COVID-19 Clinical Update
I-TECH Videoconference  October 18, 2021

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Overview

• Epidemiology & new data on HIV and COVID
• Vaccines –
  – More data on waning immunity
  – Boosters
• Molnupiravir
Global Trends in COVID-19 Diagnoses & Deaths

>237 Million Confirmed Cases
2.8 million cases/week

~4.8 Million Confirmed Deaths
46,000 deaths/week

Declines in new cases and deaths globally since late August – Europe is an exception
Global Trends in COVID-19 Diagnoses & Deaths

34%↓ Deaths – Exceptions in North Africa where numbers ↑

13%↓ Deaths – Exceptions in parts of Caribbean

11%↑ Deaths – High in Eastern Europe

34%↓ Deaths

16%↓ Deaths

16%↓ Deaths – Rates very high in Iran and Iraq
Global Trends by Country (October 15, 2021)

Week 41: New COVID-19 cases by country

Countries and territories with
twice as many new cases
more new cases
approx. the same number of new cases
fewer new cases
less than half as many new cases
zero new cases four weeks in a row

Background: Studies from the UK and South Africa have suggested increased mortality in HIV+ persons with COVID-19. Some uncertainty of relationship of HIV to COVID-19 severity persists.

Design: Analysis US National COVID Cohort Collaborative – ~1.4 million COVID19 cases, 13,170 HIV+

Outcome: Hospitalization, death, clinical severity
Association COVID-19 Severity & HIV

Variable impact of HIV on severe outcomes – higher in women, older persons, and Black/African Americans

Adjustment attenuates but does not eliminate association of HIV with severe outcomes

Source: Yang X. Lancet HIV 2021
• Severity associated with low CD4 count and lack of viral suppression

<table>
<thead>
<tr>
<th>HIV factors</th>
<th>Death, OR (95% CI)</th>
<th>Hospitalisation, OR (95% CI)</th>
<th>Mild† or moderate vs unaffected, OR (95% CI)</th>
<th>Severe† vs unaffected, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most recent CD4 count§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;500 cells per µL</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>200-500 cells per µL</td>
<td>1.49 (0.55-4.03)</td>
<td>1.28 (0.94-1.75)</td>
<td>1.15 (0.89-1.48)</td>
<td>1.62 (0.59-4.44)</td>
</tr>
<tr>
<td>&lt;200 cells per µL</td>
<td>3.10 (1.06-9.13)</td>
<td>2.73 (1.80-4.14)</td>
<td>1.51 (1.04-2.21)</td>
<td>3.91 (1.31-11.62)</td>
</tr>
<tr>
<td>Most recent viral suppression, &lt;200 copies per mL§</td>
<td>0.71 (0.27-1.89)</td>
<td>0.69 (0.49-0.97)</td>
<td>0.87 (0.64-1.17)</td>
<td>0.62 (0.24-1.57)</td>
</tr>
</tbody>
</table>

• Study is consistent with prior studies from South African and UK demonstrating that HIV, particularly with low CD4 or in the absence of viral suppression, is associated with severe COVID-19
• Large attenuation of HIV effect with adjust suggests other comorbidities are likely more important than HIV

Source: Yang X. Lancet HIV 2021
Vaccine Effectiveness at Population-Level: King County, WA, USA

For data sources and technical notes, click on the data notes section on the top-right.

Select a time period: "Past 30 Days" or "Since 1/17/2021"

### Cases
People who are **not fully vaccinated** are:

\[9x\]

more likely to test positive for COVID-19

**Relative Risk trend**

The vaccines effectively reduce a person’s risk of catching COVID-19 and spreading it to others, although they are more effective at preventing serious infections leading to hospitalization and death. Vaccinated people who do get infected tend to have mild or non-severe illness.

- 65% were not fully vaccinated (n = 10,232)
- 35% were fully vaccinated (n = 5,480)

### Hospitalizations
People who are **not fully vaccinated** are:

\[48x\]

more likely to be hospitalized for COVID-19

**Relative Risk trend**

The vaccines are highly effective at preventing severe illness from COVID-19 requiring hospitalization.

- 77% were not fully vaccinated (n = 376)
- 23% were fully vaccinated (n = 315)

### Deaths
People who are **not fully vaccinated** are:

\[69x\]

more likely to die of COVID-19 related illness

**Relative Risk trend**

Getting vaccinated dramatically reduces one’s risk of dying from COVID-19. Deaths among the unvaccinated have tended to affect younger and healthier people than the comparatively rare deaths among vaccinated people.

