Fighting a Moving Target: SARS-CoV-2 Evolution and Viral Escape

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Overview

- Update on numbers in the United States
- Persistent infection and new variants
- Monoclonal antibodies and effect of new variants
- Where could these variants have come from?

Definitions
- The virus: SARS-CoV-2
- The disease: Coronavirus Disease 2019 (COVID-19)
World: over 105 million cases and 2.2 million deaths
USA: over 27 million cases and 455,000 deaths
US COVID-19: 27,695,000

"Data from The New York Times, based on reports from state and local health agencies."

Wastewater COVID-19 Tracking

https://www.mwra.com/biobot/biobotdata.htm
How Worried Should We Be About Mutations?

Wild-Type

Mutant

Spike Mutations

RNA mutations
SARS-CoV-2 viral evolution in perspective
New variants have emerged previously
How much is SARS-CoV-2 changing over time?
Data from England

UK variant
Dec 28: 28% of cases

Lauring, JAMA 2021
How rapidly did SARS-CoV-2 spread in England?
Trajectory of B.1.1.7 variant spread across the UK
B.1.1.7 is spreading world-wide
How much more transmissible is B.1.1.7 (UK variant)?

Public Health England
How extensive was the surge in South Africa?
How quickly did B.1.351 (501Y.v2) spread in South Africa?

Lauring, JAMA 2021
How do the new variants affect transmission?
Increase in viral load in the respiratory tract

B.1.1.7 (UK)  501Y.v2 (South Africa)

CAPRISA; Kidd, medRxiv 2021

Lower CT (cycle threshold) = higher viral load
B.1.1.7 associated with increased mortality

Davies, medRxiv 2021
Variants of concern in the United States

New York Times
How did these mutations arise?
Uneven rate of SARS-CoV-2 sequencing globally

<table>
<thead>
<tr>
<th>RANK</th>
<th>COUNTRY</th>
<th>REPORTED CASES</th>
<th>SAMPLES SEQUENCED</th>
<th>PERCENTAGE OF CASES SEQUENCED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Australia</td>
<td>28,238</td>
<td>16,537</td>
<td>58.6%</td>
</tr>
<tr>
<td>2</td>
<td>New Zealand</td>
<td>2,128</td>
<td>1,034</td>
<td>48.6%</td>
</tr>
<tr>
<td>3</td>
<td>Taiwan</td>
<td>776</td>
<td>137</td>
<td>17.7%</td>
</tr>
<tr>
<td>4</td>
<td>Denmark</td>
<td>144,047</td>
<td>16,790</td>
<td>11.7%</td>
</tr>
<tr>
<td>5</td>
<td>Iceland</td>
<td>5,683</td>
<td>601</td>
<td>10.6%</td>
</tr>
<tr>
<td>6</td>
<td>Gambia</td>
<td>3,791</td>
<td>360</td>
<td>9.5%</td>
</tr>
<tr>
<td>7</td>
<td>Vietnam</td>
<td>1,421</td>
<td>113</td>
<td>8.0%</td>
</tr>
<tr>
<td>8</td>
<td>Britain</td>
<td>2,116,609</td>
<td>157,439</td>
<td>7.4%</td>
</tr>
<tr>
<td>9</td>
<td>Thailand</td>
<td>5,762</td>
<td>343</td>
<td>6.0%</td>
</tr>
<tr>
<td>10</td>
<td>Japan</td>
<td>207,001</td>
<td>9,599</td>
<td>4.6%</td>
</tr>
<tr>
<td>43</td>
<td>United States</td>
<td>18,229,260</td>
<td>51,212</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Note: Timor-Leste has sequenced 58% of its 33 reported cases.

Sources: GISAID Initiative, COVID-19 Genomics UK Consortium, Johns Hopkins University, Post reporting

HARRY STEVENS/THE WASHINGTON POST
Where could these variants have come from: an unexpected case from Boston

Key questions:
• Is this persistent COVID or reinfection?
• Are there signs of directed viral evolution and viral escape?
• Is this virus infectious?
SARS-CoV-2 viral diversity in perspective

Average pairwise distances shown in parentheses
Phylogenetic evidence of viral persistence and evolution
Reinfection vs persistent infection
Persisting virus is infectious
Disseminated SARS-CoV-2 across tissue types

Choi, NEJM 2020
Directed viral evolution, especially in the spike and receptor binding domains
Could the evolutionary “jumps” have originated from an individual with persistent infection?

