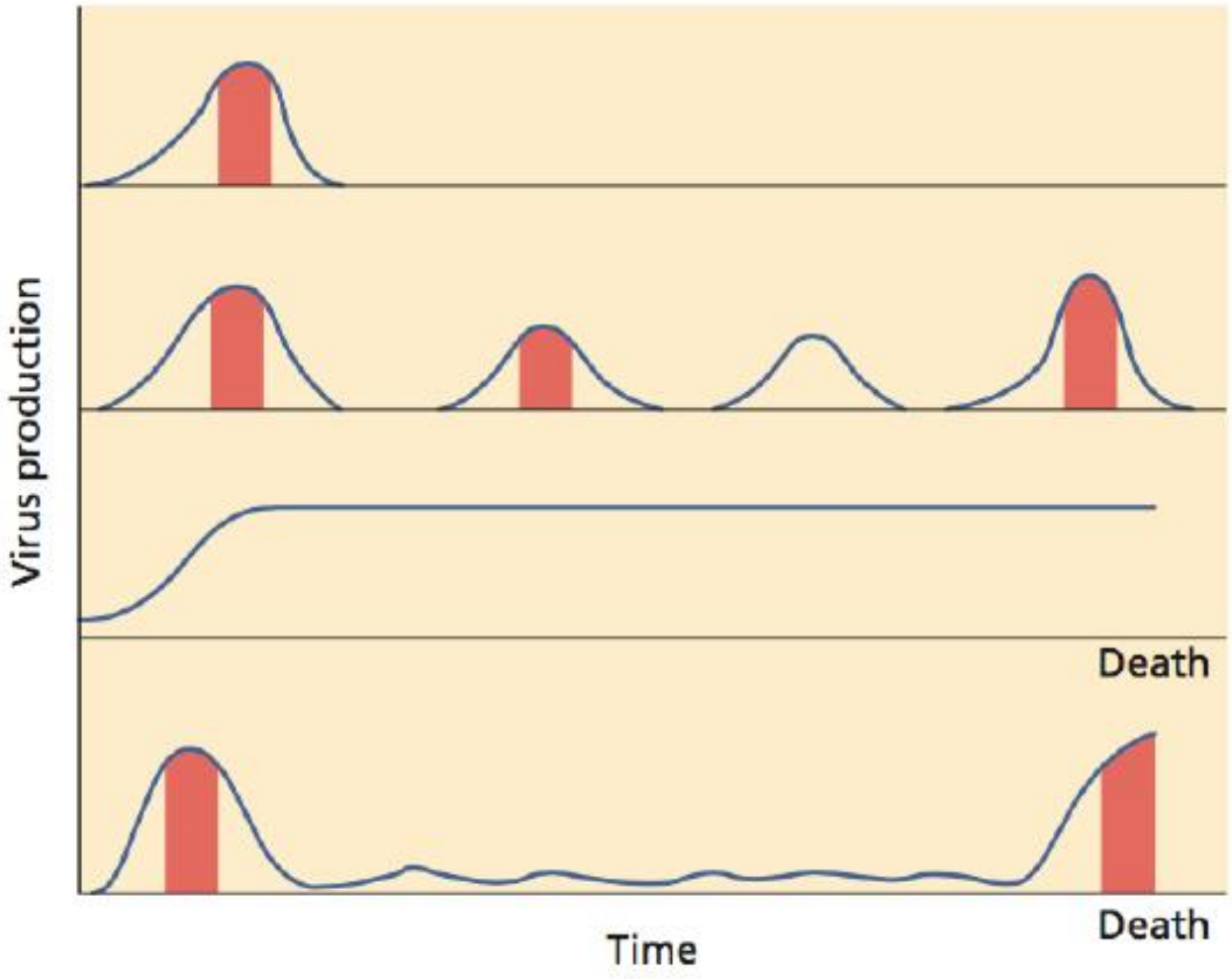
Adenoviridae
Astroviridae
Parvoviridae
Picobirnaviridae
Picornaviridae



https://www.sciencenews.org/article/vast-virome

http://www.the-scientist.com/?articles.view/articleNo/47291/title/Viruses-of-the-Human-Body/

General Patterns of Viral Infection



Examples

Acute
Influenza virus
Rhinovirus

Latent
Herpes Simplex virus 1 & 2
Epstein Barr virus

Persistent - asymptomatic
lymphocytic choriomeningitis virus

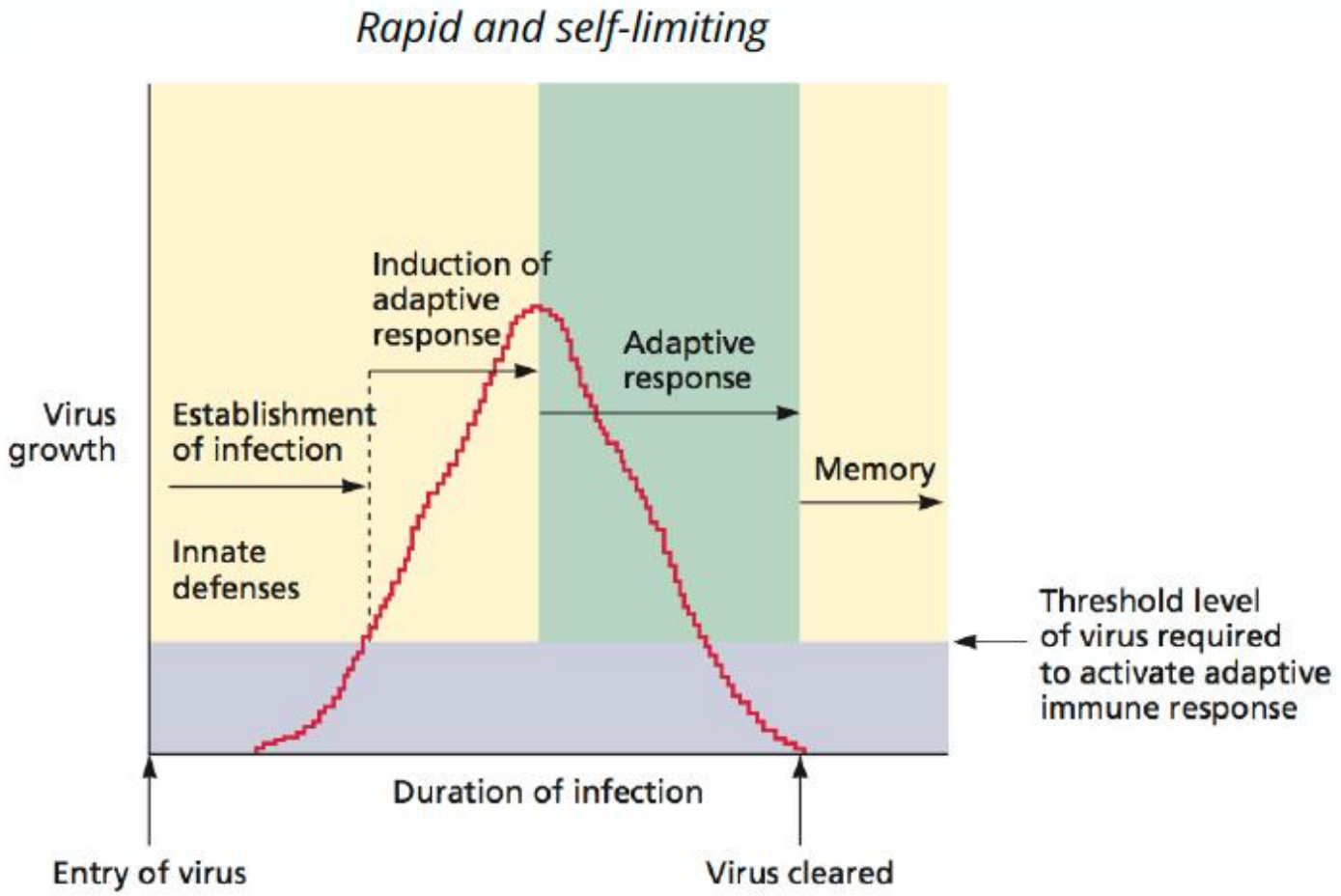
Persistent - Pathogenic
HIV

Why reactivate?

