RSV

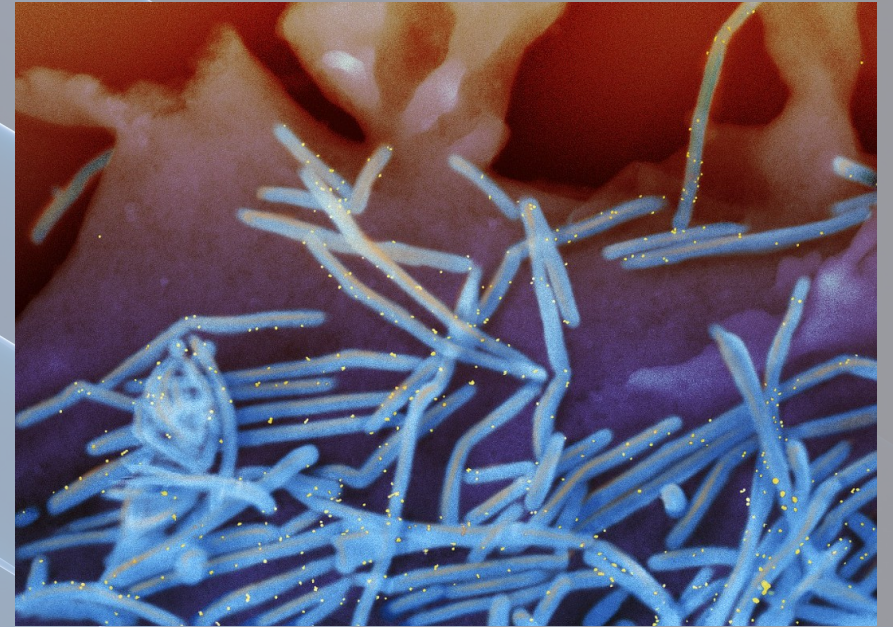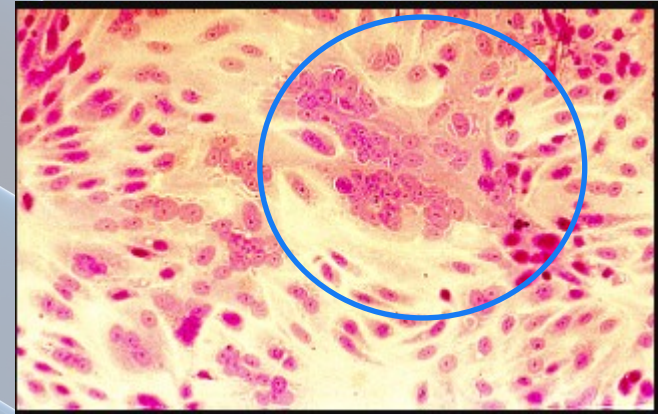## Respiratory Syncytial Virus

Scanning electron micrograph. Labeled with fluorescent anti-RSV antibodies to F (fusion) protein

WHAT'S IN A NAME?

▸ RSV

   ▸ Respiratory — causes respiratory symptoms

   ▸ Syncytial — causes fusion of epithelial cells into a single multi-nucleated cell (a syncytium).

      ▸ Elicited by the F (fusion protein) on the virus.

   ▸ Virus — An anti-sense (negative sense) single strand RNA

RSV UNDER THE HOOD

Respiratory Syncytial Virus (RSV)
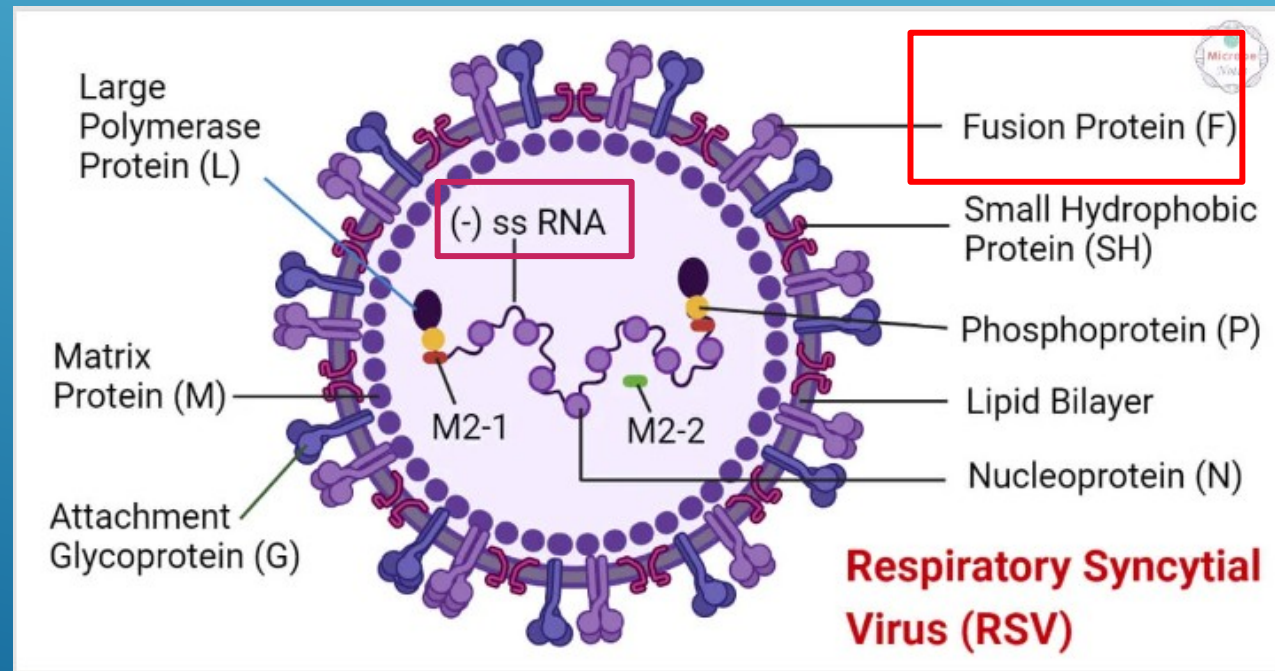
MANIFESTATIONS OF RSV INFECTION

