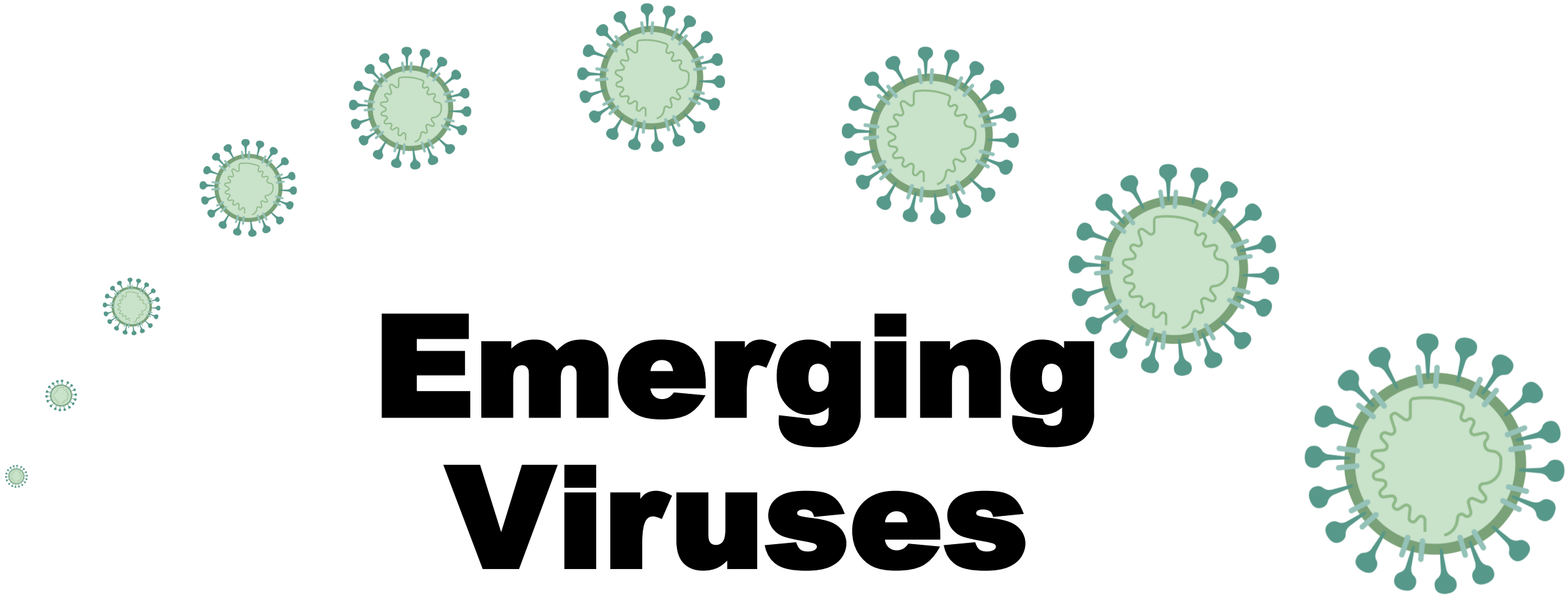


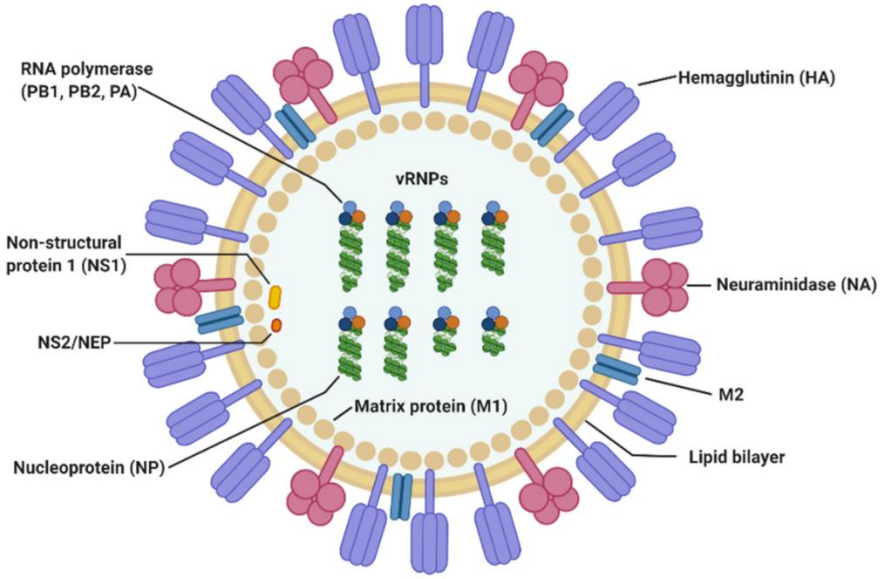
Emerging Viruses

Not Just SciFi Anymore

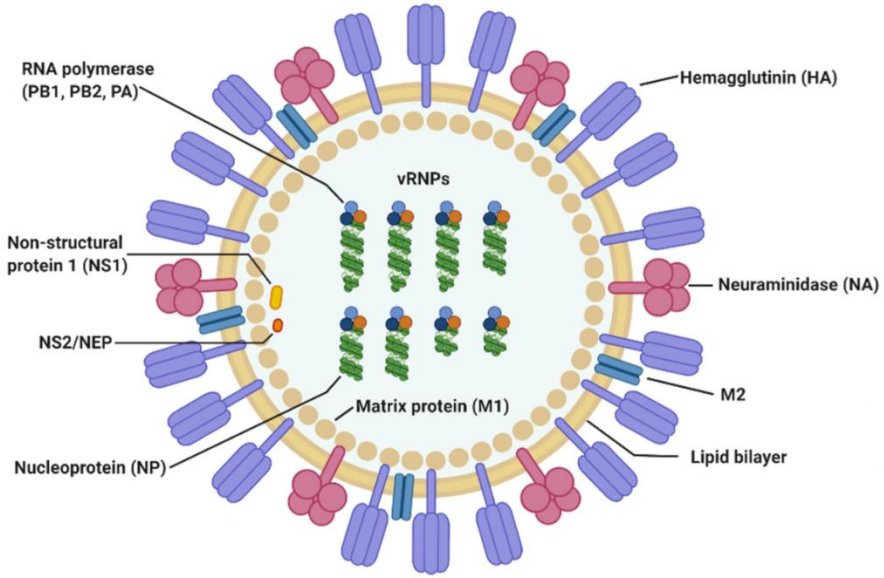
Viruses

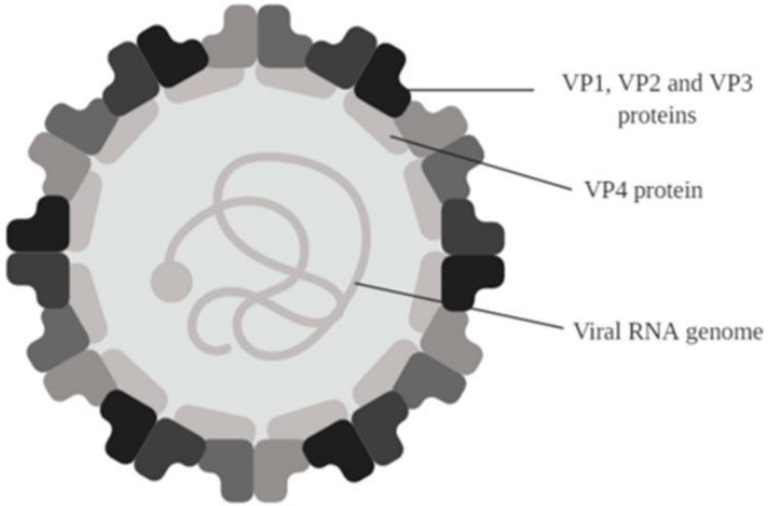
- Obligate Intracellular Pathogen
  - Nucleic Acid genome
    - RNA
    - DNA
    - Both
  - Protein structure
    - Can be enclosed in lipid envelope or protein only
  - Rely on cellular machinery
    - Synthesis of viral genomes/protein
    - Protein translation
    - Assembly
    - Transport
- Wide range of lifestyles
  - Acute
  - Chronic
  - Vector borne
  - Transmission routes