Majority of individuals with persistent COVID-19 have a B-cell immunodeficiency
Do mutations affect efficacy of Bnabs to SARS-CoV-2?
Background on monoclonal antibodies (mAbs)

• Engineered humanized mAb has been efficacious for viral infections
• First mAb was palivizumab, developed in 1988 to treat RSV
• For COVID, mAbs have been developed to bind the spike protein to prevent ACE-2 binding
• Two mAb therapies with FDA EUA
  • Lilly LY-CoV555+LY-CoV016 (Bamlanivimab, Etesevimab)
  • Regeneron 10933+10987 (Casirivimab, Imdevimab)
One mAb is good, but two is better

Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19
A Randomized Clinical Trial

Gottlieb JAMA 2021
REGN mAb Data

**Patient Population:**
- Adult, non-hospitalized COVID-19 patients
- Symptom onset ≤ 7 days from randomization
- SARS-CoV-2 confirmed by molecular testing ≤ 72 hours from randomization
- Not on any putative COVID-19 therapies

**Screening**
- Confirmation of SARS-CoV-2 infection and COVID-19 symptom evaluation

**Randomization**

**IV infusion**

**Follow Up**
- Clinical Outcome Assessment (eCOA)
- S, Con Meds, and Medically Attended Visits

**Baseline characteristics well-balanced across treatment arms**
- Mean age: 44 years
- ~ 49% male
- ~ 55% Hispanic
- ~ 13% African American
- ~ 42% Obese
- ~ 65% with ≥1 risk factors for severe COVID-19

**Biomarkers** (phase 1 only in this data cut) and NP swabs

Day 1*
- Baseline

*serum for PK (Day 3, 5, 7, 15 included in Phase 1 only)

End of Study
REGN-COV2 PROVIDED GREATER REDUCTION IN VIRAL LOAD IN THOSE WITH HIGHER VIRAL LOAD AT BASELINE
TIME TO ALLEVIATION OF SYMPTOMS (GOING TO MILD OR ABSENT) IS FASTER IN TREATMENT GROUPS COMPARED TO PBO; EFFECT MOST PRONOUNCED IN SERONEGATIVE POPULATION

**Seronegative population**

- Median Time to Alleviation:
  - Placebo: 13 days
  - Low Dose: 6 days
  - High Dose: 8 days
  - Combined: 6 days

**Overall population**

- Median Time to Alleviation:
  - Placebo: 9 days
  - Low Dose: 6 days
  - High Dose: 8 days
  - Combined: 6 days

**Seropositive population**

- Median Time to Alleviation:
  - Placebo: 7 days
  - Low Dose: 7 days
  - High Dose: 9 days
  - Combined: 7 days
**COVID-19-RELATED MEDICALLY ATTENDED VISITS ARE NUMERICALLY LOWER IN BOTH TREATMENT GROUPS (SERONEGATIVE POPULATION)**

<table>
<thead>
<tr>
<th>Baseline Serology Status: Negative</th>
<th>Placebo (N=33) n/N1 (%)</th>
<th>R10933+R10987 2.4 g IV (N=41) n/N1 (%)</th>
<th>R10933+R10987 8.0 g IV (N=39) n/N1 (%)</th>
<th>R10933+R10987 Combined (N=80) n/N1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 COVID-19 Related Medically-attended Visit through Day 29</td>
<td>5/33 (15.2%)</td>
<td>2/41 (4.9%)</td>
<td>3/39 (7.7%)</td>
<td>5/80 (6.3%)</td>
</tr>
</tbody>
</table>

95% CI [1] Proportion Difference vs Placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=33)</th>
<th>R10933+R10987 2.4 g IV (N=41)</th>
<th>R10933+R10987 8.0 g IV (N=39)</th>
<th>R10933+R10987 Combined (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI [1]</td>
<td>(5.1%, 31.9%)</td>
<td>(0.6%, 16.5%)</td>
<td>(1.6%, 20.9%)</td>
<td>(2.1%, 14.0%)</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.1370</td>
<td>0.2723</td>
<td>0.1324</td>
<td></td>
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</table>
Do mutations affect efficacy of Bnabs to SARS-CoV-2?

• Good news:
  • Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented symptomatic COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents

• Bad news:
  • Lilly's neutralizing antibody bamlanivimab (LY-CoV555) does not protect against the Brazilian (P.1) or South African (501.V2) strains
  • Convalescent sera from South African patients either do not neutralize the South African strain or do so only partially
But not all mAb combination are created equal
Anatomy of the Spike Protein: B.1.351 (501Y.V2)
K417 and E484 are key sites of Ab binding

