COVID-19: Lessons Learned?
Variants and Vaccines

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## History of Variants

<table>
<thead>
<tr>
<th>Name</th>
<th>Date of Emergence</th>
<th>Origen</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild Type</td>
<td>October 2019</td>
<td>China</td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>September 2020</td>
<td>UK</td>
<td>B.1.1.7</td>
</tr>
<tr>
<td>Beta</td>
<td>May 2020</td>
<td>South Africa</td>
<td>B.1.351</td>
</tr>
<tr>
<td>Gamma</td>
<td>November 2020</td>
<td>Brazil</td>
<td>P.1</td>
</tr>
<tr>
<td>Delta</td>
<td>October 2020</td>
<td>India</td>
<td>B.1.617.2</td>
</tr>
<tr>
<td>Lambda</td>
<td>June 2021</td>
<td>Peru</td>
<td>C.37</td>
</tr>
<tr>
<td>Mu</td>
<td>June 2021</td>
<td>Columbia</td>
<td>B1.621</td>
</tr>
<tr>
<td>Iota</td>
<td>November 2020</td>
<td>New York</td>
<td>B.1.526</td>
</tr>
</tbody>
</table>
Variants
A Few Specifics

• Alpha-
  • Binds more tightly to ACE2 binding receptor (N501Y)
  • 50% more contagious than wild type
  • May have been driven by convalescent plasma and monoclonal antibodies

• Beta-
  • Has N501Y (increased transmission)
  • Also has E484K (decreased neutralization by antibody)

• Gamma-
  • Increased transmission (N501Y)
  • Resists proteolytic cleavage (D614G) of spike protein
Variants

• Delta-
  • Now dominant variant in most of the world
  • Markely increased transmission- (similar to chicken pox)
  • Produces higher viral loads than previous variants
  • Produces longer duration of shedding
  • Evades immune response to previous (non-delta) infections
  • Less sensitive to neutralizing antibodies
  • Lower vaccine efficacy
Transmission of Delta variant vs. ancestral strain and other infectious diseases

- Delta variant is **more** transmissible than:
  - MERS & SARS
  - Ebola
  - Common cold
  - Seasonal flu & 1918 (“Spanish”) flu
  - Smallpox

- Delta variant is **as** transmissible as:
  - Chicken Pox

Note: Average case-fatality rates and transmission numbers are shown. Estimates of case-fatality rates can vary, and numbers for the new coronavirus are preliminary estimates.
The coming of Delta - Vaccines

Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant

Julia Stowe¹, Nick Andrews¹, Charlotte Gower¹, Eileen Gallagher¹, Lara Utsi³, Ruth Simmons¹, Simon Theilwall¹, Elise Tessler¹, Natalie Groves¹, Gavin Dabrera³, Richard Myers¹, Colin Campbell¹, Gayatri Amirthalingam¹, Matt Edmunds¹, Maria Zambon¹, Kevin Brown¹, Susan Hopkins¹, Meera Chand², Mary Ramsay¹, Jamie Lopez Bernal¹,²

- Single dose BioNTech/Pfizer vaccine (PHE June 2021)
  - 33% protection against symptomatic disease (Alpha > 50%)
  - 75% protection against hospitalization
- Fully vaccinated (2 weeks after second dose)
  - 80% protection against infection
  - 88% protection against symptomatic disease (Alpha 93%)
  - 94% protection against hospitalization
Variant sensitivity to neutralizing antibodies

• Sera from individuals having received one dose of Pfizer vaccine barely inhibited variants Delta and Beta

• Two doses generated a neutralizing response in 95% of individuals, with titers 3-5 fold lower against Delta than Alpha

• Delta spread is associated with an escape to antibodies targeting non-RBD and RBD Spike

https://www.nature.com/articles/s41586-021-03777-9
Variants

- **Lambda**-
  - More transmissible than alpha or gamma, but not as transmissible as delta
  - More resistant to vaccines than alpha or gamma
  - More resistant to neutralizing antibodies

- **Mu**-
  - More resistant to vaccines and natural immunity
  - Less transmissible than delta

- **Delta plus (B.1.617.2AY1/2)**
  - Spreads more easily; binds better to lung tissue
  - May not be more deadly than delta
  - AY1 or 2 adds to immune escape
  - May be a serious problem for monoclonal antibodies
  - May become the first “Variant of High Consequence”
Variants
So What??

• Variants can arise spontaneously or in response to selective pressure
• Variants can lead to increased spread or virulence
• We could be 1-2 mutations from making current vaccines ineffective
• Increasing vaccine coverage is crucial to prevent worse mutations
COVID-19 Vaccines
(Real and Potential)

• Killed Virus Vaccines
• Live Virus Vaccines
• Split Virus Vaccines
• DNA Vaccines
• Adenovirus Vector Vaccines
• mRNA Vaccines
Adenovirus Vector Vaccine

• Splice DNA of spike protein into adenovirus
• Adenovirus infects vaccine recipient
• Spike protein produced along with viral replication
• Spike protein interacts with host immune system
• Anti-spike protein antibodies are produced.
Adenovirus Vector Vaccine
mRNA Vaccine

• mRNA packaged to prevent degradation
• Packaged mRNA injected into recipient
• mRNA is transcribed by tRNA to make spike protein
• Spike protein interacts with immune system
• Anti-spike antibodies are produced
mRNA Vaccine Technology

In Deltoid Muscle

B cell

CD8 T cell

Viral peptide fragments

MHC I receptor

Protein degradation

Muscle Cell

Viral protein

Ribosome

In Deltoid Muscle and Lymph Nodes

B cell

CD4 T Cell

Viral peptide fragments

MHC II receptor

Endosome
Vaccine Efficacy

Greater risk of disease, hospitalization and death among unvaccinated vs. vaccinated people: National estimates