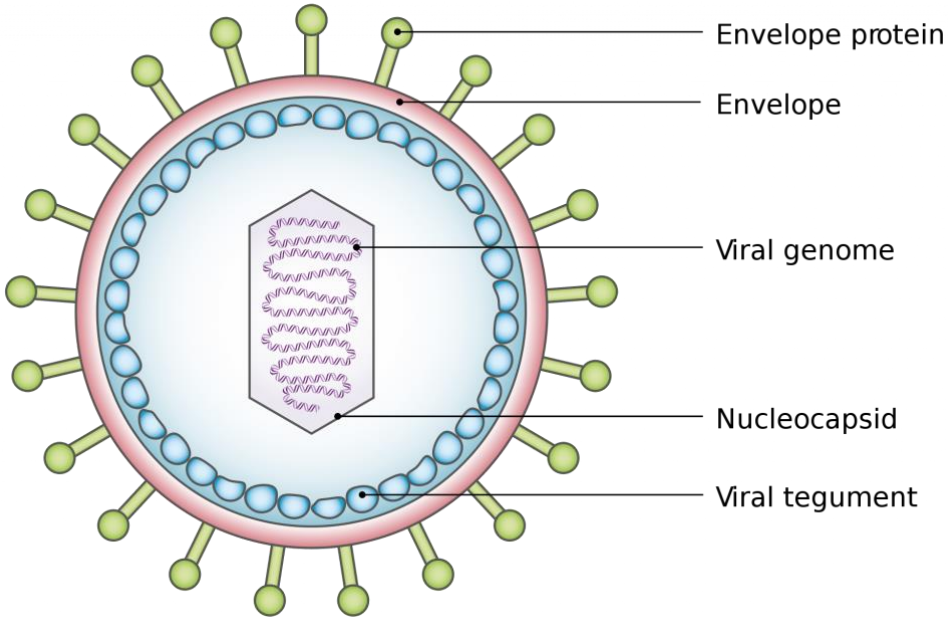
- Significant Causes of human disease



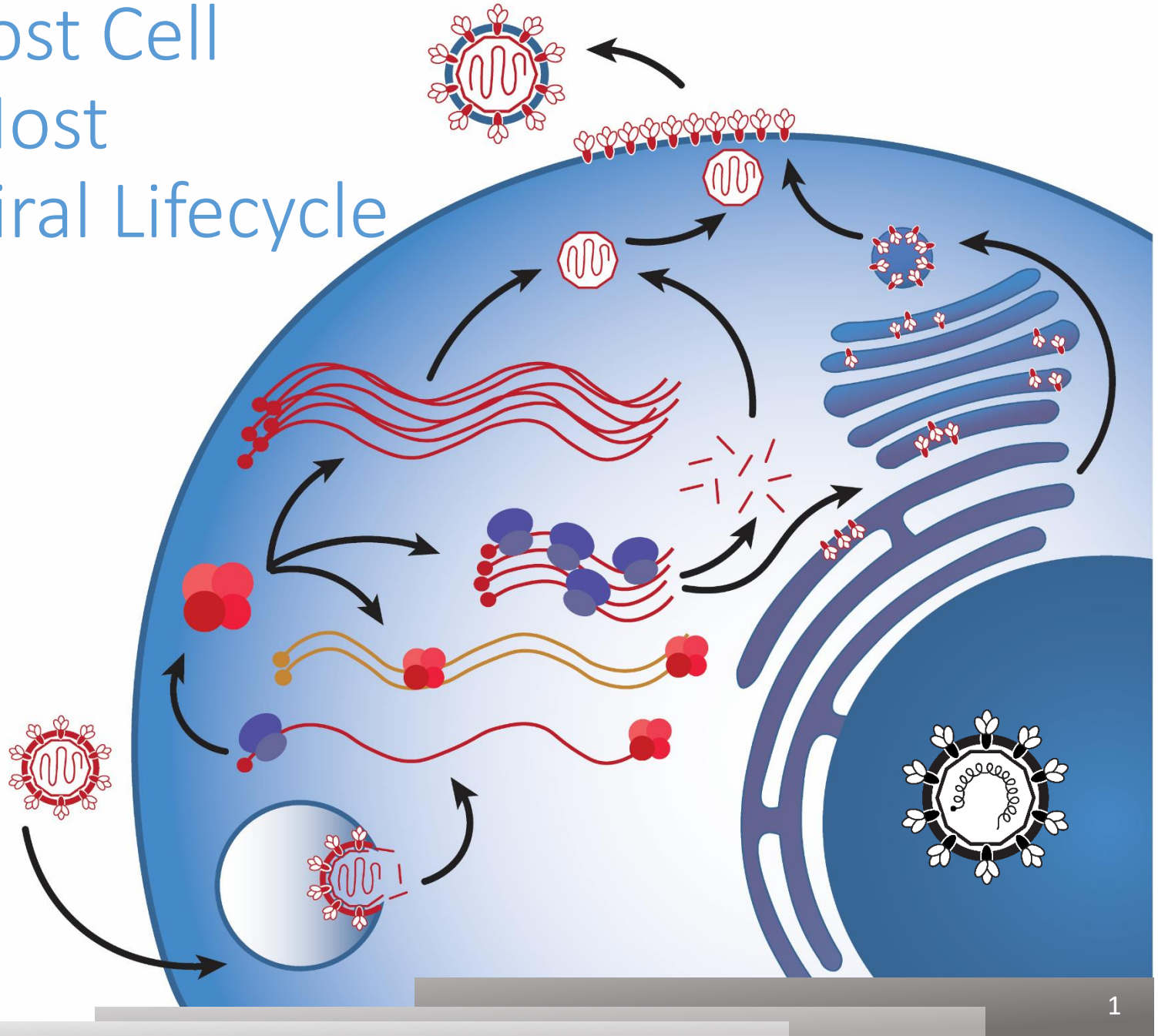
Viruses Come in a Variety of Shapes, Sizes, and Compositions



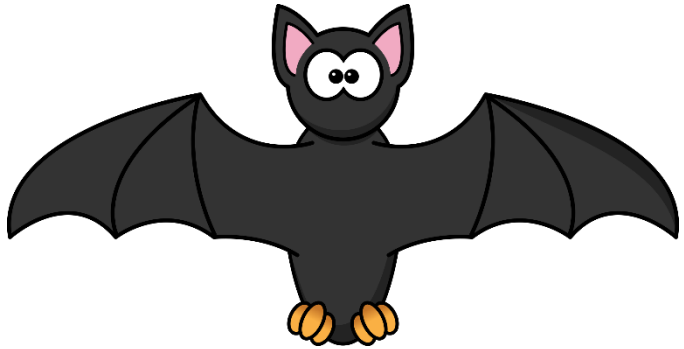


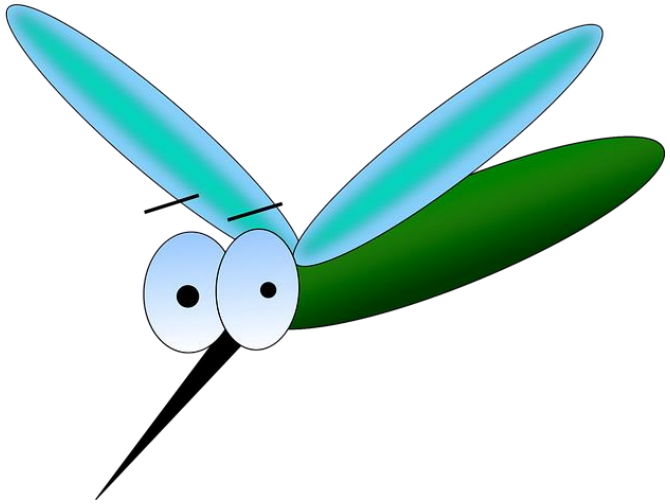


Viruses Hijack Host Cell Machinery for Most Aspects of the Viral Lifecycle



Viruses Have a Wide Variety of Life Cycles/Modes of Transmission



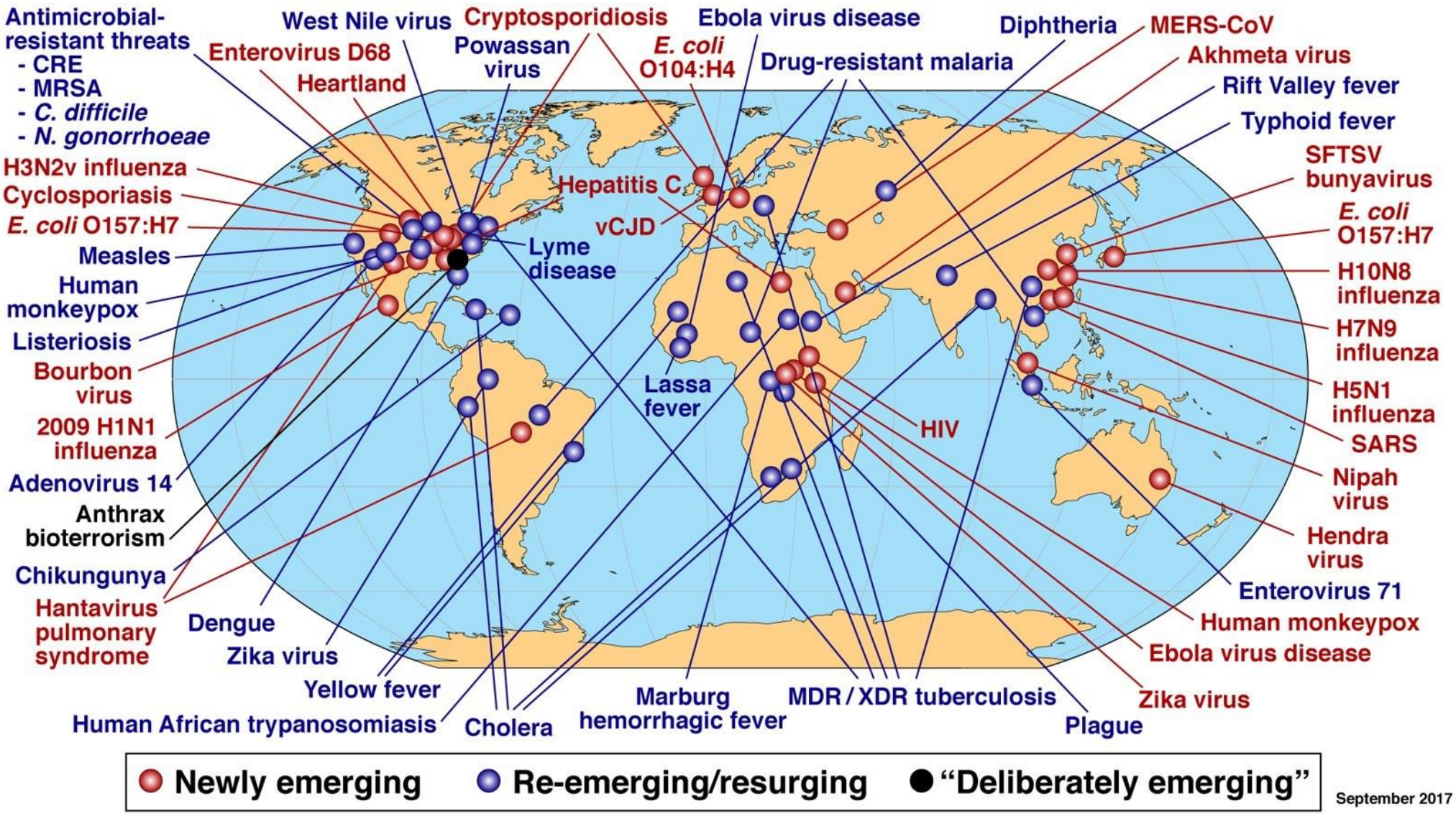


Oh So Many Emerging Viruses…

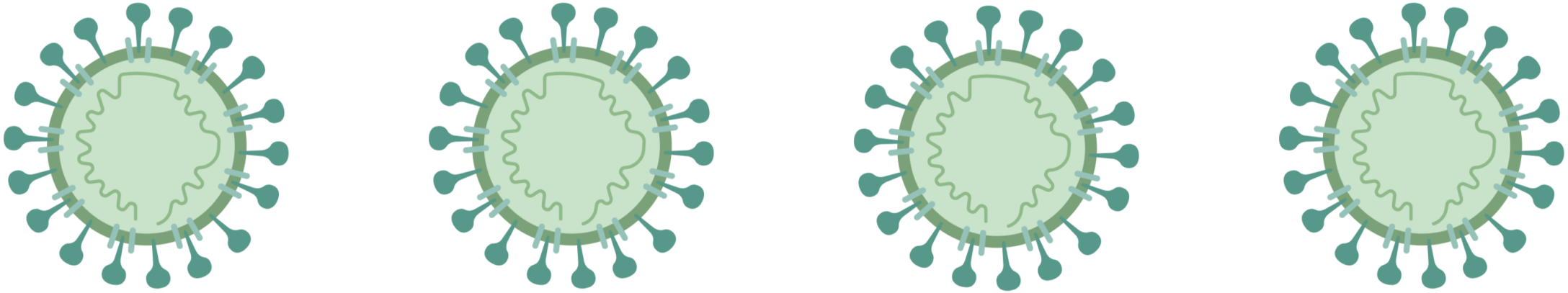
- **Major Outbreaks**
  - HIV
  - West Nile virus
  - SARS-CoV1
  - 2009 H1N1 Influenza
  - Chikungunya virus
  - MERS-CoV
  - Ebola virus
  - Zika Virus
  - **SARS-CoV2**
- **Ongoing Threats**
  - Nipah/Hedra
  - Rift Valley Fever virus
  - Hanta virus
  - Influenza virus

Global Examples of Emerging and Re-Emerging Infectious Diseases

NIAID



Why are Emerging Viruses a Problem?



