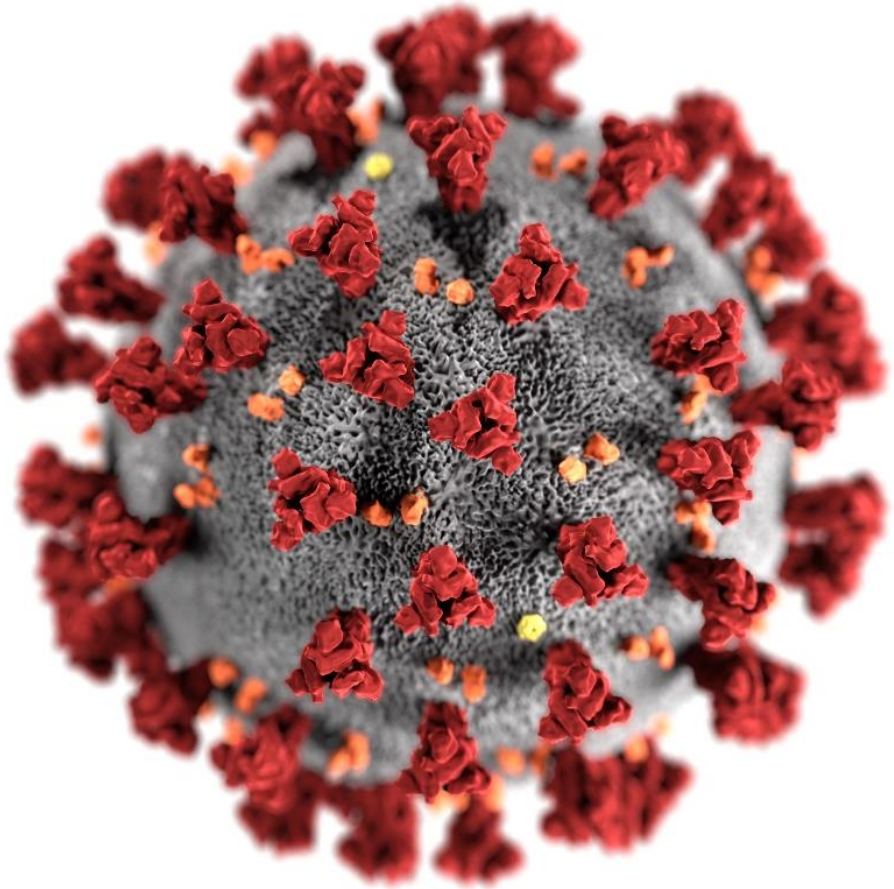
Emerging SARS-CoV-2 Variants: Considerations for Vaccine



CDR Heather Scobie PhD, MPH

ACIP Meeting

March 1, 2021

Background

SARS-CoV-2 Variants

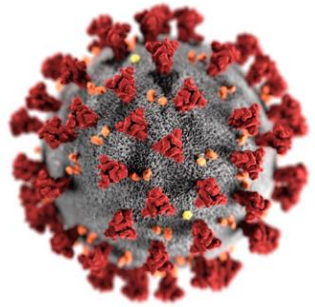
- Multiple SARS-CoV-2 variants circulating globally
  - After emerging, some disappear; others persist
- CDC and others are studying these variants to understand whether they:
  - Spread more easily from person to person
  - Cause milder or more severe disease in people
  - Detected by available diagnostic tests
  - Respond to therapeutics currently used to treat people for COVID-19
  - Change effectiveness of COVID-19 vaccines
- Variants classified, e.g., "variant of concern"

https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html
https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update

Why are new SARS-CoV-2 variants emerging?