At current incidence, 35,000 symptomatic infections per week among 162 million vaccinated Americans

Data from COVID Tracker as of July 24, 2021. Average incidence 100 cases per 100,000 persons per week. Vaccine effectiveness against symptomatic illness = 88% (Lopez Bernal et al. NEJM 2021), where risk is (1 - VE) or 12%. Vaccine effectiveness hospitalization (or death) = 96% (Stowe et al. PHE preprint), where risk is (1 - VE) or 4%. Rate in unvaccinated = Community rate/(1-fully vaccinated coverage) + (1-VE)*fully vaccinated coverage). Rate in fully vaccinated=(1-VE)*Rate in unvaccinated. Fully vaccinated coverage proportions were from COVID Data Tracker as of July 24, 2021 (50% for US).
Lower estimates of VE for mRNA vaccines among immunocompromised populations: Published evidence

- 71% (CI 37-87%) **against SARS-CoV-2 infection** 7-27 days after 2nd dose of Pfizer-BioNTech vaccine among immunosuppressed* people vs. 90% (CI 83-96%) overall\(^1\)

- 80% **against SARS-CoV-2 infection** \(\geq7\) days after 2nd dose of mRNA vaccine among people with IBD on immunosuppressive medication\(^2\)

- 75% (CI 44-88%) **against symptomatic COVID-19** 7-27 days after 2nd dose of Pfizer-BioNTech vaccine among immunosuppressed* people vs. 94% (CI 87-97%) overall\(^1\)

- 59% **against COVID-19 hospitalization** among immunocompromised \(\geq14\) days after 2nd dose of mRNA vaccine\(^3\) vs. 91% (CI 86-95%) without immune compromise\(^3\)

*Immunocompromised conditions (e.g., recipients of hematopoietic cell or solid organs transplant, patients under immunosuppressive therapy, asplenia, and chronic renal failure: advanced kidney disease, dialysis, or nephrotic syndrome)

1. Chodick et al. *Clinical Infectious Diseases*, ciab438, [https://doi.org/10.1093/cid/ciab438](https://doi.org/10.1093/cid/ciab438)
3. Tenforde et al. *medRxiv* preprint: [https://doi.org/10.1101/2021.07.08.21259776]
Is Moderna better than BioNTech/Pfizer
Herd Immunity

• May not be achievable by vaccination alone
• Decreasing vaccine efficacy increases the vaccine coverage required
• Complicated by asymptomatic infections
• Based on interaction of Ro, vaccine coverage, vaccine efficacy, and natural immunity in population
Herd Immunity
Breakthrough Infections

• Unavoidable if vaccine is less than 100% effective
• Becomes more common as vaccine coverage increases
• Depends on interaction of vaccine uptake, vaccine efficacy and (possibly) Ro
• Despite breakthroughs, there is still a 25-fold higher rate of hospitalization and death among unvaccinated
Screening Method: Relationship between % of population vaccinated, estimated vaccine effectiveness, and % of cases vaccinated
As of 21 July 2021 in the U.S.:
- For every 102K vaccinated
- There have been a TOTAL of 1,603 new hospitalizations
- And 417 COVID-19 deaths

**IMPORTANT NOTES:**
1. These are snapshots in time and compare different TOTALS over different time periods. It also compares more symptomatic infections to more severe ones that lead to hospitalization.
2. The DATA does NOT imply the chances of getting infected or the severity of the infections. It means that as of last week, only about 1 in 1000 of ALL fully-vaccinated had symptomatic infections. The likely reason is that recently, a combination of masking, social distancing, vaccinations, and milder spring/summer weather drove vaccinated AND unvaccinated infection rates to an all-time low.
3. There is every reason to believe that the Delta variant WILL infect a lot of vaccinated people.
4. BUT the vaccines are INCREDIBLY effective at preventing and reducing the severity of infections. Because Delta has 1,000X the viral load of Alpha/regular COVID, there will be CLUSTERS of vaccinated people who get infected, but their disease will be much less severe than if they were unvaccinated.

as of 26 July 2021, source: https://abcn.ws/3y9lpv
Boosters

• We have no idea about the proper dosing regime
• Antibody titers decrease after 6-8 months
• 3\textsuperscript{rd} vaccination significantly increases antibody titers
• We don’t know the significance of antibody titers.
• 3\textsuperscript{rd} doses decrease the odds of testing positive for COVID-19 for at least 3 weeks.
• There are few data on significant endpoints.
COVID-19 Vaccine: 3rd Dose Strongly Boosts Neutralizing Titers Against Delta Strain\textsuperscript{1,2}

- Post dose 3 titers vs. the Delta variant are >5-fold post dose 2 titers in 18-55 y/o & >11-fold post dose 2 titers in 65-85 y/o
- Estimated potential for up to 100-fold increase in Delta neutralization post-dose three compared to pre-dose three

1. Initial data, 2. Samples were tested against each variant separately, PRNT: Plaque Reduction Neutralizing Test, Wt. Wild Type, GMR: Geometric Mean Ratio
COVID-19 Vaccine: Neutralization Titers Much Higher Post 3rd Dose Than Post 2nd for Wild Type and Beta Variants

18-55 y/o (n=11/gp)

65-85 y/o (n=12/gp)

PRNT
PRNT
GMR<sub>B</sub>

1. Initial data, Phase 1 sentinel subjects received dose 1 & 2 of 30mcg BNT162b2 21 days apart; subjects then came back and received BNT162b2 30 mcg as a 3rd booster dose;
2. Samples were tested against each variant separately; PRNT: Plaque Reduction Neutralizing Test; GMR: Geometric Mean Ratio; WT: Wild Type; LOD: Limit of Detection

Source: Current 2021 Findings