- Naïve populations are highly susceptible to disease
  - High Mortality
  - High Morbidity
- Disruption of Health Care Systems (overwhelmed)
- Potential for massive economic disruption

Why do we need to study emerging viruses?

- **Recognize Threats and Prevent Emergence**
  - Which viruses are likely to emerge?
  - How can we decrease chances of emergence/spread?
- **Develop Therapies**
  - Understand virus biology to develop antiviral therapies
    - Which steps in the viral lifecycle should be targeted?
    - Are there host factors that the virus needs and can they be drug targets?
  - Understand disease pathogenesis to develop therapies
    - How does the virus cause disease?
      - Direct viral effects
      - Host response causes disease
- **Develop Safe and Effective Vaccines**

Where to they come from?

Ebola

Ebola

SARS-CoV2

Nipah/Hedra

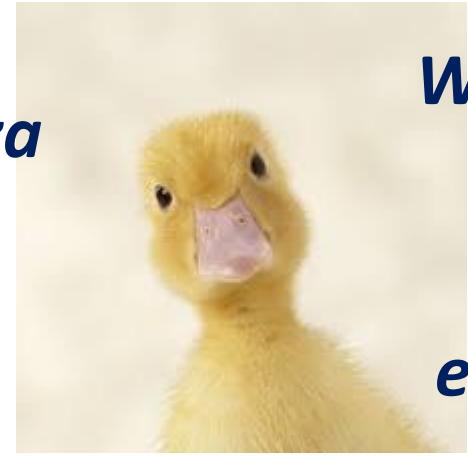
MERS-CoV

HIV

Yellow Fever virus

Chikungunya virus

Zika Virus



Influenza

West Nile virus

Eastern equine encephalitis virus

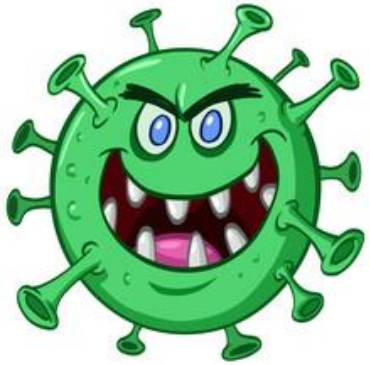
What Do Viruses Need to do to Emerge?

Essential Steps for Emergence

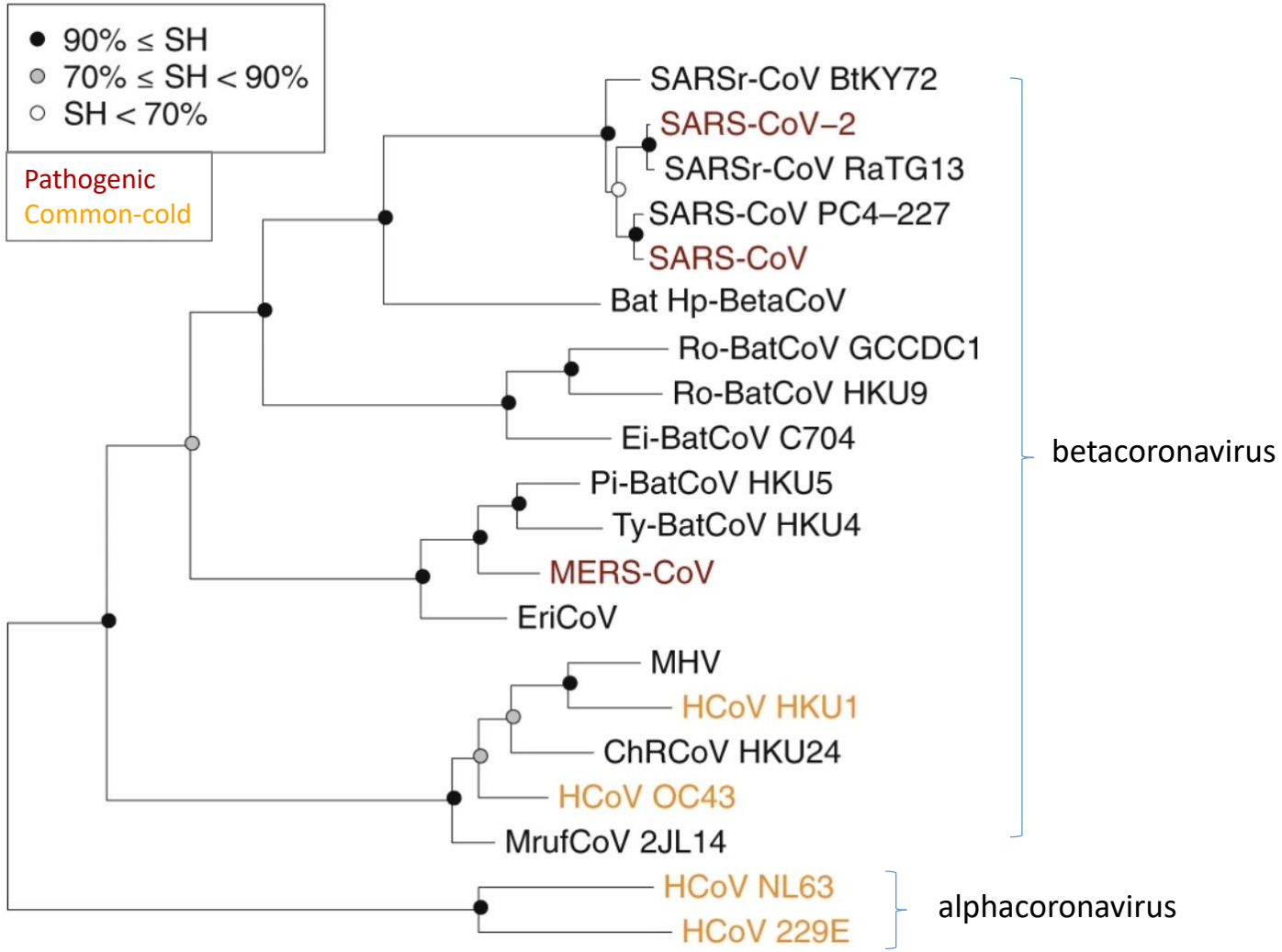
- Come in contact with humans
  - Animal interactions with humans
    - Direct/Indirect
  - Naïve populations (no immunity)
- Establish Infection
  - Functional Receptor Interactions
  - Compatible Cellular Co-Factors
  - Immune Evasion
- Transmit
  - Virus replicates to high enough levels to transmit
  - Accessible tissues
    - Lung/Airway
    - Enteric tract
    - Sexual transmission
    - Blood (vector borne or blood borne)

Things that Make it Worse

- Transmissible During Asymptomatic Phase
- Long transmissible phase
- Aerosol transmission

