Beyond COVID-19: Preparing for future pandemic threats

(Building the Plane While Flying: Research in the Time of COVID)

Sumit Chanda
Professor of Immunology and Microbiology

Our Response- Understanding the Virus to Build Antivirals

Cell

CellPress

Article

SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2

- How SARS-CoV-2 enters human cells

Cell Reports

CellPress
OPEN ACCESS

Article

MDA5 Governs the Innate Immune Response to SARS-CoV-2 in Lung Epithelial Cells

- How SARS-CoV-2 is detected by the immune system

Eli Lilly's Antibody Treatment Gets Emergency F.D.A. Approval

The authorization raised immediate questions about who would get access to the antibody treatments, which are in short supply.

Lilly

- How our cells defend against SARS-CoV-2 infection

CellPress

Molecular Cell

Resource

Functional landscape of SARS-CoV-2 cellular restriction

November 9, 2020

- Strategies to prevent severe disease

CellPress

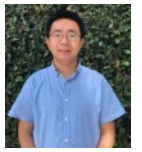
Cell

Article

TOP1 inhibition therapy protects against SARS-CoV-2-induced lethal inflammation

A Brief Timeline

December 2019: **Xin Yin returns to China for the Christmas Holidays**



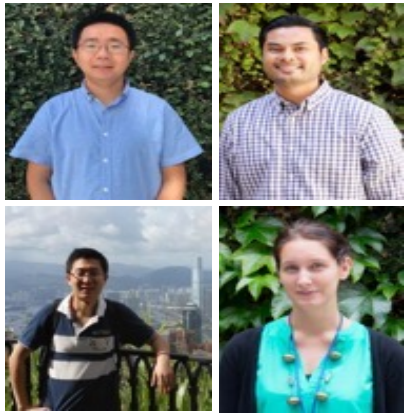
Mid-Jan 2020: **Assembly of a Virology "Dream Team" : Ren Sun (UCLA), Shuofeng Yuan & Kwok-Yung Yuen (HKU), Adolfo Garcia-Sastre (MSSM)**

BILL & MELINDA GATES *foundation*

Late Jan 2020: **Arnab Chatterjee @ Scripps/ Calibr commits to providing 12k Repurposing Library**

Early February: **Laura Riva cancels trip to Hong Kong due to travel ban**

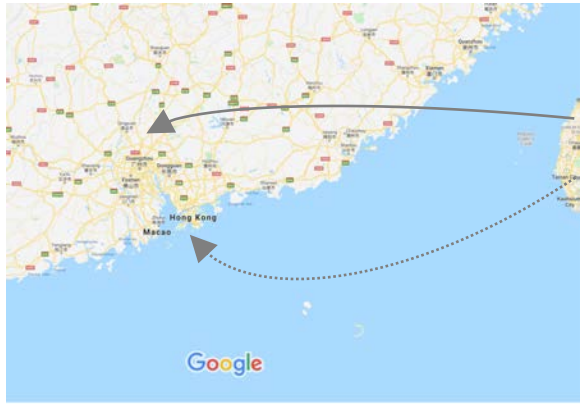
There's an App for That

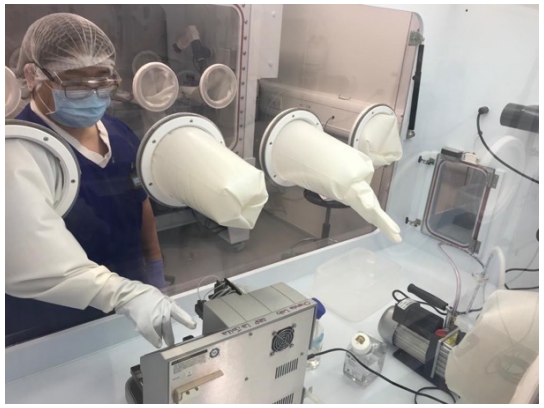


Mid-February: **Drug Discovery by iPhone**

WeChat

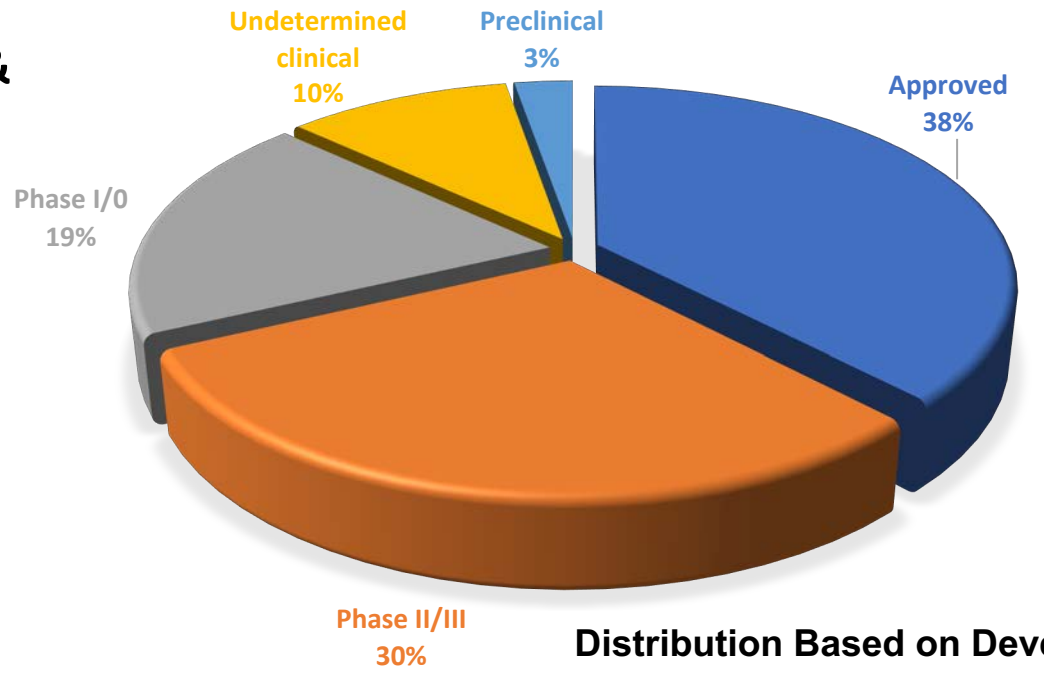
Can 'Team Science' Yield a Covid-19 Treatment?
New York Times Magazine, Kim Tingley
May 13, 2020





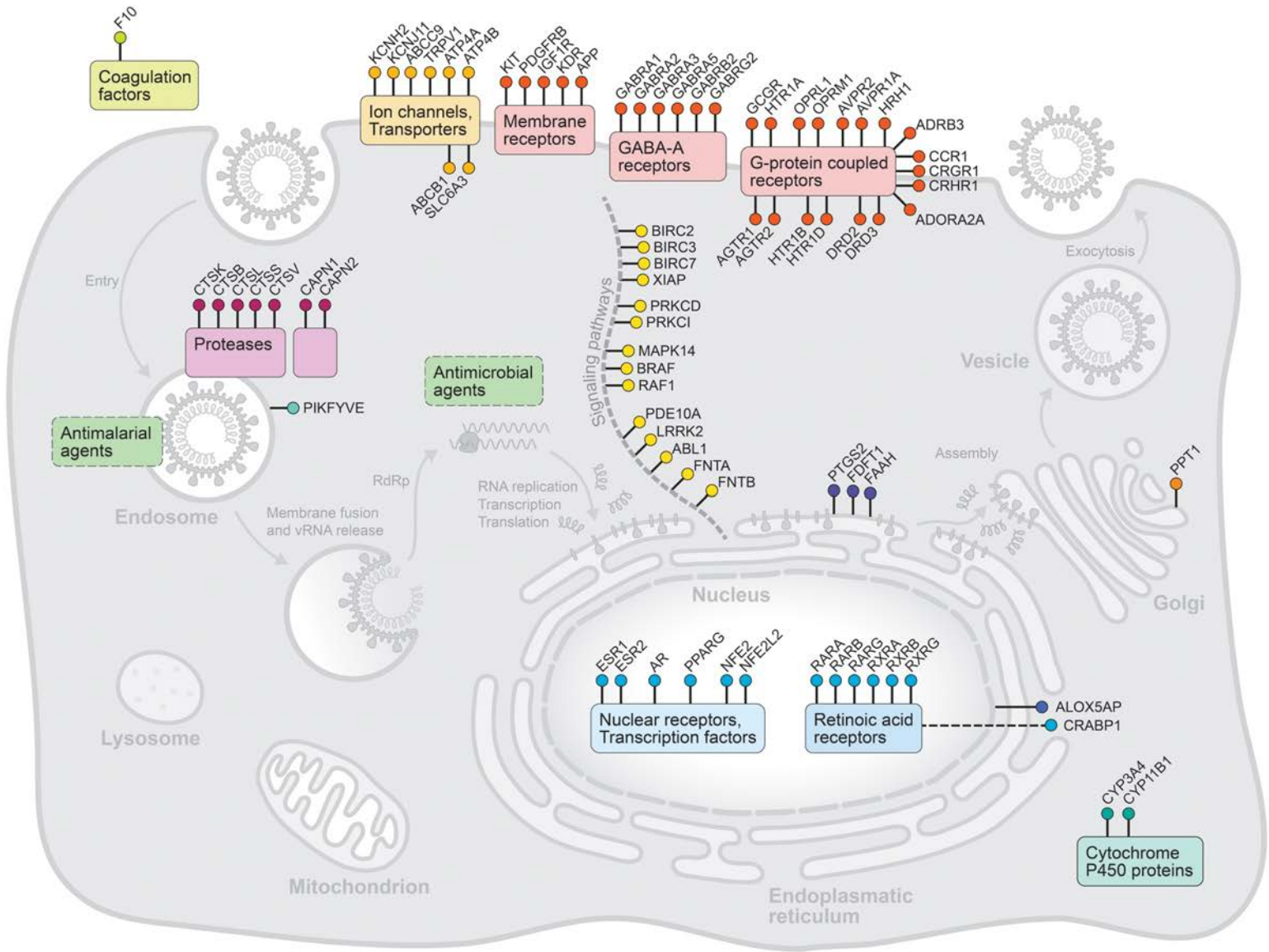
ReFRAME: The Repurposing, Focused Rescue, and Accelerated Medchem Initiative

