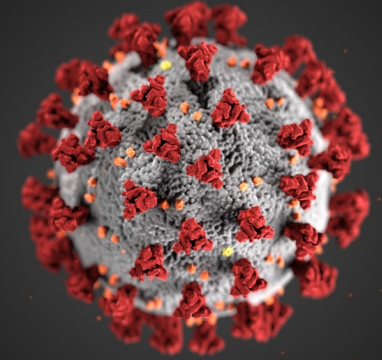
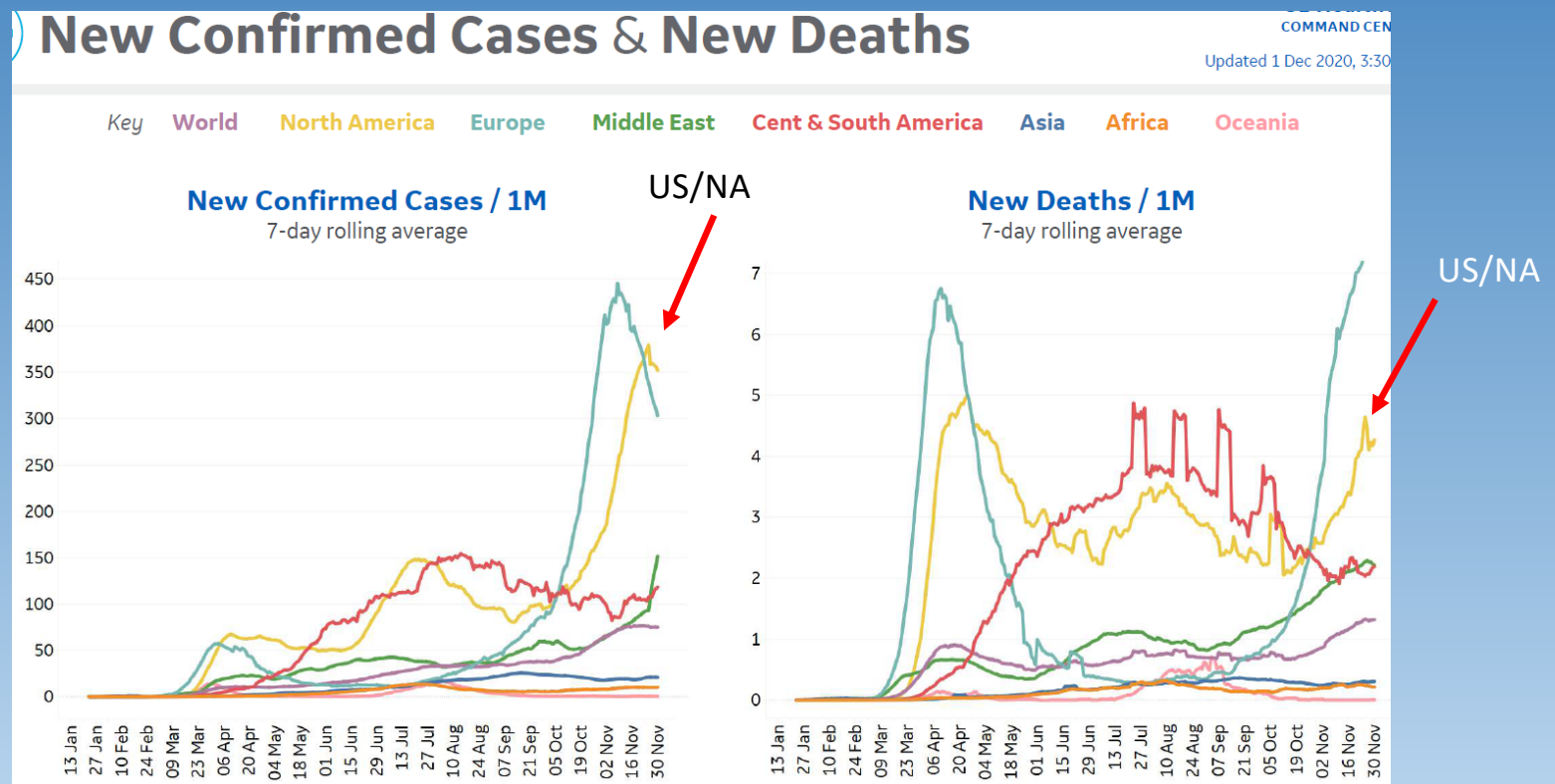


Covid-19



Alan Taege, MD
Assistant Professor of Medicine
Department of Infectious Disease
Cleveland Clinic

US: 4% World Population – 19% World Covid-19 Cases



US Coronavirus Pandemic

The Coalition believes the United States is not containing the pandemic as successfully as other nations because of:



MJH Life Sciences Covid-19 Coalition

False Accusations: Physicians and Covid Care

[Susan R. Bailey, M.D.](#)

President, American Medical Association

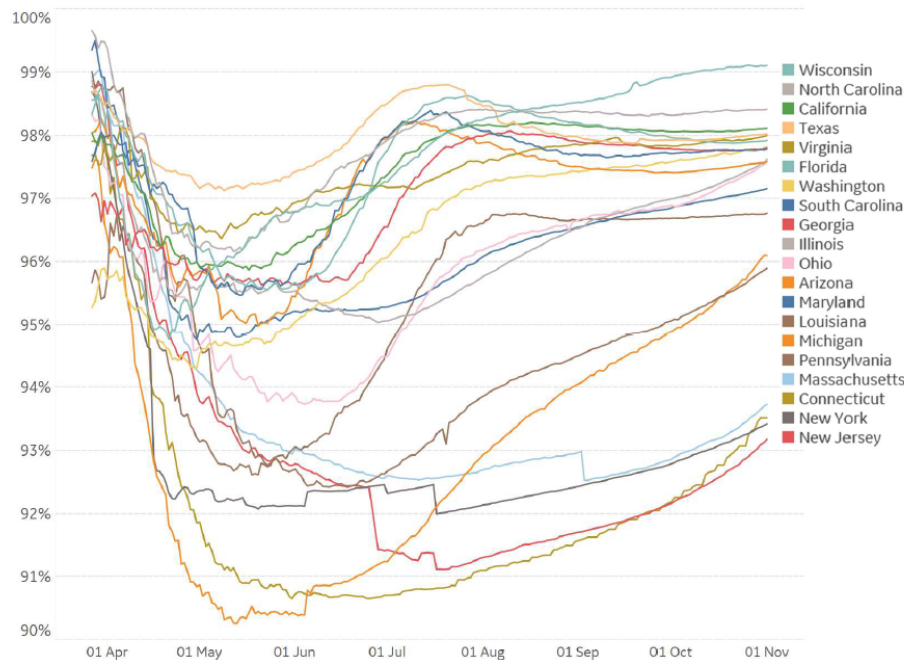
“Throughout this pandemic, physicians, nurses, and frontline health care workers have risked their health, their safety and their lives to treat their patients and defeat a deadly virus. They did it because duty called and because of the sacred oath they took. **The suggestion that doctors—in the midst of a public health crisis—are overcounting COVID-19 patients or lying to line their pockets is a malicious, outrageous, and completely misguided charge.** COVID-19 cases are at record highs today. Rather than attacking us and lobbing baseless charges at physicians, our leaders should be following the science and urging adherence to the public health steps we know work—wearing a mask, washing hands and practicing physical distancing.”