Acute Viral Infection

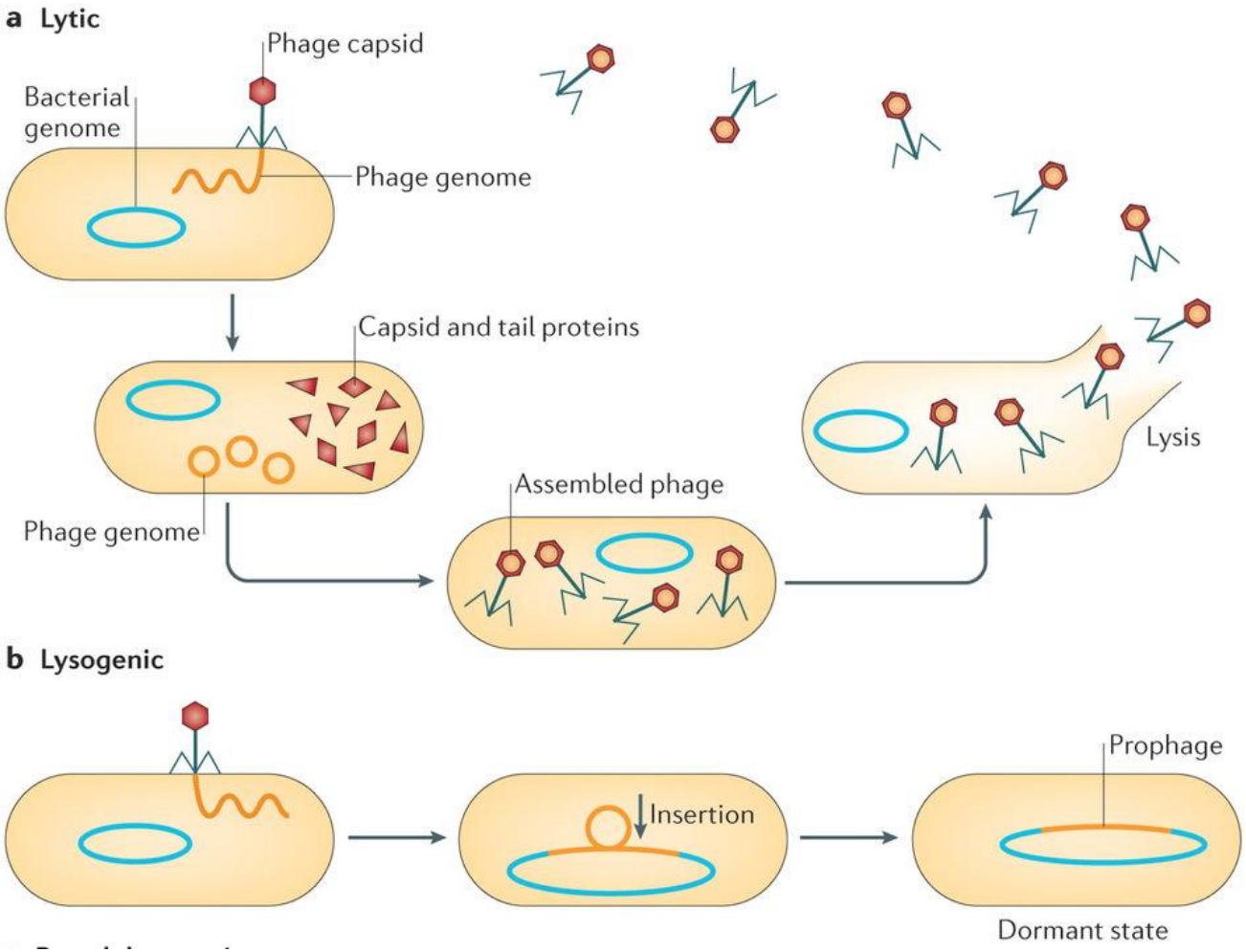
- rapid onset of viral production
- short and sometimes severe course of disease
- production of a large amount of virus
- immune clearance – usually within ~2 weeks