- 74% were not fully vaccinated (n = 75)
- 26% were fully vaccinated (n = 26)

Source: [https://kingcounty.gov/depts/health/covid-19/data/vaccination-outcomes.aspx](https://kingcounty.gov/depts/health/covid-19/data/vaccination-outcomes.aspx)
**Background:** Relative effectiveness of different vaccines is uncertain.

**Design:** Case-control study 3,689 immunocompetent persons hospitalized with COVID-19 in US March-August 2021 and controls were hospitalized persons without COVID. Second study looked at antibody levels in 100 persons 2-6 weeks post vaccine.

**Outcome:** Vaccine effectiveness comparing vaccinated and unvaccinated patients

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Period</th>
<th>Case</th>
<th>Control</th>
<th>VE COVID-19 Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderna</td>
<td>Full period</td>
<td>54/1517 (3.6)</td>
<td>422/1221 (31.9)</td>
<td>93 (91-95)</td>
</tr>
<tr>
<td></td>
<td>14-120 days</td>
<td>36/1499 (2.4)</td>
<td>345/1244 (27.7)</td>
<td>93 (90-95)</td>
</tr>
<tr>
<td></td>
<td>&gt;120 days</td>
<td>18/1481 (1.2)</td>
<td>77/976 (7.9)</td>
<td>92 (87-96)</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Full period</td>
<td>128/1591 (8)</td>
<td>610/1509 (40.4)</td>
<td>88 (85-91)</td>
</tr>
<tr>
<td></td>
<td>14-120 days</td>
<td>65/1528 (4.3)</td>
<td>495/1395 (35.5)</td>
<td>91 (88-93)</td>
</tr>
<tr>
<td></td>
<td>&gt;120 days</td>
<td>63/1526 (4.1)</td>
<td>115/1014 (11.3)</td>
<td>77 (67-84)</td>
</tr>
<tr>
<td>J&amp;J</td>
<td>Full period</td>
<td>37/1500 (25)</td>
<td>76/975 (7.8)</td>
<td>71 (56-81)</td>
</tr>
<tr>
<td></td>
<td>&gt;28 days</td>
<td>33/1496 (2.2)</td>
<td>59/958 (6.2)</td>
<td>68 (49-80)</td>
</tr>
</tbody>
</table>

Source: Self WH. MMWR 2021
Comparative Effectiveness of Vaccines

- Anti-receptor binding domain IgG (RBD) higher for Moderna vs. Pfizer (p=0.03) or J&J (p<0.001)
- Anti-spike higher for Moderna than J&J (p<.001), but not Pfizer

Source: Self WH. MMWR 2021
Waning Immunity to COVID Vaccine

**Background**: Population-based observational data from Israel suggest that vaccine effectiveness wanes over time (reviewed in Sept).

**Design**: 6-month longitudinal prospective study of 2631 Israeli healthcare workers measuring antibody to spike protein.

**Outcome**: Anti-spike IgG and neutralizing antibody levels decline over time – neutralizing anti-body seems to plateau.

Source: Levin EG. NEJM 2021
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Outcome: Anti-spike IgG and neutralizing antibody levels decline over time – neutralizing anti-body seems to plateau.

Source: Levin EG. NEJM 2021
Background: Population-based observational data from Israel suggest that vaccine effectiveness wanes over time (reviewed in Sept).

Design: Matched test negative case control study Qatar using population-based data Jan-Sept 2021. 494,859 people received 2 doses of vaccine with 10,543 breakthrough infections.

Outcome: Vaccine effectiveness against infection and against severe/critical/fatal COVID-19 declines over time.
Impact of Booster Doses in the Elderly

**Background:** In the face of waning immunity and Delta, Israel instituted 3rd dose boosters in the elderly in July, 2021.

**Design:** Retrospective cohort study of population-based data comparing persons who received booster to those who had not and, among boosted elderly, 4-6 days after booster to >=12 days.

**Outcome:** Infection rate and rate severe illness

Absolute between-group difference in the rate of severe illness was 7.5 cases per 100,000 person-days.