- Calibr's library of more than 12,000 drug compounds known to be safe in humans, with well-characterized therapeutic properties
- Open-source database containing preclinical and clinical data on these drugs
- Established in 2018 with support from the Bill & Melinda Gates Foundation



Distribution Based on Development Stage

The Initial Antiviral Map



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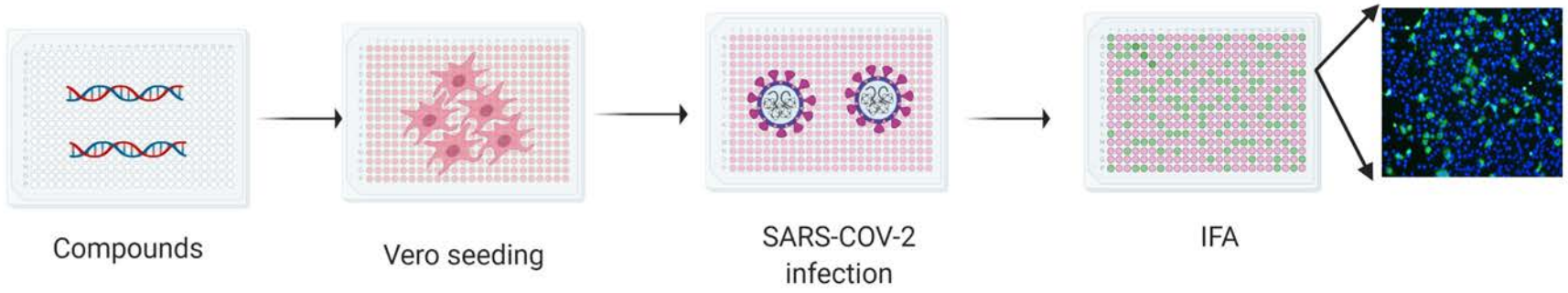
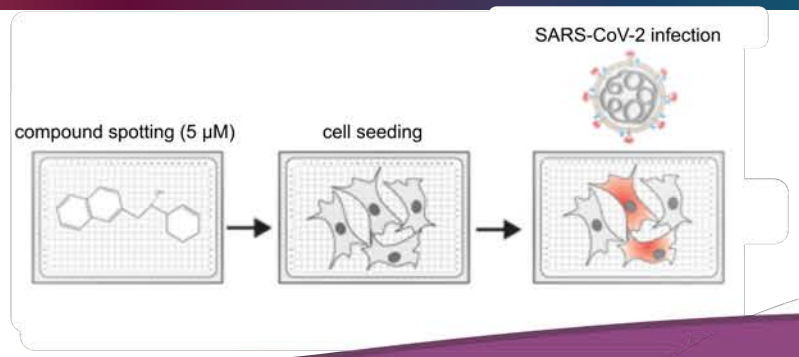
Riva et al. Nature (2020)

Getting our Hands on the Virus

SARS-Related Coronavirus 2, Isolate USA-WA1/2020 was received early March 2020

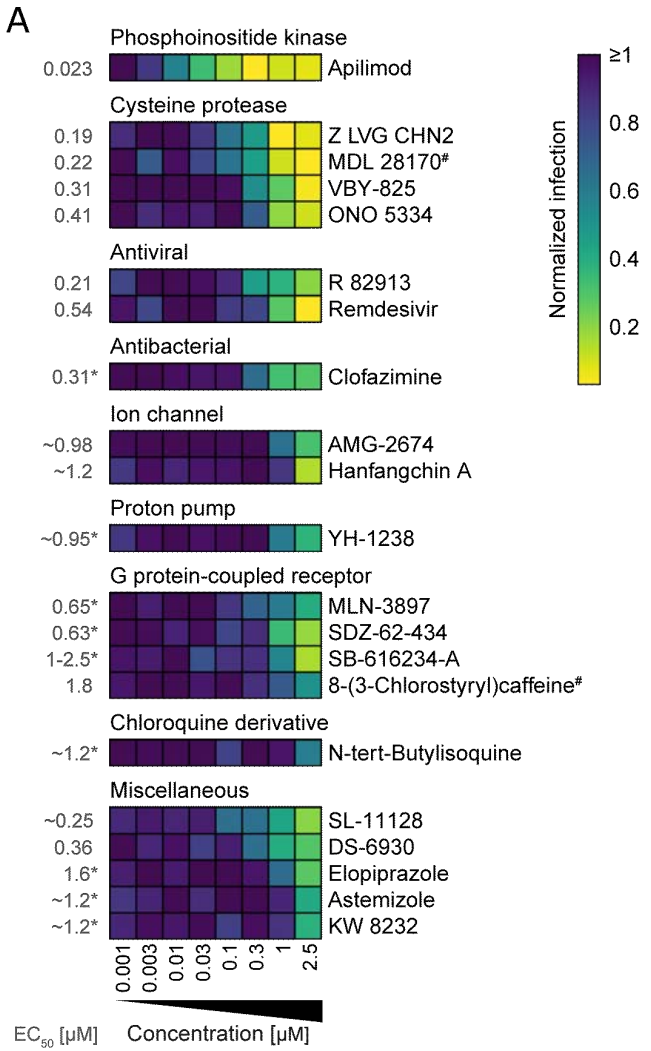


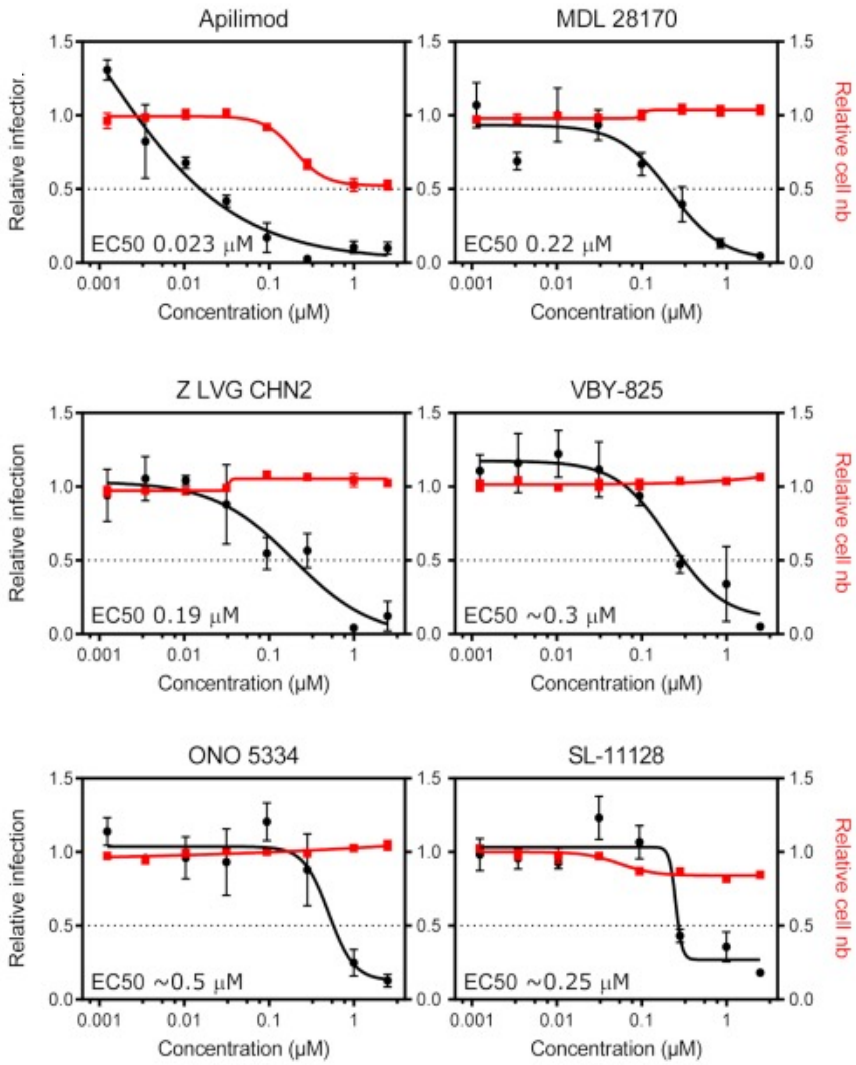
Narrowing the Haystack



Vero E6 (CPE/IF)	**Vero E6 (CPE/IF)** Selected by Z-score, GSEA (CPE) >40% inhibition of infectivity at 2.5 µM (IF)	300 100
Vero E6 (Dose-response)	**Vero E6 (Dose-response)** EC_{50} < 1 uM, SI > 10	21
Human cell lines	**293T-Ace2 and/or Huh7-Ace2 cells** EC_{50} < 1uM, SI > 10	18
Characterization/ MOA	**Remdesivir Synergy/ Impact on viral life cycle**	9
Primary Cells	**Inhibition of Replication in Human primary pneumocytes**	3
Lung Explant/ Organoids	**Inhibition of replication in a complex disease tissue**	1
In vivo POC	**Decrease in viral titers and attenuation of disease severity in an animal model (hamster, mouse, cats, NHPs)**	1

