COVID-19 Review

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Medical Director, Antimicrobial Stewardship
Disclosures

• I have a commercial relationship with the following:
  • Advisory Relationship with: Gilead (December 2020...not ongoing

• Member of the Board of Scientific Counselors to the Office of Infectious Diseases at CDC

• Huge thank you to Dr. Hannah Imlay for providing many of these slides.
Outline

• SARS COV2 Virology/Transmission/ Epidemiology
• Tools at our disposal for prevention
• Current status of outpatient treatment
• The next few years
COVID-19 pandemic

• In the US:
  • Deaths: 986,042
  • Cases: 80,440,151

https://covid.cdc.gov/covid-data-tracker/
Accessed 4/18/2022
Utah Data

COVID-19 Case Counts by Report Date

COVID-19 Hospitalizations by Admission Date

https://coronavirus.utah.gov/case-counts/
Virology

• Betacoronaviruses (RNA viruses)
• ACE-2 receptor binding by spike protein (RBD)
• Variants picked up by genomic surveillance systems
  • VOC is variant with evidence of increased transmissibility, severity, immune escape, or diagnostic detection failures
• Omicron
  • Replication advantage
  • Immune escape
  • MildER illness

Transmission

• Droplet vs contact
• Airborne vs droplet (6 ft)
  • Experimental vs epidemiologic studies
  • Barrier protection acting on airflow dynamics
• Rarely dichotomous
• Relative likelihoods of different routes of transmission
• Role of viral load?
Epidemiology

• ~1/3 of infections asymptomatic
  • Some pre-symptomatic
  • May still have subclinical findings

• Infection fatality rate ~1%

• Incubation period 14 days, peak in first 4-5 days (Omicron ~3)

• Protracted PCR pos
  • Inc w age, immunocompromise, and severity of illness.

• Infectious before sx, then 7-10 days
  • Most infectious early in the course

Oran et al Ann Int Med 2021
Levin et al Eur J Epidemiol 2020
Age strongly associated with severity

Data from 67,491,250 cases. Age group was available for 66,731,575 (98%) cases.

Data from 847,047 deaths. Age group was available for 846,693 (99%) deaths.

Infection fatality rates:
- 0.002% at age 10
- 0.01% at age 25
- 0.4% at age 55
- 1.4% at age 65
- 4.6% at age 75
- 15% at age 85
- >25% at age ≥90

https://covid.cdc.gov/covid-data-tracker/#demographics
Levin et al Eur J Epidemiol 2020
Current Variants of Concern

HHS Region 8: 1/2/2022 – 4/9/2022

Region 8 - Colorado, Montana, North Dakota, South Dakota, Utah, and Wyoming

<table>
<thead>
<tr>
<th>WHO label</th>
<th>Lineage #</th>
<th>US Class</th>
<th>%Total</th>
<th>95%PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omicron</td>
<td>B.1.1.529</td>
<td>VOC</td>
<td>76.4%</td>
<td>71.5-80.6%</td>
</tr>
<tr>
<td></td>
<td>B.1.1.529</td>
<td>VOC</td>
<td>23.6%</td>
<td>19.4-28.5%</td>
</tr>
<tr>
<td>Delta</td>
<td>B.1.617.2</td>
<td>VOC</td>
<td>0.0%</td>
<td>0.0-0.0%</td>
</tr>
<tr>
<td>Other</td>
<td>Other*</td>
<td>0.0%</td>
<td>0.0-0.0%</td>
<td></td>
</tr>
</tbody>
</table>

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other*" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates.
# AY.1, AY.133 and their sublineages are aggregated with B.1.617.2, BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. For regional data, BA.1.1 and its sublineages are also aggregated with B.1.1.529, as they currently cannot be reliably called in each region.

https://covid.cdc.gov/covid-data-tracker/#variant-proportions
BA.2 and Severity

- Differs by 40 mutations
- Replication advantage over BA.1
- Unpublished studies suggest more transmissible
- Vaccine efficacy appears similar to BA.1
- Limited data suggest no increased risk of hospitalization
“Long COVID” – estimate how many

• Post acute sequelae of SARS CoV2 infection (PASC)
• Acute COVID: symptoms up to 4 weeks following onset
• Post-COVID: broad range of symptoms that continue for ≥2 months and are otherwise unexplained
  • Fatigue
  • Dyspnea
  • Chest discomfort
  • Cough
  • Anosmia
  • Psychologic/neurocognitive
  30-40% of adults
• Unrelated to active viral replication

Davis et al. EClinical Medicine, 2021.
Logue et al. JAMA Network Open, 2021
## COVID strategies

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Early Outpatient</th>
<th>Late/Inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masking VACCINES</td>
<td>Monoclonal Abs</td>
<td>Remdesivir</td>
</tr>
<tr>
<td>Evusheld (pre-exposure)</td>
<td>• Casirivimab-imdevimab</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>• Remdesivir</td>
<td></td>
</tr>
</tbody>
</table>
Where do you still wear a well-fitting mask outside of work?