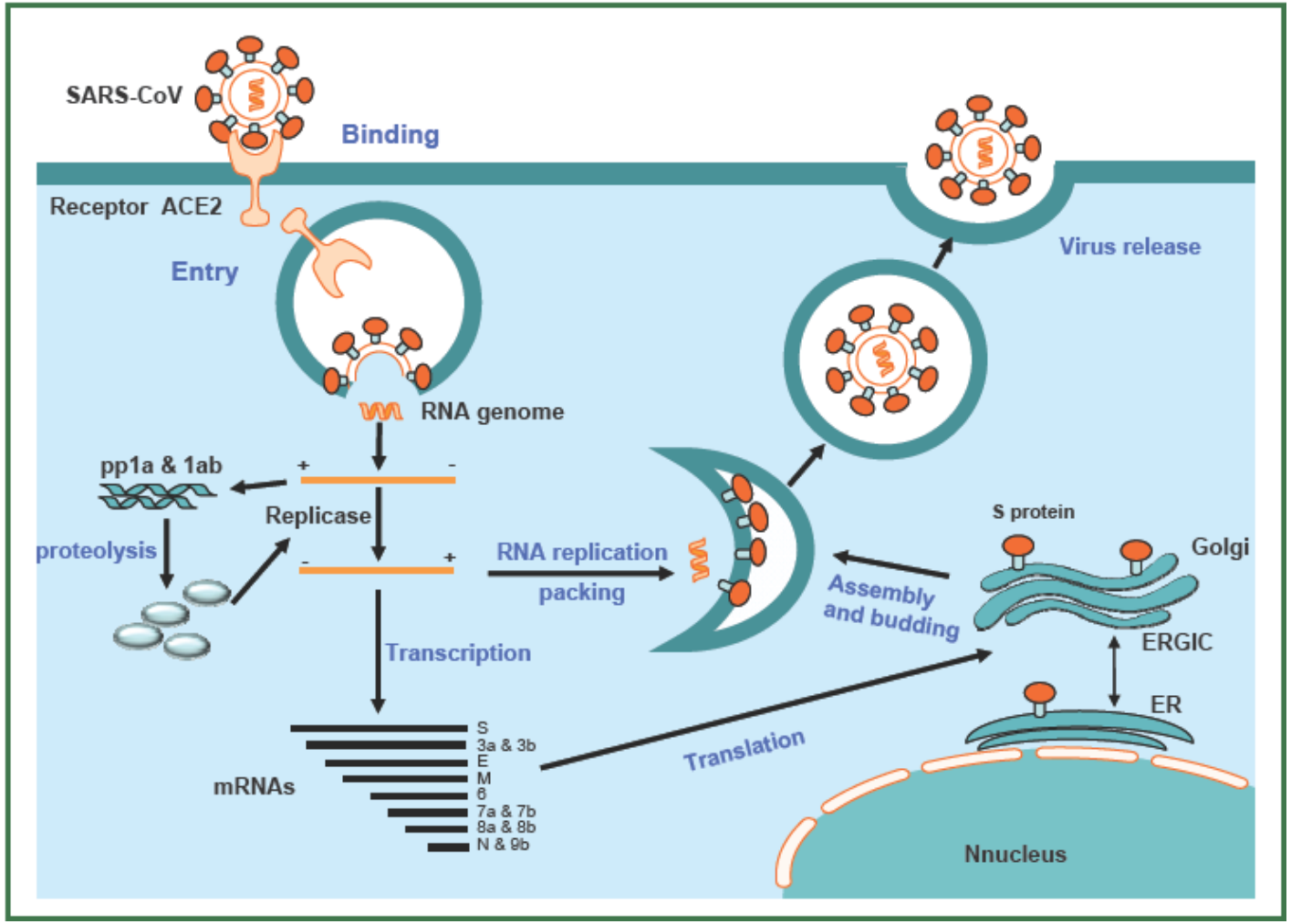


Coronaviridae



Adapted from the *International Committee on the Taxonomy of Viruses*

SARS-CoV replication



Zhu et al. 2013

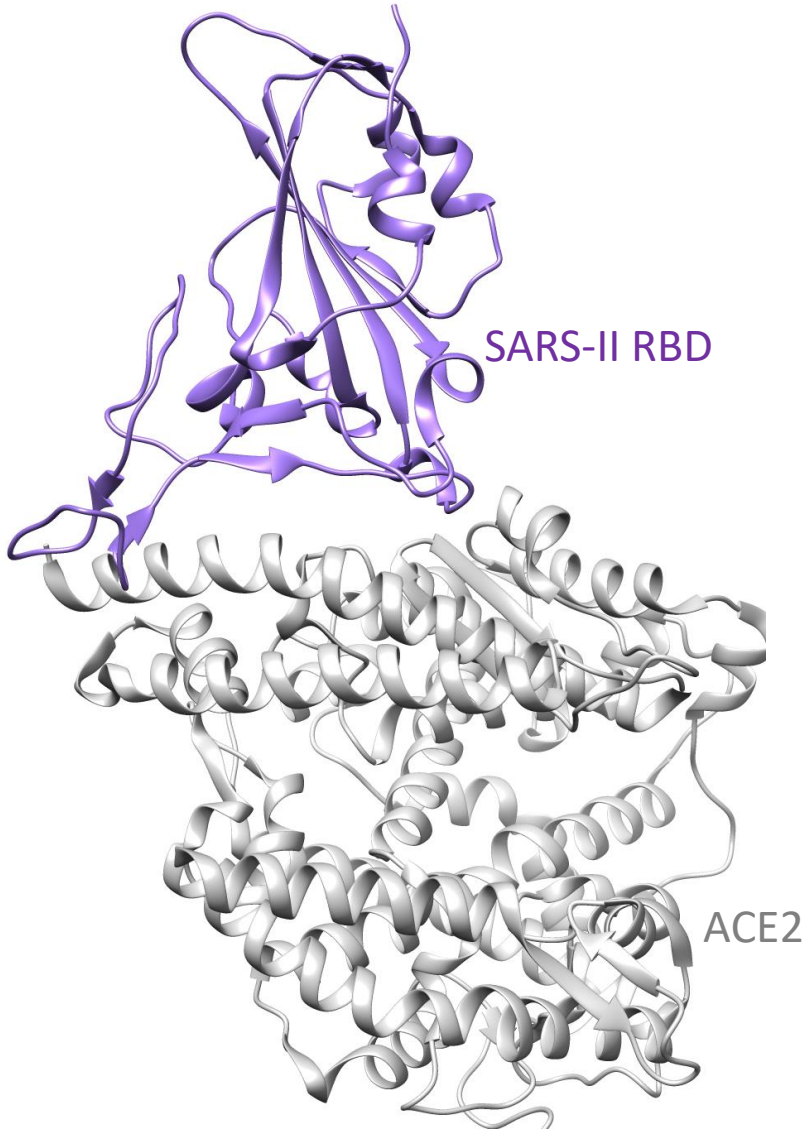
ACE2 = angiotensin converting enzyme 2

- Catalyzes hydrolysis of angiotensin 2
  - Vasoconstrictor → vasodilator
  - Lowers blood pressure
- Found on human lung, artery, heart, kidney, intestinal cells
- Binds to CoV Spike, allows for cleavage by host protease TMPRSS2

Lily Adams, unpublished

SARS-CoV-II utilizes ACE2 for cell entry

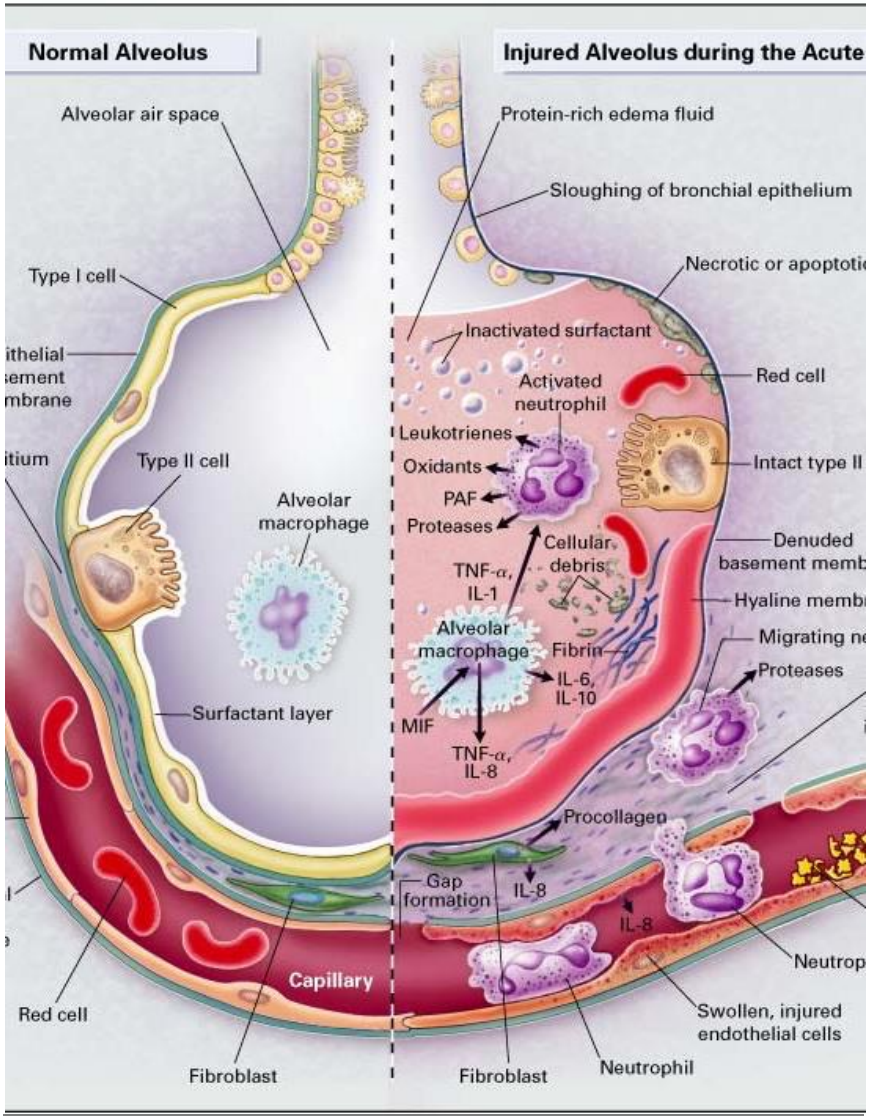
- Decades of SARS structural studies
- Drew inferences about the interactions between SARS-II and ACE2 early in the outbreak



Adapted from Shang et al. 2020, Wan et al. 2020

SARS-CoV-II

- Infects ciliated bronchial epithelial cells and type II pneumocytes
  - Facilitate gas exchange through surfactant production
- Infection causes ARDS
  - Severe inflammation
  - Fluid leakage into lungs
  - Recovery often requires intubation and supplemental oxygen



Ware et al. 2000

SARS1 vs SARS2

SARS-CoV1

- High Mortality
- Virus underwent adaptation over the course of the outbreak
- Poorly transmissible
  - With rare exceptions, only transmissible after persons become symptomatic
  - Most people don’t transmit

SARS-CoV2

- Low, but still significant mortality
- Virus efficiently uses human ACE2
- Moderately transmissible
- Asymptomatic individuals can transmit

What’s Next?

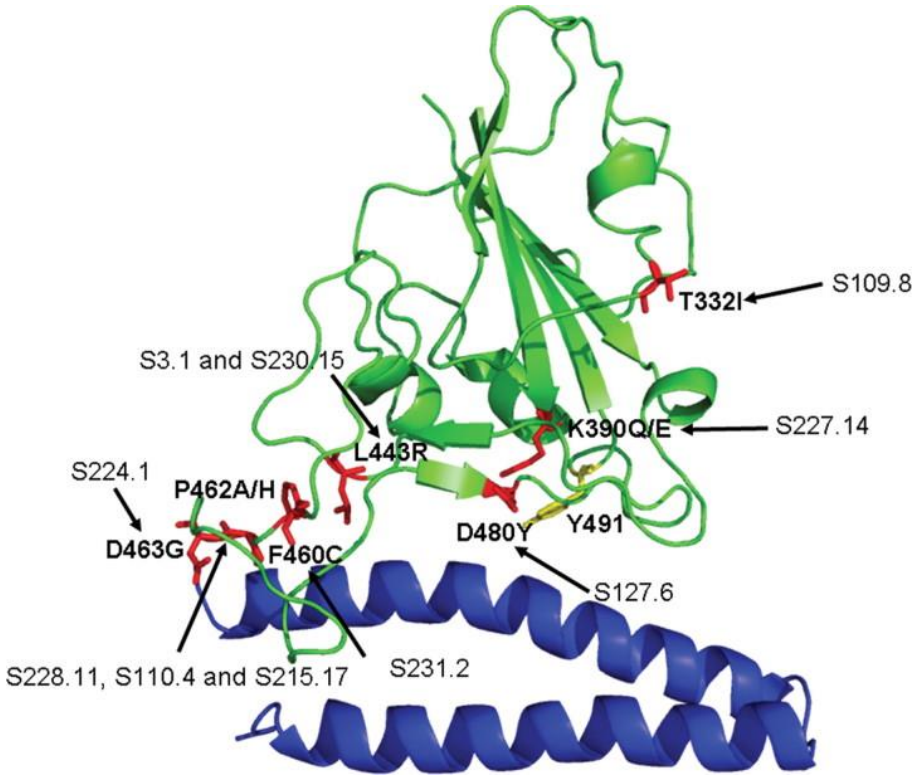
Will the virus...?

