BIMM114: Virology

Aedes aegypti mosquito vector for several arboviruses

Dustin Glasner
UCSD Division of Biological Sciences
dglasner@ucsd.edu

Outline for today's lecture

Key concepts in this lecture:

Flaviviridae:

Most human pathogens in the *Flaviviridae* family are arboviruses

Diseases caused by members of the *Flaviviridae* family

Hepatitis C

Dengue fever, dengue hemorrhagic fever and dengue shock syndrome

Viral life cycle: Enveloped, +ssRNA

Replication on the endoplasmic reticulum membrane

Dengue and Zika virus and STAT antagonism

Togaviridae:

Human pathogens in the *Togaviridae* family

Alphaviruses are arboviruses that have zoonotic and epidemic potential

Rubella, congenital rubella syndrome, and TORCH pathogens

Viral life cycle including production of subgenomic RNAs

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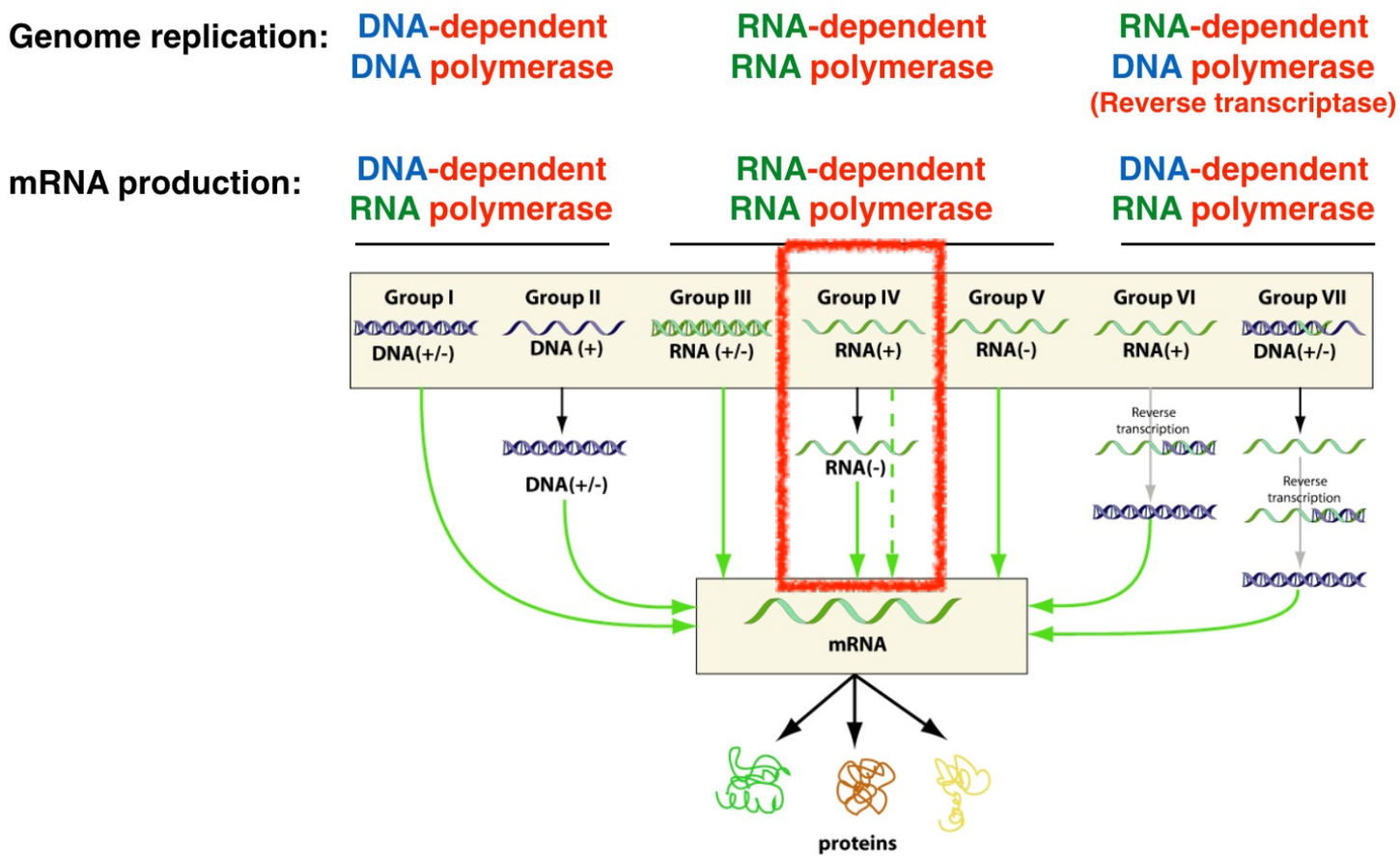
Family: *Flaviviridae*

From the latin word for yellow: Flavus

Enveloped, +ssRNA, icosahedral



Genome/mRNA → (+) ssRNA

***Viral** RNA-dependent RNA polymerase** → ** Does not need to be packaged with virus*

Antigenome/ intermediate → (-) ssRNA

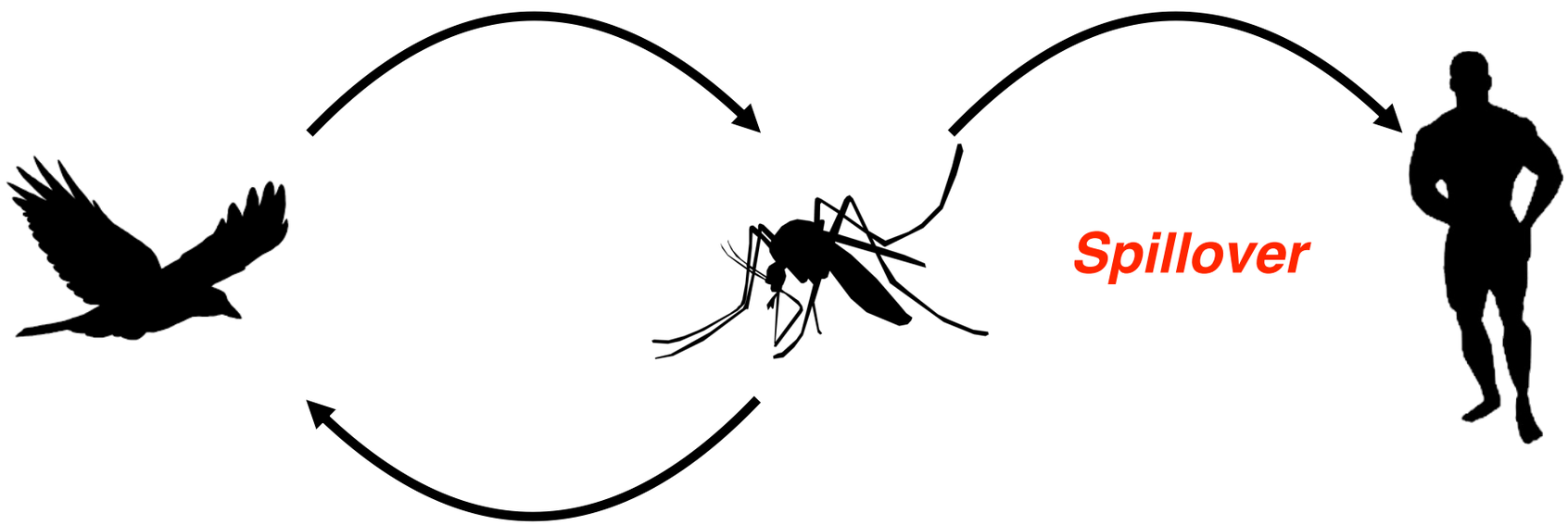
***Viral** RNA-dependent RNA polymerase* → **Genome/mRNA** → (+) ssRNA

Arboviruses: **Ar**thropod **bo**rne **viruses**

Transmission through an arthropod is an obligate part of the life cycle

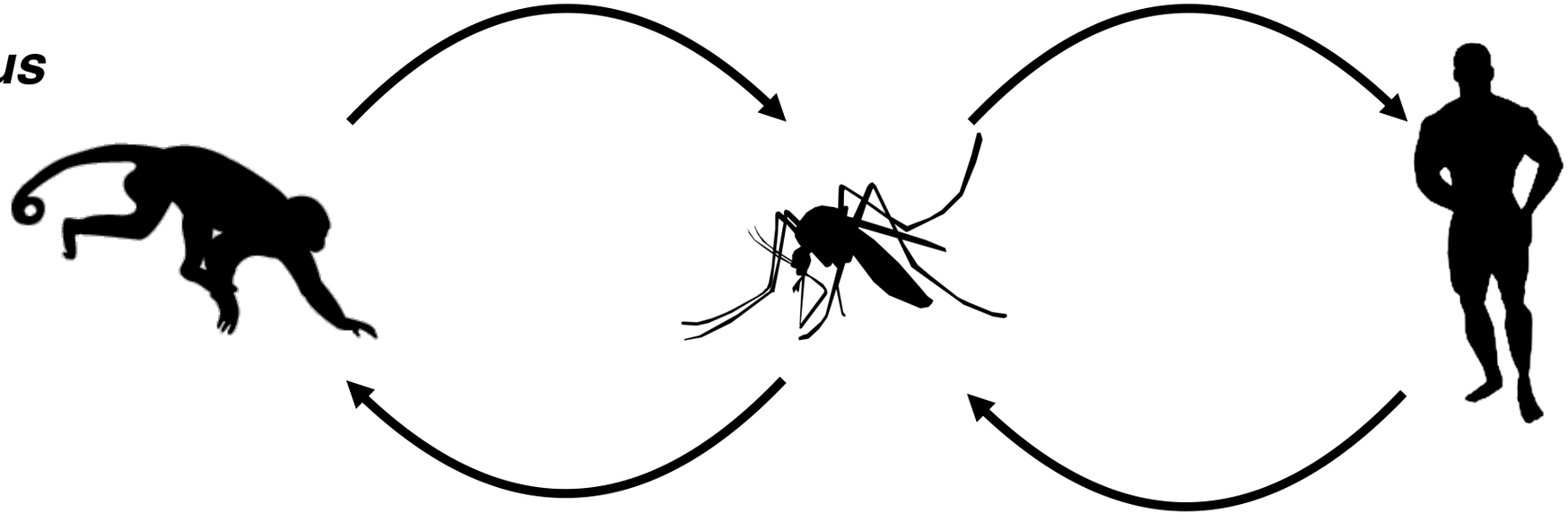
Generally mosquitos and ticks, but other insects as well.

West Nile virus



Spillover

Yellow fever virus

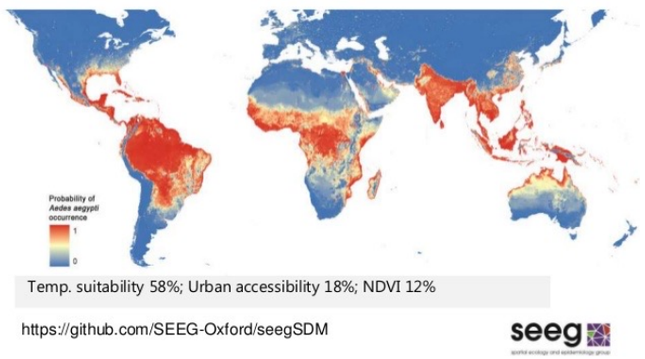


Mosquito vectors of human viruses

Aedes

Aedes aegypti, or the yellow fever mosquito, breed primarily in and around human habitations and fly short distances, usually only about 200 yards. They can carry dengue, yellow fever, chikungunya and Zika.

Aedes albopictus, or the Asian tiger mosquito, can also carry chikungunya, dengue and Zika.



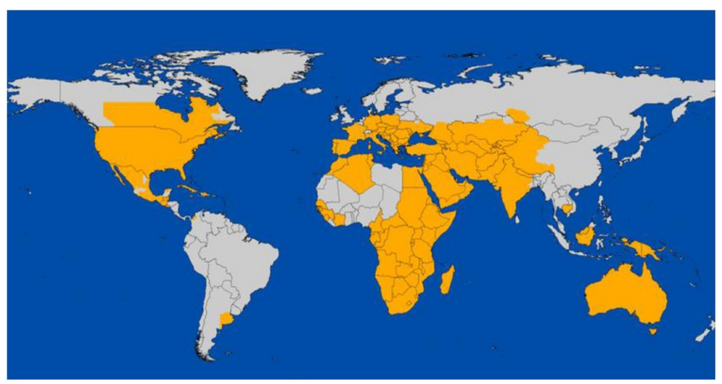
https://phc.amedd.army.mil

Yellow fever, Dengue, Zika, Chikungunya, La Crosse encephalitis

Culex

Most members of the Culex species drink the blood of birds, but some feed on humans and have been found to carry certain types of encephalitis—an inflammation of the brain—and West Nile virus.

Nineteen Culex species are found in Texas.

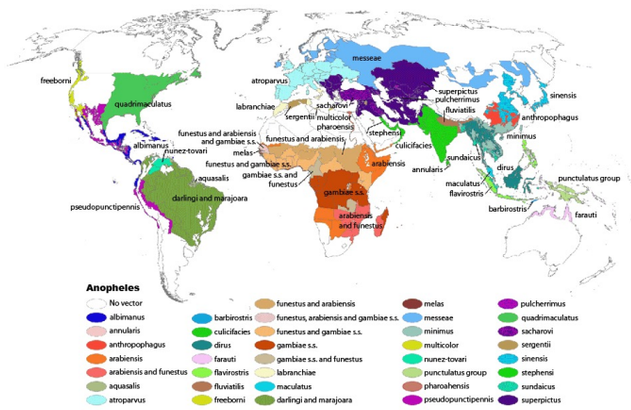


Reisen, Viruses, 2013

Japanese encephalitis, West Nile, St. Louis encephalitis, Rift Valley fever

Anopheles

Most Anopheles mosquitoes have a flight range of about 1 mile. Anopheles Psorophora have flight ranges of at least 5 miles. Anopheles quadrimaculatus are known to carry malaria—an acute chronic disease that can vary from moderately severe to fatal in humans—and are native to Central Texas.

