COVID-19 Clinical Update
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Overview

• Epidemiology
• Omicron
  – Epidemiology
  – Genetics – mechanisms of action
  – Impact on immunity
  – Disease severity
Global Trends in COVID-19 Diagnoses & Deaths

>265 Million Confirmed Cases
>4 million cases/week

~5.2 Million Confirmed Deaths
>50,000 deaths/week

Increase in new cases with stable number of deaths since last month’s review
Global Trends in COVID-19 Diagnoses & Deaths

- **African Region**: 79% increase in cases with a 3% decrease in deaths. (-10% in S. Africa)

- **Region of the Americas**: 21% increase in cases with a 38% increase in deaths.

- **European Region**: Plateauing new cases and deaths following an increase.

- **Western Pacific Region**: Plateauing cases and deaths.

- **South-East Asia Region**: 10% decrease in cases with a 49% increase in deaths.

- **Eastern Mediterranean Region**: 0% decrease in cases with an 8% decrease in deaths.
COVID-19 cases/100,000 population, November 29-December 5
COVID-19 deaths/100,000 population, November 29-December 5
Omicron (B1.1529) Variant Timeline

- November 11 & 14, 2021 – Specimens collected in Botswana and South Africa that are subsequently identified as Omicron
- November 24 – Variant reported to WHO
- November 26 – Omicron defined as VOC
  - Increase in cases in South Africa concurrent with detection of new variant
  - Large number of genetic substitutions suggest potential for increased transmission and reduced antibody neutralization
Figure 5. Presence of Variant of Concern (VOC) Omicron, data as of 7 December 2021 (4 pm CET)

Presence of Omicron variant reported
- Verified (54)
- Under verification (3)
- Presence not reported
- Not applicable
C.1.2 has been detected at ≤ 6% of sequences monthly.

B.1.1.529 was first detected in South Africa on November 14th. It makes up 76% (n=66/87) of November sequences released on GISAID.
### B.1.1.529 spike mutations compared to other VOC/VOIs

<table>
<thead>
<tr>
<th>Variant</th>
<th>Spike mutations</th>
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<tbody>
<tr>
<td>Omicron</td>
<td>26-32 mutations</td>
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<tr>
<td>C.1.2</td>
<td></td>
</tr>
<tr>
<td>Beta</td>
<td></td>
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<tr>
<td>Alpha</td>
<td></td>
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<td>Alpha+E484K</td>
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<tr>
<td>Gamma</td>
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<td>Delta</td>
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<td>Lambda</td>
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<td>Mu</td>
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- **Mutations with unknown or unconfirmed impact**

#### Multiple changes within the two immunogenic regions in S1 (NTD and RBD)
- including a three amino acid insertion

#### Accumulation of mutations surrounding the furin cleavage site
- Including combination of N679K and P681H

#### Effect of most spike S2 subunit changes have not been defined
Omicron (B1.1529): Genetics

- Virus enters cells via 2 pathways
  - Endocytosis
  - Cell surface entry
- Spikes have 2 domains
  - S1 – receptor binding ACE2
    - Omicron binds ACE2 more efficiently
  - S2 – membrane fusion for viral entry – primed by proteolytic cleavage
    - Cleavage leads to conformational changes that release the S2 fusion peptide for insertion into the cell membrane
    - Mutations may make this fusion more efficient
Rising Effective Reproductive Number (R) in South Africa
Data Through December 4, 2021

Estimated R based on admissions and reported cases
- Big increase in November

Number of cases, admissions and deaths

**Background:** Extent to which Omicron may evade immunity induced by prior infection with another variant of vaccine-induced immunity uncertain

**Design:** Viral neutralization assay

**Population:** Sera 12 Pfizer vaccine recipients, 6 with a history of D614G infection

**Outcome:** Viral neutralization comparing D614G vs. omicron

- 41-fold reduction in titer with Omicron
- People with prior infections mostly retained high levels of antibody neutralization

Source: Cele S. MedRxiv 2021
Antibody Neutralization: Omicron

- No neutralization in 2x Pfizer recipients
- No neutralization in 2x Moderna recipients
- Lower but some neutralization with Pfizer booster (3rd dose)
- No neutralization with mAb recipients
  - 2 AstraZeneca vaccine recipients
  - Inhibition mAB (imdevimab & casirivimab)

Vaccine Effectiveness
Pfizer Press Release

• Sera from persons receiving 2 doses of Pfizer - 25-fold reduction in neutralization against Omicron compared to wild-type SARS-CoV-2
• Third dose (1 month after third dose) leads to neutralization similar to that achieved with 2 doses (3 weeks after 2nd dose) against wildtype
  • Also increased CD8+ T cells against spike protein
• 80% epitopes on spike protein recognized by CD8+ T cells not affected by Omicron mutations
• Company developing vaccine against omicron variant – can be available in March
• Pfizer plans to produce 4 billion doses in 2022