US Survival Rates/Case Fatality Rates “On the ‘Brighter’ (?) Side”

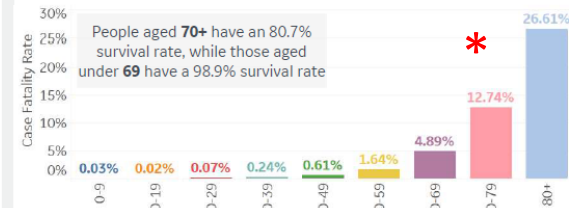


Feature: Survival Rates, US States

Survival Rates Over Time, select states



Case Fatality Rate (CFR) by Age Group



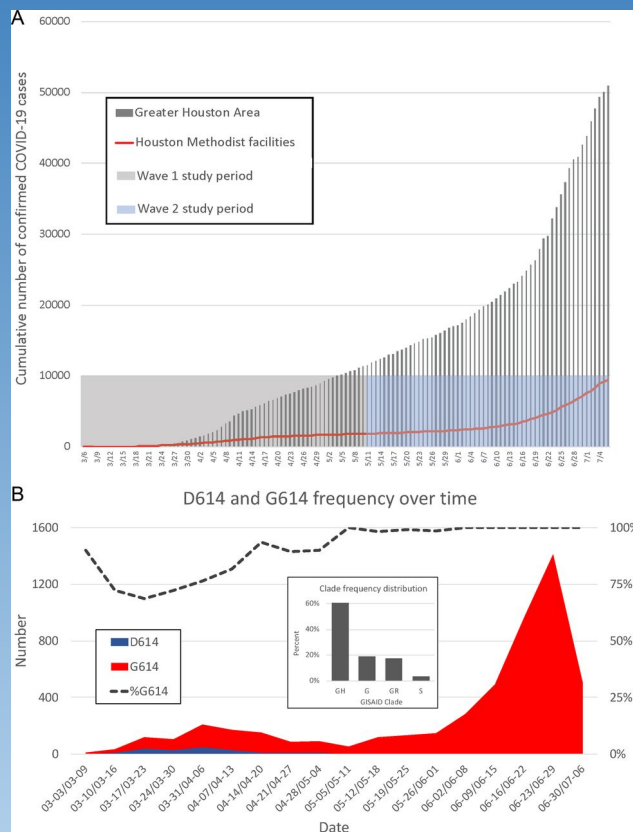
Top 5 States with Highest Survival Rates to date

State	Survival Rate	CFR to date	CFR last 30 days
Alaska	99.50%	0.50%	0.30%
Utah	99.47%	0.53%	0.37%
Wyoming	99.37%	0.63%	0.45%
Wisconsin	99.11%	0.89%	0.67%
Nebraska	99.09%	0.91%	0.63%

Top 5 States with Lowest Survival Rates to date

State	Survival Rate	CFR to date	CFR last 30 days
New Jersey	93.18%	6.82%	0.63%
New York	93.42%	6.58%	0.76%
Connecticut	93.52%	6.48%	0.78%
Massachusetts	93.73%	6.27%	1.99%
New Hampshire	95.69%	4.31%	1.45%

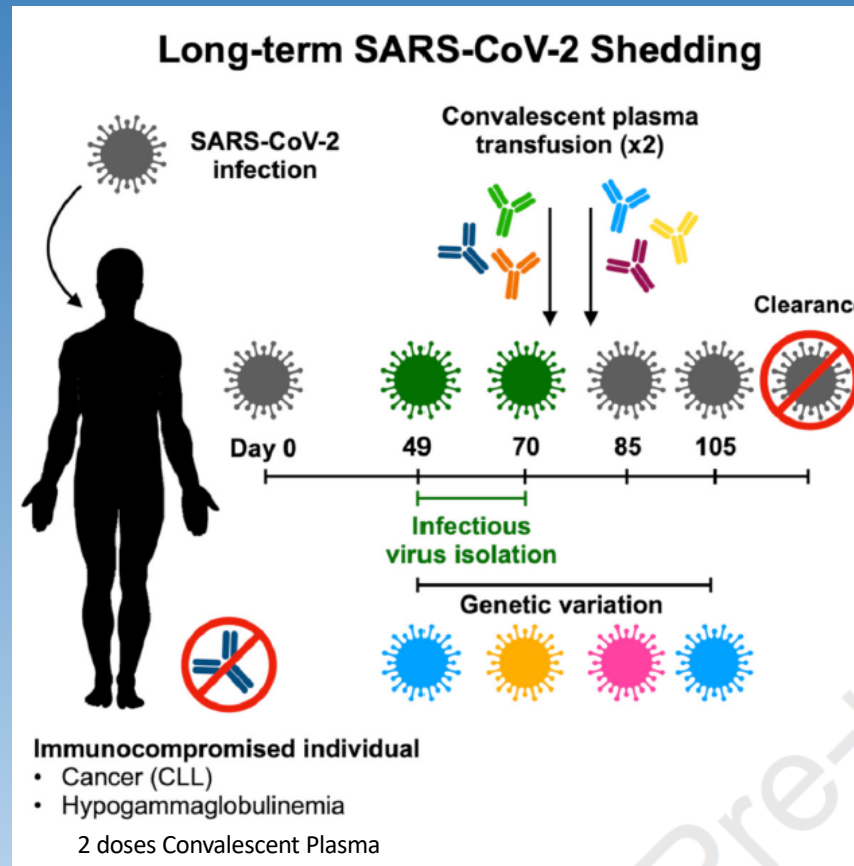
Second Wave Increased Transmission and Infectivity; not Virulence



(A) Confirmed COVID-19 cases in the Greater Houston Metropolitan region.

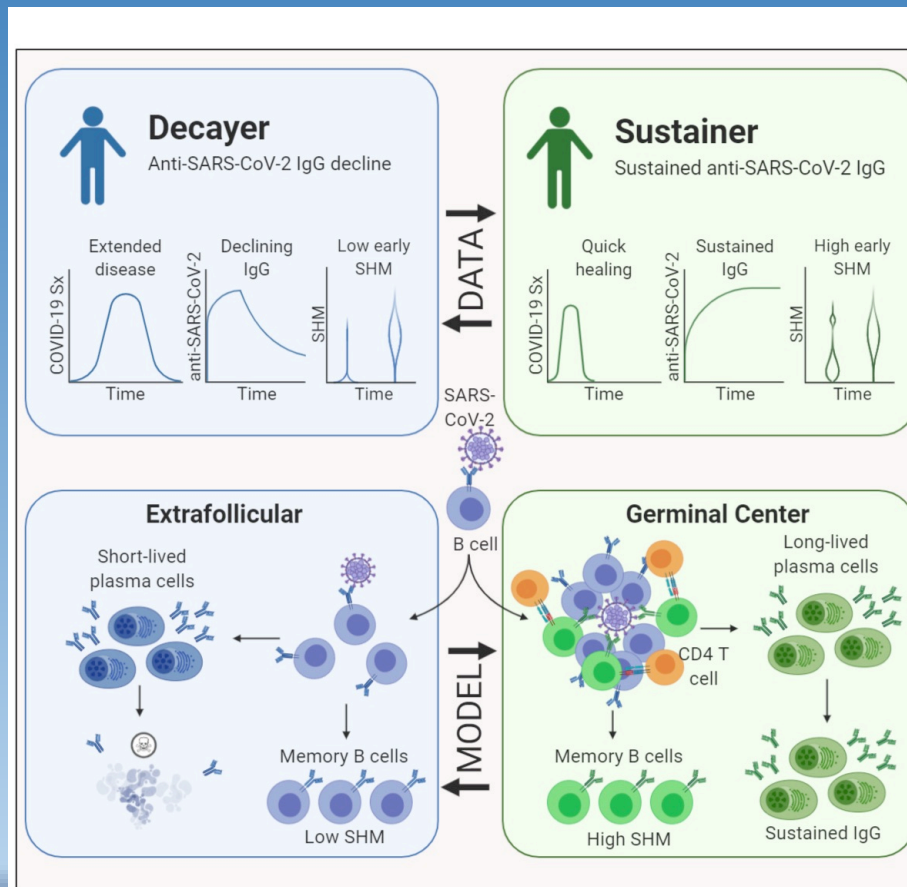
S. Wesley Long et al. *mBio* 2020; doi:10.1128/mBio.02707-20

Prolonged Shedding



Antibody Persists in Quick Healers

Virus-specific IgG decayed substantially in most individuals, whereas a distinct subset had stable or increasing antibody levels in the same timeframe despite similar initial antibody magnitudes. These individuals with increasing responses recovered rapidly from symptomatic COVID-19 disease, harbored increased somatic mutations in virus-specific memory B cell antibody genes, and had persistent higher frequencies of previously **activated CD4⁺ T cells**.