21 Known Drugs Inhibit SARS-CoV-2 Replication





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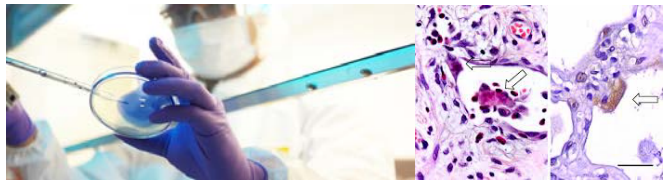
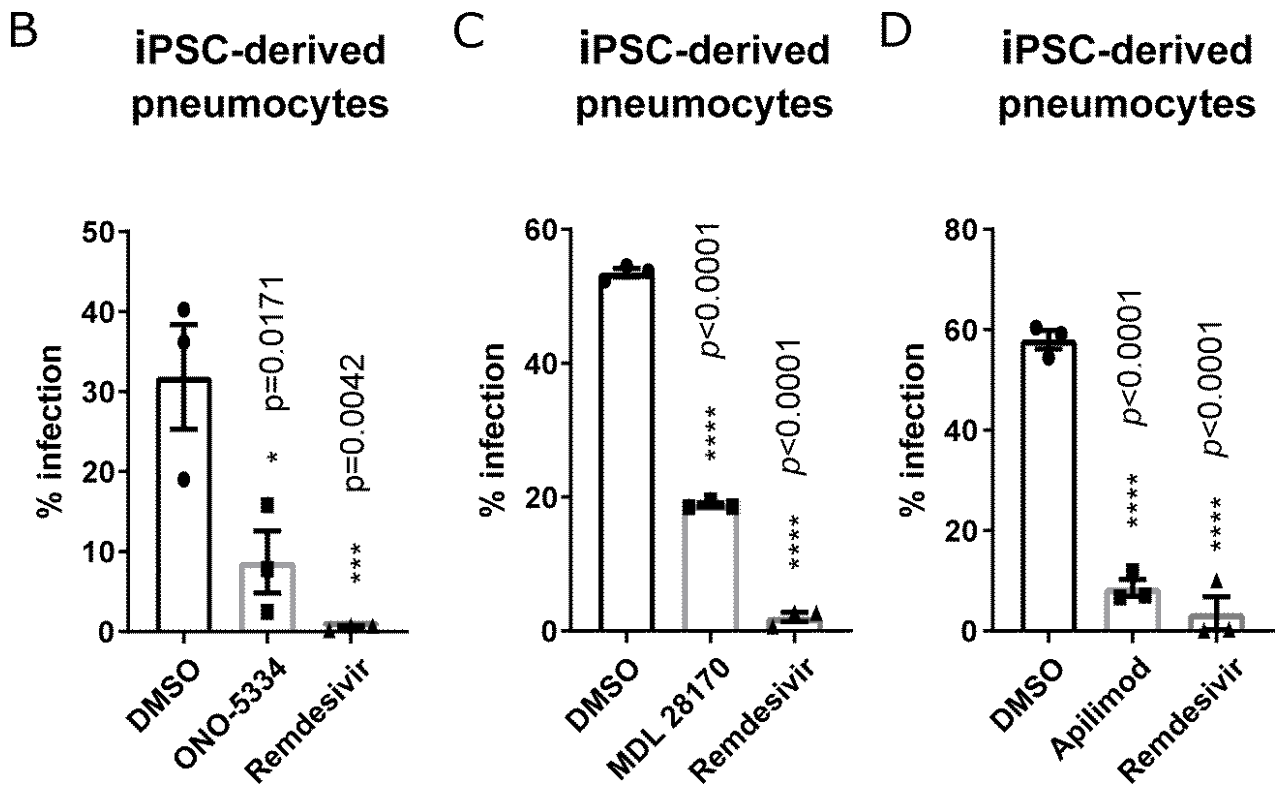
Riva et al. Nature (2020)

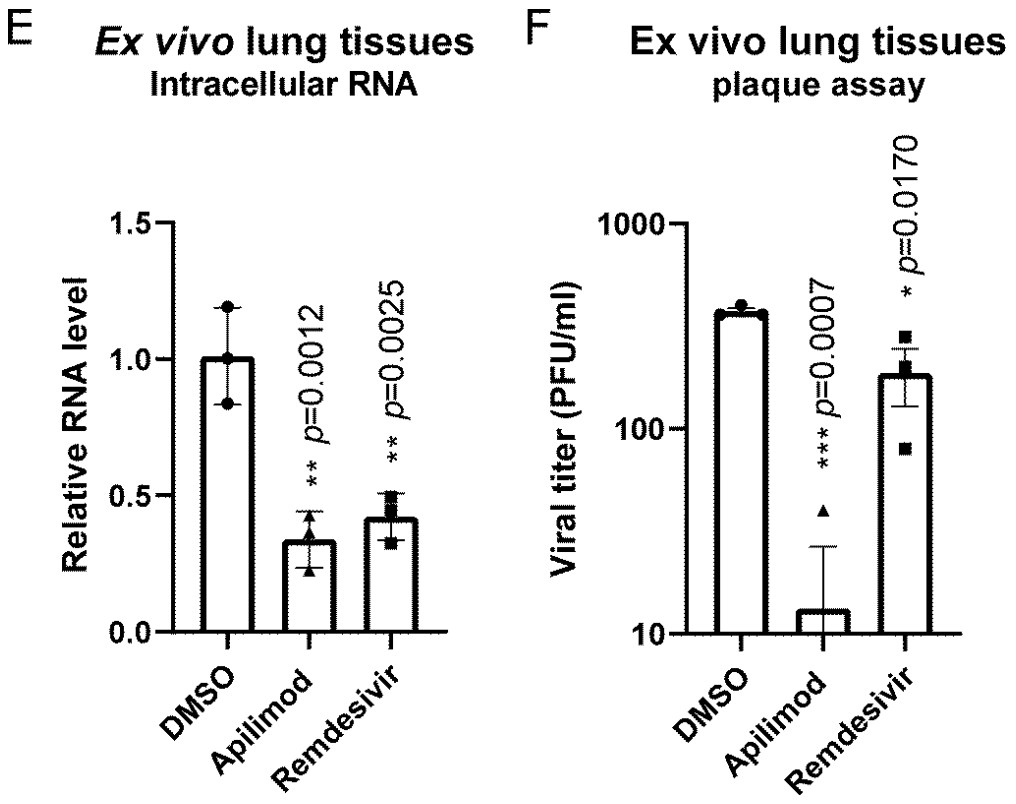
Evaluation in Disease-Relevant Cells





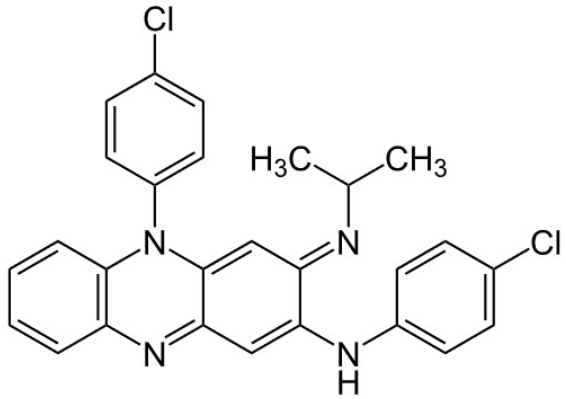
Riva et al. Nature (2020)

Evaluation in Disease-Relevant Tissue



Riva et al. Nature (2020)

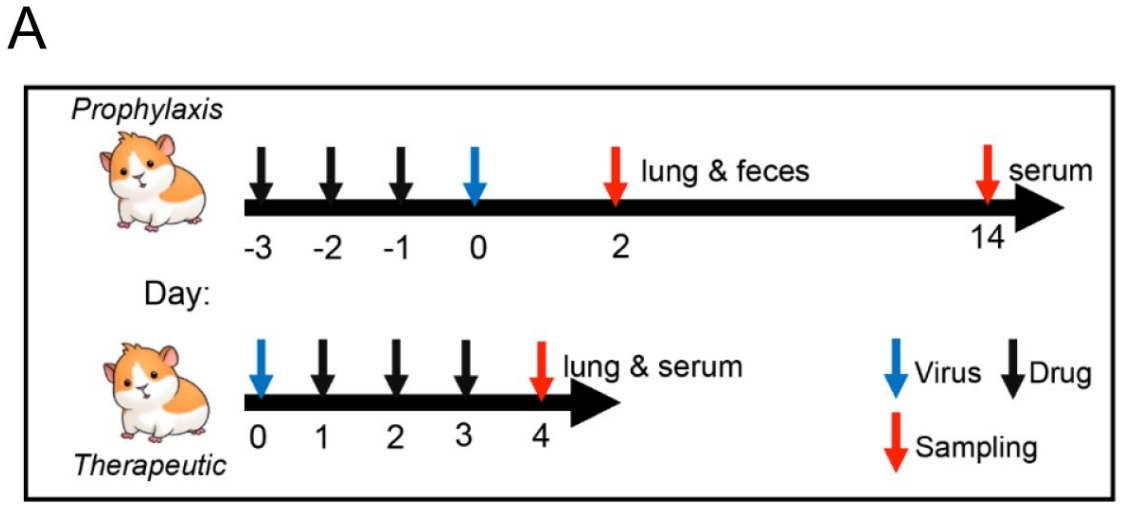
Clofazimine, LAM-320, Lamprene

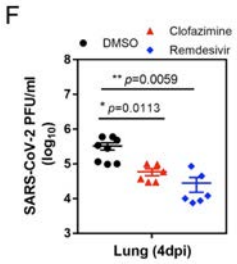


- **Discovered in the 1950's**
- **FDA-Approved (1986) ; WHO's list of Essential Medicine**
- **Treatment of leprosy/ anti-mycobacterial**
- **$1.43/day**