A. In grocery stores and restaurants.
B. Inside other people’s homes for social gatherings.
C. All social gatherings even if held outdoors.
D. A and B.
E. B and C.
F. All of the above.
## Vaccination

<table>
<thead>
<tr>
<th>Vaccine (age of authorization/approval)</th>
<th>Type</th>
<th>Doses</th>
<th>Prevents any COVID?</th>
<th>Prevents severe COVID?</th>
<th>Prevents mortality?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer BioNTech (5+)</td>
<td>mRNA</td>
<td>2</td>
<td>95%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Moderna (18+)</td>
<td>mRNA</td>
<td>2</td>
<td>94%</td>
<td>95%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100%</td>
</tr>
<tr>
<td>Johnson+Johnson (18+)</td>
<td>Adenovirus vector</td>
<td>1</td>
<td>67%</td>
<td>85%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reported in adult trial population (16+)
Well tolerated

<table>
<thead>
<tr>
<th>mRNA vaccination</th>
<th>J+J vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>(per million doses)</td>
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</tr>
<tr>
<td>Anaphylaxis</td>
<td>Thrombosis with thrombocytopenia</td>
</tr>
<tr>
<td>3-5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>10 (women 30-49)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Guillain Barre Syndrome</td>
</tr>
<tr>
<td>50-100 (males 12-24)</td>
<td>5-10</td>
</tr>
</tbody>
</table>
## Waning vaccine efficacy

<table>
<thead>
<tr>
<th>ED/UC encounters</th>
<th>Delta</th>
<th>Omicron</th>
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<tbody>
<tr>
<td>2 doses &lt;2 months</td>
<td>92</td>
<td>69</td>
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<td>48</td>
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<td>97</td>
<td>87</td>
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<td>89</td>
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<table>
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<tr>
<th>Hospitalizations</th>
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People who may not respond to vaccination

Caveat: “response” means humoral immunity (anti RBD or anti spike Ab)
- Kinetics to antibody responses
- Assay variability
- Role of T cell immunity
**Adult COVID-19 Vaccine Schedules and Doses**

### Initial series

**Pfizer-BioNTech**
- ≥ 12 yo: 0.3 mL x 2 doses 21 days apart
- 5-11 yo: 0.2 mL x 2 doses 21 days apart

**Moderna**
- 0.5 mL x 2 doses 28 days apart
- ≥ 18 yo

**Janssen (J&J)**
- 0.5 mL single dose
- ≥ 18 yo

### Additional dose

**Pfizer-BioNTech**: 0.3 mL
- ≥ 5 yo
- Mod-severe immunocompromised

**Moderna**: 0.5 mL
- ≥ 18 yo
- Mod-severe immunocompromised

### Booster dose

**Pfizer-BioNTech**: 0.3 mL
- ≥ 12 yo

**Moderna**: 0.25 mL
- ≥ 18 yo

**Janssen (0.5 mL) or Pfizer (0.3 mL) or Moderna (0.5 mL)**
- ≥ 18 yo

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*a Adapted from Dr. Monica Mahoney, PharmD. Current as of 2.8.22

*b Among HSCT, CAR-T, and recipients of B cell depleting therapies (e.g., rituximab, alemtuzumab) who were vaccinated prior to or during treatment, it is recommended to re-vaccinate for the doses received before or during treatment. Re-vaccination could be considered once immune competence is regained for people who received COVID vaccine doses during chemotherapy or radiation treatment based on provider discretion.

*c On a case-by-case basis, mod-severe immunocompromised patients may receive mRNA vaccines outside of the recommended dosing intervals based on clinical judgment.

*d Can mix and match booster dose in eligible patients following primary series with a different vaccine type.
2nd Booster

• > 12 yo and moderately or severely immunocompromised
• Anyone ≥ 50 yo eligible at least 4 months after 1st booster
• “May choose to receive...”
Waning vaccine efficacy

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Ferdinands et al. MMWR, 2022
2nd Booster

• Comparison in Israel of those ≥ 60 yo with and without 2nd booster during Omicron
• 2-fold reduction in confirmed infection
• 3.5-fold reduction in severe disease
• Overall risk of severe disease or death low
• Short follow-up period (40 – 60 days)
• Unmeasured confounders?