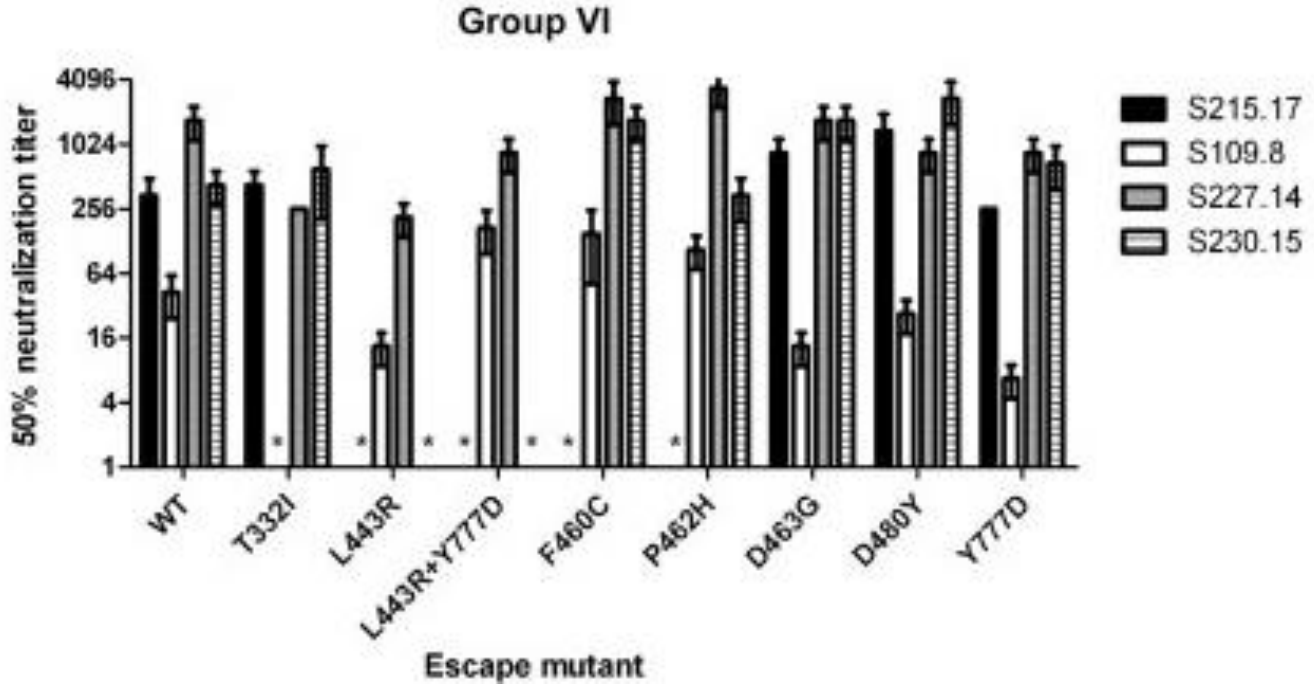
- Mutate to become less virulent?
  - **Maybe??**
- Adapt to evade host immune responses?
  - **Likely**
    - **B.1.351 (South Africa) and P.1 (Brazil)**
- Become more transmissible
  - **Yup! B.1.1.7 (UK); B.1.351 (South Africa); P.1 (Brazil)**
- Go away?
  - **Unlikely**
- Become a seasonal threat, or even a cold virus?
  - **Possible**

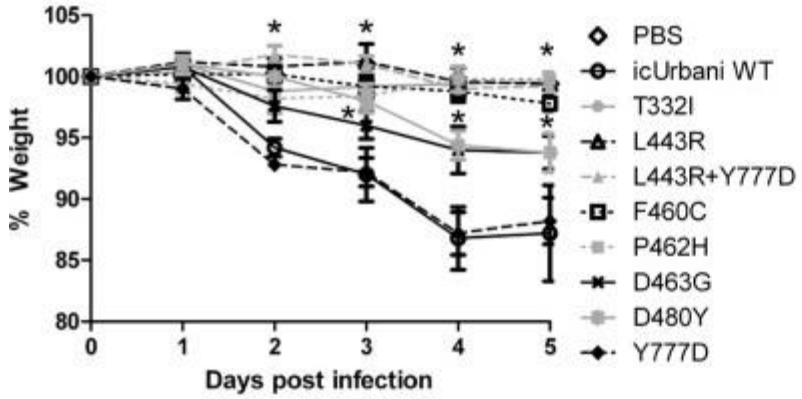
Will SARS-CoV2 Become Less Virulent? Maybe…

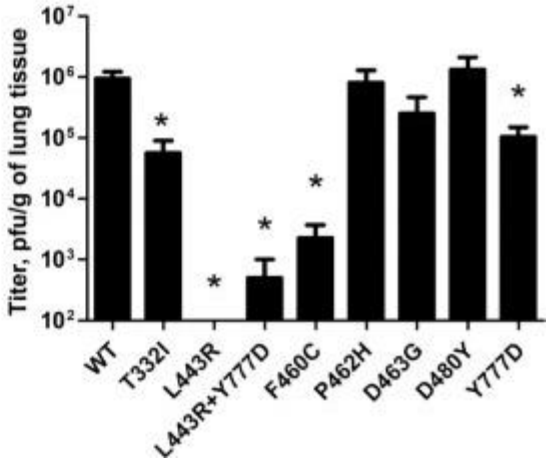
- Highly virulent pathogens may evolve to become less virulent.
  - If viruses are too virulent, they may kill the host too quickly and transmit inefficiently.
    - Myxomatosis virus in rabbits:
    - https://www.the-scientist.com/features/do-pathogens-gain-virulence-as-hosts-become-more-resistant-30219
- The host may also become resistant.
  - Selective pressure (susceptible hosts die)
  - Protective Immunity.
- What will happen with SARS2?
  - Immunity may reduce disease severity
  - Immune pressure might select for attenuated viruses
  - The virus may be in a sweet spot (not too hot, not too cold)
    - May still select for enhanced transmission (ongoing)
    - Unclear whether this will reduce or enhance virulence.

Will SARS-CoV2 Mutate to Escape Host Immunity? SARS1 says maybe…



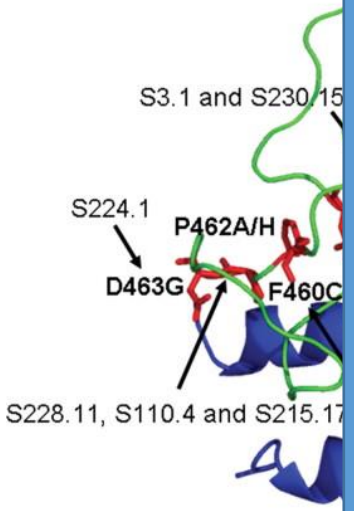






J Infect Dis. 2010 Mar 15; 201(6): 946–955.

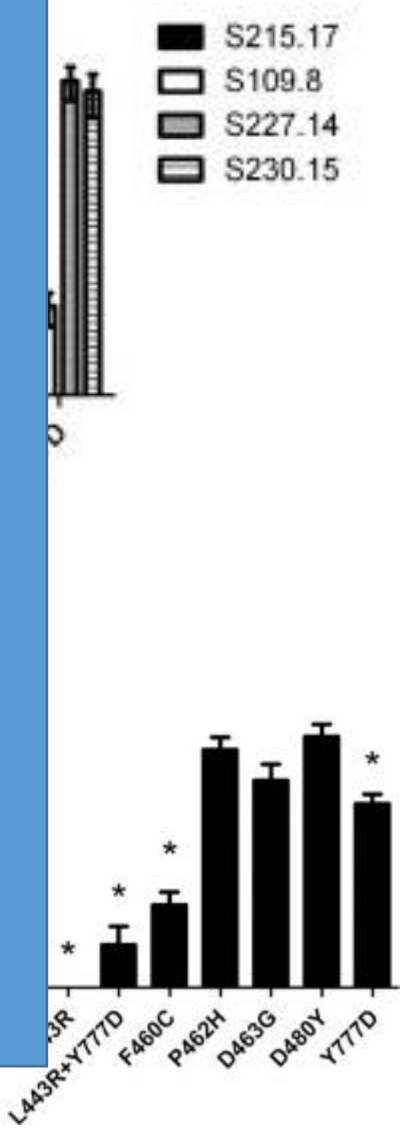
Will SARS-CoV2 Mutate to Escape Host Immunity? SARS1 say



New SARS-CoV2 Variants May Evade Prior Immunity

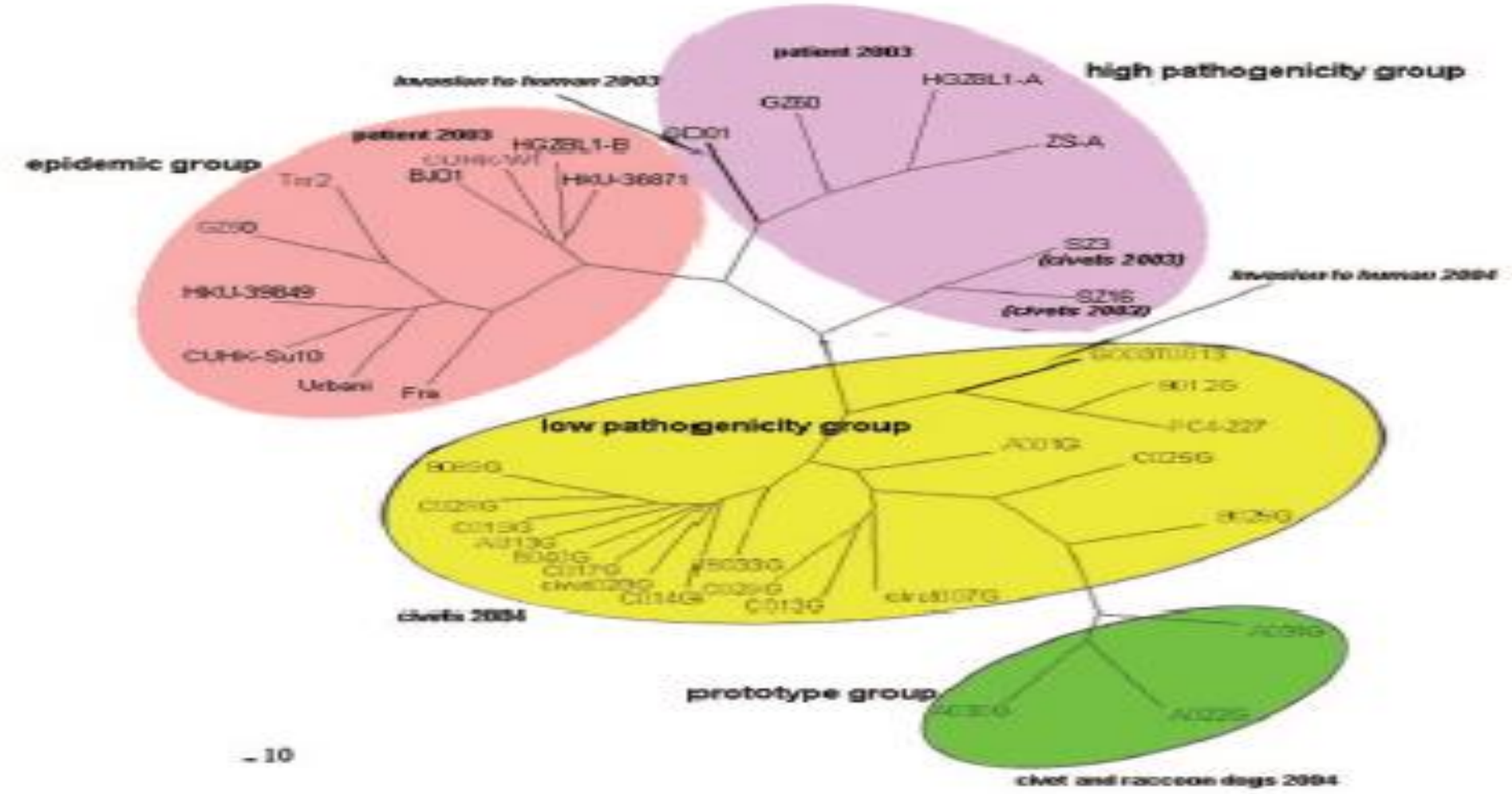
B.1.351 (South Africa) shows reduced sensitivity to neutralization by serum from individuals vaccinated against original SARS-CoV2 Strains

Vaccines also show reduced efficacy against this variant.

