An Update on SARS-CoV-2, COVID-19 and Variants

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September 16, 2021

No relevant disclosures

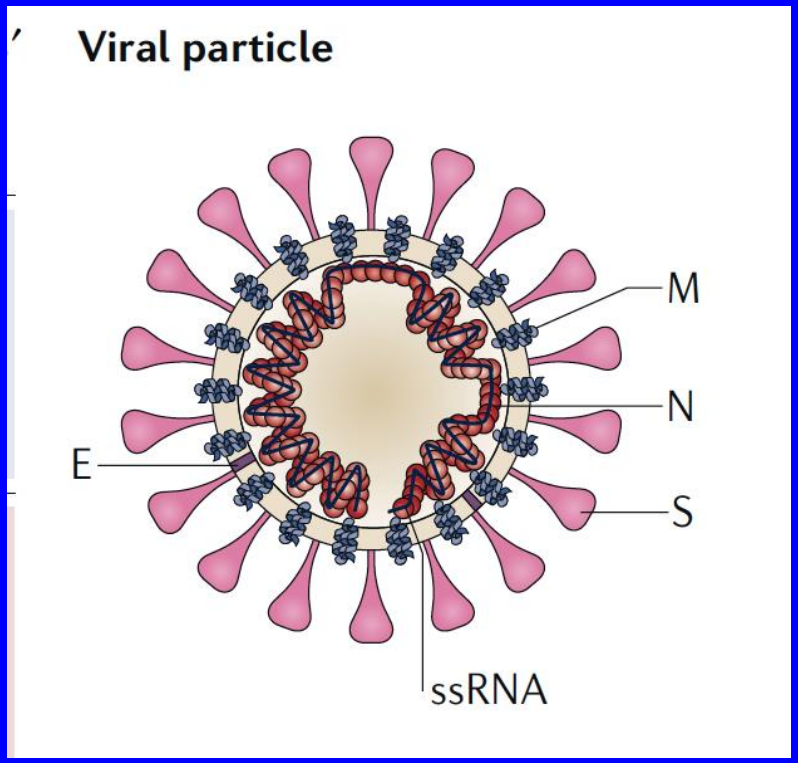
Overview

- COVID-19 update, origins and how variants emerge
- Classification of variants
- Delta, Beta and other recent variants of concern
- Vaccine effectiveness, breakthrough infections and boosters

COVID-19 update

- US 41.4 million cases, 662,620 deaths
  - 307.2/100,000 7-day average
  - CA 4.38 million cases, 67,001 deaths
    - 20.2/100,000 7-day average
  - LA County 1.44 million cases, 25,713 deaths
- 54.1% (179.9 million) Americans fully vaccinated
  - 68.5% (23.2 million) CA residents vaccinated
  - 67% (5.9 million) LA residents ≥12 vaccinated
    - https://covid.cdc.gov/covid-data-tracker/#datatracker-home; https://covid19.ca.gov/; http://publichealth.lacounty.gov/media/coronavirus/data/index.htm