*Individual risk reduction may be low and short-lived. Decision depends on individual preferences, individual risk for severe disease and risk of exposure (e.g. occupation).*
Evusheld: tixagevimab and cilgavimab

• **Prevention** of SARS CoV acquisition

• Monoclonal Abs bind to distinct, non-overlapping sites on the receptor binding domain -> block viral binding to ACE 2
  • Passive humoral protection

• Given as two intramuscular gluteal shots
PROVENT trial: tixagevimab/cilgavimab (Evusheld)

• Enrolled: ≥60 yo, high-risk of severe disease, or increased risk of SARS CoV2 infection because of living/work situation
  • <5% immunocompromised
• No known prior or current covid, unvaccinated
• 83% risk reduction at 6 months
  • 11/3,441 (0.3%) Evusheld vs 31/1,731 (1.8%) placebo

https://www.fda.gov/media/154701/download
Niche among high risk for vaccine breakthrough

• Patients ≥12 yo and ≥40kg who are **not currently infected** with SARS-CoV-2 and who have **not had a known recent exposure** to an individual infected with SARS-CoV-2 AND
  • Who have **moderate to severe immune compromise** due to a medical condition or medications or treatments and may not mount an adequate immune response to COVID-19 vaccination OR
  • For whom vaccination with any available COVID-19 vaccine...is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID19 vaccine component(s)

Lower neutralization with Omicron -> dose doubled to 300mg of each mAb
## COVID strategies

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</table>
Management of Covid-19 According to Disease Stage or Severity

<table>
<thead>
<tr>
<th>Features</th>
<th>Asymptomatic or Presymptomatic</th>
<th>Mild Illness</th>
<th>Moderate Illness</th>
<th>Severe Illness</th>
<th>Critical Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive SARS-CoV-2 test; no symptoms</td>
<td>Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea</td>
<td>Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%</td>
<td>Oxygen saturation &lt;94%; respiratory rate ≥30 breaths/min; lung infiltrates &gt;50%</td>
<td>Respiratory failure, shock, and multiorgan dysfunction or failure</td>
</tr>
</tbody>
</table>

Proposed Disease Pathogenesis
- Viral replication
- Inflammation

Potential Treatment
- Antiviral therapy
- Antibody therapy
- Antiinflammatory therapy

Mechanism of action

- Monoclonal antibodies: block binding to ACE2 receptor
- Paxlovid: protease inhibitor
- Molnupiravir: inhibits replication by lethal mutagenesis
- Remdesivir: inhibits replication by chain termination

https://www.science.org/content/article/pfizer-antiviral-slashes-covid-19-hospitalizations
Monoclonal Antibodies (mAbs)

• All are antibodies targeting the receptor binding domain of the spike protein of SARS-CoV2 -> neutralize virus early in illness

• 4 available:
  • Casirivimab-imdevimab (made by Regeneron)
  • Bamlanivimab-etesevimab (Lilly)
  • Sotrovimab (GSK/Vir biotechnology)
  • Bebtelovimab (AbCellera and Lilly)

• Multiple RCTs show 2-6% absolute risk reduction in COVID-19-related hospitalizations or all-cause deaths with monoclonal Ab vs. placebo
  • Early in disease course, among outpatients
  • 70 – 85% relative risk reduction
### RCT data: significant risk reduction in hospitalization/mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patient population</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Weinreich et al\(^a\) | RCT of casirivimab-imdevimab (2400 vs 1200mg) vs placebo (n=4057) | • Outpatients with symptomatic COVID  
  • ≤7 days of symptoms  
  • ≥1 risk factor for severe COVID | • **70% relative risk reduction** of COVID-related hospitalization or all cause mortality (1-2% vs 3-4%, p<0.01)*  
  • Median time to resolution of symptoms was 4 days shorter in mAb group (10 vs 14 days; p<0.0001)  
  • No adverse safety signals |
|                   | **Expanded use authorization (EUA) granted** |                                                                                   |                                                                         |
| Gupta et al\(^b\)  | RCT of sotrovimab vs placebo (n=583)         | • Outpatients with symptomatic COVID  
  • ≤5 days of symptoms  
  • ≥1 risk factor for severe COVID | • **85% relative risk reduction** of hospitalization or mortality (p=0.002), 3/291 (1%) in sotrovimab grp vs 21/292 (7%) in placebo  
  • All five patients admitted to intensive care received placebo  
  • No adverse safety signals |
|                   | **EUA granted**                             |                                                                                   |                                                                         |
| Dougan et al\(^c\) | RCT of bamlanivimab-etesevimab vs placebo (n=1035) | • Outpatients with symptomatic COVID  
  • ≤3 days after positive test  
  • ≥1 risk factor for severe COVID | • **70% relative risk reduction** of COVID-related hospitalization or all cause mortality (11/518 (2%) in mAb grp vs 36/517 (7%) in placebo, p<0.001)  
  • No deaths occurred in the mAb group vs 10 deaths in placebo group, 9 of which were designated by the trial investigators as Covid-19–related.  
  • No adverse safety signals |
|                   | **EUA granted**                             |                                                                                   |                                                                         |