Table 2. Primary Outcomes of Confirmed Infection and Severe Illness.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nonbooster Group</th>
<th>Booster Group</th>
<th>Adjusted Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed infection</td>
<td>4439</td>
<td>934</td>
<td>11.3 (10.4 to 12.3)</td>
</tr>
<tr>
<td>No. of cases</td>
<td>5,193,825</td>
<td>10,603,410</td>
<td></td>
</tr>
<tr>
<td>Severe Illness</td>
<td>294</td>
<td>29</td>
<td>19.5 (12.9 to 29.5)</td>
</tr>
<tr>
<td>No. of cases</td>
<td>4,574,439</td>
<td>6,265,361</td>
<td></td>
</tr>
</tbody>
</table>

* Listed are the results of the Poisson regression analysis in participants who received a booster vaccine and in those who did not receive a booster. The booster group includes data that were obtained at least 12 days after receipt of the booster dose.

† The rate ratio is the estimated factor reduction in the rate in the booster group as compared with the rate in the nonbooster group.

Source: Bar-on YM. NEJM 2021
Can We Change Vaccines When we Give Boosters? 
Vaccine Mix and Match Boosters

**Background:** The impact of using different vaccines for boosters than original immunization for COVID-19 is uncertain.

**Design:** Open-label clinical trial with 458 persons with no history of COVID-19 12 weeks post immunization received 1 of 3 vaccines: Moderna, Pfizer, J&J.

**Outcome:** Safety, immune response

- All of the boosters increased antibody and neutralizing antibody levels
- Moderna produced the highest levels

Increase was greatest for people who received J&J

**Table:**

<table>
<thead>
<tr>
<th>Primary Vaccine</th>
<th>Booster</th>
<th>IgG Day 1 GMT</th>
<th>Geo Mean rise</th>
<th>Neutralizing Ab Day 1 GMT</th>
<th>Geo Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>J&amp;J</td>
<td>Moderna</td>
<td>57</td>
<td>4.6</td>
<td>8.9</td>
<td>76</td>
</tr>
<tr>
<td>Moderna</td>
<td>J&amp;J</td>
<td>859</td>
<td>7.9</td>
<td>9.9</td>
<td>10</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Pfizer</td>
<td>357</td>
<td>17</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>J&amp;J</td>
<td>Pfizer</td>
<td>71</td>
<td>4.7</td>
<td>7.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Moderna</td>
<td>J&amp;J</td>
<td>638</td>
<td>6.2</td>
<td>62</td>
<td>4.2</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Pfizer</td>
<td>321</td>
<td>In Process</td>
<td>382</td>
<td>6.2</td>
</tr>
<tr>
<td>J&amp;J</td>
<td>Moderna</td>
<td>75</td>
<td>32.8</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>Moderna</td>
<td>Pfizer</td>
<td>534</td>
<td>9.7</td>
<td>9.4</td>
<td>12</td>
</tr>
<tr>
<td>Pfizer</td>
<td>J&amp;J</td>
<td>2235</td>
<td>14.9</td>
<td>58</td>
<td>20</td>
</tr>
</tbody>
</table>

Source: Atmar RL. medRxiv 2021
Boosters Following CoronaVac?

**THE RACE TO VACCINATE**

Out of the eight vaccines that account for the vast majority of COVID-19 vaccine doses delivered globally, China’s CoronaVac and Sinopharm jabs account for nearly half of all doses.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Doses delivered (billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoronaVac</td>
<td>1.78</td>
</tr>
<tr>
<td>Pfizer-BioNTech</td>
<td>1.57</td>
</tr>
<tr>
<td>Sinopharm</td>
<td>1.57</td>
</tr>
<tr>
<td>University of Oxford – AstraZeneca</td>
<td>1.5</td>
</tr>
<tr>
<td>Moderna</td>
<td>0.91</td>
</tr>
<tr>
<td>Sputnik V</td>
<td>0.35</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>0.06</td>
</tr>
<tr>
<td>Bharat Biotech</td>
<td>0.03</td>
</tr>
<tr>
<td>Other</td>
<td>0.03</td>
</tr>
</tbody>
</table>
• Laboratory data suggest inactivated vaccines produce lower levels of antibody that wane more rapidly than mRNA vaccines (reviewed in September) – cell mediated immunity may be different
• New preliminary data from Chile reported online on boosters following CoronaVac
• 4,785,749 people immunized with CoronaVac
• 2,017,818 received a booster shot with AstraZeneca (75%), Pfizer (18%), or Sinvac (7%)
• Data supported Chile’s decision to initiate a booster program