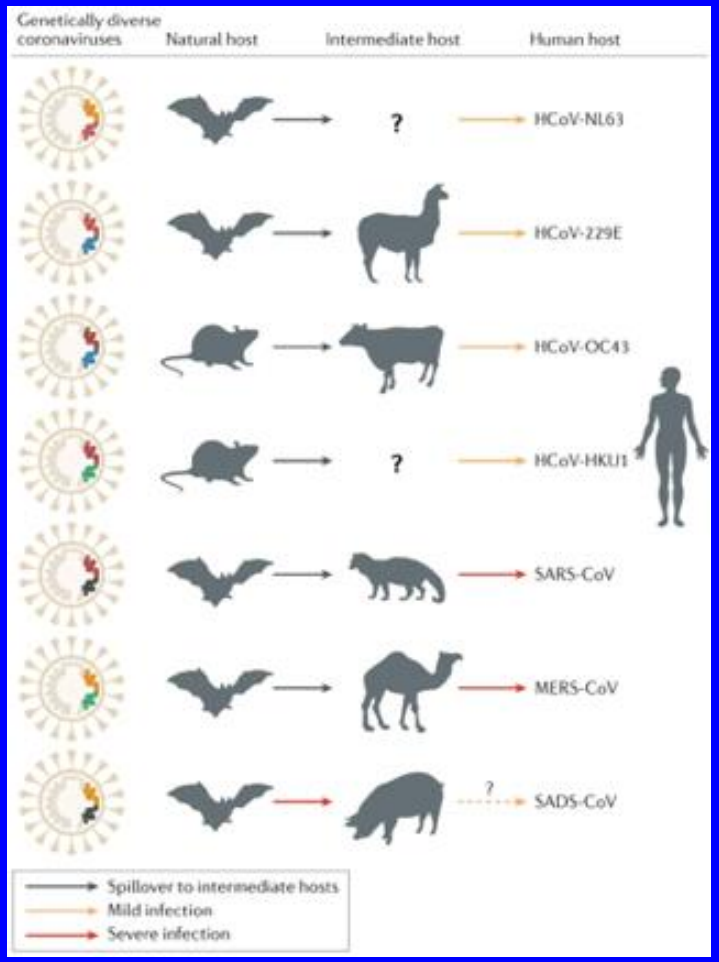
Coronaviruses



- Large single stranded enveloped RNA viruses
  - 4 genera α, β, γ, δ
  - α- and β coronaviruses
    - Respiratory tract infections in humans
    - Gastroenteritis in animals

Cui. Nature Rev Micro 2019;17:181-92.

SARS-CoV-2



Cui. Nature Rev Micro 2019;17:181-92.

- Zoonosis
  - Closely related to bat viruses (SL-CoVZC45 & SL-CoVZXC21)
  - No intermediate host identified to date
  - Binds to ACE-2 receptor in humans
    - Lu. Lancet 2020;395:565-74.
    - Giovanetti. Biochem Biophys Res Comm 2021;538:88-91.

Mutations and RNA viruses

- Mutations
  - changes in nucleic acid base pairs
  - Natural byproduct of RNA replication
    - Coronaviruses have proofreading enzyme
  - Most mutations do not impart selective advantage
    - Mutations the improve transmissibility, virulence or other advantages may become dominate
      - Lauring. JAMA 2021;325(6):529-31.

Variants

- Variants
  - SARS-CoV-2 viruses with different genomic sequences
  - Could be 1 or many mutations
  - Alpha (B.1.1.7)
    - 3 deletions and 10 substitutions in spike glycoprotein
      - Lauring. JAMA 2021;325(6):529-31.
      - https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html

Spike protein mutations and a changing virus

- Spike glycoprotein binds to ACE2 receptor for cell entry
- D614G, an early variant
  - Substitution of aspartic acid with glycine at position 614 of the Spike glycoprotein
  - Rare before March, 2020
    - 74% of sequenced viruses by June, 2020
    - 2 to 8 fold higher viral loads in human airway tissue
      - Plante. Nature 2021;592:116-121.

Variant classifications

- Variants of Interest (Eta, Iota, Kappa)
  - mutations with potential diagnostic or treatment impact, possible increase in transmissibility or disease severity
    - Limited prevalence in US or worldwide
- Variants of Concern (Alpha, Beta, Delta, Gamma)
  - Increased transmissibility, more severe disease, reduced effectiveness of treatments or vaccines, or diagnostic detection failures
- Variants of High Consequence (none)
  - Significantly reduced effectiveness of vaccines, other prevention measures or treatments
    - https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html

Variants of Concern

- Alpha (B.1.1.7; United Kingdom, Sept 2020)
  - 50% more transmissible, possible increased virulence, no change in vaccine effectiveness
- Beta (B.1.351; South Africa, May 2020)
  - 50% more transmissible, possible increased virulence, decreased response to monoclonal/vaccine antibody levels
- Gamma (P.1; Brazil, Nov 2020)
  - Unclear change transmissibility and virulence, decreased response to monoclonal/vaccine antibody levels
    - https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/
    - https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html

Delta variant (B.1.617.2, India Oct 2020)

- 98.8% of COVID-19 cases in US
  - Includes associated subtypes (AY.1, AY.2, AY.3, etc.)
- Approximately 2x more transmissible than original SARS-CoV-2 variants
  - https://www.cdc.gov/coronavirus/2019-ncov/variants/delta-variant.html
- 49% increased risk of hospitalization; 51% increased risk of death compared with Alpha
  - Fisman. https://www.medrxiv.org/content/10.1101/2021.07.05.21260050v3

Delta and risk of hospitalization Scotland, April 1 – June 6, 2021

- 19 543 SARS-CoV-2 infections
  - 377 hospitalizations for COVID-19
    - 7723 (39·5%) of cases and 134 (35·5%) hospitalizations due to Delta
- Delta cases had increased risk of COVID-19 hospitalization
    - HR 1·85 (95% CI 1·39–2·47)
  - BNT162b2 (Pfizer) 79% VE
  - ChAdOx1 nCoV-19 (AstraZeneca) 60% VE
      - Sheikh. Lancet 2021;397:2461-62.