- Viruses constantly change through mutation, so new variants are expected
  - SARS-CoV-2 has low mutation rate, compared with influenza and HIV
- Evolutionary selection — still being characterized, may be driven by:
  - Chronic infection (e.g., immunocompromised)
  - Interspecies transmission (e.g., minks)
  - Therapeutic treatment (e.g., monoclonal antibodies, convalescent sera)
  - Prior immunity to strains with limited cross-reactivity
  - Increased transmissibility
  - Founder effect — small number of genotypes seed a new population

Example of SARS-CoV-2 strain replacement



D614G – worldwide

- Greater infectivity, more open conformation of viral spike protein
- Likely increased transmissibility (20%)
- Not more clinically severe
- Current vaccines are still highly effective

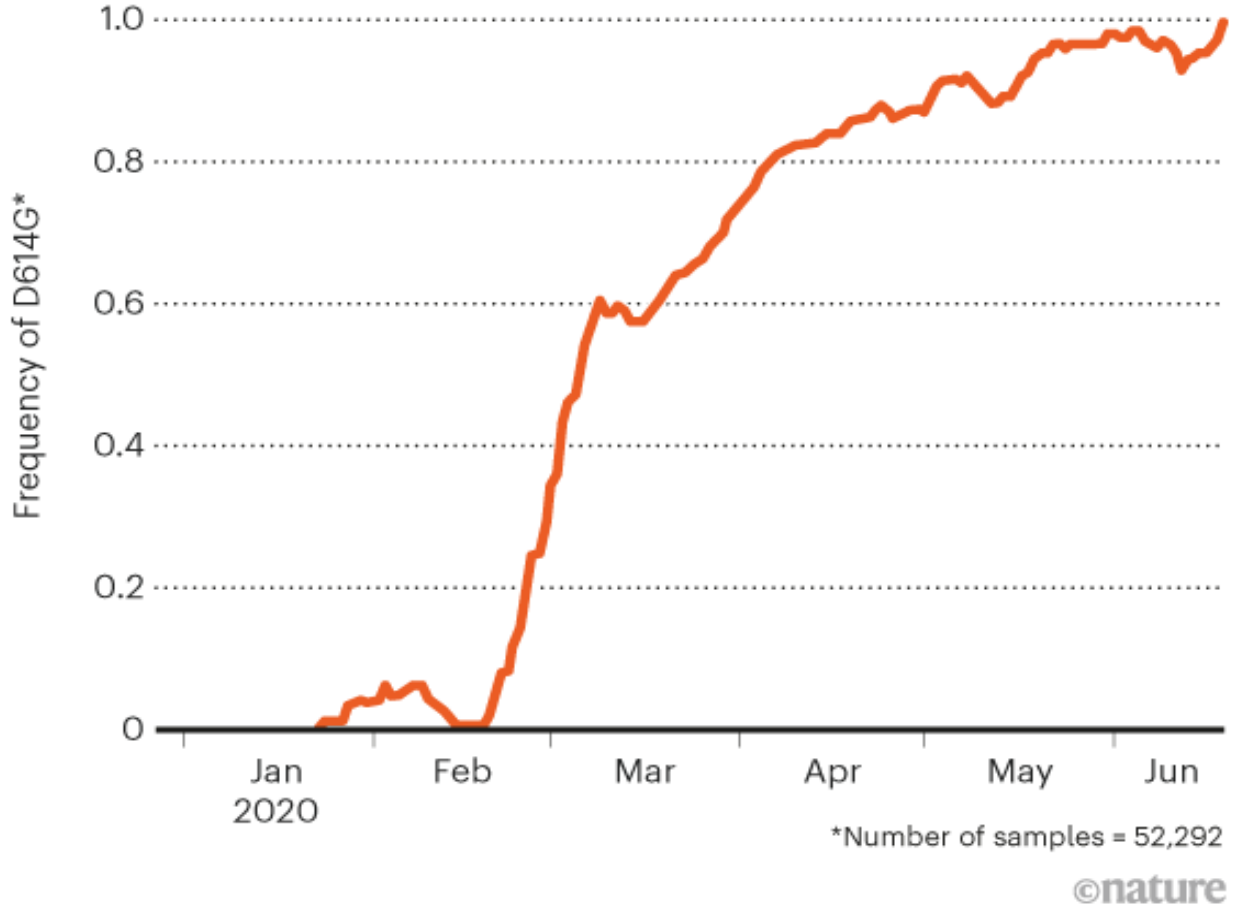


Figure source: Callaway E. *Nature* (2020). https://www.nature.com/articles/d41586-020-02544-6
Volz et al. Cell (2021). https://www.sciencedirect.com/science/article/pii/S0092867420315373
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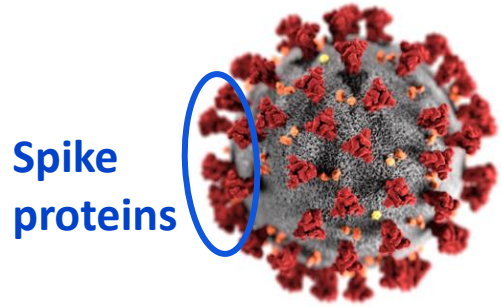