Cell Nov. 3, 2020

DOI: <https://doi.org/10.1016/j.cell.2020.10.051>

Prevalence of Covid-19 Antibodies

Figure 1. SARS-CoV-2 Prevalence Estimates by US Jurisdiction During Testing Periods From July 27 to August 13, August 10 to 27, August 24 to September 10, and September 7 to 24, 2020

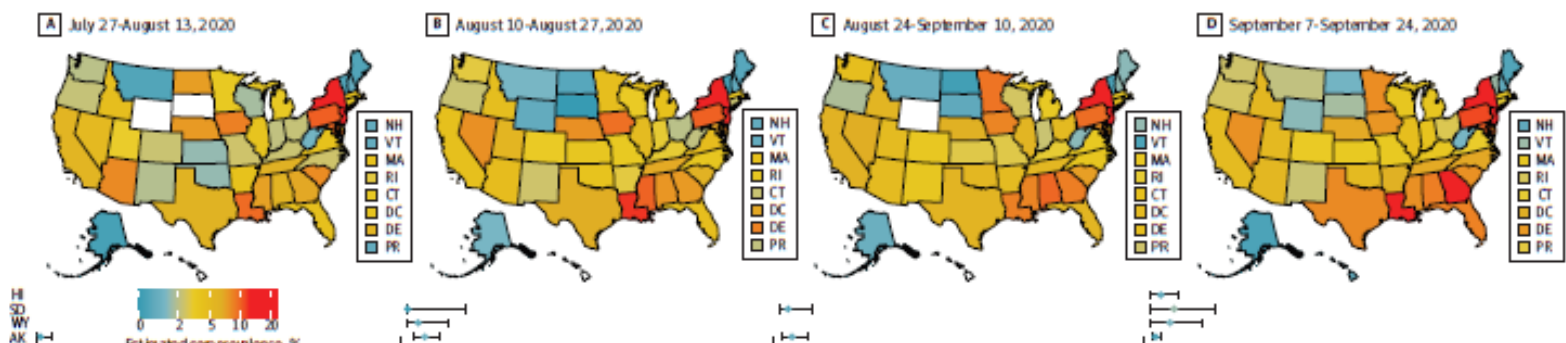


Table. Demographic and Assay Characteristics of Sampled Populations in 50 US States, Washington DC, and Puerto Rico During 4 Periods of SARS-CoV-2 Testing From July 27 to September 10, 2020

Characteristic	No. (%) ^a			
	Period 1	Period 2	Period 3	Period 4
Total samples	38 776	45 907	45 327	47 909
Dates of specimen collection ^b	July 27-August 13, 2020	August 10-27, 2020	August 24-September 10, 2020	September 7-24, 2020
Sex				
Male	16 024 (41.3)	18 794 (40.9)	18 983 (41.9)	20 343 (42.5)
Female	22 751 (58.7)	27 112 (59.1)	26 344 (58.1)	27 564 (57.5)
Age category, y				
0-17	6700 (17.3)	6920 (15.1)	6484 (14.3)	6612 (13.8)
18-49	11 237 (29.0)	14 571 (31.8)	14 079 (31.1)	15 157 (31.6)
50-64	10 367 (26.8)	12 514 (27.3)	12 426 (27.4)	13 207 (27.6)
≥65	10 408 (26.9)	11 856 (25.9)	12 316 (27.2)	12 933 (27.0)
Assay ^c				
Abbott ARCHITECT	18 467 (47.6)	20 436 (44.5)	22 378 (49.4)	23 534 (49.1)
Ortho VITROS	15 334 (39.6)	17 708 (38.6)	16 116 (35.6)	16 100 (33.6)
Roche Elecsys	4975 (12.8)	7763 (16.9)	6833 (15.1)	8275 (17.3)
Metropolitan status ^d				
Nonmetropolitan	5932 (15.3)	6339 (13.8)	6807 (15.0)	7212 (15.1)
Metropolitan	32 828 (84.7)	39 555 (86.2)	38 500 (85.0)	40 671 (84.9)

**Herd Immunity –
Not on the
Horizon!
< 10% of
Population**

Cytokine Storm Questioned

IL-6 Blockade: Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19. DOI: 10.1056/NEJMoa2028836

No difference on day 28 mortality was found. *JAMA Intern Med.* doi:10.1001/jamainternmed.2020.6820

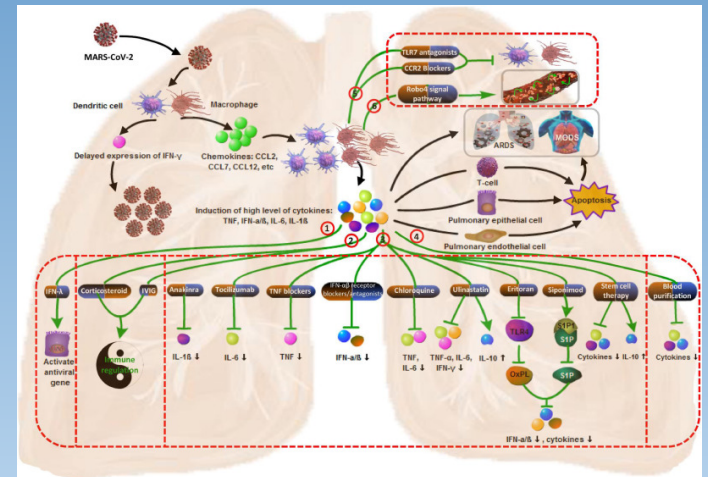
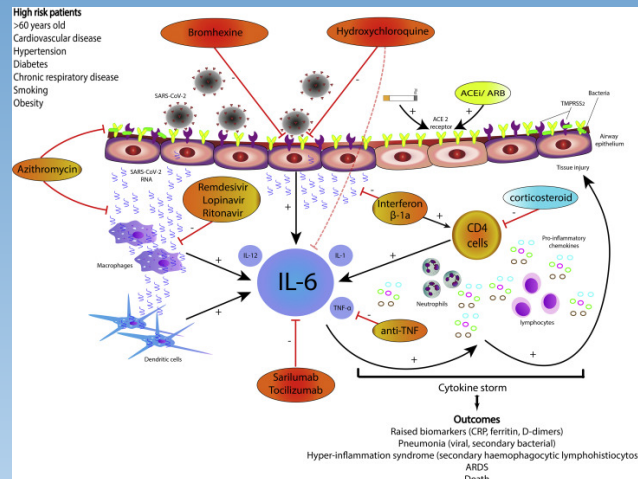
IL-1 Blockade ineffective

Steroids beneficial: In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory

Support. DOI: 10.1056/NEJMoa2021436

Wrong targets?

Too late in course?



Mink Farms – “Canary in the Coal Mine”

Thousands of Minks Dead as COVID Outbreak Escalates on Utah Farms *(Humans to Mink but not back to humans)*



