Emerging Infections –Separating Fact from Fiction

What do we know about the newest one to plague the Human Race

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Will things Ever Return to Normal?

October 2020

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TWiM
THIS WEEK IN MICROBIOLOGY

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

Emerging Infections –Separating Fact from Fiction

1. Provide a definition of an emerging infection/pathogen or re-emerging pathogen
2. Apply the information presented from the examples offered as to how they might appreciate and understand the risks associated with an emerging or re-emerging pathogens
3. Evaluate and rank the relative risk that emerging/re-emerging pathogens might represent to their community
4. Explain to colleagues, staff and patients the value proposition that routine vaccination affords to them individually, and to facilitating protection from pathogens
5. Actively contribute to the formulation of plans for the dentistry and his/her community that can mitigate the effects of emerging and extant pathogens.

Bottom Line Up front for an Emerging Infectious Disease

1. How contagious is the microbe?

- ***Look at the rate and assess the risk…***
  - *SARS-CoV-2 It seems substantially infectious, more so than SARS from 2003*
  - *Droplet secretions and fomites (like countertops, restaurant menus, etc.)*
  - *There are asymptomatic carriers are among us helping to facilitate spread.*

2. How deadly is the virus?

- *It's hard to know yet. But the fatality rate is probably going to reach ~10 %*
- *Today the global case fatality rate was 6.2%; today ~ 2.8% why?*
- *Still substantially* ***less than SARS from 2003 (10%) and MERS (36%)***

3. How long does it take to show symptoms?

- *Possibly* ***between 2 to 14 days (mean of 5)****, allowing the illness to go undetected*
- *There are asymptomatic carriers among us, helping to facilitate spread!*

Bottom Line Up front for an Emerging Infectious Disease

4. How much have infected people traveled?

- *The virus spread quickly because it started in a transportation hub in China and folks were/are shedding virus before symptomatic.*
  - *Hence the need for global & local social distancing*

5. How effective will the responses be?

- *Initially the W.H.O. has praised China's efforts, but critics feared the lockdown of 50M plus would fail given already spread to >24 countries… Feb… to April 14 ->185 countries/regions… today it's been global x2*

6. How long will it take to develop a vaccine?

- *A vaccine is still a year + away — at minimum*

The Initial Question – What is an Emerging Infection

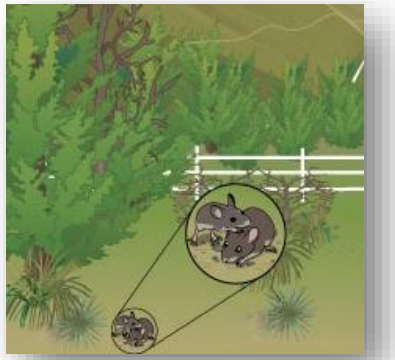
- ***Since 1970 ~40 infectious disease have emerged-***
  - *Chikungunya~1952 Tanzania (to become contorted) ~1 M*
  - *Pontiac Fever or Legionella ~1968 or 1976*
  - *Ebola ~1976*
  - *HIV-AIDS ~1981 new data reveals but really the beginning of the 20th century*
  - *Sin Nombre (1993)*
  - *SARS ~2003*
  - *Influenza ~2009*
  - *MERS ~2012*
  - *SARS-CoV-2*

The Initial Question – What is an Emerging Infection

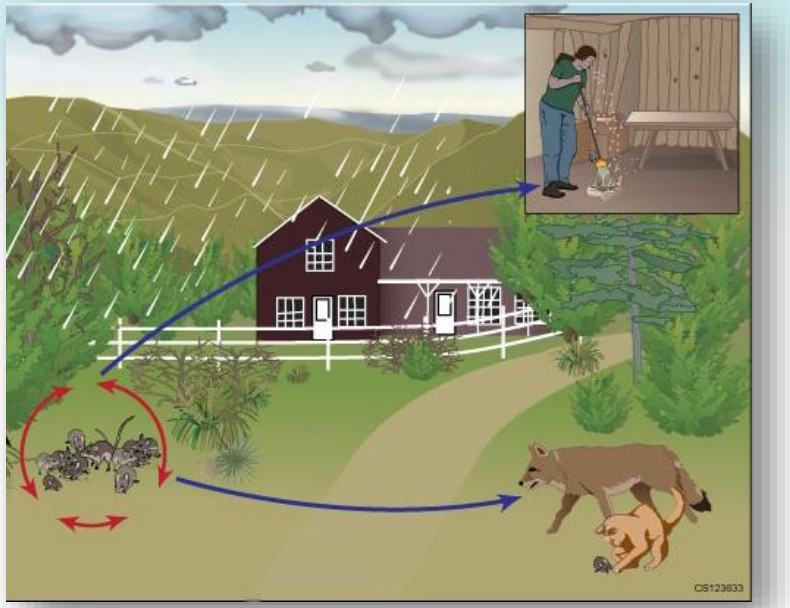
- ✓ ***Previously undetected or unknown infectious agents***
- ✓ ***Known agents that have spread to new geographic locations or new populations***
- ✓ ***Previously known agents whose role in specific diseases has previously gone unrecognized.***
- ✓ ***Re-emergence of agents whose incidence of disease had significantly declined in the past, but whose incidence of disease has reappeared. This class of diseases is known as re-emerging infectious diseases.***

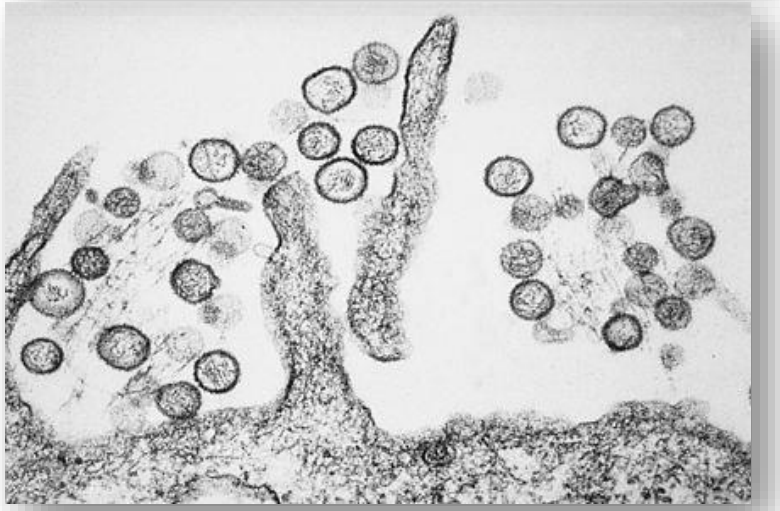
Sin Nombre orthohantavirus

- *Generally a zoonotic infection that has jumped and adapted to its new host…*
  - *An outbreak of a previously unknown disease…*
    - *Sin Nombre orthohantavirus*



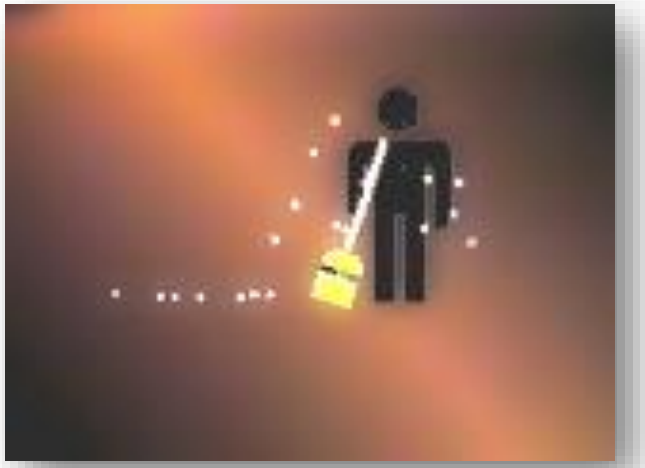
- ***May 1993 unexplained pulmonary illness in southwestern US AZ, NM, CO and Utah***
- *"A young, physically fit Navajo man suffering from shortness of breath was rushed to a hospital in New Mexico and died very rapidly."*
- *"While reviewing the results of the case, medical personnel discovered that the young man's fiancée had died a few days before after showing similar symptoms, a piece of information that proved key to discovering the disease."*
- ***What are you thinking?… bubonic plague?***

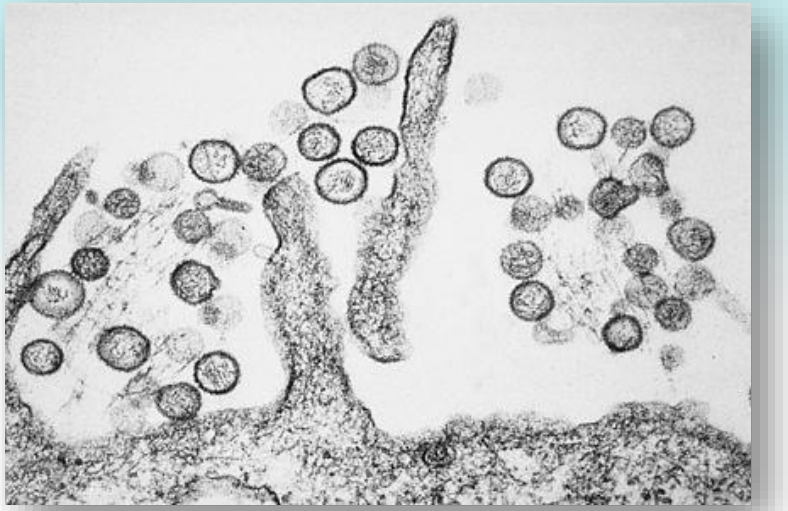


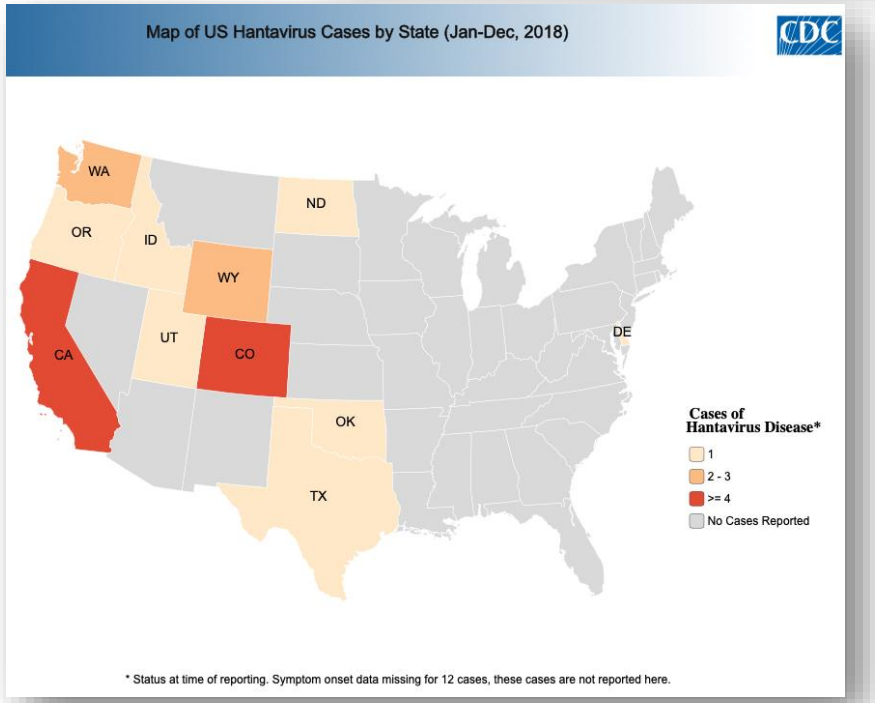


Sin Nombre orthohantavirus

- **Sin Nombre orthohantavirus**
  - Consider the following … NOT bubonic plague !







Re-Emergence…

Flint once thrived as the home of the nation's largest General Motors plant. The city's economic decline began during the 1980s, when GM downsized.

In 2011, the state of Michigan took over Flint's finances after an audit projected a $25 million deficit.

In order to reduce the water fund shortfall, the city announced that a new pipeline would be built to deliver water from Lake Huron to Flint.

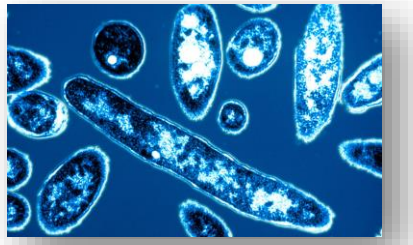
In 2014, while the pipeline was under construction, the city turned to the Flint River as a water source. Soon after the switch, residents reported changes to the water's color, smell and taste.

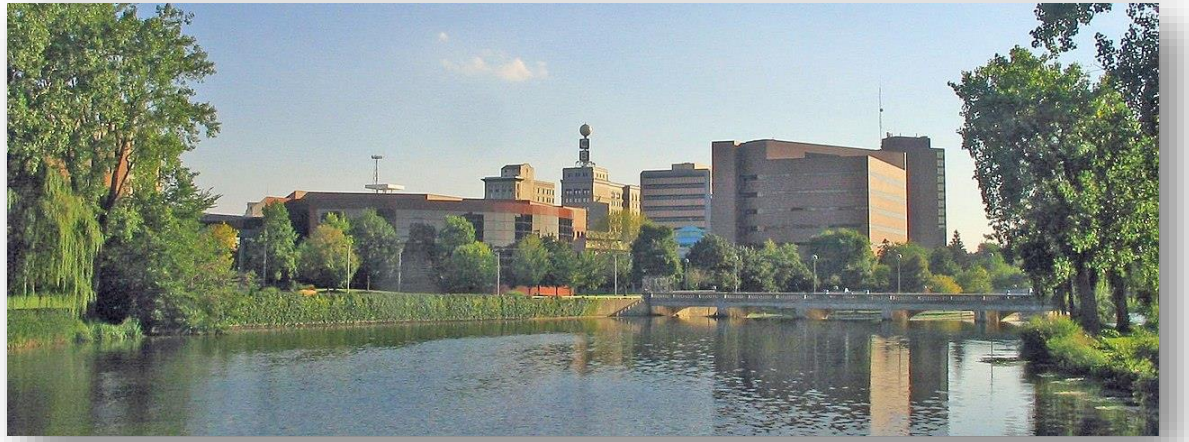
Officials failed to apply corrosion inhibitors to the water.

As a result, lead from aging pipes leached into the water supply, leading to extremely elevated levels of the heavy metal neurotoxin and exposing over 100,000 residents to elevated lead levels.

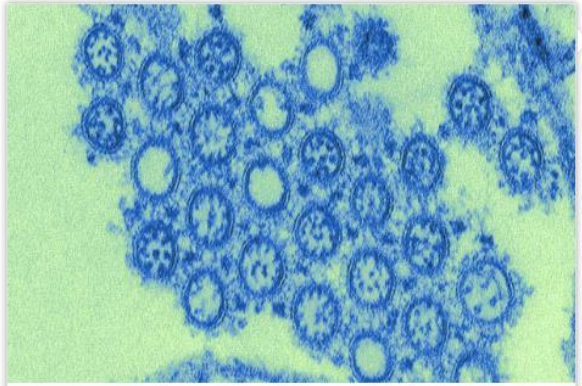
The Lead you know about… what you don't know is the second shoe to drop was the emergence of Legionella in the water that killed 12 people and sickened at least 87 in Flint between 2014 and 2015

Low Chlorine levels supported a bloom of
This pathogen, Legionella pneumophila





Re-Emergence … Influenza as an Emerging Disease



April 15
- First human infection with new influenza A H1N1 virus detected in California.

April 17
- Second human infection with the new influenza A H1N1 virus detected in California about 130 miles away from first infection, with no known connection to previous patient.

April 18
- First novel 2009 H1N1 flu infections were reported by CDC to the World Health Organization (WHO) through the U.S. International Health Regulations Program.

April 21
- CDC publicly reported the first two U.S. infections with the new H1N1 virus.
- CDC began working to develop a candidate vaccine virus.

April 22
- CDC activated it's Emergency Operations Center (EOC).

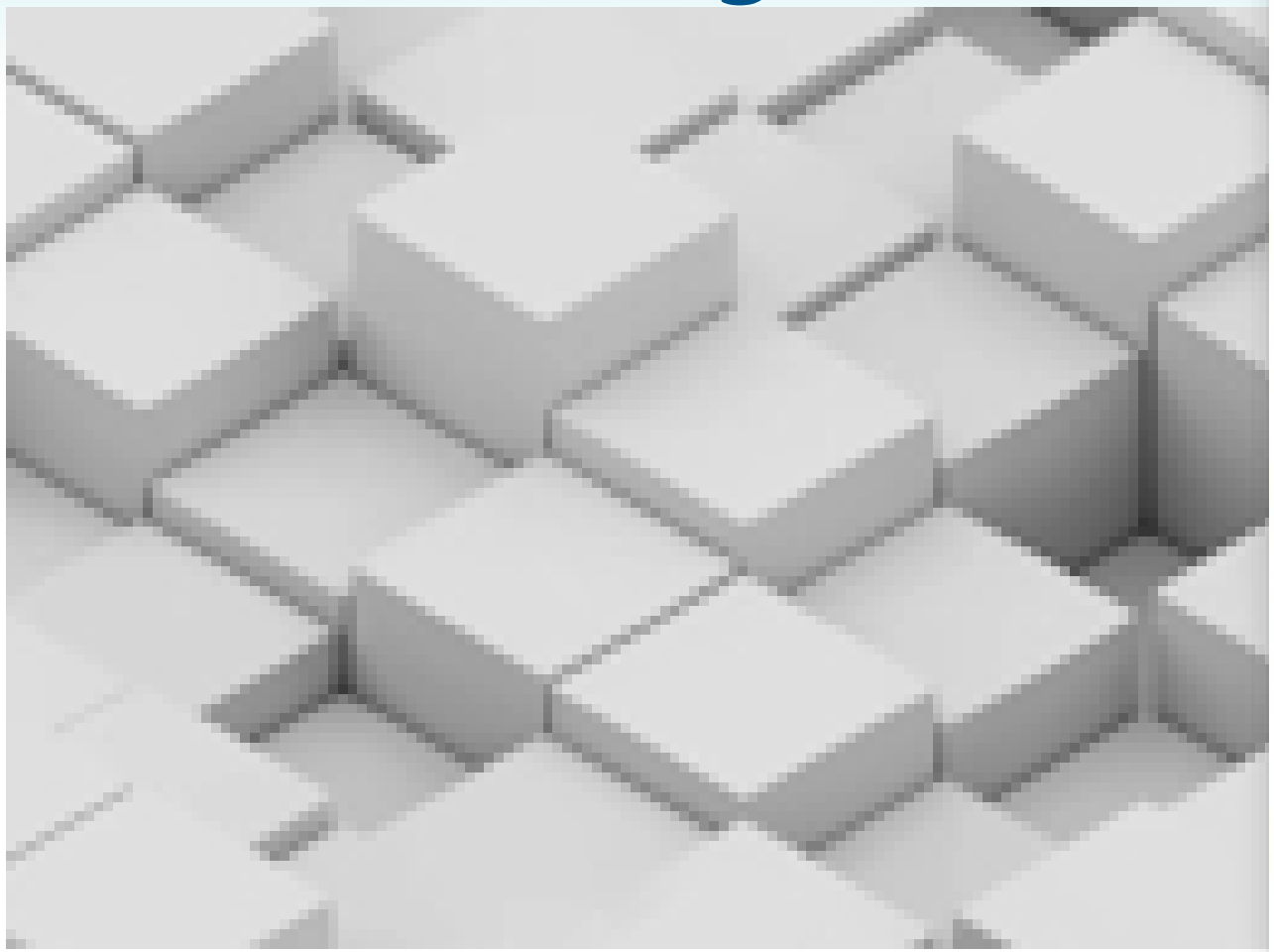
April 23
- Two additional human infections with 2009 H1N1 were detected in Texas, transforming the investigation into a multistate outbreak and response.

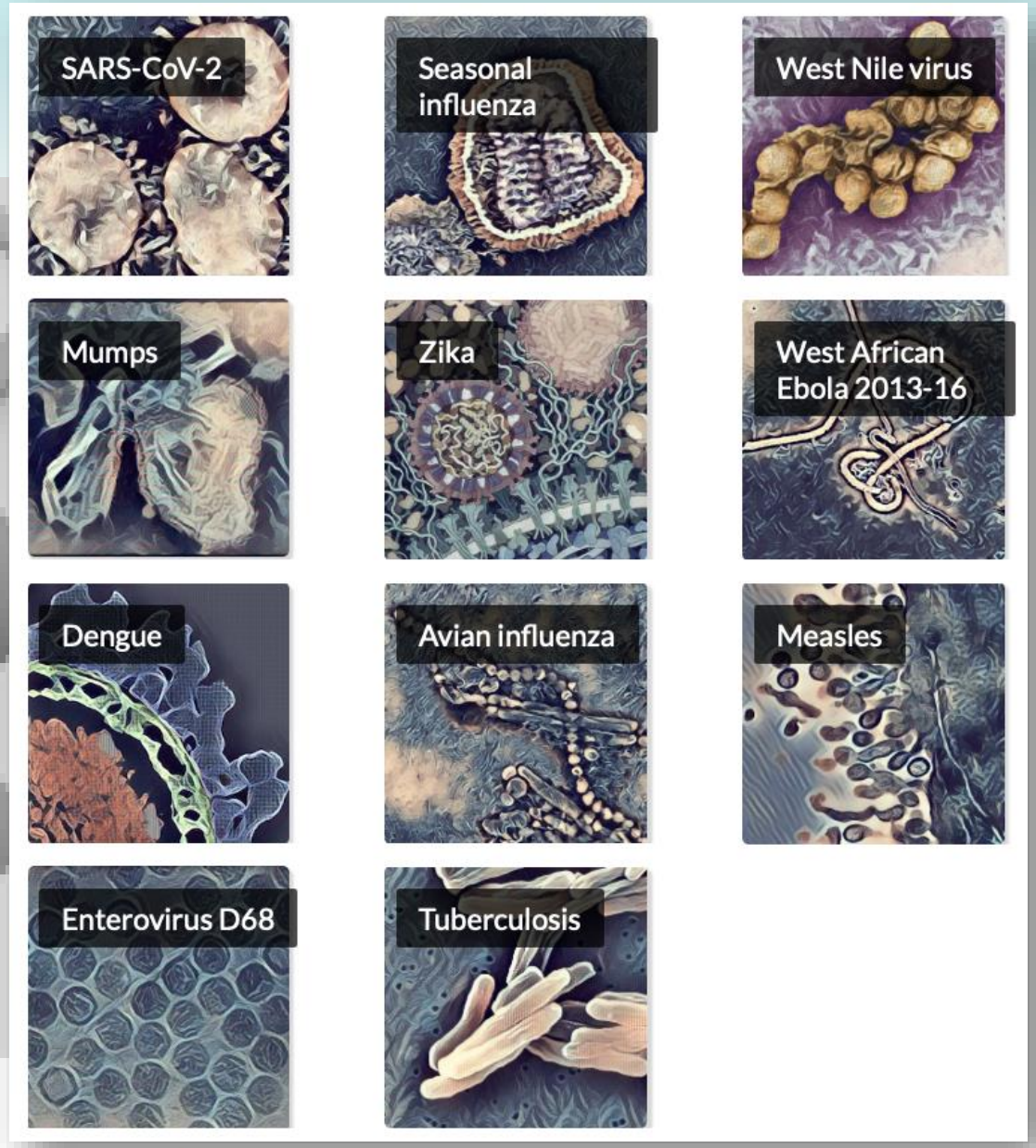
April 25
- The World Health Organization (WHO) declared a public health emergency of international concern.