Reinfection with Omicron: South Africa

**Background:** Extent to which Omicron may evade immunity induced by prior infection with another variant of vaccine-induced immunity uncertain

**Design:** Retrospective analysis surveillance data South Africa

**Population:** 2,796,982 people with lab-confirmed SARS-CoV-2 90 days prior to 11/27/21.

**Outcome:** Reinfection - Sequential positive tests ≥90 days apart – time varying relative hazard primary vs reinfection

Source: Pulliam JRC. MedRxiv 2021
Reinfection with Omicron: South Africa

Infection in wave 1 and reinfected in wave two, or infected in wave 2 and reinfected in wave 3

Infection in wave 1 and reinfected in wave 3

Reinfections Since November 1, 2021
Infection in wave 3 and reinfected in period of omicron

Source: Pulliam JRC. MedRxiv 2021
Recent trends in reinfection diverge from prior experience – much higher than predicted – suggests immune escape.

Source: Pulliam JRC. MedRxiv 2021
Reinfection with Omicron: South Africa
Empirical estimate of time-varying infection and reinfection Hazards

Primary infection

Reinfection

Hazard ratio primary vs reinfection
- Relative hazard rising since November

Source: Pulliam JRC. MedRxiv 2021
Reinfection with Omicron: South Africa
Empirical estimate of time-varying infection and reinfection Hazards

- No evidence of immune escape with Beta and Delta variants
  - Infection provided ~84% protection from reinfection during subsequent wave
  - *In vitro* neutralization studies suggest that there may be immune escape from Beta and Delta – data not consistent
  - Suggests that Beta and Delta waves were driven by increased transmissibility, not immune escape
- Omicron appears to be different

Source: Pulliam JRC. MedRxiv 2021
Background: Vaccine effectiveness against Omicron unknown

Design: Test negative control


Outcome: Symptomatic COVID-19 with Omicron – Omicron based on S-gene target failure

Cases
- 581 symptomatic Omicron cases
- 56,439 Delta
- 130,869 PCR negative controls

Vaccine Effectiveness (AZ)
- No protection from AstraZeneca against Omicron after 15 weeks
- Booster with Pfizer leads to ~71% protection

Vaccine Effectiveness Against Omicron: UK

Two doses of ChAdOx1-S with a BNT162b2 booster dose

https://khub.net/documents/135939561/430986542/Effectiveness+of+COVID-19+vaccines+against+Omicron+variant+of+concern.pdf/f423c9f4-91cb-0274-c8c5-70e8fad50074
Vaccine Effectiveness Against Omicron: UK

**Vaccine Effectiveness (Pfizer)**
- VE 88% at 2-9 weeks, dropping to 34-37% at week 15 after second dose
- Booster with Pfizer leads to 75% protection

**Conclusions**
- Concerning data on VE
- AZ recipients were different than Pfizer recipients (first vaccinated included older persons) – residual confounding
- Data support boosters
- No data on severe disease!

https://khub.net/documents/135939561/430986542/Effectiveness+of+COVID-19+vaccines+against+Omicron+variant+of+concern.pdf/f423c9f4-91cb-0274-c8c5-70e8fad50074
• Consistent laboratory data, evidence of increased rates of reinfection, and a small vaccine effectiveness study all suggest that natural and vaccine-induced immunity are diminished against Omicron
  • Lab data focus on antibody, not cell mediated immunity
• Magnitude of decrease and impact on severe disease unclear
• Existing evidence supports that idea that a booster will improve immunity against Omicron
Disease Severity Omicron: South Africa

- Rise in number of cases in Gauteng, South Africa not accompanied by increase in number of deaths
- No clear increase in number of admissions for severe COVID
- Very early data – lag in time to death

• “And yet as the Omicron variant demonstrates, the pandemic is from far over. Persistent vaccine inequity has allowed this to happen.”

Tedros Adhanom Ghebreyesus
Summary

• Epidemiology
  • Rapid emergence and spread of Omicron – most dramatic in southern Africa
  • Extent to which high reproductive number reflects the high transmissibility of Omicron vs. the virus’ ability to evade immunity is uncertain

• Clinical
  • Very limited data suggest that Omicron may be less pathogenic than Delta
    • Too early to draw firm conclusions on this
  • However, if the number of cases increases dramatically, even if the risk of severe disease per infection is lower the total number of deaths may still increase

• Vaccines
  • Vaccine-induced immunity, known to wane over time, substantially less with Omicron
  • Additional data supporting booster shots - all boosters with mRNA vaccines
Questions and Comments