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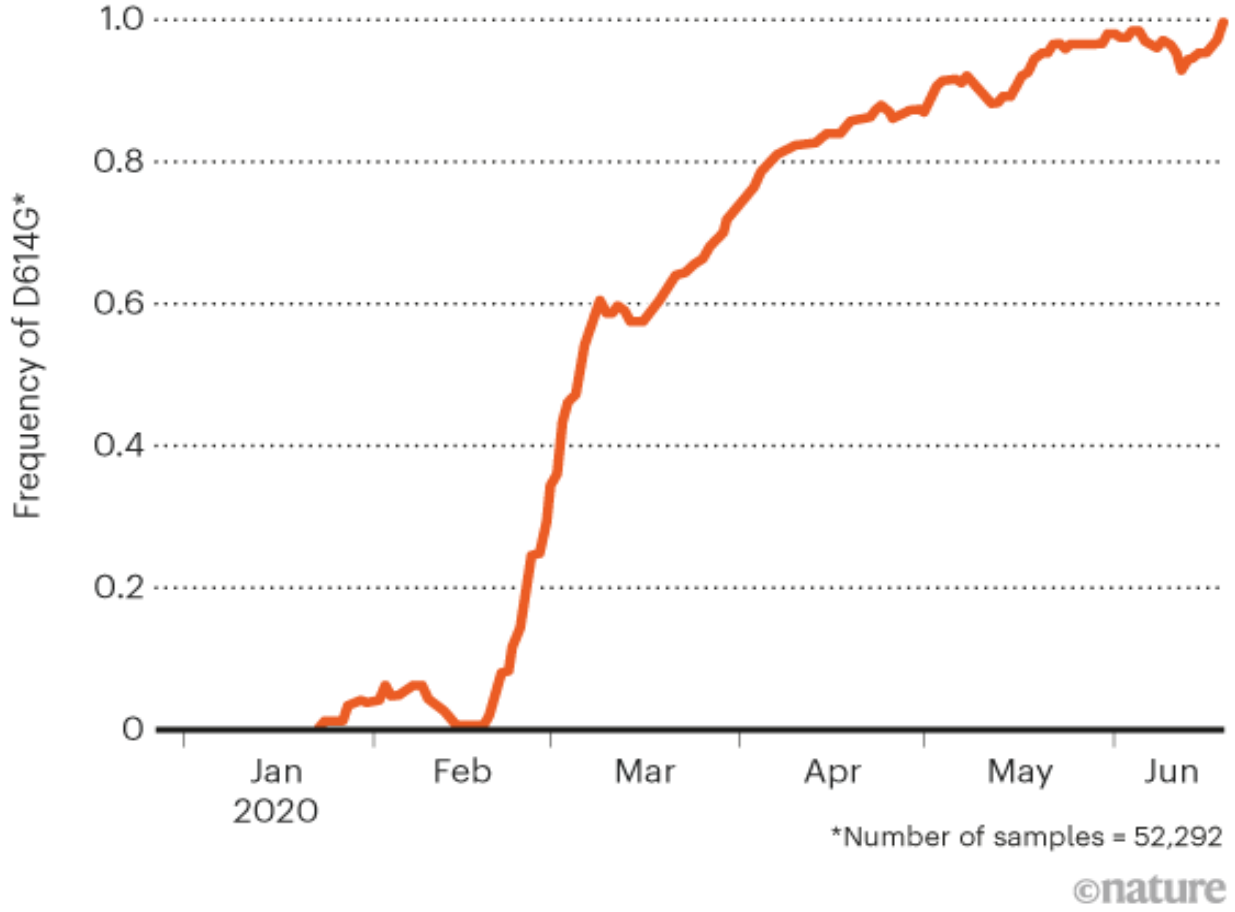