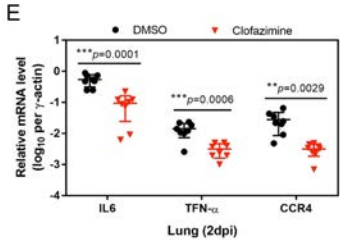
Remdesivir: ~ $3000

Efficacy of Clofazimine in Hamsters

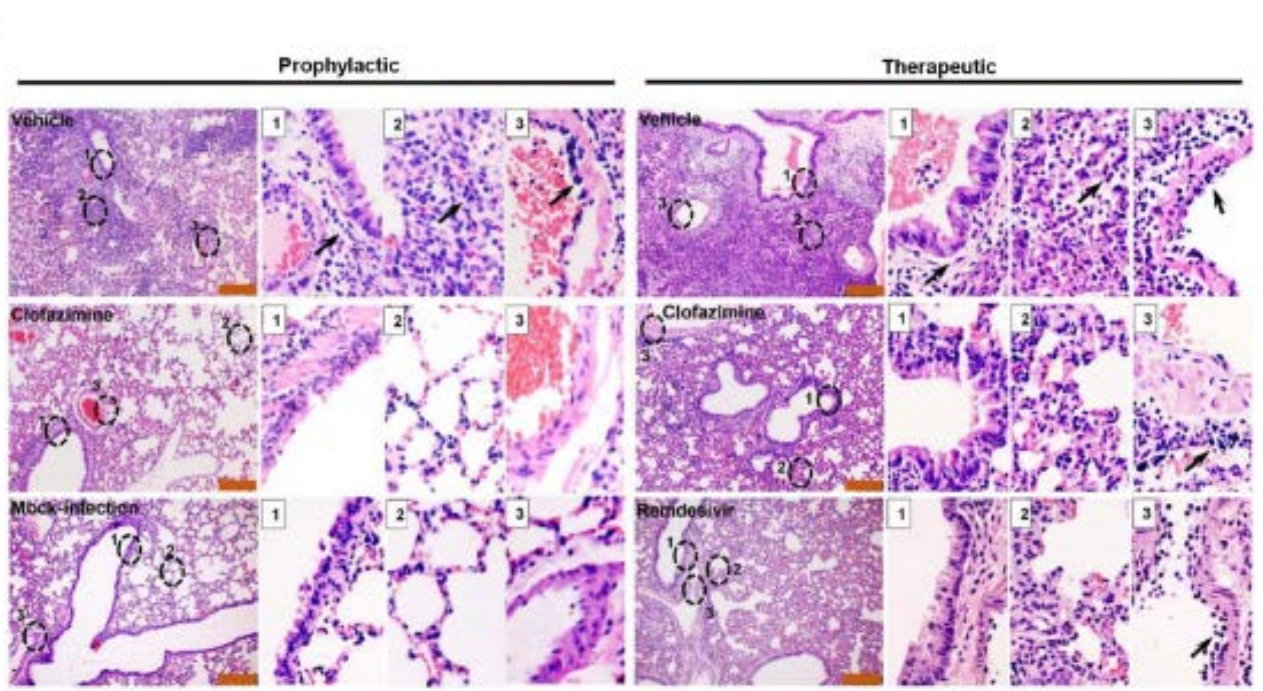




- **Administration of Clofazimine results in 10-fold lower virus in the lungs and is comparable to Remdesivir treatment**



- **Clofazimine treatment decreases inflammatory responses that lead to severe disease**



(1) bronchiolar and/or peribronchiolar cell death

(2) alveoli destruction and/or alveolar infiltration

(3) blood vessel and perivascular infiltration.

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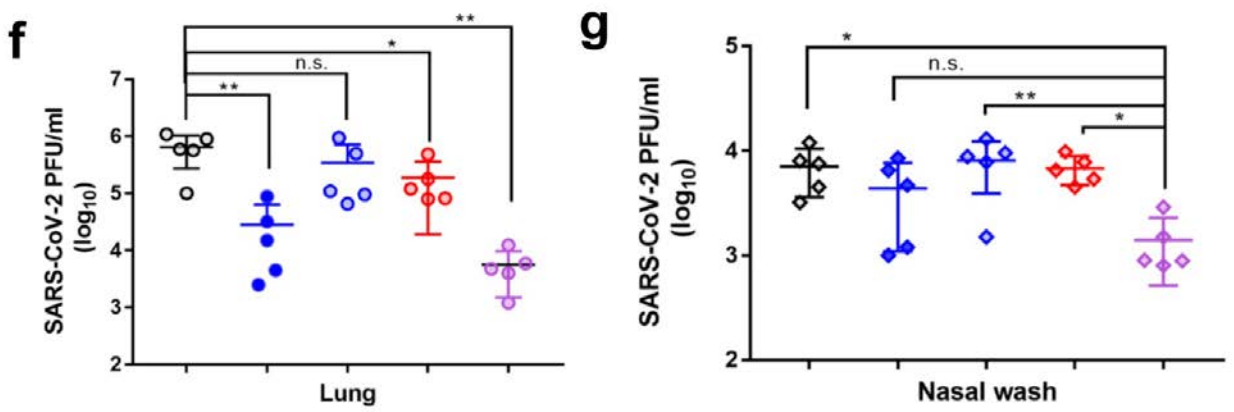
Yuan et al. Nature (2021)

Clofazimine Synergizes with Existing Antivirals



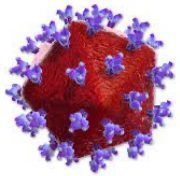
- **Combination of low-dose Clofazimine & Remdesivir works better than high-dose Remdesivir alone**
- **Combo was found to also block virus replication in the nose, which was not seen with high-dose Remdesivir alone**

Yuan et al. Nature (2021)

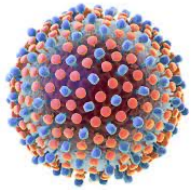
Current Approved Therapies that Work for Omicron

	Antiviral	Status/ Route
GILEAD Creating Possible	**Remdesivir (Veklury)**	Approved/ IV
MERCK INVENTING FOR LIFE	**Molnupiravir (Lagevrio)**	EUA/ Oral
Pfizer	**PF-07321332 (Paxlovid)**	EUA/ Oral
gsk	**Sotrovimab (Xevudy)**	Approved/ IV
Lilly	**LY-CoV1404 (Bebtelovimab)**	EUA/ IV
AstraZeneca	**Evusheld (AZD7442)***	EUA/ IV

The Path Forward for Therapeutics:
Resistance Isn't Futile



HIV: highly active antiretroviral therapy (HAART)
Consists of 3 or more drug combinations



HCV: Curative regimen consists of 2 or more drug combinations

Clinical Trial For Clofazimine:

FUNDACIÓ LLUITA CONTRA LA SIDA
I LES MALALTIES INFECCIOSES

together • COVID-19
clinical trials

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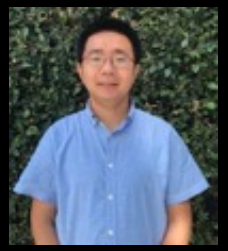