Delta and vaccine effectiveness

- 19,109 UK residents ≥ 16 with symptomatic COVID-19 caused by Alpha or Delta variants
  - 2 dose BNT162b2 vaccine (Pfizer)
    - 93.7% (95% CI 91.6-95.3%) effective against Alpha
    - 88.0% (95% CI 85.3-90.1%) effective against Delta
  - 2 dose ChAdOx1 nCoV-19 vaccine (AstraZeneca)
    - 74.5% (95% CI 68.4-79.4%) effective against Alpha
    - 67.0% (95% CI 61.3-71.8%) effective against Delta
      - Bernal et al. N Engl J Med 2021; 385:585-594.

Delta and Breakthrough Infections

- 227 healthcare workers with SARS-CoV-2 infection between March 1-July 21, 2021
  - 83.8% (109/130) fully vaccinated HCWs were symptomatic
  - 88.9% unvaccinated HCWs symptomatic
  - 93.9-96.2% effectiveness March through June
  - 65.5% vaccine effectiveness in July
    - Keehner. New Engl J Med September 1, 2021. DOI: 10.1056/NEJMc2112981

Secondary Cases of Covid-19 According to Vaccination

Vaccination Status of Index Patient	Household Contacts	Secondary Cases	Adjusted Odds Ratio (95% CI)
	no.	*no. (%)*	
Not vaccinated before testing positive	960,765	96,898 (10.1)	Reference
Vaccinated with ChAdOx1 nCoV-19 vaccine ≥21 days before testing positive	3,424	196 (5.7)	0.52 (0.43–0.62)
Vaccinated with BNT162b2 vaccine ≥21 days before testing positive	5,939	371 (6.2)	0.54 (0.47–0.62)

* Odds ratios were adjusted for the age and sex of the index patient and their household contact, geographic region, calendar week of the index case, and an index of multiple deprivation and household type and size. CI denotes confidence interval, and Covid-19 coronavirus disease 2019.

Harris et al. N Engl J Med 2021;385:759-760

Vaccines and SARS-CoV-2 Transmission, 2nd study

- 194,362 household members of 144,525 health care workers
  - HCWs vaccinated with BNT162b2 (Pfizer) vaccine or ChAdOx1 nCoV-19 (AstraZeneca)
  - December 8, 2020 - March 3, 2021
- 30% reduced risk of infection 14 days after 1st dose
  - HR 0.70 (95% CI, 0.63 to 0.78)
- 54% reduced risk 14 days after 2nd dose
  - HR 0.46 (95% CI, 0.30 to 0.70)
    - Shah. New Engl J Med September 8, 2021 DOI: 10.1056/NEJMc2106757

Vaccine effectiveness New York, May 3-July 25, 2021

- VE against new adult COVID-19 cases declined from 91.7% to 79.8%
  - 1.31 COVID-19 cases/100,000 person-days in fully vaccinated adults; 10.69 cases/100,000 person-days in unvaccinated
- VE against hospitalization was stable at 91.9% to 95.3%
  - Rosenberg. MMWR August 27, 2021 / 70(34);1150-1155.

Vaccine effectiveness in LA

- 43,127 confirmed SARS-CoV-2 cases in LA County May 1–July 25
  - 91.2% of July infections due to Delta variant
  - In July, unvaccinated persons 4.9 times more likely to be infected; 29.2 times more likely to be hospitalized
    - 29.4/100,000 vs 1.0/100,000
  - Unvaccinated COVID-19 patients were younger, less likely to have co-morbid conditions
    - Griffin. MMWR August 27, 2021 / 70(34);1170–1176.

Preventing COVID-19 hospitalizations in older adults

- 7,280 adults ≥65 years old, Feb 1-April 30, 2021
  - VE in ≥ 65–74 years old
    - 96% (95% CI 94%–98%) Pfizer
    - 96% (95% CI 95%–98%) Moderna
    - 84% (95% CI 64%–93%) for Johnson & Johnson
  - VE in ≥75 years
    - 91% (95% CI 87%–94%) Pfizer
    - 96% (95% CI 93%–98%) Moderna
    - 85% (95% CI 72%–92%) for Johnson & Johnson
      - Moline. MMWR August 13, 2021 / 70(32);1088-1093.