What we did on April 30th, 2009

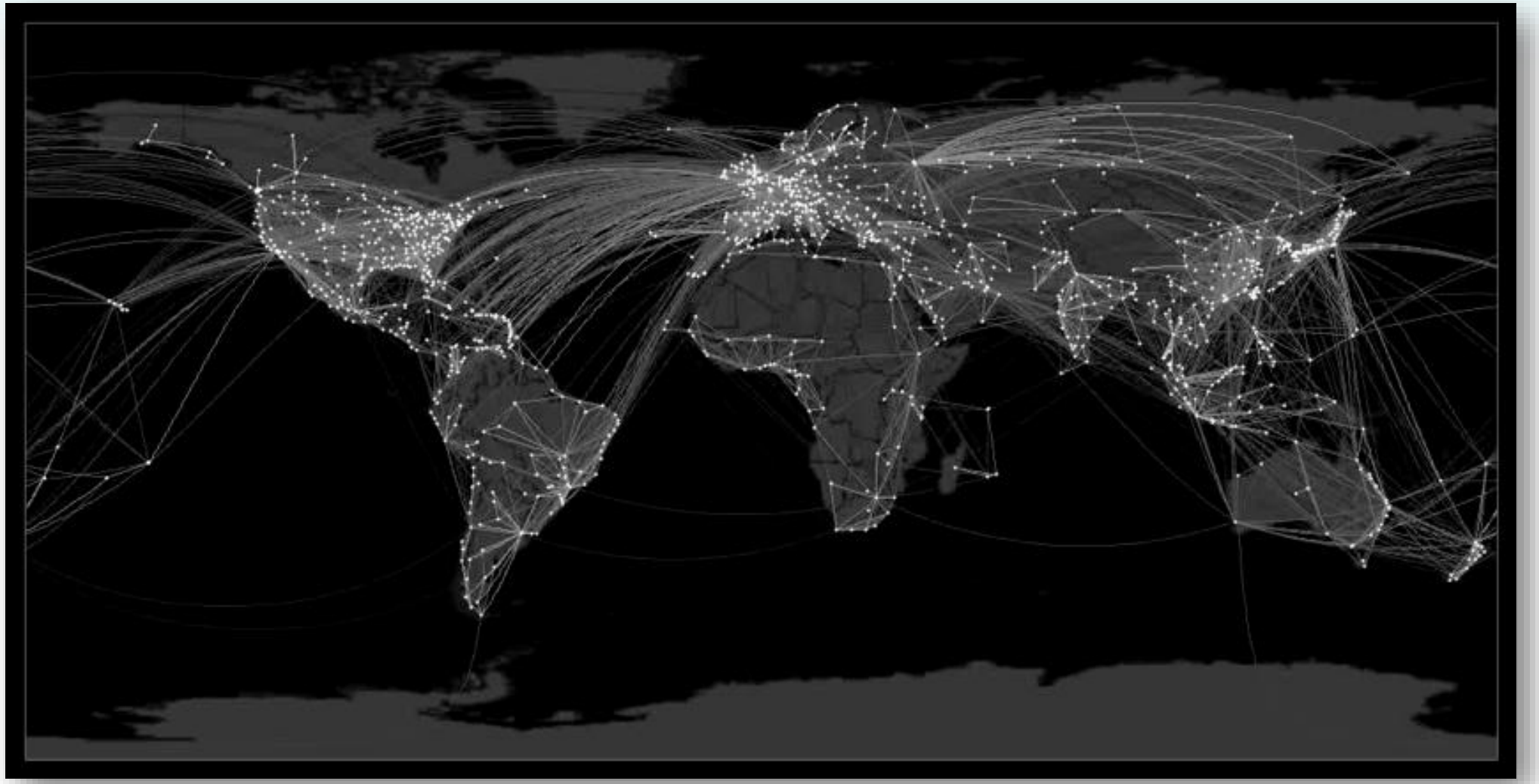
https://youtu.be/4xfiPRxcXp4

Nextstrain.org





Improved Understanding of Transmission, Natural History and Pathogenesis on our Path Towards Addressing Emerging Pathogens

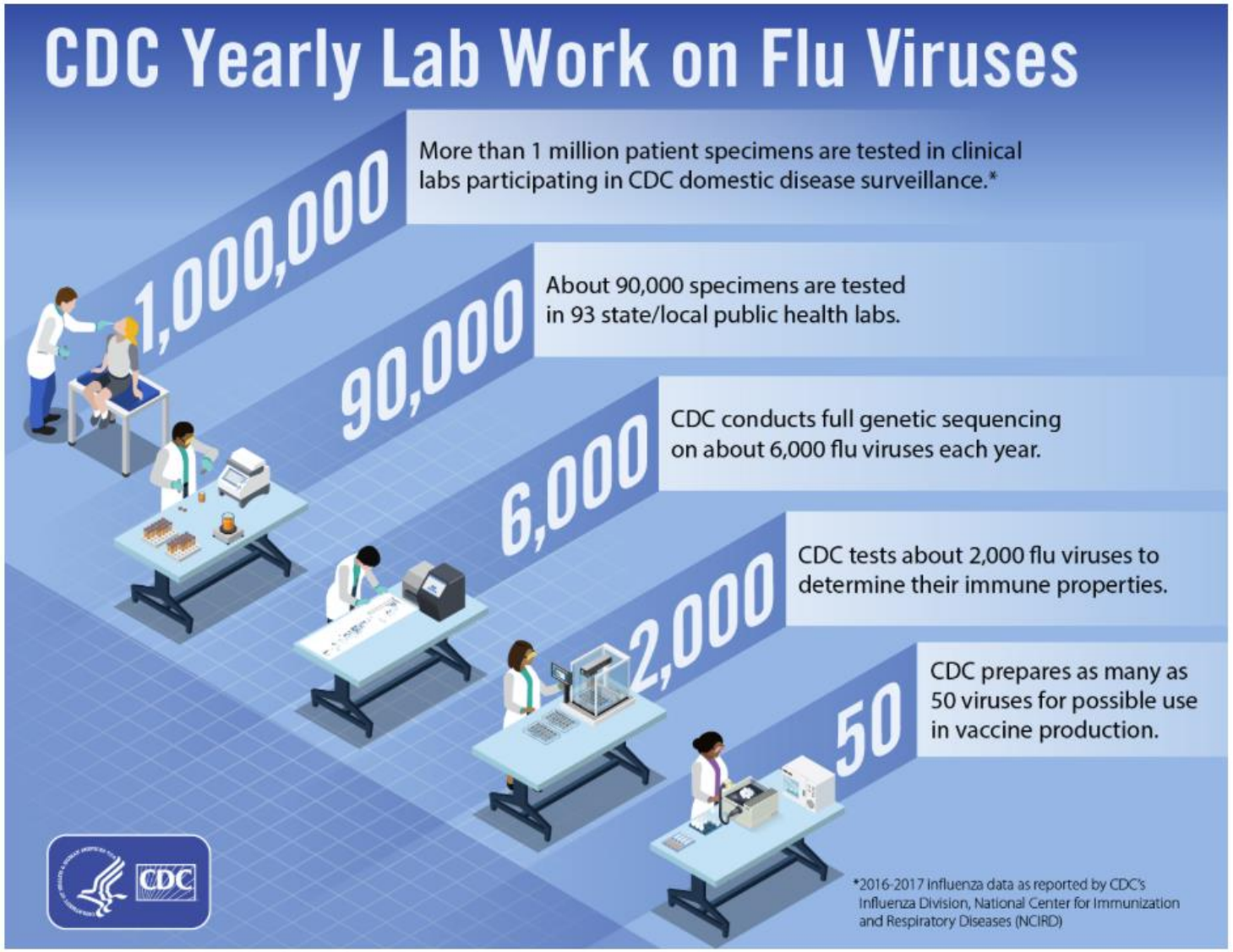


NIAID

Big Data will be key… but how?

WHAT WILL THE FUTURE OFFER FOR CONTROLLING INFLUENZA?

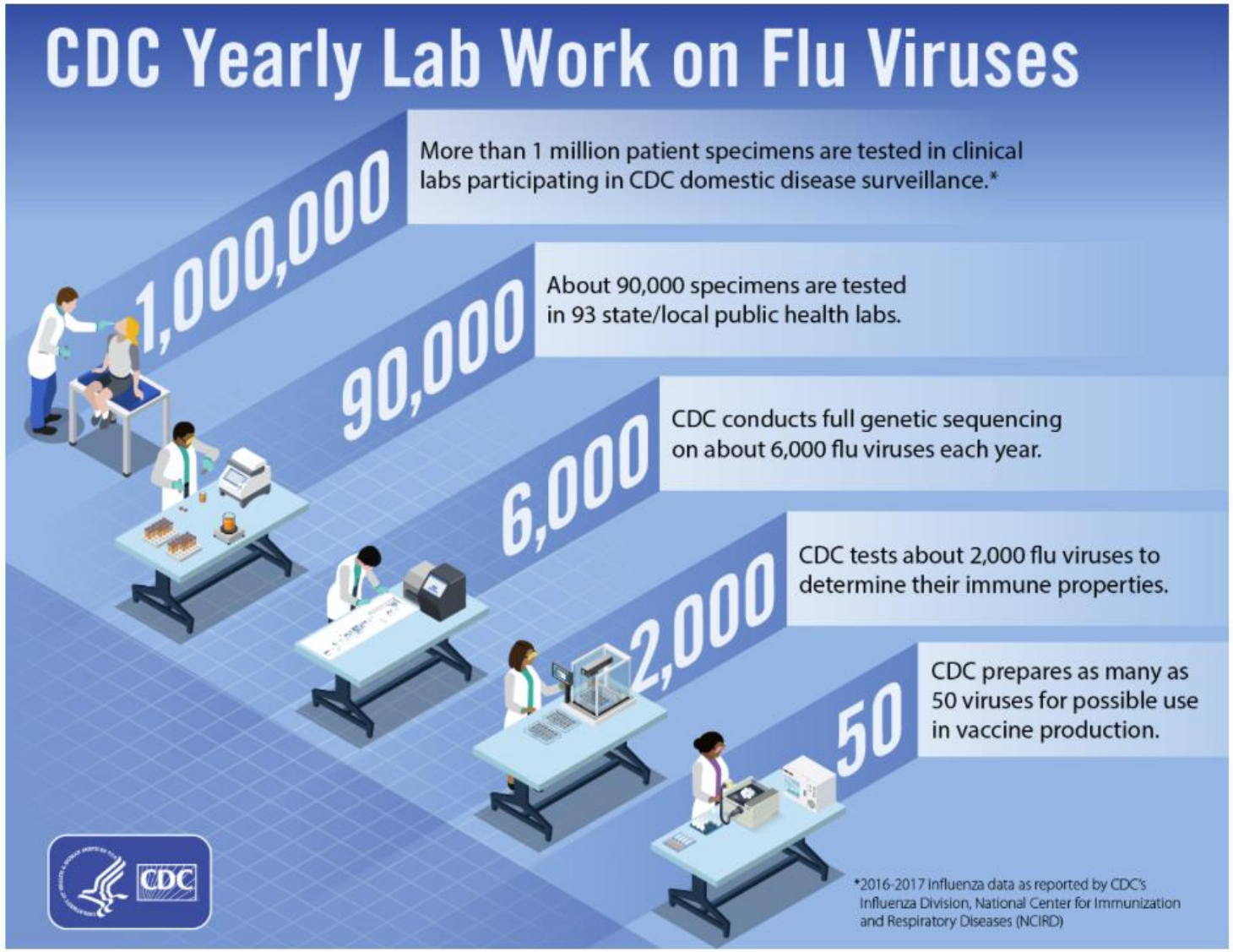
CDC Yearly Lab Work on Flu Viruses Infographic

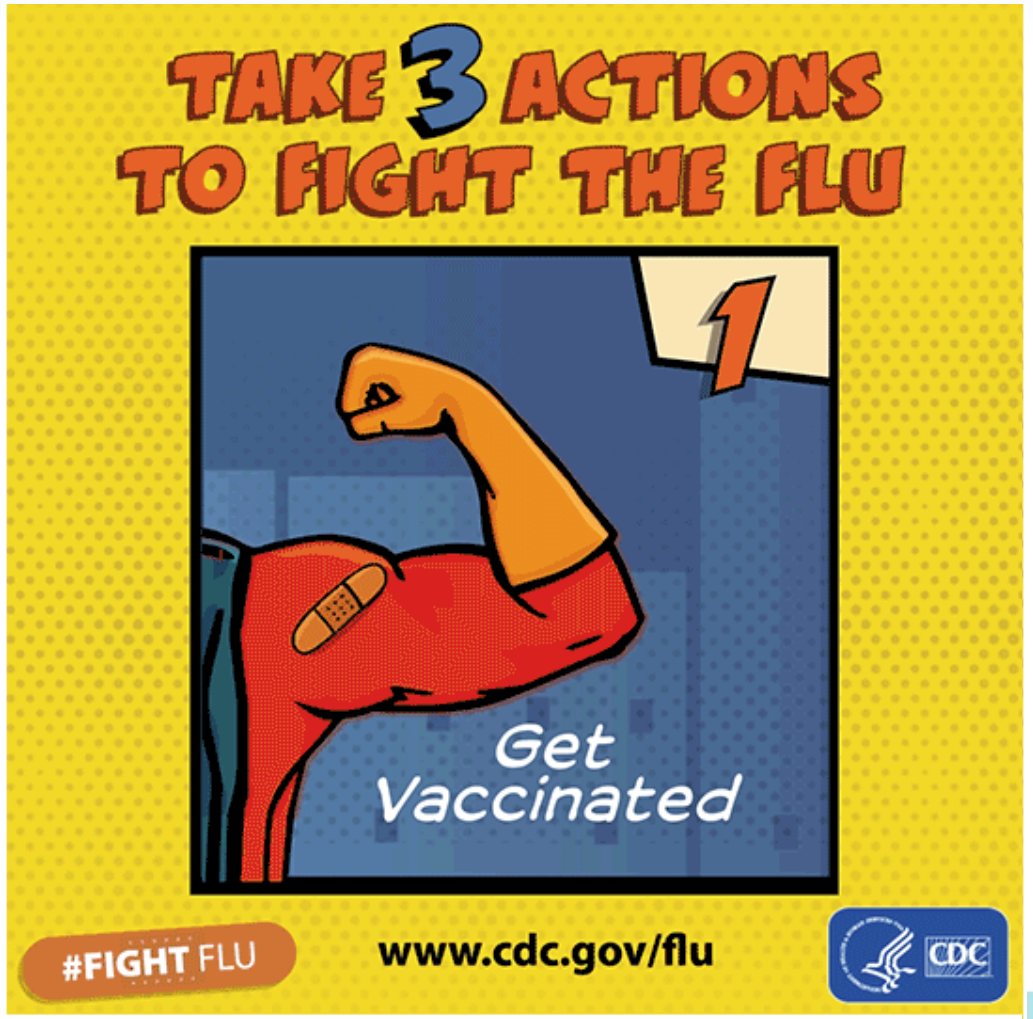


- *In 2016-2017*
  - **1,000,000**: More than 1 million patient specimens are tested in clinical labs participating in CDC domestic disease surveillance.*
  - **90,000**: About 90,000 specimens are tested in 93 state/local public health labs.
  - **6,000**: CDC conducts full genetic sequencing on about 6,000 flu viruses each year.
  - **2,000**: CDC tests about 2,000 flu viruses to determine their immune properties.
  - **50**: CDC prepares as many as 50 viruses for possible use in vaccine production.

WHAT WILL THE FUTURE OFFER FOR CONTROLLING INFLUENZA?

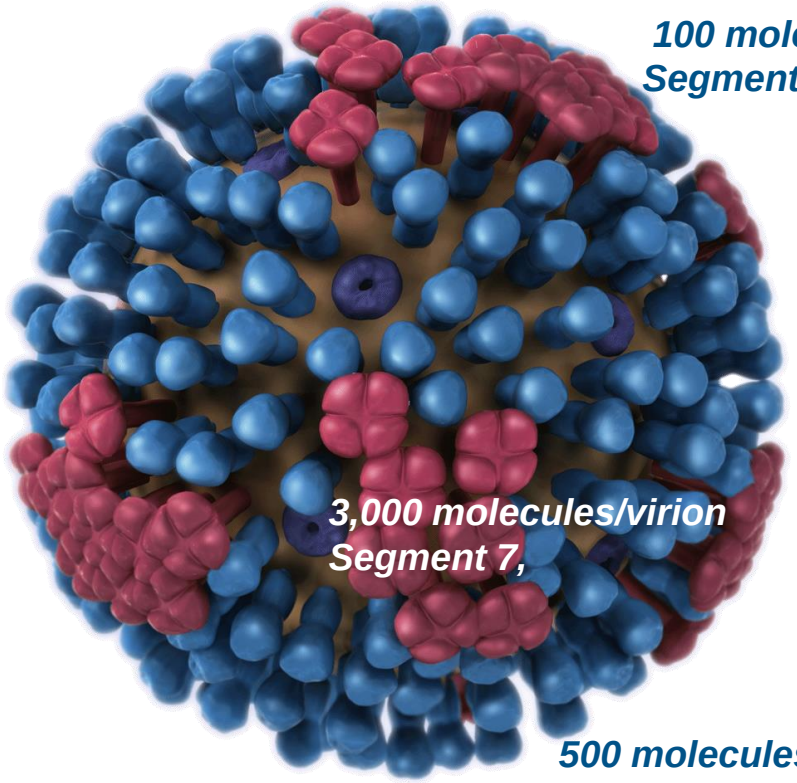
CDC Yearly Lab Work on Flu Viruses Infographic

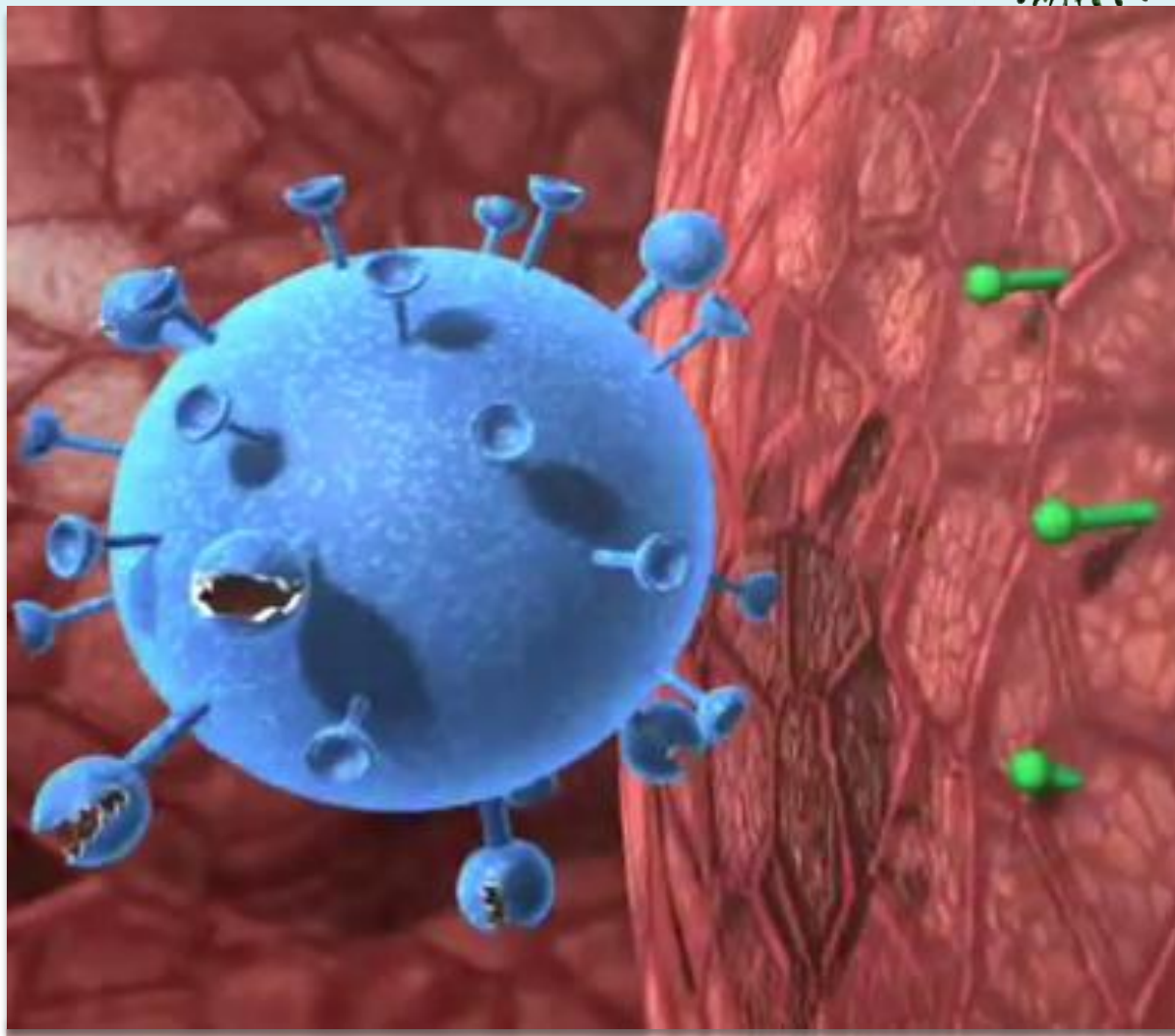




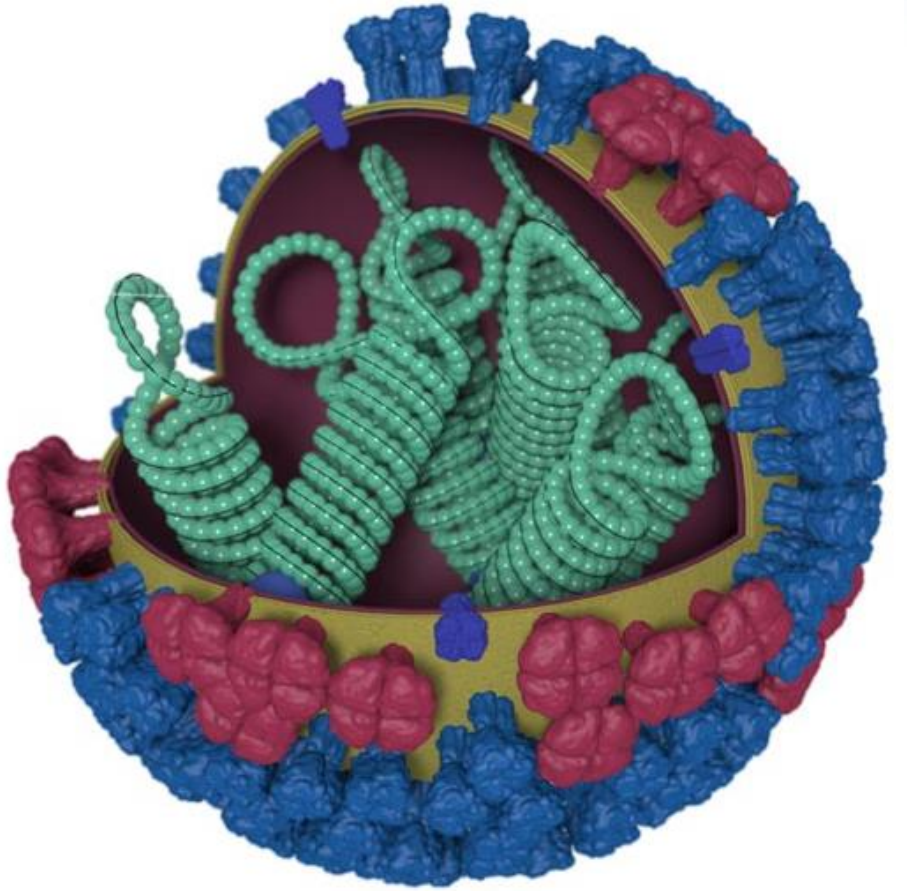
What will the future offer for controlling influenza?

Thoughts on Medications & Vaccines

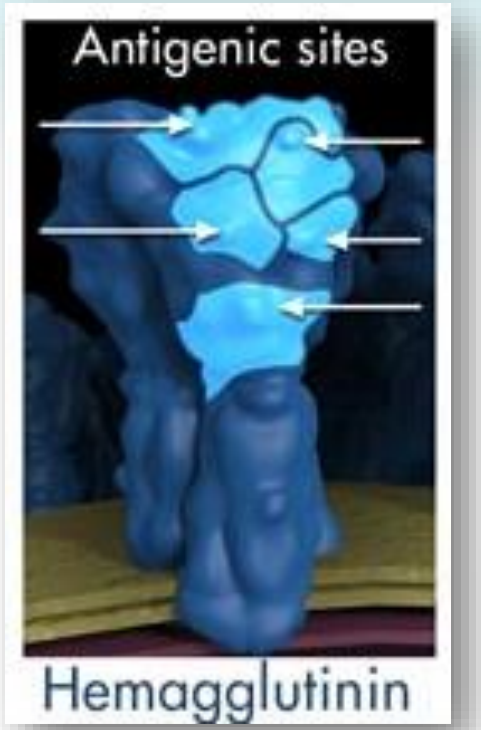


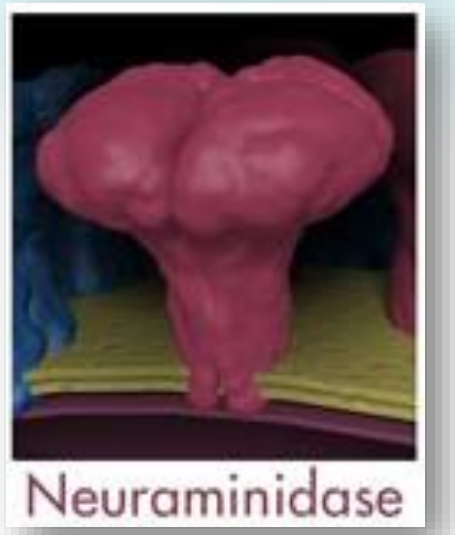


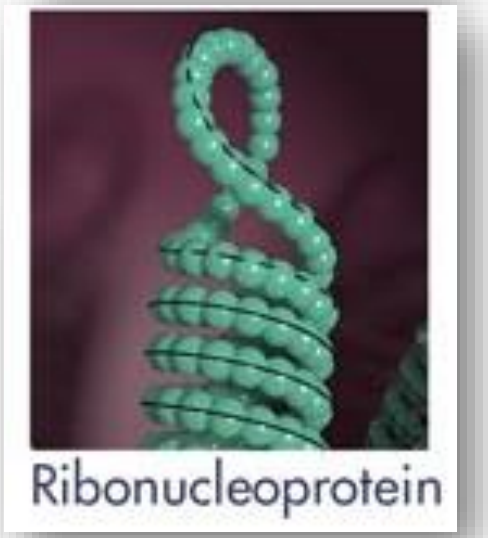
What will the future offer for controlling influenza?



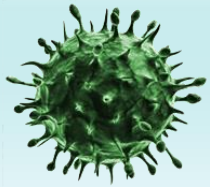
The above image shows the different features of an influenza virus, including the surface proteins hemagglutinin (HA) and neuraminidase (NA). Following influenza infection or receipt of the influenza vaccine, the body's immune system develops antibodies that recognize and bind to "antigenic sites," which are regions found on an influenza virus' surface proteins. By binding to these antigenic sites, antibodies neutralize flu viruses, which prevents them from causing further infection.