*Results were reported separately for each dose; but similar amount of benefit shown with either dosing strategy

\(^a\)NEJM, 2021. DOI: 10.1056/NEJMoa2108163  
\(^b\)NEJM, 2021.DOI: 10.1056/NEJMoa2107934  
\(^c\)NEJM, 2021. DOI: 10.1056/NEJMoa2102685
Nirmatrelvir/ritonavir (Paxlovid)

• Nirmatrelvir (Mpro inhibitor) packaged with ritonavir
  • Inhibits CYP3A-mediated metabolism -> boosted concentrations of nirmatrelvir
  • Many drug-drug interactions

• FDA EUA: “treatment of mild-moderate COVID-19 among patients ≥12 years old at high risk for progression to severe COVID-19”
  • Not for those requiring hospitalization because of severe COVID
  • Not pre- or post-exposure prophylaxis
  • Only can be used for 5 days
EPIC-HR

- Adults ≥18 years old with ≥1 risk factor for progression to severe disease
  - BMI >25, ≥60 years old
  - Chronic lung/kidney disease
  - Cardiovascular disease
  - Neurodevelopmental disorder
  - Current smoker
  - Hypertension
  - Immunosuppression/active cancer
  - Sickle Cell disease

- COVID-19 with symptoms ≤5 days
  - 66% had symptoms ≤3 days
  - Excluded vaccinated or previously infected patients

- Primary endpoint: hospitalization or death (any cause) through day 28
- Relative risk reduction of 88% (75, 94%) vs placebo

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PAXLOVID (N=1,039)</th>
<th>Placebo (N=1,048)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 related hospitalization or death from any cause through Day 28</td>
<td>8 (0.8%)</td>
<td>66 (6.3%)</td>
</tr>
<tr>
<td>Reduction relative to placebo* [95% CI], %</td>
<td>-5.62 (-7.21, -4.03)</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality through Day 28, %</td>
<td>0</td>
<td>12 (1.1%)</td>
</tr>
</tbody>
</table>
Molnupiravir (Lagevrio)

- MOVe OUT trial: 30% relative risk reduction (95% CI 1, 51) in hospitalization/mortality

- FDA EUA issued: “treatment of mild- moderate COVID-19 among patients at high risk of progression to severe COVID-19... for whom alternatives are not available”
Molnupiravir (Lagevrio) cont’d

• Works by inducing RNA mutagenesis -> safety concerns regarding mutagenesis in pregnancy

• EUA: “Molnupiravir is not recommended for use during pregnancy. Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth”
  • Patients of childbearing potential: recommended to use birth control during molnupiravir use and for 4 days after
  • Patients with partners of childbearing potential: recommended to use contraception during molnupiravir and for 3 months after
  • Lactation: Breastfeeding not recommended during molnupiravir use and for 4 days after
Remdesivir

• FDA approved for inpatient use

• PINETREE study:
  • Outpatients at high risk for severe COVID-19 ≤7 days from symptom onset randomized to 3 days of remdesivir vs placebo
  • 87% relative risk reduction

• Logistical challenge of 3-day infusion

Gottlieb et al. NEJM 2022
<table>
<thead>
<tr>
<th></th>
<th>Molnupiravir</th>
<th>Nirmatrelvir/ritonavir</th>
<th>Sotrovimab/other mAbs</th>
<th>Remdesivir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Lethal mutagenesis</td>
<td>Protease inhibitor</td>
<td>mAb – neutralization of spike</td>
<td>RNA polymerase</td>
</tr>
<tr>
<td><strong>Eligibility</strong></td>
<td>≥18 years old</td>
<td>≥12 years old</td>
<td>≥12 years old</td>
<td>≥12 years old</td>
</tr>
<tr>
<td><strong>Avoid in:</strong></td>
<td>• Pregnancy • Women trying to conceive</td>
<td>Patients with severe drug-drug interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symptom onset</strong></td>
<td>Symptoms ≤5 days</td>
<td>Symptoms ≤5 days</td>
<td>Symptoms ≤7 days</td>
<td>Symptoms ≤7 days</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>800mg PO BID x 5 days</td>
<td>300/100 PO BID x 5 days</td>
<td>Infusion x1</td>
<td>200mg x1 followed by 100mg QD x 2 days</td>
</tr>
<tr>
<td><strong>Drug Drug interactions</strong></td>
<td>None substantial</td>
<td>CYP3A4 - many</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Efficacy vs hosp/mortality</strong></td>
<td>30% relative risk reduction</td>
<td>88% relative risk reduction</td>
<td>70-85% relative risk reduction</td>
<td>87% relative risk reduction</td>
</tr>
</tbody>
</table>
Limitations of existing therapies