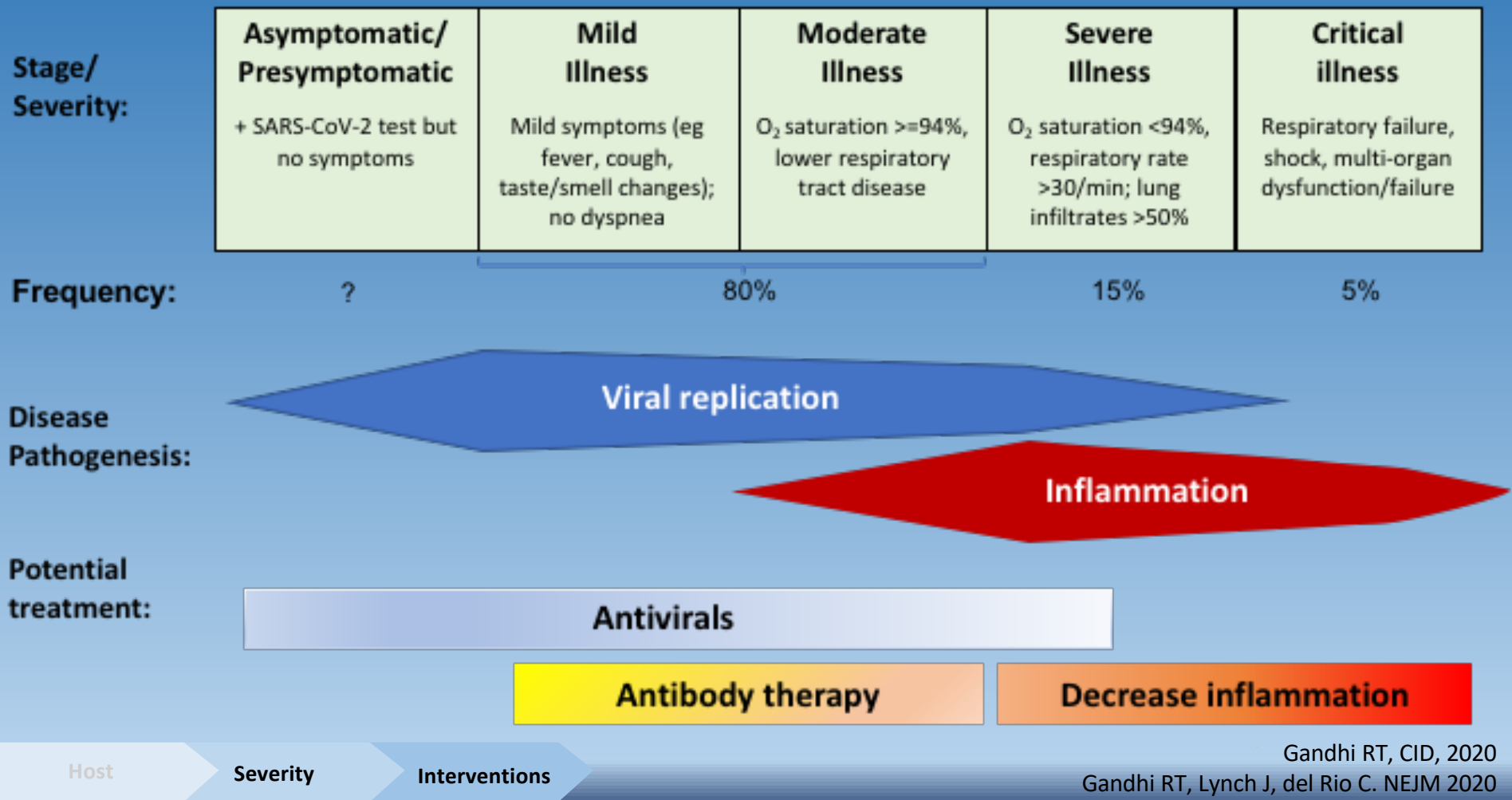
Anesthesia/Surgery after Covid-19

- Guidelines----- largely pertain to safety
- Elective Cases during surge – judicious judgment
- Urgent/emergent – potential for pulmonary complications, ↑ mortality
- Symptom resolution and complete recovery vary
 - Young vs older
 - Mild vs severe
 - Immune compromised or not
 - Pneumonia – severity; PFT? (fibrotic phase)



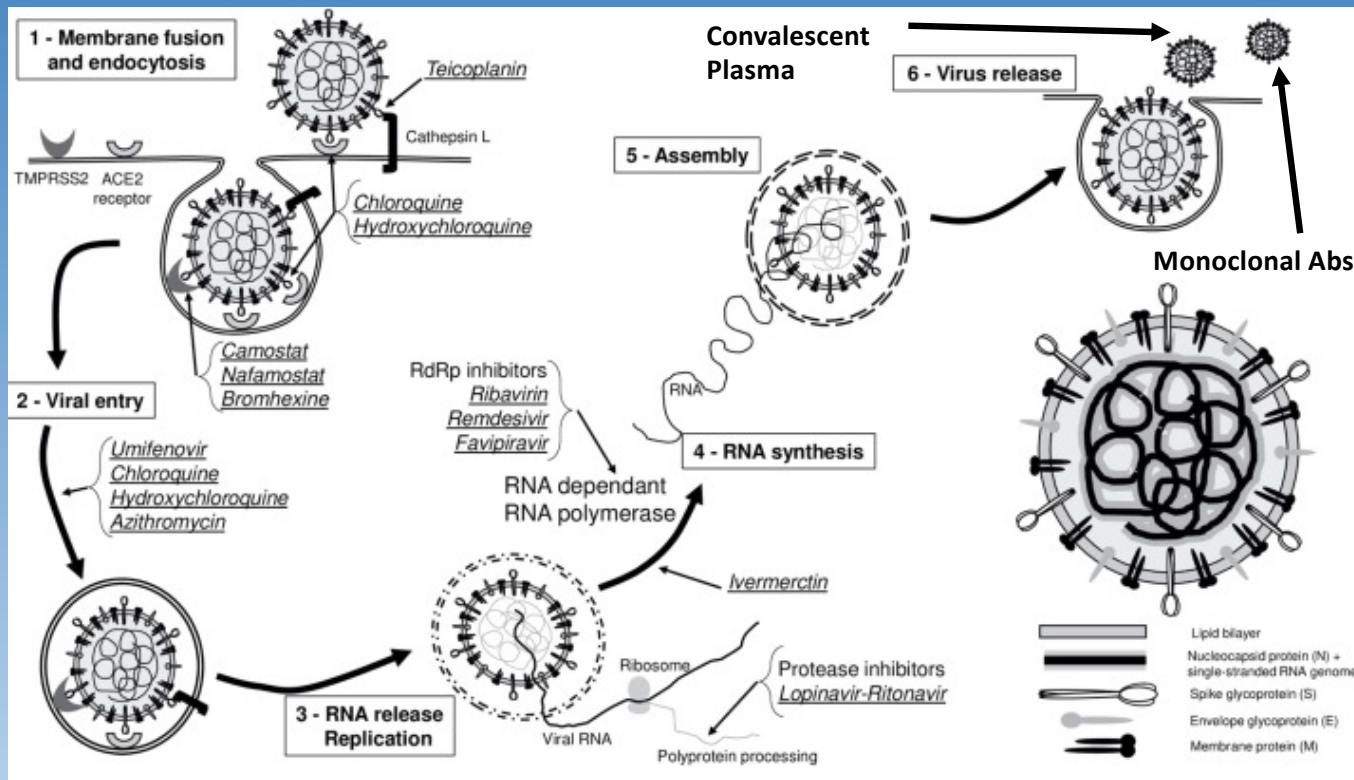
[Infect Control Hosp Epidemiol.](#) 2020 Jul 3 : 1–2.
Published online 2020 Jul 3. doi: [10.1017/ice.2020.325](https://doi.org/10.1017/ice.2020.325)
[Lancet](#) [Volume 396, Issue 10243](#), 4–10 July 2020; 27-38

