COVID-19 Update: Where are we now?

James “Brad” Cutrell, MD FIDSA
Associate Professor of Internal Medicine
Division of Infectious Diseases and Geographic Medicine
UT Southwestern Medical Center
Disclosures

- I have no financial disclosures.
- I served as an unpaid co-investigator for COVID-19 clinical trials from Gilead, Regeneron, and the NIH.
- I will be discussing off-label and emergency use authorized treatments for COVID-19.
Outline

- COVID-19 Epidemiology and Emerging Variants
- COVID-19 Management and Prevention Updates
- COVID-19 Vaccination Updates
COVID-19 in the United States

Vaccinations

<table>
<thead>
<tr>
<th>Age Group</th>
<th>At Least One Dose</th>
<th>Fully Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>77%</td>
<td>65%</td>
</tr>
<tr>
<td>5 and up</td>
<td>82%</td>
<td>70%</td>
</tr>
<tr>
<td>65 and up</td>
<td>95%</td>
<td>89%</td>
</tr>
</tbody>
</table>

New reported cases

- **Cases**: 27,621 (−12%) 79,969,941
- **Tests**: 888,308 (+7%) —
- **Hospitalized**: 17,092 (−33%) —
- **In I.C.U.s**: 2,700 (−40%) —
- **Deaths**: 702 (−44%) 978,387

COVID-19 Variants in the US

United States: 12/19/2021 – 3/26/2022

United States: 3/20/2022 – 3/26/2022 NOWCAST

Regional proportions from specimens collected the week ending 3/26/2022.
US Territories not shown are included in HHS regions:
PR, VI - Region 2
AS, FM, GU, MH, MP, PW - Region 9

Updated March 29, 2022
Omicron Subvariants: BA.1 vs. BA.2

BA.2: More transmissible, similar disease severity and vaccine efficacy to BA.1

<table>
<thead>
<tr>
<th>Feature</th>
<th>BA.1</th>
<th>BA.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission (infectiousness)</td>
<td>Reference</td>
<td>30% higher</td>
</tr>
<tr>
<td>Viral Load</td>
<td>Reference</td>
<td>Nearly 2-fold</td>
</tr>
<tr>
<td>Mutations in Spike</td>
<td>Reference</td>
<td>8 different, not shared</td>
</tr>
<tr>
<td>Neutralizing antibodies median titer</td>
<td>Reference</td>
<td>Lower level, ~70%</td>
</tr>
<tr>
<td>Disease-causing potential (virulence)</td>
<td>Reference</td>
<td>Same, but infects many more people</td>
</tr>
<tr>
<td>2-shot effectiveness vs hospitalizations*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 6 months</td>
<td>63% (95% CI 47.75)</td>
<td>69% (95% CI 27.87)</td>
</tr>
<tr>
<td>Past 6 months</td>
<td>32% (95% CI 11.49)</td>
<td>50% (95% CI 7.73)</td>
</tr>
<tr>
<td>3-shot effectiveness vs hospitalizations*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 70-days</td>
<td>81% (95% CI 75.85)</td>
<td>83% (95% CI 71.91)</td>
</tr>
<tr>
<td>Past 70-days</td>
<td>73% (95% CI 65.79)</td>
<td>70% (95% CI 50.82)</td>
</tr>
</tbody>
</table>

*Data from UKHSA March 24 report using Emergence Care dataset, includes "for" and "with" Covid so under-estimates effectiveness.
Outline

- COVID-19 Epidemiology and Emerging Variants
- COVID-19 Management and Prevention Updates
- COVID-19 Vaccination Updates
# COVID-19 Disease Severity Classification