- Logistical challenges of administration
- Distribution to a large population quickly
- Keeping up with evolving variants (Antibiotic resistance on overdrive)
- Therapies and data among immunocompromised patients
- Change to a traditional medical model
Looking forward

• Ongoing surges?
  • Vs. lower steady state level of cases
• No guarantee that pathogen becomes less virulent over time
• Endemic does not mean the way life was before
• Ideal: ability to ramp up or down restrictions depending on transmission
### New COVID-19 Cases

<table>
<thead>
<tr>
<th>Per 100,000 people in the past 7 days</th>
<th>Indicators</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New COVID-19 admissions per 100,000 population (7-day total)</td>
<td>&lt;10.0</td>
<td>10.0-19.9</td>
<td>≥20.0</td>
</tr>
<tr>
<td></td>
<td>Percent of staffed inpatient beds occupied by COVID-19 patients (7-day average)</td>
<td>&lt;10.0%</td>
<td>10.0-14.9%</td>
<td>≥15.0%</td>
</tr>
<tr>
<td>Fewer than 200</td>
<td>New COVID-19 admissions per 100,000 population (7-day total)</td>
<td>NA</td>
<td>&lt;10.0</td>
<td>≥10.0</td>
</tr>
<tr>
<td></td>
<td>Percent of staffed inpatient beds occupied by COVID-19 patients (7-day average)</td>
<td>NA</td>
<td>&lt;10.0%</td>
<td>≥10.0%</td>
</tr>
<tr>
<td>200 or more</td>
<td></td>
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</tbody>
</table>

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https://www.cdc.gov/mmwr/volumes/70/wr/mm7030e2.htm?s_cid=mm7030e2_w#T1_down

COVID in review

• We have:
  • Vaccination
  • Availability of PPE
  • Home testing and available diagnostics
  • High efficacy outpatient therapies

• We need:
  • Infrastructure to continue to provide care rapidly and cheaply
  • Active surveillance programs
  • Vaccination for kids
  • More strategies for immunocompromised patients
Thank you

**Antimicrobial Stewardship:**
Karen Fong, PharmD  
Hannah Imlay, MD  
Brandon Tritle, PharmD  
Russell Benefield, PharmD

**COVID pager:**
Hannah Imlay, MD  
Laura Certain, MD, PhD  
Adrienne Carey, MD

**Utah Allocation of Scarce Medications Subcommittee**
Erin Fox and Russell Vinik
Questions?
Common COVID fallacies

• Considering results of one study without considering the body of evidence
  • Similarly, considering poorly-performed studies on the same level as high-quality studies
• Thinking that interventions (e.g. masking, vaccines) either work 100% or they don’t work at all
• Community-level vs individual-level risk/protection
• Do recommendations follow the science or follow societal needs or a compromise of both?
Quarantine and isolation

• Quarantine: after exposure to someone with COVID
• Isolation: after diagnosis of COVID

• Knowledge that shapes recommendations regarding quarantine and isolation:
  • Lower risk of COVID-19 from vaccine
  • Lower viral loads among vaccinated infected patients
  • Replication competent virus not isolated after 10 days among most patients*

2-3 days before 8 days after

*Mild-moderate infections among immunocompetent
Quarantine

Day 0: day of exposure

Up to date on vaccination OR COVID within 90 days

Watch for symptoms until day 10, no need to quarantine

Quarantine for ≥5 days

Not up to date

Watch for symptoms until day 10

Get tested after 5 days of exposure

*Mild-moderate infections among immunocompetent
Isolation

- Among immune competent patients
- Mild infection
- Fever-free for 24 hours and symptoms improving

Day 0: day of symptoms or positive test

Isolate for ≥5 days

Optional: check antigen test; if positive, continue to isolate until day 10

Day 10

Wear a mask until day 10