▸ Very young (2 years)   Bronchiolitis

  ▸ Associated with onset of asthma then or later

▸ Middle years   Common Cold or asymptomatic

▸ Elderly (> 60 years) (Nursing home data)

  ▸ 5 – 10% per year

    ▸ Of that group,

      ▸ 10-20% pneumonia (0.5 – 2% of all NH residents)

      ▸ 2 – 5% death rate * (0.1 – 0.5 % of all NH residents)

RSV VS INFLUENZA
IN THE ELDERLY   (>60 YEARS)

▸ Influenza 37 K

▸ RSV 8 K

Annual Deaths

40000	
30000	
20000	
10000	
0	
Influenza	RSV
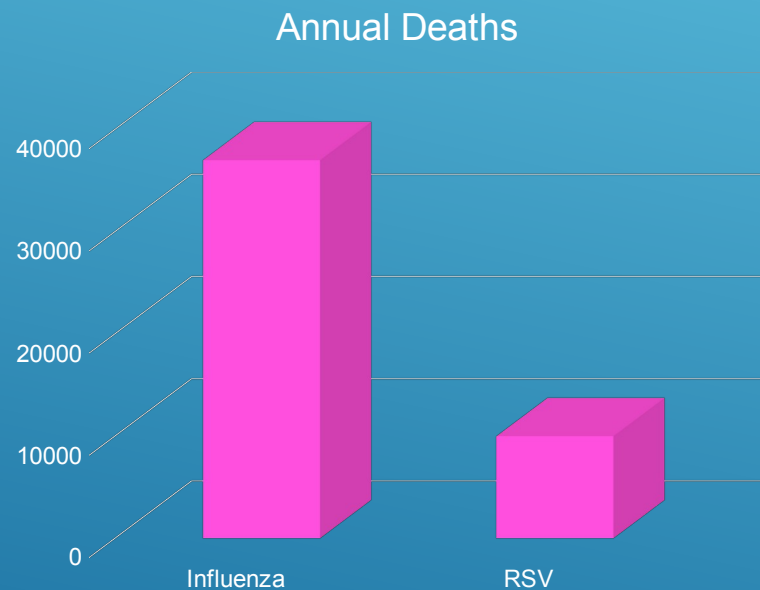
MAKING THE DIAGNOSIS

- Signs and symptoms
- Rapid Antigen Detection
  - Direct Fluorescent Antibody   (Kids only. Adults shed too little virus)
- Polymerase chain reaction (PCR) (More expensive)
- Viral culture ─ long turnaround time (3-5 days) & low sensitivity

PREVENTION

- **Avoidance**
  - Close contact
  - Sharing inanimate objects
  - Hand washing after contact
  - Covering mouth when coughing or sneezing
- **Passive immunization**
- **Active immunization**

PASSIVE IMMUNIZATION (CHILDREN)

▸ RSV- IV Ig   (Intravenous Immunoglobulin)

▸ Palivizumab (Synagis) monoclonal neutralizing antibody (for children)

▸ Nirsevimab (Beyfortis) long-acting monoclonal antibody (for children)

▸ Extended half life provided by three amino acid substitutions into the native monoclonal antibody.

ACTIVE IMMUNIZATION ADULTS (> 60 YRS)

▸ Abrysvo   PFizer

▸ Arexvy   GSK

AVREXY

- A stabilized version of the RSV F protein.

- Structure-based vaccine design...... Took about 20 years to figure out. Was used extensively in designing COVID-19 vaccine.

- Generates antibodies and long-term immunity against the RSV Fusion protein.