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Clinical Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic COVID-19</td>
<td>Viral replication without symptoms</td>
</tr>
<tr>
<td>Mild COVID-19</td>
<td>Symptomatic, no hypoxia or signs of PNA, no ongoing medical care</td>
</tr>
<tr>
<td>Moderate COVID-19</td>
<td>Symptomatic, signs of PNA or ongoing medical care <strong>but no hypoxia at rest</strong> (O₂ ≥ 94% on room air)</td>
</tr>
<tr>
<td>Severe COVID-19</td>
<td><strong>Hypoxic at rest</strong> (O₂ &lt; 94% on room air), RR &gt; 30, P/F ratio &lt; 300, &gt;50% lung infiltrates; some subdivide between low-flow vs. high-flow O₂/NIV</td>
</tr>
<tr>
<td>Critical COVID-19</td>
<td>ARDS or septic shock; requiring Mechanical ventilation or ECMO</td>
</tr>
</tbody>
</table>

Must pay attention to trial methods because some define these categories differently, particularly severe disease.
COVID-19 Therapeutics: Where are we now?

EY Bae, et al. *Curr Infect Dis Reports* 2021
Antivirals

- Agents directly targeting SARS-CoV-2 replication
- Likely work best in early viral phase or as prophylaxis
- Example Agents
  - Remdesivir (RDV)
  - Nirmatrelvir/ritonavir (Paxlovid)
  - Molnupiravir
Updated Remdesivir Meta-Analysis

- Updated RDV meta-analysis including 8 RCTs (latest CATCO trial), 9157 patients

- Risk ratio for mortality based on baseline oxygen needs:
  - MV: 1.19 (0.98-1.44)
  - On O₂: 0.83 (0.73-0.95)
  - No O₂: 0.71 (0.42-1.22)


*Excludes patients already included in SOLIDARITY (NEJM 2020)
Outpatient Short-course Remdesivir

- PINETREE trial: High-risk symptomatic outpatients ≤ 7 days of symptom onset received 3 days of RDV
- Inclusion: ≥ 60 years old or at least one high risk factor
- Exclusion: Vaccinated, Requiring O₂ or hospitalization
- 562 patient enrolled; Mean age 50, median sx duration 5 days; 62% DM2, 55% Obesity, 58% HTN, 4% immune compromised
- Primary outcome: Risk of hospitalization or death due to COVID-19 was 87% lower in RDV group
- Similar rate of ADEs in RDV and Placebo groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RDV group</th>
<th>Placebo group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 hospitalization or death, day 28</td>
<td>2 (0.7%)</td>
<td>15 (5.3%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Any death, day 28</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Any hospitalization, day 28</td>
<td>5 (1.8%)</td>
<td>18 (6.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Applying the Evidence: Remdesivir

- Best evidence in patients with severe COVID-19 but not intubated (low flow $O_2 >$ high flow or noninvasive ventilation); no clear benefit in critical disease (mechanical ventilation)

- Compelling data in very early outpatient use but logistically challenging

- Modest clinical benefit, may reduce mortality in those on $O_2$

- Practical considerations with RDV:
  - Default duration 5 d, might extend in MV/ECMO
  - Monitor LFTs daily, stop for ALT/AST $>10x$ upper limit of normal
  - Limited data in CKD (GFR $<30$), however, can be used if benefit outweighs risk$^1$
  - FDA-approved for COVID-19 hospitalized adults/teens, kids ($<12$ or $<40$ kg) via EUA

COVID-19 Oral Antivirals

- Two new EUA oral antivirals: Nirmatrelvir/ritonavir (Paxlovid) and Molnupiravir
- Demonstrated reduction in hospitalization in high-risk outpatients (89% for Paxlovid, ~30% for Molnupiravir)
- Approved for outpatient treatment of symptomatic patients with mild to moderate disease within 5 days of symptom onset
- Not approved for hospitalized patients
- Watch many drug-drug interactions with Paxlovid!
- Molnupiravir contraindication in pregnancy or caution in those trying to conceive

Liverpool COVID-19 Drug Interaction Checker

UK Liverpool COVID-19 Drug Interactions https://www.covid19-druginteractions.org/checker
Immune System Mimics