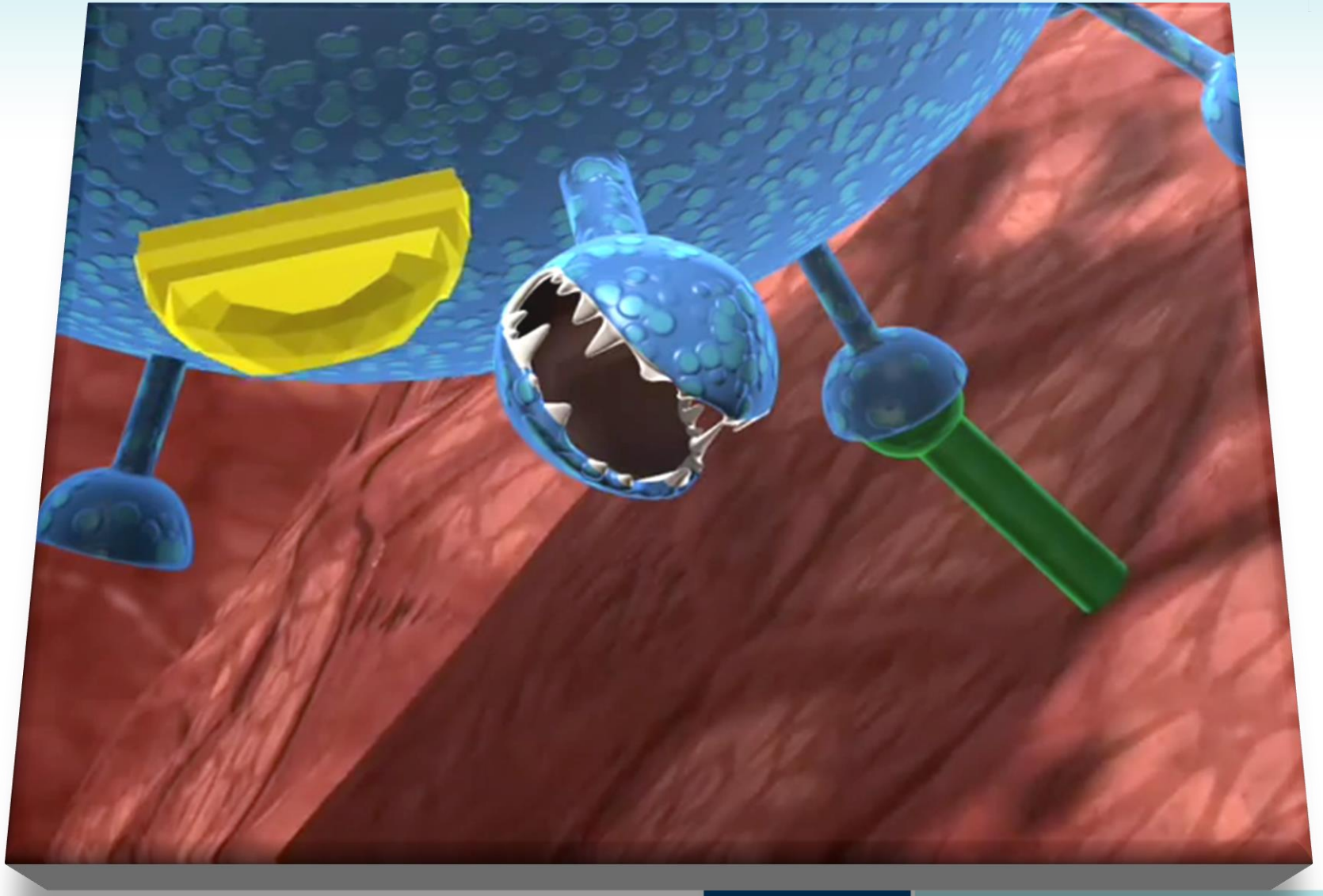
What will the future offer for controlling influenza?



Today in the US the FDA Approved Medications for influenza are

- Rapivab (peramivir)
- Relenza (zanamivir)
- Tamiflu (oseltamivir phosphate, also available as generic)
- Newest - Xofluza® (balozavir marboxil- (2018))
- See- https://www.cdc.gov/flu/treatment/whatyoushould.htm

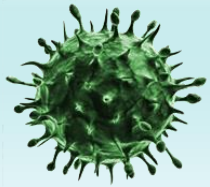
What will the future offer for controlling influenza?



Take home

Drugs **prevent new viruses from emerging from infected cells**

What will the future offer for controlling influenza?



FDA Approved Medications for influenza

- Rapivab (peramivir)
- Relenza (zanamivir)
- Tamiflu (oseltamivir phosphate, also available as generic)

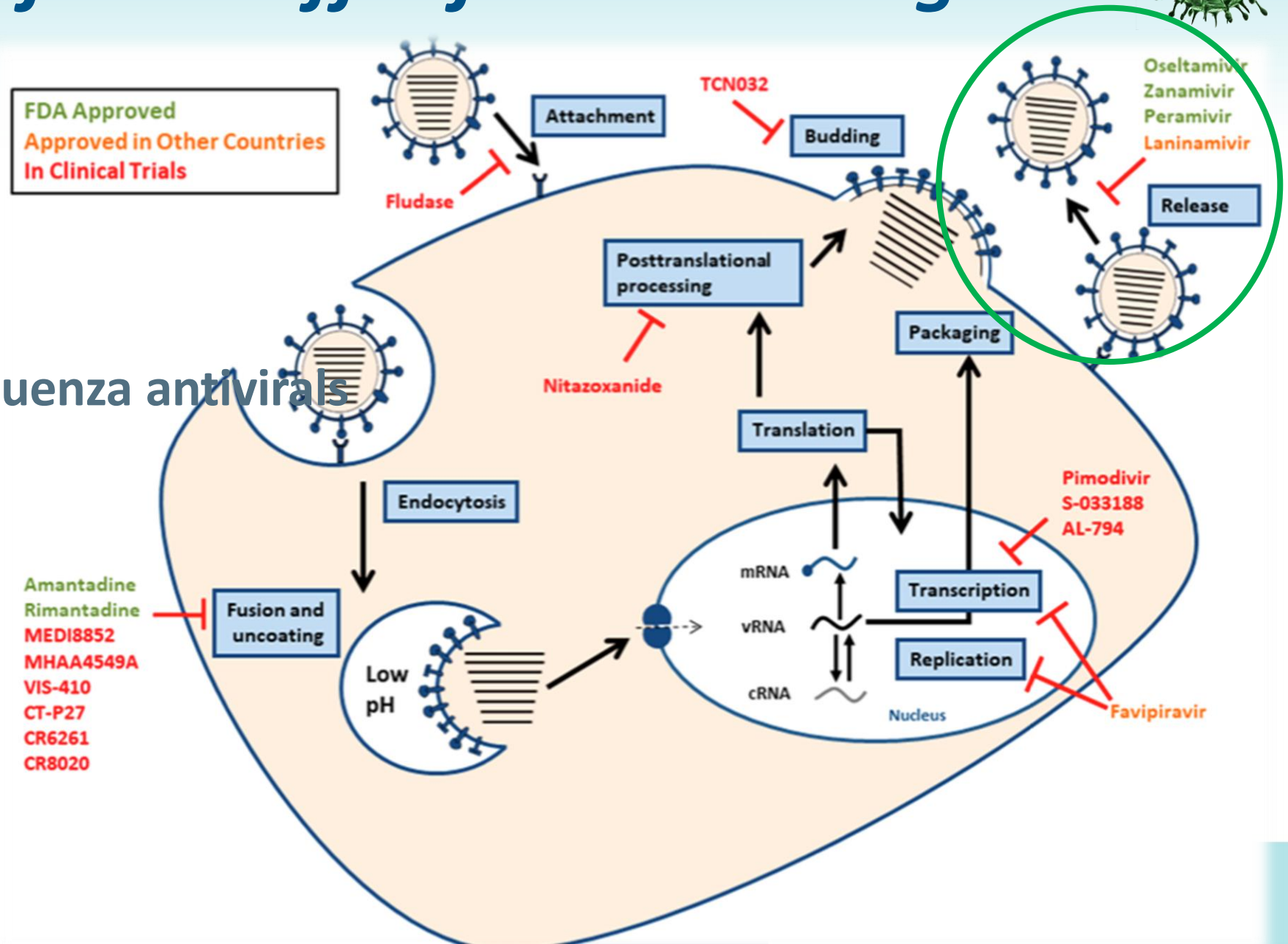
What about other targets?

What will the future offer for controlling influenza?

Medications

Targets of Opportunity?

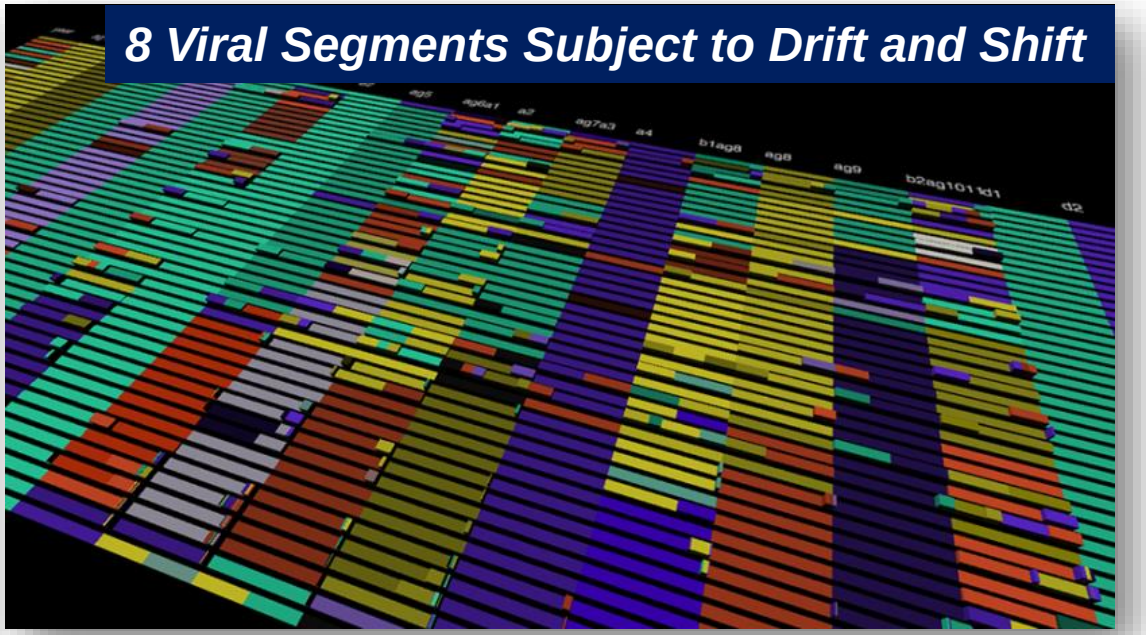
- Modes of action of influenza antivirals
- FDA approved in Green
- Other Countries Orange
- Those in trials in Red



Improved Understanding of Transmission, Natural History and Pathogenesis on our path towards a Universal Vaccine

Precise Characterization of Circulating Influenza Viruses

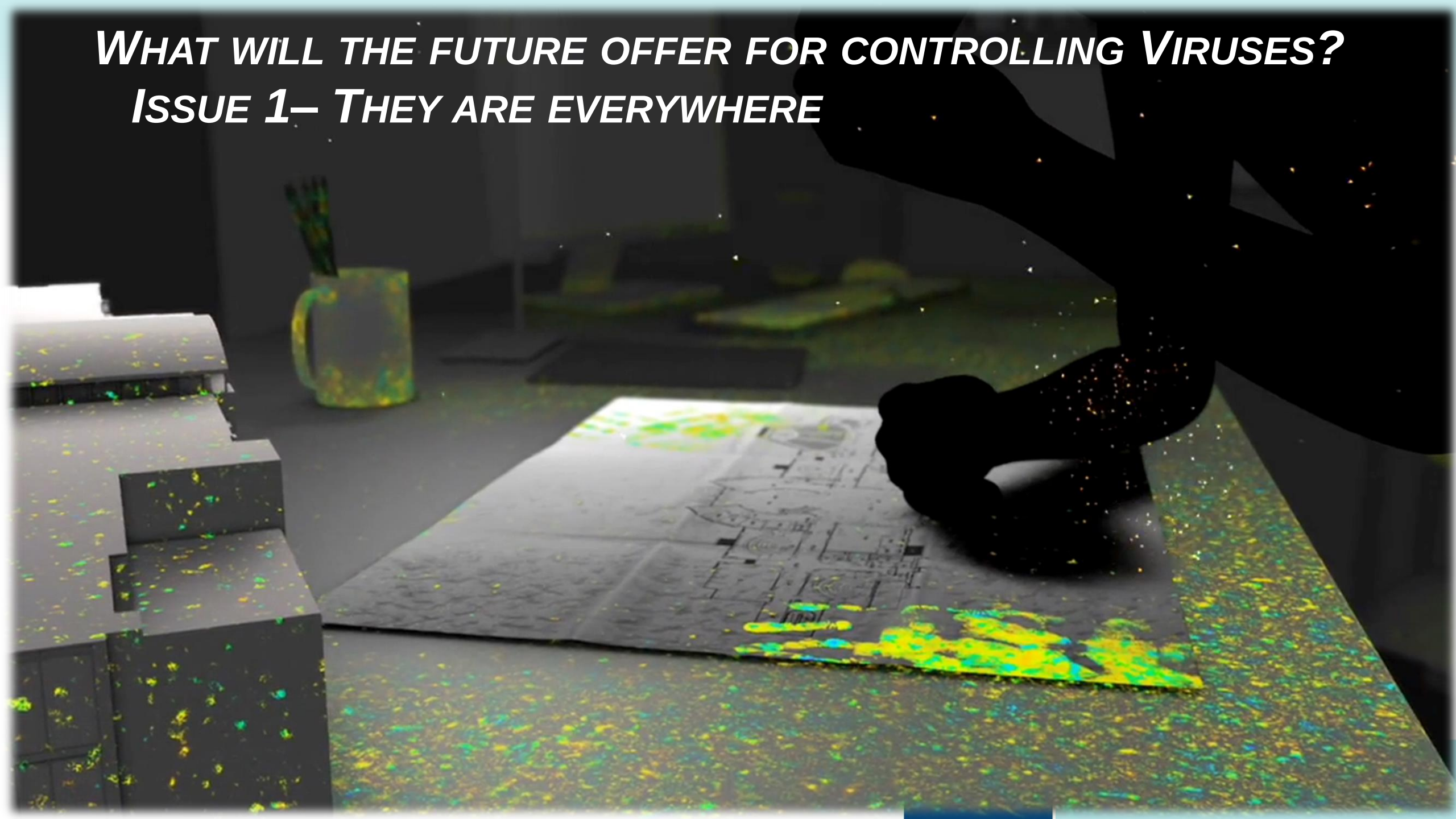
- Improve genotypic and phenotypic characterization of circulating viruses associated with adverse clinical outcomes, host immunity, and vaccine failures.



- Develop and test models predicting the influence of preexisting immunity on virus evolution to anticipate the next emerging dominant seasonal influenza virus strain.

What will the future offer for controlling Viruses?

Issue 1– They are everywhere



SARS-CoV-2 An emerging disease

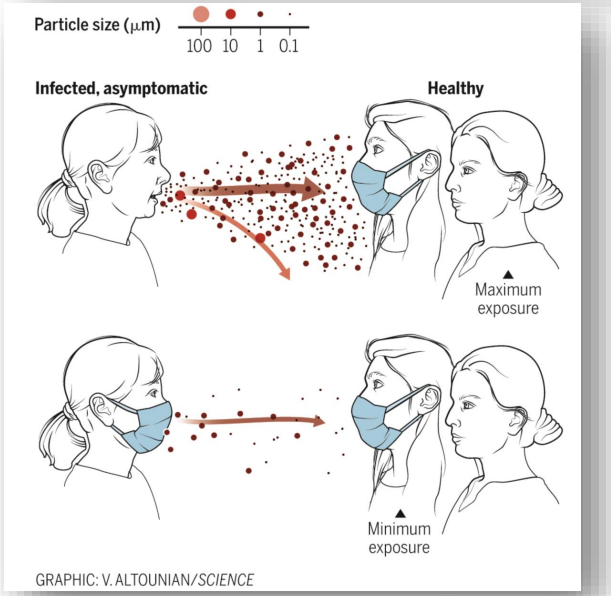
The questions…from today's perspective

WILL THINGS EVER RETURN TO NORMAL?

- ***Why are cases rising?***
  - Is a second wave inevitable? Will it be gradual or more of a spike?
- ***How can WE prevent another shut down?***
- ***How will a second wave impact us if it occurs during flu season?***
- What is the latest information on treatments that work?
- ***When will a vaccine be available?***

Why Bats?

- *Aside from humans, bats are only mammal that can fly*
- *They echo locate*
- *Congregate in caves*
- *Zoonosis that jumped into the other 'flying' mammal*



We too, echo locate Marco?…. Polo?….

SARS-CoV-2 –*ancillary questions*

1. *How long does it take a single infected person to yield one million infected people?*
2. *What is the effect of physical distancing?*
3. *Why was the initial quarantine period two weeks?*
4. *How do N95 masks block SARS-CoV-2?*
5. *How similar is SARS-CoV-2 to the common cold and flu viruses?*
6. *How much is known about the SARS-CoV-2 genome and proteome?*
7. *What can we learn from the mutation rate of the virus?*
8. *How sable and infectious is the virion on surfaces and in the air?*
9. *Are people usually diagnosed before or after they are contagious?*
10. *What is the difference between infectious or contagious and infected?*

The Homework and Cheat Sheet

eLife

FEATURE ARTICLE

SCIENCE FORUM

SARS-CoV-2 (COVID-19) by the numbers

Abstract The COVID-19 pandemic is a harsh reminder of the fact that, whether in a single human host or a wave of infection across continents, viral dynamics is often a story about the numbers. In this article we provide a one-stop, curated graphical source for the key numbers (based mostly on the peer-reviewed literature) about the SARS-CoV-2 virus that is responsible for the pandemic. The discussion is framed around two broad themes: i) the biology of the virus itself; ii) the characteristics of the infection of a single human host.

YINON M BAR-ON, AVI FLAMHOLZ, ROB PHILLIPS AND RON MILO*

Introduction

The COVID-19 pandemic has made brutally clear the need for further research into many aspects of viruses. In this article we compile data about the basic properties of the SARS-CoV-2 virus, and about how it interacts with the body (*Figure 1*). We also discuss a number of questions about the virus, and perform 'back-of-the-envelope' calculations to show the insights that can be gained from knowing some key numbers and using quantitative reasoning. It is important to note that much uncertainty remains, and while 'back-of-the-envelope' calculations can improve our intuition through sanity checks, they cannot replace detailed epidemiological analysis.

Eight questions about SARS-CoV-2

1. How long does it take a single infected person to yield one million infected people?

If everybody continued to behave as usual, how long would it take the pandemic to spread from one person to a million infected victims? The basic reproduction number, R_0, suggests each infection directly generates 2–4 more infections in the absence of countermeasures like physical distancing. Once a person is infected, it takes a period of time known as the 'latent period' before they are able to transmit the virus. The current best-estimate of the median latent time is ≈3 days followed by ≈4 days of close to maximal infectiousness (*Li et al., 2020a*; *He et al., 2020*). The exact durations vary among people, and some are infectious for much longer. Using $R_0 \approx 4$, the number of cases will quadruple every ≈7 days or double every ≈3 days. 1000-fold growth (going from one case to 10^3) requires 10 doublings since $2^{10} \approx 10^3$; 3 days × 10 doublings = 30 days, or about one month. So we expect ≈1000x growth in one month, a million-fold (10^6) in two months, and a billion fold (10^9) in three months. Even though this calculation is highly simplified, ignoring the effects of 'super-spreaders', herd-immunity and incomplete testing, it emphasizes the fact that viruses can spread at a bewildering pace when no countermeasures are taken. This illustrates why it is crucial to limit the spread of the virus by physical distancing measures. For fuller discussion of the meaning of R_0, the latent and infectious periods, as well as various caveats, see the section on 'Definitions and measurement methods' below.

2. What is the effect of physical distancing?

A highly simplified quantitative example helps clarify the need for physical distancing. Suppose that you are infected and you encounter 50 people over the course of a day of working, commuting, socializing and running errands. To make the numbers round, let's further suppose that you have a 2% chance of transmitting the virus in each of these encounters, so that you

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SARS-CoV-2 (COVID-19) by the numbers

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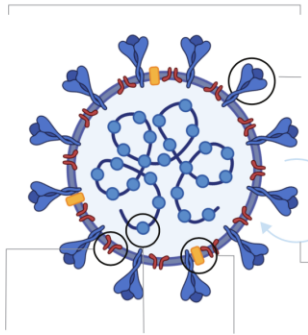
Comments are welcome; this article is being updated on an ongoing basis at: https://bit.ly/2WOeN64

Size & Content

Diameter: ≈100 nm

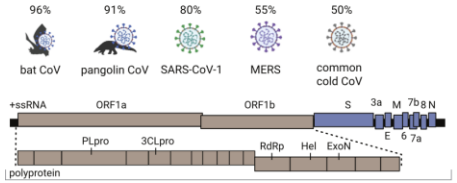
Volume: ~10^6 nm^3 = 10^{-3} fL

Mass: ~10^3 MDa ≈ 1 fg



Genome

Nucleotide identity to SARS-CoV-2



Length: ≈30kb; β-coronavirus with 10-14 ORFs (24-27 proteins)

Evolution rate: ~10^{-3} nt^{-1} yr^{-1} (measured for SARS-CoV-1)

Mutation rate: ~10^{-6} nt^{-1} $cycle^{-1}$ (measured for MHV coronavirus)

Replication Timescales

in tissue-culture

Virion entry into cell: ~10 min (measured for SARS-CoV-1)

Eclipse period: ~10 hrs (time to make intracellular virions)

Burst size: ~10^3 virions (measured for MHV coronavirus)

Host Cells

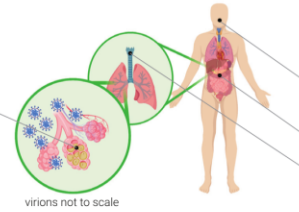
(tentative list; number of cells per person)

Type I & II pneumocytes (~10^{11} cells)

Alveolar macrophage (~10^{10} cells)

Mucous cell in nasal cavity (~10^9 cells)

Host cell volume: ~10^3 μm^3 = 10^3 fL



virions not to scale

Concentration

maximal observed values following diagnosis (Woelfel et al. 2020; Kim et al. 2020; Pan et al. 2020)

Nasopharynx: 10^6-10^9 RNAs/swab

Throat: 10^4-10^8 RNAs/swab

Stool: 10^4-10^8 RNAs/g

Sputum: 10^6-10^{11} RNAs/mL

RNA counts can markedly overestimate infectious virions

Antibody Response - Seroconversion

Antibodies appear in blood after: ≈10-20 days

Maintenance of antibody response:

≈2-3 years (measured for SARS-CoV-1)

Virus Environmental Stability

Relevance to personal safety unclear

	half-life	time to decay 1000-fold
Aerosols:	≈1 hr	≈4-24 hr
Surfaces: e.g. plastic, cardboard and metals	≈1-7 hr	≈4-96 hr

(van Doremalen et al. 2020)

Based on quantifying infectious virions. Tested at 21-23°C and 40-65% relative humidity. Numbers will vary between conditions and surface types (Otter et al. 2016).

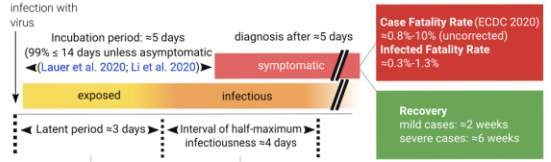
Viral RNA observed on surfaces even after a few weeks (Moriarty et al. 2020).

"Characteristic" Infection Progression in a Single Patient

Basic reproductive number R_0: typically 2-4

Varies further across space and time (Li et al. 2020; Park et al. 2020)

(number of new cases directly generated from a single case)

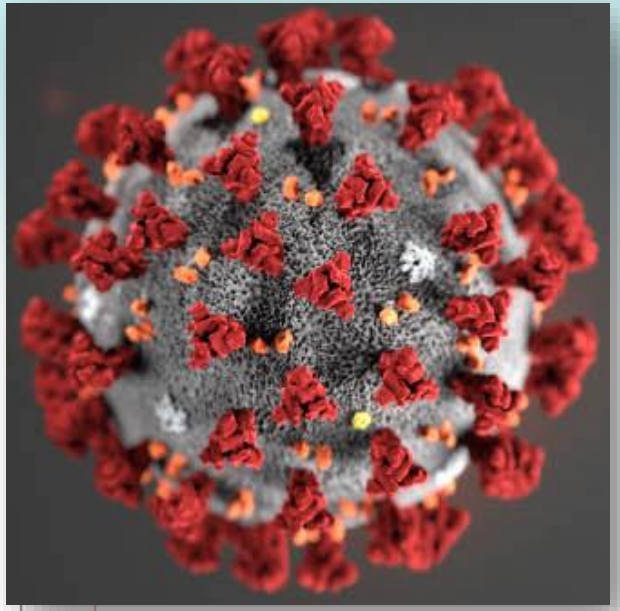


Inter-individual variability is substantial and not well characterized. The estimates are parameter fits for population median in China and do not describe this variability (Li et al. 2020; He et al. 2020).

Note the difference in notation between the symbol ≈, which indicates "approximately" and connotes accuracy to within a factor 2, and the symbol ~, which indicates "order of magnitude" or accuracy to within a factor of 10.

What is SARS-CoV-2 and COVID-19?

Human Coronavirus & Disease



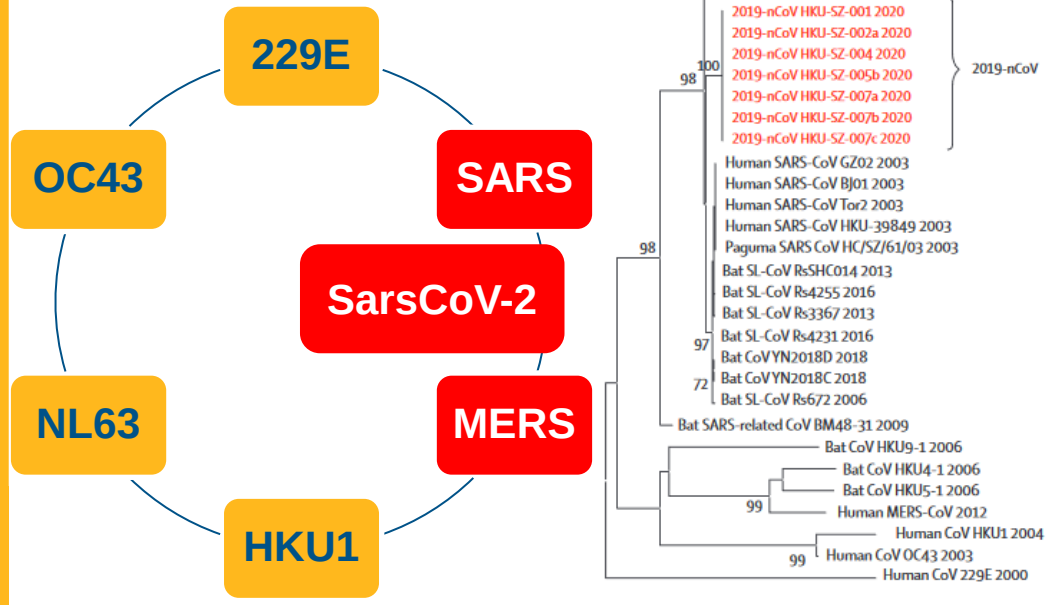
Four Common Human Coronaviruses

- 229E
- NL63
- OC43
- HKU1

+ ss non-segmented enveloped RNA virus

Uses ACE_2 Receptor in Lung (LRTI)

NL63 (mild URTI),



Three Other Human Coronaviruses

- SARS
- SARS-CoV-2
- MERS

SARS-CoV-2 Is it Changing?