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SARS-CoV-2 variants of concern

Name (Pangolin)	Name (Nextstrain)	First Detected	Cases in the US	Countries Reporting Cases	Key Amino Acid Mutations	Transmissibility Rate
B.1.1.7	20I/501Y.V1	United Kingdom	Y	101	Δ69/70 Δ144Y N501Y A570D D614G P681H	~50% increase
B.1.351	20H/501Y.V2	South Africa	Y	51	K417N E484K N501Y D614G	~50% increase
P.1	20J/501Y.V3	Brazil/ Japan	Y	29	E484K K417N/T N501Y D614G	Not determined

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html
Davies et al. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England. medrxiv.org/content/10.1101/2020.12.24.20248822v2
Pearson et al. Estimates of severity and transmissibility of novel SARS-CoV-2 variant 501Y.V2 in South Africa. https://cmmid.github.io/topics/covid19/reports/sa-novel-variant/2021_01_11_Transmissibility_and_severity_of_501Y_V2_in_SA.pdf

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B.1.351	20H/501Y.V2	South Africa	Y	51	K417N **E484K** N501Y D614G	~50% increase
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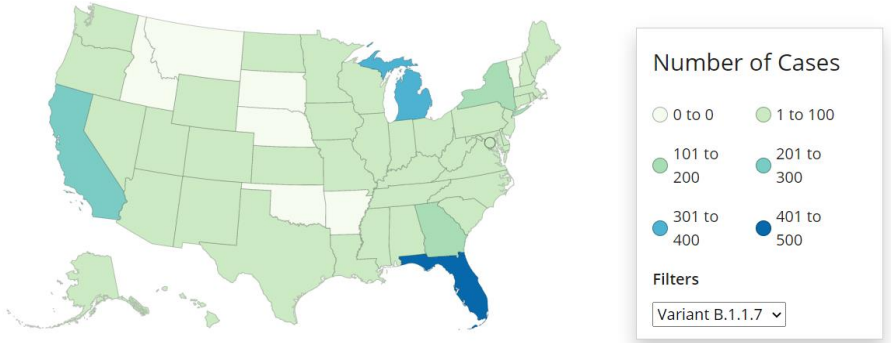
U.S. COVID-19 cases caused by variants of concern

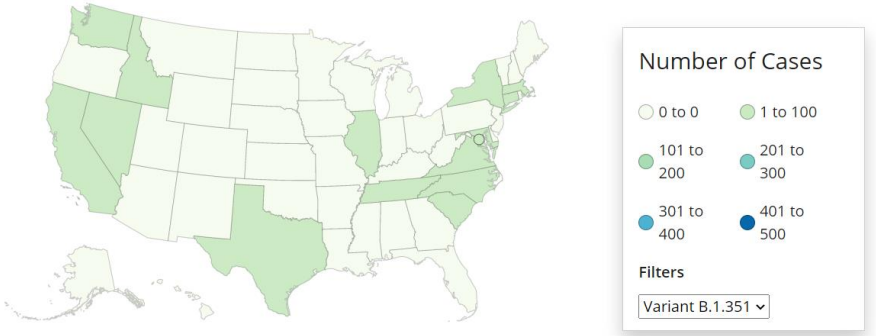
Variant	Reported cases	No. of states
B.1.1.7	2,400	46
B.1.351	53	16
P.1	10	5