Vaccine effectiveness against serious COVID-19 disease in US

- Adults ≥ 50 years old with COVID-19 like symptoms Jan 1 – June 22, 2021
  - 41,552 hospitalizations (median age 74)
    - 4321 confirmed SARS-CoV-2 infections
    - 9% Black, 11% Hispanic
  - 21,522 emergency department/urgent care clinic visits (median age 70)
    - 3251 confirmed SARS-CoV-2 infections
      - Thompson et al. New Engl J Med September 8, 2021, DOI: 10.1056/NEJMoa2110362

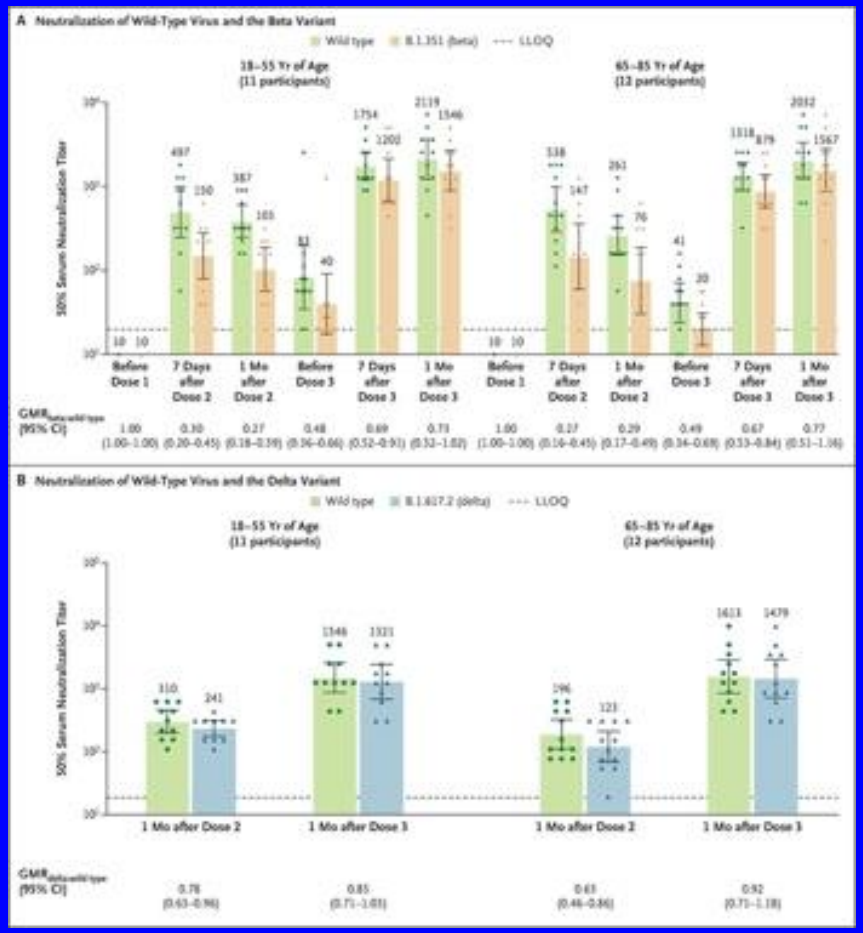
Vaccine effectiveness against serious COVID-19 disease in US

- BNT162b2 (2 doses, Pfizer)
  - 87% (85-90%) protection for hospitalization
  - 89% (85-91%) protection ER/Urgent care visit
- mRNA-1273 (2 doses, Moderna)
  - 91% (89-93%) protection for hospitalization
  - 92% (89-94%) protection ER/Urgent care visit
- Ad26.COV2.S (one dose, Johnson & Johnson)
  - 68% (50-79%) protection for hospitalization
  - 73% (59-82%) protection ER/Urgent care visit
    - Thompson et al. New Engl J Med September 8, 2021, DOI: 10.1056/NEJMoa2110362

Vaccine effectiveness after 6 months

- 44,486 participants in BNT162b2 vaccine trial (Pfizer) through March 13, 2021
  - 81 cases of Covid-19 in vaccine recipient
  - 873 Covid-19 cases in placebo recipients
- Overall VE 91.1% (95% CI, 88.8-93.0)
  - 96.7% against severe disease
  - 83.7% 4 months after the second dose to the study cutoff
- No new major adverse reactions detected
  - Thomas. New Engl J Med September 15, 2021 DOI: 10.1056/NEJMoa211034

Neutralizing Responses after 3 Doses of BNT162b2.