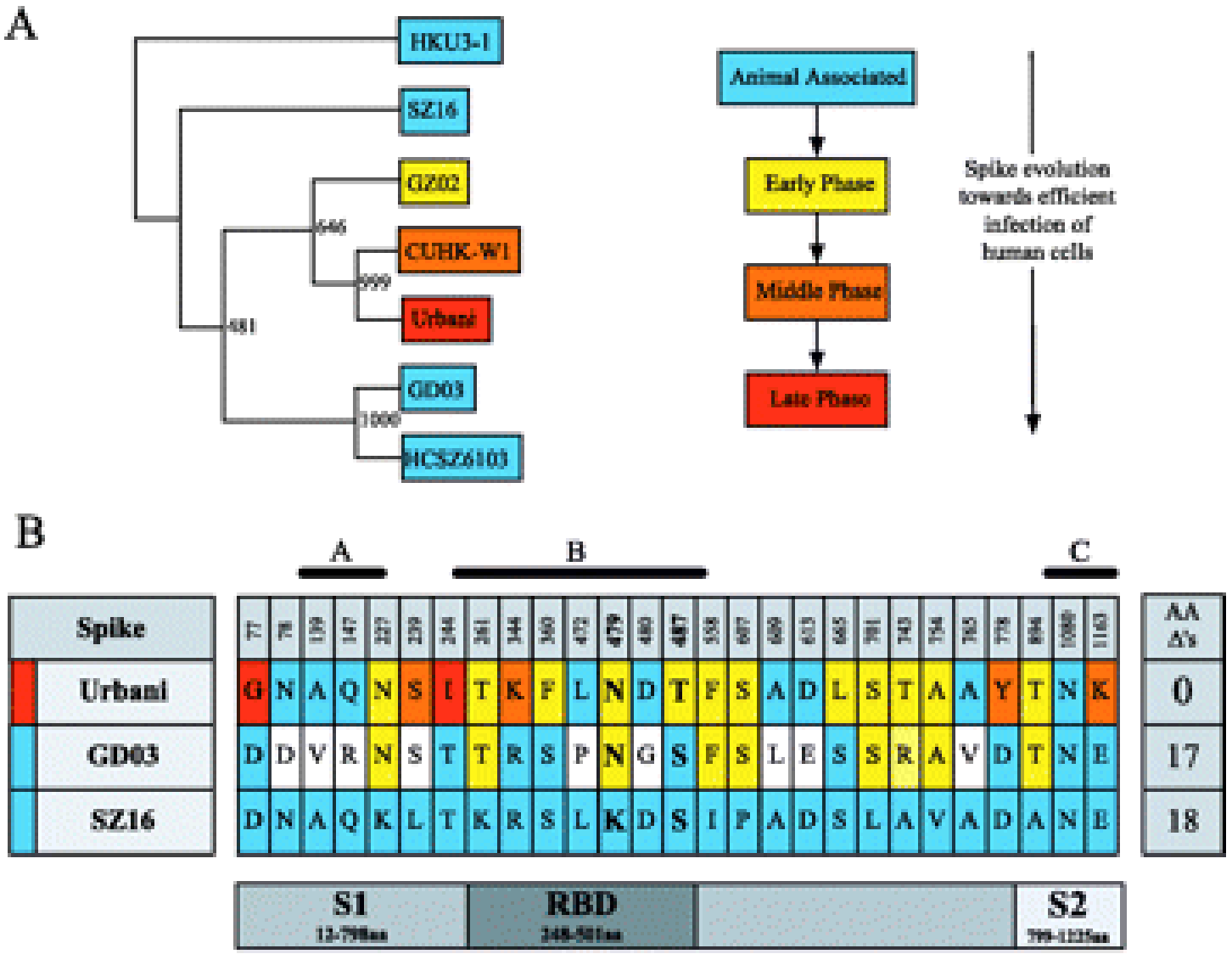


J Infect Dis. 2010 Mar 15; 201(6): 946–955.

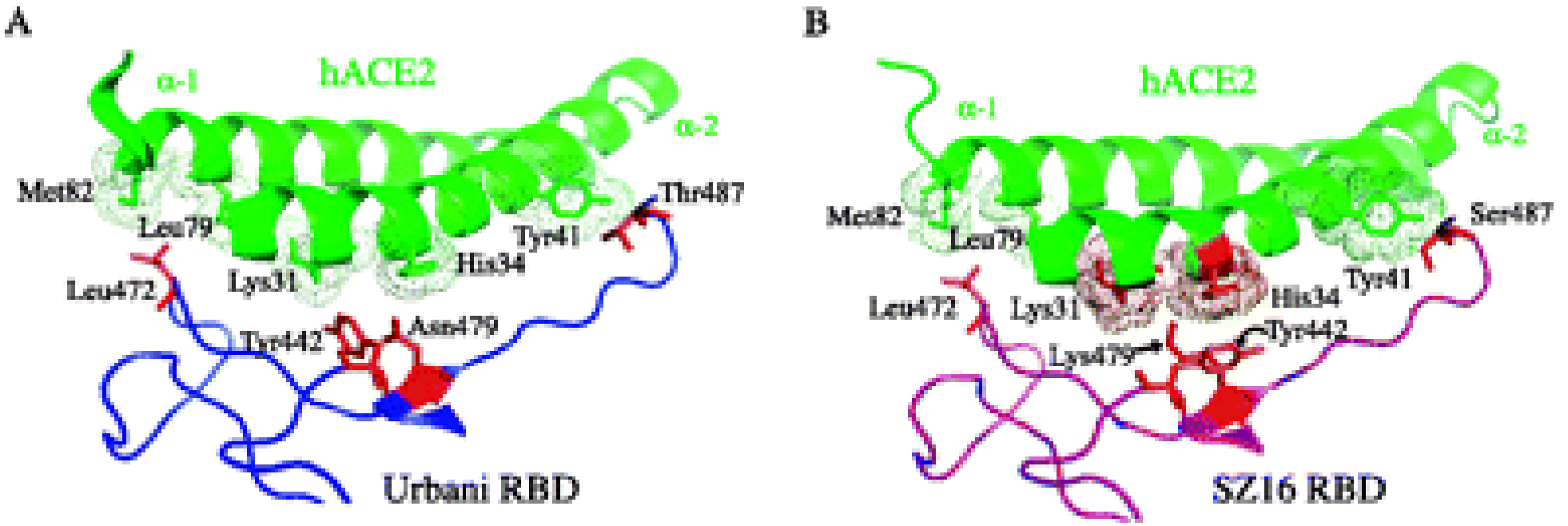
Become More Transmissible?



Changes in S1 region of the S glycoprotein, that mediate binding the ACE2
Correlate with the transition from low to high pathogenicity. J.Virol. 79:11892-11900



Sheahan et al.,2008. J.Virol. 82:2274-2285



Sheahan et al.,2008. J.Virol. 82:2274-2285

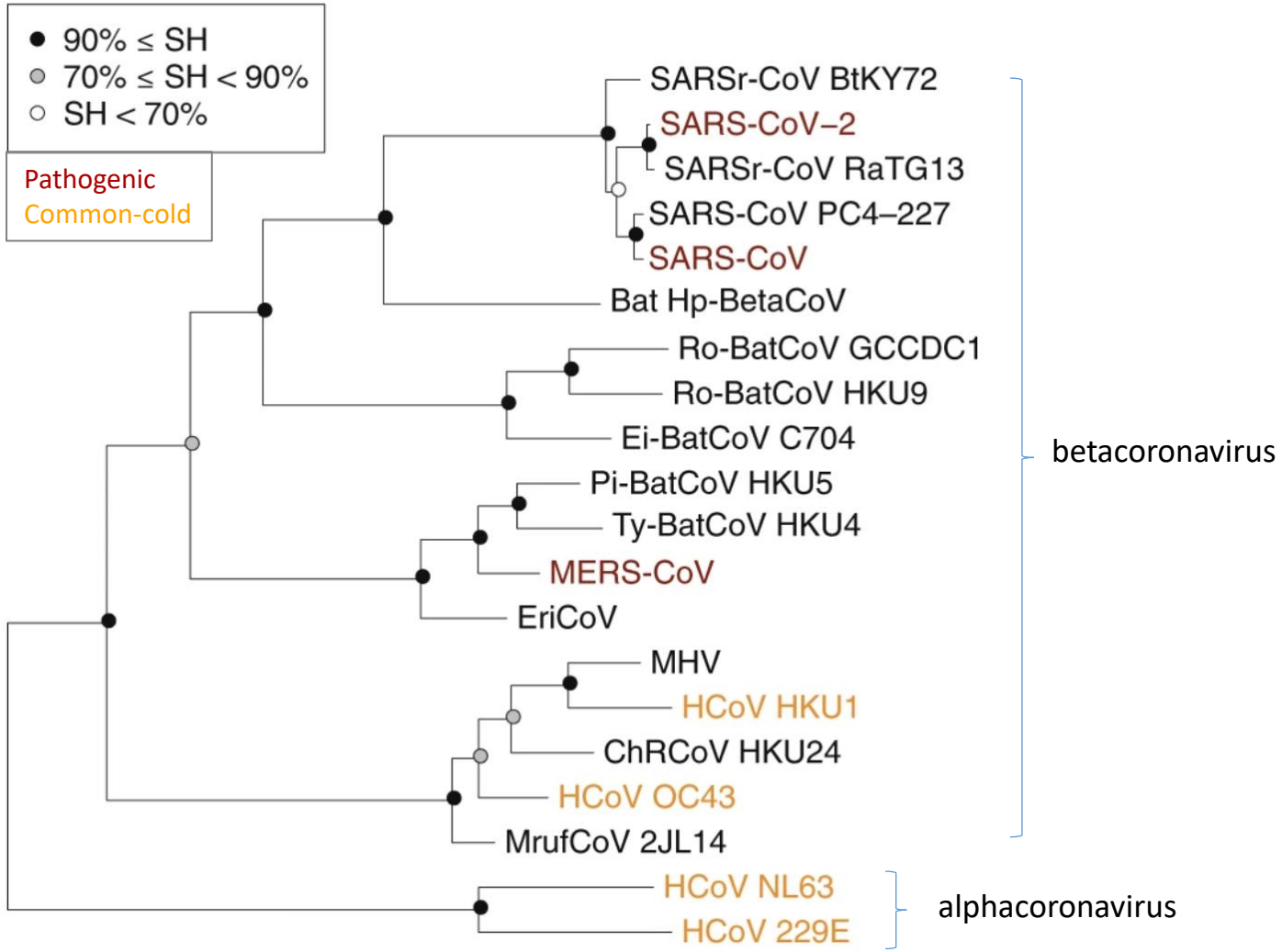
SARS-CoV2 is Adapting to Enhance Transmission