Reporting sources vary, so calculating proportions is not possible

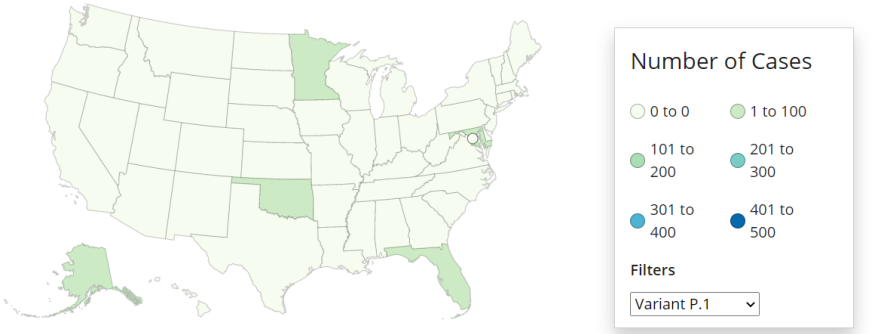
B.1.1.7



B.1.351



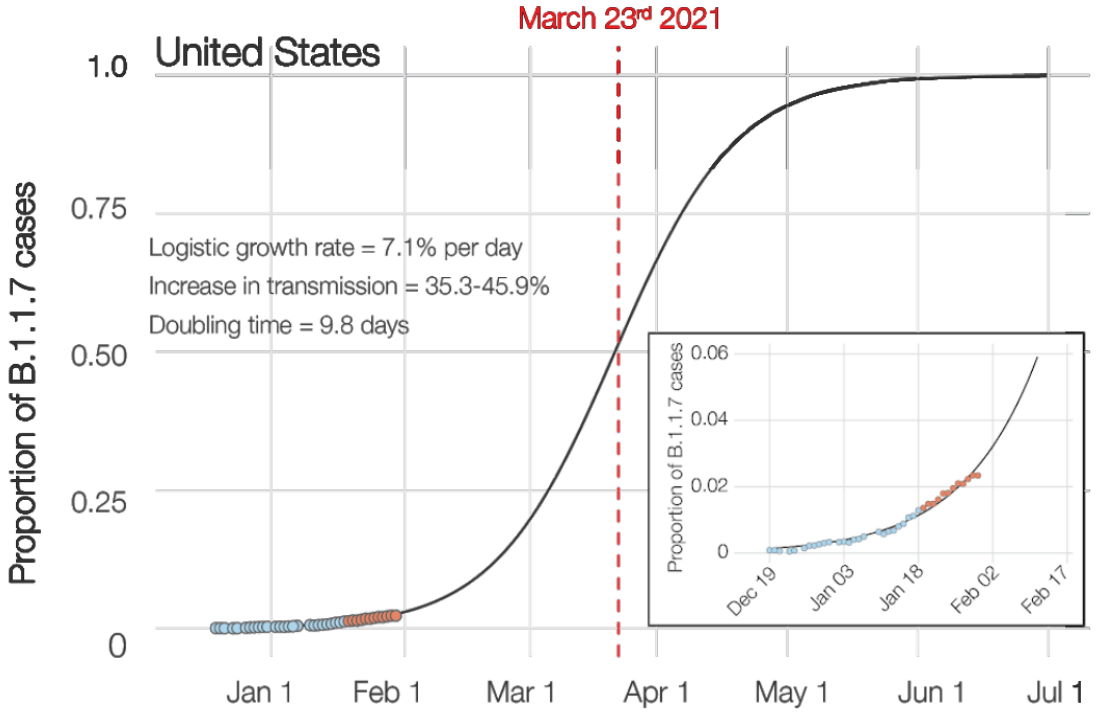
P.1



https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant-cases.html; data as of 02/28/2021

B.1.1.7 trajectory in the United States

- First identified in Dec. 2020, but likely arrived in Nov. 2020
  - Multiple introductions
- Current prevalence estimated 1-2%
  - Commercial diagnostic data suggest early phase logistic expansion
- Two models suggest B.1.1.7 may predominate by March 2021
  - One suggests high vaccine coverage will blunt impact of higher transmissibility