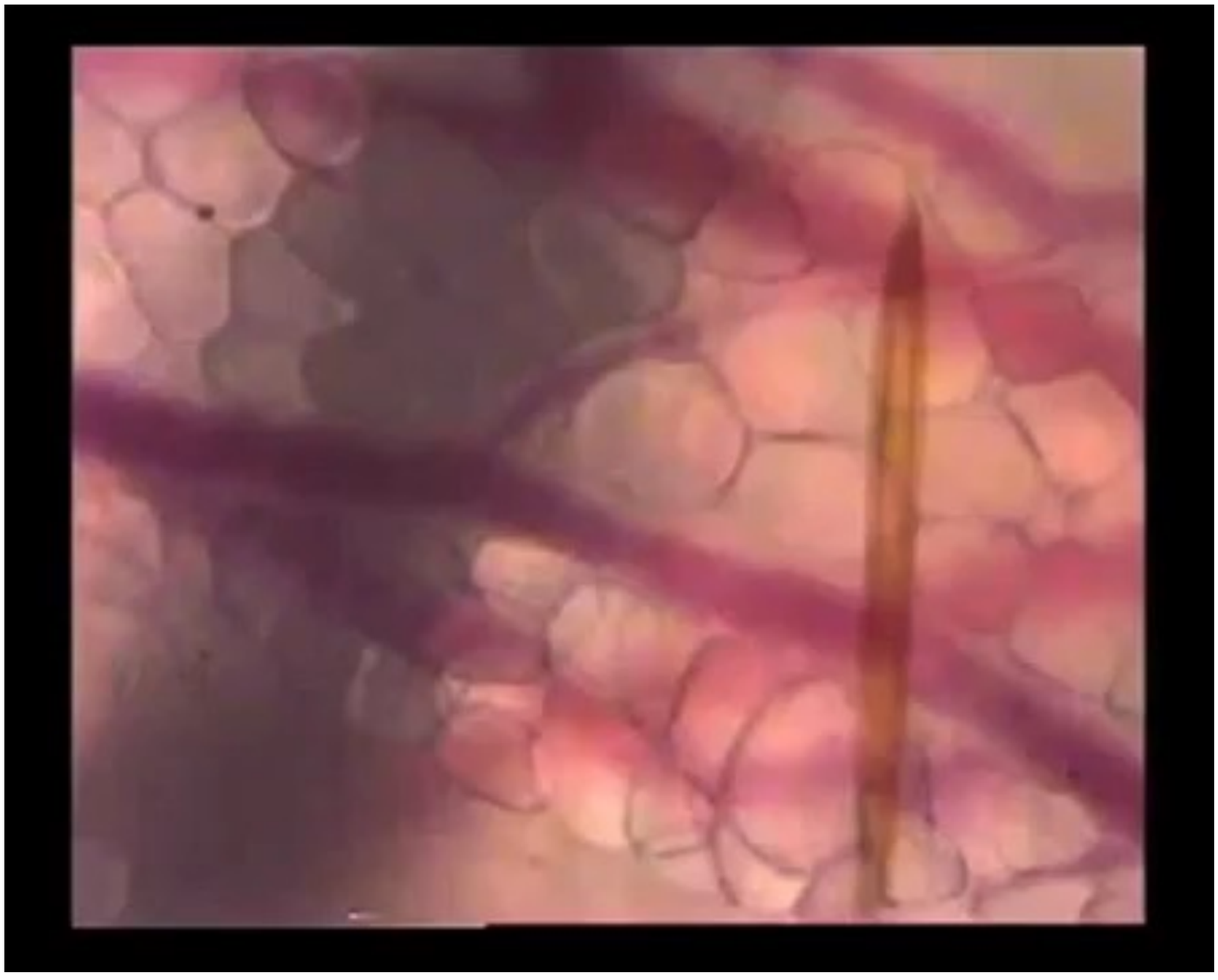


CDC

O'nyong'nyong Malaria

Glasner, BIMM114, 2/6/24

Mosquito blood feeding

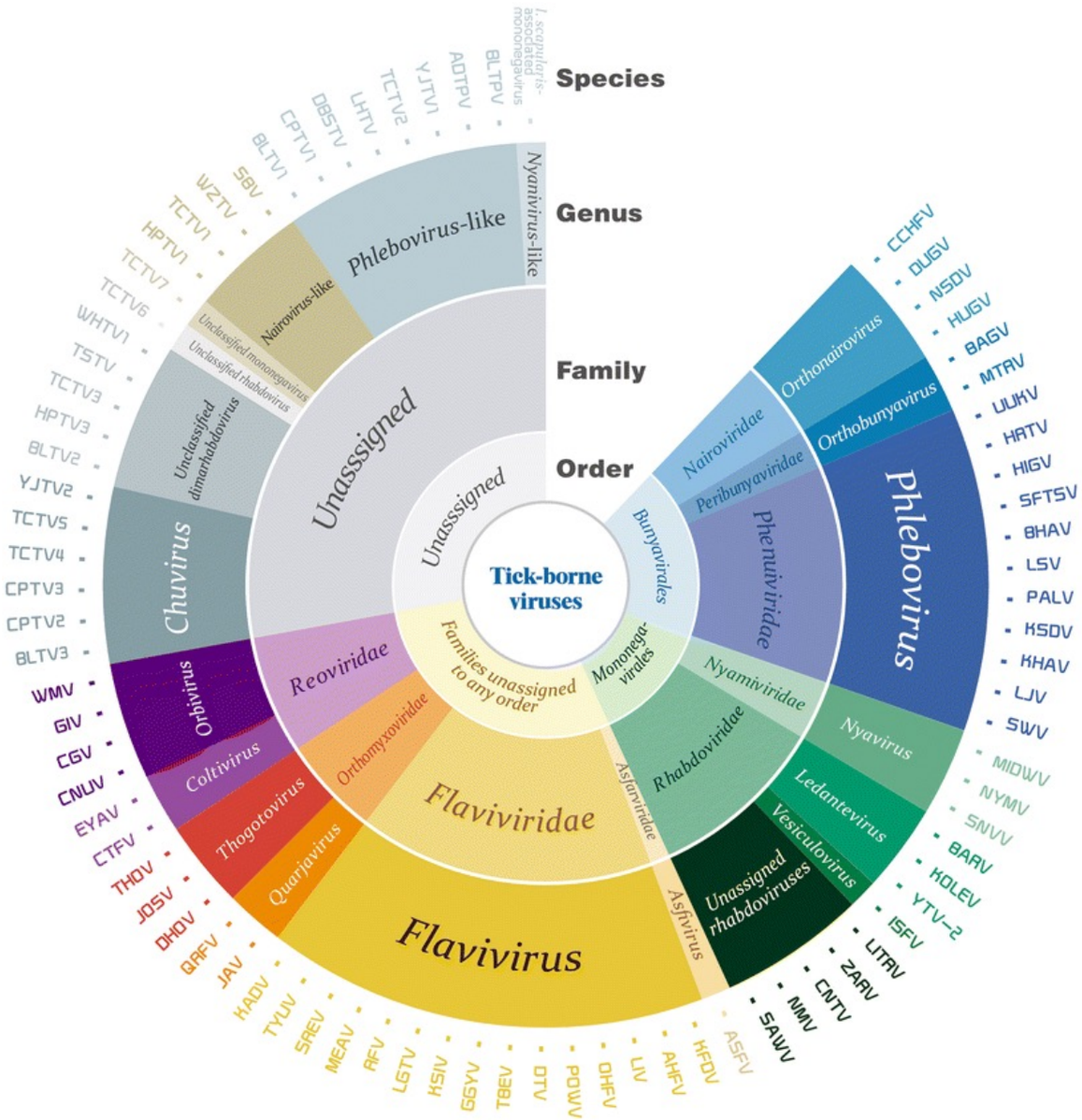


Choumet et al. (2012) PLoS One

- Mosquitoes pierce the epidermis using proboscis and probe for capillaries in the dermis

- Mosquitoes expectorate saliva containing various molecules, including anesthetics, vasodilators, and immune modulators

Ticks are also vectors of arboviruses



Tick-borne encephalitis, Powassan, Crimean-Congo haemorrhagic fever, African swine fever, Bourbon viruses

Lyme disease, Rocky-mountain spotted fever

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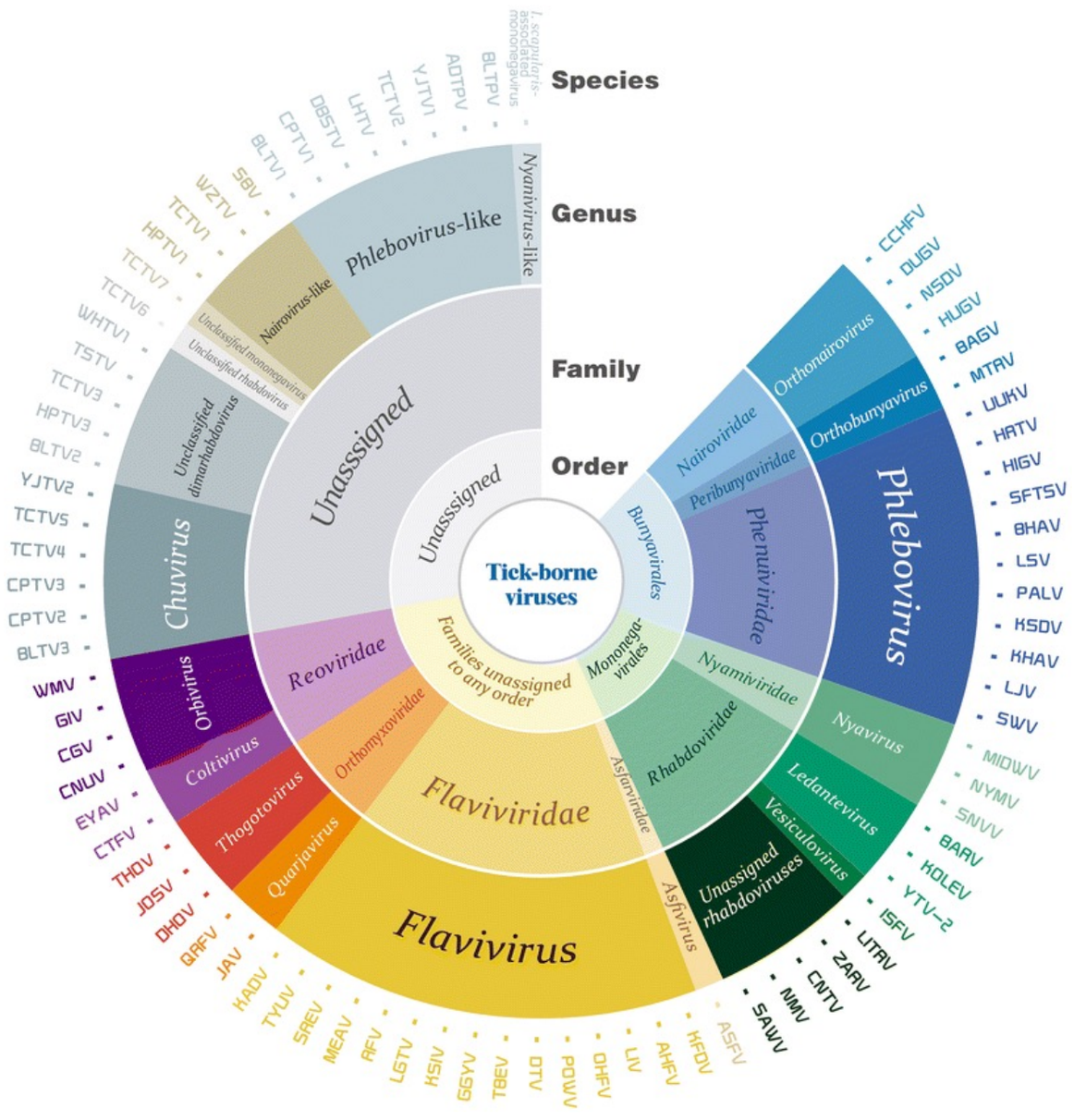

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Human pathogens in the *Flaviviridae* family

Genus: *Hepacivirus*

Hepatitis C virus (>50 million people currently infected, ~400,000 deaths/year)
Acute liver disease, can progress to liver cancer

Genus: *Flavivirus*

Dengue virus (>10 million infections/year, >20,000 deaths/year)
Carried by *Aedes* mosquitos, causes fever, sometimes hemorrhagic disease

Yellow fever virus (>100,000 infections/year, >20,000 deaths/year)
Carried by *Aedes* mosquitos, causes fever, sometimes hemorrhagic disease

Zika virus (maybe 200,000 - 1,000,000 cases since 2014, <100(?) deaths total)
Carried by *Aedes* mosquitos, causes fever, microcephaly

West Nile virus (~1000 infections/year, >10 deaths/year)
Carried by *Culex* mosquitos, bird reservoir, neurotropic, causes encephalitis

Japanese encephalitis virus (>50,000 infections/year, >10,000 deaths/year)
Carried by *Culex* mosquitos, neurotropic, causes encephalitis

Tick-borne encephalitis virus (~10,000 infections/year)
Carried by *Ixodes* ticks, neurotropic, causes encephalitis

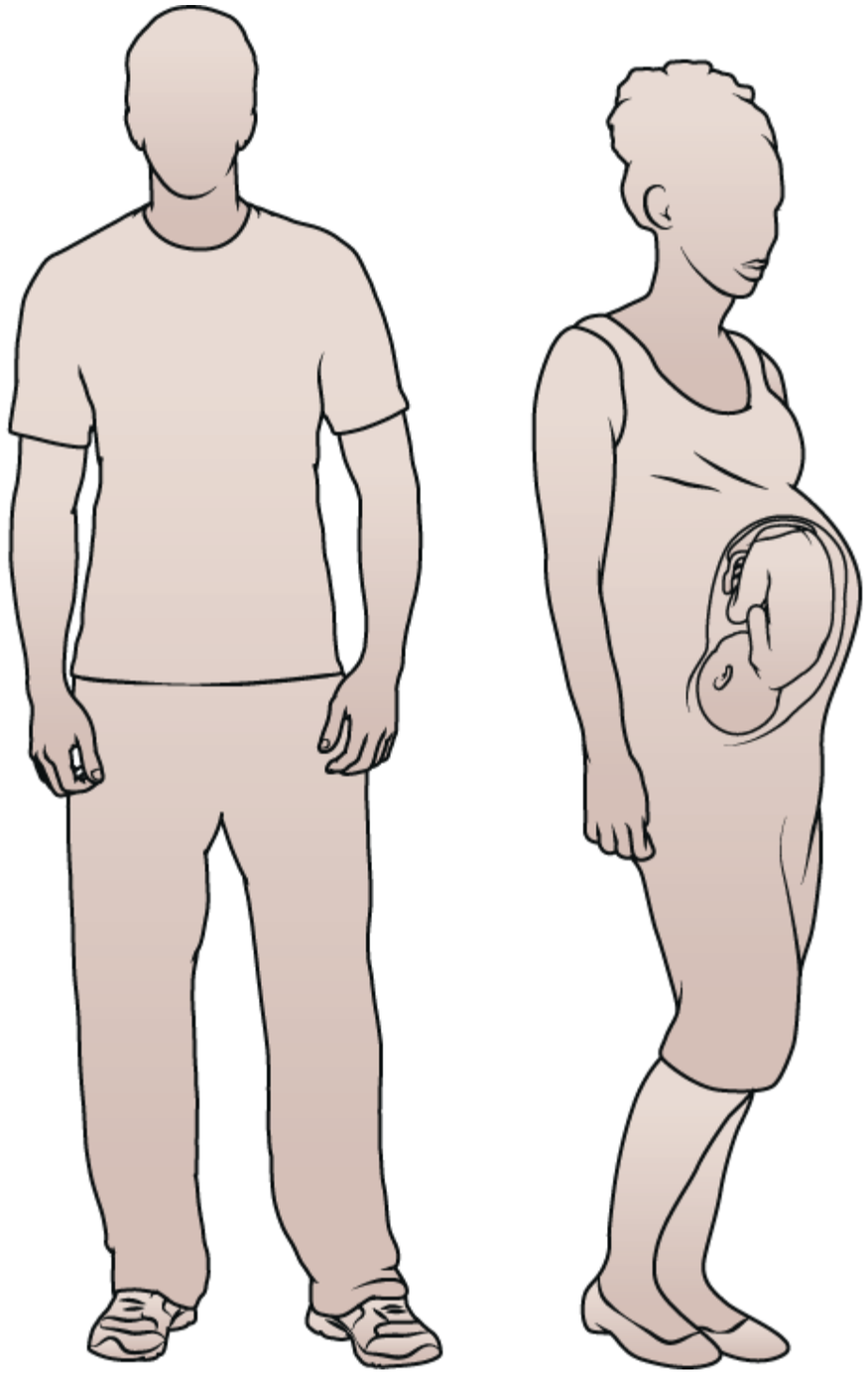
Human pathogens in the *Flaviviridae* family

Neurotropic disease

- Encephalitis
- Cognitive impairment
- Flaccid paralysis

Visceral disease

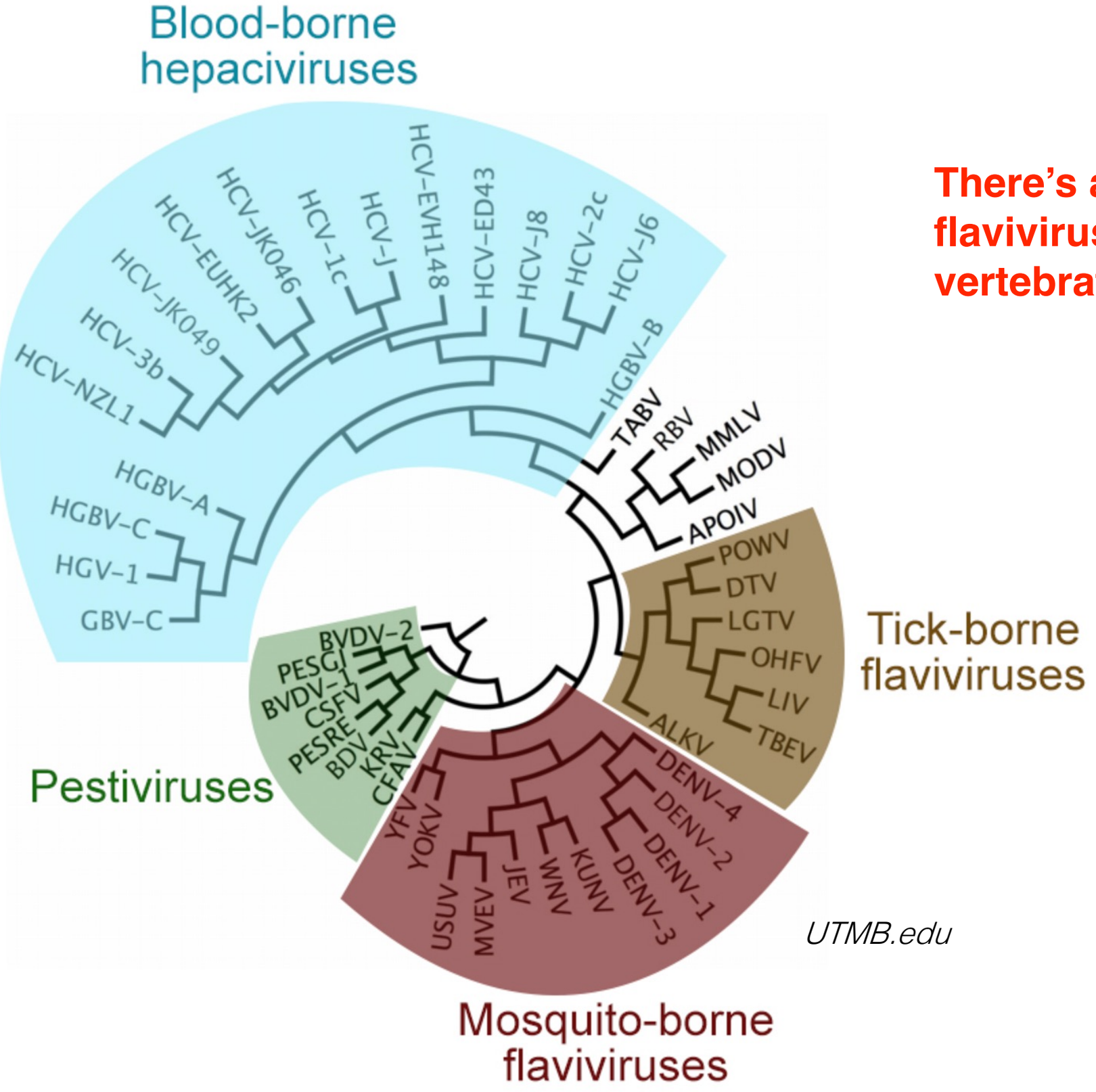
- Hepatitis
- Vascular leakage
- Haemorrhage and bleeding
- Shock syndrome



Congenital disease

- Microcephaly
- Placental insufficiency

Different hosts, cell types, and diseases



UTMB.edu

There's also a clade of insect flaviviruses that have no known vertebrate host

Hepatitis C virus

Bloodborne virus. IV drug use or other blood-contact.