▪ Agents mimic the immune system’s response to SARS-CoV-2
▪ Likely work best early prior to body’s own immune response or as prophylaxis
▪ Example Agents
  – SARS-CoV-2 Monoclonal Antibodies
  – Convalescent Plasma
SARS-CoV-2 Monoclonal Ab

- 4 Monoclonal Ab with EUA for mild to moderate COVID-19 in high-risk outpatients < 7 days from symptom onset
- NOT currently approved for patients hospitalized due to COVID-19 (but can be used if hospitalized for non-COVID-19 and meets EUA criteria)

<table>
<thead>
<tr>
<th>EUA Mab</th>
<th>Clinical Efficacy</th>
<th>Predicted Efficacy against variants</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bamlanivimab/etesevimab</td>
<td>70% RRR in hospitalization or death (2% vs. 7%)</td>
<td>Significant reduction for Delta, Gamma, and Omicron</td>
<td>No longer in use due to Omicron</td>
</tr>
<tr>
<td>Casirivimab/imdevimab</td>
<td>71% RRR in hospitalization or death (1.3% vs. 4.6%)</td>
<td>Significant reduction for Omicron</td>
<td>No longer in use due to Omicron</td>
</tr>
<tr>
<td>Sotrovimab</td>
<td>85% RRR in hospitalization or death (1% vs. 7%)</td>
<td>Significant reduction for Omicron BA.2 subvariant</td>
<td>Recommended by NIH (AIIa); distribution paused in some states</td>
</tr>
<tr>
<td>Bebtelovimab</td>
<td>More limited clinical efficacy data from phase 2 study</td>
<td>Retains in vitro activity for circulating Omicron variants</td>
<td>Recommended by NIH if others not available (CIII)</td>
</tr>
</tbody>
</table>

SARS-CoV-2 Mab Prophylaxis: Evusheld

- Two long-acting Mab (tixagevimab/cligavimab) with extended half-life up to 12 months protection
- EUA for prophylaxis in moderate/severe immunocompromised pts or those unable to be vaccinated
- PROVENT phase 3 prophylaxis trial: 5,197 participants (2:1 randomization), 75% with high-risk comorbidities, single 300 mg IM injection or saline IM placebo
- Recommended dose increased to 600 mg due to Omicron variants

<table>
<thead>
<tr>
<th></th>
<th>AZD 7442 Arm</th>
<th>Placebo Arm</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic PCR + disease</td>
<td>8</td>
<td>17</td>
<td>77% (95% CI: 46%-90%)</td>
</tr>
<tr>
<td>Severe disease</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
RCT of high-titer convalescent plasma in outpatient COVID-19 ≤ 8 days from sx onset

Pre-Omicron era, 1225 enrolled, > 80% unvaccinated

Primary outcome: 54% RRR in risk of hospitalization with CP (2.9% vs 6.3%; p=0.005)

Take-home message: Early, high-titer CP may have a role in outpatient COVID-19, particularly in unvaccinated or immunocompromised
Immunomodulators

- Agents dampen the host immune and inflammatory response to SARS-CoV-2
- Likely work best during host inflammatory phase or possibly in combination with antiviral agents
- Example Agents
  - Corticosteroids
  - Cytokine Inhibitors (e.g. IL-6)
  - JAK Pathway Inhibitors (e.g. baricitinib)
Corticosteroids: RECOVERY Trial

- Open-label, adaptive COVID-19 trial in UK
- Dexamethasone 6 mg daily up to 10d (N=2104) vs. Usual Care (N=4321)
- 28 day Mortality Rate Ratios:
  - Overall: 0.83
  - On MV: 0.64 (Absolute RR ≅ 12%)
  - On O₂: 0.82 (Absolute RR ≅ 3%)
  - No O₂: 1.19