Laura Riva, PhD

Laura Martin-Sancho, PhD

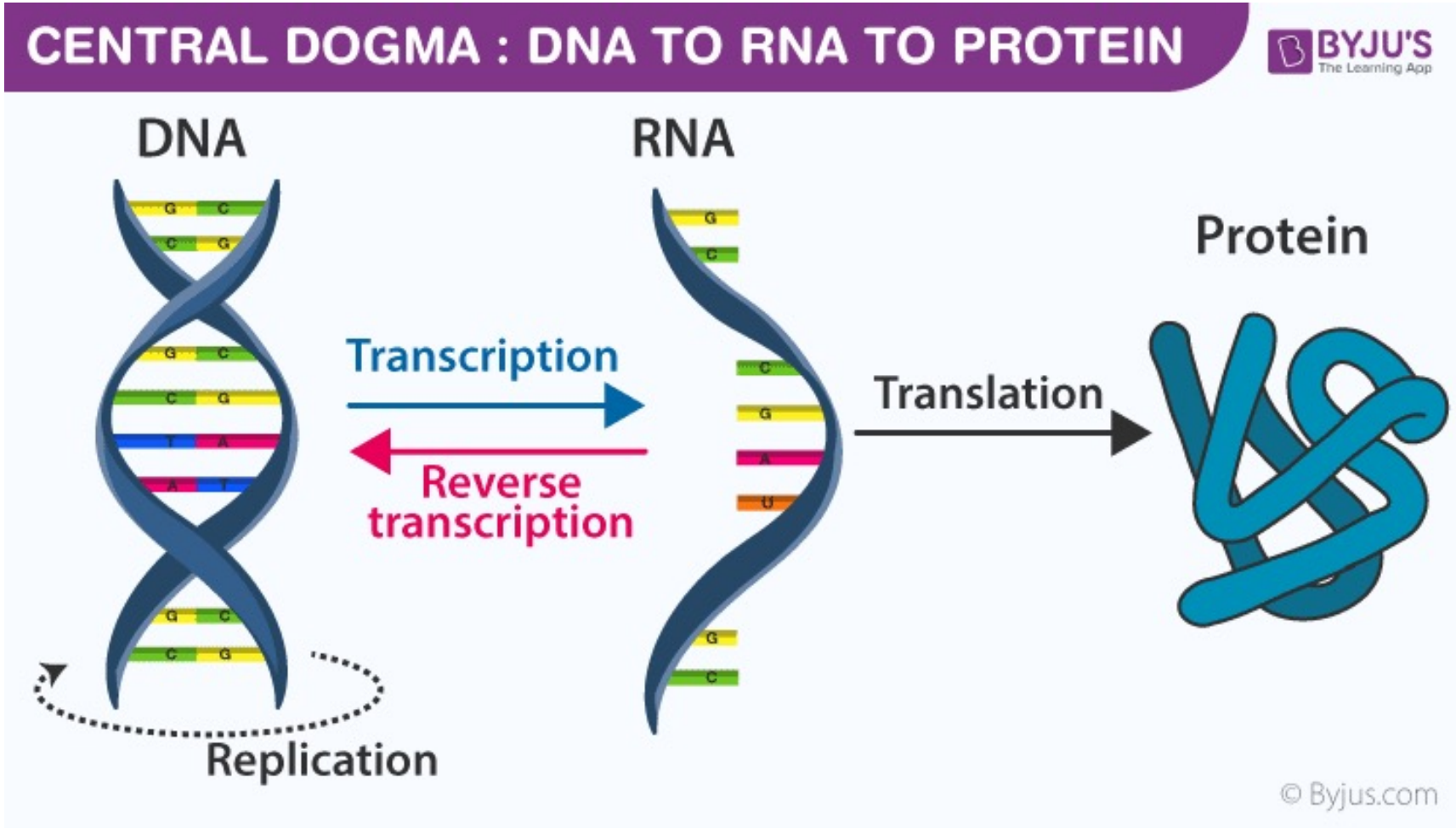
Xin Yin, PhD

Yuan Pu

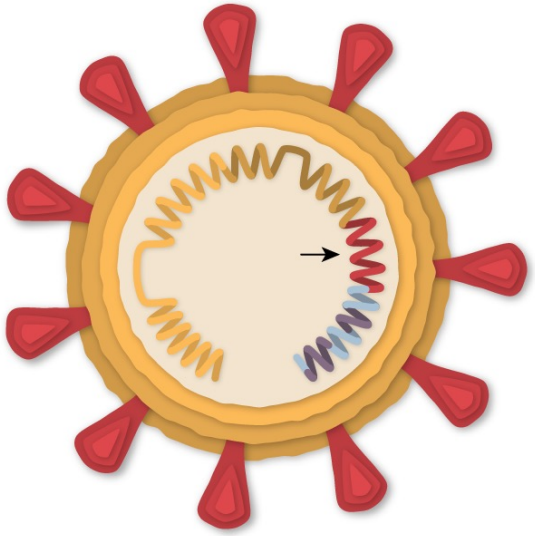
Sylvie Blondelle, PhD

FAQS: Vaccines & Boosters

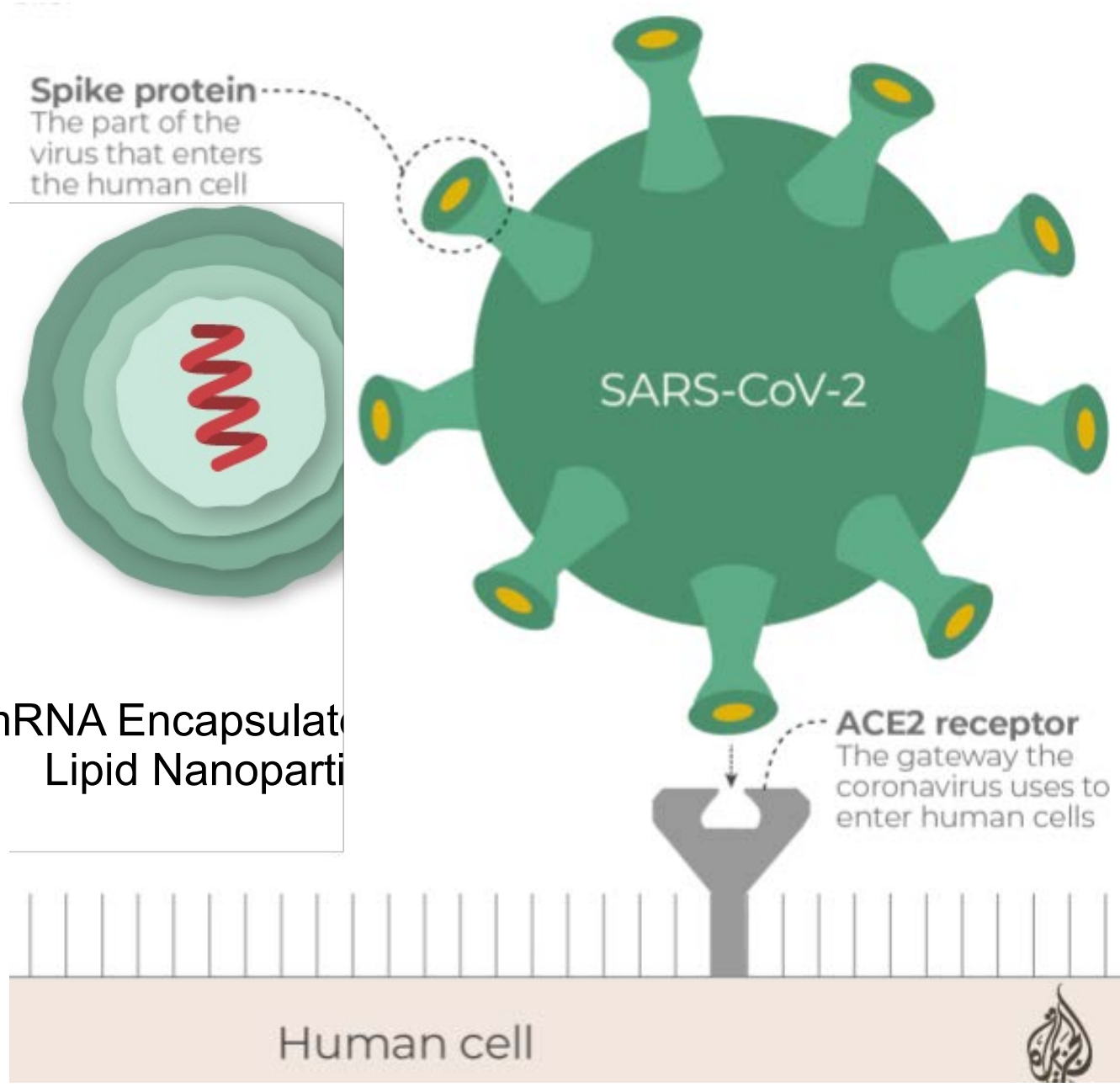
mRNA Vaccines



mRNA Vaccines



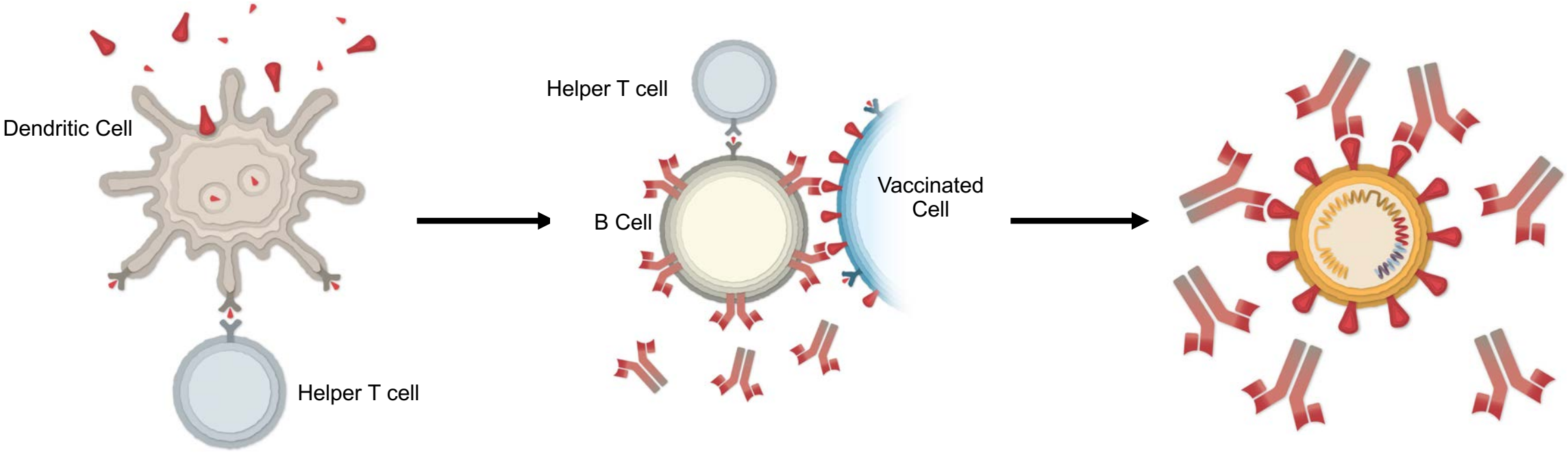
SARS-CoV-2



mRNA Encapsulat
Lipid Nanoparti

From Al Jazeera & NYtimes.com

mRNA Vaccines



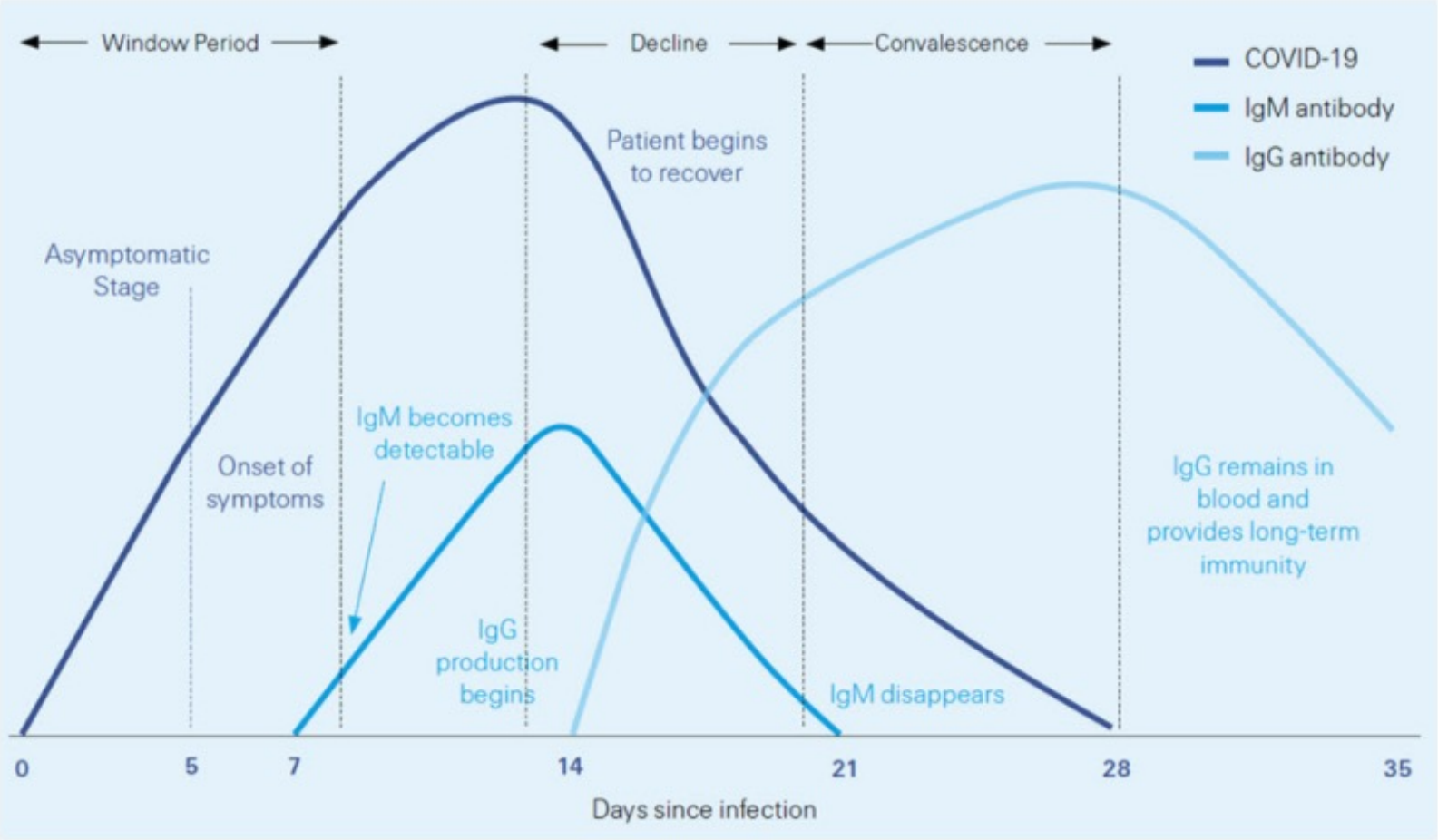
Antigen Presentation

Production of Antibodies

Blocking the Virus

Waning Antibodies

Figure 1: Timeline of Detection for COVID-19.



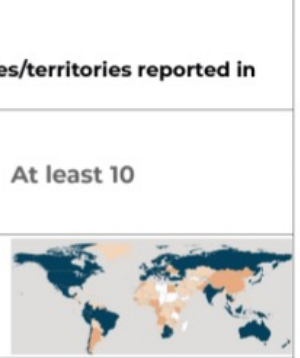
SARS-CoV-2 Variants & Boosting

COVID-19

How Omicron compares

The WHO considers Omicron's **global risk to be 'very high'**. Omicron is a highly divergent variant with a **high number of mutations.**

	Earliest documented samples	Spike protein mutations	Prevalence of analysed sequences*	Countries/territories reported in
O o Omicron B.1.1.529	Multiple countries November, 2021	32*	Unknown	At least 10
Δ δ Delta B.1.617.2	India October, 2020	10	99.8%	196
Γ γ Gamma P.1	Brazil November, 2020	12	0.1%	103