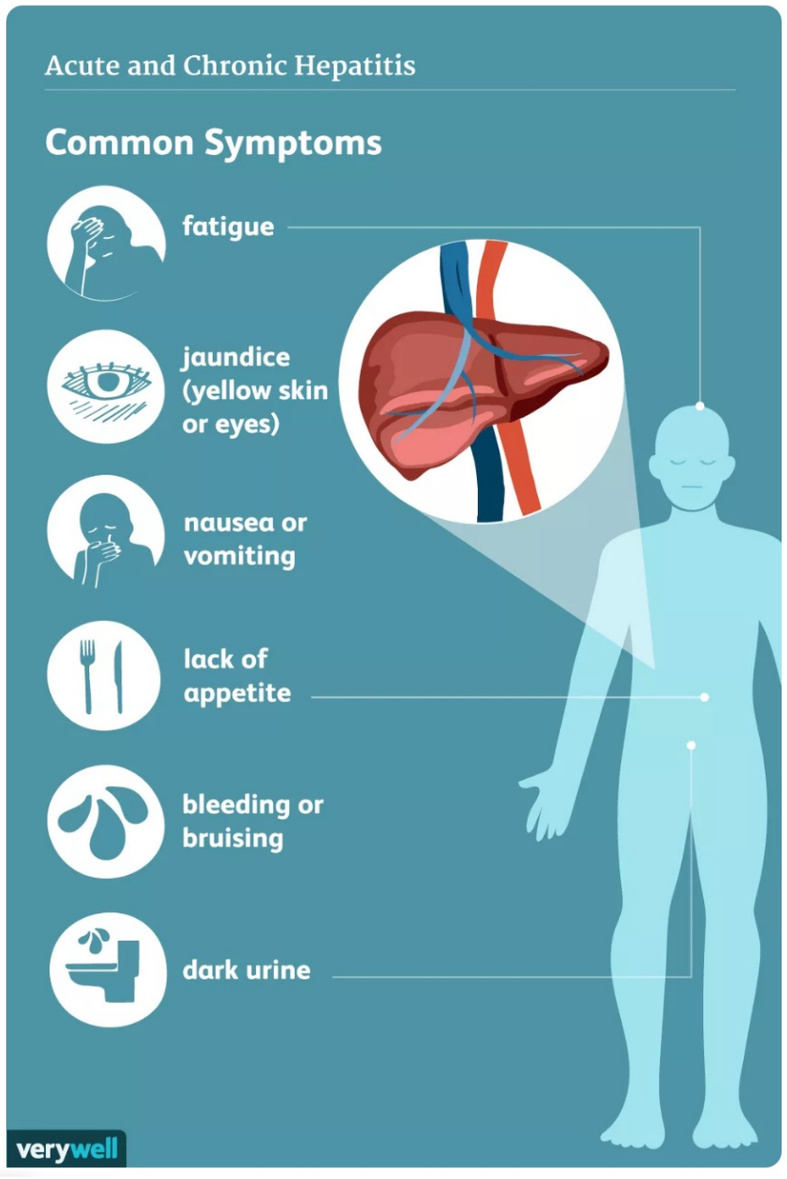
Acute infection is usually asymptomatic.
~20-40% clear infection naturally.

Rest will develop chronic infection.
15-30% develop liver cirrhosis within 20 years.

WHO estimates:
~2 million new infections per year
71 million people have chronic infection
~400,000 deaths annually
~1/3 of those are due to liver cancer

Historically, treatment was giving IFN

Recently, can get 95% cure rate, but for ~$100,000



Global burden of dengue disease

- 3.6 billion at risk for infection from DENV1-4
- ~400 million infections/year
- ~100 million dengue cases/year
- 250,000-500,000 cases of DHF/DSS/year
- 21,000 deaths attributed to dengue/year

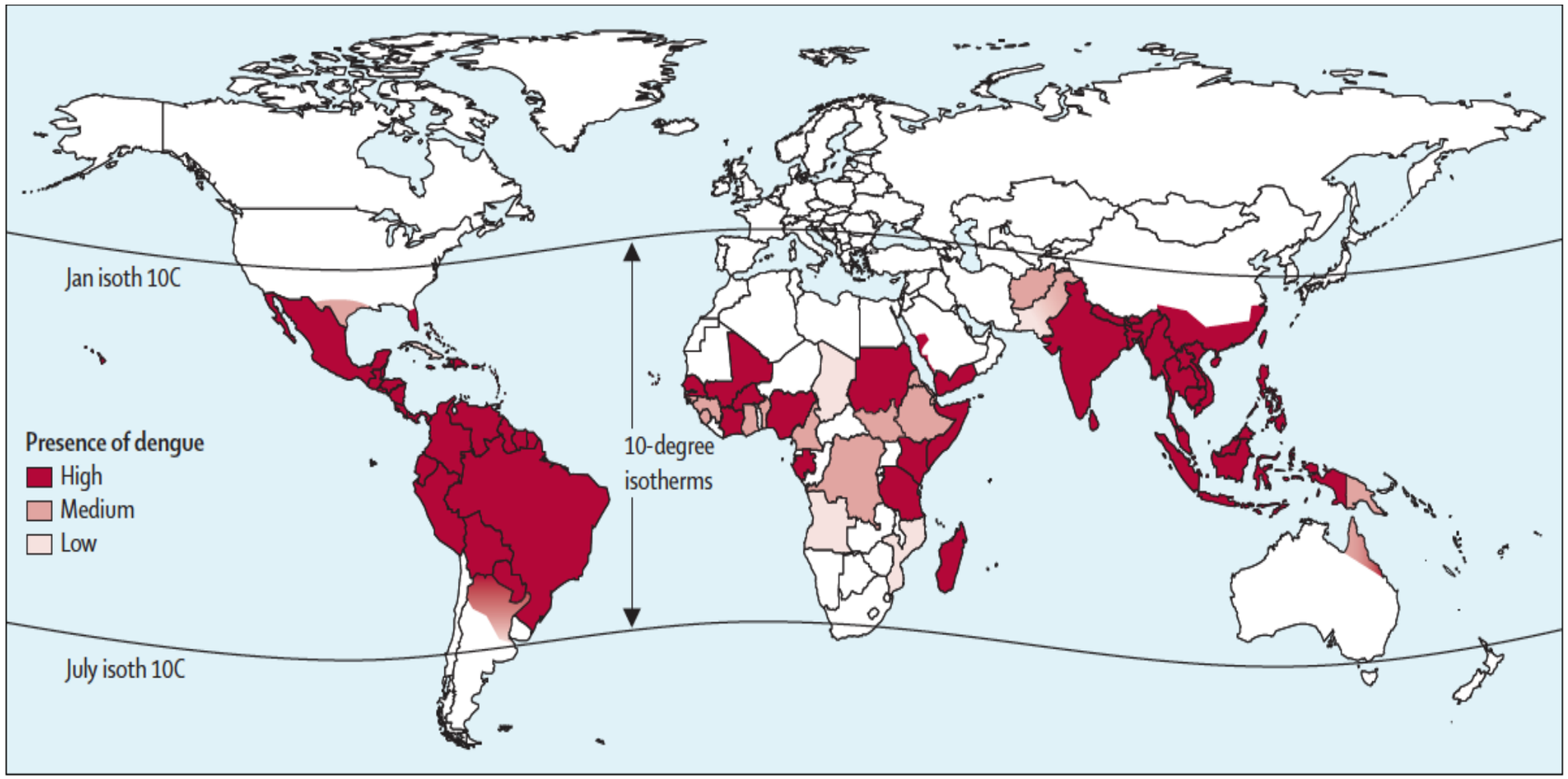


***Figure 1*: Global dengue burden, 2014**
Data from Bhatt and colleagues,[1] Healthmap,[2] and WHO[3] were integrated to indicate the relative amount of dengue globally according to best estimates.

Guzman & Harris (2015) *Lancet* 385:453-465

Two Forms of Dengue Disease

Dengue Fever

High Fever

Muscle/Bone Pain

Retro-orbital pain

Fatigue

Rash

Nausea, vomiting

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Warning Signs

Persistent vomiting

Tender abdomen

Fluid accumulation

Lethargy

Bleeding

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Increased fluid leakage

Low platelet count

Hemorrhagic manifestations

Increased cytokines

Shock from low blood volume

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Tablets Manual

DHF/DSS

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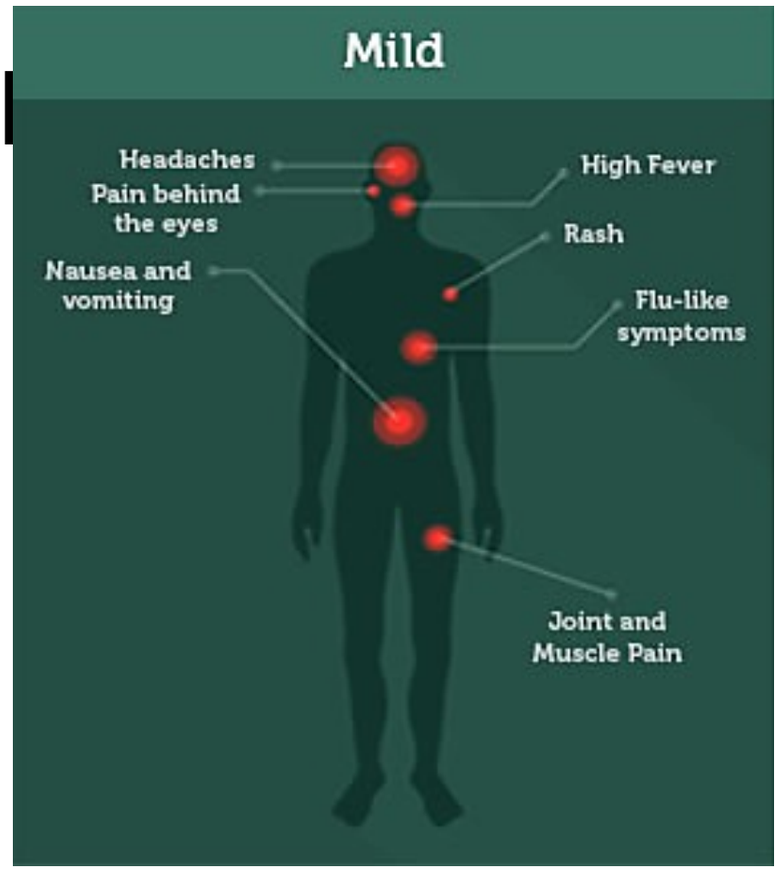
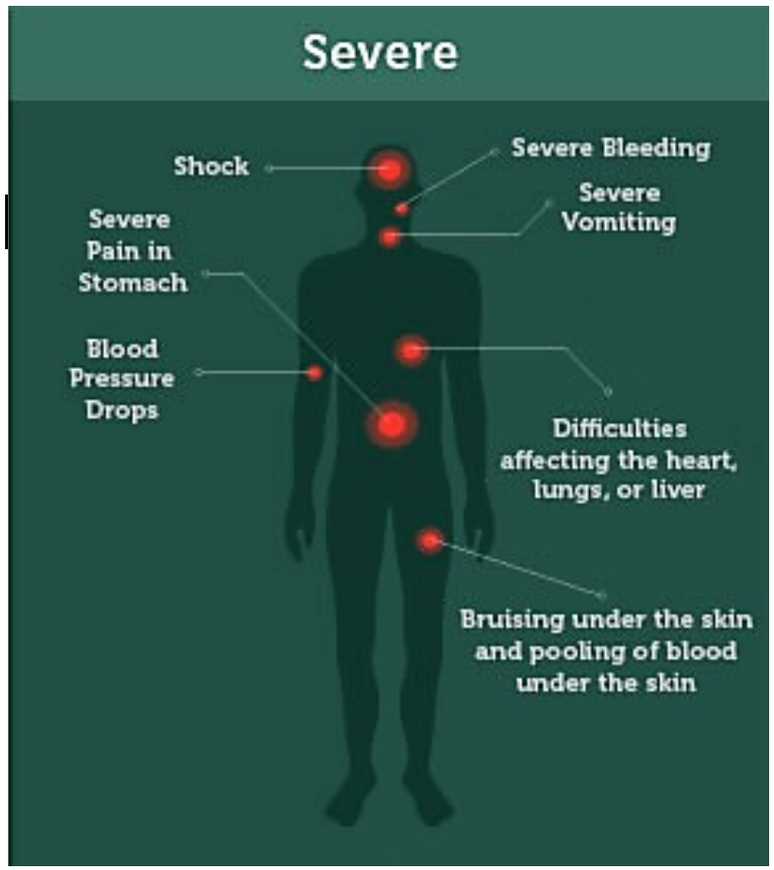
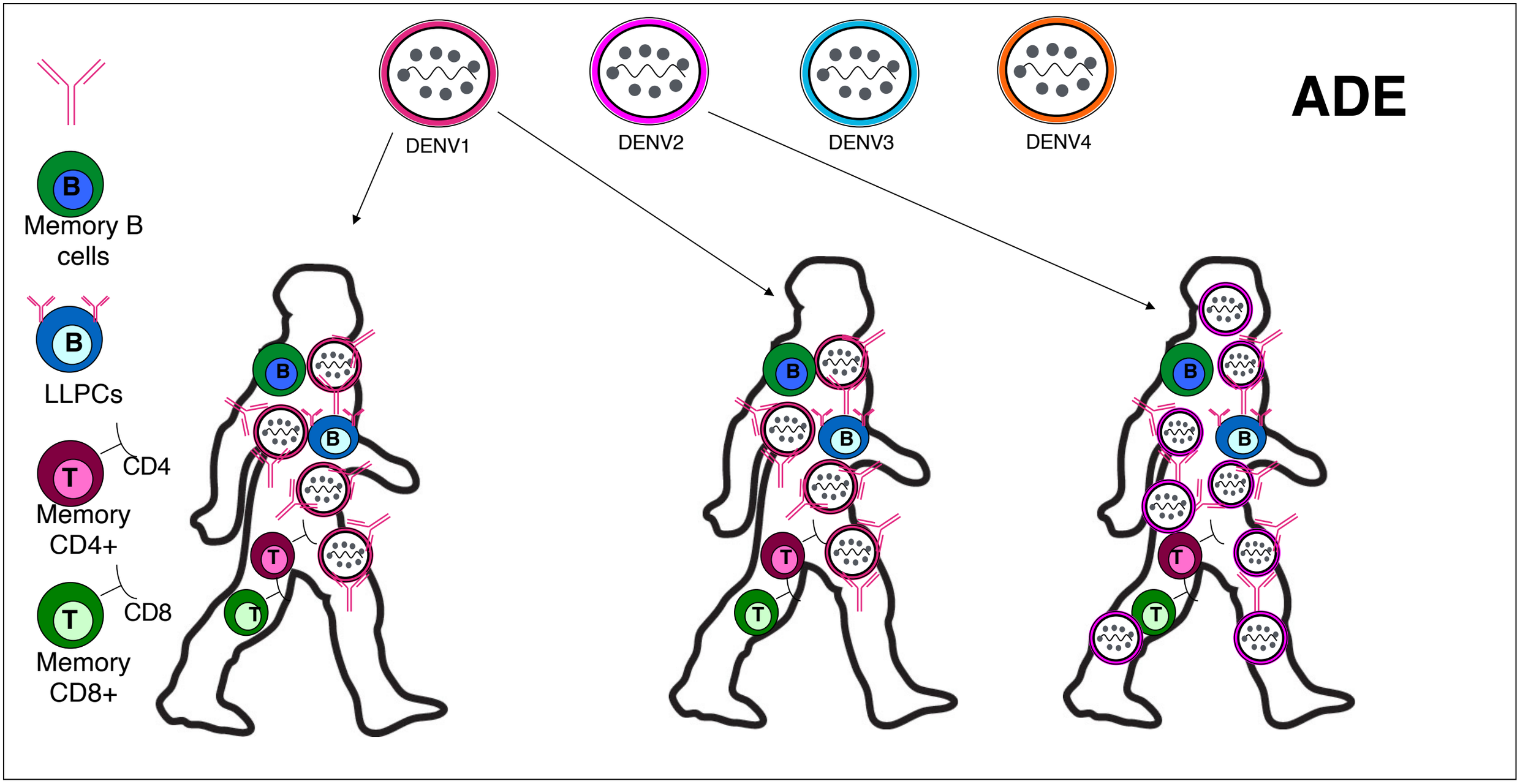


Tablets Manual



Sequential infection with different dengue serotypes can give rise to severe disease