Applying the Evidence: Corticosteroids

- Strongest data for critically ill COVID-19
  - Give to all unless clear contraindication; optimal dosing less clear
  - Dexamethasone or IV methylprednisolone (2 mg/kg x 5 days, then taper for total of 10 days)

- Strong data for severe COVID-19 on O₂ (RECOVERY)
  - Give to most unless clear contraindication, usually combined with antiviral

- Do NOT use systemic steroids in those who are outpatient or not on O₂

- Small trial supporting inhaled budesonide 800 mg BID in symptomatic outpatients
Applying the Evidence: IL-6 and JAK inhibition

- Both IL-6 receptor and JAK inhibitors have shown mortality benefit in addition to standard of care (corticosteroids +/- remdesivir)

- How to use and who is the right patient population?
  - IL-6R antagonists: Tocilizumab, weight-based dosing, single dose
  - Use in those progressing to higher $O_2$ or intubation (< 24h) despite steroids, especially if CRP > 75
  - JAK Inhibitors (baricitinib): 4 mg PO daily up to 14d, dose reduce in CKD
  - Can use either as alternative if steroids contraindicated OR in addition to steroids in those progressing to higher $O_2$ or mechanical ventilation

### COVID-19 Anticoagulation (NIH Guidelines)

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Therapeutic Dose Anticoagulation (LMWH preferred)</th>
<th>Prophylactic Dose Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically suspected or diagnosed VTE/PE (AI)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Hospitalized nonpregnant patients on low-flow O(_2) AND D-Dimer &gt; ULN*(CIIa)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Hospitalized patients requiring ICU level care or high-flow O(_2)/NIV (AI)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>All other hospitalized patients (including all pregnant patients) (BIII)</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

* Contraindications to therapeutic anticoagulation include: Platelets < 50k, Hgb < 8 mg/dL, Need for dual antiplatelet, ED visit or hospitalization for major bleeding in last 30 days, Inherited or known history of bleeding disorder.

What is NOT currently recommended

▪ Routine bacterial antibiotics
▪ Hydroxychloroquine
▪ HIV protease inhibitors
▪ Ivermectin
▪ Colchicine
▪ IVIG
▪ Azithromycin (for COVID-19)
▪ Zinc, Vitamin C, Vitamin D (for COVID-19)

Case #1

- 45 year old male with PMHx of NYHA III CHF, obesity, DM type 2 contacts the clinic with 2 days of fevers, cough, fatigue. His home pulsox is reading 96% on room air. He received 2 doses of Moderna vaccine in May. He had a prolonged exposure to a family friend last week who is now COVID+. What do you recommend?

- Immediate COVID-19 rapid Ag +/- PCR testing, Isolation

- Counsel and strongly recommend one of the following:
  - Monoclonal Ab treatment (Bebtelovimab or Sotrovimab)
  - Oral nirmatrelvir/ritonavir (Paxlovid)
  - Outpatient IV Remdesivir x 3 days
Key Pearls: Prioritize early outpatient therapy in high risk patients; **Every high risk patient should have Mab action plan**

- Selling Point: 70-85% reduction in risk of hospitalization or death
- Oral nirmatrelvir/ritonavir also a good option if within 5 days of symptoms and no drug-drug interactions
- IV Remdesivir x 3 days also a choice but outpatient logistics more challenging

**Mab EUA Criteria:**
- Sx onset < 7 days
- Not hospitalized due to COVID
- No new or ↑ oxygen
- “High risk for progression”

**Mab High Risk Criteria:**
- Age > 65
- BMI > 25
- DM, CKD, Chronic heart/lung dz
- Immunosuppressed
- Others....
Case #2