AREXVY

- RSV reduction 82% in healthy people
  - 12,466 subjects
    - Placebo   40 cases
    - Arexvy   7 cases
- RSV reduction 95% in people with at least one comorbidity
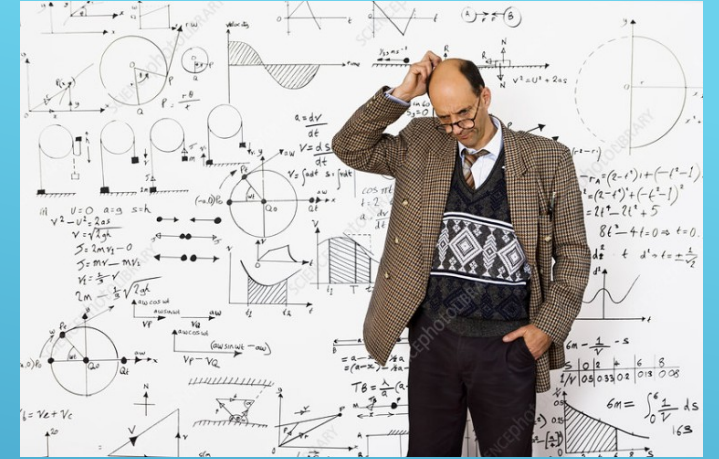- Cost per dose: $300

Side Bar: Death rate.

- Directly from the disease.

- Include death from a secondary complication
  of the disease

- Include death from any disease or condition of any sort
  while having active RSV disease.

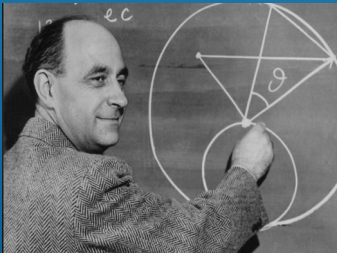- Death the time of or shortly after having the disease.

Death Rate
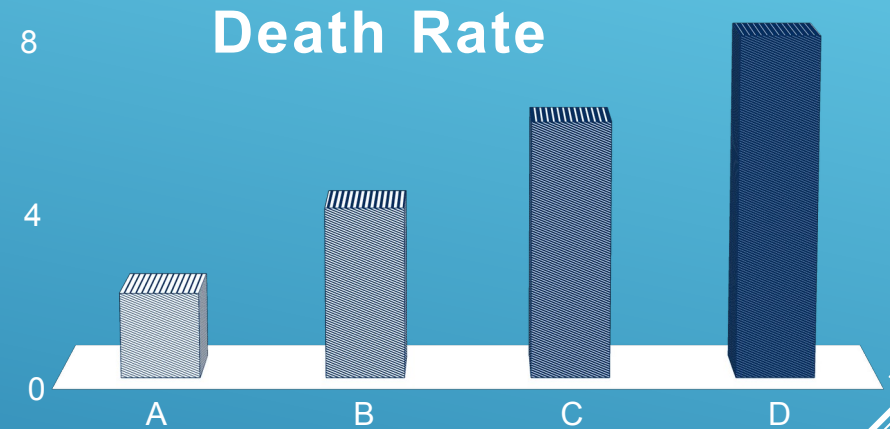
DO THE MATH....

Rough numbers

- RSV reduction 82% in healthy adults

- If we immunized the entire US population over 65 (50 million) with Arexvy, we would prevent 8,000 deaths per year.

- Soooo... $300 x 5 x 10^7 / 8 x 10^3 = $190,000 per death saved.

Enrico Fermi
1901 – 1954

OR... A LONG RUN FOR A SHORT SLIDE.

- Upper Bound

  - Upper bound: about 10% of nursing home residents have RSV annually, i.e., one RSV cold every 10 years in adults over 65 years old.

  - It would take an annual RSV injection for 12.5 years to prevent one infection, almost all of which are colds.

  - Chance of dying... 1/25,000 - 0.00004%

AND THE CDC SAYS...

▶ Adults 60 years of age and older may receive a single dose of RSV vaccine using shared clinical decision-making (SCDM).
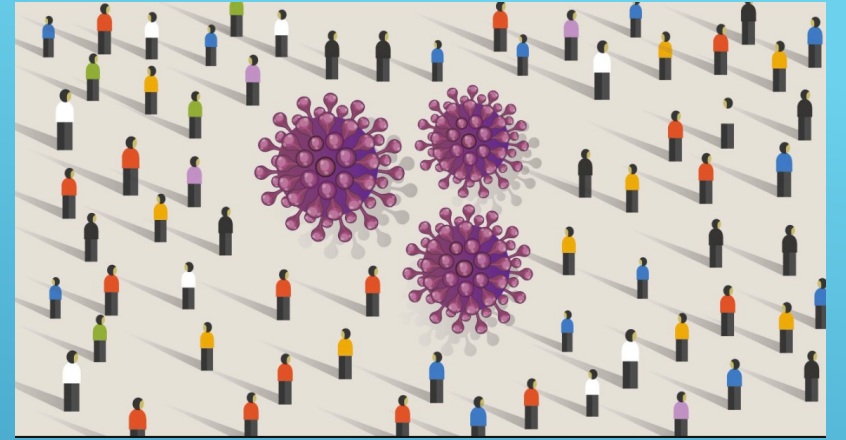
CHANGING GEARS TO COVID