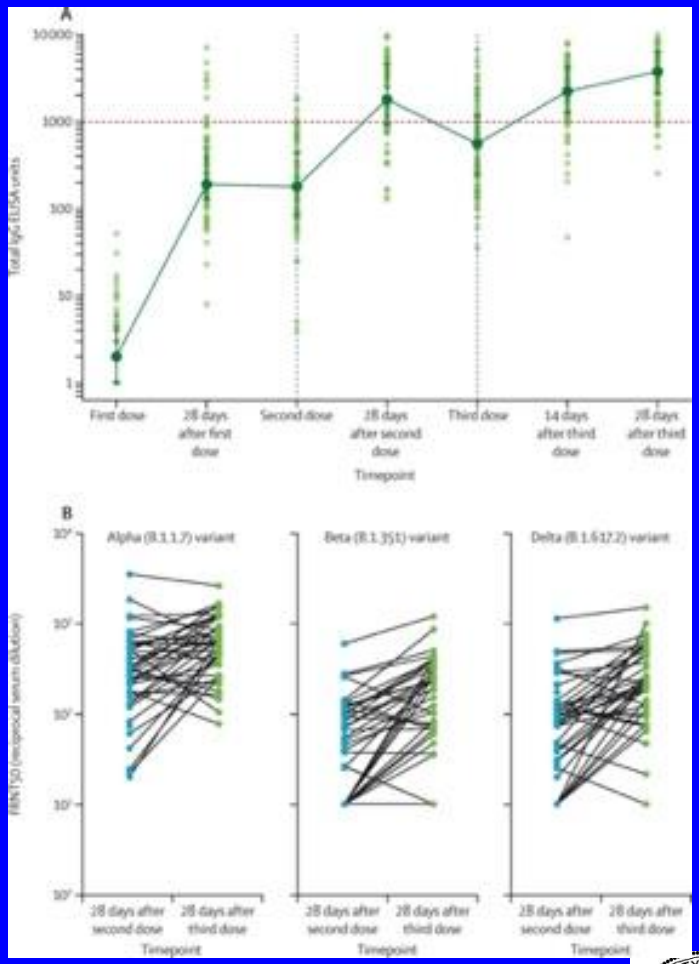


- 3rd vaccine dose ~ 8 months after dose 2
  - 11 participants 18-55
  - 12 participants 65-85
- Neutralizing titers 5 to 7 times higher 1 month after dose 3 compared with dose 2

AR Falsey et al. N Engl J Med 2021. DOI: 10.1056/NEJMc2113468

ChAdOx1 vaccine delayed dosing and booster

- 321 participants with 2nd dose vaccine
  - 8–12 weeks (267, 83%)
  - 15–25 weeks (24, 7%)
  - 44–45 weeks (30, 9%)
- 90 participants vaccinated 3rd dose ChAdOx1 nCoV-19.



Flaxman. Lancet 2021;398(103040):981-990.

Effectiveness of vaccine booster

- 1,186,779 Israeli residents ≥ 60 years old vaccinated with BNT162b2 (Pfizer)
  - Compared booster with no booster between July 30 – August 31, 2021
  - 4439 infections, 294 cases of severe disease
- Infection lowered by 11.3
- Severe disease lowered by 19.5
  - Severe illness difference 7.5 cases/100,000 person-days
    - Bar-On. New Engl J Med September 15, 2021 DOI: 10.1056/NEJMoa2114255

Vaccine Adverse Reactions

- 884,828 persons
  - myocarditis (risk ratio, 3.24; 95% CI, 1.55 to 12.44) risk difference, 2.7 events per 100,000 persons
  - Myocarditis in SARS-CoV-2 infection (risk ratio, 18.28; 95% CI, 3.95 to 25.12; risk difference, 11.0 events per 100,000 persons)
  - appendicitis (risk ratio, 1.40); risk difference, 5.0 events per 100,000 persons
  - Herpes zoster infection (risk ratio, 1.43); risk difference, 15.8 events per 100,000 persons
    - Barda. N Engl J Med 2021; 385:1078-1090.

Summary

- Delta variant currently the dominant variant in the US
  - Increased transmissibility, possible increased virulence
- Vaccine induced neutralizing antibodies decline over time
  - Increased risk of breakthrough infections (? Delta, waning immunity, both)
- Boosters increase immune responses
  - Limited data suggest may reduce serious disease
- Current vaccines remain highly effective against serious COVID-19 disease

Thank you

Questions