B β Beta B.1.351	South Africa May, 2020	10	<0.1%	146
A α Alpha B.1.1.7	United Kingdom September, 2020	11	<0.1%	197



Analysed sequences uploaded to GISAID with specimen collected from 20 September to 19 November 2021.

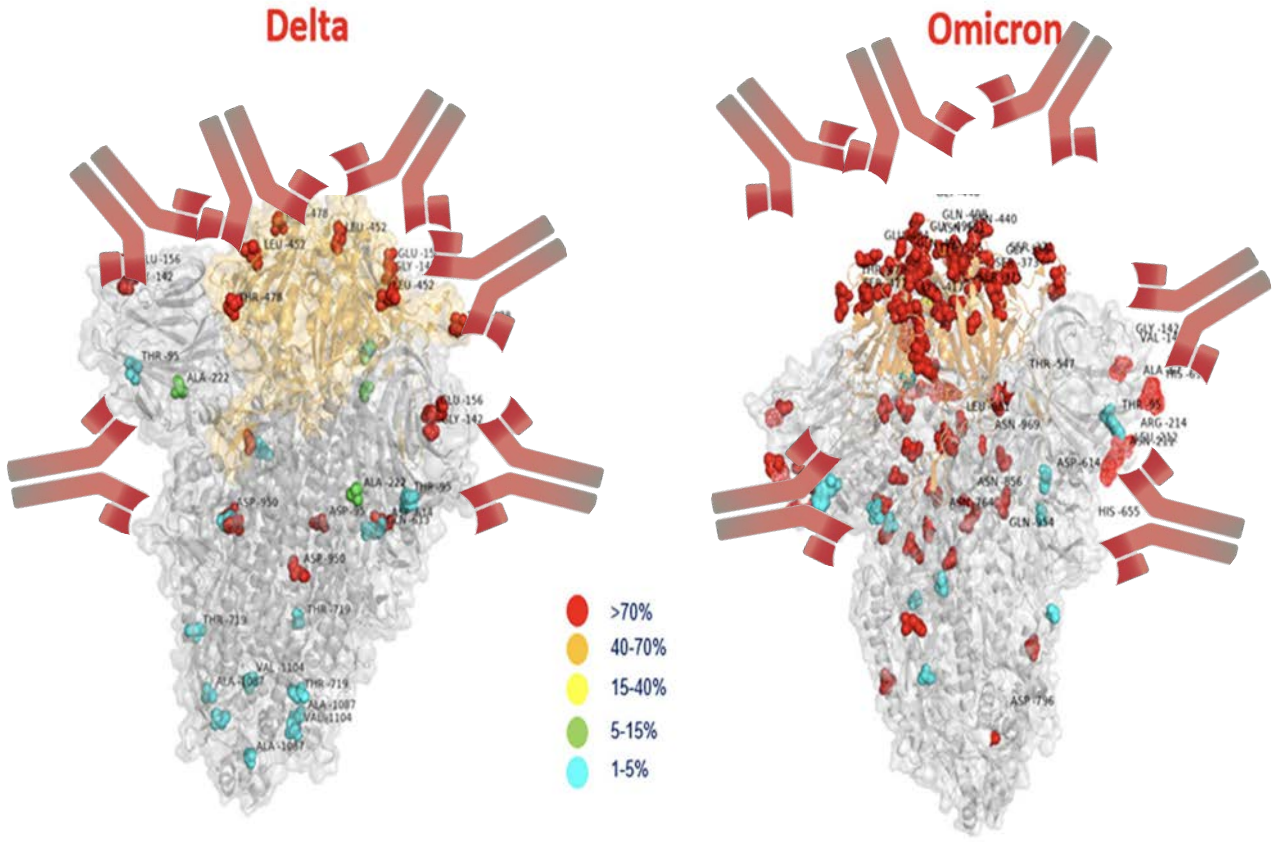
Proportion of variant
0.5-1
0.1-0.5
0.011-0.1
>0.01
Too few samples
No new samples
Not reported to WHO

* Known number as of November 28, 2021
Source: WHO, nference.com | November 29, 2021

@AJLabs ALJAZEERA

From Al Jazeera

Variant-specific Vaccines?



The structure of SARS-CoV-2 spike protein showing the active site in orange and the residues coloured against different mutational rate.

Safety Data on Vaccines: Benefits Considerably Outweigh Risks

Common

Site of Administration: Pain, Redness, Swelling

Systemic: Tiredness, Headache, Muscle Pain, Chills, Fever, Nausea

Rare

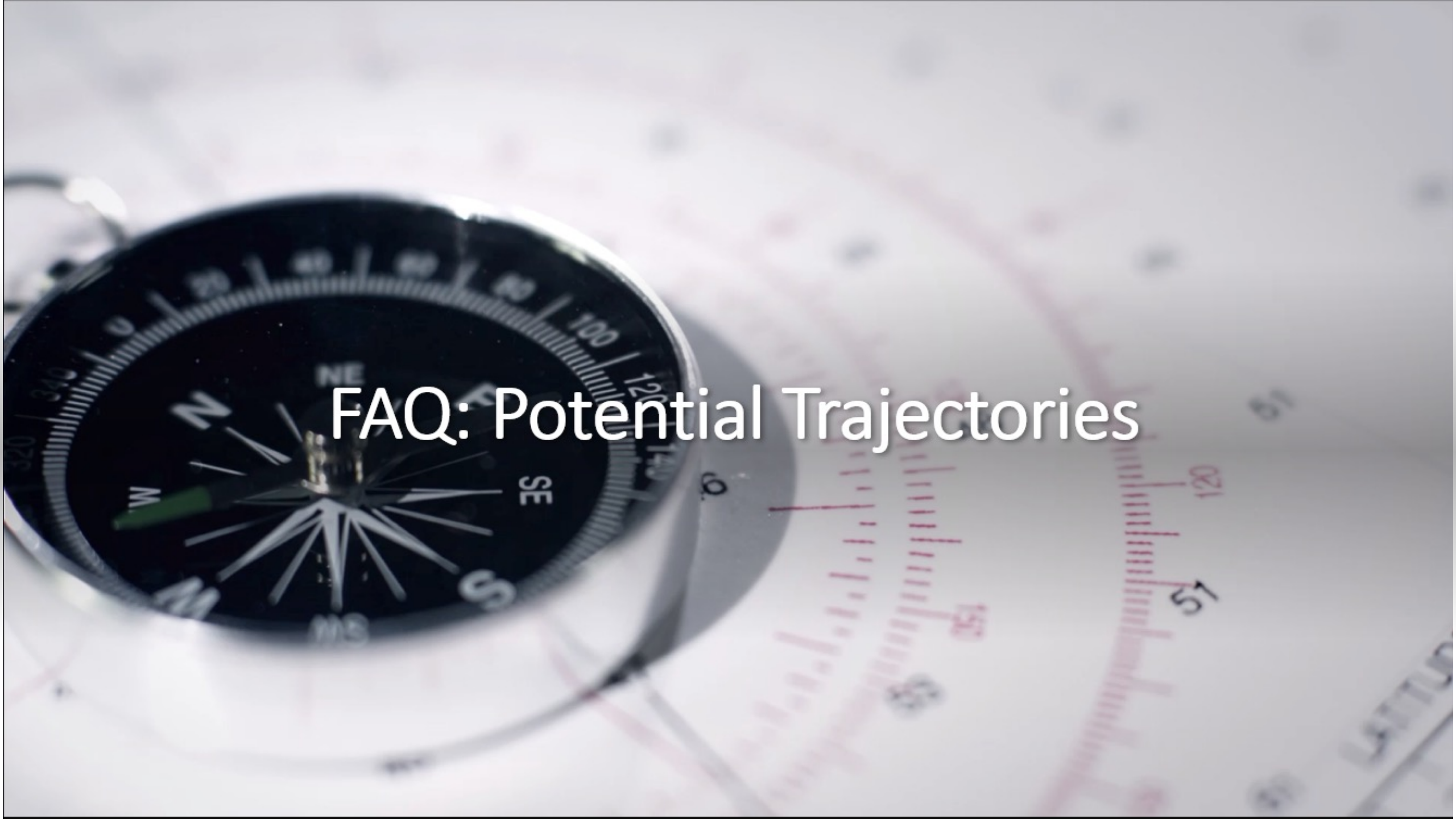
Anaphylaxis- all (~5/ 1Million)
Thrombosis with thrombocytopenia syndrome (TTS)- J&J & AZ (~3/ 1Million)
Guillain-Barré Syndrome- J&J & AZ (~16/1 Million)
Myocarditis – Pfizer & Moderna (~10/ 1 Million)