What's new pussycat?
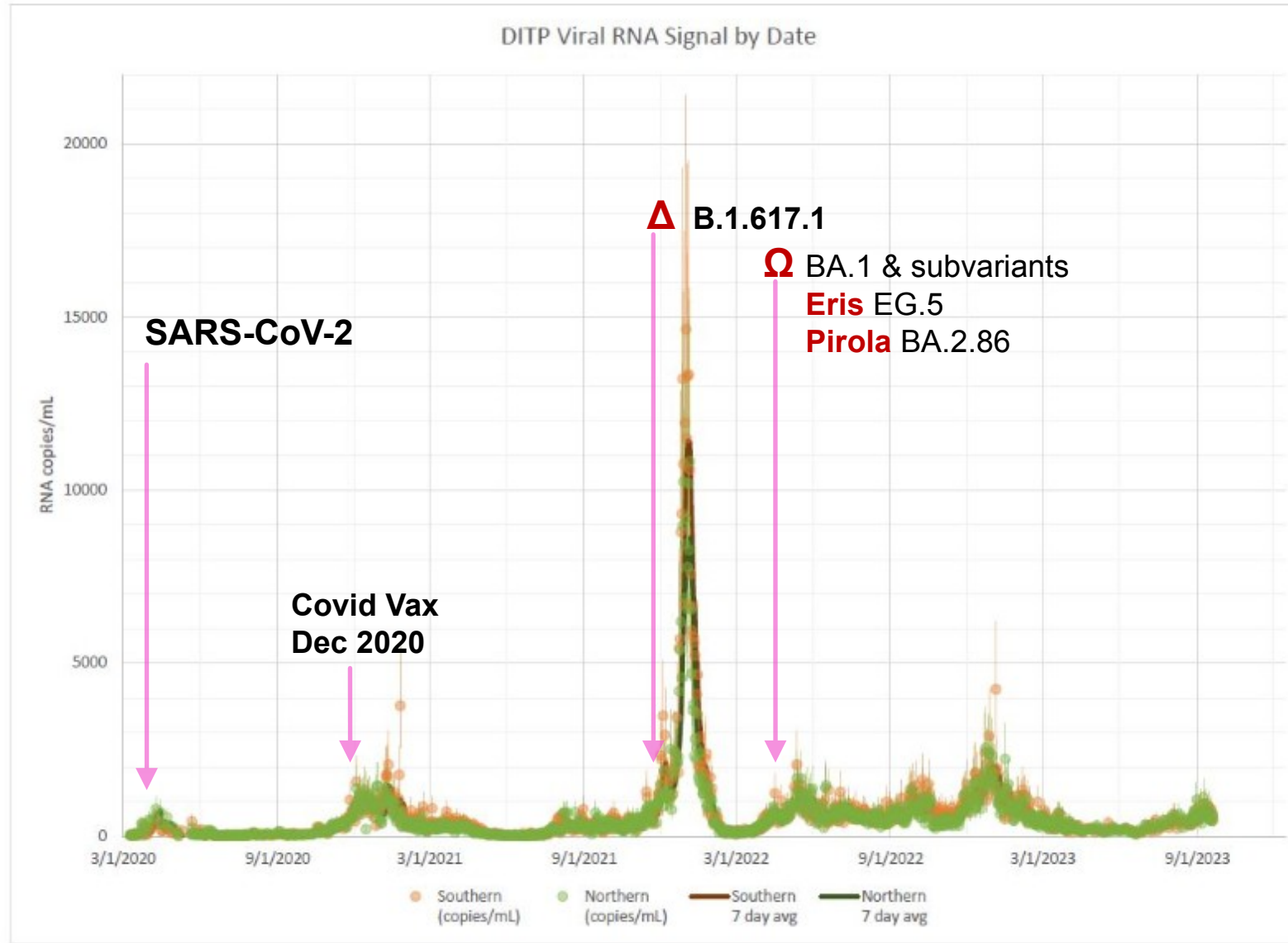
EPIDEMIOLOGY

Evolve from Pandemic

⟶ to Epidemic

⟶ to Endemic

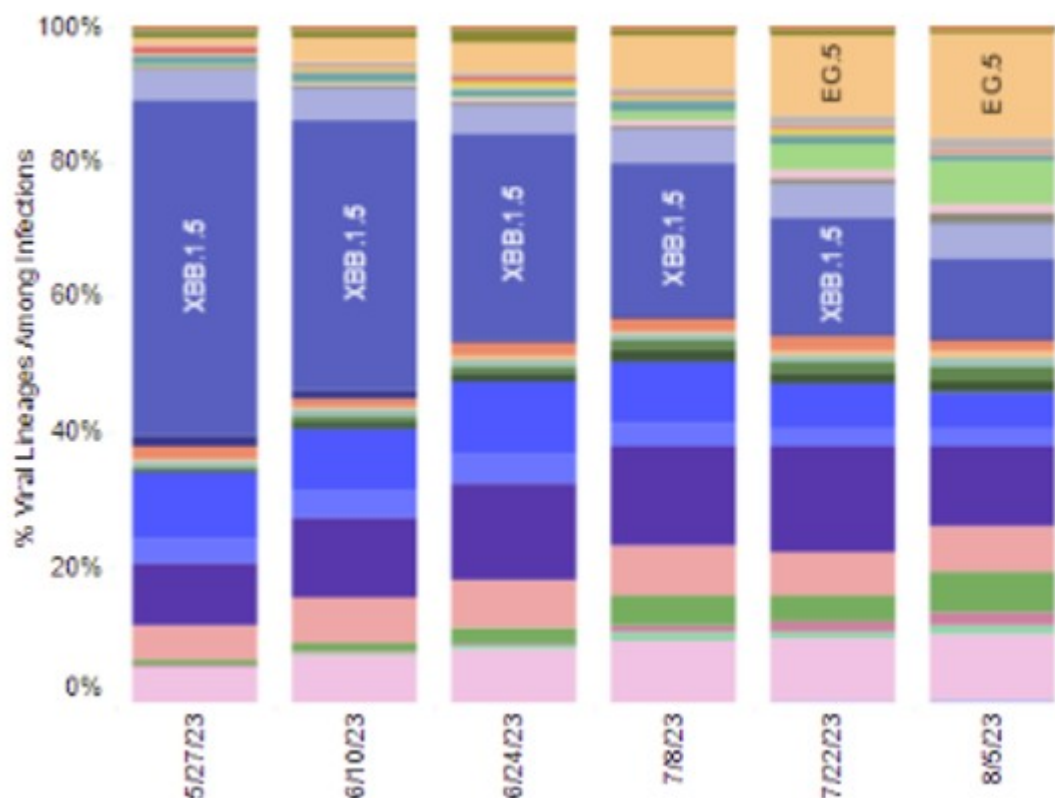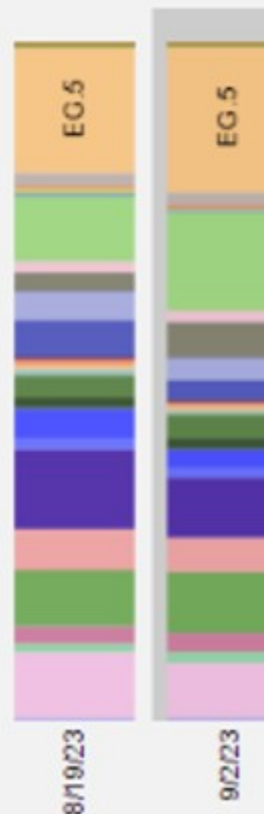Likely to self-attenuate through mutations.

MWRA VIRAL RNA SIGNALS

Eris: Greek goddess of discord, chaos, and strife.

Pirola: a combination of the Greek letters π & ρ.