Treatment Across the COVID-19 Spectrum

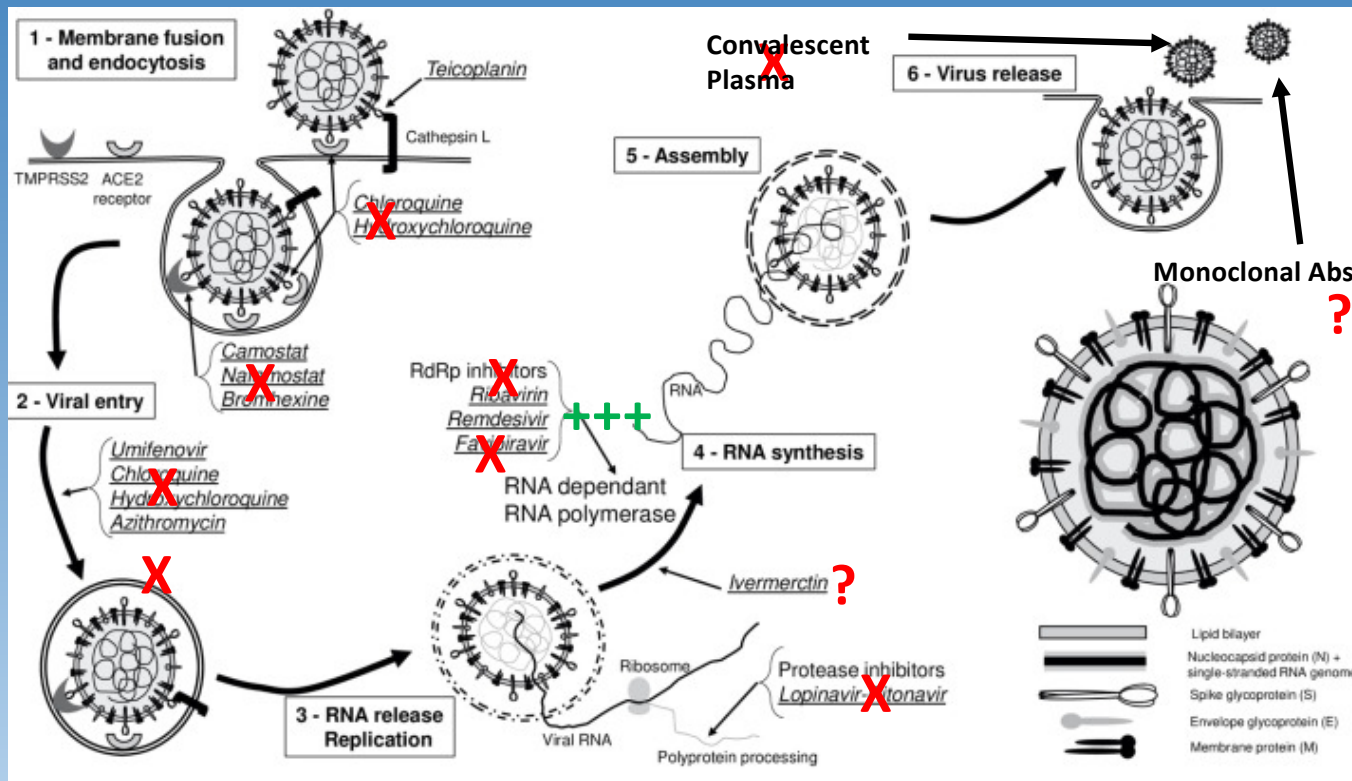


Gandhi RT, CID, 2020
 Gandhi RT, Lynch J, del Rio C. NEJM 2020

Lifecycle and Medication



Lifecycle and Medication



Monoclonal Antibodies

Boost immune responses

- Monoclonal antibodies against SARS-CoV-2 being studied for treatment and prevention
- In outpatients with mild to moderate disease (n=452), participants randomized to received IV infusion of placebo or one of three doses of a neutralizing antibody directed against SARS-CoV-2 spike protein (LY-CoV555)

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Klekotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators*

Monoclonal vs Polyclonal----

Host

Severity

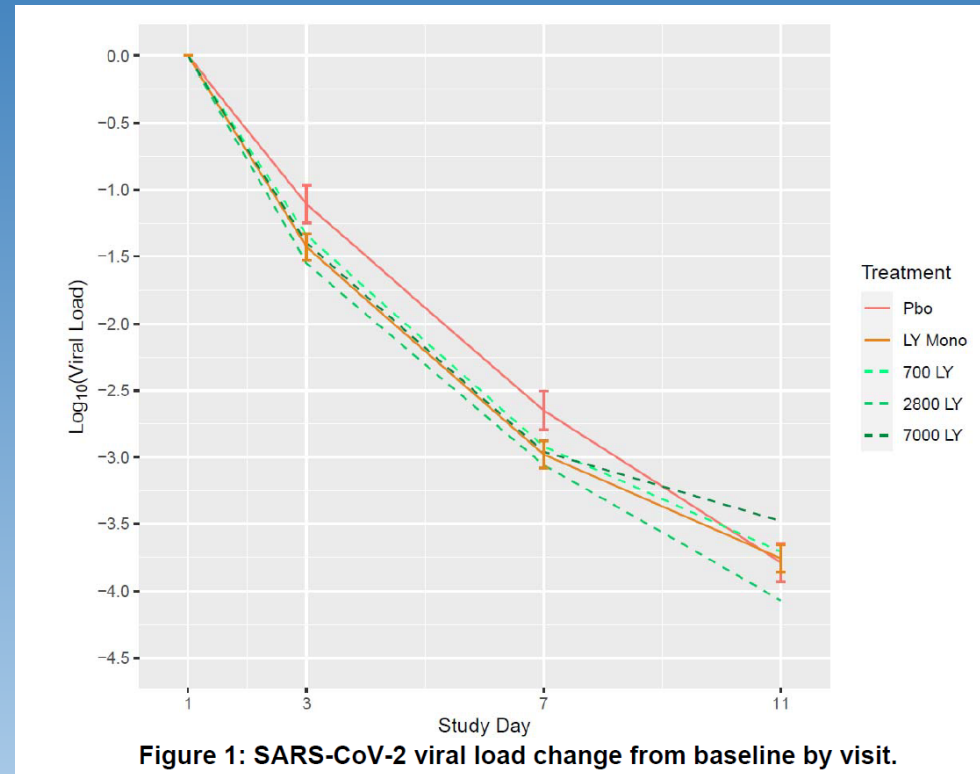
Interventions

Chen P et al, NEJM, 2020

LY-CoV555 (Bamlanivimab)

Boost immune responses

- At day 11, 2800 mg dose of antibody appeared to accelerate decline in viral load as compared to placebo
 - 3.4-fold lower in 2800 mg group than in the placebo group
 - Viral load decline did not differ significantly between other antibody doses and placebo
- In all 3 dose groups, there appeared to be a separation in virus level decay as compared to placebo



Host

Severity

Interventions

Chen P et al, NEJM, 2020; <https://www.fda.gov/media/143602/download>

Monoclonal Antibody Therapy EUA

[Reuters](#) (11/9, Beasley) reports the Food and Drug Administration authorized on Monday emergency use of Eli Lilly's "COVID-19 antibody treatment for non-hospitalized patients older than 65 or who have certain chronic medical conditions." The FDA found that clinical trials indicated the treatment, **bamlanivimab**, "reduced the need for hospitalization or emergency room visits in high-risk COVID-19 patients."

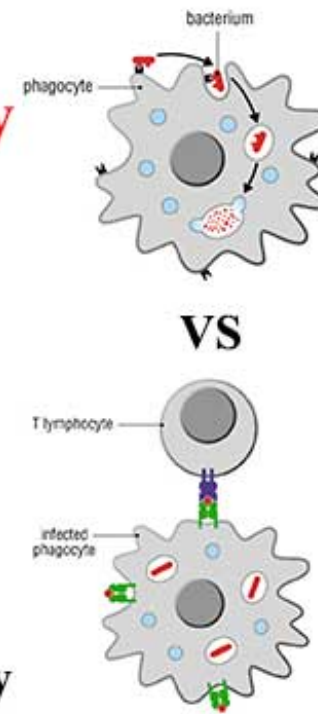
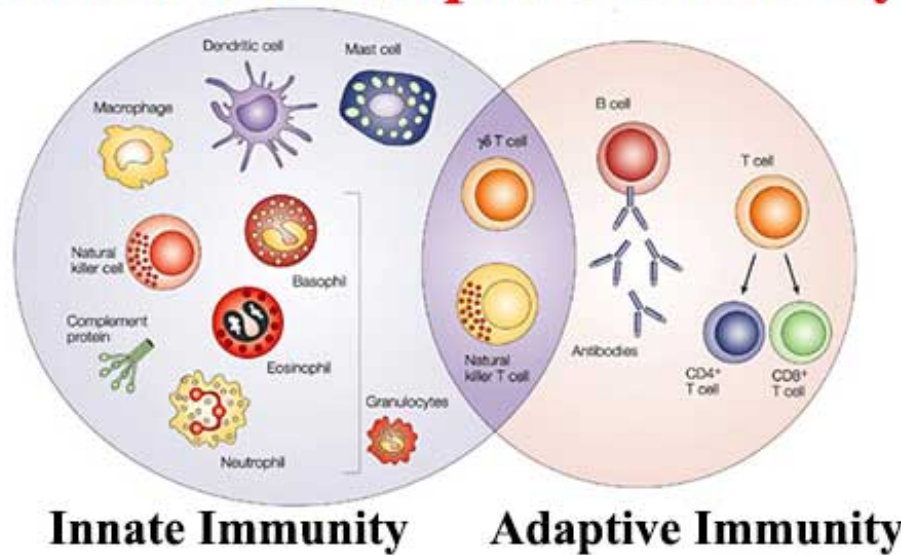
The FDA (11/23) [issued an emergency use authorization](#) to Regeneron Pharmaceuticals for its monoclonal antibodies — **casirivimab and imdevimab** — to be administered together to treat mild-to-moderate COVID-19 in adults and kids over age 12.