Boosters

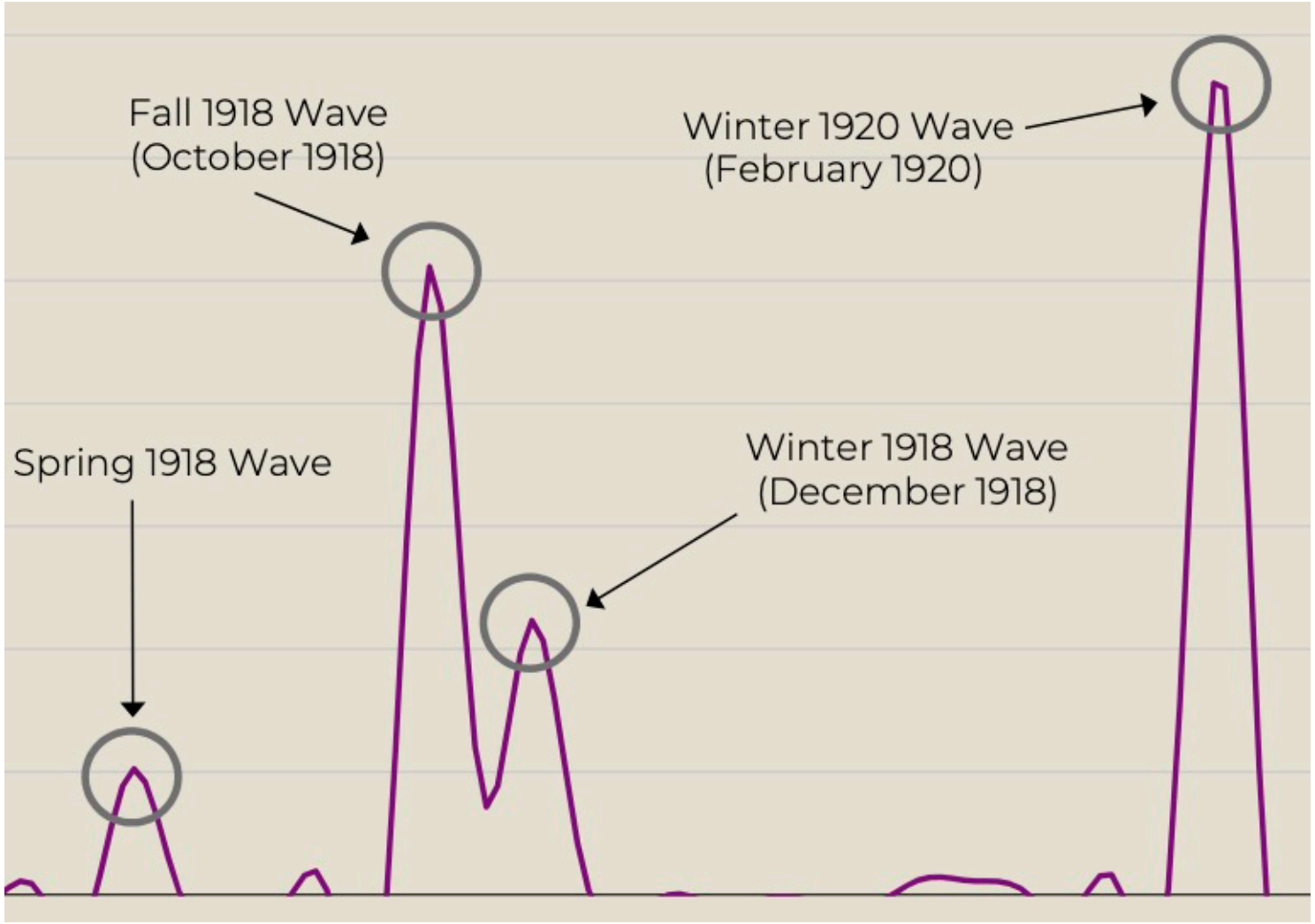
Similar Side Effects to Vaccines

For Perspective

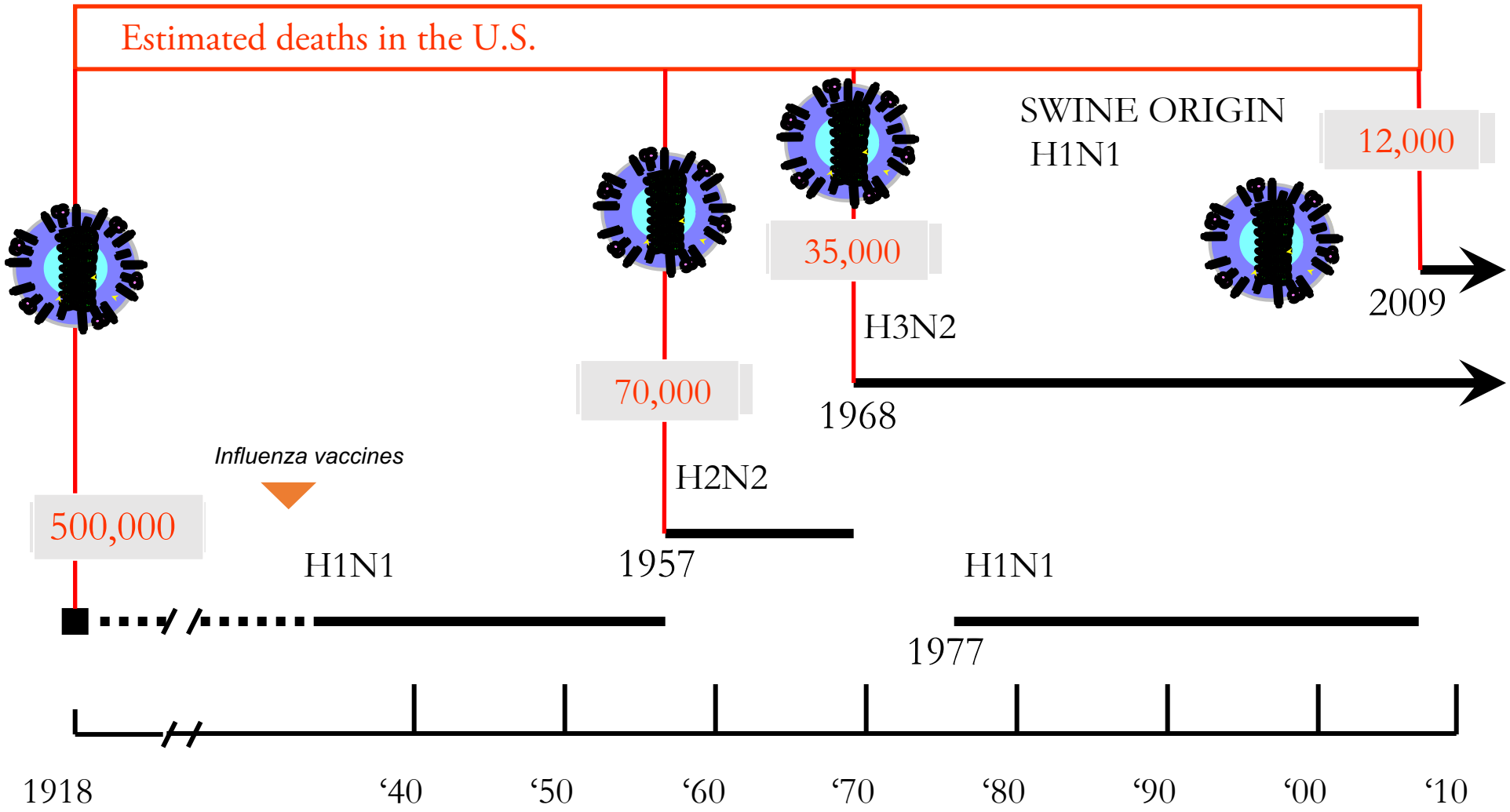
Dying in a Car Accident: 1/ 107
Killed on a Bike: 1/ 3,825
Struck by Lightening: 1/ 15,000
Killed in a Dog Attack: 1/ 86,781
Winning Olympic Gold: 1/ 662,000
Death by Asteroid: 1/ 700,000


FAQ: Potential Trajectories

Where do we go from here? Lessons from 1918



HUMAN INFLUENZA VIRUS PANDEMICS



Likely Trajectories

‘”It's tough to make predictions, especially about the future”