Regeneron mAbs have fewer overlapping escape sites

<table>
<thead>
<tr>
<th>Escape mutants</th>
<th>REGN10989</th>
<th>REGN10987</th>
<th>REGN10933</th>
<th>REGN10934</th>
<th>REGN10933/10987</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>7.27 × 10⁻¹²</td>
<td>3.65 × 10⁻¹¹</td>
<td>5.57 × 10⁻¹¹</td>
<td>5.99 × 10⁻¹¹</td>
<td>3.28 × 10⁻¹¹</td>
</tr>
<tr>
<td>K417E</td>
<td>2.49 × 10⁻¹¹</td>
<td>3.10 × 10⁻¹¹</td>
<td>8.33 × 10⁻⁹</td>
<td>2.70 × 10⁻¹¹</td>
<td>4.15 × 10⁻¹¹</td>
</tr>
<tr>
<td>K444Q</td>
<td>2.47 × 10⁻¹¹</td>
<td>NC</td>
<td>7.81 × 10⁻¹¹</td>
<td>5.38 × 10⁻⁹</td>
<td>1.23 × 10⁻¹⁰</td>
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<tr>
<td>V445A</td>
<td>2.65 × 10⁻¹¹</td>
<td>NC</td>
<td>8.82 × 10⁻¹¹</td>
<td>1.42 × 10⁻¹⁰</td>
<td>1.54 × 10⁻¹⁰</td>
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<tr>
<td>N450D</td>
<td>4.10 × 10⁻¹¹</td>
<td>1.20 × 10⁻⁹</td>
<td>7.60 × 10⁻¹¹</td>
<td>1.88 × 10⁻¹⁰</td>
<td>1.88 × 10⁻¹⁰</td>
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<tr>
<td>Y453F</td>
<td>2.77 × 10⁻¹¹</td>
<td>1.04 × 10⁻¹⁰</td>
<td>NC</td>
<td>2.17 × 10⁻¹⁰</td>
<td>1.15 × 10⁻¹⁰</td>
</tr>
<tr>
<td>L455F</td>
<td>1.77 × 10⁻¹¹</td>
<td>3.87 × 10⁻¹¹</td>
<td>NC</td>
<td>4.34 × 10⁻¹¹</td>
<td>5.87 × 10⁻¹¹</td>
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<tr>
<td>E484K</td>
<td>NC</td>
<td>6.25 × 10⁻¹¹</td>
<td>1.13 × 10⁻⁹</td>
<td>NC</td>
<td>6.19 × 10⁻¹¹</td>
</tr>
<tr>
<td>G485D</td>
<td>NC</td>
<td>2.34 × 10⁻¹¹</td>
<td>2.05 × 10⁻¹⁰</td>
<td>4.47 × 10⁻¹¹</td>
<td>4.71 × 10⁻¹¹</td>
</tr>
<tr>
<td>F486V</td>
<td>NC</td>
<td>3.16 × 10⁻¹¹</td>
<td>NC</td>
<td>3.50 × 10⁻¹¹</td>
<td>8.8 × 10⁻¹¹</td>
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<tr>
<td>F490L</td>
<td>3.10 × 10⁻⁹</td>
<td>3.56 × 10⁻¹¹</td>
<td>4.53 × 10⁻¹¹</td>
<td>1.94 × 10⁻⁹</td>
<td>3.64 × 10⁻¹¹</td>
</tr>
<tr>
<td>F490S</td>
<td>2.23 × 10⁻¹⁰</td>
<td>4.42 × 10⁻¹¹</td>
<td>6.63 × 10⁻¹¹</td>
<td>8.91 × 10⁻⁹</td>
<td>3.4 × 10⁻¹¹</td>
</tr>
<tr>
<td>Q493K</td>
<td>NC</td>
<td>4.19 × 10⁻¹¹</td>
<td>NC</td>
<td>3.45 × 10⁻¹⁰</td>
<td>3.24 × 10⁻¹⁰</td>
</tr>
</tbody>
</table>

Wang bioRxiv 2021
Rapid emergence of resistance to Regeneron mAbs in the immunocompromised patient

Starr, Science 2021
Will the new variants compromise vaccine efficacy?

Data from this sample set shows mRNA-1273 maintained activity against all circulating strain variants tested to date, and only the B.1.351 variant showed reduced neutralizing titers, as assessed from vaccinated human and NHP sera. **Viral escape was not detected from any sample and neutralizing titers remained above those previously found to be protective in NHP challenge studies.**
Concerns about other vaccines and new variants
Key Points

• Sudden emergence of novel SARS-CoV-2 variants with a large set of mutations suggests a “hidden” source of viral evolution in the community
  • Potential viral sequencing blind spots and a need to ramp up efforts
  • Immunosuppressed individuals (especially B-cell suppression) may cause persistent COVID and accelerated viral evolution with mAb resistance

• Novel variants have greater transmissibility, potentially from higher viral shedding and some evidence of more severe disease

• Novel variants (especially B.1.351 and P.1) are a threat to current monoclonal antibody treatments and vaccines
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