Typical acute infection



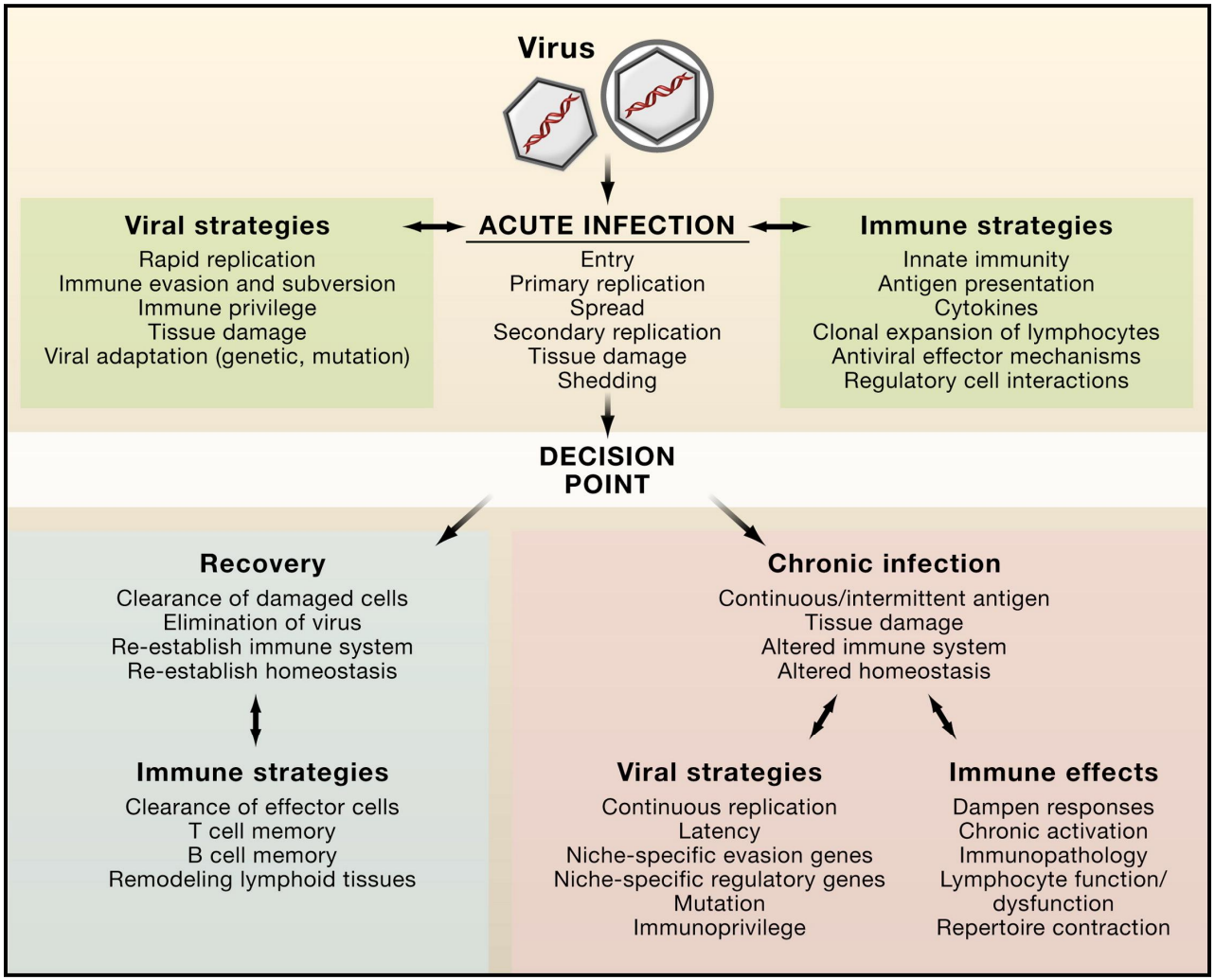
Principles of Virology

Basic virus replication – phage and bacteria



http://www.nature.com/nrmicro/journal/v13/n10/full/nrmicro3527.html

Persistent infection is a balancing act between the virus and the host



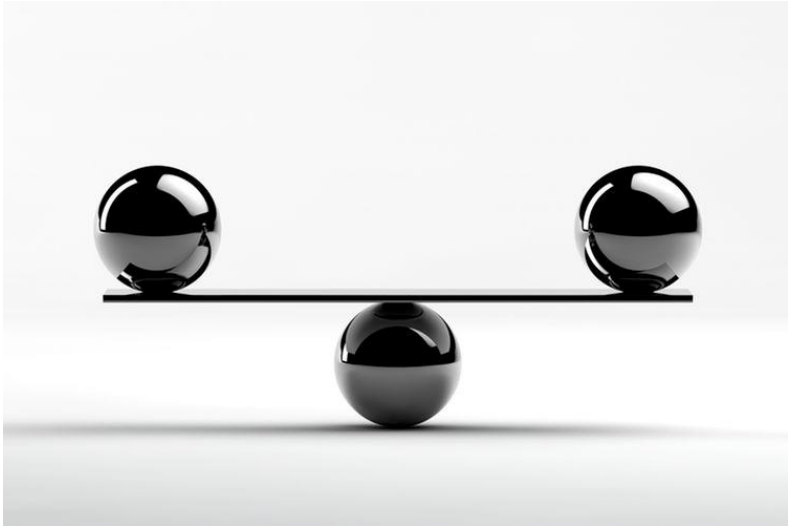
Virgin, et al. Cell 2009
http://www.sciencedirect.com/science/article/pii/S0092867409007831

Characteristics of persistence

- Occurs when primary infection is not cleared
- Usually occurs after a period of acute replication
- Evasion of sterilizing immunity
  - What is sterilizing immunity?
- Immune system must limit viral replication to an ‘acceptable’ level such that damage to tissues is limited.
- Latency allows survival of genomes integrated into DNA or as nuclear episomes without continuous replication
- Persistence in specialized niches e.g. Herpes simplex virus in neurons

Persistent viral infection is a balancing act between the virus and the host

- Chronic infection is dynamic
- All of us are infected with 8-12 chronic viruses
- The most successful persistent viruses cause little damage to the host
- Persistence usually reflects a long-term evolutionary relationship
- What happens when the immune system is compromised?

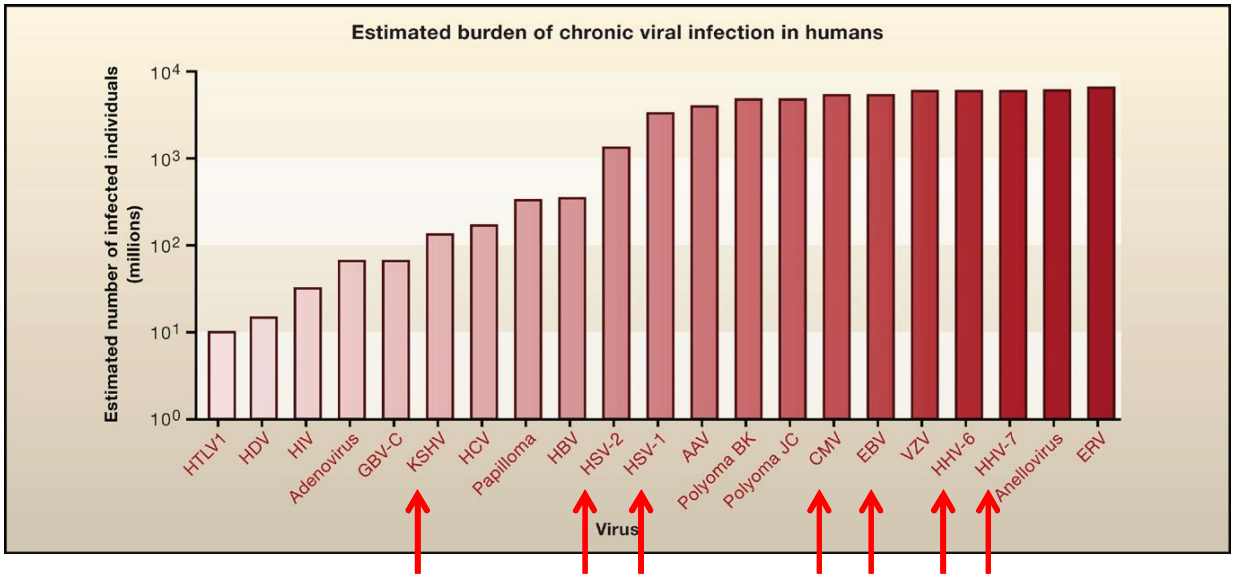


The most successful persistent viruses cause little disease

Table 1. Chronic Virus Infections in Humans

			Disease during Chronic Infection		
Virus, Primary Nucleic Acid, Estimated Percent of Humans Infected	Major Site of Persistence (Organ or Cell)	Acute Infection Examples	Within Normal Hosts	Within Immunocompromised Hosts	References
Endogenous retroviruses (ERV), DNA, 100%	All	Not applicable	Unknown	Unknown	Seifarth et al., 2005; Virgin, 2007b
Anellovirus/Circovirus, DNA, 90%–100%	Many tissues	Unknown	Unknown	Unknown	Davidson and Shulman, 2008; Ninomiya et al., 2008; Hino and Miyata, 2007
Human herpesvirus 6 (HHV-6), DNA, >90%	Lymphocytes?	Roseola	Unknown	Meningoencephalitis, secondary infections, immunomodulatory?	Straus, 2000; Yamanishi et al., 2007
Human herpesvirus 7 (HHV-7), DNA, >90%	Lymphocytes?	Roseola	Unknown	Unknown	Straus, 2000; Yamanishi et al., 2007
Varicella zoster virus (VZV), DNA, >90%	Sensory ganglia neurons and/or satellite cells, lymphocytes	Chicken pox	Herpes zoster	Disseminated disease, hepatitis, pneumonitis	Zerboni and Arvin, 2008; Straus, 2000
Cytomegalovirus (CMV), DNA, 80%–90%	Myelomonocytic cells	Mononucleosis	Rare	Disseminated disease, vasculitis, pneumonitis, retinitis, hepatitis, gastroenteritis, meningoencephalitis	Mocarski et al., 2007
Epstein-Barr virus (EBV), DNA, 80%–90%	Pharyngeal epithelial cells, B cells	Mononucleosis	Burkitt's lymphoma, nasopharyngeal carcinoma, non-Hodgkin's lymphoma	CNS lymphomas, oral hairy leukoplakia, lymphoproliferative disease	Rickinson and Kieff, 2007; Straus, 2000; Kieff and Rickinson, 2007

Herpesviruses as part of our virome

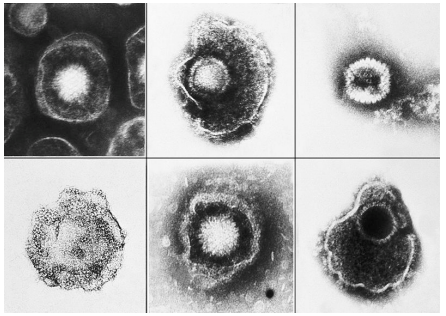


http://www.sciencedirect.com/science/article/pii/S0092867409007831

https://www.flickr.com/photos/tsevis/11645535103/in/photostream/

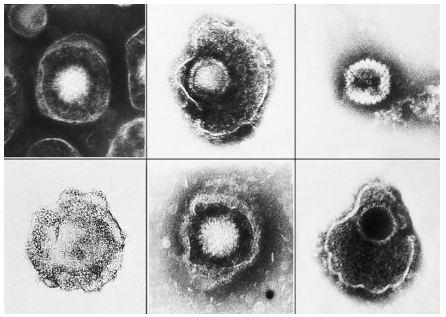
- We all harbor ~10 chronic viral infections
- Every single one of us is infected with at least one herpesvirus
- Herpesviruses can be both harmful and beneficial to the host
- “Virus-plus-host gene” effects on disease phenotypes
- Virome influences the host in ways independent of classic viral disease
- Immune system is not static; dynamic equilibrium with components of the microbiome