- 63 year old male with PMHx of obesity, COPD, HTN admitted with 6 days of fevers, HA, rhinorrhea, SOB. He was unvaccinated. COVID-19 PCR positive on admission, CXR shows bilateral interstitial infiltrates. O$_2$ sat 94% on 3L NC. LFTs 2x ULN. CRP 25 mg/L. **What do you recommend?**
- Dexamethasone 6 mg daily up to 10 days plus IV Remdesivir x 5 days
- At least ppx anticoagulation, possibly therapeutic
- Trend O$_2$ sats, LFTs, D-dimer, CRP
- No antibacterial antibiotics; Awake proning
Case #2: Severe COVID-19 on low flow O2

Key Pearls:

- Dexamethasone and Remdesivir mainstay of Rx
- Secondary bacterial infection rare, no abx needed in most cases
- Assess anticoagulation level based on bleeding risk
- Awake proning may benefit, no cost intervention
- Trend O2, LFTs, D-dimer and CRP
- If O2 needs progressing rapidly, can consider adding baricitinib or tocilizumab
- Cannot use Mab via EUA but can consider compassionate use if Ab negative
Outline

- COVID-19 Epidemiology and Emerging Variants
- COVID-19 Management and Prevention Updates
- COVID-19 Vaccination Updates

Prospective UK cohort of > 35,000 HCWs from Dec 2020-Sept 2021 (pre-Omicron)

Robust vaccine immune protection against infection (esp. mRNA) that wanes > 6 months

Robust infection-induced immune protection that is further boosted with vaccination
## COVID-19 Vaccination Schedule*

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>0 month</th>
<th>1 month</th>
<th>2 month</th>
<th>3 month</th>
<th>4 month</th>
<th>5 month</th>
<th>6 month</th>
<th>7 month</th>
<th>8 month</th>
<th>9 month</th>
<th>10 month</th>
<th>11 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Booster Dose² (at least 5 months after 2ⁿ Booster Dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ages 5-11 years)</td>
<td>Booster Dose¹ (3 weeks after 1ⁿ dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfizer-BioNTech</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Booster Dose² (at least 5 months after 2ⁿ Booster Dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ages 12 years and older)</td>
<td>1ⁿ Dose</td>
<td>2ⁿ Dose (3-8 weeks after 1ⁿ dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderna</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Booster Dose¹ (at least 5 months after 2ⁿ Booster Dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ages 18 years and older)</td>
<td>1ⁿ Dose</td>
<td>2ⁿ Dose¹ (4-8 weeks after 1ⁿ dose)</td>
<td>Booster Dose¹ (at least 5 months after 2ⁿ Booster Dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janssen</td>
<td>1ⁿ Dose</td>
<td>Booster Dose¹ (at least 2 months after 1ⁿ dose)</td>
<td>2ⁿ Booster Dose³ (See footnote)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ages 18 years and older)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Timeline is approximate. Intervals of 3 months or fewer are converted into weeks per the formula “1 month = 4 weeks.” Intervals of 4 months or more are converted into calendar months.

---

2ⁿ Booster Dose now an option for those ≥ 50 years old

- Greatest likely benefit in those ≥ 65 years old or with chronic medical conditions
- Those with recent Omicron infection can likely delay booster shot

---

CDC Vaccine clinical considerations [https://www.cdc.gov/vaccines/covid-19/index.html](https://www.cdc.gov/vaccines/covid-19/index.html)
michigan dhhs [https://www.michigan.gov/coronavirus/0,9753,7-406-98178_103214---,00.html](https://www.michigan.gov/coronavirus/0,9753,7-406-98178_103214---,00.html)
## COVID-19 Vaccination Schedule