Expanded Use Authorization Criteria: Ambulatory Patients with Mild to Moderate COVID-19 at High Risk for Progression - 1

- Body mass index (BMI) ≥ 35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or receiving immunosuppressive treatment
- ≥ 65 years of age
- ≥ 55 years of age AND have
 - cardiovascular disease, OR
 - hypertension, OR
 - chronic obstructive pulmonary disease/other chronic respiratory disease

Adaptive vs Innate Immunity

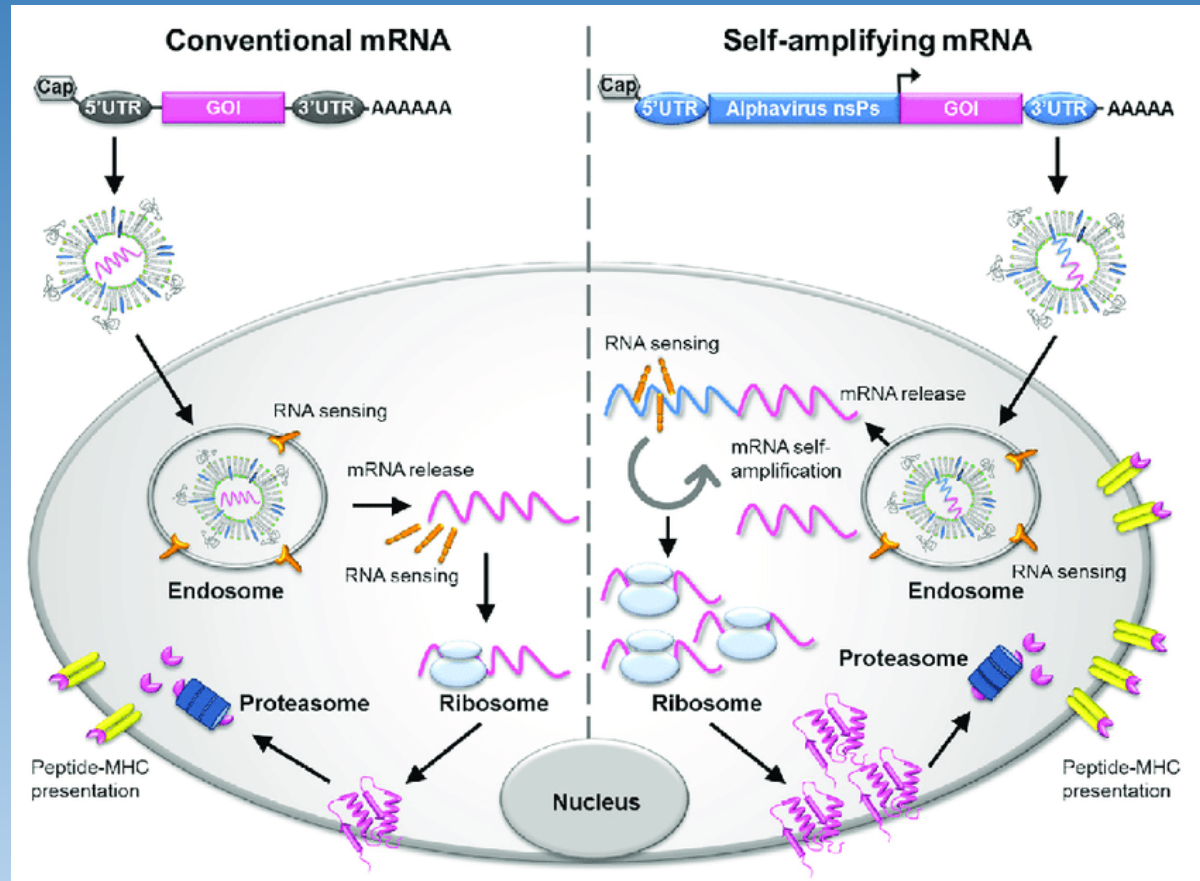
Difference between Innate and Adaptive Immunity



Nonspecific
Quick Response

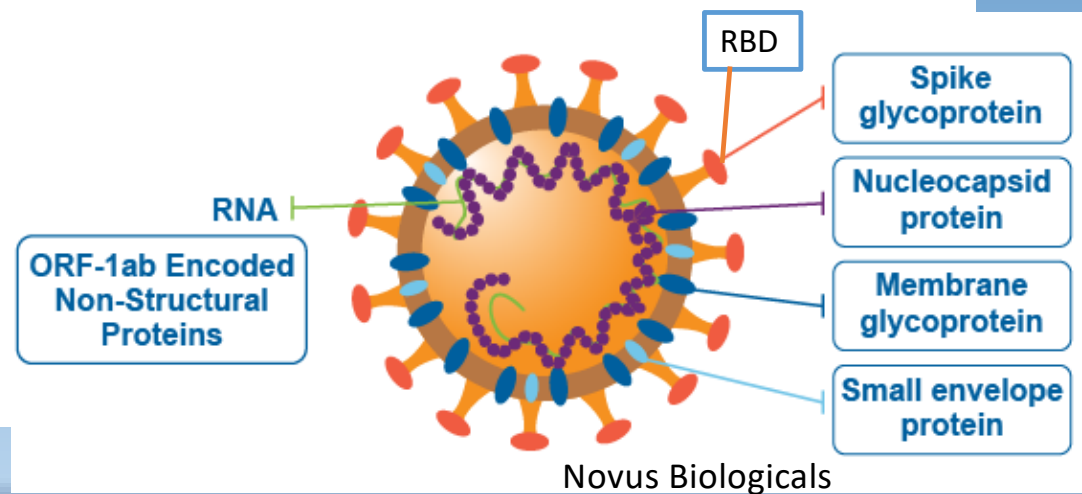
Quick Specific
Response, 1st Time

mRNA Vaccines

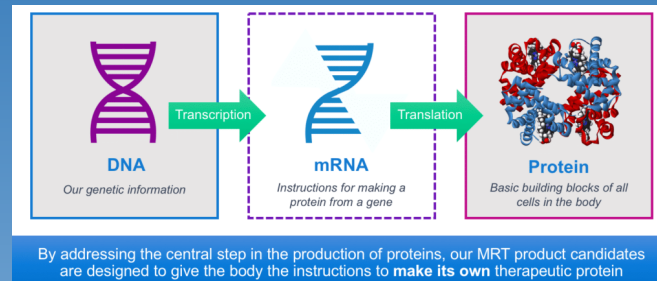


Vaccines

- Ideal: long-lasting humoral and/or cellular immunity with memory
- Live Attenuated Vaccine (LAV)
- Inactivated Whole-virus Vaccine (IWVV)
- Nucleic Acid vaccines
- Vector Based Vaccines
- Recombinant Protein Vaccines
- Sampling of what's available



mRNA Vaccines



Delivery: challenging - since free RNA in the body is quickly broken down. lipocorporated into a larger molecule to help stabilize it and/or packaged into particles or liposomes.

Safety: RNA does not integrate itself into the host genome and the RNA strand in the vaccine is degraded once the protein is made.

Storage: many RNA vaccines, like conventional vaccines, need to be frozen or refrigerated. Thus far, **RNA vaccines are not stable at normal temperatures**