Early Change in the Viral Spike Protein (D614G) Enhanced Transmission (Hou et al., Science 370, 1464–1468 (2020))

B.1.1.7 (UK); B.1.351 (South Africa); P.1 (Brazil) show enhanced Transmissibility Compared to Common SARS-CoV2 Isolates

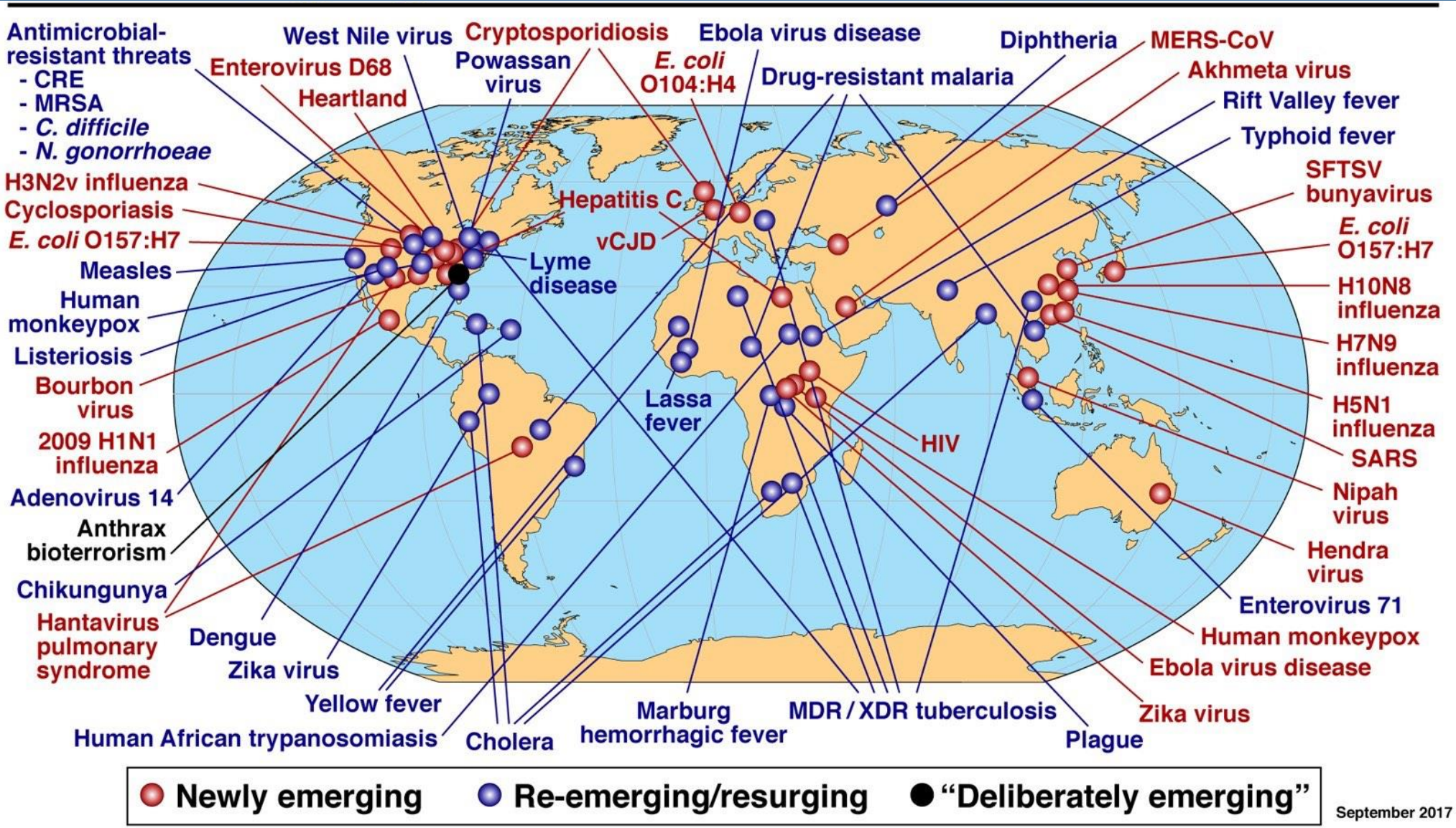
Sheahan et al.,2008. J.Virol. 82:2274-2285

Will it go away? Unlikely
Become a seasonal cold virus? Maybe



Adapted from the *International Committee on the Taxonomy of Viruses*

Which One Emerges Next?



How Can We Prepare for the Next Pandemic?

- Learn from this one
  - Communication Failures
  - Education
  - Rebuild Trust in Science
- Strengthen Public Health Systems
  - Surveillance
    - International Cooperation
  - Testing
- Drugs and Vaccines

Without bold action now, the next pandemic is inevitable

- Novel viruses are emerging more frequently
- Viruses can emerge from anywhere
- The costs are staggering
- Response to COVID-19 continues to reveal multiple system failures

The world urgently needs a better solution.

THE PROBLEM

Antiviral drugs play a critical role in pandemic response

Vaccines are required to end pandemics to provide protection from disease and end spread

- However, vaccine development begins when a new virus emerges
- **Creates a crucial gap** between virus emergence and vaccine delivery

We need broad spectrum antiviral drugs ready for use when a new virus emerges

- *Immediate treatment options and limit virus spread until a vaccine can be developed*

READDI

Contact: Nat Moorman 609-651-2013

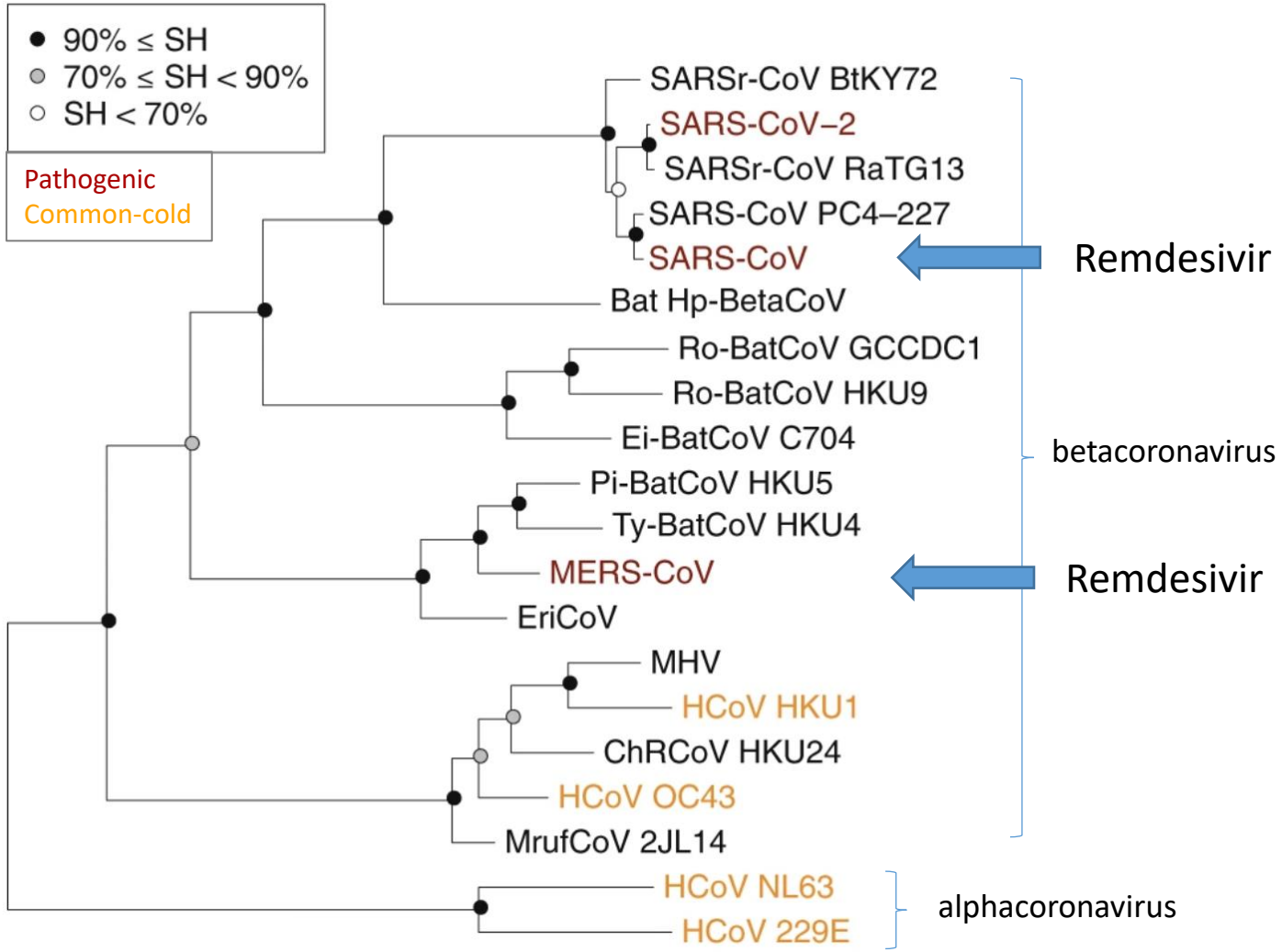
THE PROBLEM

Filling the gap in drug discovery

- **There's no market force to drive drug discovery for *potential* future pandemics**
  - making a product for a market that doesn't yet exist
- **Current fundamental gap in research enterprise**
  - expertise in virology almost always separated from expertise in drug development
  - few paths linking basic science with drug discovery process
- ***Fills that gap*** by teaming discovery and development expertise from around the globe

READDI

How Do We Identify Broad Spectrum Drugs Against Unknown Viruses?