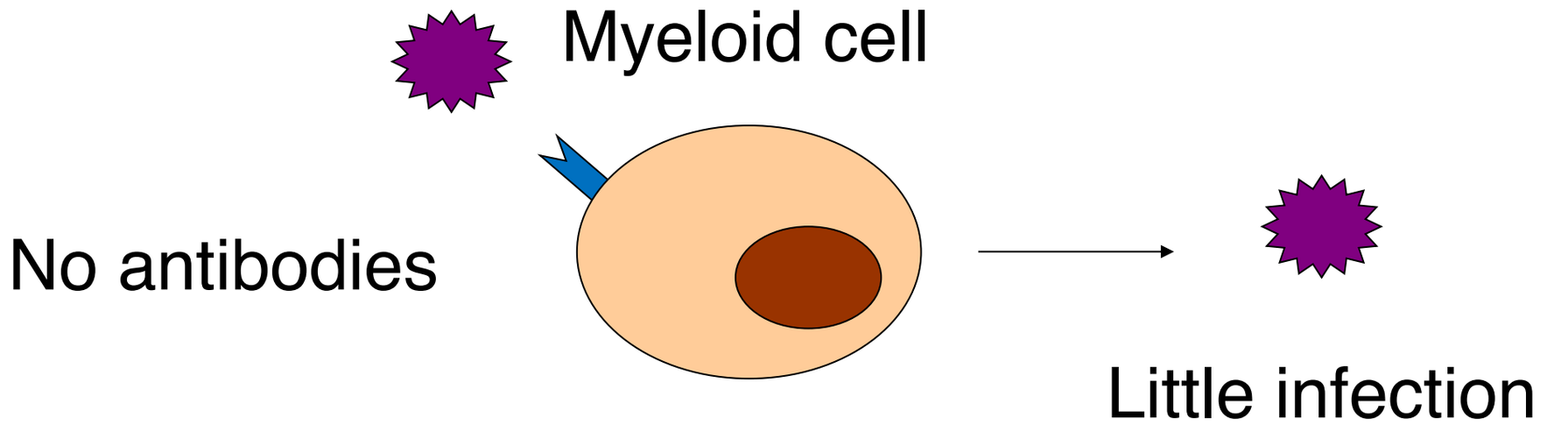


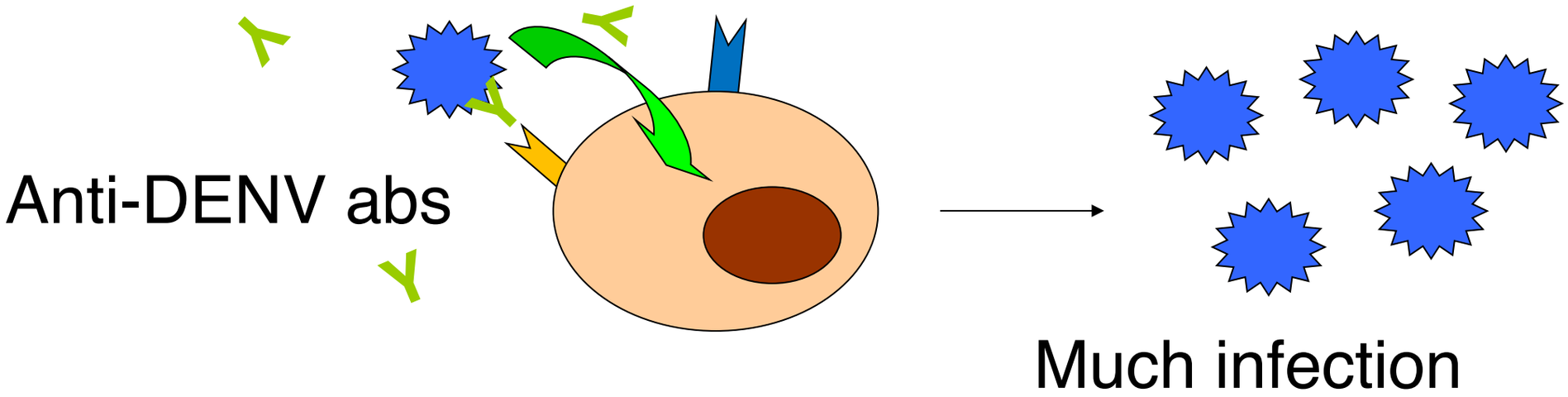
Primary Infection
Asymptomatic infection OR mild disease

Secondary Infection
Increased risk of severe dengue (DHF/DSS) disease

Courtesy of Dr. Eva Harris

Antibody-dependent enhancement (ADE)





Zika virus

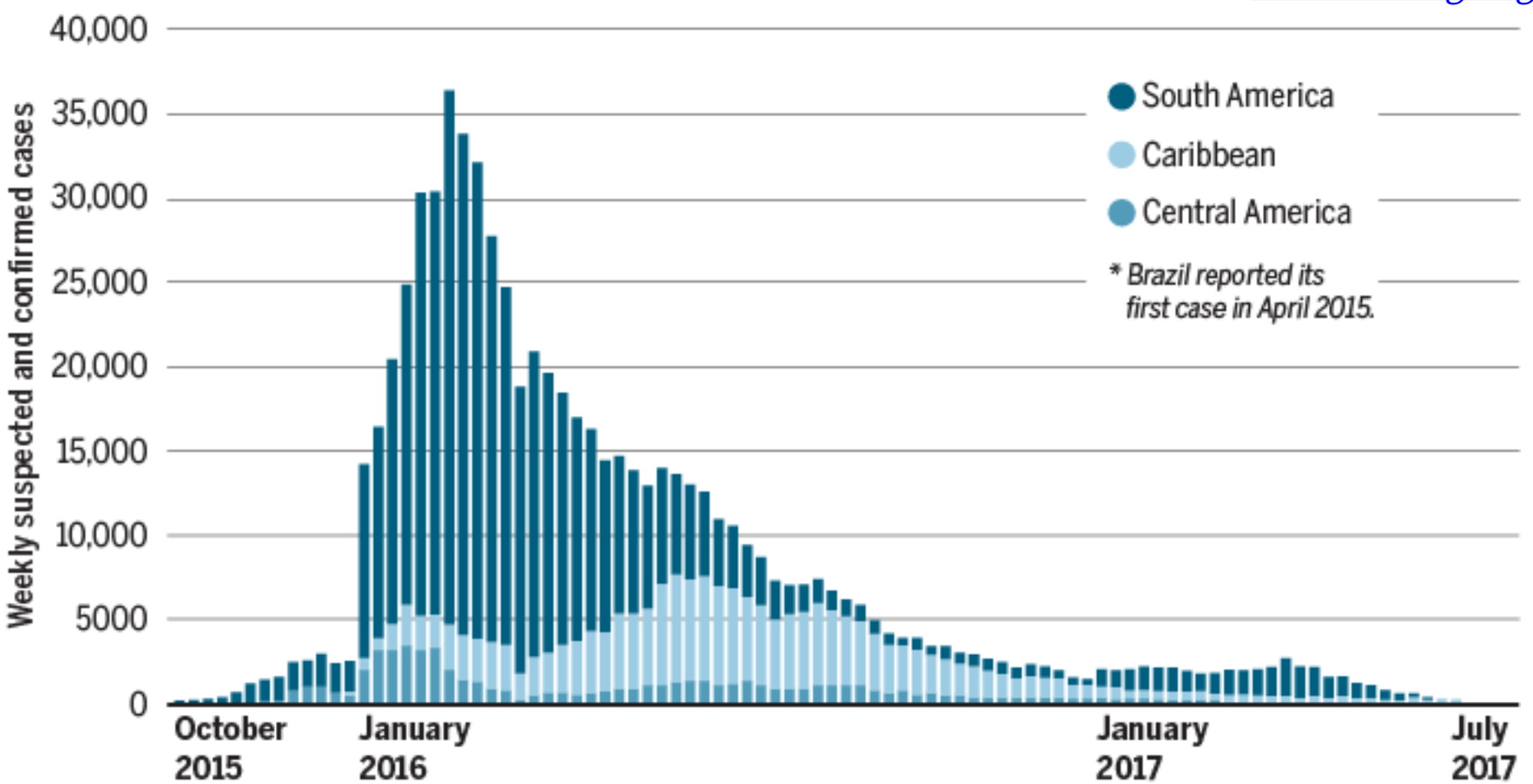
Mostly asymptomatic infections

Symptoms include fever, rash … sound familiar?

Until 2007, few cases were in Africa and was of minor concern

2014 - 2016: Major outbreak in South and Central America

sciencemag.org



Major problem is that virus gets to unborn fetus, causing brain abnormalities

Why such a sharp rise and sharp fall?

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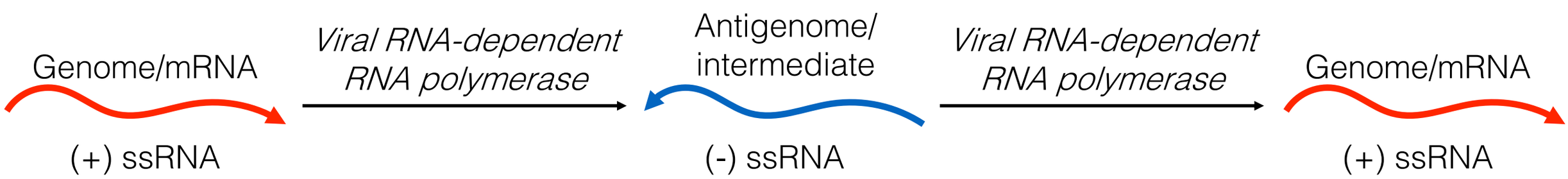
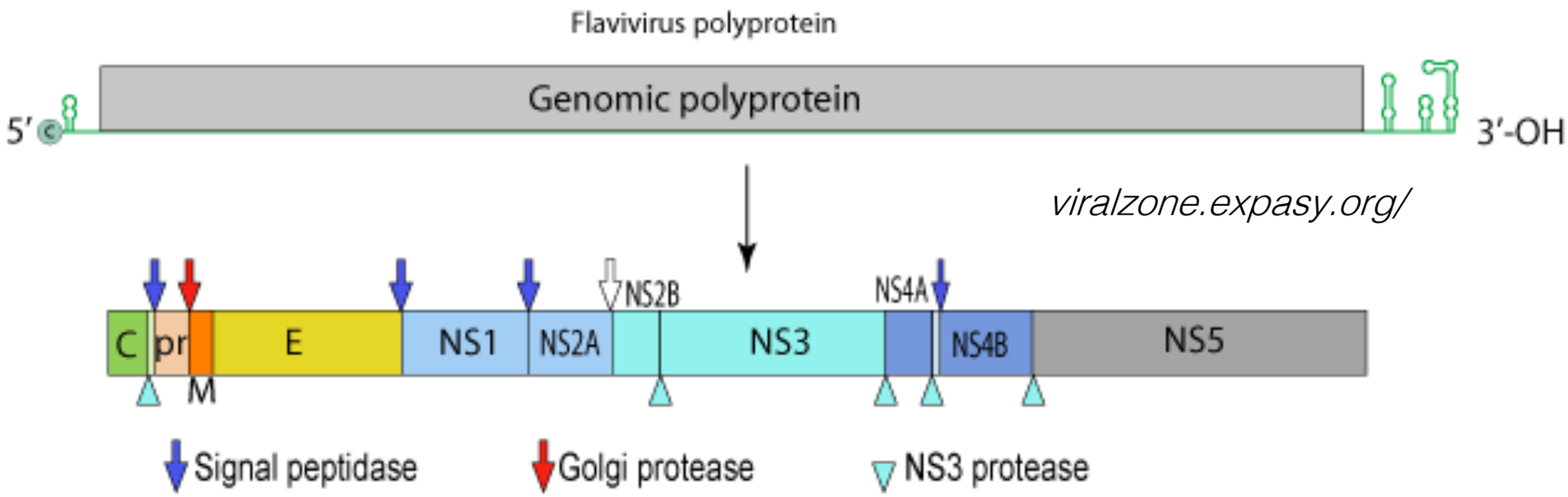
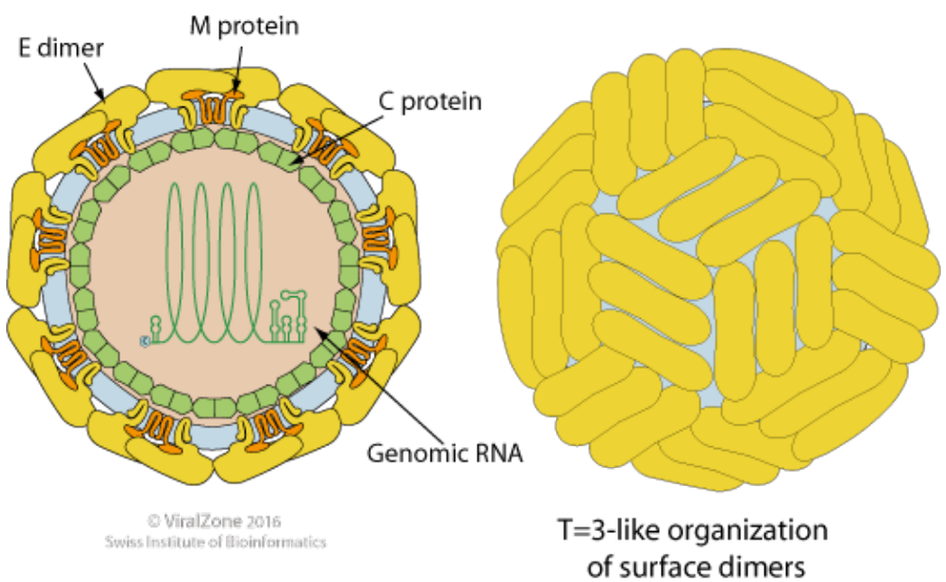
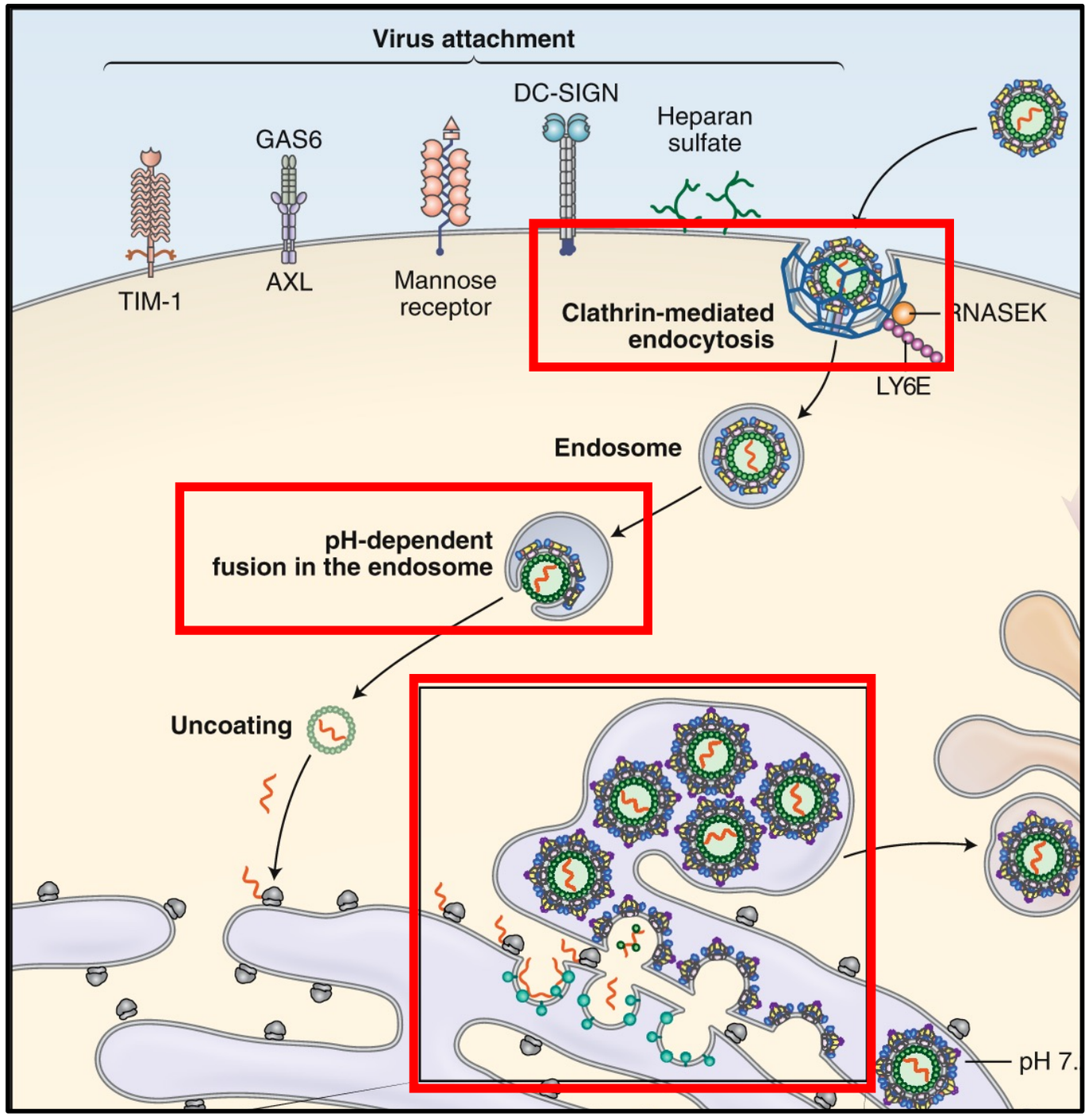
Flaviviridae genome structure