For Those who are Moderately or Severely Immunocompromised

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>0 month</th>
<th>1 month</th>
<th>2 month</th>
<th>3 month</th>
<th>4 month</th>
<th>5 month</th>
<th>6 month</th>
<th>7 month</th>
<th>8 month</th>
<th>9 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech (ages 5-11 years)</td>
<td>1st Dose</td>
<td>2nd Dose</td>
<td>3rd Dose</td>
<td>Booster Dose¹</td>
<td>2nd Booster Dose³ (See footnote)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ages 12 years and older)</td>
<td>1st Dose</td>
<td>2nd Dose</td>
<td>3rd Dose</td>
<td>Booster Dose¹</td>
<td>2nd Booster Dose³ (See footnote)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderna (ages 18 years and older)</td>
<td>1st Dose</td>
<td>2nd Dose</td>
<td>3rd Dose</td>
<td>Booster Dose¹</td>
<td>2nd Booster Dose³ (See footnote)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janssen (ages 18 years and older)</td>
<td>1st Dose</td>
<td>2nd (Additional) Dose² using an mRNA COVID-19 Vaccine (at least 4 weeks after 1st dose)</td>
<td>Booster Dose¹</td>
<td>2nd Booster Dose³ (See footnote)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Timeline is approximate. Intervals of 3 months or fewer are converted into weeks per the formula “1 month = 4 weeks.” Intervals of 4 months or more are converted into calendar months.

CDC Vaccine clinical considerations: [https://www.cdc.gov/vaccines/covid-19/index.html](https://www.cdc.gov/vaccines/covid-19/index.html)

Michigan DHHS: [https://www.michigan.gov/coronavirus/0,9753,7-406-98178_103214--,00.html](https://www.michigan.gov/coronavirus/0,9753,7-406-98178_103214--,00.html)
Conclusions

- Cases and hospitalizations are currently at nadir after Omicron surge but likely to see a new wave in the summer due to new variants, waning immunity

- Outpatient therapies focus on early initiation of oral antivirals, Mabs, or short course IV Remdesivir (if available)

- Cornerstone of inpatient treatment for those with severe disease (on O2) remains IV remdesivir plus steroids (+/- other immunomodulators)

- Vaccine recommendations on boosters continue to evolve with changing science and new variants
Questions?

Winning shot.
Let’s get the vaccine.

utswmed.org/taketheshot
4th Dose COVID-19 Booster: Israel Clalit Health

Pre-print retrospective cohort of > 560k patients > 60 yo in large Israeli Health System

Mortality Reduction at Clalit Health for Initial Booster and Second Booster

3rd shot vs 2 shots, age 50+
90% Reduction

4th shot vs 3-shots, age 60+
78% Reduction

Eric Topol Substack https://erictopol.substack.com/p/a-new-wave-and-a-new-booster?s=r
Largest and most rigorous RCT of early ivermectin treatment in COVID-19 showed no benefit in reducing disease progression.

**METHODS**
We conducted a double-blind, randomized, placebo-controlled, adaptive platform trial involving symptomatic SARS-CoV-2-positive adults recruited from 12 public health clinics in Brazil. Patients who had had symptoms of Covid-19 for up to 7 days and had at least one risk factor for disease progression were randomly assigned to receive ivermectin (400 µg per kilogram of body weight) once daily for 3 days or placebo. (The trial also involved other interventions that are not reported here.) The primary composite outcome was hospitalization due to Covid-19 within 28 days after randomization or an emergency department visit due to clinical worsening of Covid-19 (defined as the participant remaining under observation for >6 hours) within 28 days after randomization.

**RESULTS**
A total of 3515 patients were randomly assigned to receive ivermectin (679 patients), placebo (679), or another intervention (2157). Overall, 100 patients (14.7%) in the ivermectin group had a primary-outcome event, as compared with 111 (16.3%) in the placebo group (relative risk, 0.90; 95% Bayesian credible interval, 0.70 to 1.16). Of the 211 primary-outcome events, 171 (81.0%) were hospital admissions. Findings were similar to the primary analysis in a modified intention-to-treat analysis that included only patients who received at least one dose of ivermectin or placebo (relative risk, 0.89; 95% Bayesian credible interval, 0.69 to 1.15) and in a per-protocol analysis that included only patients who reported 100% adherence to the assigned regimen (relative risk, 0.94; 95% Bayesian credible interval, 0.67 to 1.35). There were no significant effects of ivermectin use on secondary outcomes or adverse events.