Yes, but no…

The New York outbreak has cosmopolitan origins, but the majority of cases are attributable to introductions from Europe.

The outbreak in New York City shows mixing of cases across all 5 boroughs.

The outbreak in California is related to both nearby Washington State and distant New York.

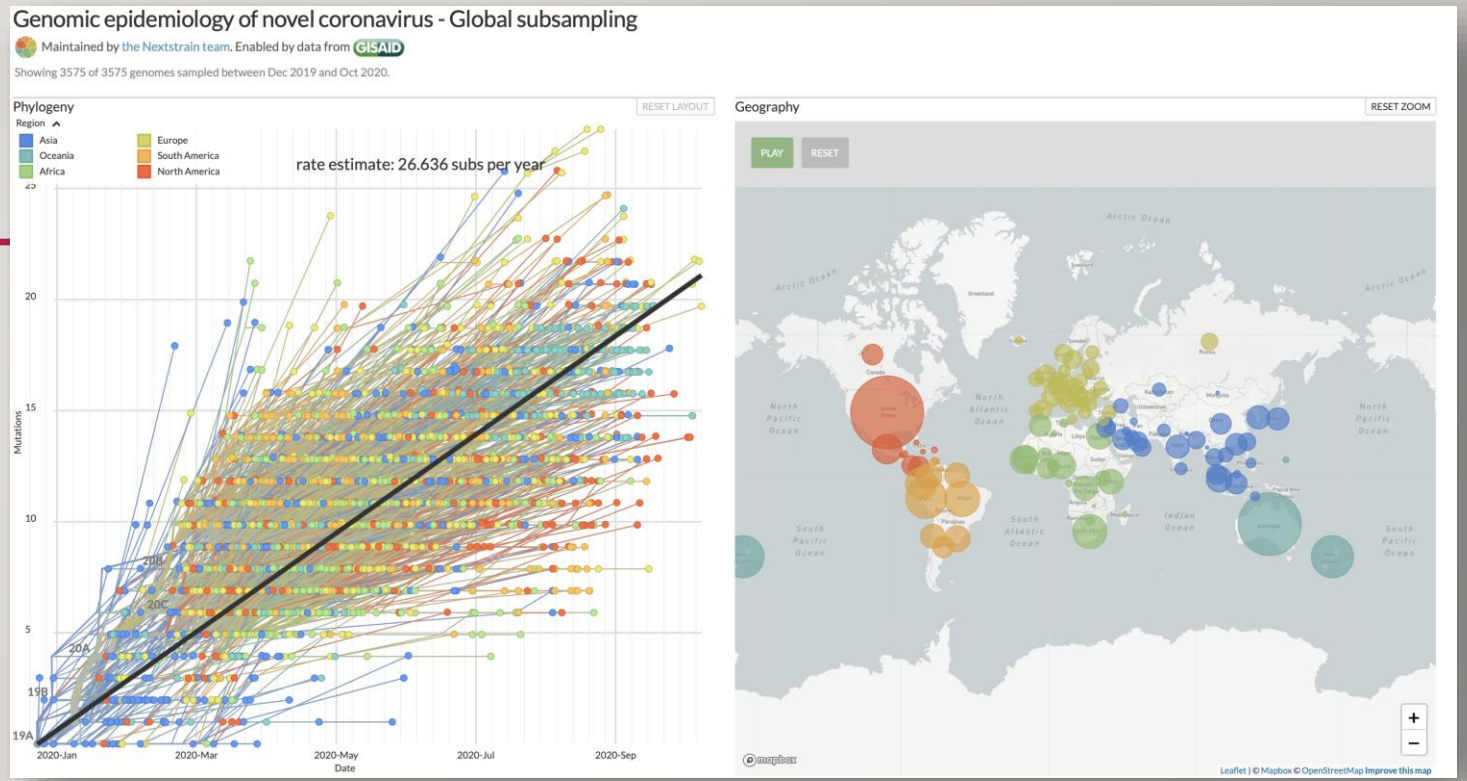
The Midwest outbreak is heterogeneous and is the result of many independent introductions.

Ongoing outbreaks in Utah and Idaho are closely related.

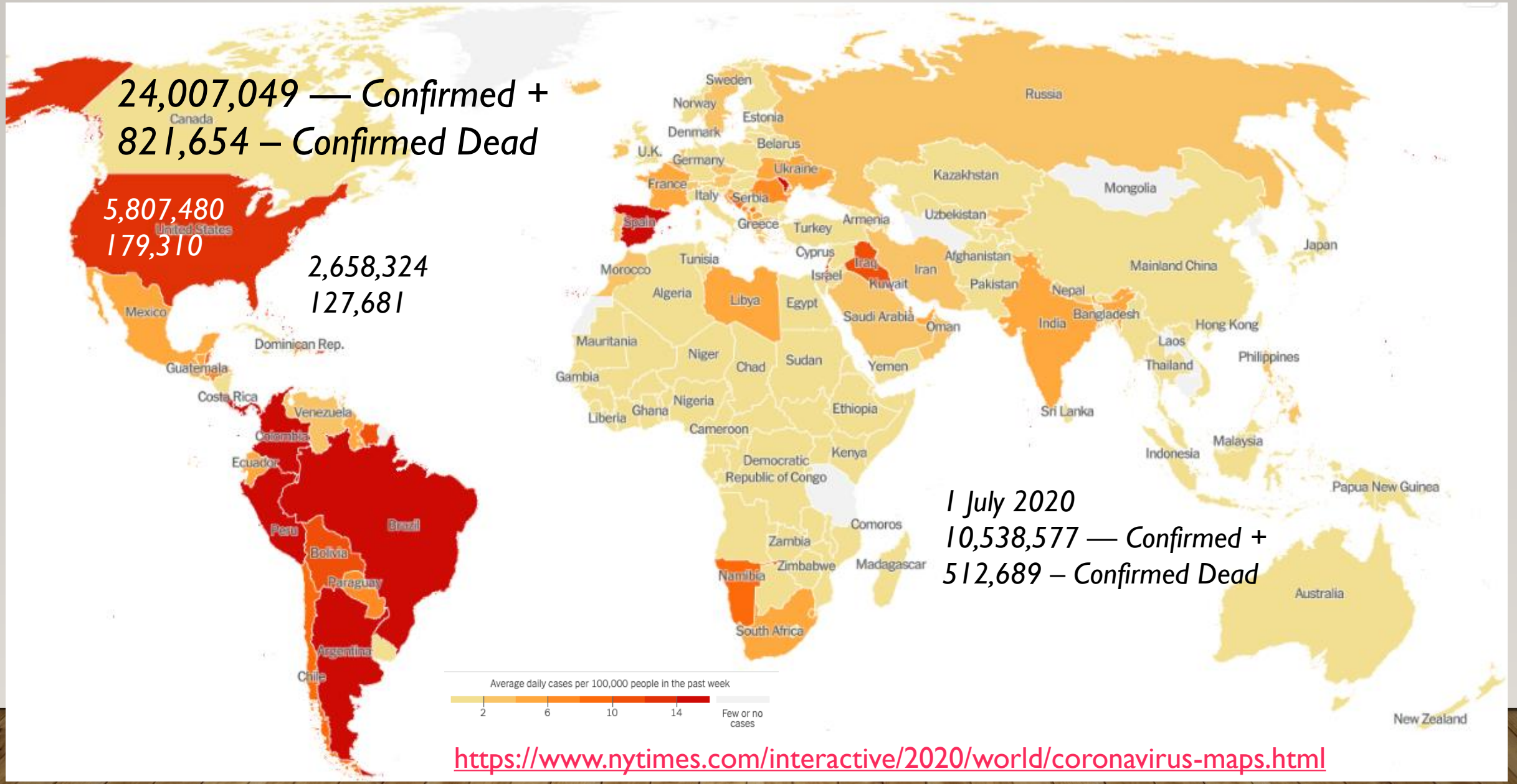
26.636 substitutions per year

3,575 genomes Dec 2019-Aug 2020

The decisions made by each state profoundly impacts the fate of the others. Safely easing restrictions in any state will require coordinated containment, with all states acting to protect each other.

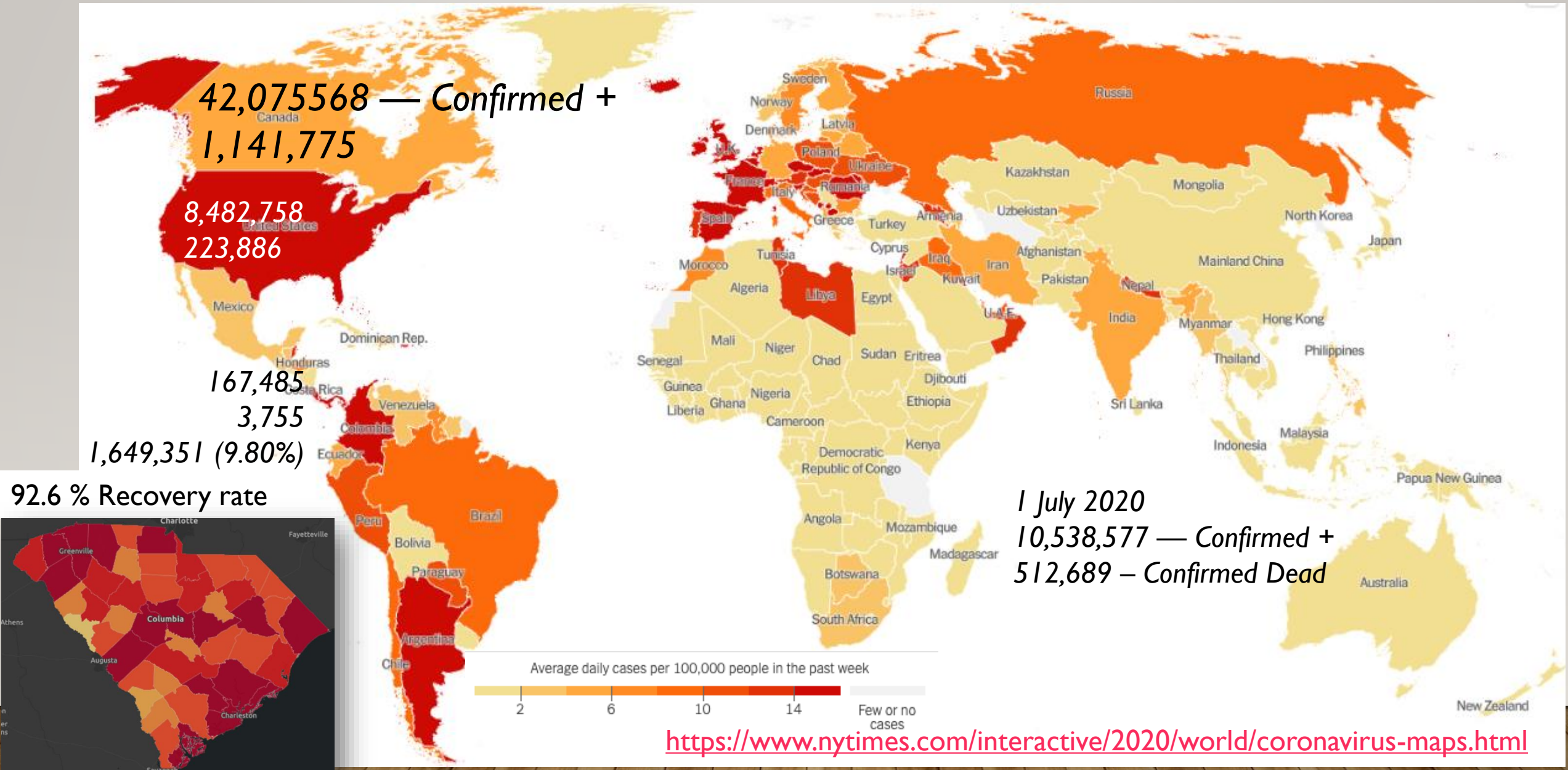


THE GLOBAL SITUATION AS OF 26 AUG 2020

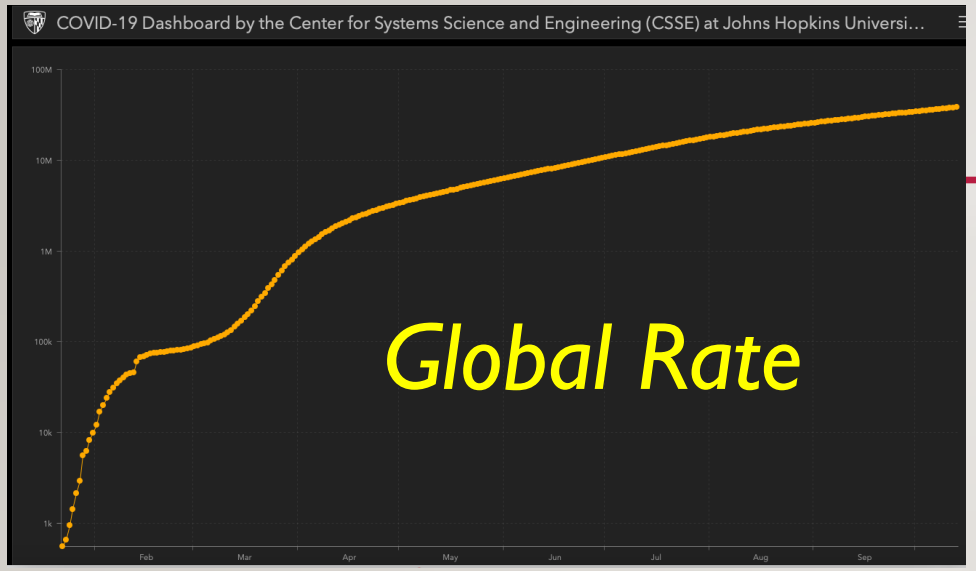


https://www.nytimes.com/interactive/2020/world/coronavirus-maps.html

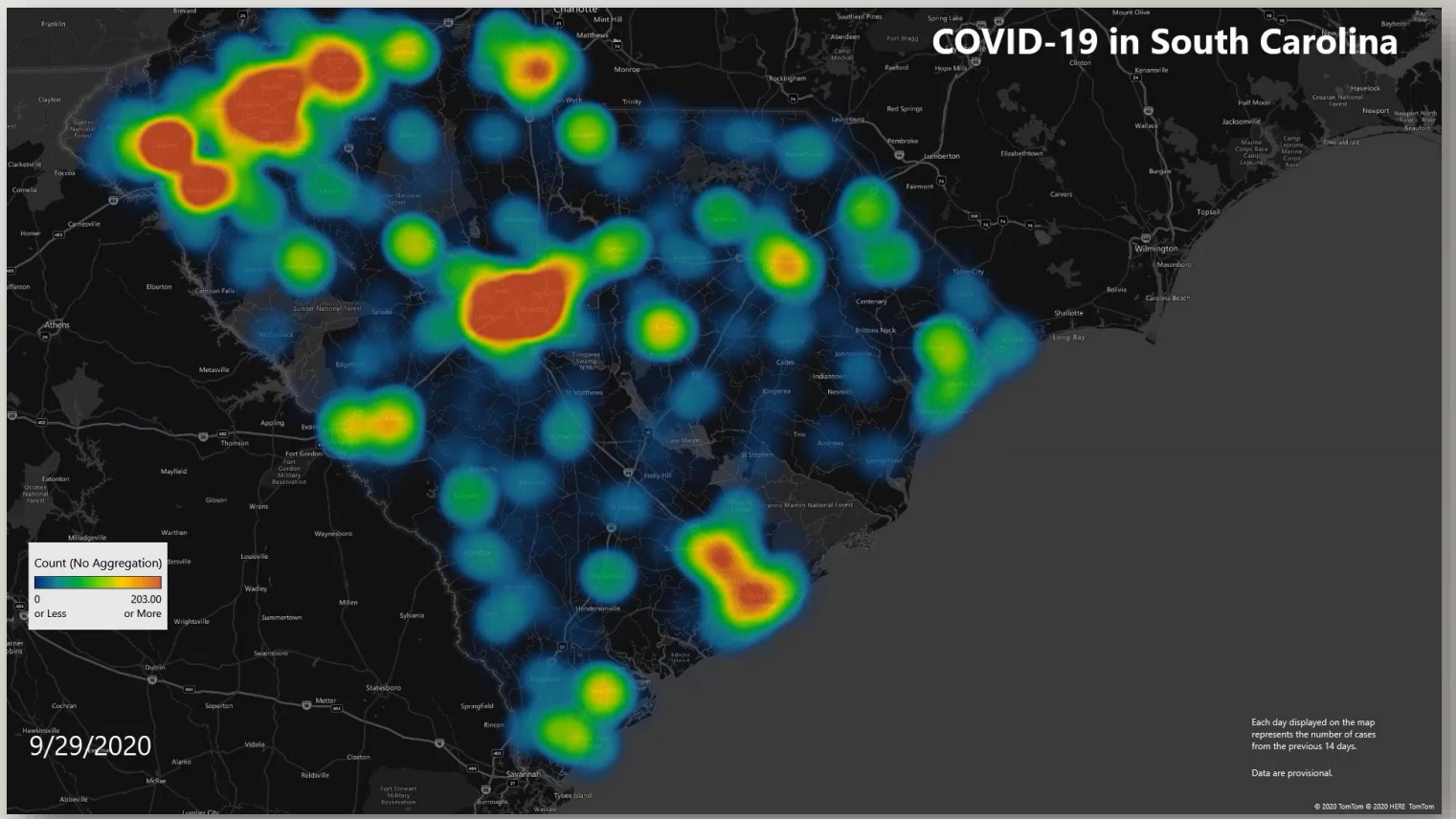
THE GLOBAL SITUATION AS OF TODAY 23 OCT 2020



Are we in the second wave?



Not yet… the globe is trying to level off
but in SC (5.1M) we are seeing our initial surge…
Colorado, 32,715; 1,690 dead 5,456,574



Why are cases rising?

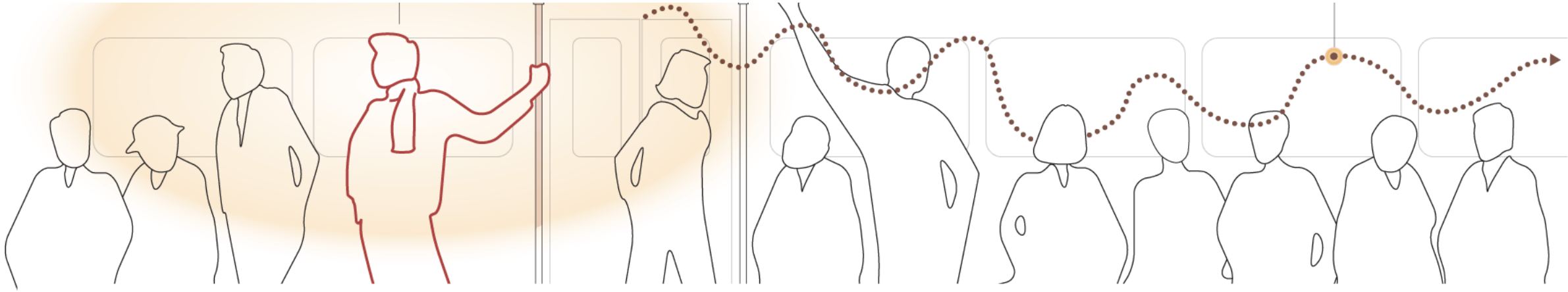
Is a second wave inevitable?

Will it be gradual or more of a spike?

How contagious is the virus? 2 Part Answer…

Part 1 of the answer…

- ✓ ***Coronaviruses can move using air currents, small particles move further, larger particles fall out of the air***
- ✓ ***Can survive on surfaces for ~ 28 days at room temperature*** *(PMCID-PMC7538848)*



- ***Likely, large larger particles, CDC guidance, N-95, will limit inhalation risk, other mask types help control expiration risk from the asymptomatic/pre-symptomatic/symptomatic***
- ***Enveloped Virus, so, soap and water & ethanol hand sanitizers will work…***

How contagious is the virus? 2 Part Answer…

Let's consider that 4th of July Barbecue

~15 folks…

Ro of **2** = ***225***

2.5 = 871

3.0 = 3,375

3.5 = 13,071

4.0 = 50,625

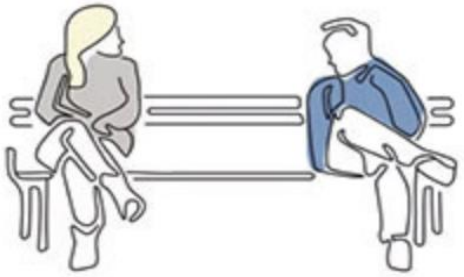
4.5 = 196,070

5.0 = 759,375 infected

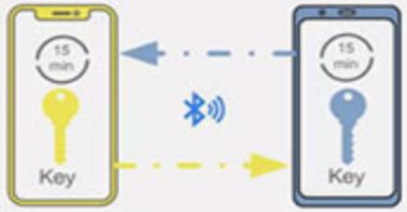
TESTING TRACING AND ISOLATION (TETRIS)

Apple and Google's effort

Alice and Bob meet each other for the first time and have a 10-minute conversation.



Their phones exchange anonymous identifier beacons (which change frequently).



A few days later...

Bob is positively diagnosed for COVID-19 and enters the test result in an app from a public health authority.

With Bob's consent, his phone uploads the last 14 days of keys for his broadcast beacons to the cloud.

Apps can only get more information via user consent

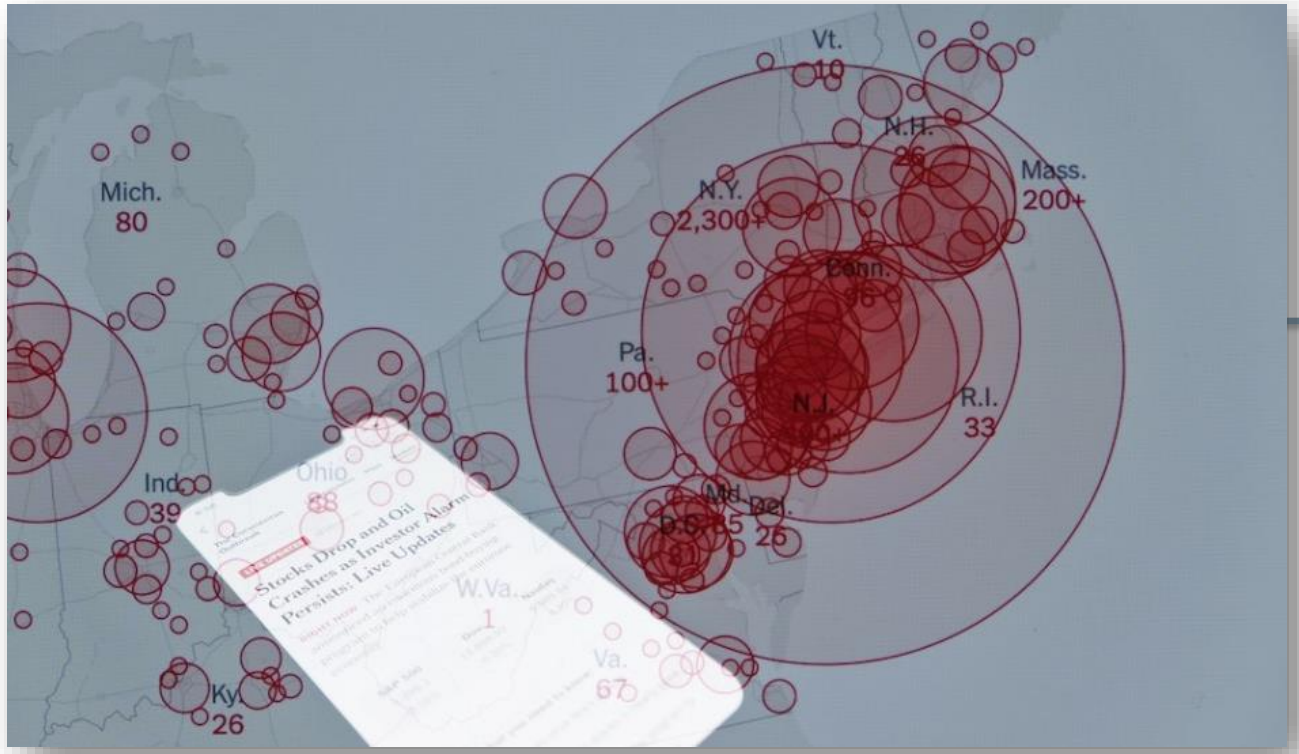
Google

CONTACT TRACING, AND ISOLATION

Tract and Trace Technology and then isolate

- *Bluetooth based… Class 2 device ~33 feet/10 meters*

- ***Three step process…***
  - **Step 1, asks *have our phones been within 'spitting distance' of each other?* …already in your current operating system, you opt in…**
  - **Step 2, Government health agencies deploy an app where again, you opt in, that when you test positive and the application on the government server matches your phone**
  - ***No personal information is stored, simply who you have been near***
  - **Step 3, A text is sent automatically to the positive person's Bluetooth interactions alerting them that they have been exposed.**
  - **Digital tracing will not replace protective measures!**



South Carolina

In a joint Apple-Google statement to *AppleInsider*, the two companies said that South Carolina would be one of the first U.S. states to build out a contact tracing app, tentatively called "SC-Safer-Together," using their Exposure Notification framework.

