COVID-19 Clinical Update
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Overview

• Epidemiology
  – Trends
  – Omicron – new subvariants
• Treatment – Remdesivir
• Natural Immunity & Vaccines
  – Boosters and Omicron
• Long COVID
Global Trends in COVID-19 Diagnoses & Deaths

>392 Million Confirmed Cases
>19 million cases/week

~5.7 Million Confirmed Deaths
~68,000 deaths/week

Decrease in new cases with increase in number of deaths over the last week
Global Trends in COVID-19 Diagnoses & Deaths

**Africa**
- Cases plateauing at high level

**Americas**
- Cases overall, but highly variable – stable in Brazil – Death no change overall – increase in Mexico, Brazil

**Western Pacific**
- Cases plateauing at high level

**South-East Asia**
- ↓ Cases ↑ Deaths

**Europe**
- Plateau at high level – Very high in Russia

**Eastern Mediterranean**
- ↑ Cases and Deaths
COVID-19 cases/100,000 population, January 31-February 6, 2022

97% Sequenced viruses worldwide are Omicron
Omicron Evolution: Trends in Omicron Pango Lineage

Increase proportion of BA.2
Omicron Evolution: BA2 in Denmark
Secondary Attack Rate (SAR)

**Background:** BA.2 differs from BA.1 by ~40 mutations. Little is known about its transmissibility or ability to evade vaccine-induced immunity.

**Design:** Analysis of national surveillance data Denmark

**Population:** Persons testing SARS-CoV-2 positive by PCR in Denmark 12/20/21-1/11/22 – 2,122 households with BA.2 and 6,419 BA.1

**Outcome:** Secondary attack rate (SAR) in household members & vaccine efficacy

Source: Lyngse FP. MedRxIV 2022
Omicron Evolution: BA2 in Denmark
Effect of Vaccination

- Comparing vaccinated vs. unvaccinated - Both susceptibility and transmissibility were lower in people who had received boosters
  - Vaccines still provided some protection

### Table 2: Effect of Vaccination

<table>
<thead>
<tr>
<th></th>
<th>Susceptibility</th>
<th>Transmissibility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Omicron BA.2 households</td>
<td>Omicron BA.1 households</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>1.10 (0.92-1.32)</td>
<td>1.23 (1.09-1.40)</td>
</tr>
<tr>
<td>Fully vaccinated</td>
<td>ref (ref)</td>
<td>ref (ref)</td>
</tr>
<tr>
<td>Booster vaccinated</td>
<td>0.80 (0.67-0.94)</td>
<td>0.65 (0.58-0.73)</td>
</tr>
</tbody>
</table>

Source: Lyngse FP. MedRxIV 2022
Omicron Evolution: BA2 in Denmark

- BA.2 associated with greater susceptibility to infection regardless of vaccine status
  - Relative effect of BA.2 greater in vaccinated - ↓Vaccine effectiveness

- BA.2 associated with great transmissibility than BA.1 if initial case was unvaccinated but lower transmissibility than BA.1 if the initial case was vaccinated
  - Unvaccinated cases had lower PCR Ct values – c/w higher viral loads

### Table 3: Relative effect of Omicron VOC BA.2 vs. BA.1

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<tr>
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<tbody>
<tr>
<td></td>
<td>Unvaccinated</td>
<td>Fully vaccinated</td>
</tr>
<tr>
<td>Omicron BA.2 households</td>
<td>2.19 (1.58-3.04)</td>
<td>2.45 (1.77-3.40)</td>
</tr>
<tr>
<td>Omicron BA.1 households</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Number of observations</td>
<td>17,945</td>
<td>17,945</td>
</tr>
<tr>
<td>Number of households</td>
<td>8,541</td>
<td>8,541</td>
</tr>
<tr>
<td></td>
<td>Unvaccinated</td>
<td>Fully vaccinated</td>
</tr>
<tr>
<td>Omicron BA.2 households</td>
<td>2.62 (1.96-3.52)</td>
<td>0.60 (0.42-0.85)</td>
</tr>
<tr>
<td>Omicron BA.1 households</td>
<td>ref</td>
<td>ref</td>
</tr>
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Source: Lyngse FP. MedRxIV 2022
Background: Remdesivir previously shown to improve outcomes in hospitalized patients in one RCT, but not in a 2nd trial.