Herpesviruses – key features



- Large enveloped double stranded DNA virus
- Found in all vertebrates examined
- Narrow host range
- In mammals they likely coevolved during speciation
- Infection persists for life and is never cleared
- Establishes *noncytopathic* infection with limited viral gene expression and no virus production – Latency
- Genome maintenance in the nucleus as an episome
- Ability to turn on replication-associated genes leading to viral progeny production – Reactivation

Herpesviridae



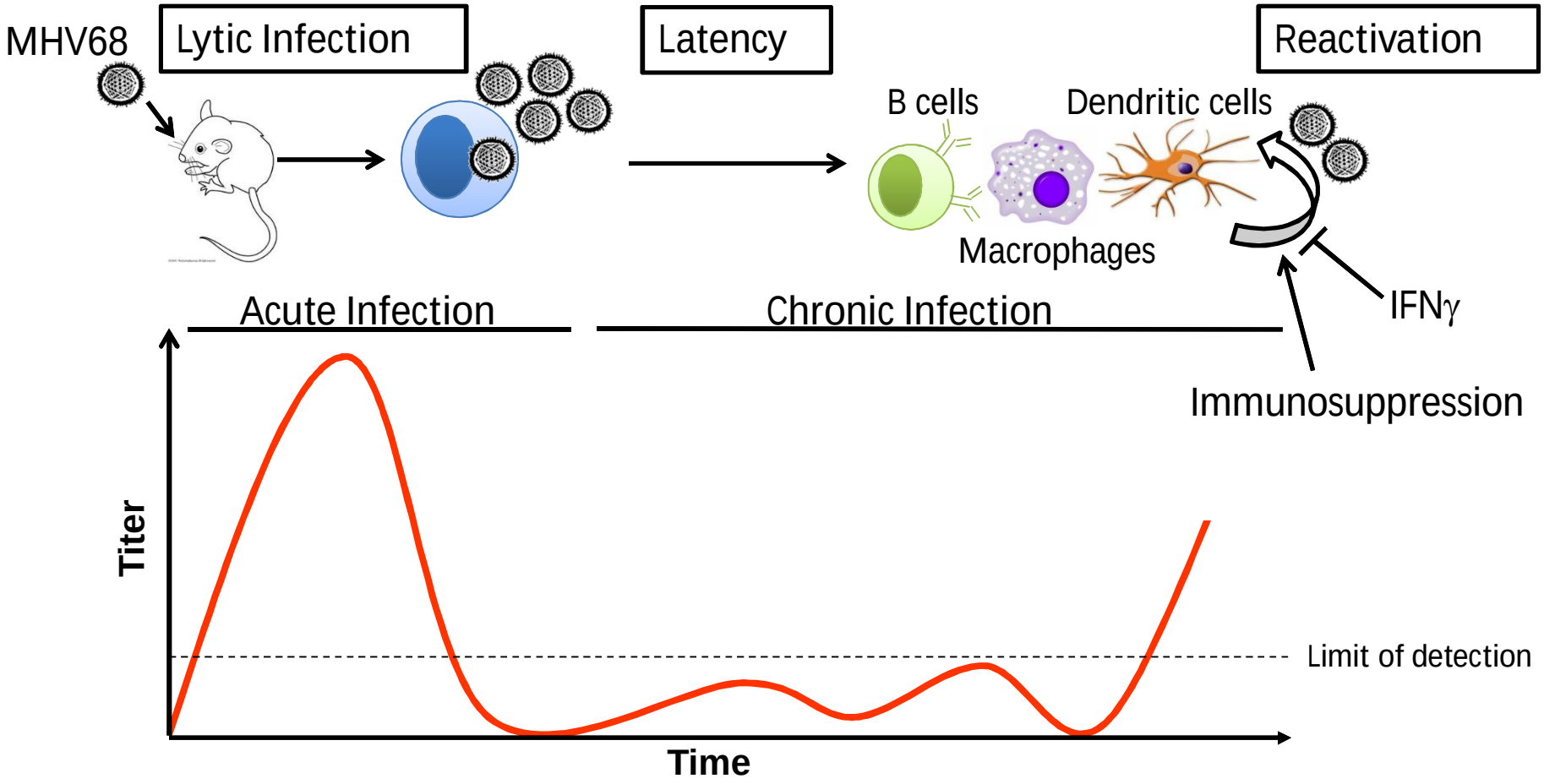
Herpesviridae	Gammaherpesvirinae	lymphocryptovirus (γ1)	**EBV**	B cells, ?
		rhadinovirus (γ2)	**KSHV**	B cells, endothelial cells
			MHV68	B cells, macs, DCs
	Betaherpesvirinae	cytomegalovirus	**CMV (HHV5)**	Monocytes, lymphocytes, ?
		roseolovirus	**HHV6**	T cells, ?
	Alphaherpesvirnae	simplexvirus	**HSV-1, HSV-2**	neurons
		varicellovirus	**VZV**	neurons
		mardivirus	**MDV**	

Diseases associated with gammaherpesvirus infection

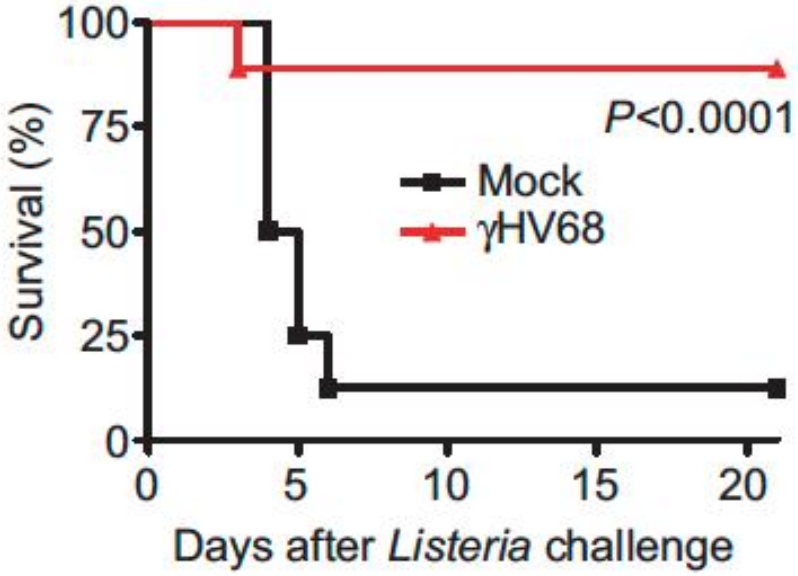
- Kaposi's sarcoma-associated herpesvirus (KSHV)
  - Kaposi's sarcoma
  - Primary effusion lymphoma
  - Multicentric Castleman's disease

- Epstein Barr Virus
  - mononucleosis
  - Lymphomas including Burkitts lymphoma
  - Nasopharyngeal and gastric carcinomas