However, a spokesperson for South Carolina's Department of Health and Environmental Control has since clarified that the state has "no plans to pursue this application." The DHEC had only received a memorandum of understanding from the Medical University of South Carolina authorizing it to "explore the potential development" of an app using the Apple-Google framework

A spokesperson for MUSC added that they are still in the "development, evaluation and state-level discussion and review stage of things," adding that the project has not been approved or deployed by any state-level agency.

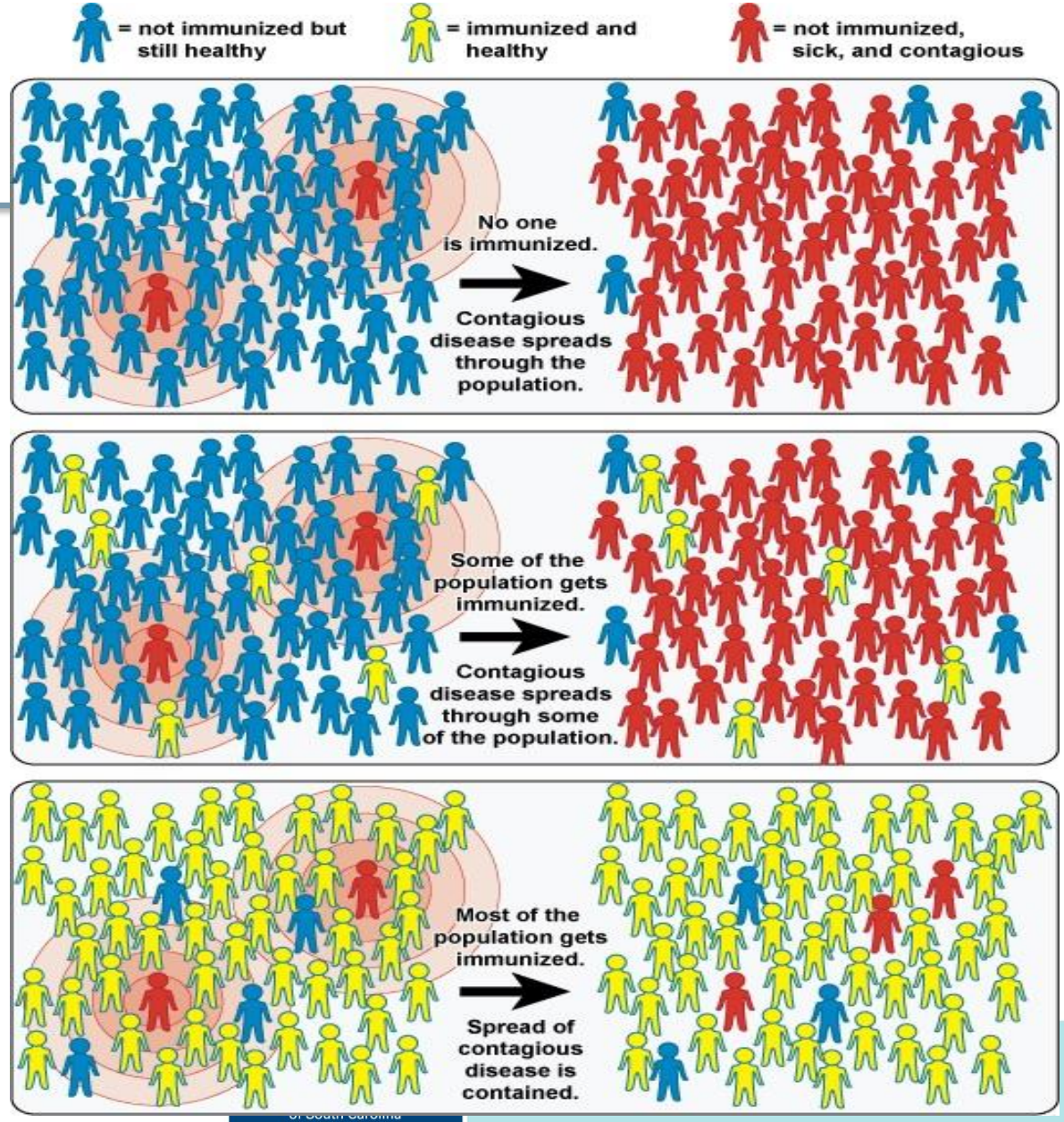
As of Aug. 26, South Carolina has not yet released its app.

How U.S. states are using digital contact tracing to stop COVID-19
Mike Peterson, August 26, 2020.

When will we achieve Herd Immunity?

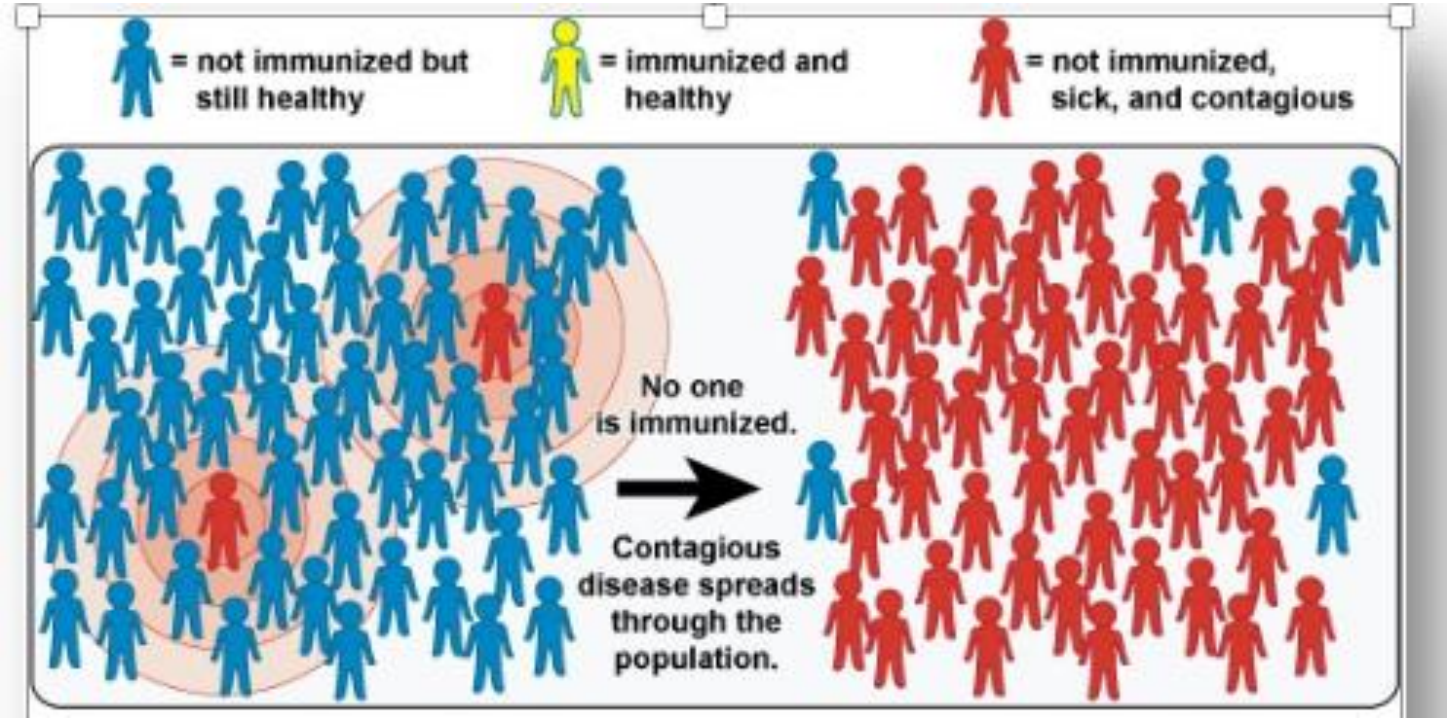
Definition

- When most of a population is immune to an infectious disease,
- ✓This provides indirect protection
  - —How?
    - **Virus struggles to find a host!**



Masks – What is all the fuss over?
How can we prevent another shutdown?

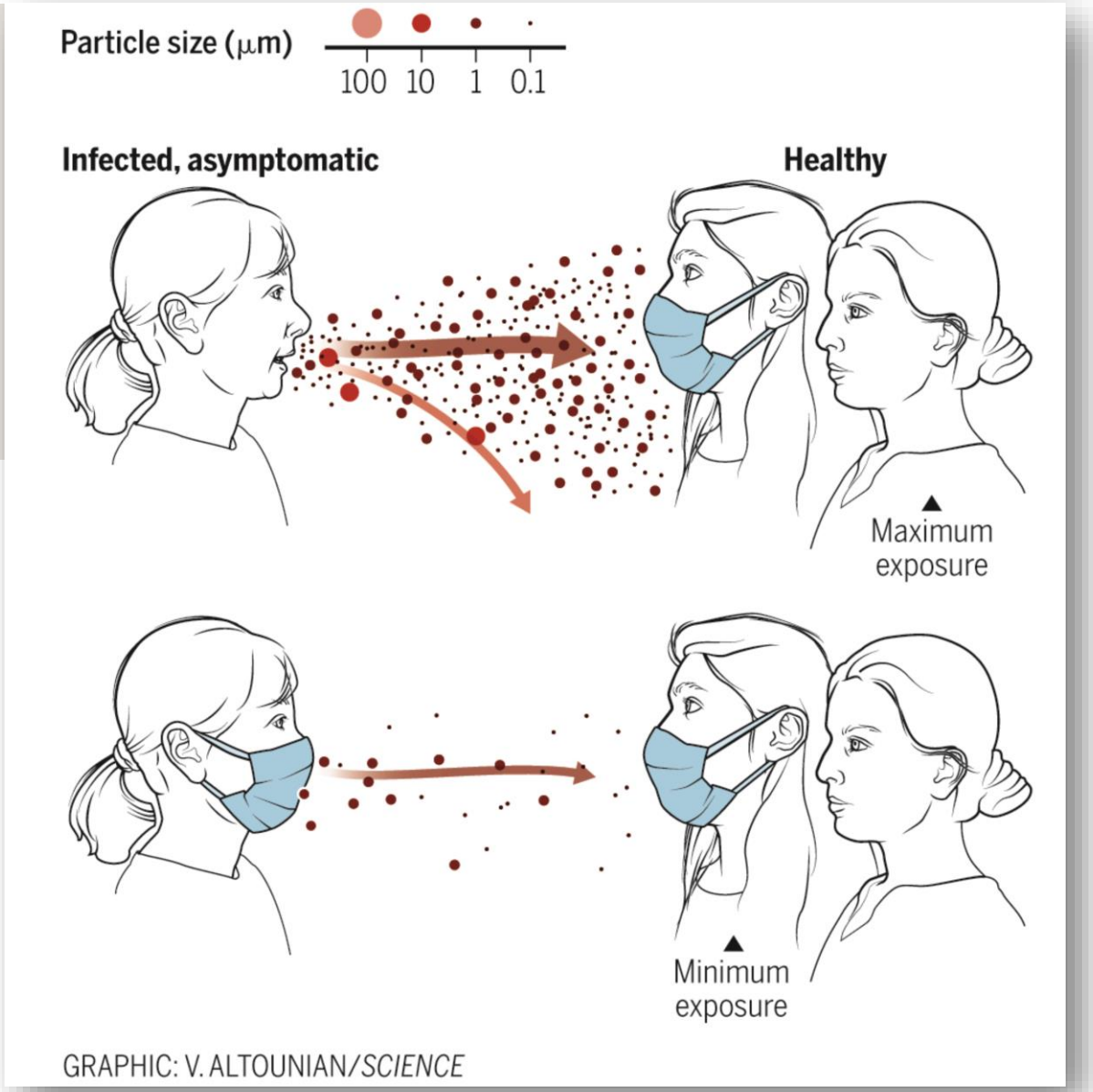
- *How could something so simple work?*
- *Limits the spread,*
- *Virus struggles to find a host*



Masks – What is all the fuss over?

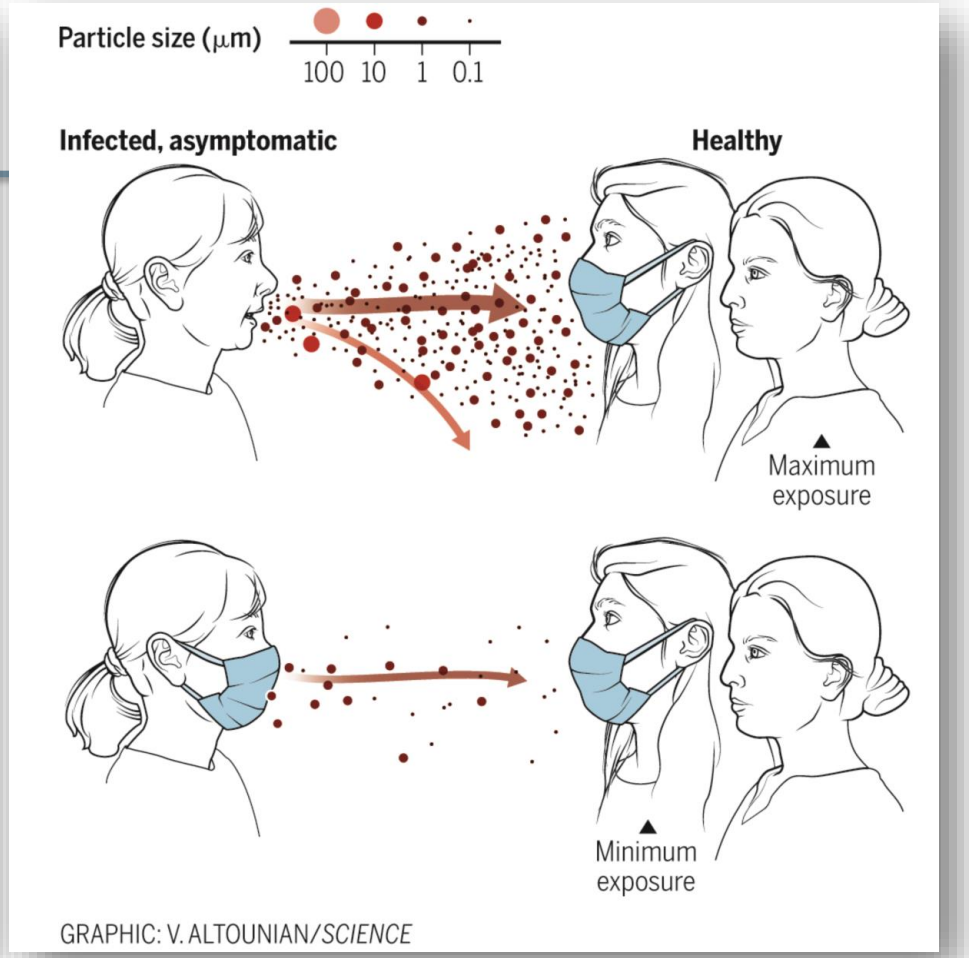
How? –

- ✓ *Containment*
- ✓ *Virus struggles to find a host!*



If not masks, then what?

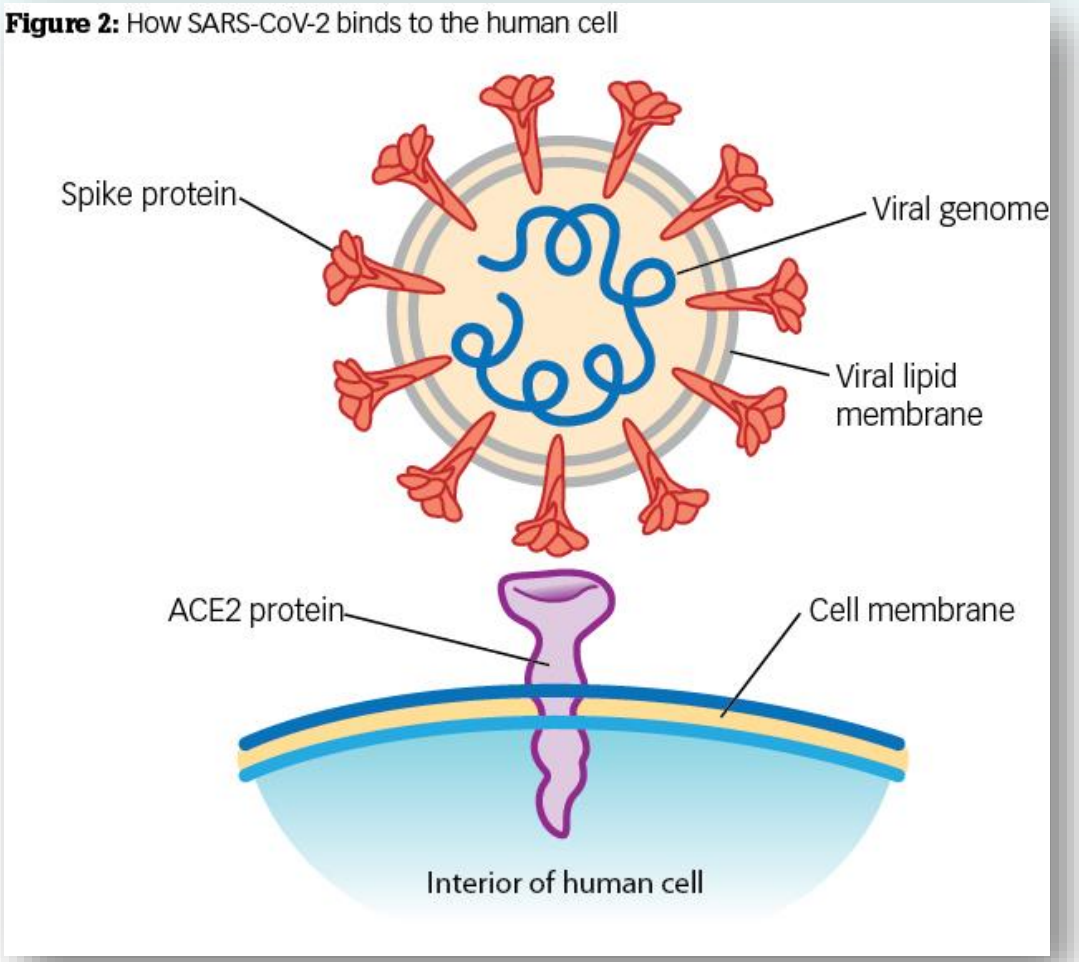
MASKS – MUST I WEAR ONE? I FIND THEY INHIBIT MY STYLE



Full Face Shields Can achieve the same goal and have advantages

Aerosols and Splatter in the Dental Operatory

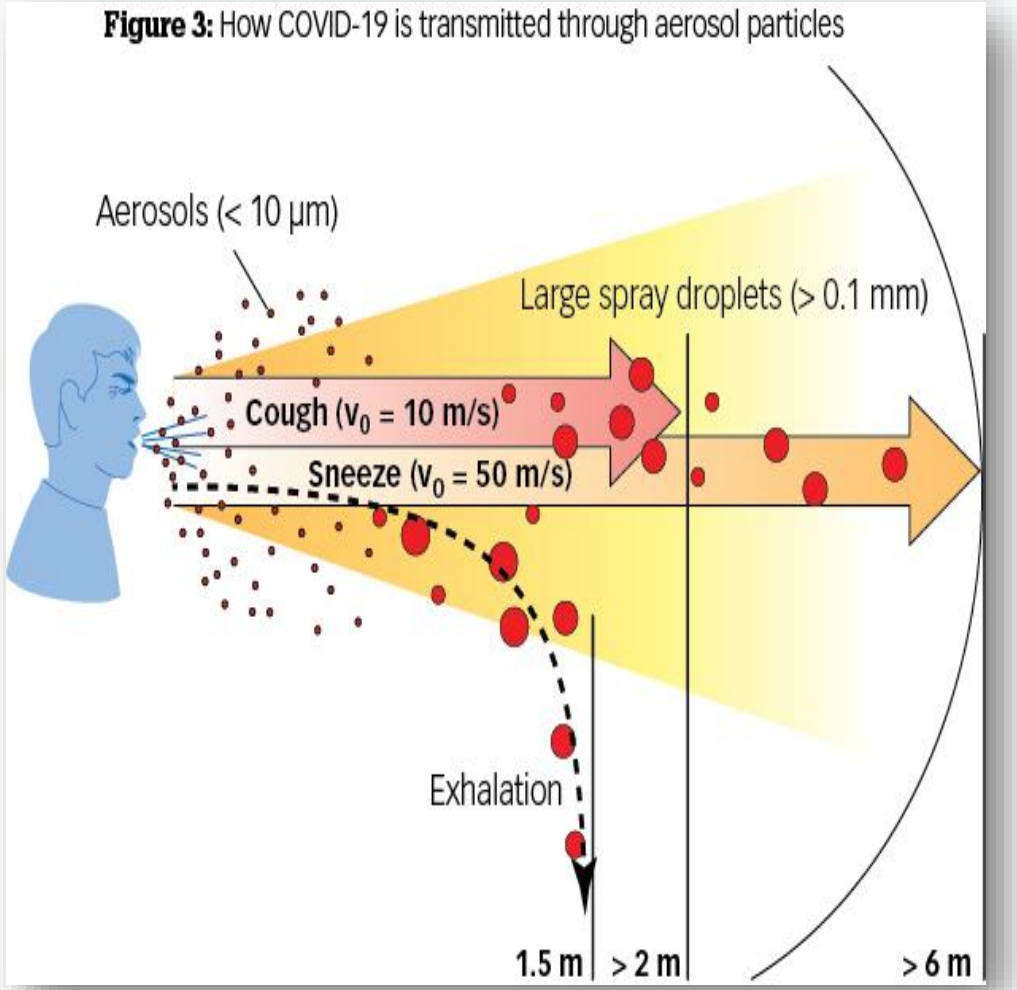
1. ***What do we know?***
2. ***How do we control them?***



Aerosols and Splatter in the Dental Operatory

1. What do we know?

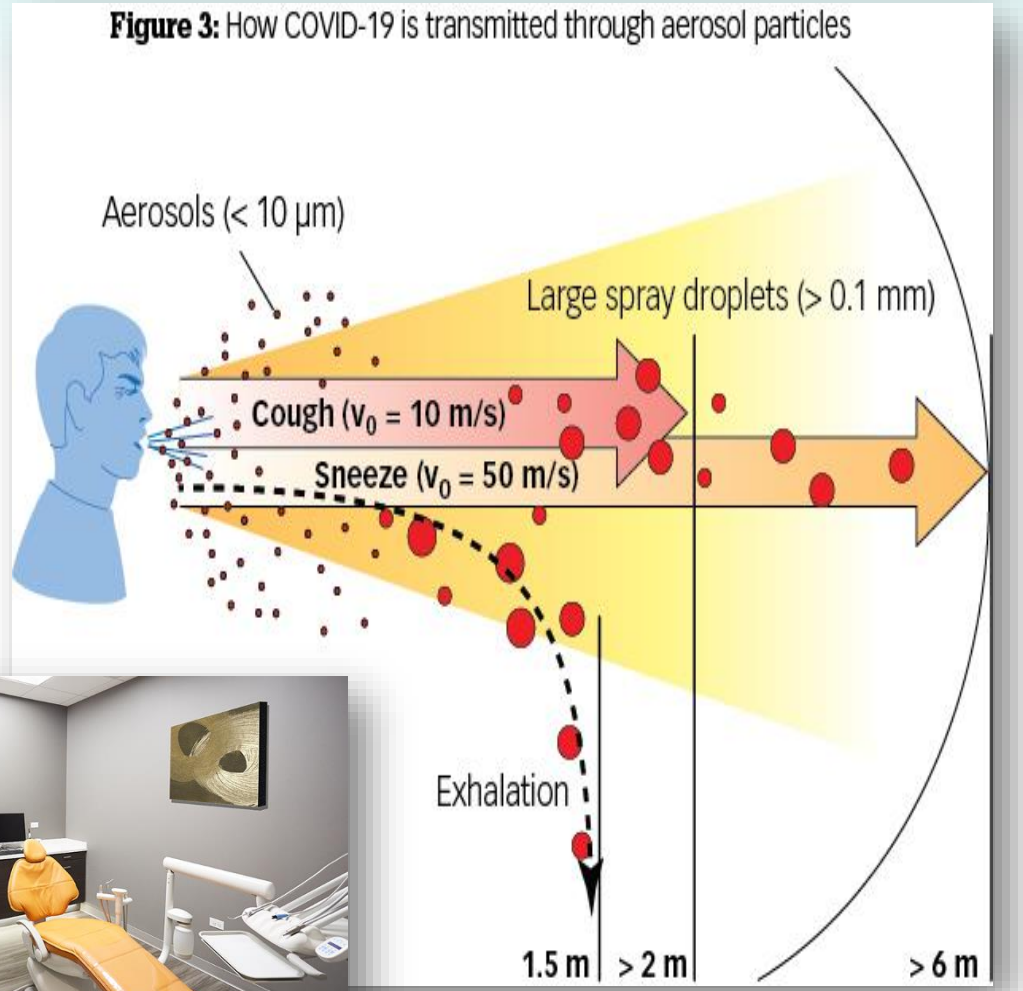
- ***Particle transmission is dependent on the size of the particle…***
  - *Course 2.5 to 10 µm*
  - *Fine, < 2.5 µm*
  - *Ultrafine < 0.1µm*
    - *These can enter the blood stream and then scanning for the ACE-2 receptor infect those tissues.*
- ***Dentistry classified as***
  - *Very High Risk*
    - *Tools of the trade generate aerosols*
      - *Bacteria, Fungi and Viruses*
      - ***Dental Particles generated are < 50µm***
      - *Others are in the sweet spot of between 0.5 µm to 10 µm*