Design: Randomized double-blind placebo-controlled trial

Intervention: 3 days IV Remdesivir

Population: 562 people with COVID-10 and symptoms <7 days with risk for severe disease (DM, HTN, obesity)

Outcome: Hospitalization or death

Difficult to administer an IV medication to large number of outpatients

Source: Gottlieb RL NEJM 2021
**Background**: The effectiveness and duration of immunity induced by COVID-19 infection is uncertain beyond 5-6 months.

**Design**: Retrospective cohort study

**Population**: 52,656 persons tested 3/20-8/20 with subsequent testing through 9/21 in Cleveland Clinic System (pre-omicron)

**Outcome**: Reinfection >90 days after initial infection

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**Effectiveness of Symptomatic and Asymptomatic Natural Infection in Preventing Subsequent COVID-19**

- **Any Infection**:
  - 90-150: 64%
  - 151-210: 93%
  - 211-270: 94%
  - 271-330: 91%
  - 3331-390: 87%
  - >390: 93%

- **Symptomatic**
  - 90-150: 83%
  - 151-210: 96%
  - 211-270: 92%
  - 271-330: 89%
  - 3331-390: 95%
  - >390: 96%

- **Asymptomatic**
  - 90-150: 78%
  - 151-210: 80%
  - 211-270: 89%
  - 271-330: 100%
  - >390: -35%

**Key Points**:
- Durable protection against symptomatic infection
  - Less protection asymptomatic infection (92% vs. 52%)
- Protection lower for those ≥65 than <65 (76% vs 89%)

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Source: Kim P. CID 2022 (epub ahead of print)
Background: The effectiveness and duration of immunity induced by COVID-19 infection is uncertain.

Design: Test negative case-control design

Population: Analysis of national data from Qatar that includes all vaccine, hospitalization and PCR data

Outcome: Effectiveness against symptomatic infection and severe COVID-19
  - Effect variants

Source: Altarawneh HN; NEJM 2022
# Natural Immunity

Table S4. Effectiveness of SARS-CoV-2 prior infection against reinfection with Alpha, Beta, Delta, or Omicron variant, adjusting for time between prior infection and PCR test.

|            | Cases\(^1\) (PCR-positive) | Controls\(^1\) (PCR-negative) | Effectiveness in % (95% CI)
|------------|-----------------------------|-------------------------------|-----------------------------
|            | Prior infection | No prior infection | Prior infection | No prior infection |                      |
| Alpha      |                |                   |                |                   |                      |
| 3-8 months | 1              | 334               | 43             | 1,548             | 89.4 (22.6 to 98.5)  |
| 9-14 months| 1              | 334               | 51             | 1,548             | 91.0 (34.5 to 98.8)  |
| ≥15 months | --             | --                | --             | --                | --                  |
| Beta       |                |                   |                |                   |                      |
| 3-8 months | 3              | 1,322             | 6,084          | 92.6 (76.7 to 97.6)|                      |
| 9-14 months| 11             | 1,322             | 6,084          | 81.2 (65.5 to 89.8)|                      |
| ≥15 months | --             | --                | --             | --                | --                  |
| Delta      |                |                   |                |                   |                      |
| 3-8 months | 10             | 2,153             | 602            | 93.4 (87.6 to 96.5)|                      |
| 9-14 months| 10             | 2,153             | 454            | 91.1 (83.3 to 95.3)|                      |
| ≥15 months | 3              | 2,153             | 98             | 87.1 (59.4 to 95.9)|                      |
| Omicron    |                |                   |                |                   |                      |
| 3-8 months | 94             | 5,284             | 460            | 64.0 (54.7-71.4)  |                      |
| 9-14 months| 191            | 5,284             | 630            | 47.2 (37.5-55.4)  |                      |
| ≥15 months | 127            | 5,284             | 530            | 59.6 (50.7-67.0)  |                      |

\(^1\)Cases and controls were exact matched one-to-five by sex, 10-year age group, nationality, and calendar week of PCR test in the Alpha, Beta, and Delta analyses (March 23-November 18, 2021, Figure S1), and one-to-three by sex, 10-year age group, nationality, and PCR test date in the Omicron analysis (December 23, 2021-Jan 2, 2022; Figure S2).

\(^2\)Effectiveness of prior infection in preventing reinfection was estimated using the test-negative, case-control study design.**
**Background:** COVID-19 vaccine immunity wanes over time. A 3rd dose of mRNA vaccines increases VE, but the durability of that increase is unknown.

