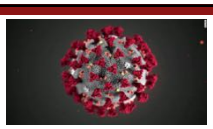

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SAAAPM 2020 Annual Meeting

Update on COVID-19

Yvonne (Bonnie) Maldonado, MD, FAAP, FPIDS, FIDSA
Senior Associate Dean for Faculty Development and Diversity
Professor of Pediatrics, Epidemiology and Population Health
Stanford University School of Medicine

November 7, 2020

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First 425 Confirmed Cases of SARS-CoV-2

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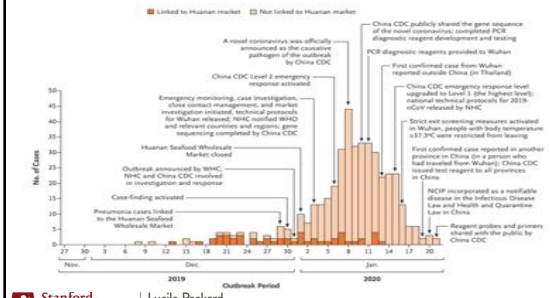

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Li et al, NEJM 2020, DOI: 10.1056/NEJMoa2001316
January 29, 2020

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Outline

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- The Virus
- Global and US Overview
- Epidemiology
- Risk Groups
- Disparities
- Therapeutics and Vaccines

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Coronavirus (CoV) Virology

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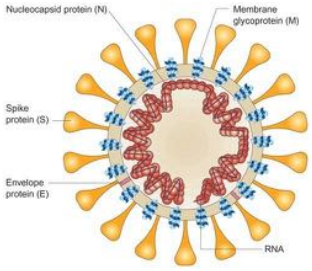
- CoVs are enveloped, single positive-stranded RNA viruses with a nucleocapsid.
- ~ 30 kb in length — the largest known RNA viruses
- Structural proteins include spike (S), membrane (M), envelope (E), nucleocapsid (N) proteins and accessory proteins chains
- Seven known human strains
- A spike mutation, which probably occurred in late November 2019, likely **triggered spillover into humans**



https://www.ncbi.nlm.nih.gov/books/NBK554776/

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Human Endemic Coronaviruses (HCoVs)

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- 229E, HKU1, NL63, OC43
- Up to 15-30% of human colds
- No durable immunity – frequent cycles of infection
- Upper respiratory infections – most common
- Lower respiratory infections – immunocompromised patients
- Worldwide circulation
- Winter and early spring
- No vaccines or antivirals licensed or in use

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Emerging Coronaviruses

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- SARS-CoV (2002-2004) – Severe Acute Respiratory Syndrome
  - > 8,000 cases, 10% mortality, 32 countries in 3 months
  - Bats → Civet Cats / Racoon Dogs → Humans
- MERS-CoV
  - > 2,500 cases, ~ 35% mortality, 27 countries
  - Bats → Camels → Humans
- SARS-CoV-2
  - ~50M cases, 1-2% mortality, pandemic
  - Bats → Pangolins??? → Humans

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Global COVID-19 Cases November 7, 2020

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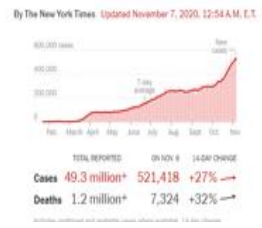

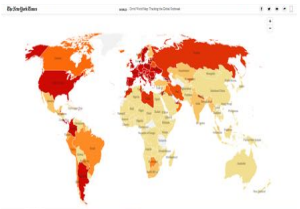

More than 500,000 new cases per day

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US COVID-19 Cases - November 7, 2020

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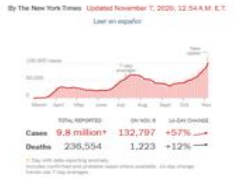

- >9,830,800 US COVID-19 cases and 236,500 deaths
- 1,223 new deaths and 132,797 new cases on Nov. 6
- Average of 100,991 cases per day, an increase of 57 percent from the average two weeks earlier

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Epidemiology of SARS-CoV-2 Infection

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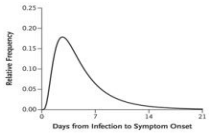
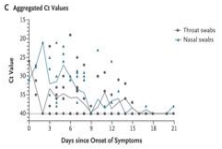
- Incubation period 2-14 days, peak at day 5 after exposure
- Viral shedding for ~48 hours before onset of symptoms and generally for up to 3-4 weeks
- Infectious for ~10 days, longer if immunocompromised
- Occasional shedding for several weeks, not associated with high risk of transmission to others
- Approximately 40% of infections are asymptomatic, 40% mild to moderate symptoms, 20% moderate to severe symptoms requiring hospitalization
- About 5% of hospitalized patients require intensive care with an overall 1-2% mortality rate





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COVID-19 Disease Severity

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- 36,160 cases (81%) reported mild symptoms
- 6,168 cases (13.8%) reported severe symptoms
- 2,087 cases (4.7%) critically ill
- Case fatality higher among those with comorbid conditions (2-12%) compared with those with no comorbid conditions (0.9%)

China CDC Weekly Report February 17, 2020

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COVID-19 Clinical Symptoms

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- Fever (83-98%)
- Cough (46-82%)
- Myalagia or fatigue (11-44%)
- Shortness of breath (31%)
- Less common symptoms: diarrhea, productive sputum
- Potential for worsening clinical course during second week of symptoms
- ARDS developed in 17-29% of hospitalized patients
- Secondary infection in 10% of hospitalized patients

Chen et al., Lancet 2020
Huang et al., Lancet 2020

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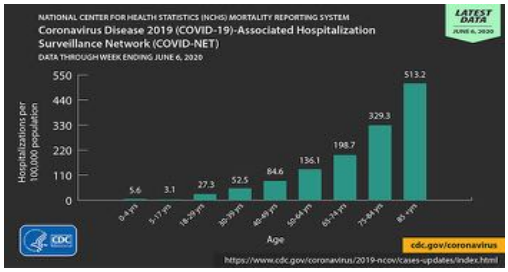

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COVID-19 and Age

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COVID-19 Hospitalization and Death by Age

Rate ratios compared to 18–29 year olds

	Hospitalization*	Death*
0-4 years	4x lower	9x lower
5-17 years	9x lower	18x lower
18-29 years	Comparison Group	Comparison Group
30-39 years	2x higher	4x higher
40-49 years	3x higher	10x higher
50-64 years	4x higher	30x higher
65-74 years	5x higher	90x higher
75-84 years	8x higher	220x higher
85+ years	13x higher	630x higher

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https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html

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Risk Factors for Severe Disease

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D. Wolff et al.

Table 4 Overview of risk factors reported by leading institutions

Robert Koch Institute [54]	U.S. CDC [55]	Johns Hopkins Medicine [56]	NHS UK [57]
Higher age (increase from 50–60 years)	Higher age (increase from 65 years)	Higher age (increase from 65 years)	Higher age (increase from 70 years)
Heart diseases	Living in a nursing home or long-term care facility	Diabetes	Organ transplant recipients
Diabetes	Chronic lung disease	Male gender	Lung diseases
Diseases of the respiratory system	Asthma	USA: obesity (BMI ≥ 30)	Blood or bone marrow cancer
Liver diseases	Heart diseases	USA: African American ethnicity	Heart diseases
Renal diseases	Immunosuppression	Comorbidities	Pregnancy
Obesity	Severe obesity (BMI ≥ 40)		Severe obesity (BMI ≥ 40)
Smoking	Diabetes		Chronic kidney diseases
Multimorbidity	Chronic kidney disease undergoing dialysis		Conditions affecting brain or nerves
Immunosuppression	Liver disease		Liver diseases

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7453858/pdf/15010_2020_Article_1509.pdf

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COVID-19 Outcomes in Young Adults

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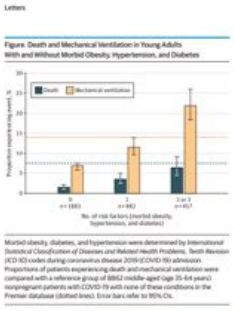
- 3,222 young adults age 18 to 34 years hospitalized with COVID-19 experienced high rates of adverse outcomes:
  - 21% required intensive care
  - 10% required mechanical ventilation
  - 2.7% died
- In-hospital mortality rate lower than for older adults but ~2X that of young adults with acute myocardial infarction
- Morbid obesity, hypertension, and diabetes were common and associated with greater risks of adverse events
- Young adults with >1 of these conditions faced risks comparable to in middle-aged adults without them
- More than half requiring hospitalization were Black or Hispanic



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https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2770542

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Epidemiology Impact on Designing Clinical Treatments for COVID-19

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- Epidemiologic data indicates that ~80% of patients have no symptoms or mild COVID-19 infection.
- Although these individuals may not need hospitalization, they still experience respiratory symptoms, need to quarantine, and consequently lose productivity.
- More importantly, patients with mild disease still contribute to community disease transmission.
- **Limiting viral shedding from this group is crucial to controlling the spread of COVID-19, especially in households and close personal contacts.**

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Contact/Droplet/Airborne Transmission

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- Infections with respiratory viruses are principally transmitted through three modes: contact, droplet, and airborne.
- **Contact transmission** is infection spread through direct contact with an infectious person (e.g., touching during a handshake) or through fomite transmission
- **Droplet transmission** is infection spread through exposure to virus-containing respiratory droplets (i.e., larger and smaller droplets and particles) exhaled by an infectious person. Transmission is most likely to occur when someone is close to the infectious person, generally within about 6 feet.
- **Airborne transmission** is infection spread through exposure to those virus-containing respiratory droplets comprised of smaller droplets and particles that can remain suspended in the air over long distances (usually greater than 6 feet) and time (typically hours).

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Scientific Brief: SARS-CoV-2 and Potential Airborne Transmission

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- **The principal mode of SARS-CoV-2 infection is through exposure to infectious respiratory droplets**
- **Respiratory droplets** are produced during exhalation (e.g., breathing, speaking, singing, coughing, sneezing) and span a wide spectrum of sizes that may be divided into two basic categories based on how long they can remain suspended in the air:
- **Larger droplets** some of which are visible and that fall out of the air rapidly within seconds to minutes while close to the source.
- **Smaller droplets and particles** (formed when small droplets dry very quickly in the airstream) that can remain suspended for many minutes to hours and travel far from the source on air currents.
- Once respiratory droplets are exhaled and as they move outward from the source, their concentration decreases through fallout from the air (largest droplets first, smaller later) combined with dilution of the remaining smaller droplets and particles into the growing volume of air they encounter.

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https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-sars-cov-2.html
Updated Oct. 5, 2020

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The epidemiology of SARS-CoV-2 indicates that most infections are spread through close contact, not airborne transmission

- Diseases that are spread efficiently through airborne transmission tend to have high attack rates because they can quickly reach and infect many people in a short period of time.
- We know that a significant proportion of SARS-CoV-2 infections (estimated 40-45%) occur without symptoms and that infection can be spread by people showing no symptoms.
- Thus, were SARS-CoV-2 spread primarily through airborne transmission like measles, experts would expect to have observed considerably more rapid global spread of infection in early 2020 and higher percentages of prior infection measured by serosurveys.
- Available data indicate that SARS-CoV-2 has spread more like most other common respiratory viruses, primarily through respiratory droplet transmission within a short range (e.g., less than six feet).
- There is no evidence of efficient spread (i.e., routine, rapid spread) to people far away or who enter a space hours after an infectious person was there.

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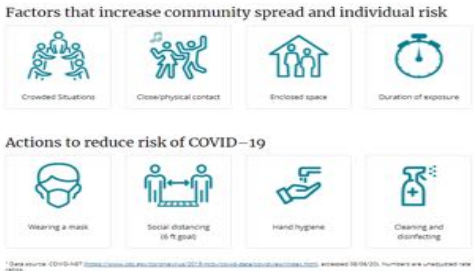
Risk For Spread and Mitigation



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How important is aerosol transmission of SARS-CoV-2?

ACCEPTED MANUSCRIPT

It is Time to Address Airborne Transmission of COVID-19

Lidia Morawska, Donald K Milton

Clinical Infectious Diseases, ciaa939, https://doi.org/10.1093/cid/ciaa939

"We appeal to the medical community and to the relevant national and international bodies to recognize the potential for airborne spread of COVID-19. There is significant potential for inhalation exposure to viruses in microscopic respiratory droplets (microdroplets) at short to medium distances (up to several meters, or room scale), and we are advocating for the use of preventive measures to mitigate this route of airborne transmission."

- Size matters
  - Smaller (<5 μ) droplets can travel beyond 1-2 m
  - Viral RNA associated with droplets <5 μ can be recovered from air
- Analogy with SARS, MERS and other respiratory viruses
- One outbreak in a Chinese restaurant suggested aerosol transmission

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Airborne Transmission of SARS-CoV-2 Theoretical Considerations and Available Evidence

VIEWPOINT

- "Demonstrating that speaking and coughing can generate aerosols or that it is possible to recover viral RNA from air does not prove aerosol-based transmission; infection depends as well on the route of exposure, the size of inoculum, the duration of exposure, and host defenses."
- R0 = 2.5 – this is a small number given that people are infectious for about a week

Klompas M, Baker MA, Rhee C. JAMA 2020 Jul 13 [Epub ahead of print].

- Secondary attack rates low (5%) but higher among close contacts (10-40%)
  - Risk to unmasked HCW 3%
- Few outbreaks suggest aerosol transmission
- Simple face masks highly effective
- **"…the balance of currently available evidence suggests that long-range aerosol-based transmission is not the dominant mode of SARS-CoV-2 transmission."**

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Business

The outbreak that didn't happen: Masks credited with preventing coronavirus spread inside Missouri hair salon

Springfield, Mo., health officials braced for an outbreak. Now they say face coverings prevented one.

- 2 PCR-positive hairdressers in Springfield, Mo.
  - Worked 8 and 5 days, respectively
  - Both symptomatic
  - 139 customers exposed
- Posted sign "a mask is required to enter salon"
- Both hairdressers and all customers wore masks
- **No** secondary cases detected

Public health officials braced for a coronavirus outbreak after two stylists at this Great Clips hair salon in Springfield, Mo., tested positive for the virus last month. (USA Today Network/Reuters)

See also Hendrix MJ, Walde C, Findley K, Trotman R. Absence of apparent transmission of SARS-CoV-2 from two stylists after exposure at a hair salon with a universal face covering policy – Springfield, Missouri, May 2020. MMWR 2020 Jul 14; 69 [early release].

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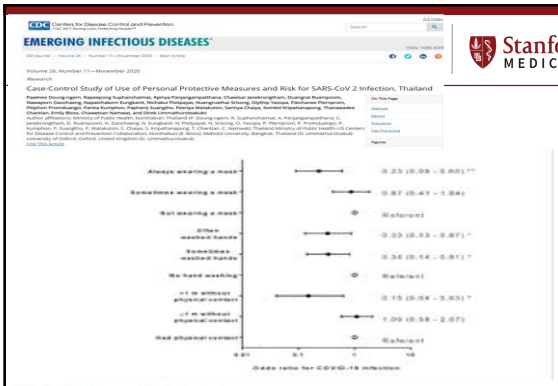

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COVID-19 DATA BY RACE/ETHNICITY

Rate ratios compared to White

	American Indian or Alaska Native	Asian	Black or African American	Hispanic or Latino persons
CASES	2.8x higher	1.1x higher	2.6x higher	2.8x higher
HOSPITALIZATIONS	5.3x higher	1.3x higher	4.7x higher	4.6x higher
DEATHS	1.4x higher	No increase	2.1x higher	1.1x higher

Source: CDC.gov

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Social Determinants of Health Relevant to COVID-19

poverty	limited job and economic security
frontline jobs (e.g. public transportation, pharmacy, grocery, and warehouse distribution workers)	jobs with lack of adequate PPE
crowded living spaces	social distancing is impossible
reliance on crowded public transportation	social distancing is impossible
food deserts or swamps	no access to healthy food
Inadequate insurance coverage	self-rationing of health care

Owen, W. F., Carmona, R., & Pomeroy, C. (2020). Failing Another National Stress Test on Health Disparities. *Jama*. doi: 10.1001/jama.2020.6547

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HEALTH DISPARITIES AND EQUITY

PRIORITY POPULATIONS FOR TREATMENT AND PREVENTION OF COVID-19

- Racial and ethnic **minority** populations
- People living in **rural** or frontier areas
- People experiencing **homelessness**
- Essential and **frontline** workers
- People with **disabilities**
- People with **substance use** disorders
- People who are justice-involved **(incarcerated persons)**
- **Non-U.S.-born** persons

Source: CDC.gov

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Therapeutic and Preventive Approach to SARS-CoV-2 and COVID-19

- Factors that drive approaches include
  - Virology
  - Disease Pathophysiology
  - Immune Correlates
- Much of this information is either unknown or derived from other viral models

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Therapeutic Management of COVID-19 in the United States

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Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

DISEASE SEVERITY | PANEL'S RECOMMENDATIONS

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https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/

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SARS-CoV-2 Infection

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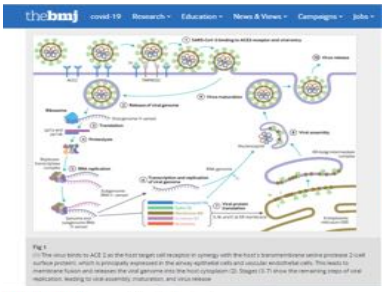

- SARS-CoV-2 binds to ACE 2 as the host target cell receptor in synergy with the host's transmembrane serine protease 2 (cell surface protein)
- Principally expressed in the airway epithelial cells and vascular endothelial cells.
- This leads to membrane fusion and releases the viral genome into the host cytoplasm.
- Remaining steps of viral replication lead to viral assembly, maturation, and virus release

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https://www.bmj.com/content/371/bmj.m3862

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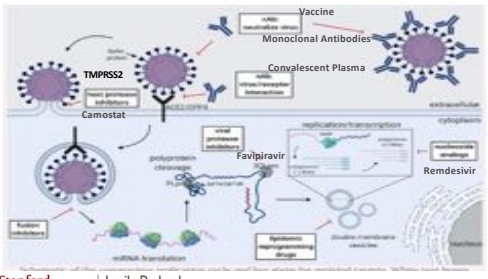
SARS-CoV2 Targets for Therapy



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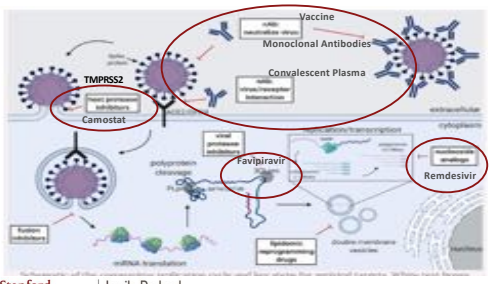
SARS-CoV2 Targets for Therapy



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Pathophysiology and Clinical Manifestations

- Direct viral effects
- Indirect inflammatory effects
- Direct and indirect immunomodulatory effects

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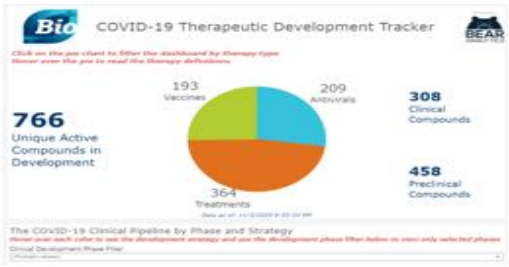
Therapeutics in Development or in Clinical Trials



https://www.bio.org/policy/human-health/vaccines-biodefense/coronavirus/pipeline-tracker

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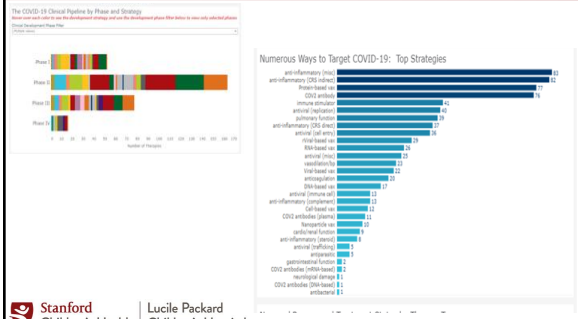
Therapeutic Trials by Phase and Location



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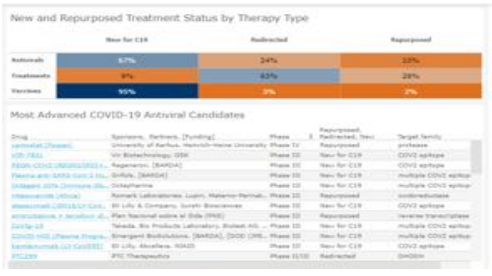

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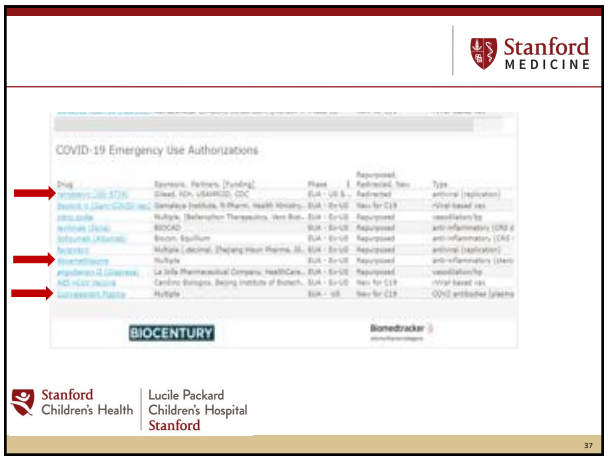

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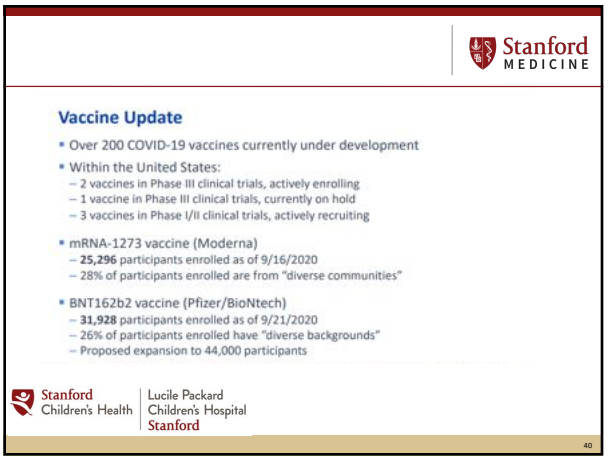

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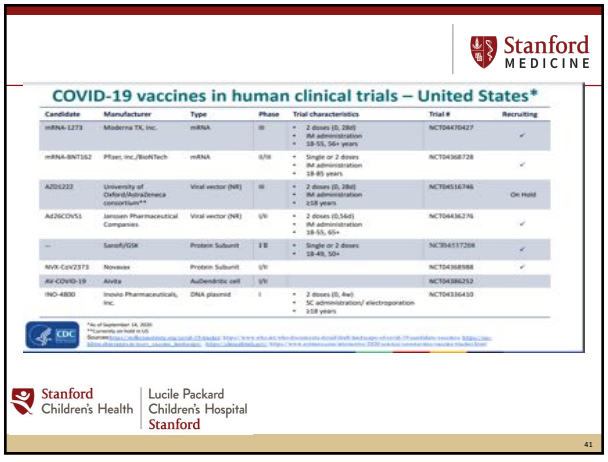

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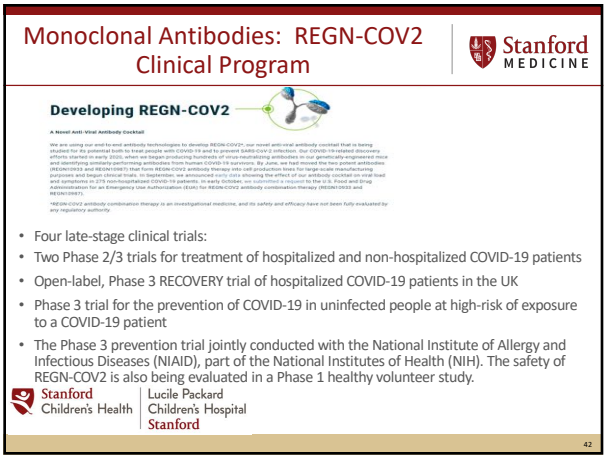

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Monoclonal Antibodies: REGN-COV2 Clinical Program

- **Serological status highly correlated with baseline viral load (p<0.0001) and predicted time to alleviation of COVID-19 clinical symptoms.**
  - Seropositive placebo patients had a median time to alleviation of symptoms of **7 days**, compared to seronegative patients at **13 days**.
- **REGN-COV2 reduced viral load through Day 7 in seronegative patients (key virologic endpoint).**
- Overall **a 0.51 log10 copies/mL greater reduction (p=0.0049)** for high dose and a 0.23 log10 copies/mL greater reduction (p= 0.20) for low dose, compared to placebo.
- **Patients with higher baseline viral levels had greater reductions at Day 7 with REGN-COV2.**
- **Small number of medically-attended visits given that most non-hospitalized patients recover well at home**. 10 of the 12 medically-attended visits occurred in patients who were seronegative at baseline.

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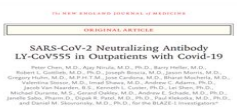
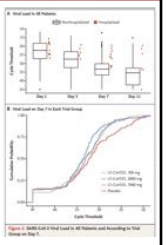
Monoclonal Antibodies: Eli Lilly





- Phase 2 outpatient trial with mild or moderate Covid-19 (n=452)
- Single intravenous infusion of neutralizing antibody LY-CoV555 in one of three doses:
  - 700 mg, 2800 mg, or 7000 mg or placebo and evaluated virologic end points and clinical outcomes.
- Primary outcome was the change from baseline in the viral load at day 11
- Mean decrease from baseline in the log viral load for the entire population was −3.81; elimination of more than 99.97% of viral RNA
- For the 2800-mg dose of LYCoV555, the difference from placebo in the decrease from baseline was −0.53 (95% confidence interval [CI], −0.98 to −0.08; P=0.02), for a viral load that was lower by a factor of 3.4.
- No significant differences from placebo observed for the 700-mg dose (−0.20; 95% CI, −0.66 to 0.25; P=0.38) or the 7000-mg dose (0.09; 95% CI, −0.37 to 0.55; P=0.70)
- Slightly lower severity of symptoms, compared to placebo.

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2029849

(Funded by Eli Lilly; BLAZE-1 ClinicalTrials.gov number, NCT04427501.)

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Convalescent Plasma?

Recommendations for Investigational COVID-19 Convalescent Plasma

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Three COVID-19 Clinical Trials Paused

Pathophysiology and Clinical Manifestations

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3 Covid-19 Trials Have Been Paused for Safety. That's a Good Thing.

Experts were comforted that companies are following safety precautions. They pointed out that pauses in vaccine trials are common, but pauses in treatment trials like Eli Lilly's are rare.

With AstraZeneca's vaccine trial still on pause in US, questions abound about study participants' mysterious illnesses

Study of Eli Lilly Covid-19 Drug Paused Due to Safety Concern

Drugmaker halted trial testing that explored use of its antibody drug in combination with remdesivir

Johnson & Johnson - October 13

Johnson & Johnson Covid-19 vaccine study paused due to unexplained illness in participant

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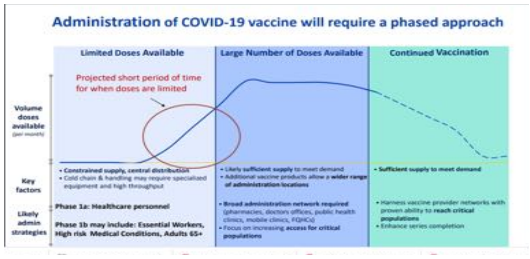
Phases of COVID-19 Vaccination in the US



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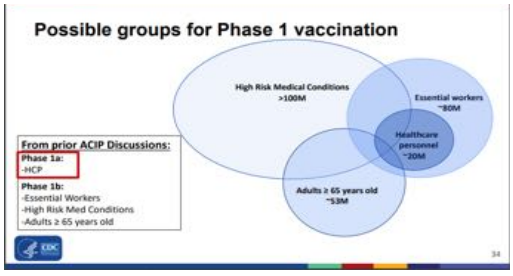
Phasing of COVID-19 Vaccines in the US



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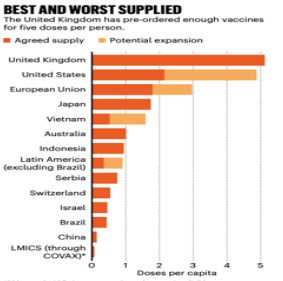
Global Scramble for Coronavirus Vaccines



Callaway, Ewen. Image from *"The unequal scramble for coronavirus vaccines — by the numbers"* by Nature. 24AUG2020. Received from: https://www.nature.com/articles/d41586-020-02432-4

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What Does the Future Hold?

- Combination therapy
  - Antiviral, immunomodulatory, anti-inflammatory, monoclonal
  - Clinical trials approaches must be flexible and adaptive
  - Ideally development of biomarkers or clinical indices to measure outcomes
- Vaccines
  - Herd immunity is the ultimate goal but may not happen rapidly
  - Degree and durability of immunity to be determined
  - Vaccine associated immune effects unknown
- Non-pharmacologic interventions to continue for an undefined period

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Critical Questions About SARS-CoV-2

- How effective are mitigation efforts to prevent SARS-CoV-2 spread, especially ventilation and masking?
- What proportion of SARS-CoV-2 infections are acquired through airborne transmission?
- What are the conditions that facilitate airborne transmission?
- What is the infectious dose for SARS-CoV-2 (how many virions are required for infection to occur)?
- Do inoculum size and route of inoculation affect risk of infection and disease severity?
- What is the risk for reinfection?

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