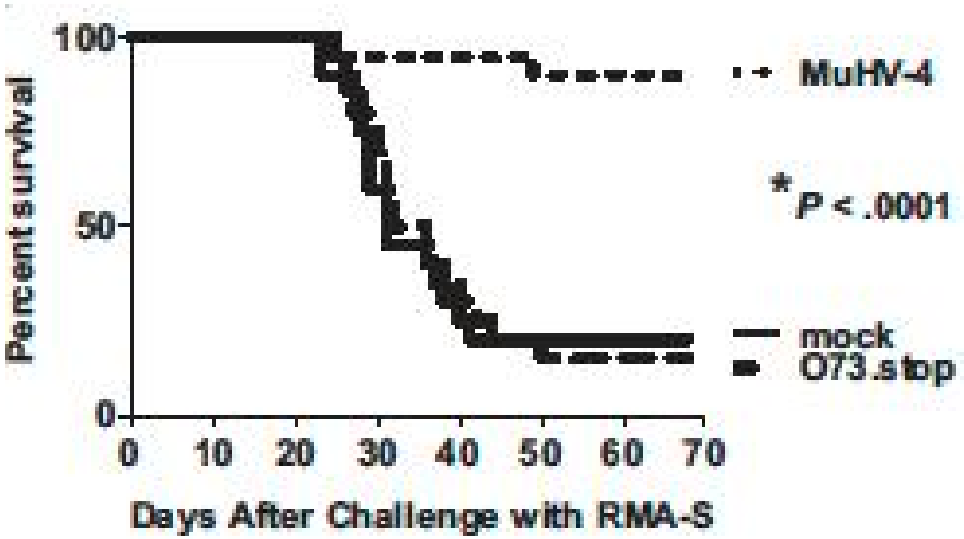
Murine gammaherpesvirus-68 (MHV68 or γHV68) establishes latent infection.



Mutualistic symbiosis – a herpesvirus protects infected mice from lethal bacterial or tumor challenge.

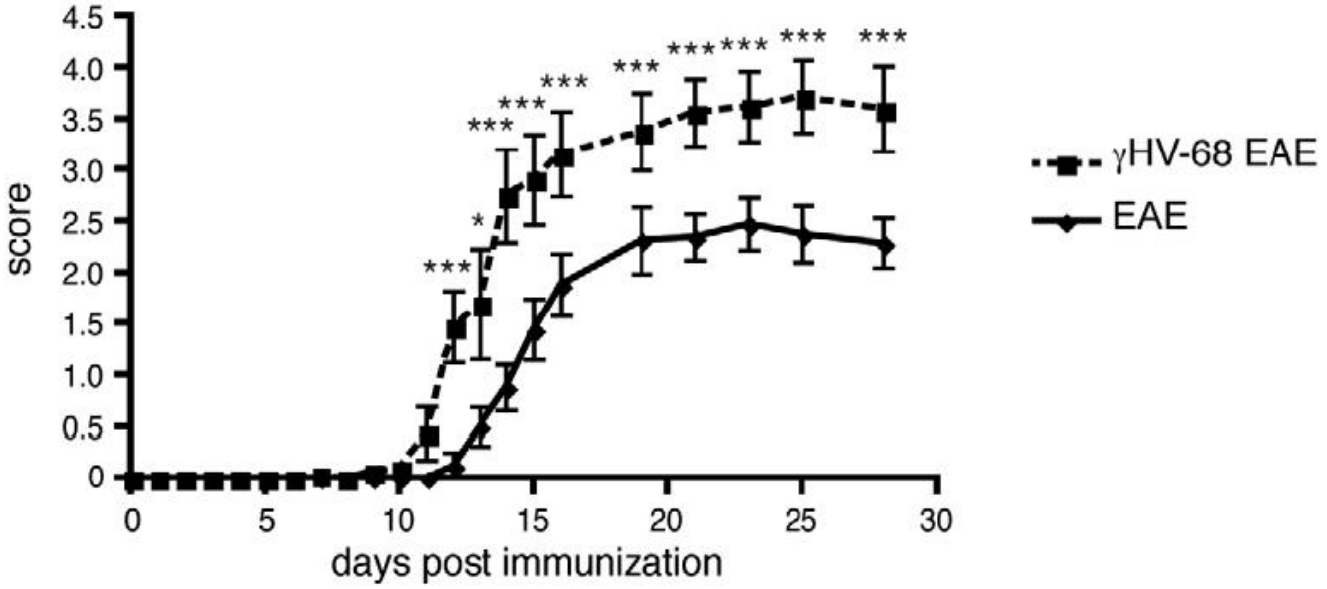


Barton, et al. *Nature* 2007



White, et al. *Blood* 2010

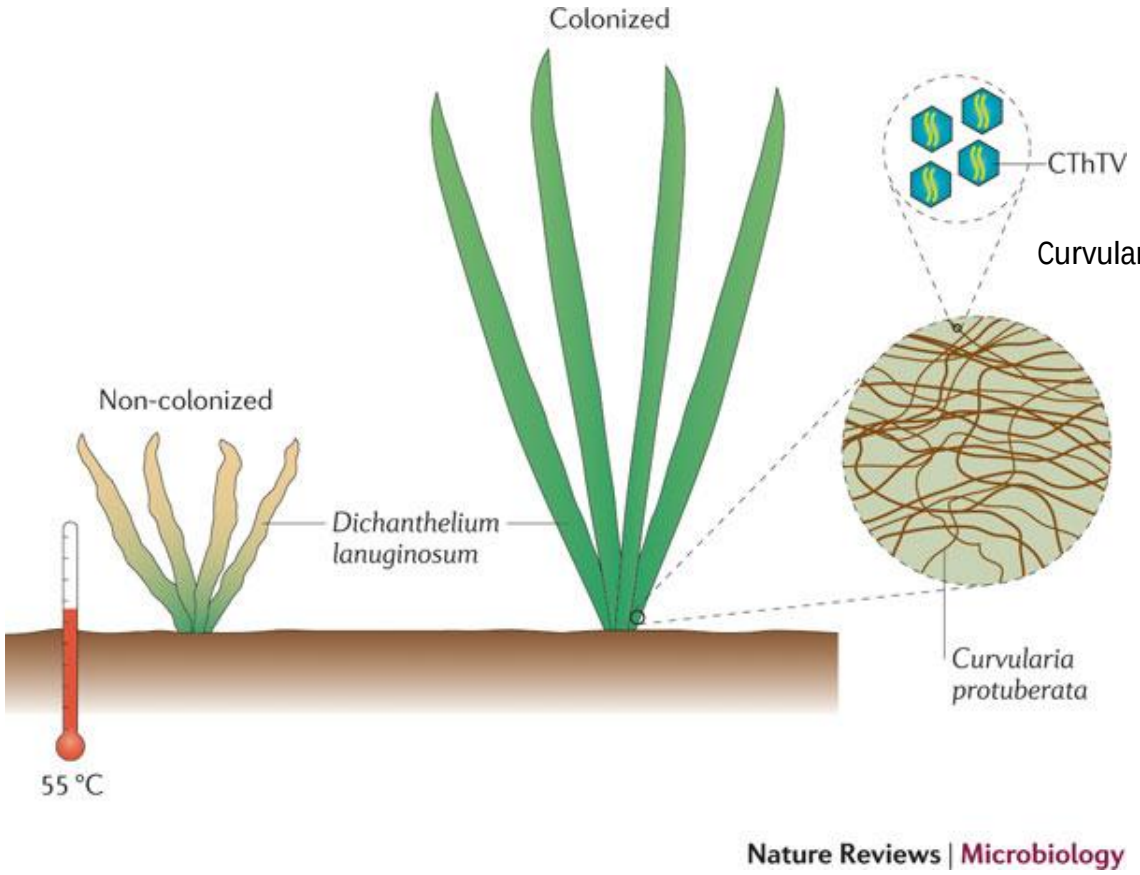
Herpesviruses aren't always good for you!