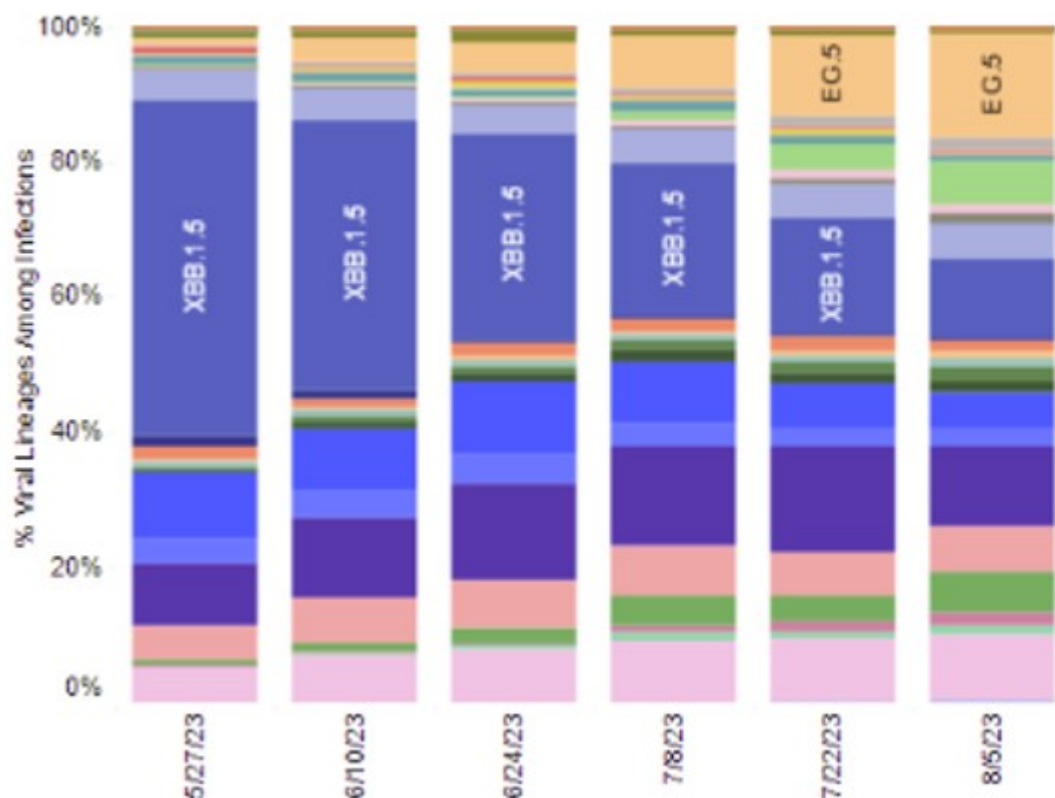Weighted Estimates: Variant proportions based on reported genomic sequencing results | projected estimates of variant proportions
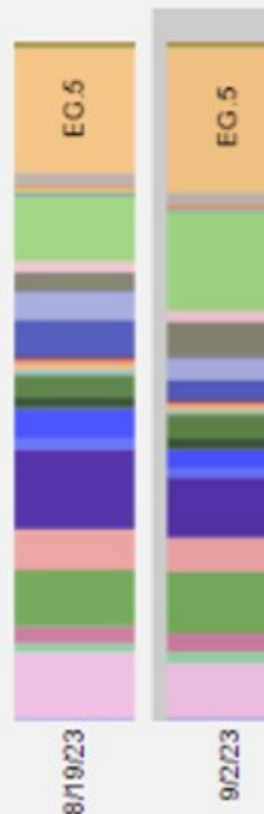
WHO label	Lineage #	%Total	95%PI	
Omicron	EG.5	21.5%	19.0-24.3%	
	FL.1.5.1	14.5%	10.5-19.6%	
	XBB.1.16.6	9.2%	7.6-11.0%	
	XBB.1.16	8.9%	7.8-10.3%	
	XBB.2.3	8.1%	7.0-9.2%	
	HV.1	5.1%	3.3-7.9%	
	XBB.1.16.1	5.0%	4.2-6.0%	
	XBB.1.5.70	3.5%	2.6-4.7%	
	XBB	3.3%	2.7-4.1%	
	XBB.1.5	3.1%	2.6-3.7%	
	XBB.1.9.1	3.0%	2.5-3.5%	
	XBB.1.16.11	2.8%	1.8-4.5%	
	EG.6.1	1.8%	1.2-2.7%	
	GE.1	1.6%	1.1-2.4%	
	XBB.1.5.72	1.6%	1.2-2.1%	
	XBB.1.42.2	1.3%	0.7-2.3%	
	XBB.1.9.2	1.1%	0.9-1.3%	
	XBB.1.5.10	0.9%	0.7-1.2%	
	XBB.1.5.68	0.8%	0.5-1.1%	
	XBB.2.3.8	0.7%	0.4-1.2%	
	FD.1.1	0.6%	0.4-0.8%	
	FE.1.1	0.5%	0.3-0.8%	
	XBB.1.5.59	0.4%	0.3-0.6%	
	CH.1.1	0.4%	0.3-0.6%	
	EU.1.1	0.1%	0.1-0.2%	
	XBB.1.5.1	0.0%	0.0-0.1%	
	BA.2.12.1	0.0%	0.0-0.1%	
	BA.5	0.0%	0.0-0.0%	
	BQ.1	0.0%	0.0-0.0%	
	FD.2	0.0%	0.0-0.1%	
	B.1.1.529	0.0%	0.0-0.1%	
Other	Other[a]	0.0%	0.0-0.1%	

Weighted Estimates: Variant proportions based on reported genomic sequencing results