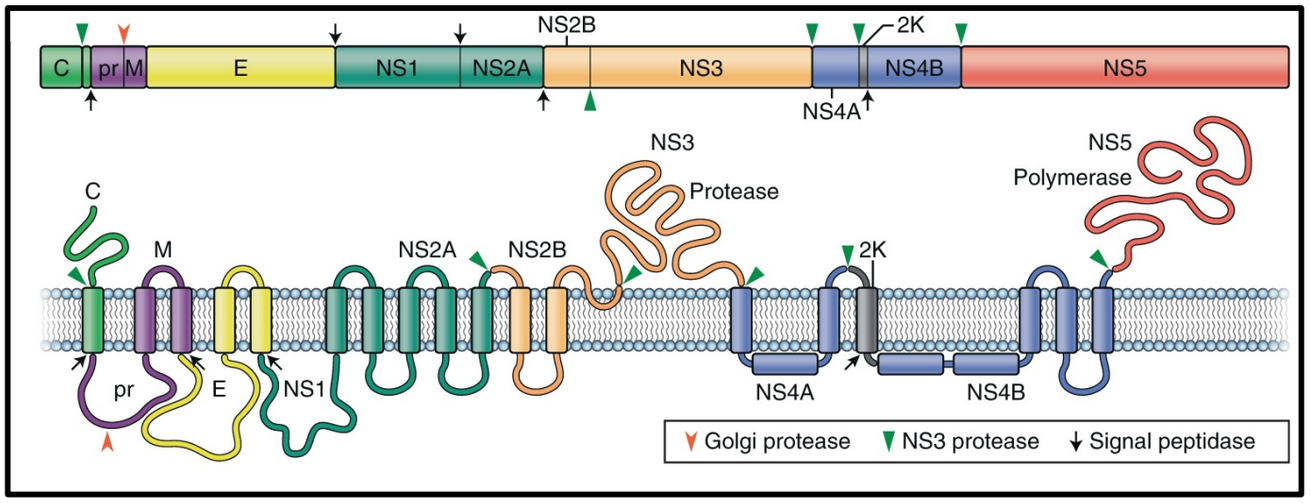
Flaviviridae life cycle



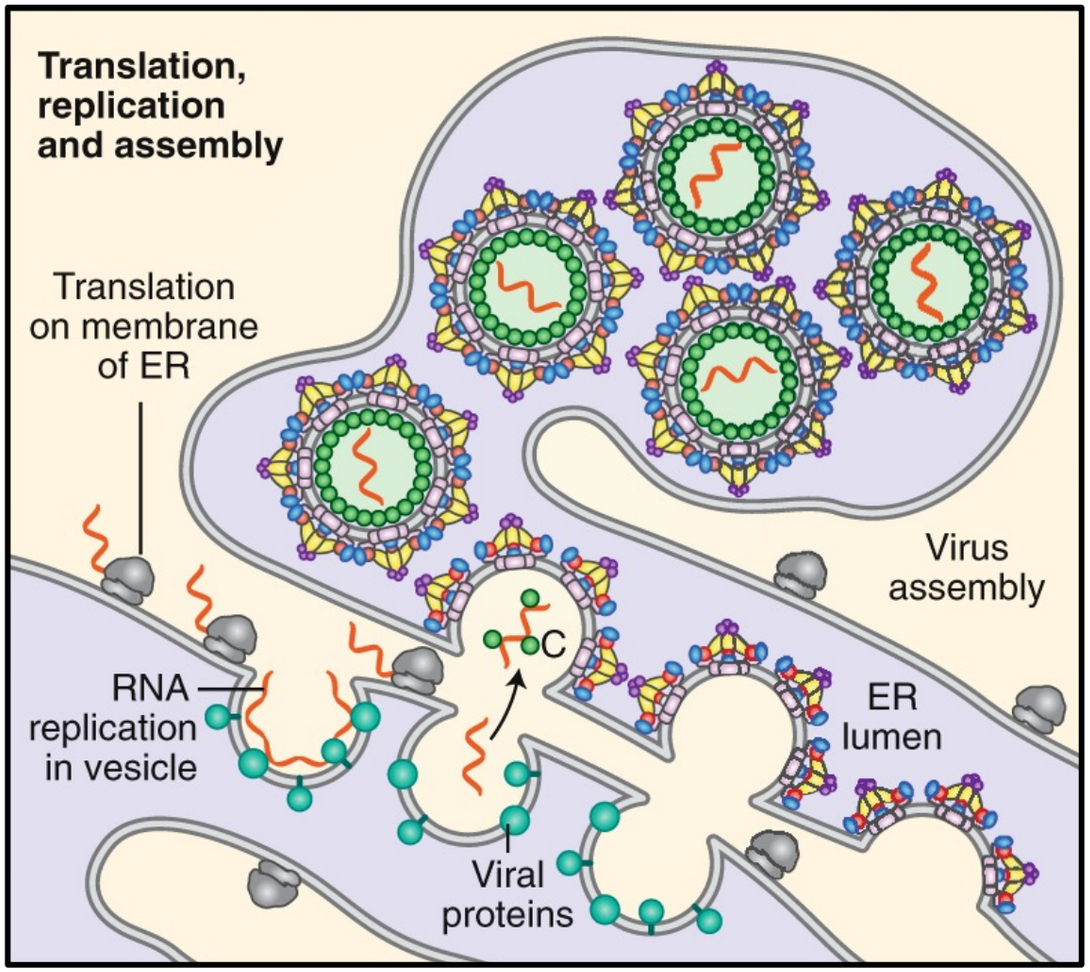
Pierson & Diamond, Nature Microbiology, 2020

- Entry by endocytosis
- Unpackaging in the cytoplasm
- Replication and assembly on cellular membranes

Replication on cellular membranes

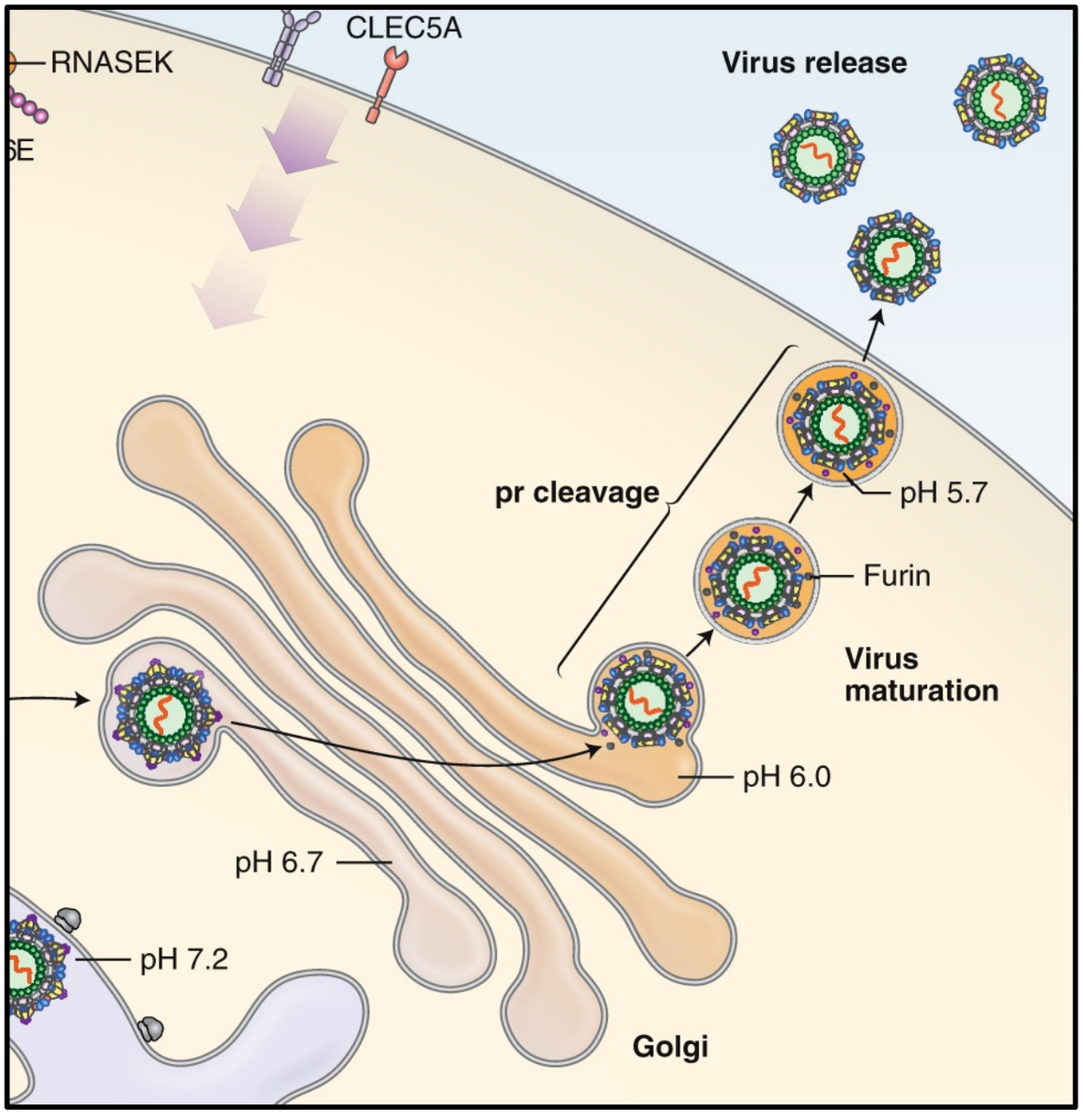


Pierson & Diamond, Nature Microbiology, 2020



- Viral proteins are translated on ER membrane
- RNA replication occurs in virus-induced membrane structures
- Structural proteins arrange on the ER lumen
- Viral particles assemble and bud into the ER

Virus maturation and release



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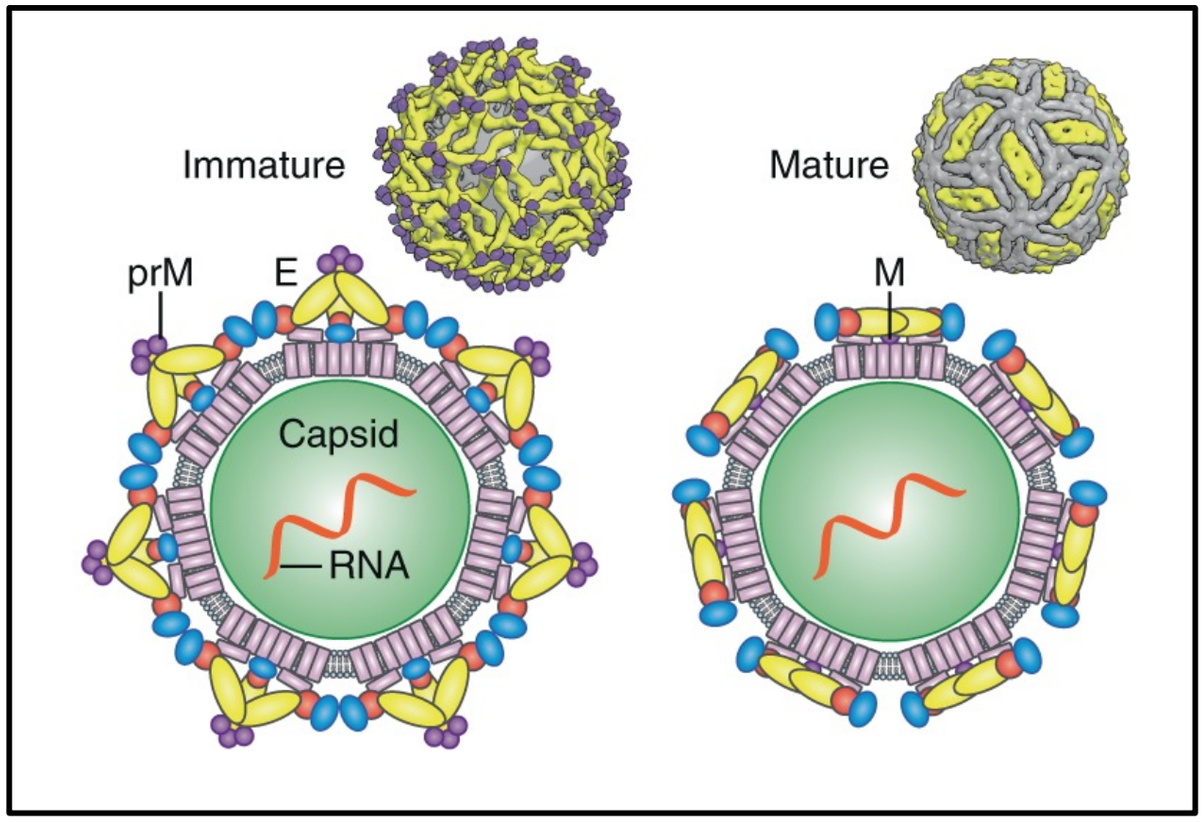
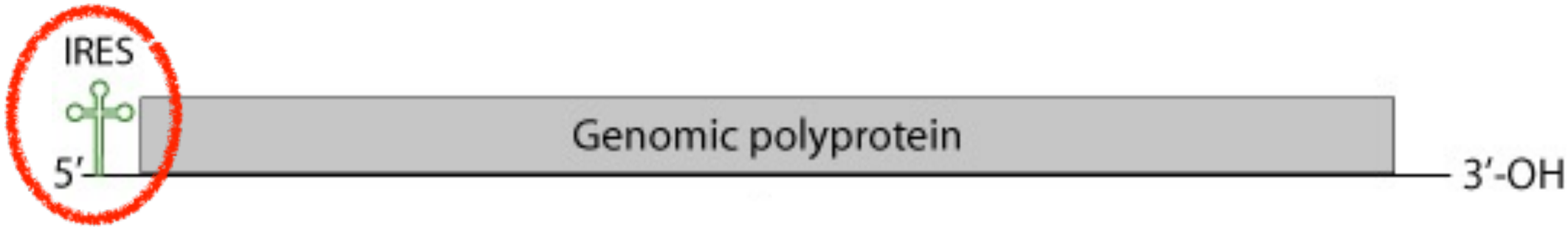


Immature virions are thought to be non-infectious

Hepatitis C virus



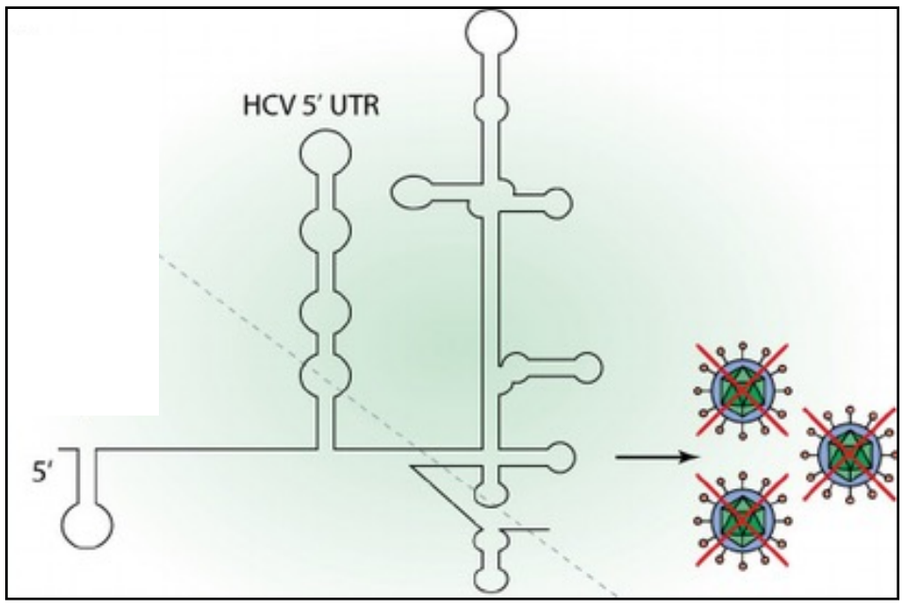
Two unique aspects of Hepatitis C virus at 5’ end of genome:

IRES -> Cap-independent translation

miRNA binding site provides stability to RNA

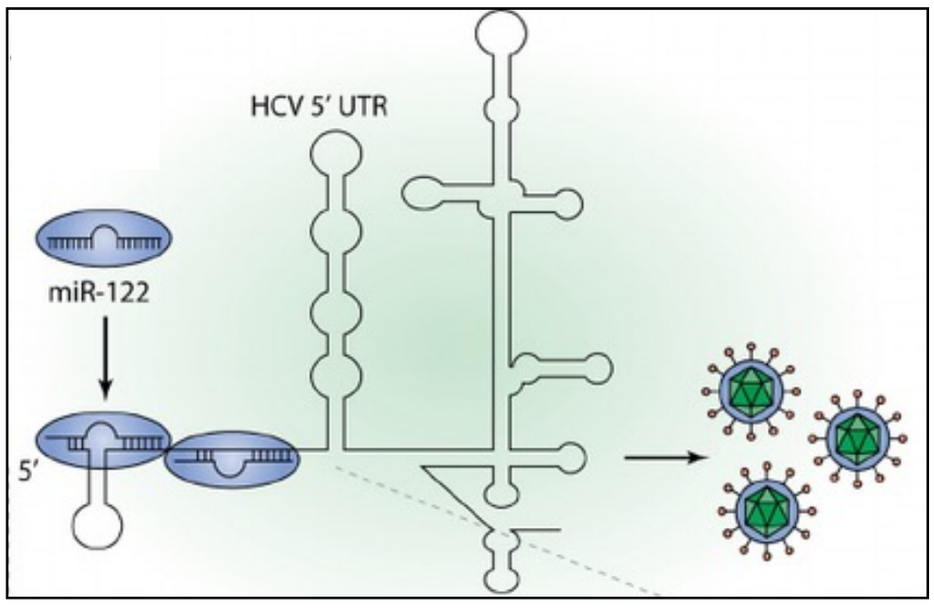
Most tissues

No miRNA 122, viral RNA unstable



Liver

miRNA 122 expressed, viral RNA stable



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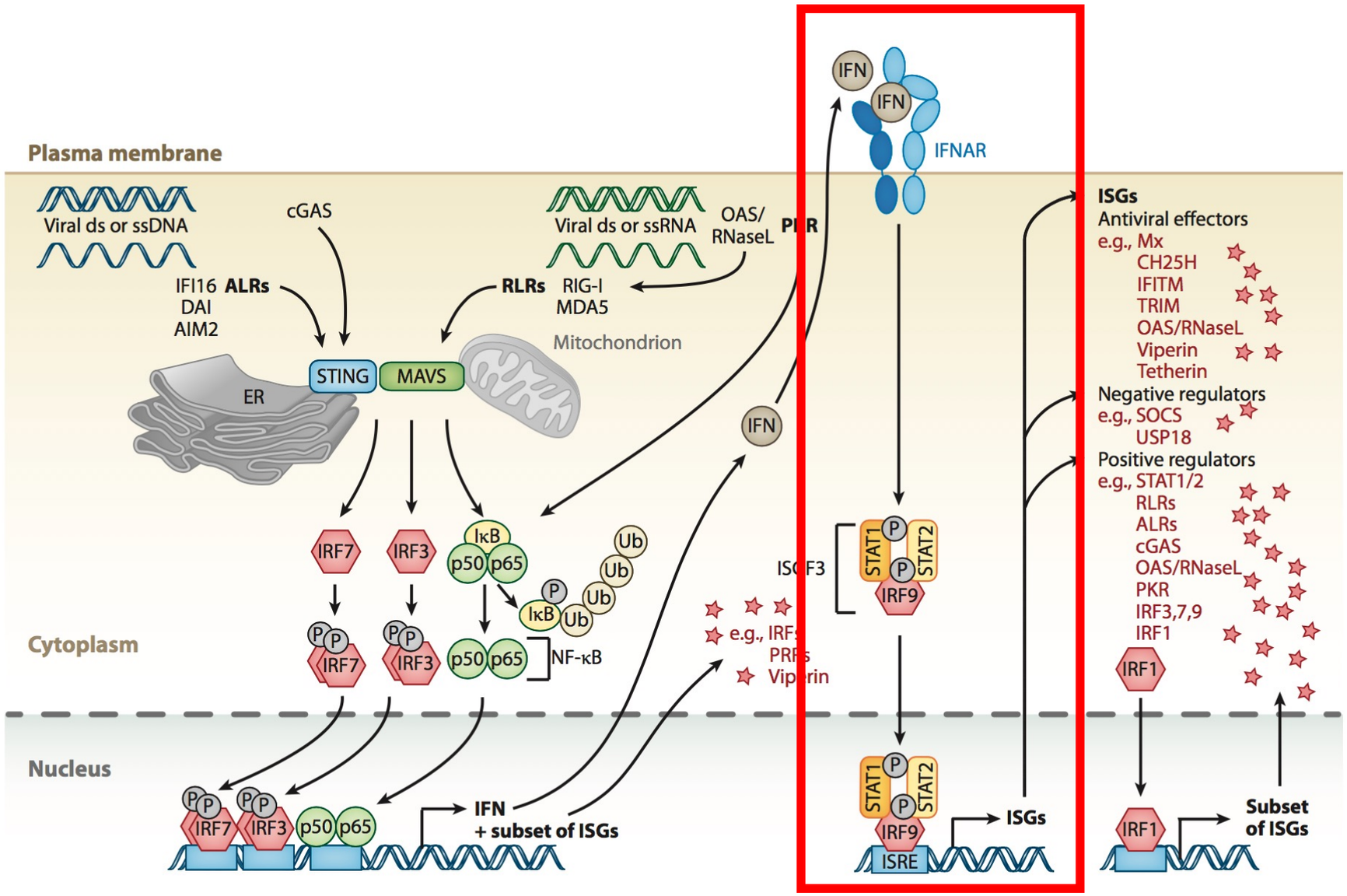
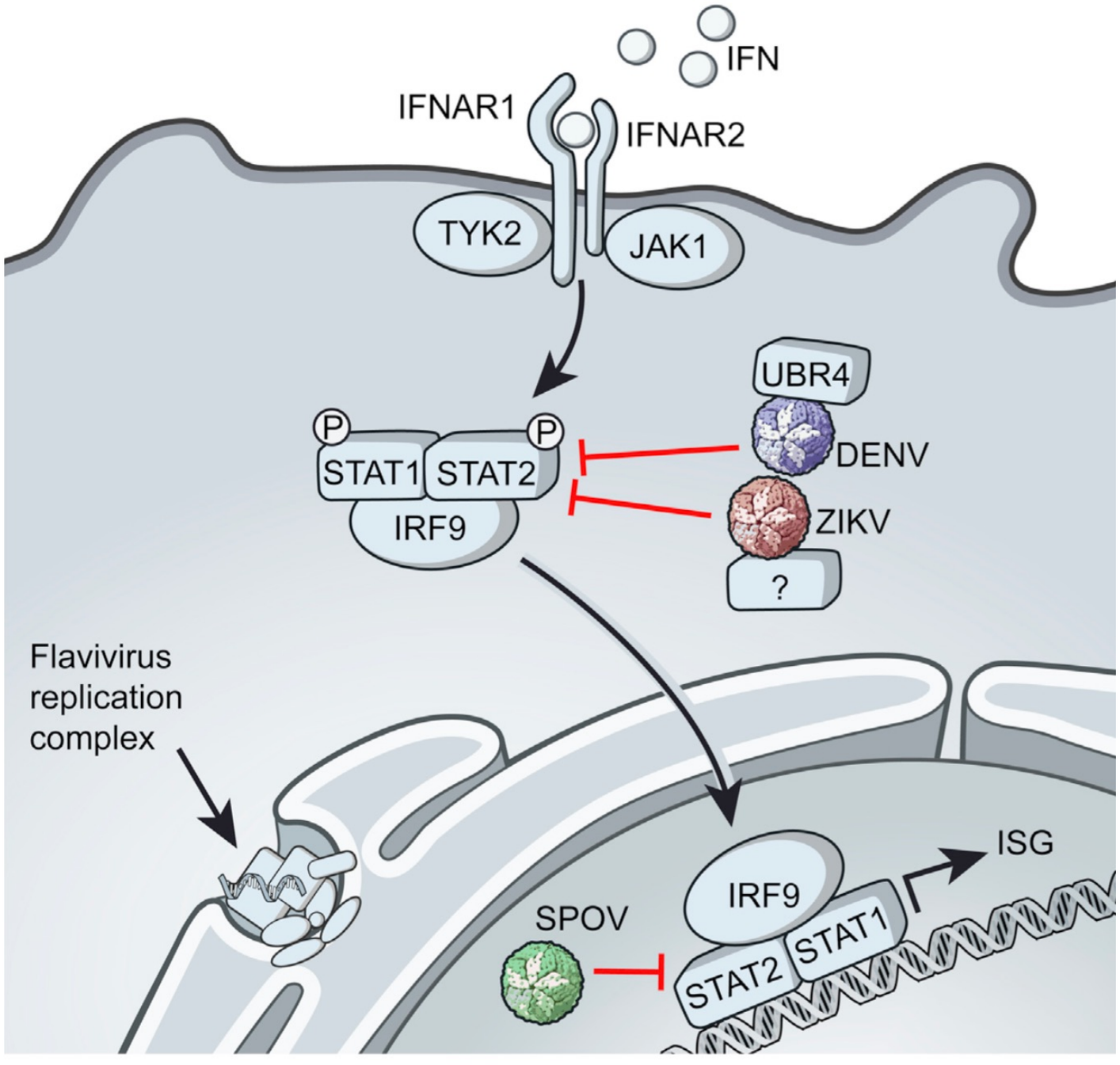
STAT proteins are critical for IFN response



Schneider, Ann Rev Immunol, 2014

STAT proteins are the primary transcription factors that mediate ISG induction

Flaviviruses target the STAT signaling pathway



Grant, Cell Host & Microbe, 2016

Dengue virus and Zika virus both target STAT2 for degradation

Cause degradation in mechanistically distinct ways: Convergent evolution?

Replacing mouse STAT2 with human STAT2 makes mouse a model for studying Zika

Questions?

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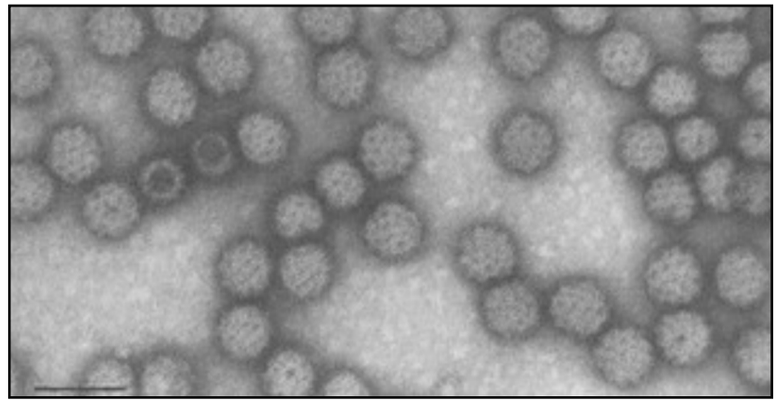
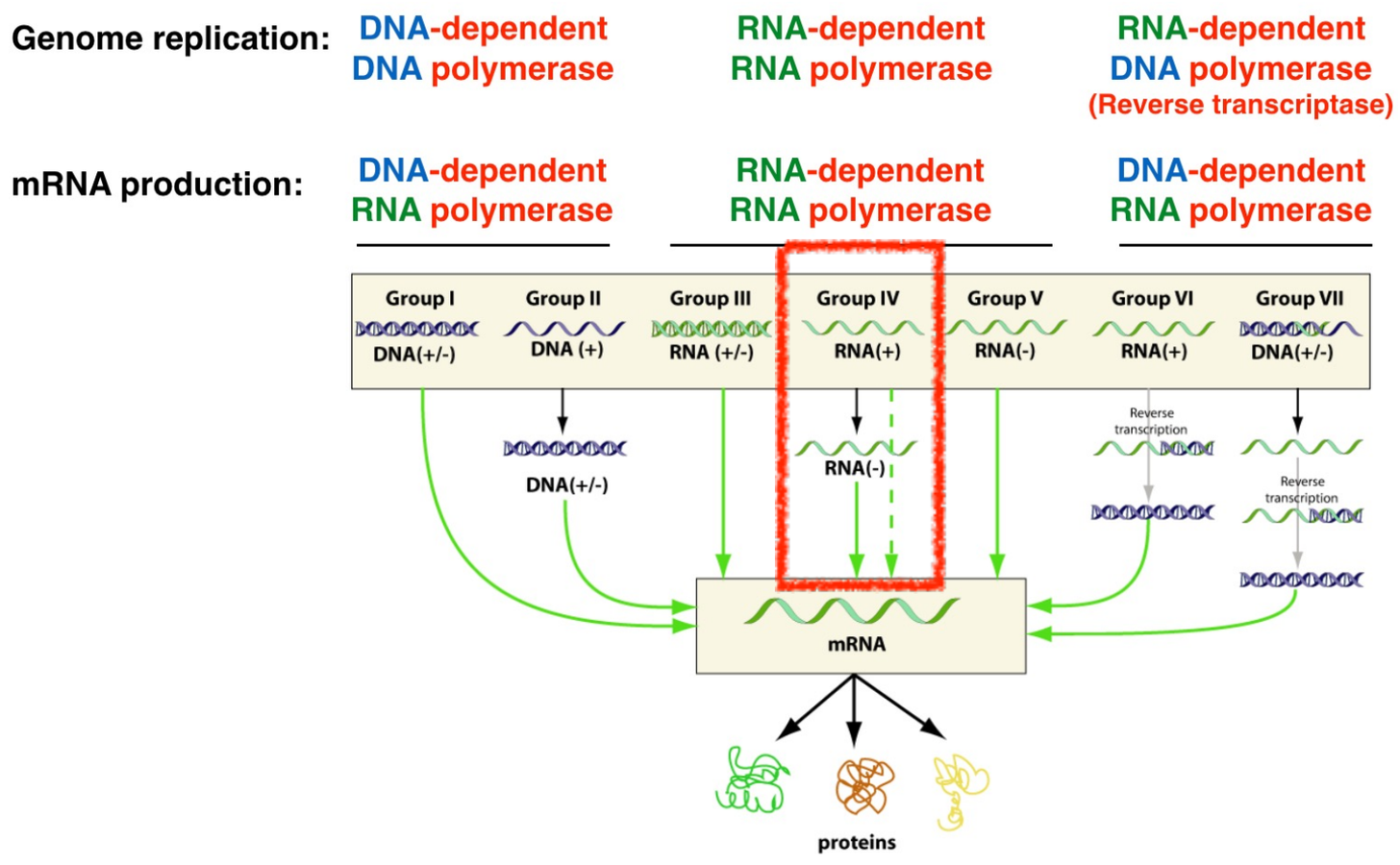