Murine gammaherpesvirus-68 infection exacerbates EAE in mice (a model of multiple sclerosis)

Peacock, et al. Eur J Immunol 2003
Casiraghi, et al. *PLOS Pathog.* 2012

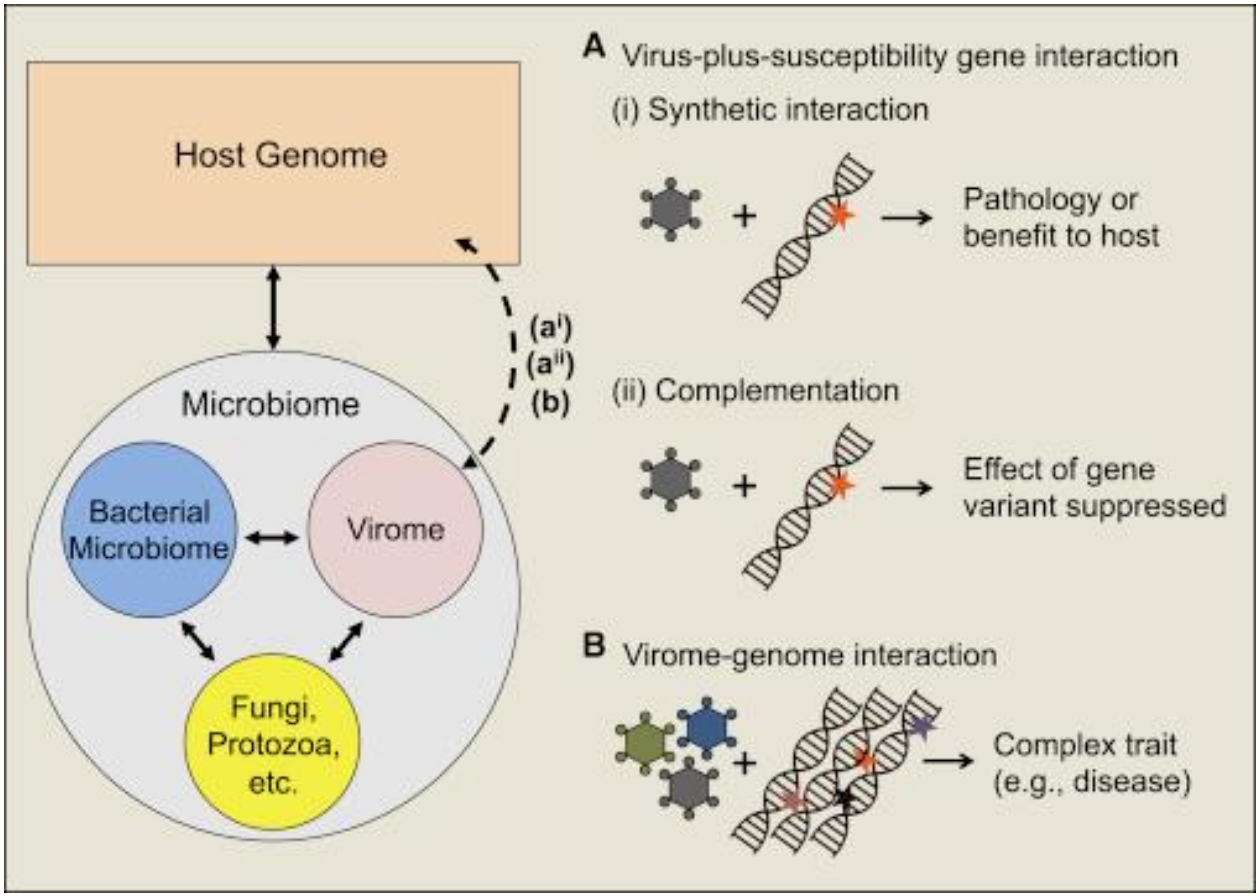
Many examples in the eukaryotic world of mutualistic symbiosis



Grass requires a fungus, which in turn requires a virus to grow in geothermal soils of Yellowstone!