Aerosols and Splatter in the Dental Operatory

2. How do we control them

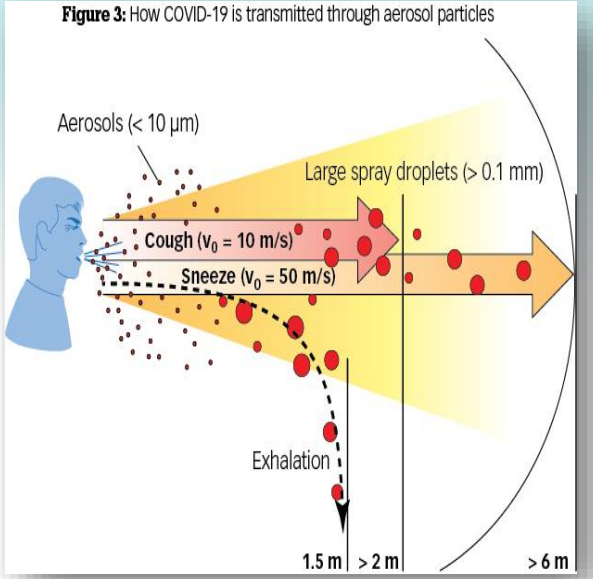
- ***Mitigative Step 1***
  - *Ideally negative pressure…*
    - *Air should flow from the hallways into the isolation rooms but at a minimum*
- ***Mitigative Step 2***
  - *CDC-At least 6 air changes per hour (some say 8-12)*
  - *CDC-12 ACH for new construction/renovations*



Aerosols and Splatter in the Dental Operatory

2. What do we know?

- ***Mitigative Step 3***
  - *Testing of the Patients*
    - *Telephone Triage*
    - *Temperature readings*
    - *Viral Testing*
- ***Mitigative Step 4***
  - *Testing of the Providers*
    - *Daily Triage*
    - *Daily Temperature readings*
    - *Routine Viral Testing*
- ***Mitigative Step 5***
  - *Inactivation of the Virus and other Microbes*
    - *Colgate Proxyl and Listerine Whitening*
      - *Time on target 1 Minute*
      - *DO NOT SWALLOW*

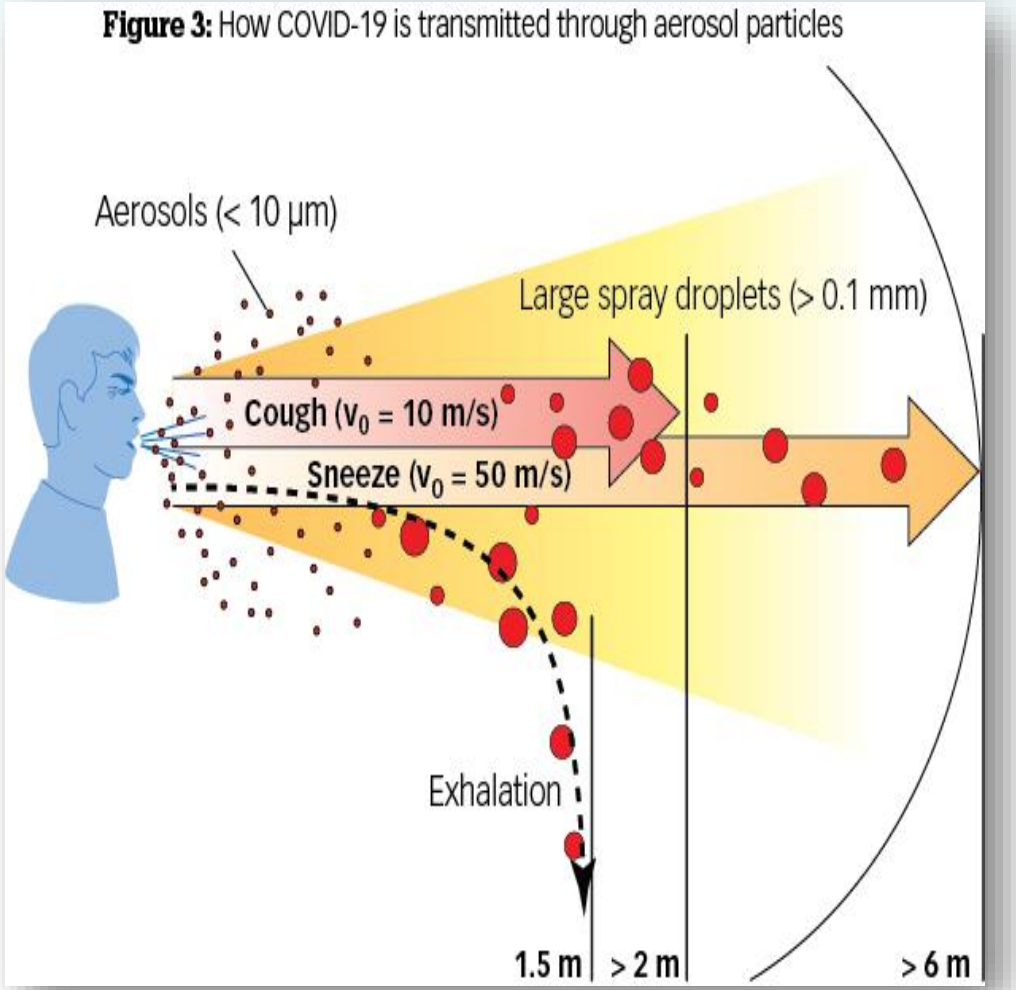


Both Contain 1.5% Hydrogen peroxide

Aerosols and Splatter in the Dental Operatory

2. What do we know?

- ***Mitigative Step 5***
  - ***Inactivation of the Virus and other Microbes***
    - ***Citrox® -***
      - ***Bioflavonoids thought to interfere with coronaviral chymotrypsin protease***
      - ***Also strong oxidants***
    - ***Amphilphilic Cylcodextrins***
      - ***Modified sugar molecules attract viruses before they irreversibly inactivate them***



Aerosols and Splatter in the Dental Operatory

2. What do we know?

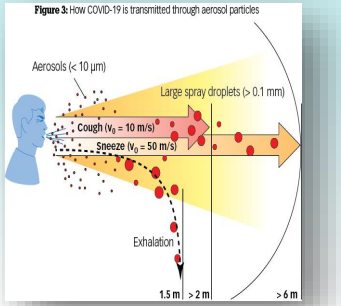
- **Mitigative Steps 5- Mouth Rinses**

Table 1. Overview of Oral Rinses Used in the Study With Product Name, Active Compounds, and Calculated Reduction Factors

			Log Reduction Factor (Mean of n = 3)		
Product	Trade Name	Active Compound[a]	Strain 1	Strain 2	Strain 3
A	Cavex Oral Pre Rinse	Hydrogen peroxide	0.78	0.61	0.33
B	Chlorhexamed Forte	Chlorhexidinebis (D-gluconate)	1.00	0.78	1.17
C	Dequonal	Dequalinium chloride, benzalkonium chloride	≥3.11	≥2.78	≥2.61
D	Dynexidine Forte 0.2%	Chlorhexidinebis (D-gluconate)	0.50	0.56	0.50
E	Iso-Betadine mouthwash 1.0%	Polyvidone-iodine	≥3.11	≥2.78	≥2.61
F	Listerine Cool Mint	Ethanol, essential oils	≥3.11	≥2.78	≥2.61
G	Octenident mouthwash	Octenidine dihydrochloride	1.11	0.78	0.61
H	ProntOral mouthwash	Polyaminopropyl biguanide (polyhexanide)	0.61	≥1.78	≥1.61

[a]The exact formulations for these oral rinses are not publicly available due to patent-related restrictions.

One study aims to compare 3 antiseptic mouthwash/gargling solutions compared to a control (distilled water) to reduce SARS-CoV-2 load in 120 individuals with confirmed COVID-19. (https://clinicaltrials.ucsf.edu/trial/NCT04409873).



The Journal of Infectious Diseases

BRIEF REPORT

Virucidal Efficacy of Different Oral Rinses Against Severe Acute Respiratory Syndrome Coronavirus 2

Toni Luise Meister,[1] Yannick Brüggemann,[1] Daniel Todt,[1,2] Carina Conzelmann,[3] Janis A. Müller,[3] Rüdiger Groß,[3] Jan Münch,[3] Adalbert Krawczyk,[4,5] Jörg Steinmann,[6,7] Jochen Steinmann,[8] Stephanie Pfaender,[1,a] and Eike Steinmann[1,a]

[1]Department for Molecular and Medical Virology, Ruhr University Bochum, Bochum, Germany, [2]European Virus Bioinformatics Center, Jena, Germany, [3]Institute of Molecular Virology, Ulm University Medical Center, Ulm, Germany, [4]Department of Infectious Diseases, West German Centre of Infectious Diseases, Universitätsmedizin Essen, University Duisburg-Essen, Essen, Germany, [5]Institute for Virology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, [6]Institute of Clinical Hygiene, Medical Microbiology and Infectiology, General Hospital Nürnberg, Paracelsus Medical University, Nuremberg, Germany, [7]Institute of Medical Microbiology, University Hospital of Essen, Essen, Germany, and [8]Dr. Brill + Partner GmbH Institute for Hygiene and Microbiology, Bremen, Germany

The ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic creates a significant threat to global health. Recent studies suggested the significance of throat and salivary glands as major sites of virus replication and transmission during early coronavirus disease 2019, thus advocating application of oral antiseptics. However, the antiviral efficacy of oral rinsing solutions against SARS-CoV-2 has not been examined. Here, we evaluated the virucidal activity of different available oral rinses against SARS-CoV-2 under conditions mimicking nasopharyngeal secretions. Several formulations with significant SARS-CoV-2 inactivating properties in vitro support the idea that oral rinsing might reduce the viral load of saliva and could thus lower the transmission of SARS-CoV-2.

Keywords. SARS-CoV-2; oral rinses; inactivation; suspension test; transmission.

Aerosols and Splatter in the Dental Operatory

2. What do we know?

- **Mitigative Steps 5- Mouth Rinses**

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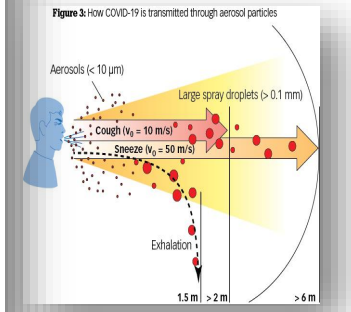
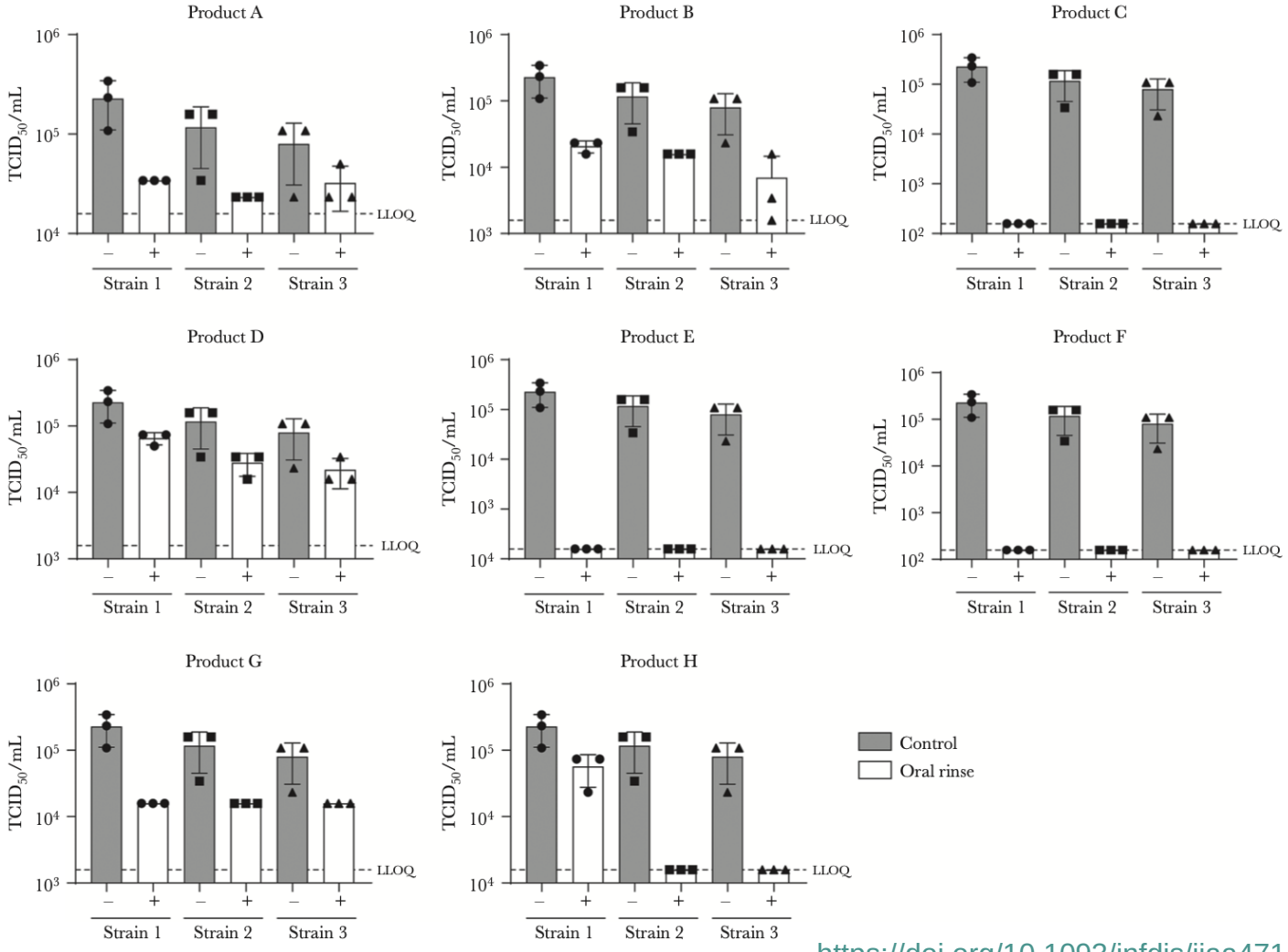




https://doi.org/10.1093/infdis/jiaa471

Figure 1. Virucidal activity of oral rinses against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 strains 1 (dot; UKEssen), 2 (square; BetaCoV/Germany/Ulm/01/2020), and 3 (triangle; BetaCoV/Germany/Ulm/02/2020) were incubated with medium (control) or various oral rinses for 30 seconds. Both conditions were supplemented with an interfering substance mimicking respiratory secretions. Viral titers were determined upon titration on Vero E6 cells. The cytotoxic effect was monitored using noninfected cells incubated with the different products, defined as the lower limit of quantification (LLOQ). The 50% tissue culture infectious dose ($TCID_{50}$/mL) was calculated according to Spearman–Kärber. Data indicate averages and standard deviation of 3 independent experiments.

Aerosols and Splatter in the Dental Operatory

2. What do we know?

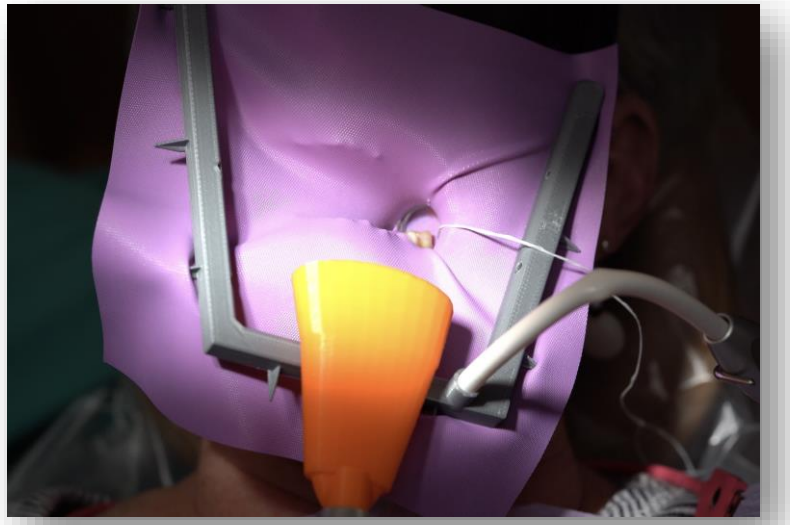
- ***Mitigative Step 6***
  - *Saliva Ejectors and/or high- volume evacuator*
    - *Backflow values a must*
    - *Reduces splatter by 90%*
- ***Mitigative Step 7***
  - *Decontamination immediately after patient-care*

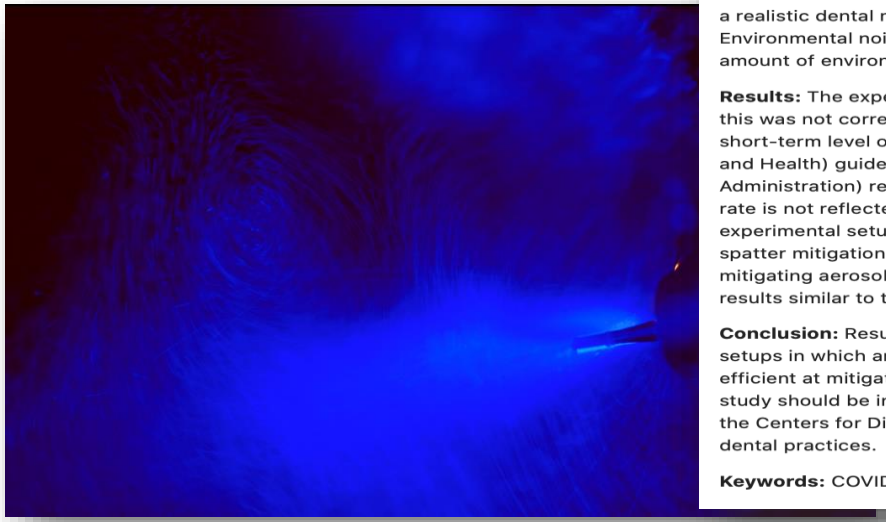
  Product must remain in contact for full recommended time
    - *SARS-CoV-2 remains infectious for for up to 3 days!*

Aerosols and Splatter in the Dental Operatory

2. What do we know?

- **Mitigative Step 8**
  - Rubber Dams and Dry Field Isolation Techniques
    - Use of high-volume evacuators





> Quintessence Int. 2020;51(8):660-670. doi: 10.3290/j.qi.a44919.

Evaluation of the spatter-reduction effectiveness and aerosol containment of eight dry-field isolation techniques

Theodore D Ravenel, Raymond Kessler, John C Comisi, Abigail Kelly, Walter G Renne, Sorin T Teich

PMID: 32661521 DOI: 10.3290/j.qi.a44919

Abstract

Objective: The novel coronavirus that was first identified in Wuhan, China, in December 2019, created a pandemic that has the potential to change the paradigm of health care delivery. Of interest to the dental community is the presence of SARS-CoV-2 in the saliva of the affected patients that can potentially cause transmission of COVID-19 via droplets. The highly infectious nature of the pathogen has created a sense of urgency and a need for extra caution to prevent the spread of the disease and the potential infection of patients and the entire dental team. Spatter consists of droplets up to 50 µm in size that are effectively stopped by barriers such as gloves, masks, and gowns. Aerosols are defined as droplet particles smaller than 5 µm that can remain airborne for extended periods and that have been reported to be significant in viral respiratory infections. In this study, aerosol represented by particulate matter with a size of 2.5 µm (PM2.5) was measured.

Method and materials: Eight dry-field isolation methods were tested in a setup that included a realistic dental manikin and a high-speed handpiece that generated air-water spray. Environmental noise generated by the suction devices, suction flow rate of each setup, and the amount of environmental spatter and aerosols, were measured.

Results: The experimental setups showed significant variability in the suction flow rate, but this was not correlated to the level of sound generated. Some experimental setups caused a short-term level of noise that exceeded the NIOSH (National Institute for Occupational Safety and Health) guidelines and were close to the OSHA (Occupational Safety and Health Administration) recommended thresholds. It is also worth noting that the variability in the flow rate is not reflected in the efficacy of the experimental setups to mitigate spatter. All experimental setups, except the IsoVac system, provided statistically significantly better spatter mitigation compared to the control. All experimental setups also were efficient in mitigating aerosols compared with the positive control ($P < .0001$) and most systems yielded results similar to the negative control ambient PM ($P > .05$).

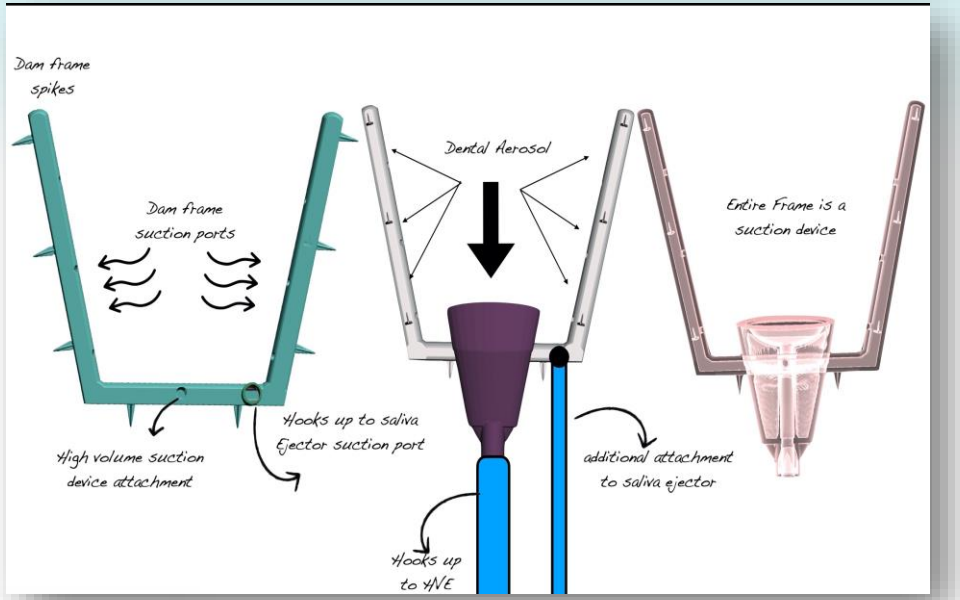
Conclusion: Results indicate that spatter reduction was significantly better amongst the setups in which an additional high-volume evacuator (HVE) line was used. All setups were efficient at mitigating PM2.5 aerosols in comparison to the control. The conclusions of this study should be interpreted with caution, and additional mitigation techniques consistent with the Centers for Disease Control and Prevention recommendations must be implemented in dental practices.

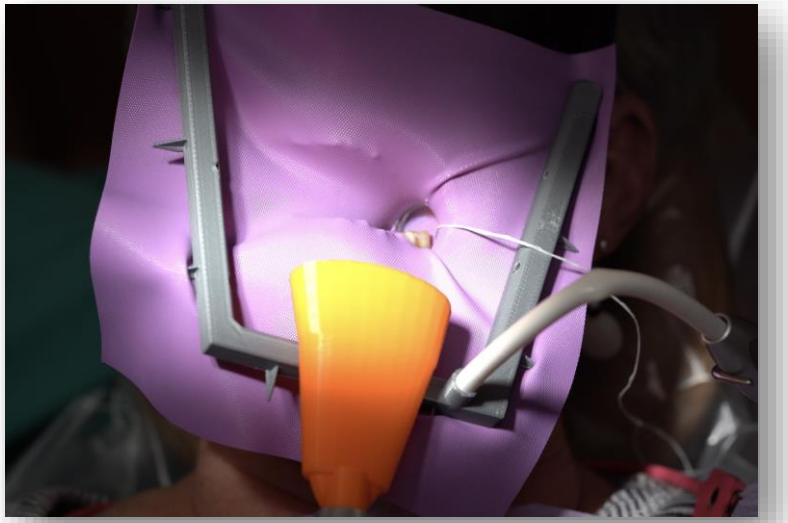
Keywords: COVID-19; high-volume evacuator (HVE); infection control; suction; aerosol.

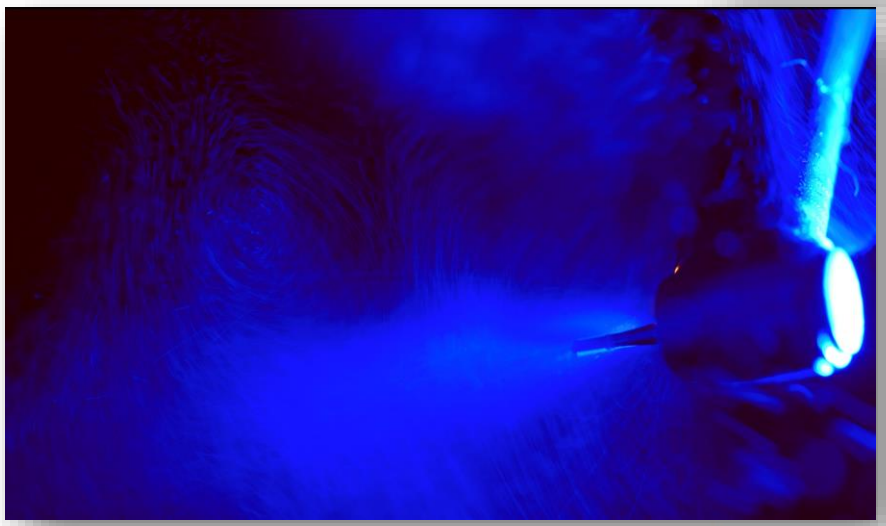
Aerosols and Splatter in the Dental Operatory

2. What do we know?

- ***Mitigative Step 8***
  - ***Rubber Dams and Dry Field Isolation Techniques***
    - ***Use of high-volume evacuators***







Is There Hope?

