Covid-19

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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:

- Widespread misinformation: 33.3%
- Lack of a comprehensive national strategy: 33.3%
- Lack of public health leadership: 22.2%
- Other: 11.1%

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
- People aged 70+ have an 80.7% survival rate, while those aged under 69 have a 98.9% survival rate

Top 5 States with Highest Survival Rates to date

<table>
<thead>
<tr>
<th>State</th>
<th>Survival Rate</th>
<th>CFR to date</th>
<th>CFR last 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaska</td>
<td>99.50%</td>
<td>0.50%</td>
<td>0.50%</td>
</tr>
<tr>
<td>Utah</td>
<td>99.47%</td>
<td>0.53%</td>
<td>0.57%</td>
</tr>
<tr>
<td>Wyoming</td>
<td>99.37%</td>
<td>0.63%</td>
<td>0.45%</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>99.11%</td>
<td>0.89%</td>
<td>0.67%</td>
</tr>
<tr>
<td>Nebraska</td>
<td>99.09%</td>
<td>0.91%</td>
<td>0.63%</td>
</tr>
</tbody>
</table>

Top 5 States with Lowest Survival Rates to date

<table>
<thead>
<tr>
<th>State</th>
<th>Survival Rate</th>
<th>CFR to date</th>
<th>CFR last 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Jersey</td>
<td>93.18%</td>
<td>6.82%</td>
<td>0.63%</td>
</tr>
<tr>
<td>New York</td>
<td>93.42%</td>
<td>6.58%</td>
<td>0.76%</td>
</tr>
<tr>
<td>Connecticut</td>
<td>93.52%</td>
<td>6.48%</td>
<td>0.78%</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>93.73%</td>
<td>6.27%</td>
<td>1.99%</td>
</tr>
<tr>
<td>New Hampshire</td>
<td>95.69%</td>
<td>4.31%</td>
<td>1.45%</td>
</tr>
</tbody>
</table>
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

November/December 2020 Volume 11 Issue 6 e02707-20 http://mbio.asm.org/ on
Prolonged Shedding

Long-term SARS-CoV-2 Shedding

SARS-CoV-2 infection

Convalescent plasma transfusion (x2)

Clearance

Day 0 49 70 85 105

Infectious virus isolation

Genetic variation

Immunocompromised individual
- Cancer (CLL)
- Hypogammaglobulinemia

2 doses Convalescent Plasma

https://doi.org/10.1016/j.cell.2020.10.049
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.
Prevalence of Covid-19 Antibodies

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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total samples</td>
<td>38776</td>
<td>45907</td>
<td>45227</td>
<td>47900</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16024 (41.3)</td>
<td>18734 (40.3)</td>
<td>18983 (41.9)</td>
<td>20343 (42.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22751 (58.7)</td>
<td>27112 (55.1)</td>
<td>26344 (58.1)</td>
<td>27564 (57.5)</td>
<td></td>
</tr>
<tr>
<td>Age category, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-17</td>
<td>6700 (17.3)</td>
<td>6930 (15.1)</td>
<td>6484 (14.3)</td>
<td>6612 (13.8)</td>
<td></td>
</tr>
<tr>
<td>18-49</td>
<td>11237 (29.0)</td>
<td>14571 (31.8)</td>
<td>14079 (31.1)</td>
<td>15157 (31.5)</td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>10367 (26.8)</td>
<td>12514 (27.3)</td>
<td>12426 (27.4)</td>
<td>13207 (27.6)</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>10408 (26.9)</td>
<td>11858 (25.9)</td>
<td>12316 (27.2)</td>
<td>12913 (27.0)</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott ARCHITECT</td>
<td>18467 (47.6)</td>
<td>20436 (44.5)</td>
<td>22378 (49.4)</td>
<td>23534 (49.1)</td>
<td></td>
</tr>
<tr>
<td>Ortho VITROS</td>
<td>15234 (39.6)</td>
<td>17708 (38.8)</td>
<td>16116 (35.6)</td>
<td>16100 (33.6)</td>
<td></td>
</tr>
<tr>
<td>Roche Elecsys</td>
<td>4973 (12.8)</td>
<td>7763 (16.9)</td>
<td>8833 (15.1)</td>
<td>8275 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Metropolitan status</td>
<td>Nonmetropolitan</td>
<td>Metropolitan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5032 (15.3)</td>
<td>6329 (13.8)</td>
<td>6807 (15.0)</td>
<td>7212 (15.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32828 (84.7)</td>
<td>39555 (86.2)</td>
<td>38500 (85.0)</td>
<td>40671 (84.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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)

Lancet Volume 396, Issue 10243, 4–10 July 2020; 27-38
Treatment Across the COVID-19 Spectrum

**Stage/Severity:**
- Asymptomatic/Presymptomatic: + SARS-CoV-2 test but no symptoms
- Mild Illness: Mild symptoms (e.g., fever, cough, taste/smell changes); no dyspnea
- Moderate Illness: O₂ saturation ≥94%, lower respiratory tract disease
- Severe Illness: O₂ saturation <94%, respiratory rate >30/min; lung infiltrates >50%
- Critical illness: Respiratory failure, shock, multi-organ dysfunction/failure

**Frequency:**
- ?
- 80%
- 15%
- 5%

**Disease Pathogenesis:**
- Viral replication
- Inflammation

**Potential treatment:**
- Antivirals
- Antibody therapy
- Decrease inflammation

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

1 - Membrane fusion and endocytosis
   - TMPRSS2 and ACE2 receptor
   - Chloroquine and Hydroxychloroquine
   - Remdesivir
   - Lopinavir-Ritonavir

2 - Viral entry
   - Darunavir
   - Darunavir/Prosidavir/Favipiravir

3 - RNA release and replication
   - Ribosomyl polymerase
   - Polyprotein processing
   - Lopinavir-Ritonavir

4 - RNA synthesis
   - RNA dependent RNA polymerase
   - Ivermectin

5 - Assembly
   - Cathepsin L
   - Tegafirin
   - Convalescent plasma

6 - Virus release
   - Monoclonal Abs

- Lamivudine
- Nucleos(t)ide reverse transcriptase inhibitor
- Envelope glycoprotein (E)
- Membrane protein (M)
Lifecycle and Medication

1 - Membranes fusion and endocytosis
- Teicoplanin
- Cathepsin L
- Chloroquine
- Hydroxychloroquine
- Azithromycin

2 - Viral entry
- Remdesivir
- Amprenavir
- Darunavir
- Lopinavir
- Ivermectin

3 - RNA release
- Ribavirin
- Lopinavir
- Remdesivir

4 - RNA synthesis
- RNA dependent RNA polymerase

5 - Assembly
- RNA
- Protease inhibitors
- Lopinavir
- Remdesivir

6 - Virus release

Convalescent Plasma

Monoclonal Abs

Lipid bilayer
- Nucleocapsid protein (N) + single stranded RNA genome
- Spike glycoprotein (S)
- Envelope glycoprotein (E)
- Membrane protein (M)
Monoclonal Antibodies

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)
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

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

Figure 1: SARS-CoV-2 viral load change from baseline by visit.
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

https://www.fda.gov/media/143602/download
Adaptive vs Innate Immunity

Difference between Innate and Adaptive Immunity

Nonspecific Quick Response

Quick Specific Response, 1st Time
mRNA Vaccines

Conventional mRNA

Self-amplifying mRNA
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 (Tfh) 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

Pro: Scalability – making RNA is easy, cheap

Cons: New technology = unknown risks
  Autoimmunity?

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
## COVID-19 Vaccine Pipeline Summary

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

**EUA submitted**

*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

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/8</td>
<td>- FDA to make VRBPAC background material publicly available</td>
</tr>
</tbody>
</table>
| 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

- Phase 1c: Adults with high-risk medical conditions
  - Adults 65+

- Phase 1b: Essential workers
  - (examples: Education Sector, Food & Agriculture, Utilities, Police, Firefighters, Corrections Officers, Transportation)

- Phase 1a: HCP, LTCF residents

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

A Discrete choice (average marginal component effects)

- Efficacy, %
  - 50
  - 70
  - 90
- Protection duration, y
  - 1
  - 5
- Major side effects
  - 1 in 10000
  - 1 in 100000
- Minor side effects
  - 1 in 10
  - 1 in 30
- FDA approval
  - Full approval
  - Emergency use authorization
- Origin
  - US
  - UK
  - China
- Endorsement
  - Trump
  - Biden
  - CDC
  - WHO

B Individual vaccine evaluation (marginal means)

- Efficacy, %
  - 50
  - 70
  - 90
- Protection duration, y
  - 1
  - 5
- Major side effects
  - 1 in 10000
  - 1 in 100000
- Minor side effects
  - 1 in 10
  - 1 in 30
- FDA approval
  - Full approval
  - Emergency use authorization
- Origin
  - US
  - UK
  - China
- Endorsement
  - Trump
  - Biden
  - CDC
  - WHO

Marginal mean willingness to receive vaccine

Change in probability of choosing vaccine

JAMA Netw Open. 2020;3(10):e2025594.
“We will sell no wine before it’s time” – I mean vaccine

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