projected estimates of variant proportions

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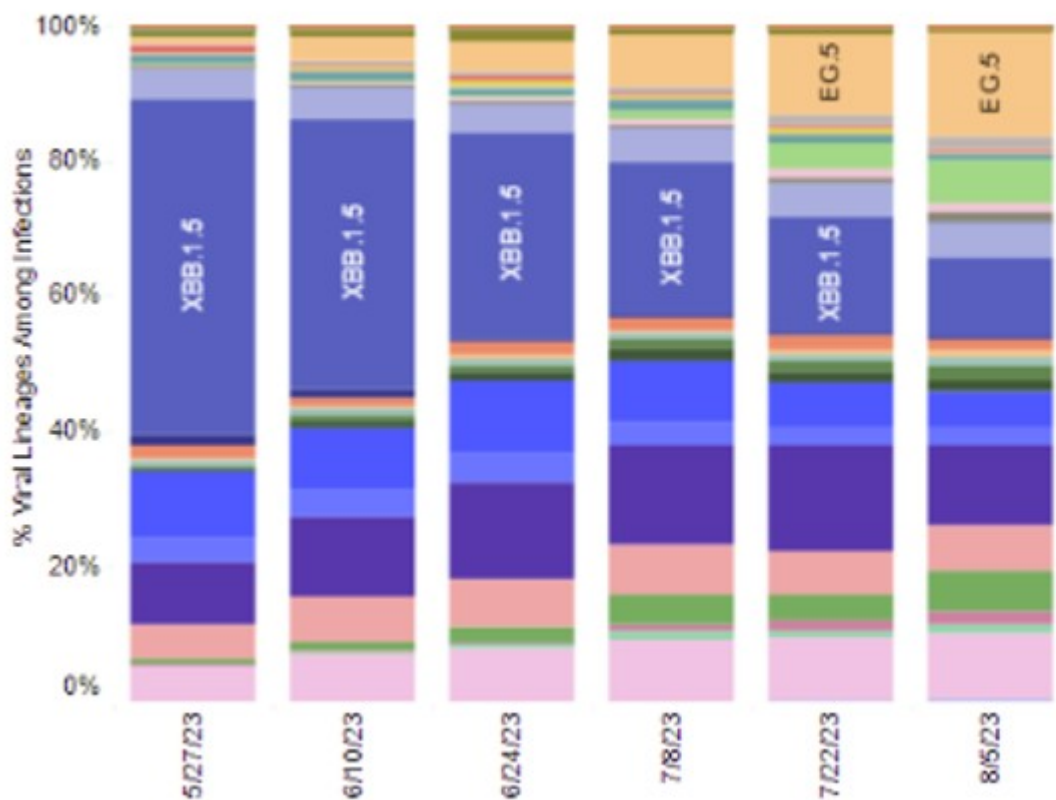Weighted Estimates: Variant proportions based on reported genomic sequencing results
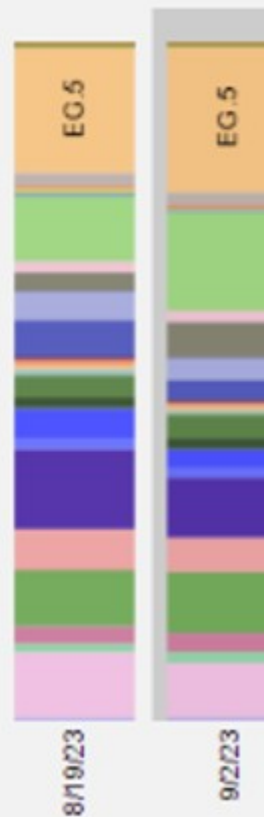
projected estimates of variant proportions

BA.2.86 not forecast in August when chart was made.

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COVID IMMUNIZATION BOOSTER

What we know about the Moderna monovalent booster against XBB.15

Neutralizing immunoglobulin levels rise from the monovalent vaccine against XBB.1.5

XBB.1.5 is rapidly disappearing

It provides a significant boost in neutralizing antibodies
against rising variants EG.5 and FL.1.5.1 variants.

BA.2.86 has 30 mutations to the spike protein. Questions have arisen
about its match for the Moderna XBB.1.5 booster.

BIOLOGICAL NICHES

When a biologic niche is emptied,
a different organism will move in.

If the population is immunized against XBB.1.5, EG.5, FL.1.5.1 , and
B.2.86, will other strains move in to fill the empty niche?

DO THE COVID TESTS WORK ON THE NEW STRAINS ?

▸ The home test to detect Covid antigen seem to work for XBB.1.5, EG.6. and BA.2.86.   (I assume FL.1.5.1 as well.)

▸ A PCR test can be designed to detect universal RNA fragments or strain-specific ones.

WHAT WE DON'T KNOW.

How much protection from current strains is provided by:

- Past Covid infection

- Past Covid immunization

- Hybrid immunity (Past infection & immunization)
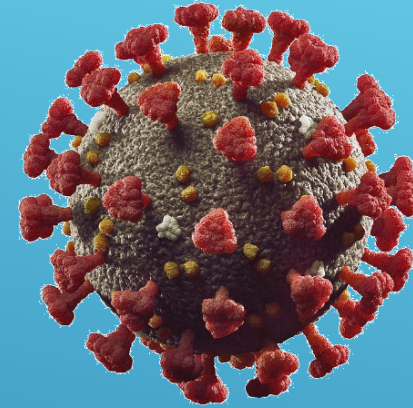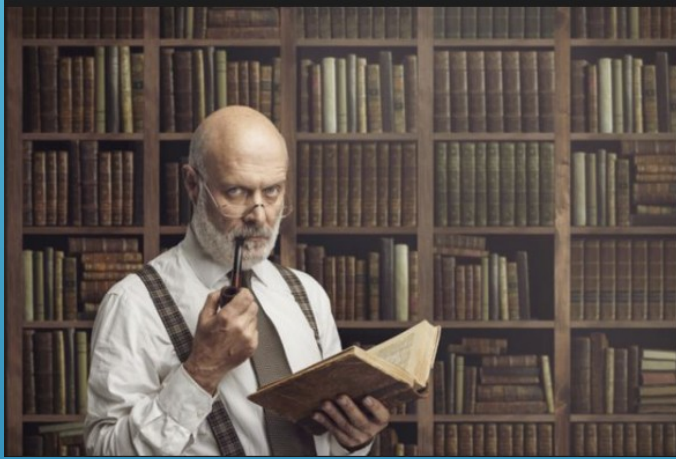
DATA PROBLEM

Past infection

- Does infection from one of the multiple strains provide a different level of protection from current strains?
  - If you had a previous Covid infection, which strain did you have?
- Covid tests, antigen or PCR, identified antigens or RNA segments found in all strains, i.e., the test was designed to establish the presence of Covid virus, nothing more.
- Were the specimens saved? Doubt it. They could be retested for unique RNA segments to identify a specific viral strain.   (Ah, given the zillions of tests, that'll never happen.)