Big Data will be key…

For Quick Coronavirus Testing, Israel Turns to a Clever Algorithm

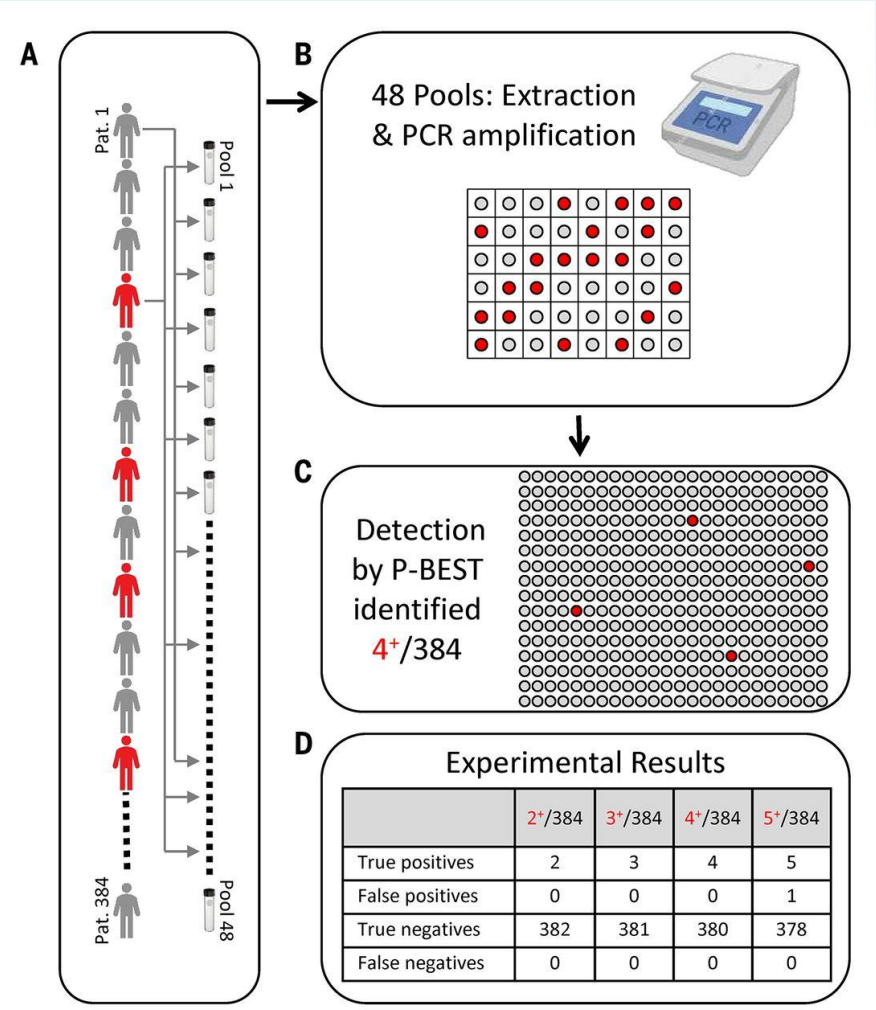
Inspired by a mother's question, the new method will be introduced across Israel this fall, just in time for flu season, and could be coming soon to the U.S.

Israeli scientists successfully detected coronavirus positives in pools of 16 and 48 samples with a new testing procedure. Dan Balilty for The New York Times

Efficient high-throughput SARS-CoV-2 testing to detect asymptomatic carriers

Science Advances
Noam Shental et al. Sci Adv 2020;sciadv.abc5961

Big Data will be key



	2+/384	3+/384	4+/384	5+/384
True positives	2	3	4	5
False positives	0	0	0	1
True negatives	382	381	380	378
False negatives	0	0	0	0

P-BEST design and detection results obtained for a set of 384 samples with a carrier rate of ~1%.

a. Pooling design – Pools are generated using a combinatorial pooling design based on an error correcting code that optimizes carrier detection.

The P-BEST pooling design for a carrier rate of **~1%** uses 48 pools to test 384 subjects simultaneously providing both an 8-fold increase in testing efficiency, as well as an 8-fold reduction in testing reagent costs.

Each sample is distributed to six pools and there are a total of 48 subjects per pool. Subjects in red represent the four unidentified infected individuals within the set of 384 samples. **b.** Pooled samples are then treated as individual samples – RNA is extracted, followed by standard PCR amplification. Positive pools are designated by red circles. **c.** P-BEST identifies the positive samples out of the 384 samples using an optimization-based algorithm based on compressed sensing. **d.** Results of the four experiments performed, containing 2, 3, 4 or 5 positive samples, respectively. All positive carriers were correctly identified in all experiments. When five positive carriers were tested (carrier rate of 1.3%), a single false positive sample was added to the true positive ones.

Fig. 1 P-BEST design and detection results obtained for a set of 384 samples with a carrier rate of ~1%. a.

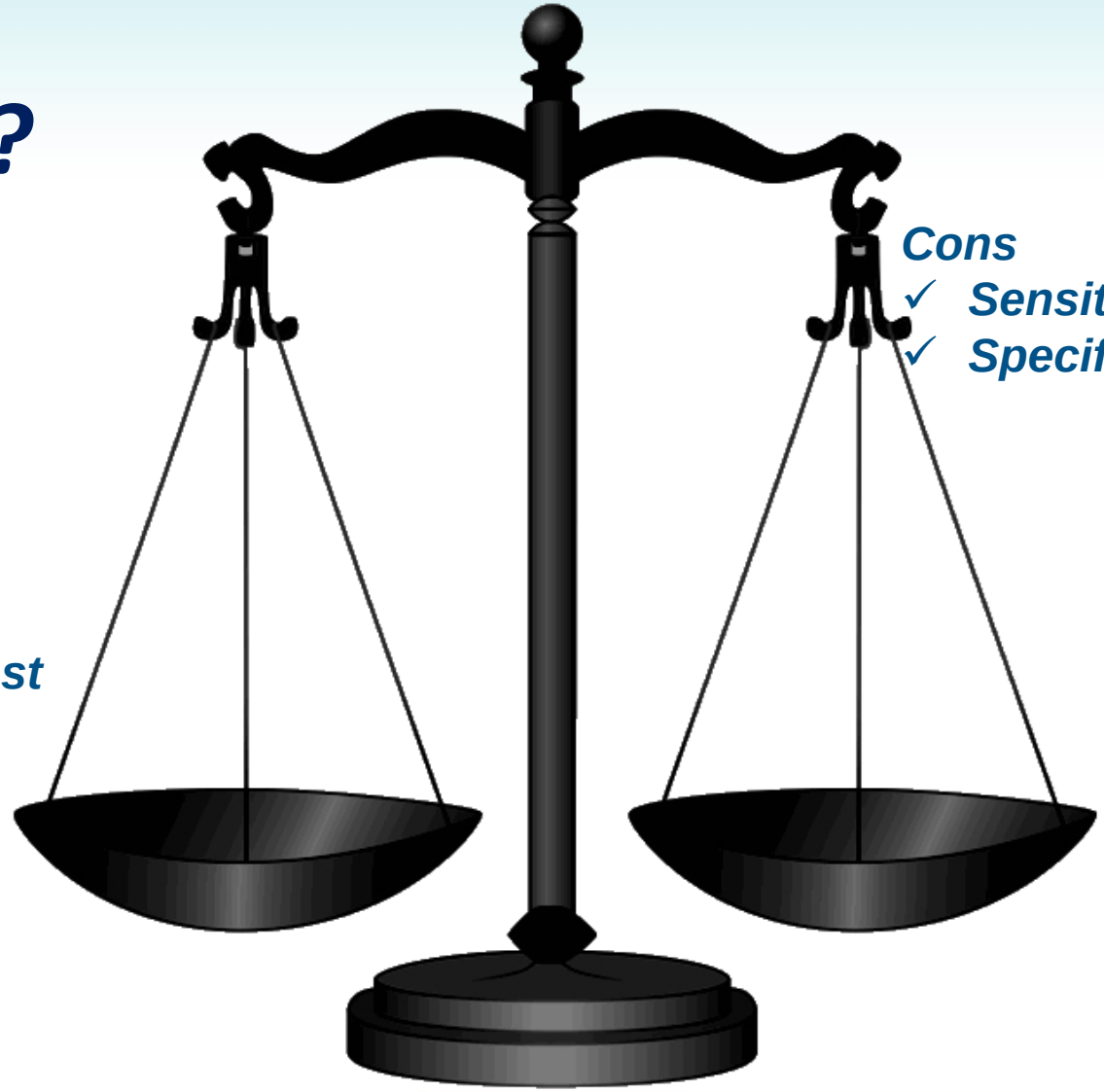
How can we prevent another shutdown?

Testing – What is its role?

The Antigen test …

- *What question does it ask of the patient?*

Pros
- ✓ **Speed and Cost**



Cons
- ✓ **Sensitivity (TP)**
- ✓ **Specificity (TN)**

How can we prevent another shutdown?

Testing – What is its role?

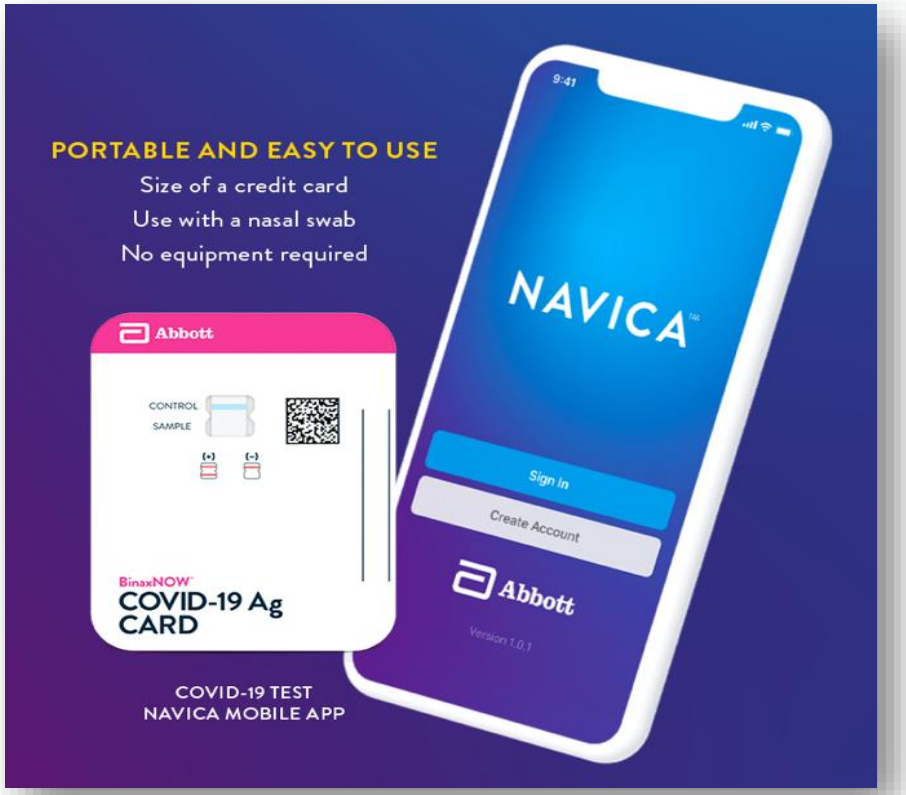
The Serology test …

- *What question does it ask of the patient?*
  - *Have you been exposed?*
- *What role does it serve?*
  - *Unknown… but in general, absent symptoms*

Testing Terms – What do they mean?

- ***Sensitivity***
  - Assesses the true positive
    - Dependent upon what question is being asked by the test
- ***Specificity***
  - Assesses the true negatives
    - Dependent upon what question is being asked by the test

Headline News - 26 August 2020
What's Next? - Lick Stick Tech

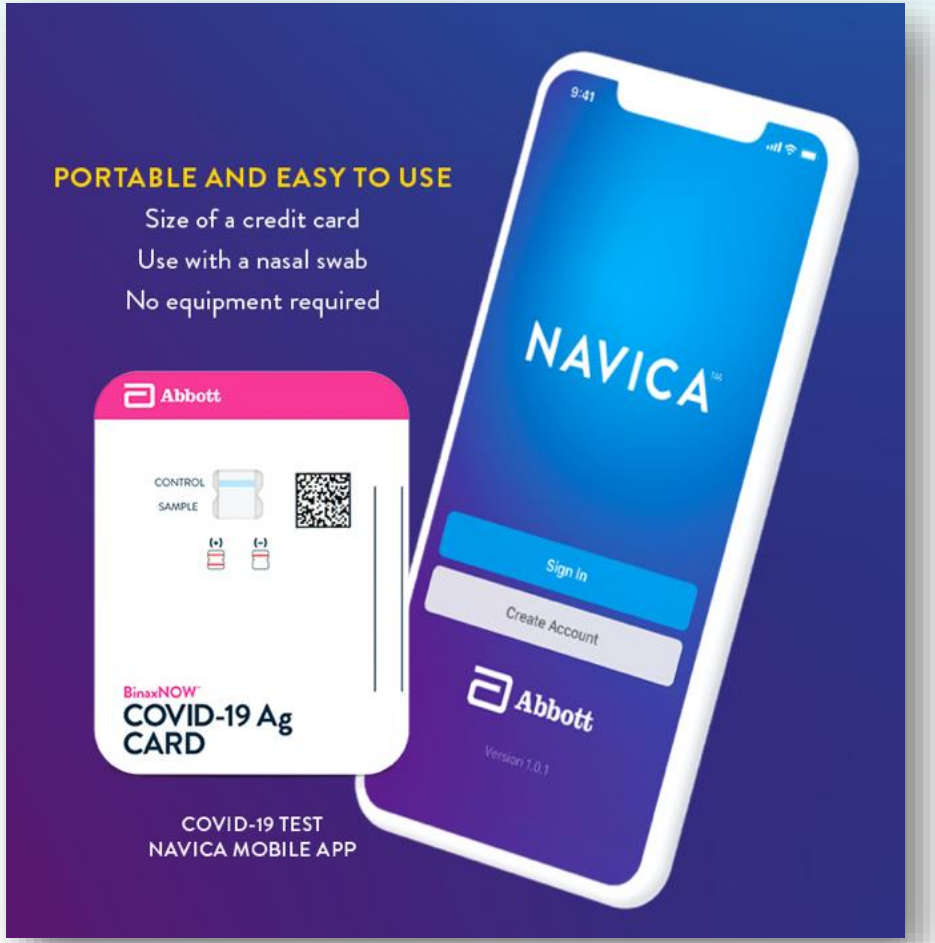


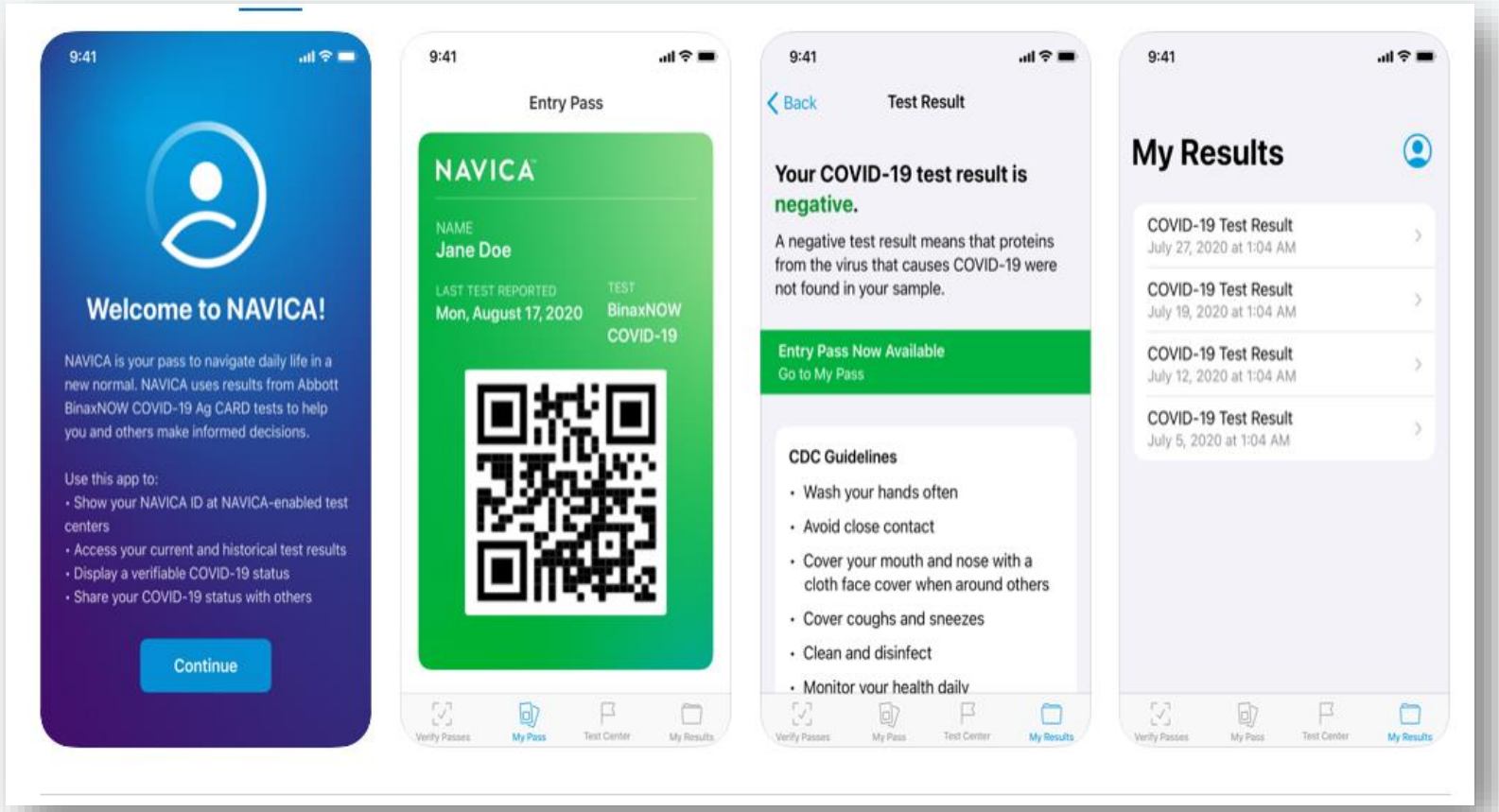
ABBOTT PARK, Ill., Aug. 26, 2020 /PRNewswire/ -- Abbott (NYSE: ABT) announced today that the U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorization (EUA) for its BinaxNOW™ COVID-19 Ag Card rapid test for detection of COVID-19 infection.

Abbott will sell this test for $5. It is highly portable (about the size of a credit card), affordable and provides results in 15 minutes. BinaxNOW uses proven Abbott lateral flow technology, making it a reliable and familiar format for frequent mass testing through their healthcare provider. With no equipment required, the device will be an important tool to manage risk by quickly identifying infectious so they don't spread the disease to others.

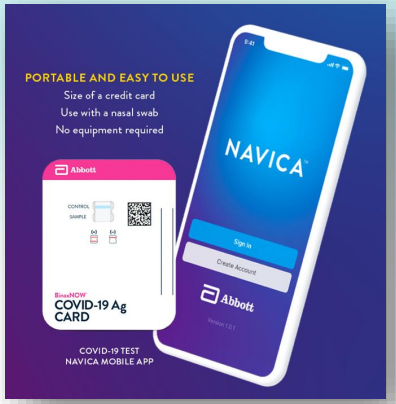
Abbott will also launch a complementary mobile app for iPhone and Android devices named NAVICA™. This first-of-its-kind app, available at no charge, will allow people who test negative to display a temporary digital health pass that is renewed each time a person is tested through their healthcare provider together with the date of the test result. Organizations will be able to view and verify the information on a mobile device to facilitate entry into facilities along with hand-washing, social distancing, enhanced cleaning and mask-wearing.

BinaxNOW™ and Navica™





BinaxNOW™ Covid-19 Ag Card Navica™



Pros-

- ✓ *Fast – 15 minutes for result*
- ✓ *Affordable $5*
- ✓ *Available 50 million per month*
- ✓ *Use with Nasal Swab*
- ✓ *No equipment needed*

Cons

- ✓ *Nasal Swab rather than Saliva*
- ✓ *Expensive if used daily ~~$5~~ (ideal $0.05 to 0.25/test)*
- ✓ *Available ~~50~~ 500 million per month*
- ✓ *Need for HCP to read*

Medications - How should we prime the pump?

Lessons learned from HIV and HEP-C

- ***It should be more than 1***
- **Remdesivir - IV only**

Passive Immunization

- ***Monoclonal Antibodies***
  - **Regeneron**
  - **Eli Lilly**

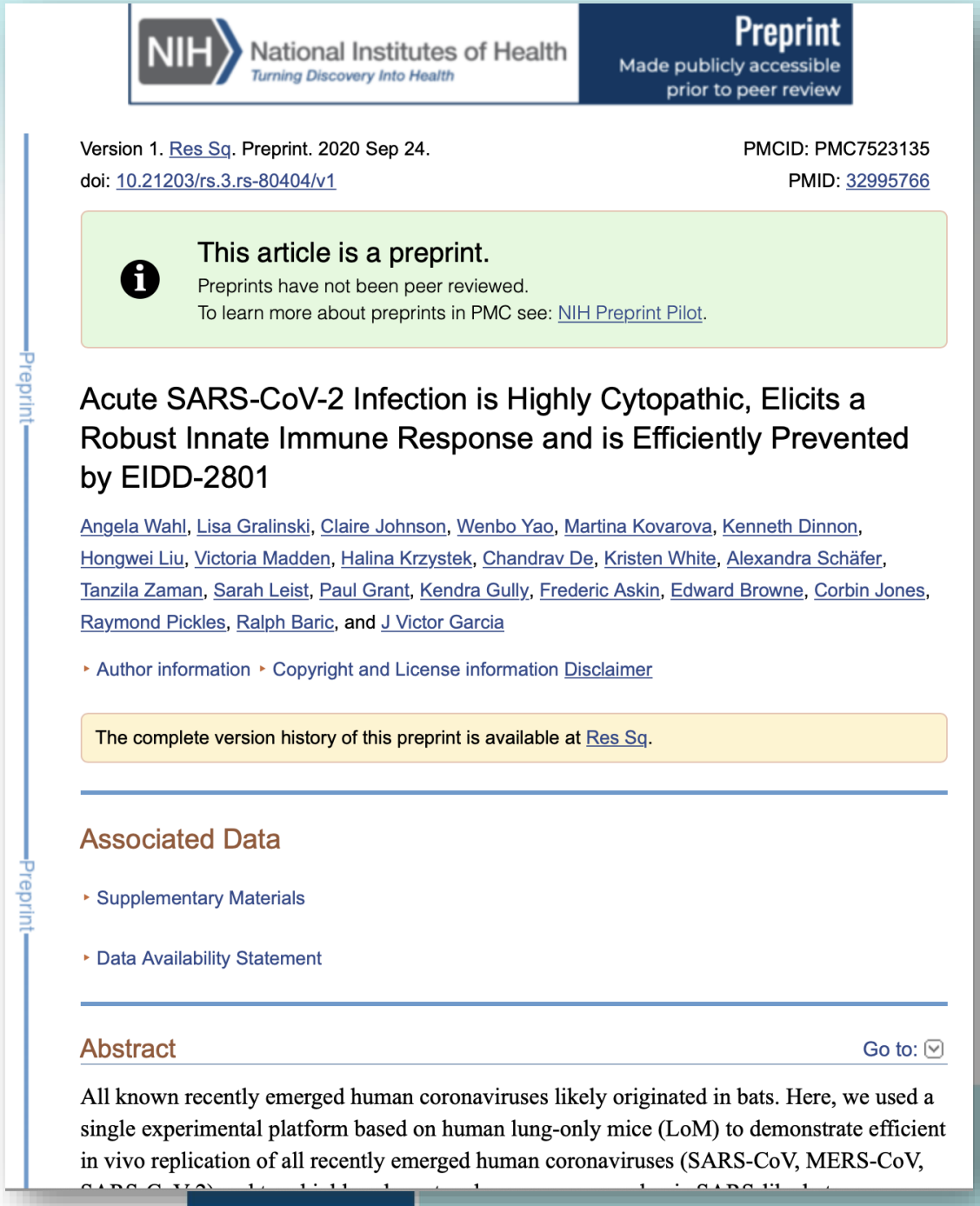
https://youtu.be/GZucJzAmYhM

https://youtu.be/5AXApBbj1ps

Part of our hope…EIDD-2801

- *Nucleoside analog of Cytosine…proofreader then puts in a U…*
- **Works as an oral medication !**
- *Passed phase I safety trials*
- *Currently in phase II human clinical trials*
- *Works well and safely in mice.*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7523135/



NIH National Institutes of Health
Turning Discovery Into Health

Preprint
Made publicly accessible prior to peer review

Version 1. Res Sq. Preprint. 2020 Sep 24.
PMCID: PMC7523135
doi: 10.21203/rs.3.rs-80404/v1
PMID: 32995766

This article is a preprint.
Preprints have not been peer reviewed.
To learn more about preprints in PMC see: NIH Preprint Pilot.

Acute SARS-CoV-2 Infection is Highly Cytopathic, Elicits a Robust Innate Immune Response and is Efficiently Prevented by EIDD-2801

Angela Wahl, Lisa Gralinski, Claire Johnson, Wenbo Yao, Martina Kovarova, Kenneth Dinnon, Hongwei Liu, Victoria Madden, Halina Krzystek, Chandrav De, Kristen White, Alexandra Schäfer, Tanzila Zaman, Sarah Leist, Paul Grant, Kendra Gully, Frederic Askin, Edward Browne, Corbin Jones, Raymond Pickles, Ralph Baric, and J Victor Garcia

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The complete version history of this preprint is available at Res Sq.