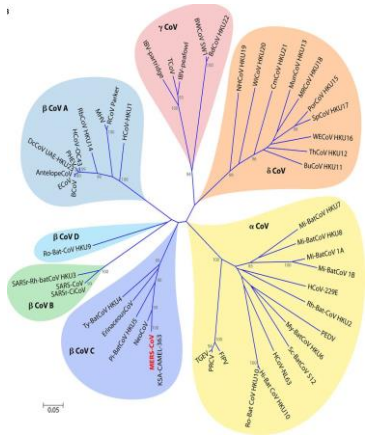


Adapted from the *International Committee on the Taxonomy of Viruses*

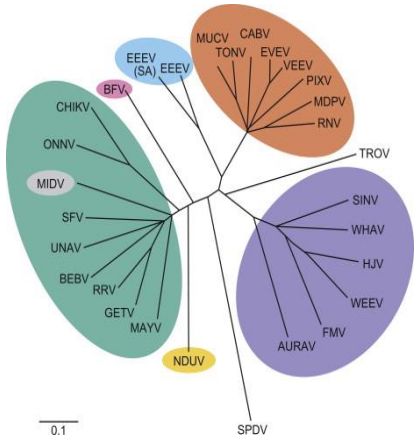
READDI Deliverables

Broad spectrum antiviral drugs ready for immediate deployment when the next viral outbreak emerges

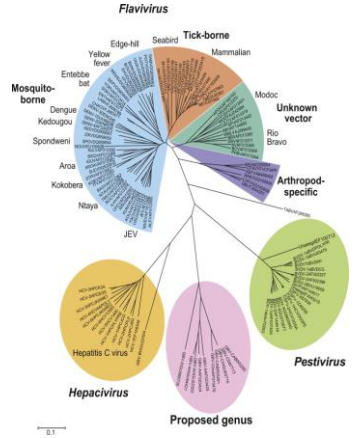
MEDICINES EFFECTIVE AGAINST EXISTING VIRUSES THAT LACK THERAPEUTICS AND/OR VACCINES



coronavirus



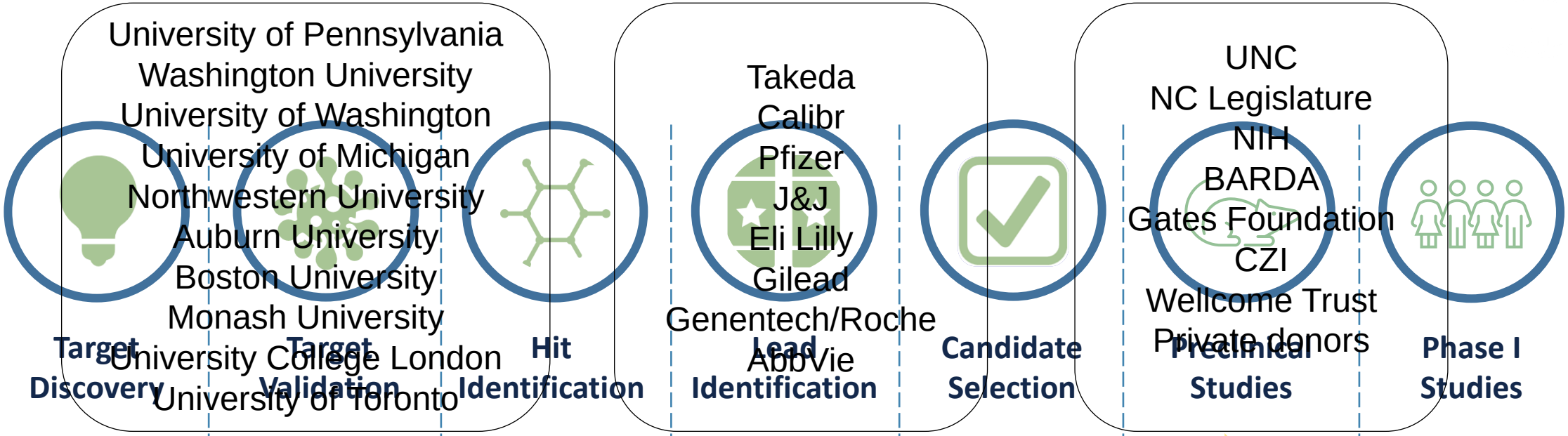
alphavirus



flavivirus

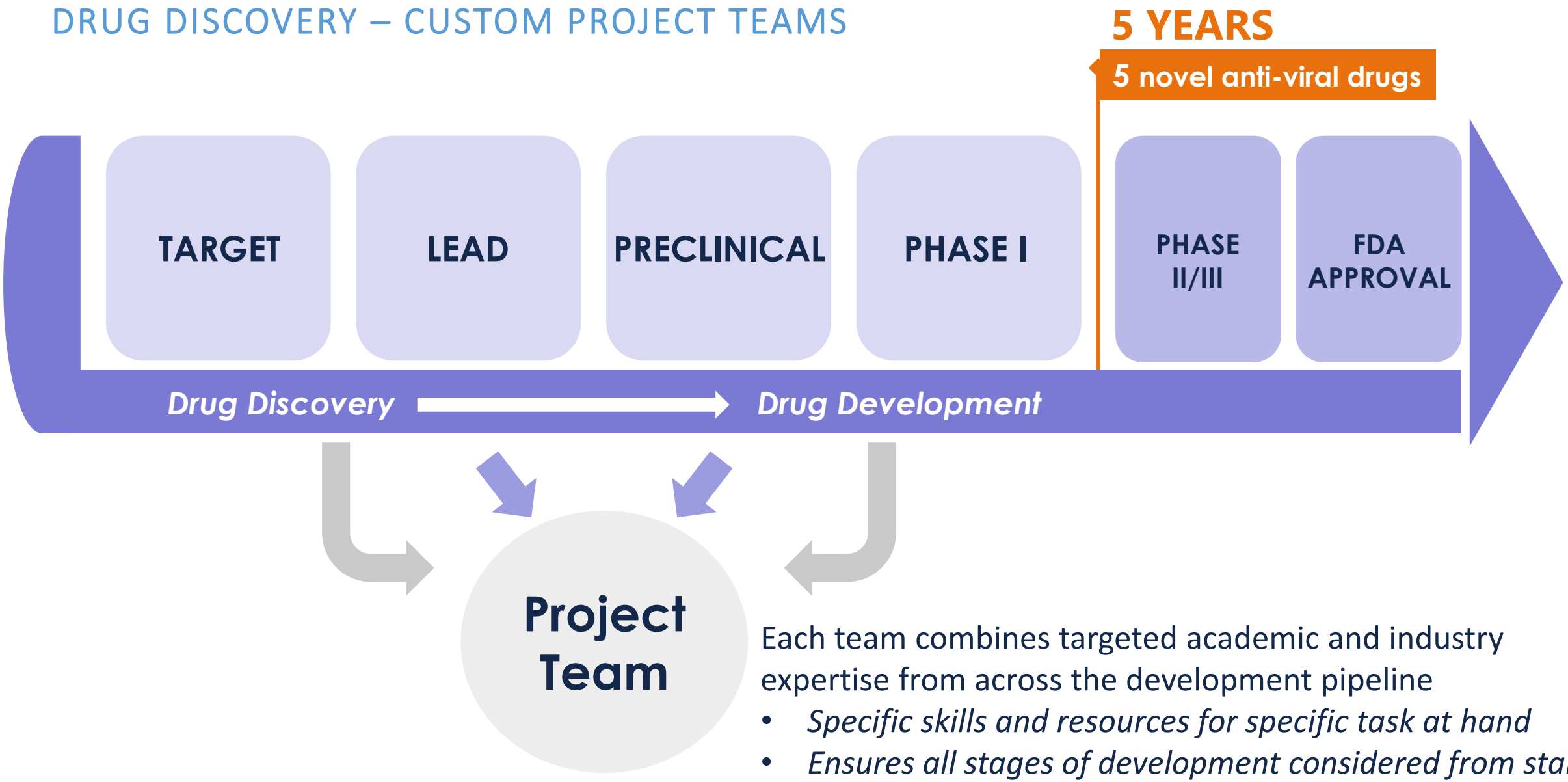
READDI

DRUG DISCOVERY – DRUG DEVELOPMENT ENGINE



READDI

DRUG DISCOVERY – CUSTOM PROJECT TEAMS



Each team combines targeted academic and industry expertise from across the development pipeline

- *Specific skills and resources for specific task at hand*
- *Ensures all stages of development considered from start*

READDI

What will READDI do?

Accelerate new antiviral drug development

Target factors that viruses need to replicate

Fund and facilitate projects at all stages

Aggregate and advance existing assets

Identify promising antiviral compounds shelved by industry

Develop stalled antivirals from academic labs

Expedite treatment availability

Prepare Phase II & III trial design

Identify manufacturing partners in advance

LEADING THE WAY

We’re already collaborating for success

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Industry Partners

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Calibr at Scripps Research

Pfizer

RTI INTERNATIONAL

Takeda

LOVELACE BIOMEDICAL

Patheon

University Partners

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

VANDERBILT UNIVERSITY

UCL

Washington University in St. Louis

MONASH University

University of Colorado Boulder

UNIVERSITY OF TORONTO

UNIVERSITY OF OXFORD

OREGON HEALTH & SCIENCE UNIVERSITY

Strategic Partners

DNDi Drugs for Neglected Diseases *initiative*

SGC

sas

DEERFIELD Advancing Healthcare®

NC Policy Collaboratory

NIH National Institutes of Health

The research team is already at work

- 20+ active projects with partners from around the world
- Focus on multiple viral families with high pandemic potential

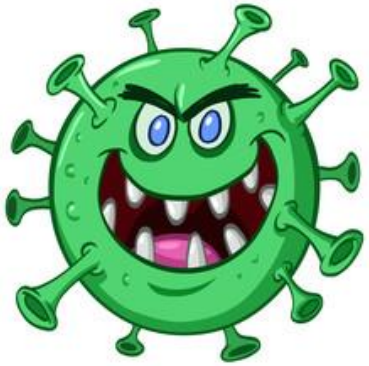
Project example:

- COVID-19 – Repurpose kinase inhibitors as SARS2 antiviral drugs

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

SGC

Calibr at Scripps Research



Questions?