**CONCLUSIONS**
Treatment with ivermectin did not result in a lower incidence of medical admission to a hospital due to progression of Covid-19 or of prolonged emergency department observation among outpatients with an early diagnosis of Covid-19. (Funded by FastGrants and the Rainwater Charitable Foundation; TOGETHER ClinicalTrials.gov identifier NCT04369054.)
Figure 1: Algorithm for Inpatient Use of Remdesivir and Monoclonal Antibodies

- Supportive care and isolation
- May consider other therapies targeted at inflammatory phase of COVID-19 if appropriate
- Exceptions may be discussed with SWAT for approval

Criteria for Inpatient Remdesivir and Monoclonal Ab Therapy: (Should meet ALL Criteria)
- Positive SARS-CoV-2 test ≤ 10 days
- Symptom onset ≤ 10 days (if present and known)

Assess for symptoms related to COVID-19 and oxygen status

Yes

- Symptomatic from COVID-19 AND
  - Not requiring supplemental oxygen or SpO2 > 94% on room air
  - One of the following:
    1. Moderate to severely immunocompromised†
    2. ≥ 3 risk factors for severe disease§

- Symptomatic from COVID-19 AND
  - Requiring supplemental oxygen at screening or SpO2 ≤ 94% on room air

Exclusions: Mechanical ventilation > 24 hours or currently on ECMO; enrolled in clinical trial with remdesivir for COVID-19

- Can consider either:
  1. Remdesivir for 3 days or until discharge, whichever is first OR
  2. Monoclonal Ab (symptom onset ≤ 7 days)

- Recommend remdesivir for 5 days or until ready for discharge, whichever is first
  - May request SWAT approval for extended duration if protracted clinical response or on MV/ECMO

- Asymptomatic from COVID-19 ("incidental COVID-19")
  - Not candidate for remdesivir or monoclonal Ab based on lack of symptoms
  - Monitor for development of symptoms related to COVID-19 and re-evaluate for Rx if develop

- Monitor for progression to require O2
- Exceptions may be discussed with SWAT for approval

UTSW Inpatient RDV and Mab Algorithm

UTSW SWAT COVID-19 Inpatient Guidance (as of 3/31/22)

---

†Moderate to severely immunocompromised per CDC definitions [https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html]

§Risk factors for severe disease: Unvaccinated, Age ≥ 65, DM2, Obesity (BMI > 30), and Chronic cardiac, pulmonary, renal, neurologic or liver disease
Figure 1. Recommended Treatment Approach for Non-Hospitalized Patients with COVID-19

Criteria for Outpatient COVID-19 Rx (must meet ALL criteria):
- Symptomatic and within 7-10 days of symptom onset
- Not requiring O₂ or no worsening baseline O₂ needs
- Not requiring hospitalization for COVID-19
- Unvaccinated and/or risk factors for progression to severe disease¹
- Those who are unvaccinated, immunocompromised, age ≥ 65 and/or have multiple risk factors for progression are most likely to benefit from specific outpatient Rx

Yes

SARS-CoV-2 variant by PCR genotyping if available

Omicron BA.2 variant or unknown variant status

Moderate to Severe Immunosuppression² OR Pregnancy OR severe renal (eGFR < 30) or hepatic dysfunction (CTP class C):
- Bebtelovimab Mab Rx (if within 7 days of symptom onset)

If Bebtelovimab unavailable:
- Assess drug-drug interactions and consider Paxlovid (nirmatrelvir/RTV)
- If Paxlovid unavailable or contraindicated: may consider alternatives (see Table 1) if < 5-7 days from symptom onset
- Follow-up variant genotype if pending

UTSouthwestern
Medical Center


UTSW SWAT COVID-19 Outpatient Guidance (as of 3/31/22)