mRNA Vaccines

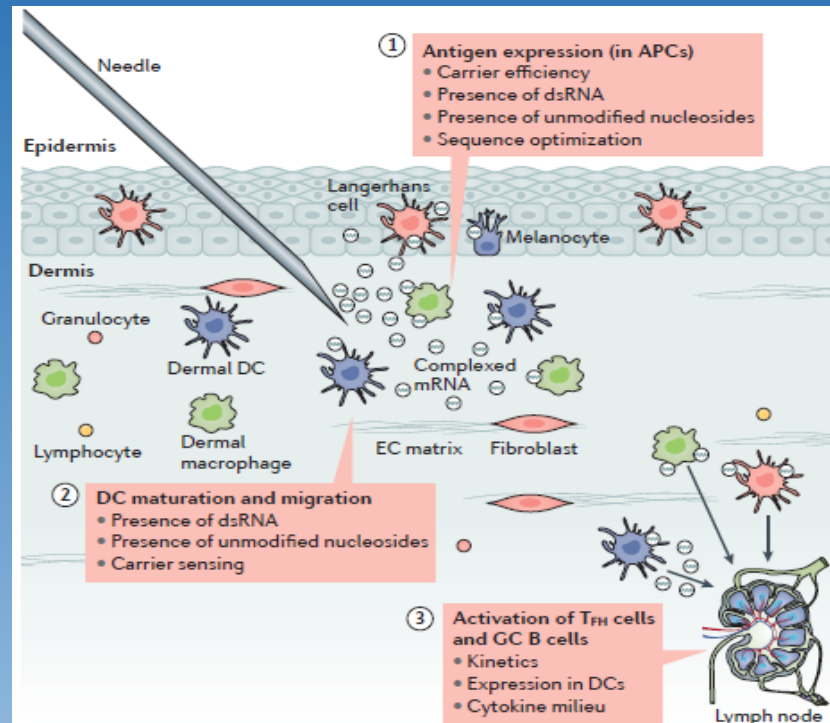
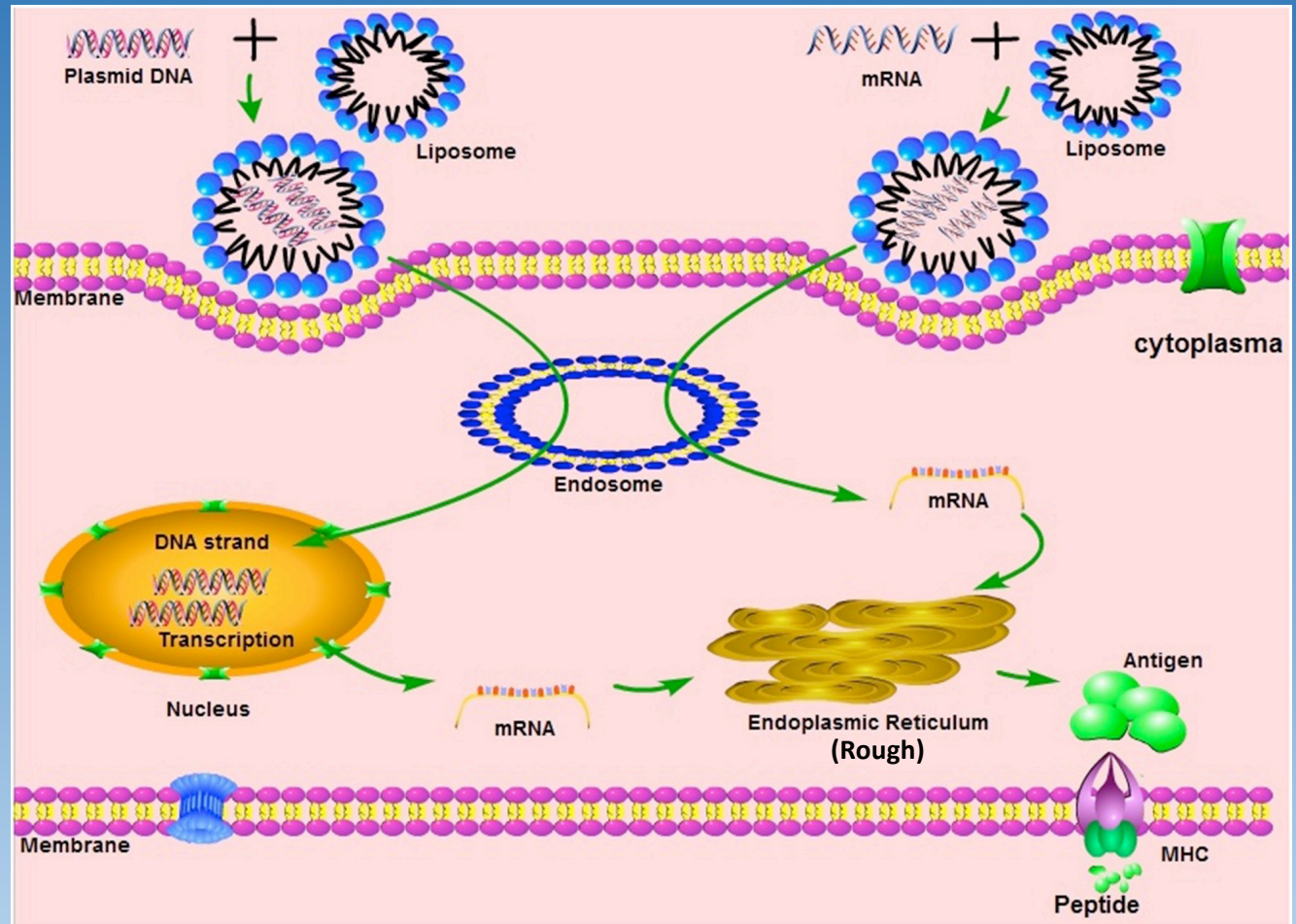


Figure 3 | Considerations for effectiveness of a directly injected mRNA vaccine. For an injected mRNA vaccine, major considerations for effectiveness include the following: the level of antigen expression in professional antigen-presenting cells (APCs), which is influenced by the efficiency of the carrier, by the presence of pathogen-associated molecular patterns (PAMPs) in the form of double-stranded RNA (dsRNA) or unmodified nucleosides and by the level of optimization of the RNA sequence (codon usage, G:C content, 5' and 3' untranslated regions (UTRs) and so on); dendritic cell (DC) maturation and migration to secondary lymphoid tissue, which is increased by PAMPs; and the ability of the vaccine to activate robust T follicular helper (T_{FH}) cell and germinal centre (GC) B cell responses — an area that remains poorly understood. An intradermal injection is shown as an example. EC, extracellular.

mRNA Vaccines



RNA Vaccines – never before in humans

RNA Vaccines



Pros

- Scalability – making RNA is easy, cheap

Front-runner in US

Lipid nanoparticles-encapsulated mRNA

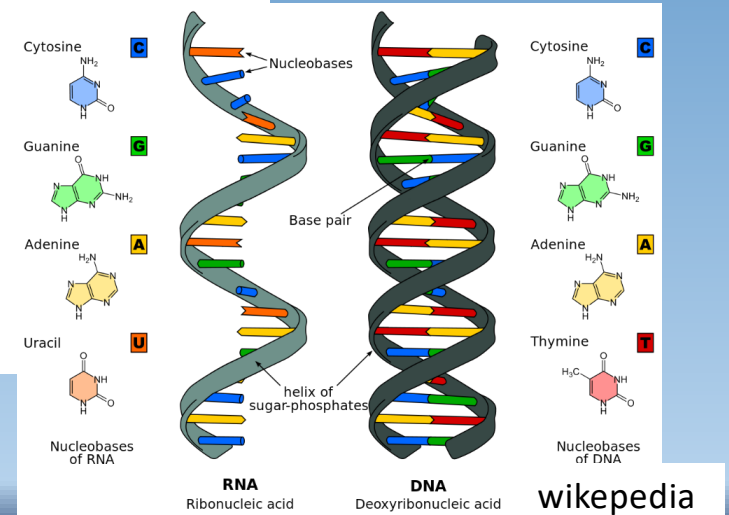
Moderna – robust T-cell activity

BioNTech: BNT162b1 & 2 targets RBD; Ab and neutralizing Ab responses; Fast Track designation

Now Phase III; 162b1 requires -20 C

Cons

- New technology = unknown risks
- Autoimmunity?