**Design:** Test negative control

**Population:** 241,204 symptomatic emergency room & 93,408 hospitalized patients tested for SARS-coV-2 in US 8/21-1/22.

**Outcome:** Vaccine effectiveness against ED visit infection and hospitalization

Source: Ferdinands JM; MMWR 2022
Boosters: Waning Immunity

Vaccine Effectiveness of 2 and 3 doses of mRNA Vaccine Against COVID-19 Hospitalization During Delta & Omicron Predominant Periods in the US

- VE for Omicron is lower and wanes substantially within 4 months
- Boosters increase VE, but effect also wanes
- Efficacy higher against more severe disease

Source: Ferdinands JM; MMWR 2022
**Background:** Impact of COVID-19 vaccine boosters other Pfizer vaccine ill-defined.

**Design:** Phase 4 safe and immunogenicity study comparing 4 vaccine boosters given at ~6 months – AZ, Pfizer, J&J, and Coronavac

**Population:** 1240 Brazilian adults

**Outcome:** Anti-spike IgG antibodies 28 days after the booster dose

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All heterologous boosters were significantly better than a 3rd dose of CoronaVac.
Boosters in Persons Receiving CoronaVac
Neutralizing Antibody Delta & Omicron

Source: Clemens SAC. Lancet 2022
Boosters: Waning Immunity - Summary

• **Good news**
  • Natural immunity is pretty durable
  • mRNA Boosters increased VE – 54%->78% against hospitalizations at >=4 months
    • Effect greater on hospitalizations than ED visits
  • Heterologous booster for persons receiving CoronaVac increased antibody levels
  • Supports strategy of giving boosters

• **Bad news**
  • VE wanes over relatively short period of time
  • VE lower for Omicron than Delta
    • Complex issue – less virulent virus – is lower VE reflective of a more compromised population seeking care?
  • CoronaVac boosters don’t look to be effective
  • Would an mRNA vaccine designed to induce immunity against more contemporary strains perform better?
Long COVID: WHO Definition

- Post COVID-19 condition – 10-20% of patients
  - History of probable or confirmed SARS CoV-2 infection
  - Usually 3 months from the onset of COVID-19
  - Symptoms persisting >2 months
  - Not explained by an alternative diagnosis
- Common symptoms: fatigue, shortness of breath, cognitive dysfunction - impact on everyday functioning
  - New onset following initial recovery or persist from the initial illness
  - May fluctuate or relapse over time
Late Onset Cardiovascular Morbidity

Background: The long-term health impacts of COVID-19 are ill-defined

Design: Retrospective cohort study

Population: Veterans Affairs cohort 153,760 people with COVID, 5.6 million contemporary controls and 5.8 million historical controls

Outcome: Cardiovascular outcomes >30 days-1 year post diagnosis

Risk and 12-month burden incident post-COVID CV Outcomes vs. Contemporary Control

MACE = all-cause mortality, stroke & myocardial infarction

Source: Xie Y. Nature Medicine 2022
Long COVID

Risk and 12-month burden incident post-COVID CV Outcomes vs. Contemporary Control, Stratified by Acute COVID-19 Severity

- Risk highest in those with more severe disease
- Risk was elevated even in those who were not hospitalized

Excess Burden per 1000

Source: Xie Y. Nature Medicine 20
I use the term pandemic to refer to the extraordinary societal efforts over the past 2 years to respond to a new pathogen that have changed how individuals live their lives and how policy responses have developed in governments around the world.

The era of extraordinary measures by government and societies to control SARS-CoV-2 transmission will be over. After the omicron wave, COVID-19 will return but the pandemic will not.

“This framing that the pandemic is ending is really unfortunate,” said Jeff Duchin, the chief health officer for Seattle and King County, and also affiliated with the UW, when I asked him about the predictions.

The thing that makes pandemics so challenging, as we all ought to know by now, is that they feature a novel, evolving pathogen.

“It’s by its nature unpredictable,” Duchin said. “We’ve just seen that evolving unpredictability, twice, since last summer” — the delta and omicron waves, which combined have killed nearly 300,000 more Americans. The key is having some humility about it. There’s no reason to think another variant like that can’t happen again.”
Summary

• Epidemiology
  • Case numbers declining though mortality still not declining consistently
  • New Omicron variant – more transmissible with lower vaccine effectiveness

• Treatment
  • Remdesivir – looks good in outpatients – hard to give IV meds

• Immunity & Vaccines
  • Natural immunity less for Omicron, but durable for severe disease for all variants to date
  • Boosters are protective - effectiveness wanes relatively quickly, though less for severe disease
  • Heterologous boosters for CoronaVac recipients

• Clinical
  • Long COVID is concerning – we have a lot we don’t know about this