Veterinary Virology, 3rd edition

Toga - latin for "cloak" due to the viral envelope

Enveloped, +ssRNA



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Glasner, BIMM114, 2/6/24

Pathogens in the *Togaviridae* family

Alphaviruses

Arboviruses transmitted by *Aedes* and *Culex* mosquitoes

Chikungunya virus

Means ‘that which bends up’ for the severe joint pain and arthritic symptoms

In 2013, found in Americas transmitted by *Aedes* mosquitoes

The virus people worried about before Zika, Ebola and SARS-CoV-2 outbreaks

Equine encephalitis viruses

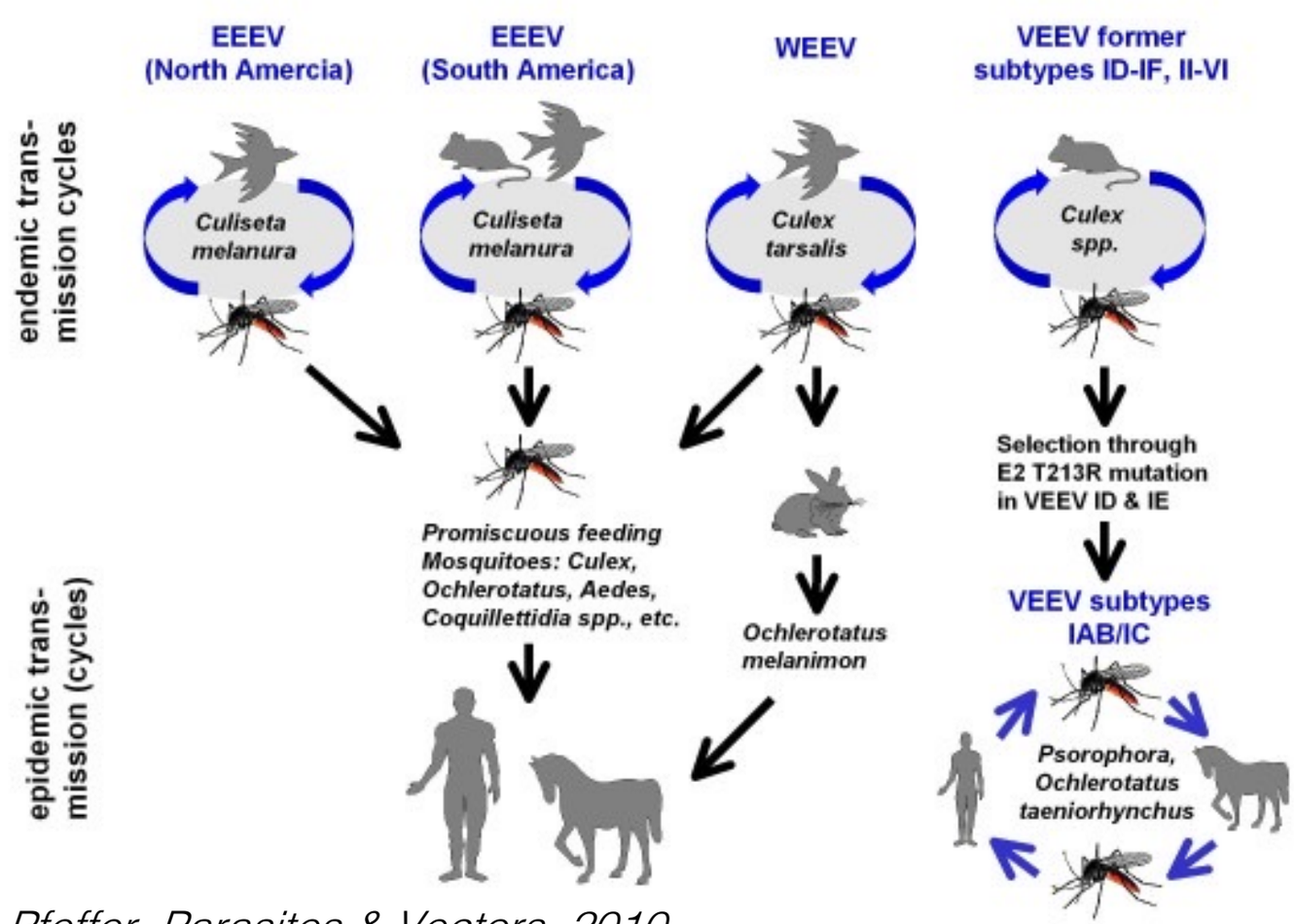
Most transmitted by *Culex* mosquitoes

Occasionally cause outbreaks in horses with fatalities in up to 90% of cases

Can spread to humans. Estimated fatalities up to 75%

In 2019, 38 cases, 15 deaths

Developed as a biological weapon by pre-1992 USSR and pre-1969 USA



Pfeffer, Parasites & Vectors, 2010

Pathogens in the *Togaviridae* family

Rubella (aka German measles) - genus Rubivirus

Mild infection, but can pass through placenta to fetus

Used to be a leading cause of birth defects

e.g. 1962-65 US epidemic 12.5 million infections, 20000 congenital abnormalities

TORCH pathogens

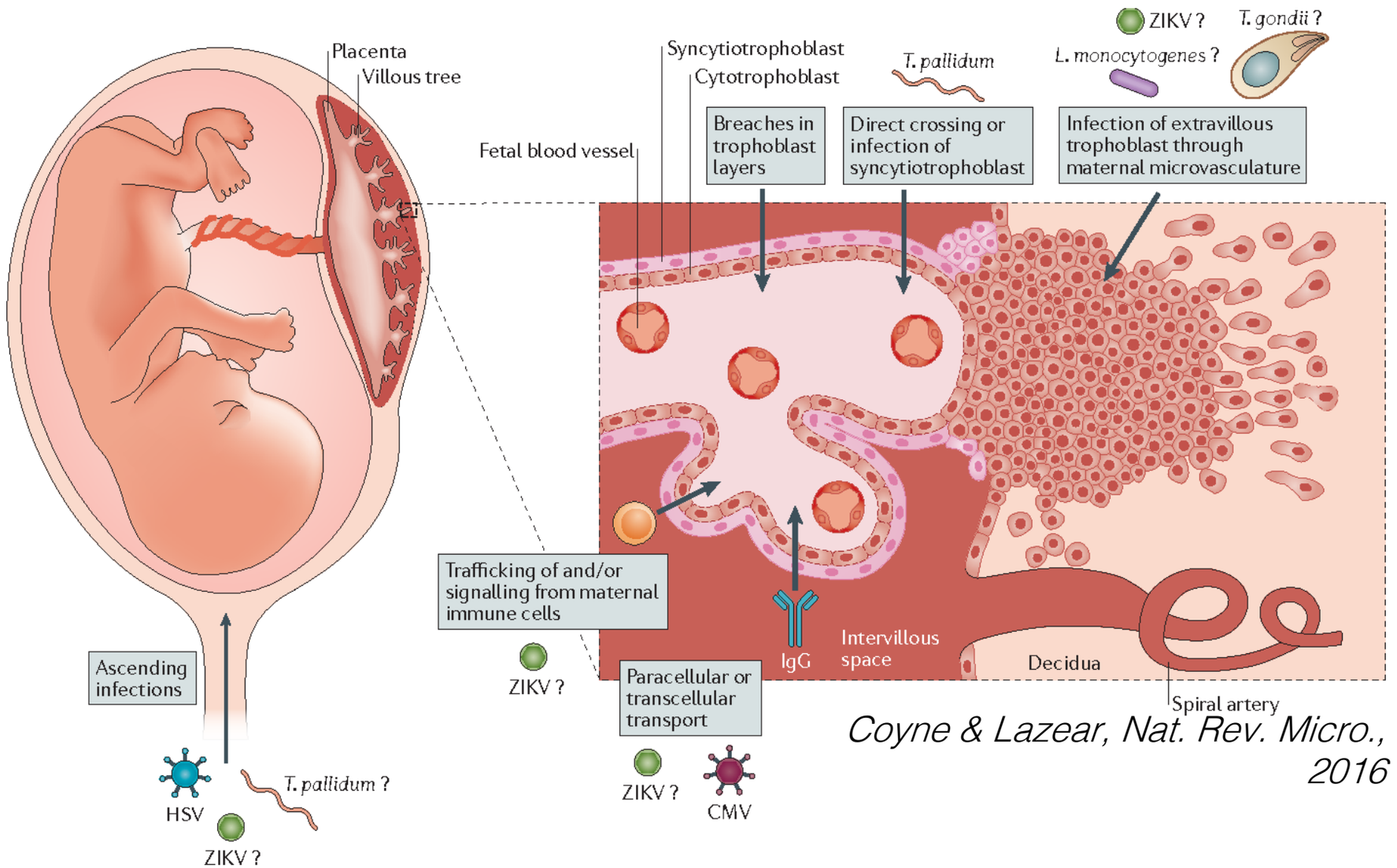
Toxoplasma

Other (syphilis, Zika virus, parvovirus)

Rubella

Cytomegalovirus (CMV)

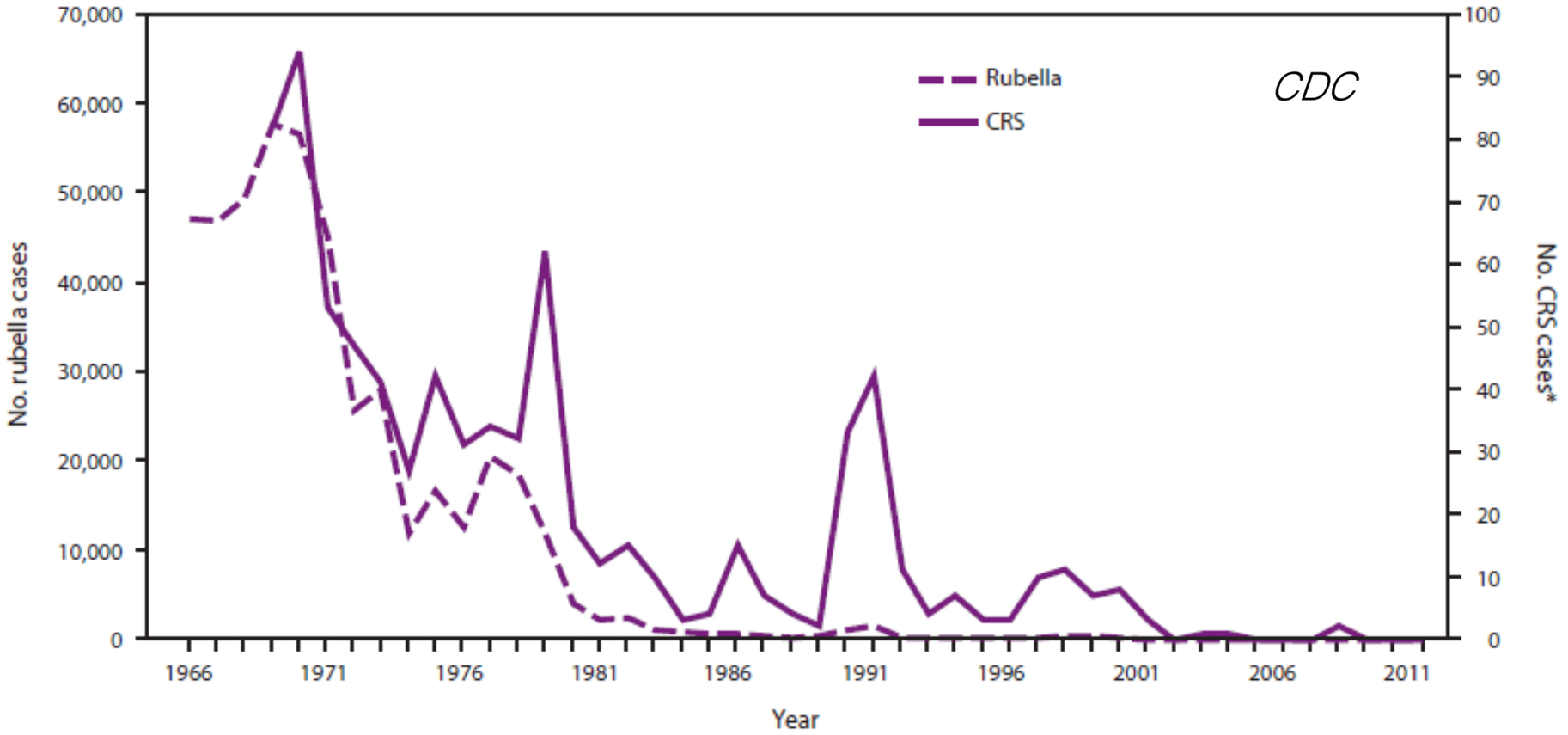
Herpes



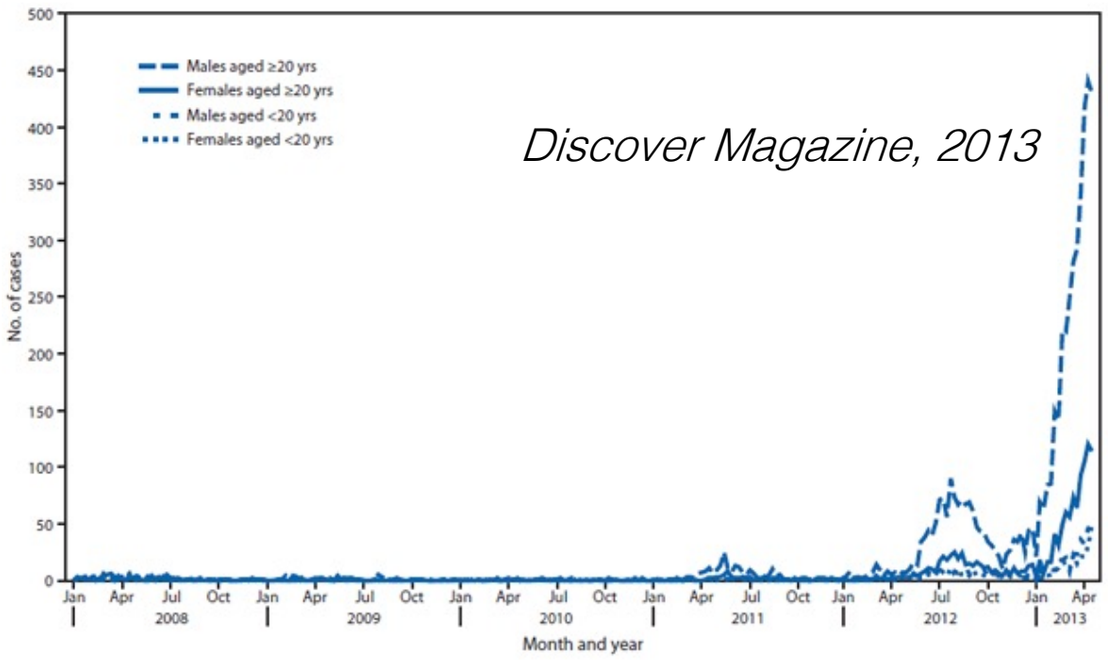
Coyne & Lazear, Nat. Rev. Micro., 2016

Pathogens in the *Togaviridae* family

Part of MMR (measles, mumps, rubella) vaccine - virus considered eradicated in US



Why can we hope to eradicate rubella virus?



Still ~100,000 infants both with congenital abnormalities globally

Several outbreaks in Japan since 2000 due to lack of vaccination in men

Outline for today's lecture

Key concepts in this lecture:

Flaviviridae:

Most human pathogens in the *Flaviviridae* family are arboviruses

Diseases caused by members of the *Flaviviridae* family

Hepatitis C

Dengue fever, dengue hemorrhagic fever and dengue shock syndrome

Viral life cycle: Enveloped, +ssRNA

Replication on the endoplasmic reticulum membrane

Dengue and Zika virus and STAT antagonism

Togaviridae:

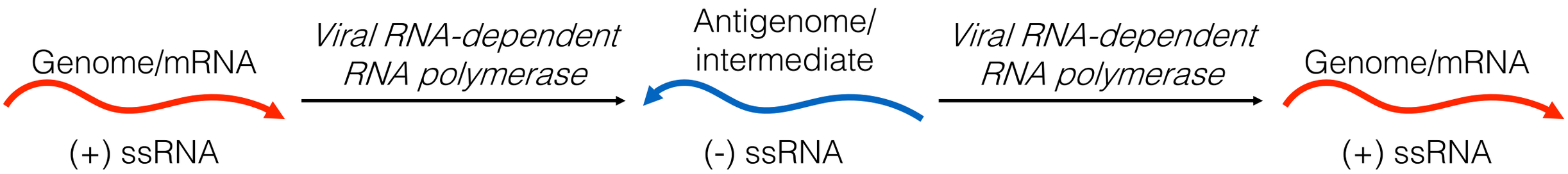
Human pathogens in the *Togaviridae* family