COVID-19 Vaccine Pipeline Summary

	mRNA vaccines		Adenovirus Vector		Recombinant/ Adjuvant
Product	mRNA 1273	BNT162b2	ChAdOx1/ AZD1222	AD26.CoV2.S	NVX-CoV2373
Company	* Moderna/ NIAID (EUA submitted)	* BioNTech/ Pfizer (EUA submitted)	Oxford/ AstraZeneca	J&J	Novavax
Series	0, 28 days	0, 21 days	0, 28 days	1-dose	0, 21 days
Ages Studied	≥ 18 years	12-85 years*	≥ 18 years**	≥ 18 years***	18-84 years
Phase of Development	Phase III	Phase III	Phase III	Phase III	Phase III
Efficacy	94.5%	95%	70%	NR	NR
Storage	-20°C	* -70 ± 10 °C	-20°C or Fridge	Fridge	Fridge
Stability	Fridge: 30d RT: 6 hours	Fridge: 5d RT: 6 hours	NR	Fridge: 3 mo RT: 6 h	NR

*Phase III expanded to include patients ≥ 12 years of age and patients with controlled HIV, Hepatitis B, Hepatitis C

**Phase II-III in pediatric patients 5-12 years in UK

***Requesting approval to enroll patients 12-18 years of age

COVID-19 Vaccine Key Dates – Pfizer Moderna ~ 1 week later

12/8

- FDA to make VRBPAC background material publicly available

12/10

- VRBPAC Meeting
 - VRBPAC will make recommendation to FDA whether to approve EUA

12/11-
12/15

- FDA announcement EUA approval
 - could take longer, but earliest will be 12/11

12/14-
12/18

- ACIP Emergency meeting to publish recommendations for COVID-19 use

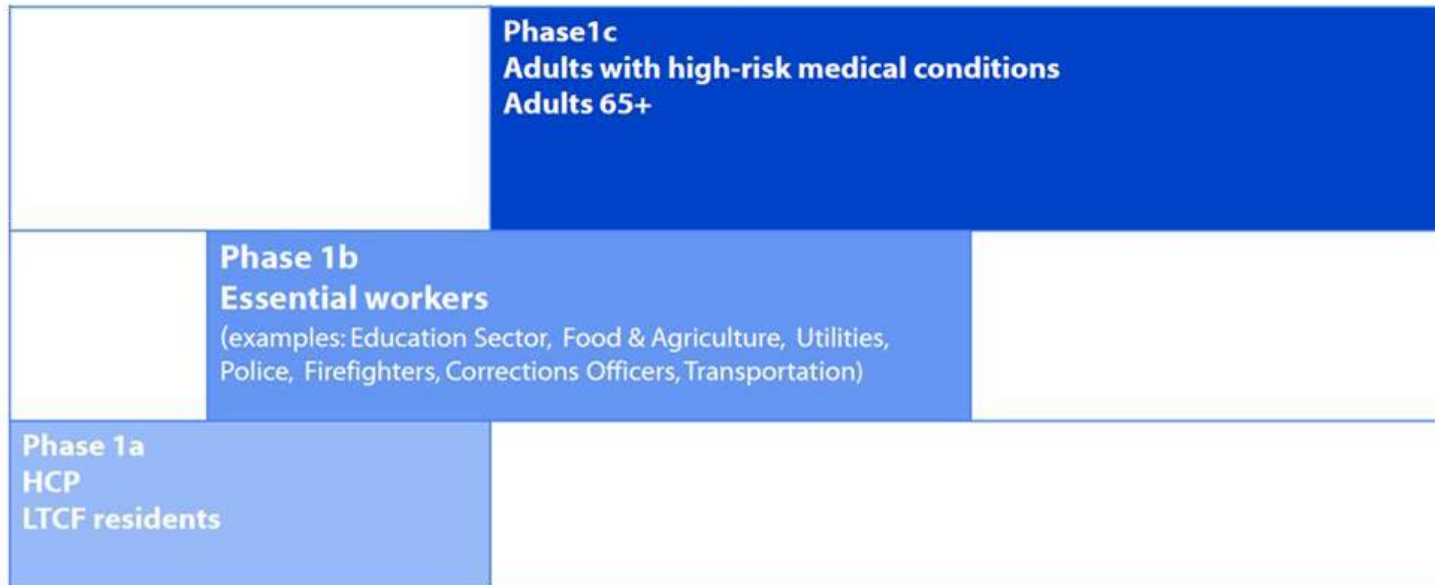
12/15-
12/21

- COVID-19 vaccine shipment and initiation of vaccination

Interim Phase 1 Sequence per ACIP

(Proposal Vote 12/1/20)

Proposed Interim Phase 1 Sequence



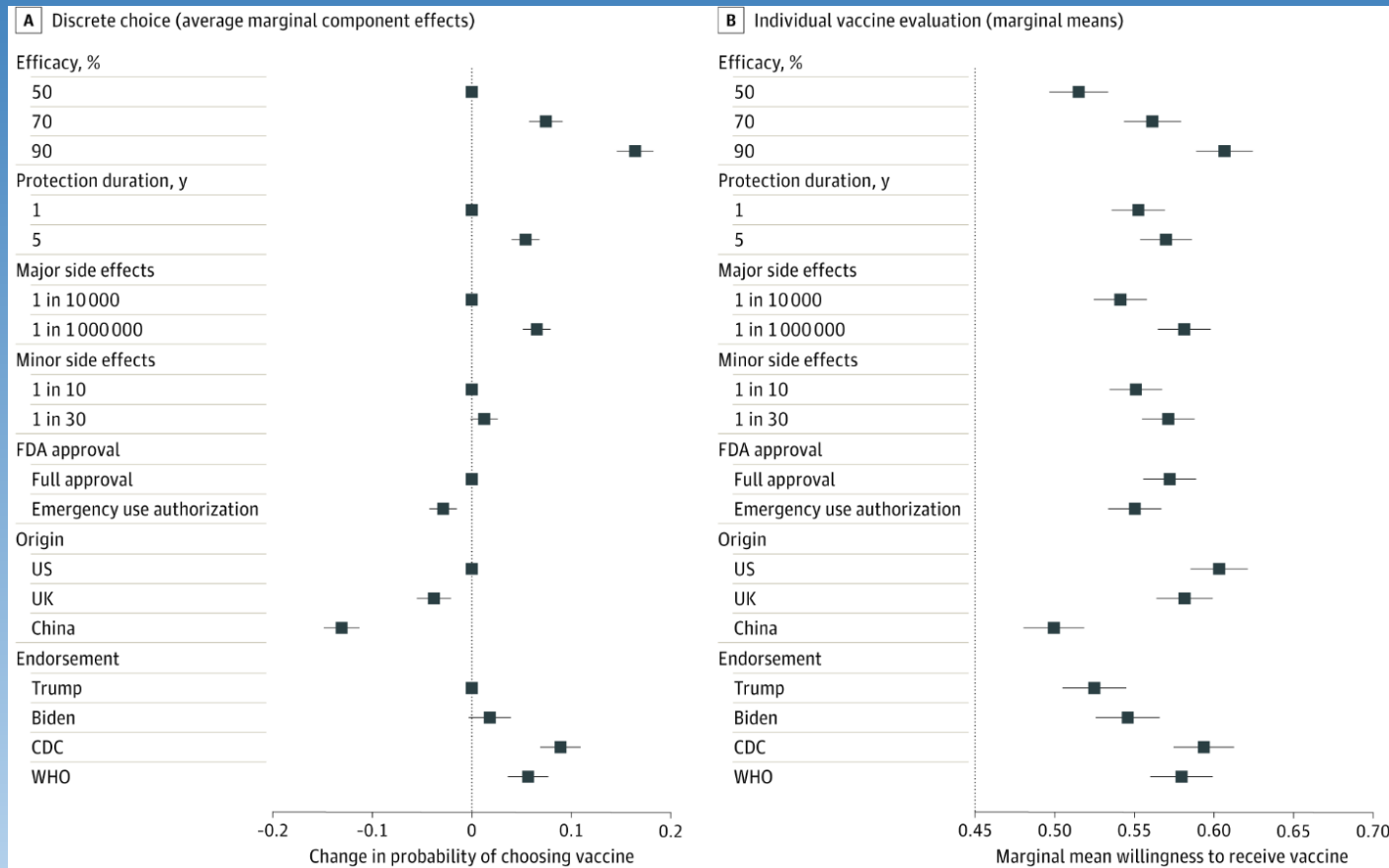
Time

ACIP Proposed Vaccine Distribution

Healthcare personnel as phase 1A. This group includes personnel who work in: hospitals, long-term care facilities, outpatient home health care, pharmacies, emergency medical personnel, and public health workers.

1b, essential workers, people with high-risk medical conditions, and adults 65 years and older. Essential workers include people who work in food and agriculture, food service, transportation, education, energy, police, firefighters, manufacturing, IT, communication, water and wastewater. People with high risk medical conditions include: obesity, and severe obesity, diabetes, COP, heart condition, chronic kidney cancer, smoking, solid organ transplant, and sickle cell disease

Factors Associated with Vaccine Acceptance



“We will sell no wine before it’s time” –
I mean vaccine



The New York Times

F.D.A. to Release Stricter Guidelines for Emergency Vaccine Authorization

The new guidelines underscore the fact
that a vaccine is highly unlikely before
the election.

Nearly 50% US population hesitant to receive a vaccine – should not be used as a political tool