- Omicron is highly transmissible and likely less pathogenic (high level of adaptation to humans)

  > Will become an enduring strain that goes endemic or seasonal (high likelihood)

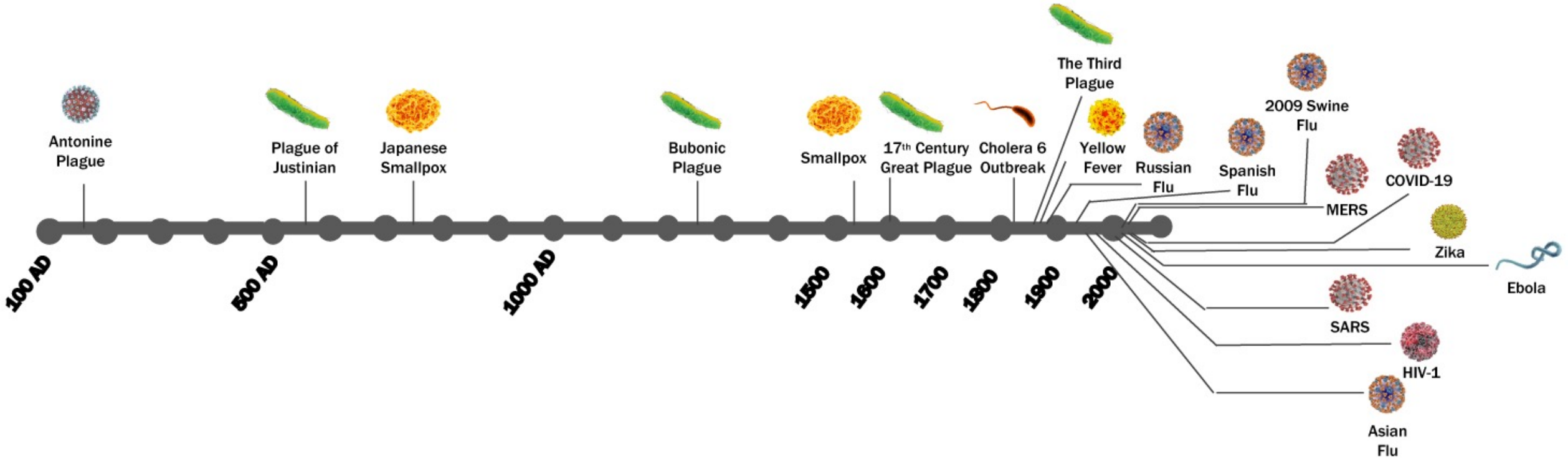
  > Caveats: Emergence of a more transmissible variant with enhanced immune evasion capacity (low likelihood)

  > Annual or bi-annual vaccines to strengthen global immunity to variants

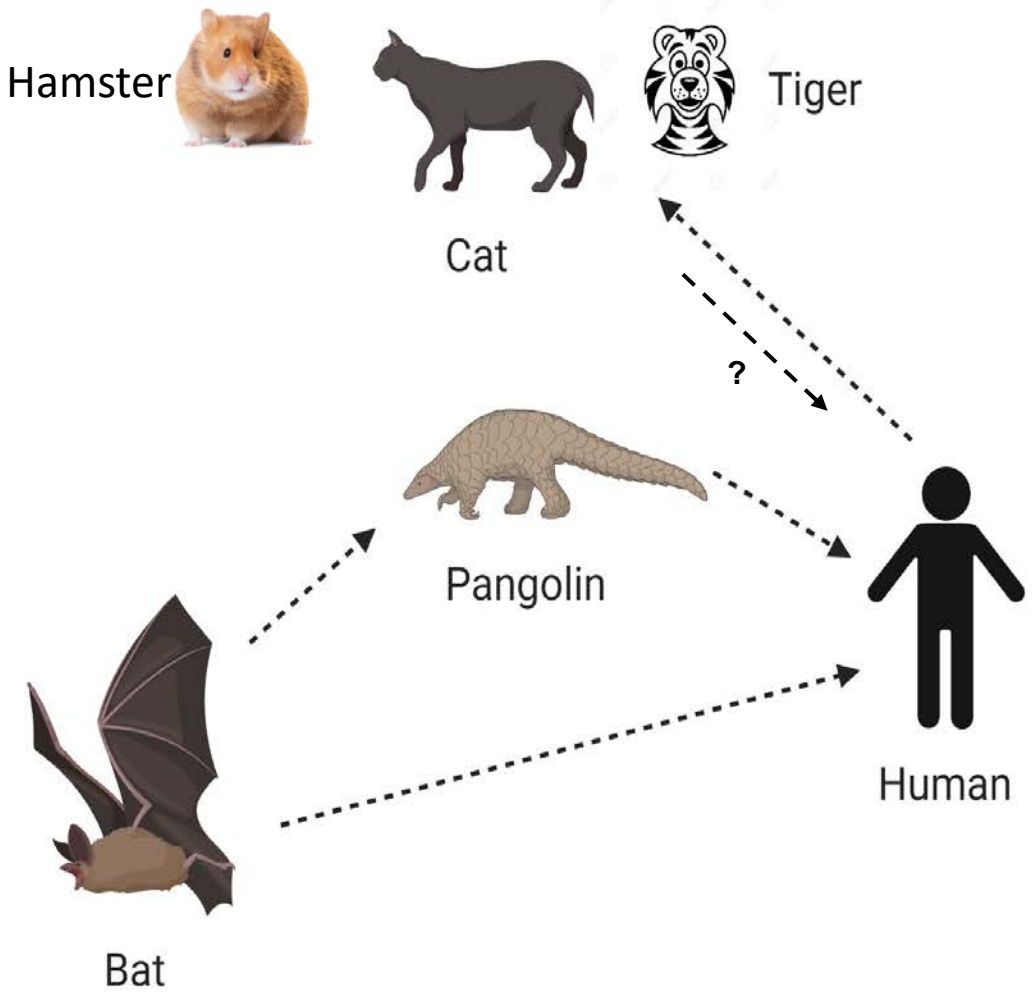
FAQ: Understanding Future Pandemic Risks

A Brief History of Pandemics

No longer a 100-year event



Zoonotic Transmission & Pandemic Spread



Climate Change

Habitat Encroachment/ Wild Animal Trade

Global Interconnectivity

Threat Matrix

Viruses with Epidemic & Pandemic Potential


Novel Influenza Virus


Novel Coronavirus


Nipah Virus


Monkeypox


Enterovirus


Ebola/ Marburg/ Lassa


Crimean-Congo hemorrhagic fever


Rift Valley Fever


Zika/ Dengue/ West Nile Virus/ Yellow Fever


Disease X

Transmission:
Respiratory Droplets
Bodily Fluids/ Close contact
Vectors (e.g. mosquitos, ticks)

Mitigation Strategies- Lives & Livelihoods

- *Global **Surveillance** & Coordinated **Response Strategies***

(information, treatments/vaccines, travel, and supply chains)

- *Prepositioning & Stockpiling of Broad-Spectrum **Antivirals and Vaccines***

- *Increased **Scientific Literacy***

- ***Pandemic Preparedness Programs** to Minimize Global Health & Economic Impacts*

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Surveillance • Scientific Outreach • Vaccines • Antibodies • Therapeutics

Center for Antiviral Medicines & Pandemic Preparedness

www.CAMPP.org

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Tell Congress You Want Us to Be Better Prepared!

Scripps Research Philanthropy:
Meredith Johnston (merejohn@scripps.edu)

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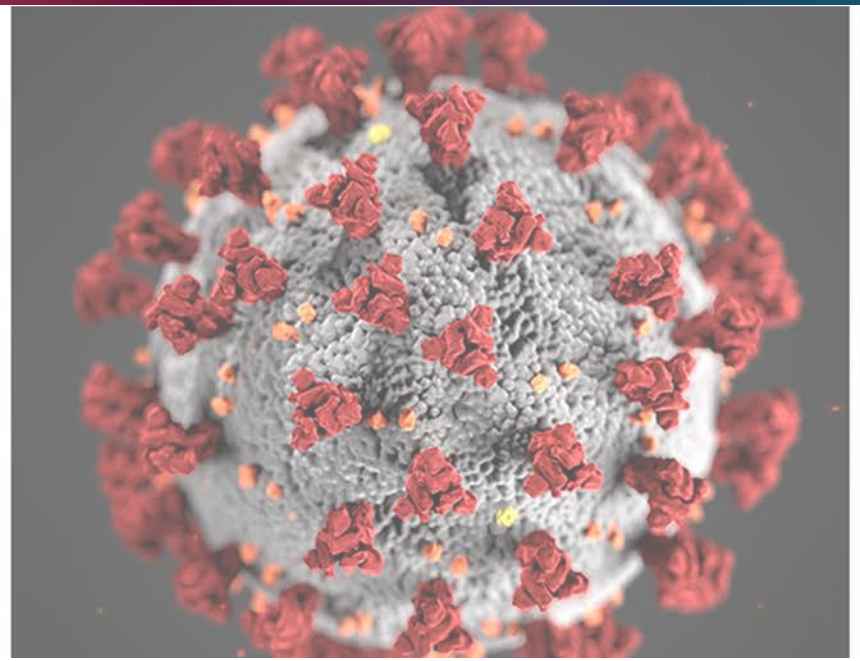

Future Pandemics Are Inevitable, But We Can Be Better Prepared

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UPCOMING LECTURES

Taking a new view of vital signs

Wednesday, April 20
1:00 PM PT/4:00 PM ET

Jay Pandit, MD
Director of Digital Medicine
Scripps Research Translational Institute

Assistant Professor
Department of Molecular Medicine
Scripps Research

The hunt for regenerative medicines

Wednesday, June 29
1:00 PM PT/4:00 PM ET

Michael Bollong, PhD
Assistant Professor
Department of Chemistry
Scripps Research

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