<table>
<thead>
<tr>
<th>No Booster</th>
<th>CoronaVac Booster</th>
<th>Pfizer Booster</th>
<th>AZ Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>56%</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>84%</td>
<td>88%</td>
<td>87%</td>
</tr>
</tbody>
</table>

CDC Guidance on Boosters

- Age 65
- 50-64 with underlying medical conditions
- Age 18-49 with underlying medical conditions – individual decision
- Employees and residents at increased risk for COVID-19 exposure because of occupational or residential exposure

Recommendation currently only for Pfizer, but Moderna will likely be recommended in next week

Medical conditions: cancer, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes, Down syndrome, dementia, HIV, heart disease, immunocompromised
Molnupiravir - A Mutagenic ribonucleoside

- β-D-N4-hydroxycytidine (NHC, ribonucleoside form = rNHC)
- Similar to ribavirin and favipiravir, but >100 fold more active
- Drug interferes with RNA synthesis through a 2 step process
  - Viral RNA-dependent RNA polymerase (RdRp) uses rNHC as a substrate instead of cytidine or uridine triphosphate
  - Mutated –gRNA strand leads to mutanized +gRNA strand
  - Resultant RNA does not support functional virus – “error catastrophe”
- Broad spectrum anti-RNA virus activity

https://www.nature.com/articles/s41594-021-00651-0
**Background:** There is a need for COVID-19 treatments, particularly orally administered drugs.

**Design:** RCT

**Population:** ~1400 unvaccinated persons at high risk for COVID-19 (obesity, age >60, DM, heart disease) within 5 days of symptom onset – interim analysis 775 through day 29

**Outcome:** Hospitalization or death

<table>
<thead>
<tr>
<th></th>
<th>Hospitalization or Death</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molnupiravir</td>
<td>28/385 (7.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Placebo</td>
<td>53/377 (14.1%)</td>
<td>8</td>
</tr>
</tbody>
</table>

\[P=0.0012\]

- Similar results for all variants
- Lower rate of discontinuation in Molnupiravir than placebo

**Background:** Impact of molnupiravir on viral shedding unknown. Decreased shedding would suggest that the drug would decrease transmission.

**Design:** RCT placebo, 200mg, 400mg, or 800mg bid

**Population:** 202 untreated patients within 7 days symptom onset

**Outcome:** Nasopharyngeal viral shedding day 3 and 5

<table>
<thead>
<tr>
<th></th>
<th>200mg</th>
<th>400mg</th>
<th>800mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>50%</td>
<td>42%</td>
<td>38%</td>
<td>47%</td>
</tr>
<tr>
<td>Day 3</td>
<td>18%</td>
<td>12%</td>
<td>2%*</td>
<td>17%</td>
</tr>
<tr>
<td>Day 5</td>
<td>4%</td>
<td>0*</td>
<td>0*</td>
<td>11%</td>
</tr>
</tbody>
</table>

* P<0.05 vs. placebo

https://www.medrxiv.org/content/10.1101/2021.06.17.21258639v1.full.pdf
Merck is committed to providing timely access to molnupiravir globally, if it is authorized or approved, and plans to implement a tiered pricing approach based on World Bank country income criteria to reflect countries’ relative ability to finance their health response to the pandemic.

As part of its commitment to widespread global access, Merck previously announced that the company has entered into non-exclusive voluntary licensing agreements for molnupiravir with established generic manufacturers to accelerate availability of molnupiravir in more than 100 low- and middle-income countries (LMICs) following approvals or emergency authorization by local regulatory agencies.
Summary

• **Epidemiology** – Declining epidemic in most of the world

• **Vaccines**
  - Moderna likely the most effective vaccine
  - Vaccine-induced immunity wanes over time – not so clear how much this is true for the most severe disease in all people
  - Boosters work – greater impact on infection than severe disease
  - Probably OK and even good to use different boosters than initial vaccine – particularly true of using mRNA boosters following inactivated vaccine
    - It would be good to see published data
  - Molnupiravir looks promising
    - May be less effective than mAb treatments (50% vs. 85%), but likely much easier to deploy
    - Exciting to have a new, possibly broad spectrum anti-viral against RNA viruses
    - We need to see the data in a publication and additional safety data will be important