Associated Data

Supplementary Materials

Data Availability Statement

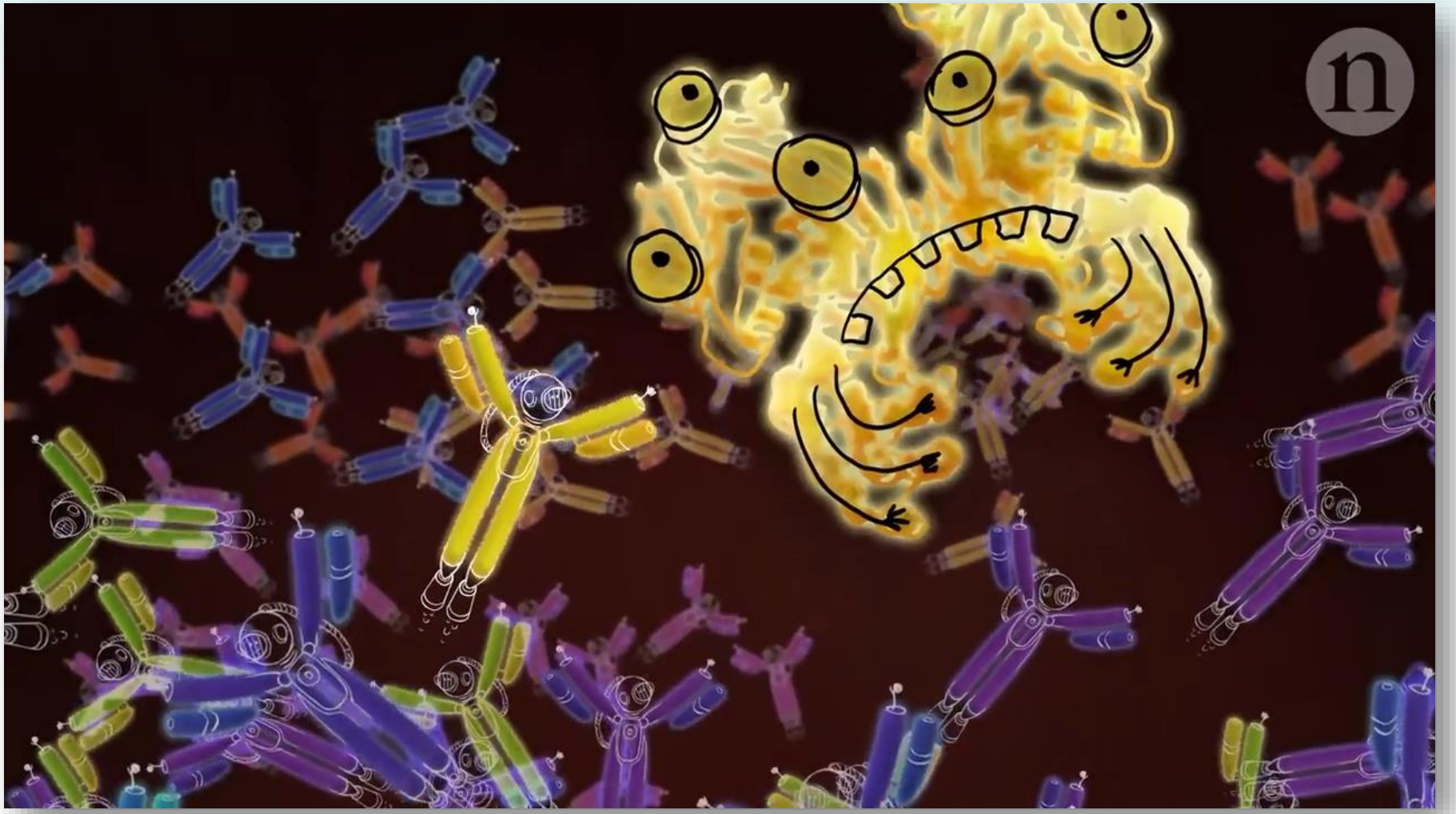
Abstract Go to:

All known recently emerged human coronaviruses likely originated in bats. Here, we used a single experimental platform based on human lung-only mice (LoM) to demonstrate efficient in vivo replication of all recently emerged human coronaviruses (SARS-CoV, MERS-CoV,

Medications - How should we prime the pump?

Passive Immunization

- ***Monoclonal Antibodies***
  - **Regeneron**
  - **Eli Lilly**



https://youtu.be/5AXApBbj1ps

Medications - How should we prime the pump?

Passive Immunization

- ***Monoclonal Antibodies***
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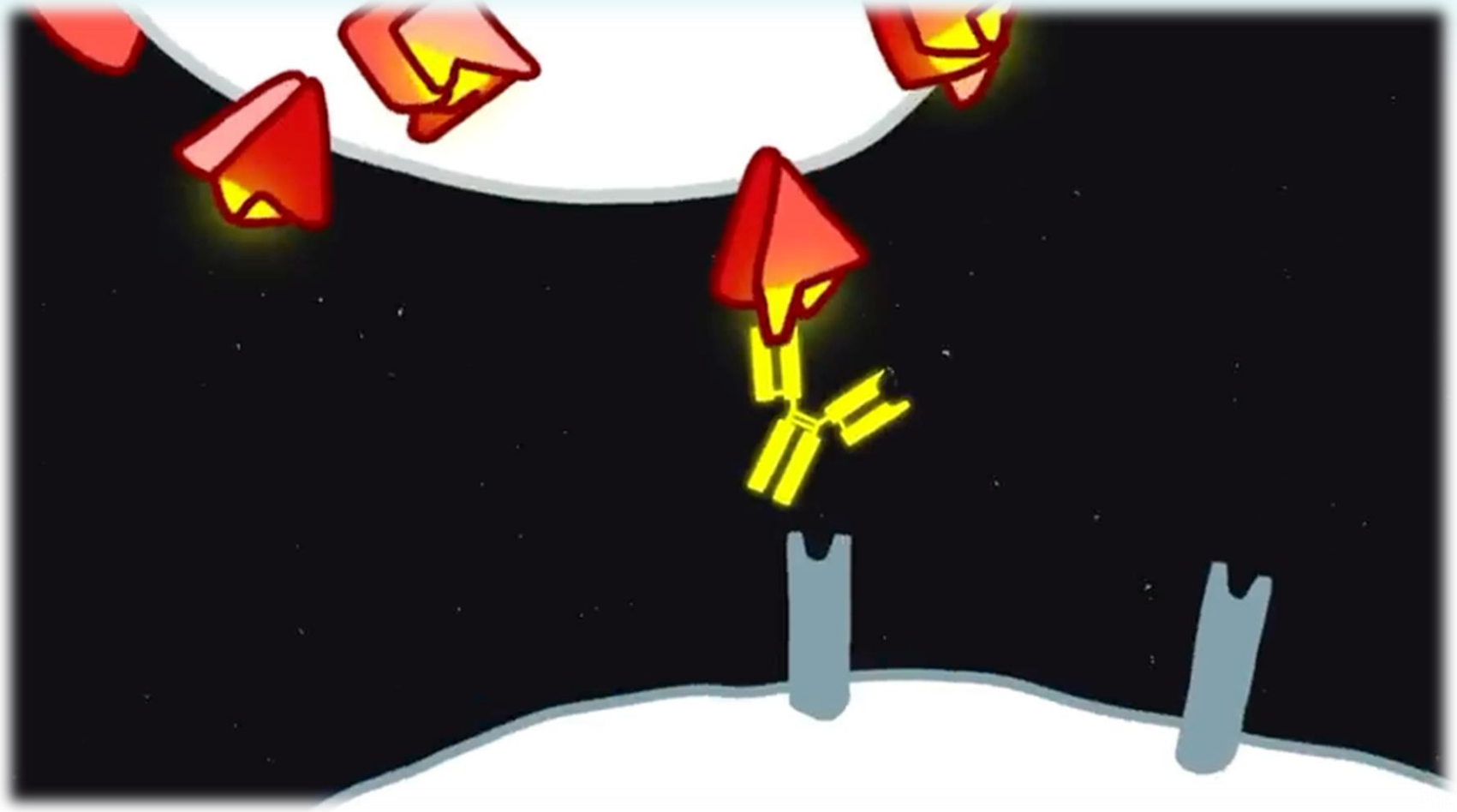


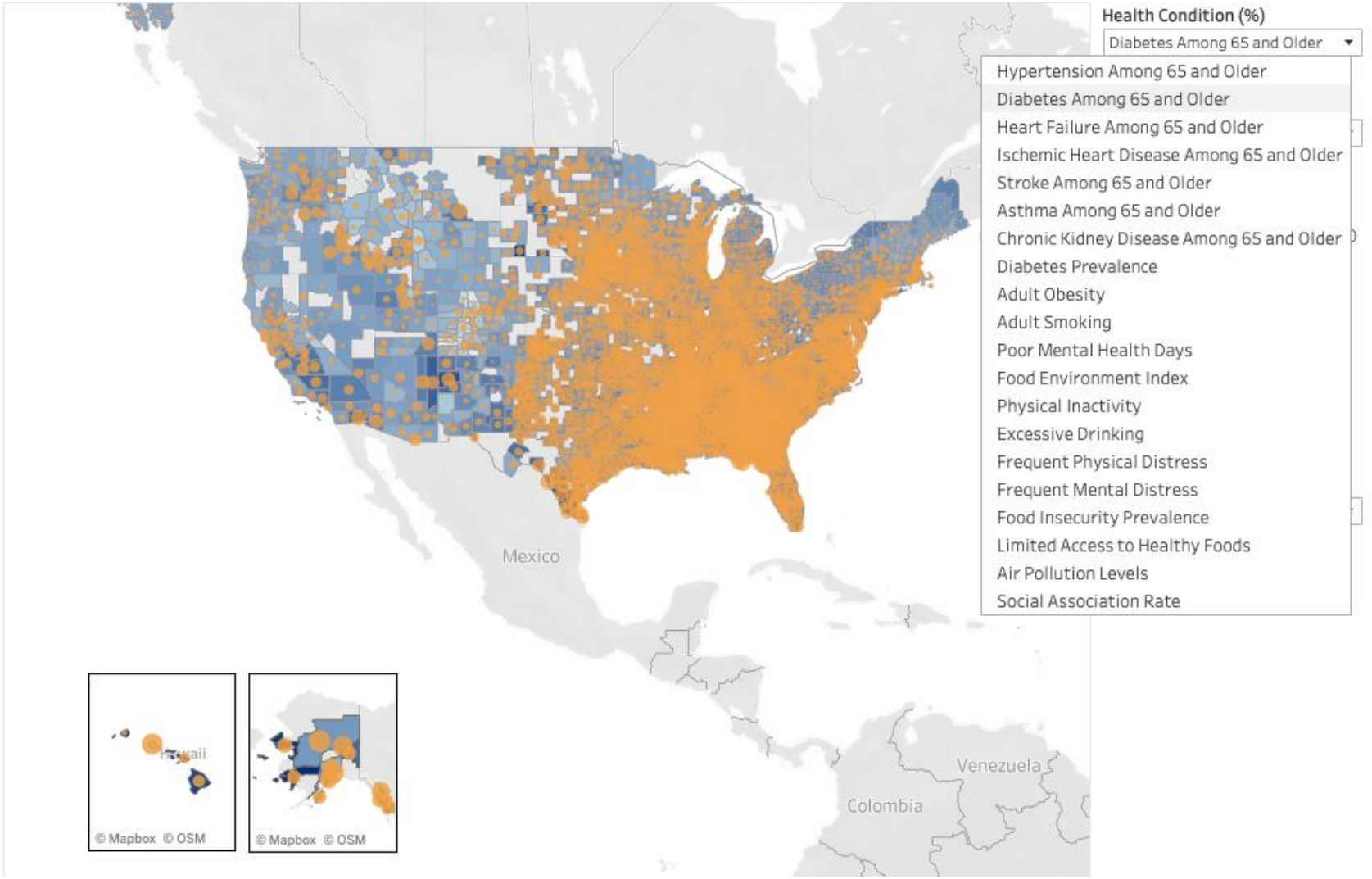
https://youtu.be/RqYD7taehrU

Folks are busy!

The MI COVID-19 Community Explorer provides a simple way to explore geographic clusters of communities affected by the pandemic and their socioeconomic, demographic, and health-related features.

Community Characteristics of US Counties

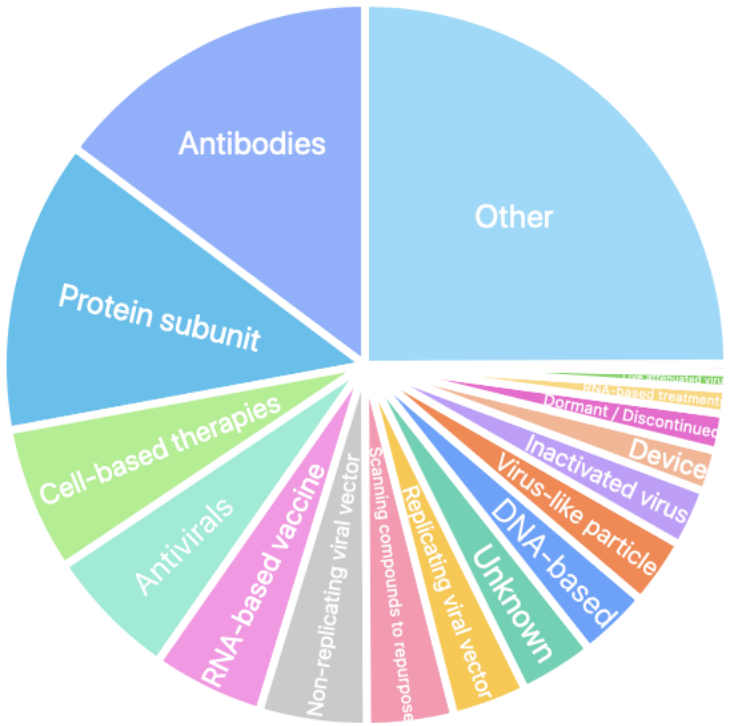
Their interactive map provides a simple but informative way for users to gain necessary insights into what makes communities more vulnerable.



- ***https://milkeninstitute.org/research/COVID-19-community-explorer***

Folks are busy!

- *Tracking websites*



QUICK LINKS

MILKEN INSTITUTE FasterCures

COVID-19 TREATMENT AND VACCINE TRACKER

LAST UPDATED: **OCTOBER 16, 2020 10:40 AM** PACIFIC

FasterCures, a center of the Milken Institute, is currently tracking the development of treatments and vaccines for COVID-19 (coronavirus). This tracker contains an aggregation of publicly-available information from validated sources.

Explore detailed information on each development:

TREATMENTS	VACCINES
319 TOTAL	213 TOTAL

FIRST PERSON

See the race for a vaccine visualized

https://covid-19tracker.milkeninstitute.org/#home

Vaccines – When? Warp Speed NOW!

What does the vaccine need to do?

- **Vaccines don't cure…. They either**
  - ✓ **Prevent an infection or**
  - ✓ **Prevent disease**
    - ❑ **Over 213 under development**
      - ✓ *Early safety data promising…*
      - ✓ *Early challenge experiments of some, worked safely in animals…*

https://covid-19tracker.milkeninstitute.org/#home

There are currently	These fall into	At this time,
213	9	36
vaccines in development for COVID-19.	different product categories/platforms.	vaccines are in one of four phases of clinical testing.

Leading Candidates

FARTHEST ALONG*	CLINICAL PHASE
Univ. of Oxford/AstraZeneca	III
Sinovac/Instituto Butantan	III
Wuhan Inst./Sinopharm	III
Beijing Inst./Sinopharm	III
Moderna	III
Gamaleya Research Inst.	III
CanSino Biologics	III
Janssen Pharma	III
BioNTech/Fosun/Pfizer	II/III
Novavax	II

* Ranked by entry into latest phase of development. Clinical phases move when it is publicly reported that the product has been dosed in a trial.

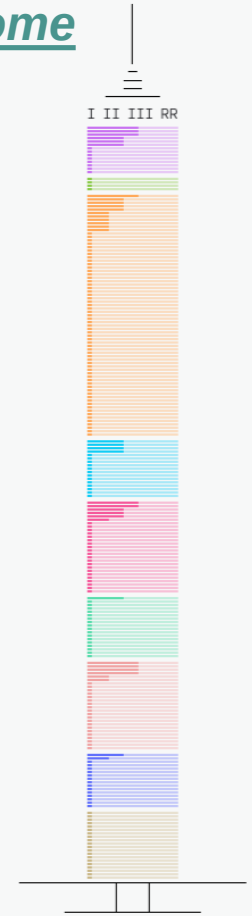
Key

VACCINE CATEGORIES

- Inactivated Virus
- Live Attenuated Virus
- Protein Subunit
- DNA-Based
- RNA-Based
- replicating viral vector
- Non-Replicating VIral Vector
- Virus-Like Particle
- Other Vaccines

CLINICAL TRIAL PHASE

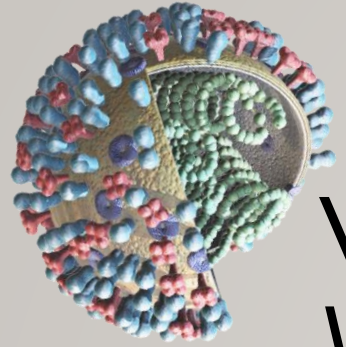
- I Phase One
- II Phase Two
- III Phase Three
- RR Regulatory Review



Clinical trial phases read in columns from left to right on the syringe.

Vaccines still in the pre-clinical phase remain transparent.

- ➢ **Normally ~ 10 to 15 years from concept to clinic**
- ➢ **With COVID-19 -12-18 months!**
  9 candidates in Phase III



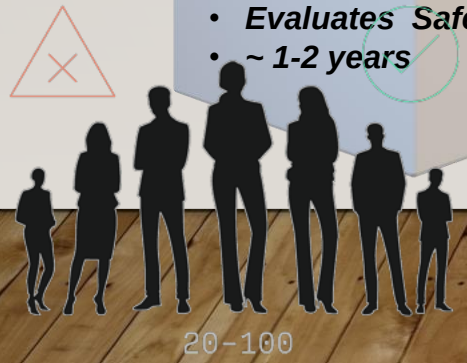
Vaccine Pipeline – *Why so long?*

Pre-Clinical Phase

- *Feasibility*
- *Iterative Non-human testing*
- *Toxicity& Pharmacology*

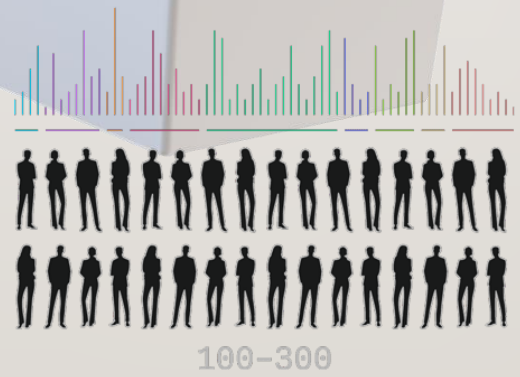
Phase 1-Clinical Phase 20 to 100

- *Small Study of Healthy Folk*
- *Evaluates Safety, Dose & Effect*
- *~ 1-2 years*



Phase 2-Clinical Trial 100 to 300

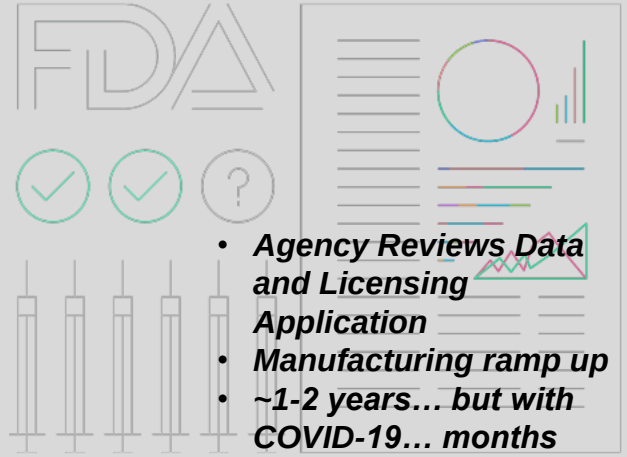
- *Evaluates Safety, Dose & Effect*
- *Outcome informs optimal dose*
- *Schedule, once, prime, boast, etc.*
- *~2 to 3 years*



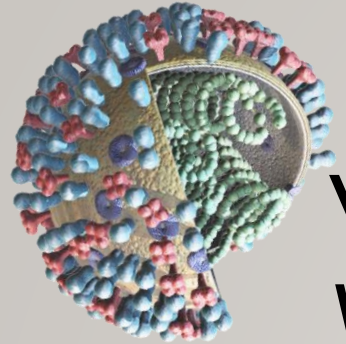
Phase 3-Clinical Trials Studies 1000s

- *Evaluates Safety & Efficacy*
- *Typically 2 to 4 years but with COVID-19 Phase II & III may be combined*

Regulatory Review



- *Agency Reviews Data and Licensing Application*
- *Manufacturing ramp up*
- *~1-2 years… but with COVID-19… months*



Vaccine Pipeline – *Why so long?*

Manufacturing

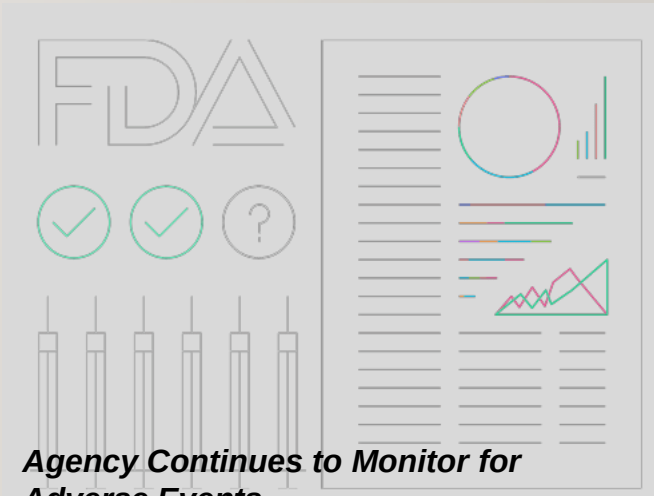
- *What works?*
- *In widespread circulation*
- *US already invested ~4 Billion*

Developer gets fast approval and is concurrently manufacturing the vaccine during the clinical trials Ready for Mass Distribution

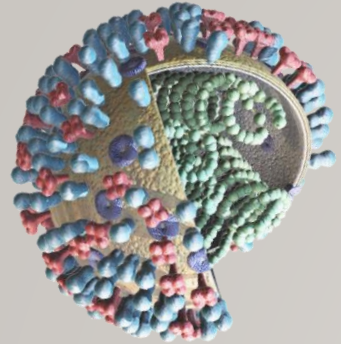
Phase 4 Clinical Use

- *Monitors Effectiveness under Real World Conditions*

Continuous Regulatory Review



- *Agency Continues to Monitor for Adverse Events*



WHILE WE WAIT … THERE MAY BE HOPE!

Manufacturing

- *What works?*
- *In widespread circulation*
- *US already invested ~4 Billion*

Phase 4 Clinical Use

- *Monitors Effectiveness under Real World Conditions*

Developer gets fast approval and is concurrently manufacturing the vaccine during the clinical trials Ready for Mass Distribution

Continuous Regulatory Review

VIEWPOINT: COVID-19

Can existing live vaccines prevent COVID-19?

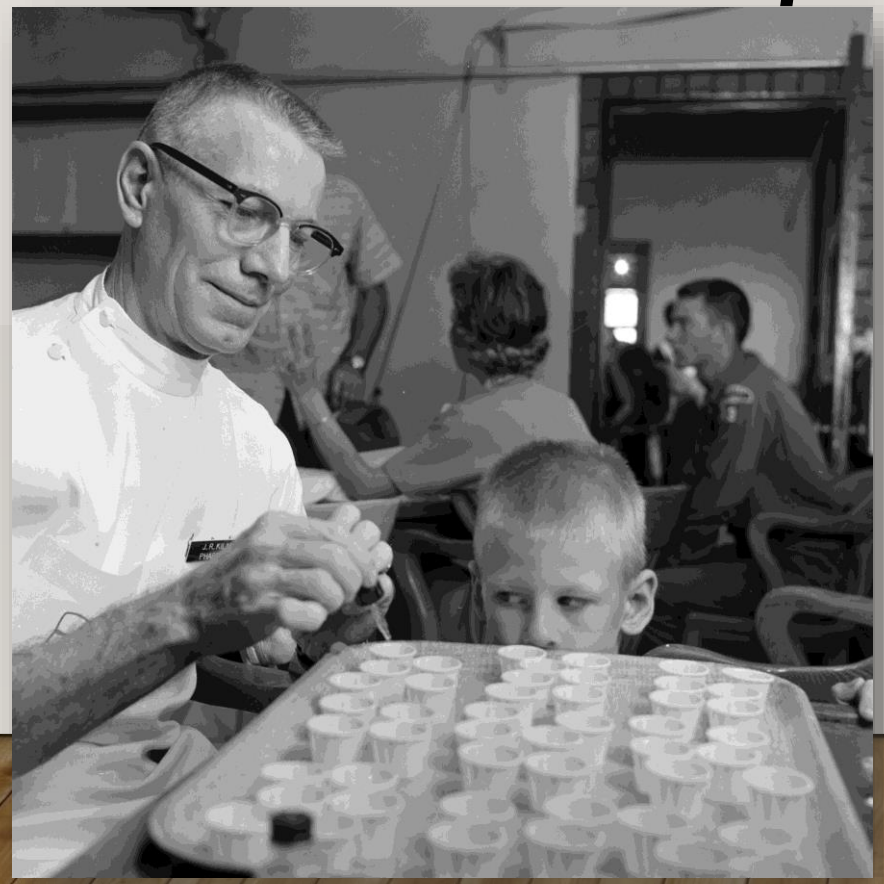
Live vaccines can prevent unrelated infections and may temporarily protect against COVID-19

By Konstantin Chumakov[1,2], Christine S. Benn[3], Peter Aaby[4], Shyamasundaran Kottilil[5], Robert Gallo[2,5]

Prophylactic vaccination is the most effective intervention to protect against infectious diseases. The commonly accepted paradigm is that immunization with both attenuated virus (live but with substantially reduced virulence) and inactivated (killed virus particles) vaccines induces adaptive and generally long-term and specific immunity in the form of neutralizing antibodies and/or activating pathogen-specific cellular immune responses. However, an increasing body of evidence suggests that live attenuated vaccines can also induce broader protection against unrelated pathogens likely by inducing interferon and other innate im-

THANK YOU…

- *The only thing more contagious than this virus is hope…*



Will things Ever Return to Normal?

25 October 2020

Michael G. Schmidt, Ph.D. FAAM, FACD (hon)
Professor of Microbiology & Immunology
Medical University of South Carolina
schmidtm@musc.edu

TWiM
THIS WEEK IN MICROBIOLOGY

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA