Update in COVID-19 diagnostics, therapeutics and vaccines

Claudia Hawkins MD, MPH
Associate Professor of Medicine and Infectious Diseases
Northwestern Feinberg School of Medicine
Chicago, Il
Overview

• Global and Local COVID-19 epidemiology
• Updates in COVID-19 diagnostics, treatment and vaccines

Slide credit:
clinicaloptions.com
Michael Ison MD, MS
Robert Murphy MD
Global and local epidemiology
A year into COVID-19, where are we now?

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 17, 2019</td>
<td>First detectable COVID-19 case in China</td>
</tr>
<tr>
<td>December 31, 2019</td>
<td>Chinese Health officials inform the WHO about a cluster of 41 patients with a mysterious pneumonia</td>
</tr>
<tr>
<td>January 7, 2020</td>
<td>Chinese authorities identify virus that cause pneumonia as novel type of coronavirus</td>
</tr>
<tr>
<td>January 11th, 2020</td>
<td>Chinese researchers publish the virus’ genetic sequence</td>
</tr>
<tr>
<td>January 20th, 2020</td>
<td>The first US Case reported in Washington</td>
</tr>
<tr>
<td>January 30th, 2020</td>
<td>WHO declares a global public health emergency</td>
</tr>
<tr>
<td>February 21st, 2020</td>
<td>COVID-19 cases start to spike in Italy, followed by lockdown for all 60 million residents</td>
</tr>
<tr>
<td>March 11th, 2020</td>
<td>WHO declares COVID-19 outbreak a pandemic</td>
</tr>
<tr>
<td>March 13th, 2020</td>
<td>Trump declares National Emergency in the US</td>
</tr>
<tr>
<td>March 23rd, 2020</td>
<td>New York becomes epicenter of US outbreak with 21,000 cases</td>
</tr>
<tr>
<td>April 2nd, 2020</td>
<td>The world passes 1 million COVID-19 infections</td>
</tr>
<tr>
<td>June 28th, 2020</td>
<td>Global COVID-19 cases surpass 10 million</td>
</tr>
<tr>
<td>September 2nd, 2020</td>
<td>The WHO recommends steroids for seriously ill COVID-19 patients</td>
</tr>
<tr>
<td>October 23rd, 2020</td>
<td>US enters its third surge of coronavirus cases, beginning of its deadliest phase yet</td>
</tr>
<tr>
<td>November 9th, 2020</td>
<td>Global cases top 50 million</td>
</tr>
<tr>
<td>December 11th, 2020</td>
<td>FDA authorizes Pfizer and BioNTechs COVID-19 vaccine</td>
</tr>
<tr>
<td>December 18th, 2020</td>
<td>FDA authorizes Modernas COVID-19 vaccine</td>
</tr>
<tr>
<td>January 16th, 2021</td>
<td>Global deaths to 2 million</td>
</tr>
</tbody>
</table>
The CSSE at Johns Hopkins: Global COVID-19 Dashboard

<table>
<thead>
<tr>
<th>Confirmed Cases</th>
<th>Deaths</th>
<th>Recovered*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global</strong>: 94,132,992</td>
<td><strong>Global</strong>: 2,015,323</td>
<td><strong>Global</strong>: 41,544,026</td>
</tr>
</tbody>
</table>

- **US**: 23,575,628
- **India**: 10,542,841
- **Brazil**: 8,393,492
- **Russia**: 3,507,201
- **UK**: 3,336,988

- US: 393,049
- Brazil: 208,246
- India: 152,093
- Mexico: 139,022
- UK: 88,747

- India: 9,520,827
- Brazil: 6,301,547
- Russia: 2,207,398
- Turkey: 1,753,552
- Argentina: 1,352,556

Last updated: January 16th, 2021, 9.30am ET


Slide credit: clinicaloptions.com
CDC: US COVID-19 Tracker

Illinois cases: 1.07 million
Illinois deaths: 20,021

Cases:
- 0-31,875
- 39,775-95,010
- 121,299-203,797
- 368,187-570,602
- 856,118-1,585,044

Deaths:
- 0-321
- 604-1555
- 1978-3273
- 3969-6845
- 7358-12,620
- 15,455-24,561

Last updated: December 15, 2020 12:17 PM ET

https://www.cdc.gov/covid-data-tracker
Daily trends in number of COVID-19 cases in the US reported to CDC
CDC Data: Cases, Hospitalization, and Mortality Trends in the US

- COVID-19 mortality data in the US (deaths due to COVID-19/total deaths) have generally followed the infection data trends, with a 2- to 3-wk delay

![Graph showing COVID-19 Cases, Hospitalizations, and Mortality (March-November 2020)]

*The percentage of deaths due to PIC and hospitalizations are expected to increase for the most recent wks as additional data are received.


Slide credit: clinicaloptions.com
Risk-Adjusted Fatality Rates for Patients Hospitalized With COVID-19 in NYC

- Assessment of in-hospital case fatality rates or discharge to hospice in persons hospitalized with laboratory confirmed COVID-19 from March through August 2020 at 3 academic hospitals in NYC (N = 5,121)
  - Decrease in case fatality observed across age groups

<table>
<thead>
<tr>
<th>Month</th>
<th>Fatality or Discharge to Hospice (%)</th>
<th>Total COVID-19 Admissions (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>March</td>
<td>25.6%</td>
<td>2,500</td>
</tr>
<tr>
<td>April</td>
<td>7.6%</td>
<td>2,000</td>
</tr>
<tr>
<td>May</td>
<td>10.0%</td>
<td>1,500</td>
</tr>
<tr>
<td>June</td>
<td>5.0%</td>
<td>1,000</td>
</tr>
<tr>
<td>July</td>
<td>5.0%</td>
<td>500</td>
</tr>
<tr>
<td>August</td>
<td>0.0%</td>
<td>0</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race/ethnicity, BMI, smoking history, admission oxygen saturation, D-dimer, ferritin, C-reactive protein, and high-risk comorbidities.

COVID-19 Mortality: Potential Improvements and Lessons Learned

• Increasing clinical experience
  • Appropriate timing of ventilation
  • Best way to supply supplemental oxygen

• Decreasing hospital volume

• Pharmacologic treatments: systemic corticosteroids and remdesivir

• Nonpharmacologic management, such as proning

• Lower viral load exposure from mask wearing and social distancing?
COVID-NET: Lab-Confirmed COVID-19–Associated Hospitalizations Stratified by Age and Race/Ethnicity

Characteristics of Covid-19-associated Hospitalizations

- White
- Black
- Hispanic/Latino
- Asian/Pacific Islander
- American Indian/Alaska Native
- Other

Age:
- 0-1 yr
- 5-17 yr
- 18-49 yr
- 50-64 yr
- 55+ yr
- Overall

Percent:
- 0
- 20
- 40
- 60
- 80
- 100

Last updated: December 5, 2020
https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html
Slide credit: clinicaloptions.com
COVID-19 Cases, Hospitalizations, and Deaths by Race/Ethnicity in NYC

*Age-adjusted. Last updated December 15, 2020, 1:00 PM ET. Data not provided on those identified as other categories (e.g., Native American/Alaska Native or multiracial). Latino/Hispanic includes people of any race. Race/ethnicity data most complete for those hospitalized or who have died.


Slide credit: clinicaloptions.com
Factors Influencing Racial and Ethnic Minority Group Health

Living/Work Conditions

- Discrimination promotes chronic and toxic stress
- Work in essential industries with increased exposure, lack paid sick leave
- Reside in economically depressed areas with high housing density and limited access to healthy foods
- Multigenerational households and limited space may make it more difficult to follow prevention strategies

Health & Access to Care

- High prevalence of comorbid conditions that can increase likelihood and severity of COVID-19
- Factors restricting access to care: language barriers; lack of insurance, transportation, or child care; financial implications of missing work to receive care; cultural differences between patients and providers; distrust of government and healthcare systems

Diagnostic tests for COVID-19
Types of SARS-CoV-2 tests

- Molecular tests- RNA detection  
  \textit{(nasopharyngeal, nasal, oral, saliva)}
- Antibody tests \textit{(finger stick or blood draw)}
- There are also viral antigen tests that detect viral proteins
Common COVID-19 Diagnostic Methods: RNA

### Viral Nucleic Acid Assays

<table>
<thead>
<tr>
<th>Typically indicate</th>
<th>Current infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen sources</td>
<td>Upper (eg, nasopharyngeal swabs or washes, oropharyngeal swabs, nasal aspirates) or lower (eg, sputum, bronchoalveolar lavage fluid, tracheal aspirates) respiratory tract</td>
</tr>
<tr>
<td>Considerations</td>
<td>Primary method for COVID-19 diagnosis with multiple RT-PCR kits available</td>
</tr>
<tr>
<td></td>
<td>False negatives may result from improper sampling or handling, low viral load, or viral mutations</td>
</tr>
<tr>
<td></td>
<td>SARS-CoV-2 RNA undetectable by ~ Day 14 following onset of illness in some cases/samples</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
# Common COVID-19 Diagnostic Methods: Antibodies

**Serologic Assays**

<table>
<thead>
<tr>
<th>Typically indicate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past infection, but may have some utility in diagnosis of current infection among</td>
</tr>
<tr>
<td>those presenting late or when RT-PCR negative/unavailable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimen sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most often blood serum or plasma, but may include saliva, sputum, or other</td>
</tr>
<tr>
<td>biological fluids</td>
</tr>
<tr>
<td>Provides a delayed but wider window of time for detection</td>
</tr>
<tr>
<td>May be useful for COVID-19 surveillance and identification of convalescent plasma</td>
</tr>
<tr>
<td>donors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>False negatives</strong>: Low sensitivity in first wk after symptoms with subsequent</td>
</tr>
<tr>
<td>rises during second/third wks and scant data thereafter; unclear if low-level</td>
</tr>
<tr>
<td>antibody detectable in cases of mild/asymptomatic disease</td>
</tr>
<tr>
<td><strong>False positives</strong>: Due to cross-reactivity</td>
</tr>
<tr>
<td>Uncertain if positive read = immune protection if re-exposed</td>
</tr>
</tbody>
</table>
Temporal Considerations for Diagnosis

<table>
<thead>
<tr>
<th>Before symptom onset</th>
<th>After symptom onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection unlikely</td>
<td>PCR – Likely positive</td>
</tr>
</tbody>
</table>

Antibody detection

- Nasopharyngeal swab PCR
- Virus isolation from respiratory tract
- Bronchoalveolar lavage/sputum PCR
- Stool PCR
- IgM antibody
- IgG antibody

Symptom onset:
- Wk -2
- Wk -1
- Wk 1
- Wk 2
- Wk 3
- Wk 4
- Wk 5
- Wk 6

SARS-CoV-2 exposure

Increasing probability of detection

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Challenges with SARS-CoV-2 diagnostic testing

• Problems with sensitivity both during infection and afterwards*
• Testing capacity limits
• Processing large numbers can also disrupt the normal workflow of testing laboratories
• Safety requirements
• Specimen collection and transport issues
• Reagents and equipment needs
• Most approved require in-house lab facilities, not POC/at home, other settings.
Rapid Acceleration of Diagnostics (RADx) Initiative

Signed into law, April 24 → Launched April 29 (2020)

Innovate: Expand Number, Type, Access, Throughput of Testing Technologies

Optimize: Technology Performance for Range of Essential “Use Cases”

- Home-based
- Point of Care (POC)
- Hospital
- Testing Laboratory

**Totally RADx @NIH**

**RADx Tech – $500M**
Highly competitive, rapid three-phase challenge to identify the best candidates for at-home or point-of-care tests for COVID-19 and to make millions of accurate and easy-to-use tests per week available.

**RADx Underserved Populations (RADx-UP) – $500M**
Interlinked community-based demonstration projects focused on implementation strategies to enable and enhance testing of COVID-19 in underserved, under-resourced, rural, and/or vulnerable populations.

**RADx Radical (RADx-Rad) – $200M**
Develop and advance novel, non-traditional approaches or new applications of existing approaches for testing, including unconventional screening, biological or physiological markers, new platforms, POC devices, etc.

**RADx Advanced Testing Program (RADx-ATP) – $230M**
Rapid scale-up of advanced technologies to increase rapidity and enhance and validate throughput – create ultra-high throughput machines and facilities.

*Remaining $70M of OD funds for Data Management Support for Testing for Safe Release Project*
Results to Date Have Been Robust

NATIONAL CALL FOR INNOVATIVE TECHNOLOGIES

PHASE 0: "Shark Tank"-Like Rapid Selection Process
PHASE 1: Validation and Risk Review
PHASE 2: Clinical Tests, Regulatory Approval, and Scaling Up
END OF SUMMER/FALL 2020

Rolling submission open April 29, 2020

Applications Started

>3000

Projects in each Phase

707  136  46  22

5-6 Months

FAST TRACK FOR ADVANCED DIAGNOSTIC TECHNOLOGIES

>6 M tests/day by end of year

DEPLOY MILLIONS of tests per week

Validation, Clinical Testing, Regulatory, Manufacturing, Distribution

NIH National Institute of Biomedical Imaging and Bioengineering
New RADx Supported Technologies

Rapid Ag 30m, Battery RT-PCR 40m, F-imm Ag 15m, RT-PCR 30m
M2Dx DASH SARS-CoV-2 Test

- **Indication**: asymptomatic and symptomatic
- **Sample Type**: Saliva, direct nasal or nasopharyngeal swab, or nasal or nasopharyngeal in VTM / UTM
- **Method**: RT-qPCR
- **Analytical Sensitivity**: 100 cp/ml
- **Time to result**: <15 minutes
- **Result Format**: semi-quantitative with thresholds calibrated against copies of the virus (1 = Very Weak Positive up to 4 = Strong Positive)
- **Connectivity**: Yes

Northwestern Spinoff: Minute Molecular Diagnostic’s DASH Platform Diagnostic Analyzer for Specific Hybridization

1. Scan sample
2. Scan cartridge
3. Insert swab
4. Insert cartridge
5. Read result
6. Discard cartridge
Clinical studies at NU under RADx

• **RADx Test at Home** will test the accuracy of the at-home testing kits. Participants will be asked to self-test for 14 days utilizing an at-home kit provided by the RADx team.

• **RADx 6313** will observe changes to the virus over 14 days by asking participants with a recent positive test result or close exposure to a confirmed positive test result to self-test daily for 14 days. (NU College students)

• Contact: Amelia M Kelly [amelia.kelly@northwestern.edu](mailto:amelia.kelly@northwestern.edu) if you are interested in enrolling in RADx Test at Home.
Therapeutic options for COVID-19
## Key Therapeutic Classes Under Investigation for Treatment of COVID-19

<table>
<thead>
<tr>
<th><strong>Antivirals</strong></th>
<th><strong>Immune-based therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baloxivir</td>
<td>Immunomodulators:</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Corticosteroids <em>(eg, dexamethasone)</em></td>
</tr>
<tr>
<td>*(Hydroxy)*chloroquine</td>
<td>IL-1 inhibitors <em>(eg, anakinra)</em></td>
</tr>
<tr>
<td>Interferon</td>
<td>IL-6 inhibitors <em>(eg, tocilizumab, sarilumab)</em></td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>JAK inhibitors <em>(eg, baricitinib)</em></td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>Neutralizing monoclonal antibody</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td><em>(eg. bamlanivimab LY-CoV555 and LY3819253)</em></td>
</tr>
<tr>
<td><strong>Remdesivir</strong></td>
<td>Blood derived products <em>(eg. Convalescent plasma)</em></td>
</tr>
<tr>
<td>Ribavirin</td>
<td></td>
</tr>
</tbody>
</table>
COVID-19: How and When to Intervene?

Stage I (Early Infection)
- Viral response phase
- Mild constitutional symptoms
  - Fever >99.6°F
  - Dry Cough, diarrhea, headache

Stage II (Pulmonary Phase)
- Host inflammatory response phase
- Shortness of Breath
- Hypoxia (PaO2/FiO2 ≤300 mmHg)
- Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)
- Abnormal chest imaging
- Transaminitis
- Low-normal procalcitonin

Stage III (Hyperinflammation Phase)
- ARDS
- SIRS/Shock
- Cardiac Failure
- Elevated inflammatory markers
  - (CRP, LDH, IL-6, D-dimer, ferritin)
  - Troponin, NT-proBNP elevation

Potential Therapies
- Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions
- Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors
- Reduce immunosuppression

Remdesivir (GS-5734): IV Antiviral Drug for SARS-CoV-2

Antivirals: Remdesivir

- FDA approved 10/20
  - 1,062 hospitalized COVID-19 patients to receive remdesivir (10 days) or a placebo plus standard treatment
  - shortened time to recovery (10 days [remdesivir] vs. 15 days [placebo]).
  - improved mortality rates for those receiving supplemental oxygen (4% with remdesivir versus 13% with placebo at day 29 of treatment)*
  - In this open-label trial, 11,330 patients in 30 countries were randomized to receive standard of care (no trial drug) or one of the four antivirals depending on local availability- remdesivir, hydroxychloroquine, lopinavir, and beta interferon. 8% were receiving mechanical ventilation.
  - Remdesivir no better than standard of care overall or for subgroup with mechanical ventilation
COVID-19: Monoclonal Antibodies

Image of an antibody binding to the surface of a virus, blocking entry into a human cell. *Lisa Donohue, CoVPN*
Monoclonal antibodies:

Bamlanivimab

• EUA to outpatients at high risk for severe disease and/or hospitalization.
• Phase 2 BLAZE-1 study Chen. NEJM. 2020; treatment reduced the need for hospitalization among outpatients — especially those deemed at high risk for poor COVID-19 outcomes. For this group, 3% of bamlanivimab versus 10% of placebo recipients required admission.

• Casirivimab and Imdevimab (REGN-COV2)
  • EUA administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients at high risk for progressing to severe COVID-19
  • Weinreich D et al., NEJM, 2020-For patients at high risk for disease progression, hospitalizations and emergency room visits occurred in 3% of casirivimab and imdevimab-treated patients on average compared to 9% in placebo-treated patients.

• Problems with administering as outpatient- supply is limited, needs to be given IV and within 10 days of symptom onset, infusion center logistics and risks, takes 3 hours for infusion; only stable for 7 hours after prep, serious AE can occur

• No benefits in hospitalized patients*

DOI: 10.1056/NEJMoa2035002
COVID-19: Immune Modulation Therapy

- IL6R: Tocilizumab, Sarilumab
- JAK: Barcitinib, Ruxolitinib
- IL-1: Canakinumab, Anakinra
- BTK Inhibitor: Ibrutinib
- Steroids

JAK inhibitors: Baricitinib

• JAK inhibitor selective for JAK1 and JAK 2; prevents cellular immune activation and inflammation

• EUA for use in combination with remdesivir for hospitalized patients requiring supplemental oxygen, mechanical ventilation or ECMO

• NIAID ACTT-2 *Kalil et al. NEJM 2020* - Baricitinib + Remdesivir vs Remdesivir in Hospitalized Patients With Severe COVID-19
  • Reduced median time to recovery in hospitalized COVID-19 patients from eight days to seven days. Most benefit seen in those on high-flow oxygen or non-invasive ventilation (18-10 days)
  • Patients condition a 8 days improved in those with combination therapy
Steroids

• Dexamethasone is a corticosteroid with **anti-inflammatory effects** that has been used to treat allergies, asthma, dermatitis, rheumatic disorders, MS, other autoimmune disorders, etc

• Can be administered IV or orally

• Contraindicated by FDA in patients with systemic fungal infections

• Pregnancy category C

• **Warnings:** can cause elevation in blood pressure, left ventricular free wall rupture in patients with recent MI, adrenocortical insufficiency, increased susceptibility to infection, and cataracts/glaucoma with possible damage to the optic nerve
Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial Among Hospitalized Patients

- Hospitalized patients in the UK with clinically suspected or laboratory confirmed SARS-CoV-2
  - Initial recruitment was in patients ≥ 18 yrs of age but age limit was removed on 5/9/2020
- Patients randomized to usual care plus: no additional treatment, lopinavir/ritonavir, dexamethasone, hydroxychloroquine, or azithromycin
  - Factorial design with simultaneous allocation to no additional tx vs convalescent plasma
  - If progressive disease (hyper-inflammatory state), subsequent randomization to no additional treatment vs tocilizumab
- > 11,500 patients enrolled from > 175 NHS hospital organizations in the UK
- Addition of dexamethasone to usual care associated with lower mortality at 28 days among subsets receiving invasive mechanical ventilation or oxygen alone but not in those receiving no baseline respiratory support


Slide credit: clinicaloptions.com
## COVID-19: Steroids

<table>
<thead>
<tr>
<th>Drug and trial</th>
<th>ClinicalTrials.gov identifier</th>
<th>Initial dose and administration</th>
<th>No. of deaths/total No. of patients</th>
<th>Odds ratio (95% CI)</th>
<th>Favors steroids</th>
<th>Favors no steroids</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>DEXA-COVID 19 NCT04325061</td>
<td>High: 20 mg/d intravenously</td>
<td>2/7 2/12</td>
<td>2.00 (0.21-18.69)</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>CoDEX</td>
<td>NCT04327401</td>
<td>High: 20 mg/d intravenously</td>
<td>69/128 76/128</td>
<td>0.80 (0.49-1.31)</td>
<td></td>
<td></td>
<td>18.69</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>NCT04381936</td>
<td>Low: 6 mg/d orally or intravenously</td>
<td>95/324 283/683</td>
<td>0.59 (0.44-0.78)</td>
<td></td>
<td></td>
<td>57.00</td>
</tr>
<tr>
<td>Subgroup fixed effect</td>
<td></td>
<td></td>
<td>166/459 361/823</td>
<td>0.64 (0.50-0.82)</td>
<td></td>
<td></td>
<td>76.60</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>CAPE COVID NCT02517489</td>
<td>Low: 200 mg/d intravenously</td>
<td>11/75 20/73</td>
<td>0.46 (0.20-1.04)</td>
<td></td>
<td></td>
<td>6.80</td>
</tr>
<tr>
<td>COVID STEROID</td>
<td>NCT04348305</td>
<td>Low: 200 mg/d intravenously</td>
<td>6/15 2/14</td>
<td>4.00 (0.65-24.66)</td>
<td></td>
<td></td>
<td>1.39</td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>NCT02735707</td>
<td>Low: 50 mg every 6 h intravenously</td>
<td>26/105 29/92</td>
<td>0.71 (0.38-1.33)</td>
<td></td>
<td></td>
<td>11.75</td>
</tr>
<tr>
<td>Subgroup fixed effect</td>
<td></td>
<td></td>
<td>43/195 51/179</td>
<td>0.69 (0.43-1.12)</td>
<td></td>
<td></td>
<td>19.94</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Steroids-SARI NCT04244591</td>
<td>High: 40 mg every 12 h intravenously</td>
<td>13/24 13/23</td>
<td>0.91 (0.29-2.87)</td>
<td></td>
<td></td>
<td>3.46</td>
</tr>
<tr>
<td>Overall (random effects)</td>
<td>222/678 425/1025</td>
<td></td>
<td>0.70 (0.48-1.01)</td>
<td></td>
<td></td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

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Treatment guidelines - WHO, NIH, IDSA

• All three guidelines advise against the use of chloroquine, hydroxychloroquine, lopinavir/ritonavir, or azithromycin for the treatment of COVID-19 patients.

• The IDSA and NIH guidelines recommend 5 days of remdesivir for patients on supplemental oxygen, but not for those on mechanical ventilation or extracorporeal membrane oxygenation.

• The NIH guideline suggests co-administration of remdesivir and dexamethasone for patients with severe disease as well as for those on noninvasive ventilation and those who were recently intubated.

• The WHO guideline recommends against the use of remdesivir in any situation.

• All three guidelines agree that dexamethasone at a dose of 6 mg once daily (or an equivalent corticosteroid) should be administered to hospitalized critically ill patients with requirement for oxygen supplementation or ventilation (noninvasive or invasive), and they advise against its use in those with mild disease without oxygen requirement, even if hospitalized.

• The IDSA and NIH guidelines do not recommend routine use of tocilizumab, bamlanivimab, or reconvalescent plasma.
Approach to COVID-19: *Gaps in Our Understanding*

- We need to identify ideal study endpoints
  - Initial enthusiasm for ordinal scale; challenges noted
  - There’s more to drugs than prevention of death
- We need to know more about impact of interventions
  - Serial virology and resistance emergence
  - Biomarkers and the clinical correlates of their change
- We need to figure out how to learn from EUA/EAP
- We need more personalized approach to therapy
  - Especially true for immunomodulation
- Better therapies for outpatient care and more potent antivirals
COVID-19 Vaccine Development
Vaccine Development Pathway

- **Traditional vaccine development pathway**[1]
  - Target discovery/validation, preclinical stage, manufacturing development, clinical assay optimization: **3-8 yrs**
  - Phase I (safety), phase II (safety/immunogenicity), phase III (safety/efficacy) clinical trials: **2-10 yrs**
  - Regulatory review: **1-2 yrs**

### SARS-CoV-2 Vaccine Candidates in Development[2]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>86+</td>
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<tr>
<td>Phase I (safety)</td>
<td>41</td>
</tr>
<tr>
<td>Phase II (expanded safety trials)</td>
<td>16</td>
</tr>
<tr>
<td>Phase III (large-scale efficacy tests)</td>
<td>16</td>
</tr>
<tr>
<td>Approval</td>
<td>2</td>
</tr>
</tbody>
</table>

How were these vaccines developed so fast?

• Shared data and global collaboration
  • The SARS-CoV-2 virus genetic sequence became available on January 10, 2020
    ➔ Scientists were able to start working before there were ever cases in the United States

• Existing knowledge of other coronaviruses
  • existing data on the structure, genome, and life cycle of this type of virus.
  • previous work in mRNA vaccine technology (BioNTech and Moderna)

• Funding
  • Operation Warp Speed (US), European Commission, UK Government Vaccine taskforce
Vaccine platforms

**DNA-based vaccines** work by inserting synthetic DNA of viral gene(s) into small DNA molecules (called plasmids). Cells take in the DNA plasmids and follow their instructions to build viral proteins, which are recognized by the immune system, and prepare it to respond to disease exposure.

**Viral vector vaccines** insert a gene for a viral protein into another, harmless virus (replicating or non-replicating), which delivers the viral protein to the vaccine recipient, triggering an immune response.

**RNA vaccines** introduce an mRNA sequence coded for a disease-specific antigen. Once this antigen is reproduced within the body, it is recognized and triggers an immune response.

**Subunit vaccines** introduce a fragment of the virus into the body. This fragment is enough to be recognized by the immune response and stimulate immunity.

**Inactivated vaccines** consist of the whole virus, which has been killed with heat or chemicals so it can't cause illness.

**Live attenuated vaccines** are made up of whole viruses that have weakened in a lab. They tend to elicit a stronger immune response than inactivated vaccines.
Types of SARS-CoV-2 Vaccines

• **Goal:** have immune system learn to recognize COVID proteins so it can quickly fight the virus

• **mRNA** Vaccines (DNA). (2 doses)
  - Moderna mRNA-1273
  - BioNTech Pfizer mRNA-BNT162

• **Viral Vector** Vaccines (2 doses (Ox); 1 dose (Janssen))
  - AstraZeneca/Univ of Oxford (chimpanzee adenovirus) AZD1222
  - Janssen/Johnson & Johnson (human adenovirus 26)* Ad26COVS1

• **Protein-Based** Vaccines
  - Novavax*
  - Sanofi*
How does an mRNA Vaccine Work?

- The red protrusions on the surface of the virus = spike proteins
- The vaccine contains the temporary genetic instructions messenger RNA (mRNA) for how to make a spike protein
- Your cells use those instructions to make spike proteins
- Your immune system then learns how to recognize the spike protein and makes antibodies to it, so that it will also react to a coronavirus particle in the future
# mRNA Vaccines Against SARS-CoV-2

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Description</th>
<th>Phase (Total N)</th>
<th>Case Count, n</th>
<th>Primary Endpoint: Prevention of Symptomatic COVID-19</th>
<th>Additional Analyses Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT162b2 (Pfizer)</td>
<td>Vaccinations on Day 1 and Day 21 in persons ≥ 16 yrs of age with nucleoside-modified mRNA (modRNA) encoding the membrane-bound full-length spike protein</td>
<td>II/III (43,661)*</td>
<td>170 (final)</td>
<td>95% 7 days after second dose (P &lt; .0001)</td>
<td>▪ &gt; 94% efficacy in adults &gt; 65 yrs of age</td>
</tr>
<tr>
<td>mRNA-1273 (Moderna)</td>
<td>Vaccinations on Day 1 and Day 29 in persons ≥ 18 yrs of age with mRNA encoding a prefusion stabilized spike protein</td>
<td>III (30,000)†</td>
<td>95 (interim)</td>
<td>94.5% 14 days after second dose (P &lt; .0001)</td>
<td>▪ 11/11 severe cases occurred in placebo group</td>
</tr>
</tbody>
</table>

*41,135 had received second dose as of November 13, 2020. 42% of volunteers had diverse ethnic backgrounds; 41% were 56-85 yrs of age.
†Includes more than 7000 persons > 65 yrs of age and more than 5000 < 65 yrs of age with high-risk chronic diseases, such as diabetes, severe obesity, and cardiac disease. 37% of volunteers from racial and ethnic minorities.

mRNA vaccines: CDC guidance

Indications

• Pfizer-BioNTech: ≥16 years (30 µg, 0.3 ml each): 3 weeks (21 days) apart
• Moderna: ≥18 years (100 µg, 0.5 ml): 1 month (28 days) apart
• mRNA COVID-19 vaccines are not interchangeable
• Avoid other vaccines within 14 days
• Vaccination should be offered to persons regardless of history of prior symptomatic or asymptomatic SARS-CoV-2 infection
• Vaccination should be deferred in those with active infection (can delay until 90 days)
• Similar recommendations to those who have received monoclonal antibody therapies or convalescent plasma
• Can be administered to HIV and patients with immunocompromised immune systems
• Can be used in pregnant women and lactating

Contraindications

• Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components
• Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG])*
• Immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG)*
• Precautions history of any immediate allergic reaction to any other vaccine or injectable therapy (i.e., intramuscular, intravenous, or subcutaneous vaccines or therapies not related to a component of mRNA COVID-19 vaccines or polysorbate)

Oxford- Astrazeneca AZD1222

- Uses a replication-deficient chimpanzee adenovirus viral vector that contains the genetic material of the SARS-CoV-2 virus spike protein; After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.
- 20,000 participants enrolled across four clinical trials in the UK (COV001 and COV002), Brazil (COV003) and South Africa (COV005)
- **Interim results (UK and Brazil)** Voysey M et al. *Lancet Dec 2020*
  - vaccine 70.4% (95.8% CI: 54.8% to 80.6%) effective at preventing symptomatic COVID-19 occurring more than 14 days after receiving two doses of the vaccine.
  - No cases of severe infections or hospitalizations in the vaccine group.
  - When vaccine was given as two full doses, vaccine efficacy was 62.1% (n=8,895; CI 41.0% to 75.7%), and 90.0% (n=2,741; CI 67.4% to 97.0%) in participants who received a half dose followed by a full dose.
- **Most participants 18-55, so efficacy for older adults limited**
- Can be stored at regular fridge temperatures
COVID-19 Vaccines: Unanswered Questions

- Primary endpoint in mRNA vaccine trials was *symptomatic* illness, therefore not yet known if these effectively prevent transmission
- Duration of vaccine immunity still unknown
- Long-term safety data will require years of vaccination follow-up
- No data yet on efficacy or safety in children and pregnant women
- < 200 participants/trial developed symptomatic COVID-19, ie, too few to draw conclusions about efficacy in subpopulations
- SARS-CoV-2 genome appears relatively stable, but not known how virus will respond to selection pressure of mass vaccination


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Vaccine distribution strategy in Illinois

• Phase 1 a—c priority groups
  • a) Healthcare personnel and residents from Long-Term care Facilities (LTCF)
  • b) Those aged 65+ & Frontline Essential Workers
  • c) Those persons aged 16-64 years with medical conditions that increase the risk for severe COVID-19 & other essential workers

• Phase 2
  • Possible group- the rest of the population

• Recommendations for groups on which to focus will likely change after vaccine is available, depending on characteristics of each vaccine, vaccine supply, and disease epidemiology.

• Both doses of the vaccine will be with the same vaccine type, produced by the same manufacturer, but not the same lot of the vaccine.

• Work with local pharmacies, LHDs hospitals, mobile units

• Vaccination will be voluntary

Vaccine hesitancy- myths and disinformation

• **Myth:** the process was rush and compromised safety
• **FACT:** the vaccine was studied in thousands of persons over 2 month period, has undergone rigorous review by FDA, CDC, and data published

• **Myth:** People who get vaccinated don’t have to wear masks anymore
• **FACT:** evidence shows that vaccination will prevent people from getting sick but they may still acquire and transmit virus to others

• **Myth:** The vaccine has microchips that allow the government to track people
• **FACT:** No

• **Myth:** More people will die as a result of a negative side effect to the COVID-19 vaccine than would actually die from the virus
• **FACT:** mortality rate from COVID high (much higher than flu), You cannot get COVID-19 infection from the COVID-19 vaccines; they are inactivated vaccines and not live viruses; the vaccine is not all about survival, it protects others too

• **Myth:** COVID-19 vaccines will alter my DNA
• **FACT:** mRNA vaccines work by instructing cells in the body how to make a protein that triggers an immune response. Injecting mRNA into your body will not interact or do anything to the DNA of your cells.
Global Data: Survey of 15 Countries in October 2020

- Online survey of 18,526 adults aged 16-74 yrs
- "If a vaccine for COVID-10 were available, I would get it"
  - In total, 73% agree
  - Overall vaccination intent declined 4% from Aug to Oct

<table>
<thead>
<tr>
<th>Country</th>
<th>Strongly agree</th>
<th>Somewhat agree</th>
<th>Somewhat disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>73%</td>
<td>33%</td>
<td>40%</td>
<td>17%</td>
</tr>
<tr>
<td>India</td>
<td>87%</td>
<td>54%</td>
<td>34%</td>
<td>8%</td>
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<td>China</td>
<td>85%</td>
<td>28%</td>
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<td>South Korea</td>
<td>83%</td>
<td>24%</td>
<td>59%</td>
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<td>Brazil</td>
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<td>Australia</td>
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<tr>
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<td>29%</td>
<td>36%</td>
<td>21%</td>
</tr>
</tbody>
</table>


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Global Data: Reasons for Vaccine Hesitancy

• “Which best describes why you would not take a vaccine for COVID-19?”

• Overall:
  • 67% cite 2 main concerns: side effects and speed of approval process
  • ~ 10% generally against vaccines
  • ~ 8% believe risk of getting COVID-19 is low

The World Economic Forum.
Online survey of 2050 US adults, weighted sample to match US demographics

“How likely are you to get a COVID-19 vaccine as soon as it becomes available?”

In Oct, 58%, on average, likely to take the vaccine, declining from Aug

Black Americans were less likely to say they would get vaccinated

US Data: July to November 2020

• “If an FDA-approved vaccine to prevent COVID-19 was available right now at no cost, would you take it?”

- Online survey of 2985 US adults; weighted sample to match US demographics
- Response was binary yes-no; in Oct, 58% would take the vaccine
- This survey found vaccine intent increased between Sep and Oct


Slide credit: clinicaloptions.com
Conclusions

• COVID-19 isn’t going anywhere soon…..but we know what works to contain it

• There continues to be urgent need for more effective therapies and better diagnostics – we cannot vaccinate our way out of this pandemic

• While it’s good news on the vaccine front we need to ensure that enough vaccines are distributed in a rapid, effective, and equitable way

• And we need to build trust with transparent and informative communication about vaccine safety and efficacy
Thank you and any questions?