http://www.nature.com/nrmicro/journal/v9/n2/full/nrmicro2491.html

Virome-genome interaction

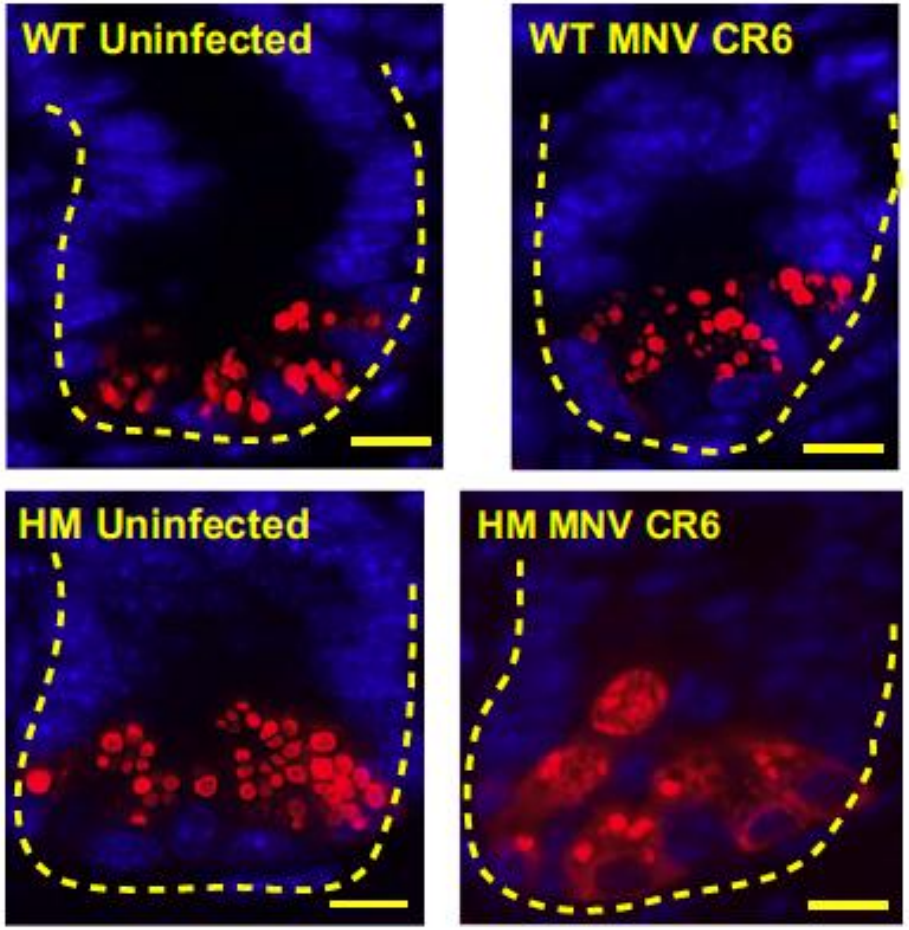


http://www.sciencedirect.com/science/article/pii/S1074761315001831

Genetic deficiency plus viral infection required to cause disease

Gene mutation + Virus Trigger = Disease

crypts of small intestine, red staining for paneth cell granules

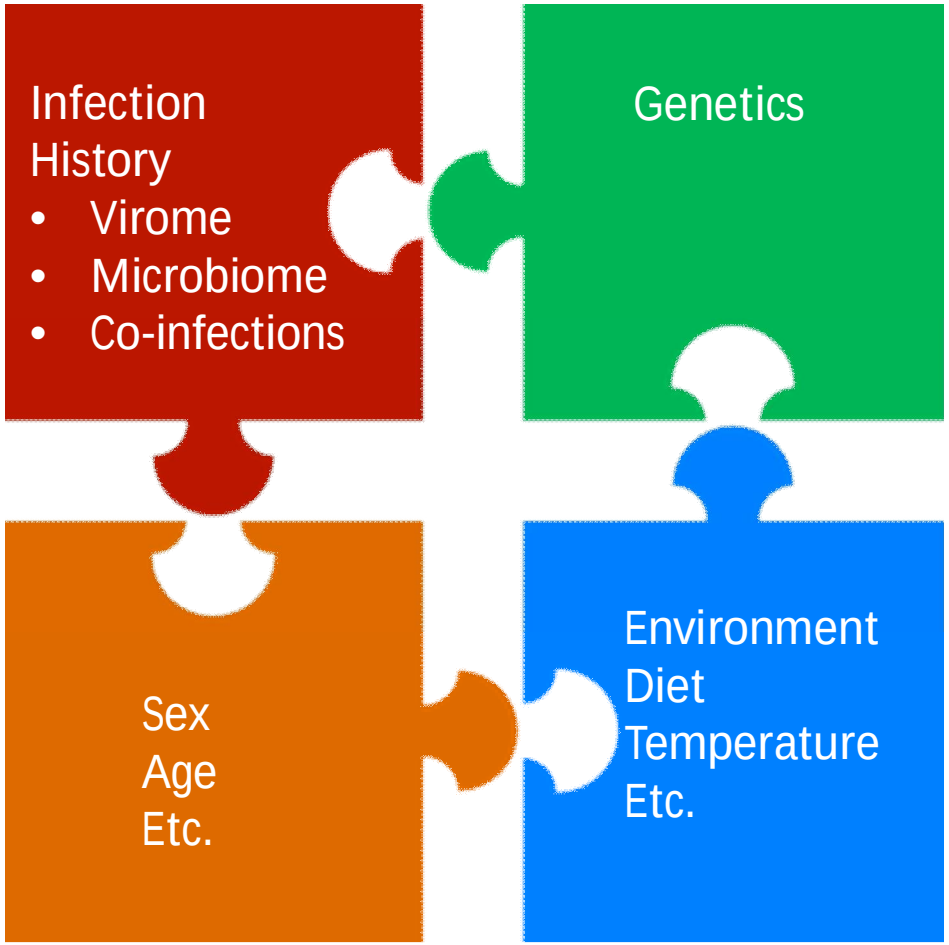


WT, no virus = no disease
WT, virus = no disease
Atg16L1 HM, no virus = no disease
Atg16L1 HM, virus = Crohn's disease phenotype

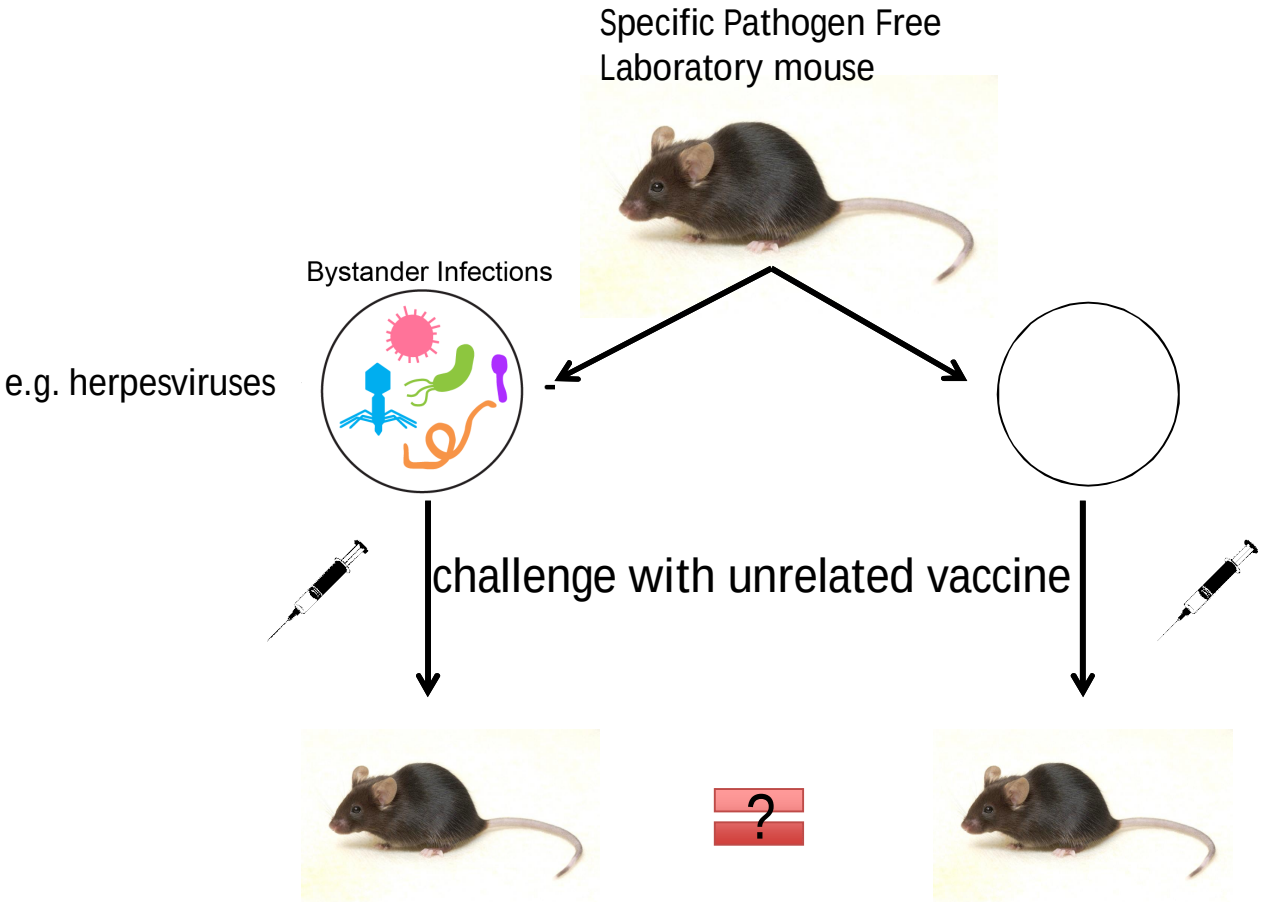
MNV: murine norovirus, persistent strain
HM: *Atg16L1* hypomorphic mice

Cadwell, et al. *Cell* 2010

Factors that influence the “basal” level of activation of an immune response and disease state.

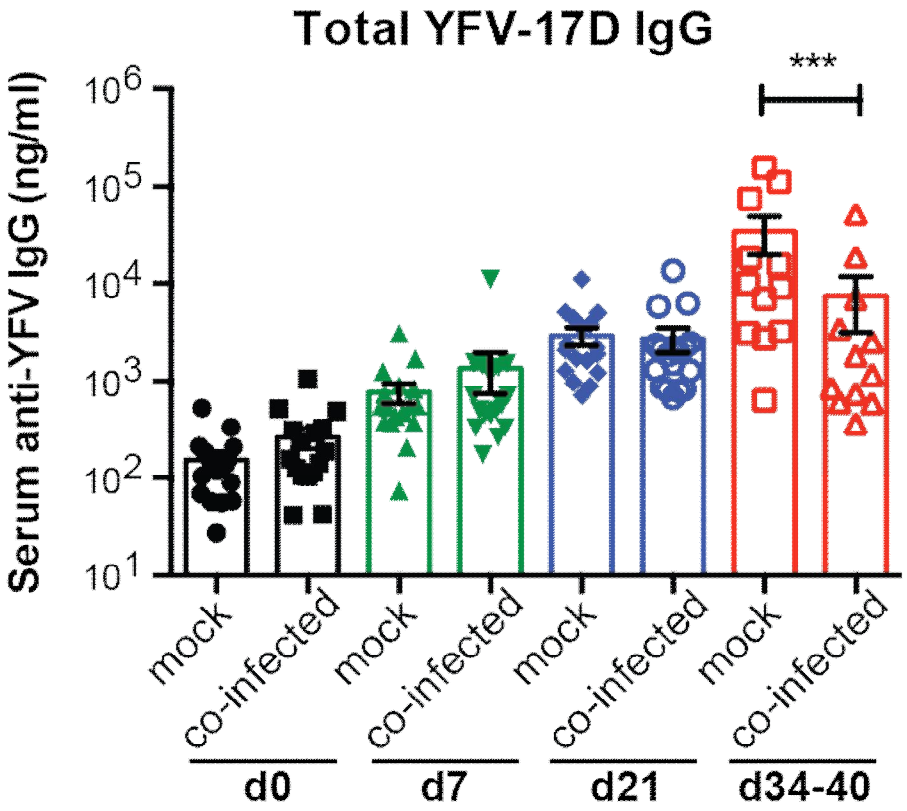


Does the presence of bystander infections in mice change immune response to a vaccine?