Alphaviruses are arboviruses that have zoonotic and epidemic potential

Rubella, congenital rubella syndrome, and TORCH pathogens

Viral life cycle including production of subgenomic RNAs

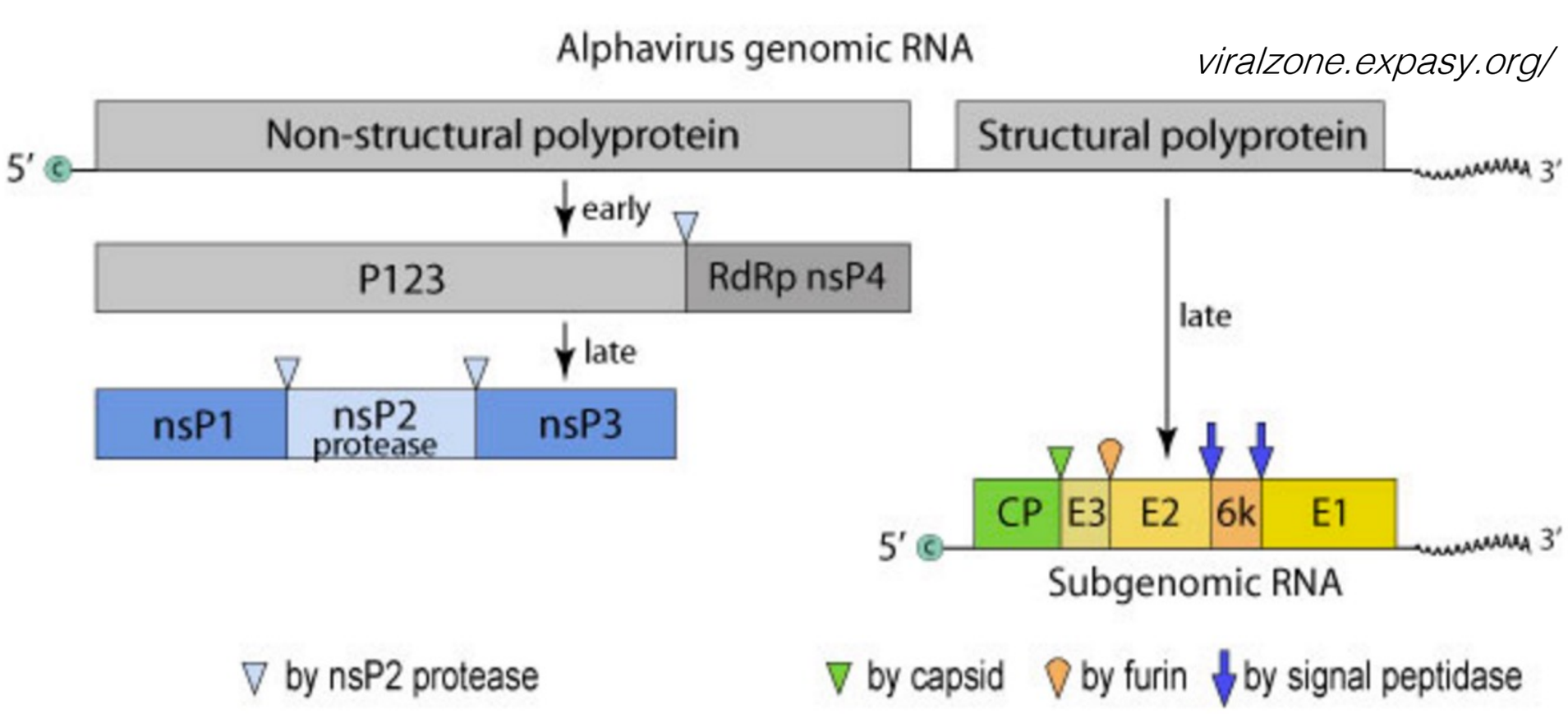
Togaviridae life cycle



Made as polyprotein

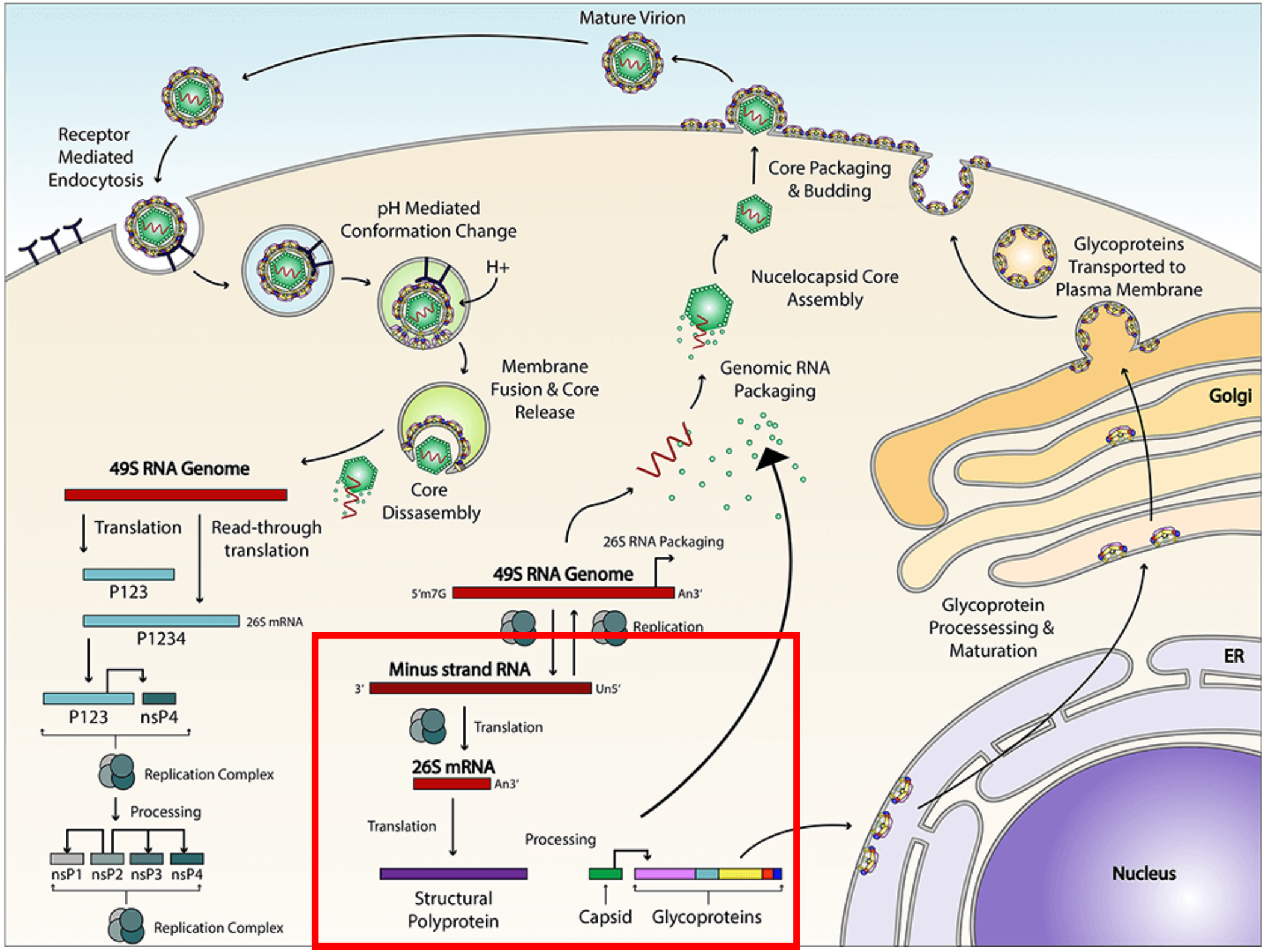
Cleaved by viral and host proteases

One major difference: more than one mRNA made



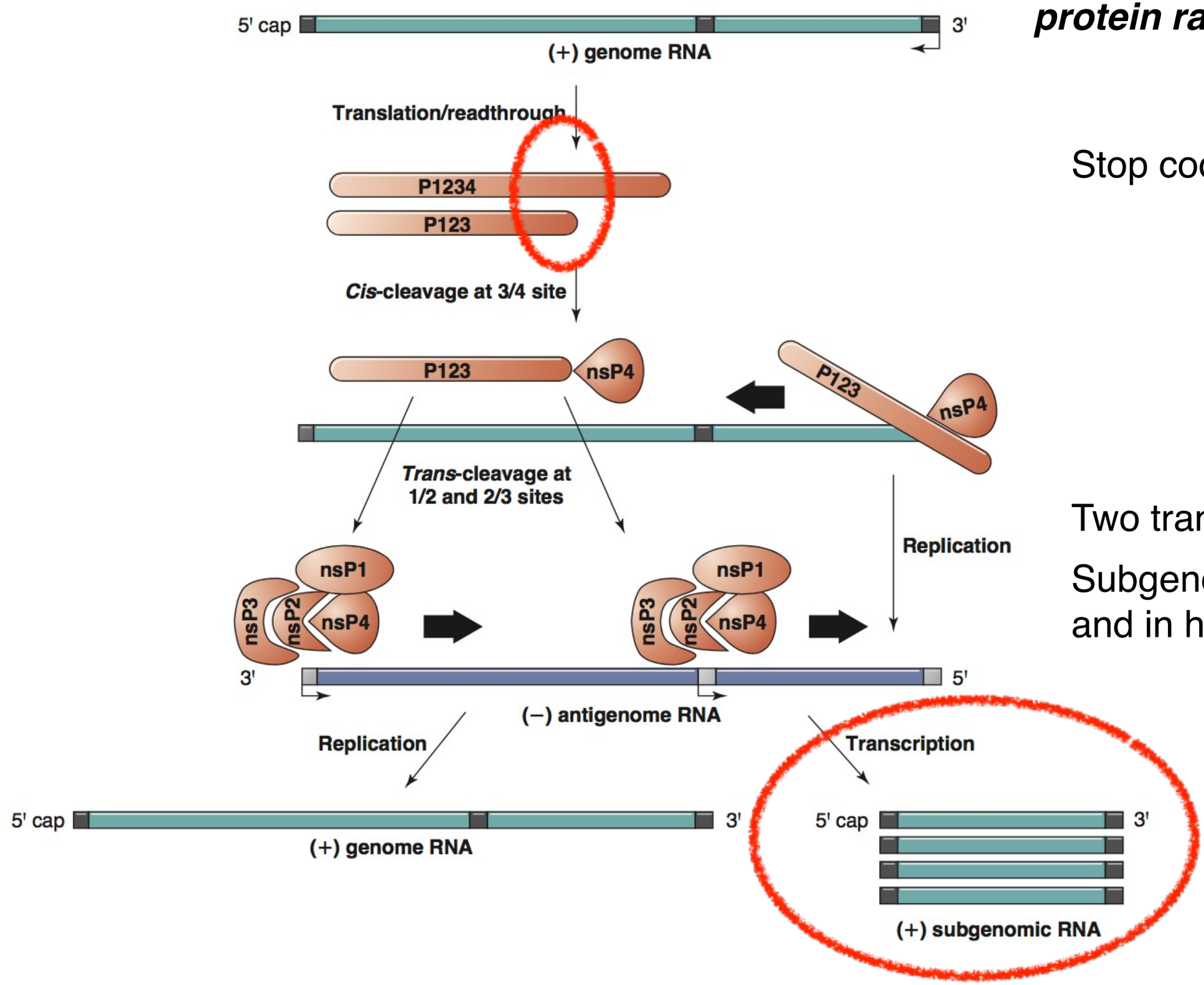
Glasner, BIMM114, 2/6/24

Togaviridae life cycle



https://www.bio.purdue.edu/lab/kuhn

Production of subgenomic RNAs



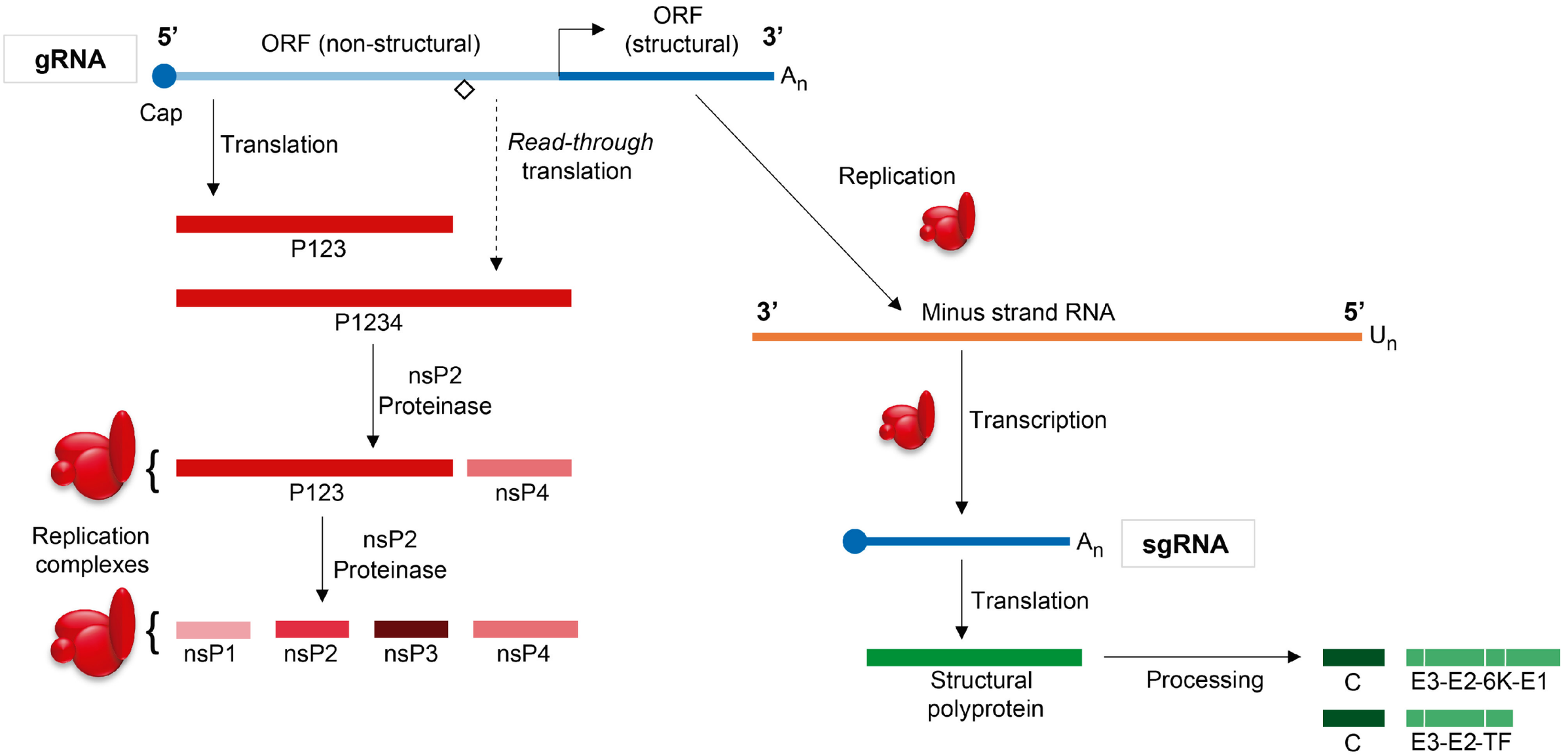
Ways to regulate timing and protein ratios:

Stop codon readthrough

Two transcripts:

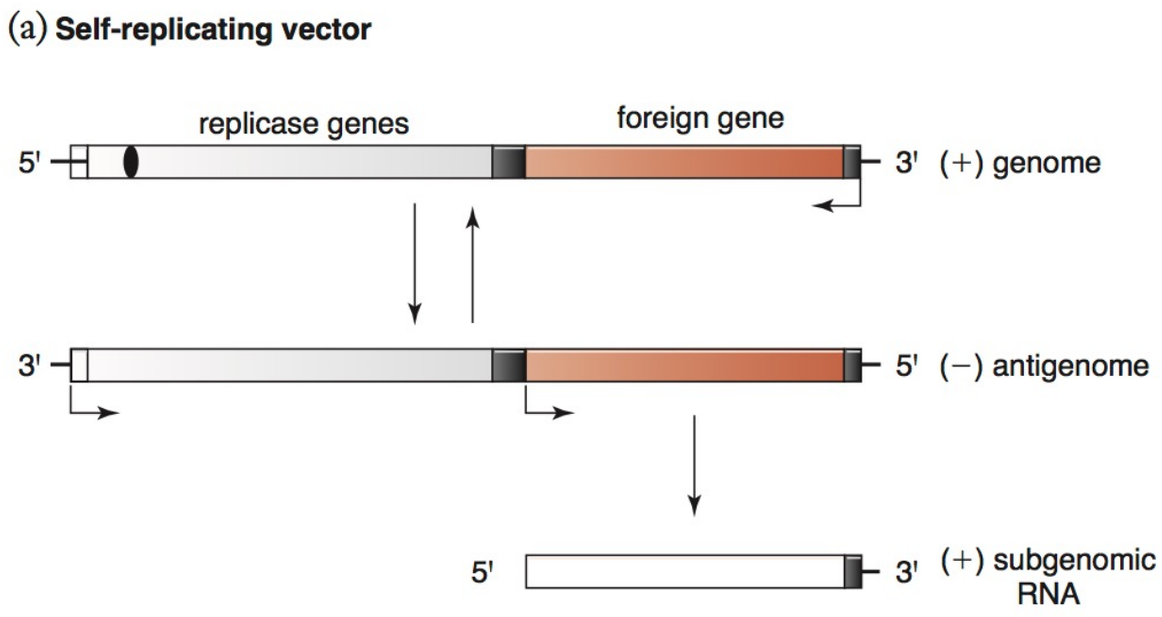
Subgenomic RNAs made later and in higher abundance

Production of subgenomic RNAs



- Stop codon read-through leads to expression of different polypeptides and, later, replication complexes
- Different complexes preferentially transcribe genomic RNA, subgenomic RNA, and/or minus strand RNA
- Orchestrated via several factors including transcript and protein abundance and replication complex stability

Use as viral vectors and vaccines



This life cycle makes it easy to engineer alphaviruses

Can introduce additional subgenomic mRNAs

Can take advantage of natural recombination that has shuffled non-structural and structural genes

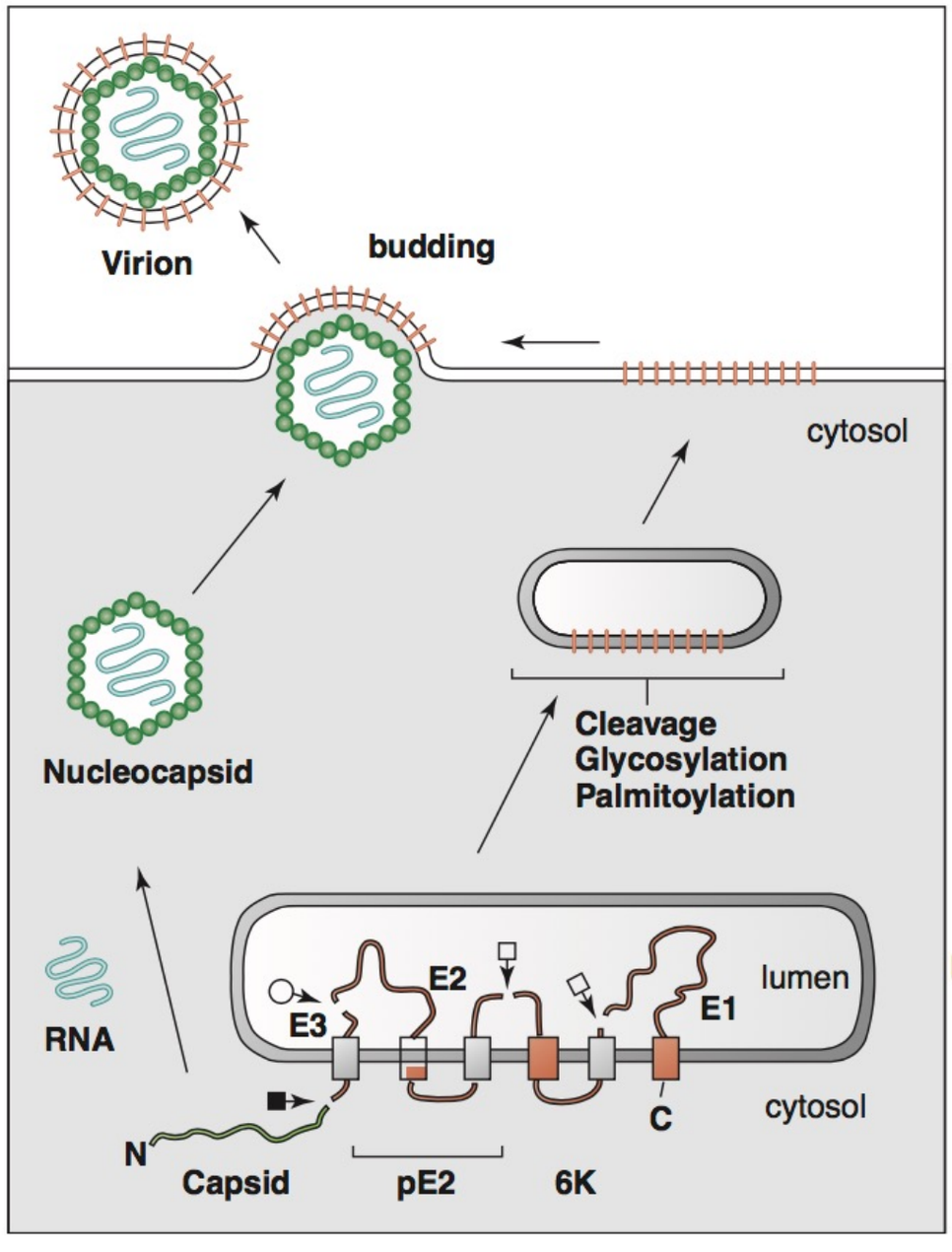
Can take advantage of recent discovery of an insect specific virus (no pathogenesis in humans)

Enveloped viruses that bud from cells

Enveloped, icosahedral virion

Replicate on cellular membranes

Escape cell by budding from cell membrane



Questions?