DATA PROBLEM

— PAST INFECTION PROTECTION

So if you have had Covid, we don't know how much protection you have against the current strains.

DATA PROBLEM — PAST IMMUNIZATION

How much does past immunization protect against current covid strains?

XBB.1.5 is as far genetically from SARS-CoV-2 as SARS-CoV-2 is from the original SARS. (2003)

DATA PROBLEM — HYBRID IMMUNITY

Much of the imprinted hybrid immunity was acquired when the original Omicron strain was circulating.

How much does this immunity extend to XBB.1.5, etc.?

SINGAPORE STUDY ON HYBRID IMMUNITY

- XBB.1.5 wave in Singapore — real world picture on hybrid immunity.

- Studied breakthrough infections by BA.4, BA.5, and an XBB subvariant.

SINGAPORE STUDY

Hybrid immunity provided by pre-2022 Omicron variants, i.e, original SARS-CoV-2, did not confer protection against XBB.1.5 infection.

Hybrid immunity from previous BA.2 infection provided protection against BA.4 and BA.5, but less against XBB strains, especially to XBB over time since original infection. "Waning immunity."
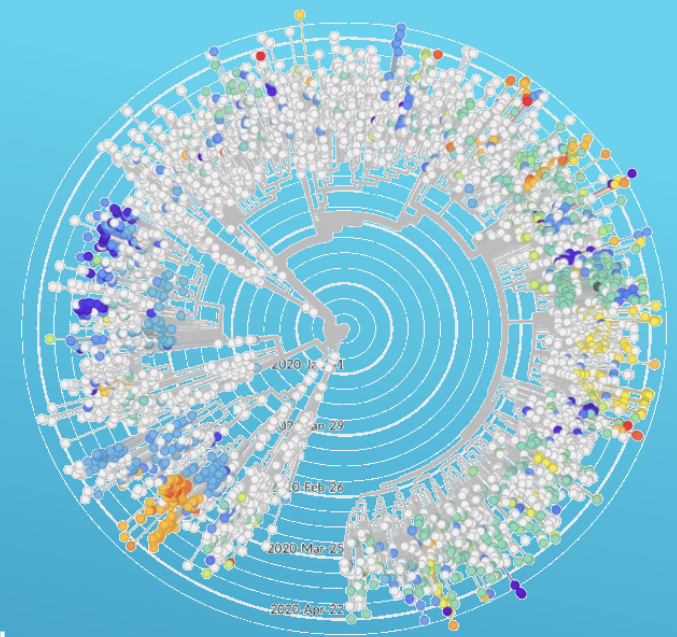
Technical term: Differential quantity and quality of imprinted protective immunity varies with virus type and date of past infection.

TO MAKE MATTERS WORSE

All of the above isn't the real problem....

COVID EVOLUTION

- The strains change so fast that constructing an updated immunization and testing it with two shots six weeks apart and then studying its effect for six months results in an outdated study.

- New strains inevitably emerge during that time so the "updated" immunization can be obsolete by the time that its efficacy has been established.

- ...And you still have to get it out there for immunization.

MODERNA SAYS…..

The Moderna updated XBB.1.5 vaccine generates a strong immune response against BA.2.86
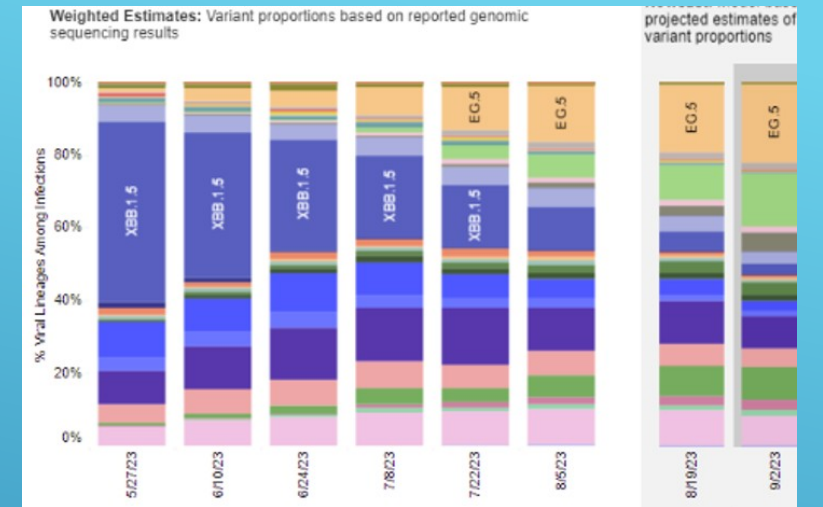
BA 2.86 causes 0.5 % cases of cases (September 13)

BA.2.86 prevalence over the coming months is unknown.

SO, THE CDC SAYS....

"A booster is recommended for everyone."

Crystal clear....