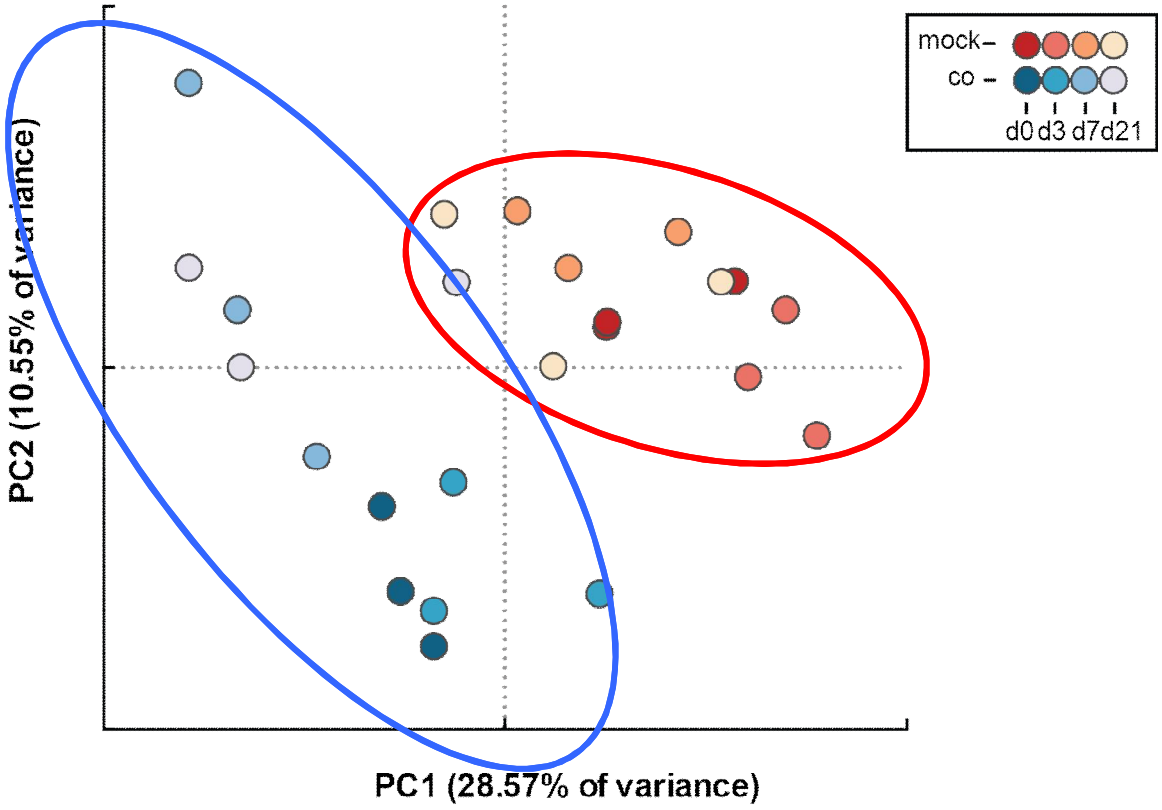
Reese, et al. *Cell Host Microbe* 2016.

Co-infection leads to reduced antibody response following vaccination.



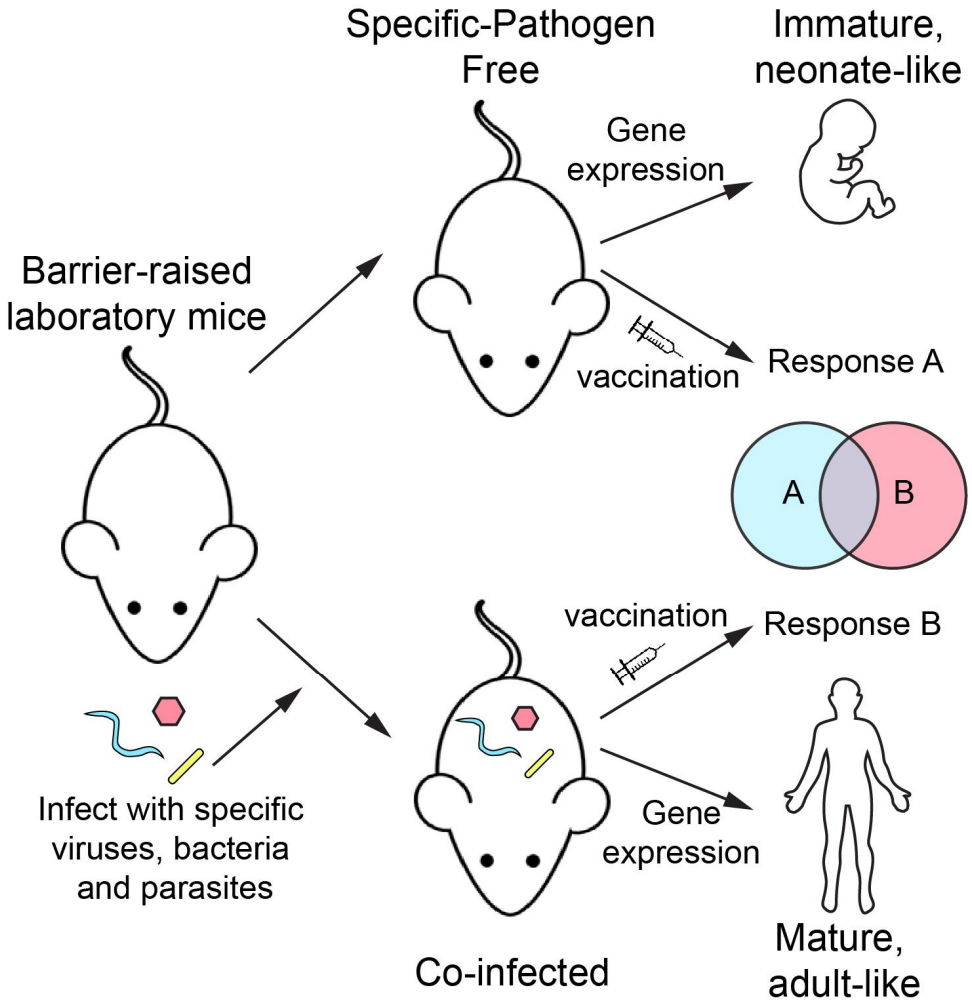
Reese, et al. *Cell Host Microbe* 2016.

Gene expression is significantly different between co-infected and mock-infected mice.



Reese, et al. *Cell Host Microbe* 2016.

Bystander infections may partially humanize the mouse immune system.



Reese, et al. Cell Host Microbe 2017.
Tao and Reese. *Trends in Immunol*. 2017.

- Viruses are part of our microbiome
- Most viruses are not pathogens
- Persistent viruses play important roles in host biology independent of classic virologic disease
- Chronic herpesvirus infection may change host immune responses to bystander infections or challenges

Additional Reading

The Scientist » November 2016 Issue » Features

Viruses of the Human Body

Some of our resident viruses may be beneficial.

By Eric Delwart | November 1, 2016

The good viruses: viral mutualistic symbioses

Marilyn J. Roossinck

NATURE REVIEWS | MICROBIOLOGY VOLUME 9 | FEBRUARY 2011 | 99

Immunity
Review

CellPress

The Virome in Host Health and Disease

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http://dx.doi.org/10.1016/j.immuni.2015.05.003

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