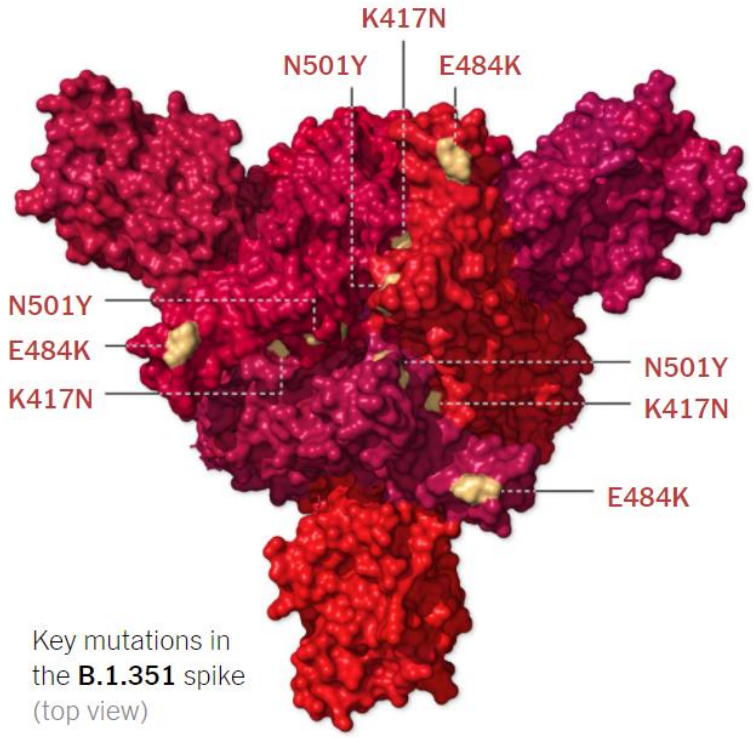
https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html

Figure source: Washington et al. medRxiv preprint (Feb 7 2021): https://www.medrxiv.org/content/10.1101/2021.02.06.21251159v1
Galloway et al. MMWR 2021;70:95–99. https://www.cdc.gov/mmwr/volumes/70/wr/mm7003e2.htm?s_cid=mm7003e2_w

Changes in receptor-binding domain (RBD) of spike protein

- RBD binds host ACE2 receptor – essential for infection
- Majority of neutralizing antibodies bind RBD in most convalescent human sera
- Convergent evolution of several RBD mutations
  - ↑ binding, ↑ infectivity, ↓ efficacy of antibody therapies

Amino acid change in spike protein	**United Kingdom** (B.1.1.7)	**South Africa** (B.1.351)	**Brazil** (P.1)
No. of spike changes	8	10	12
N501Y	✓	✓	✓
E484K		✓	✓
K417T/N		✓	✓



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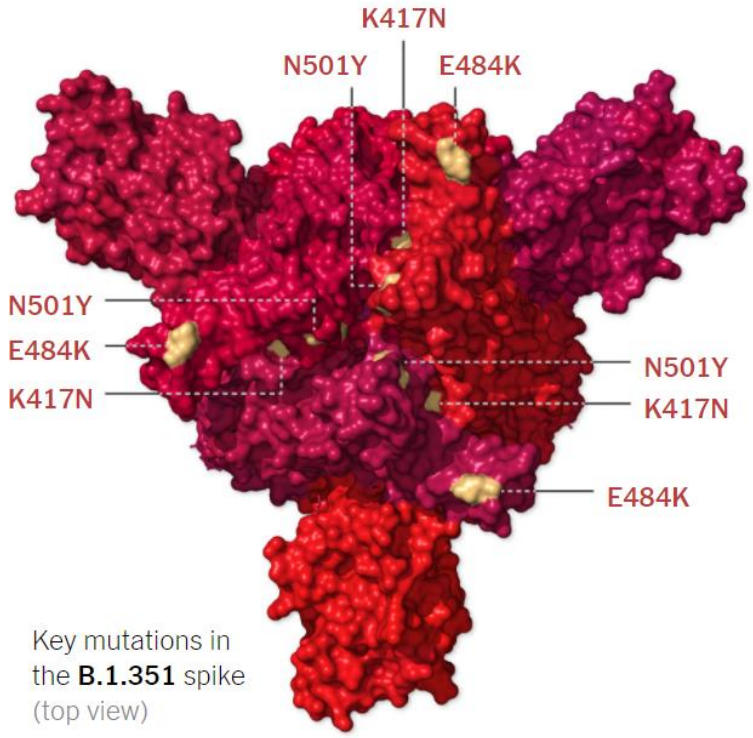
N501Y	✓	✓	✓	
E484K		✓	✓	P.2
K417T/N		✓	✓	



https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html

Vaccine effectiveness data

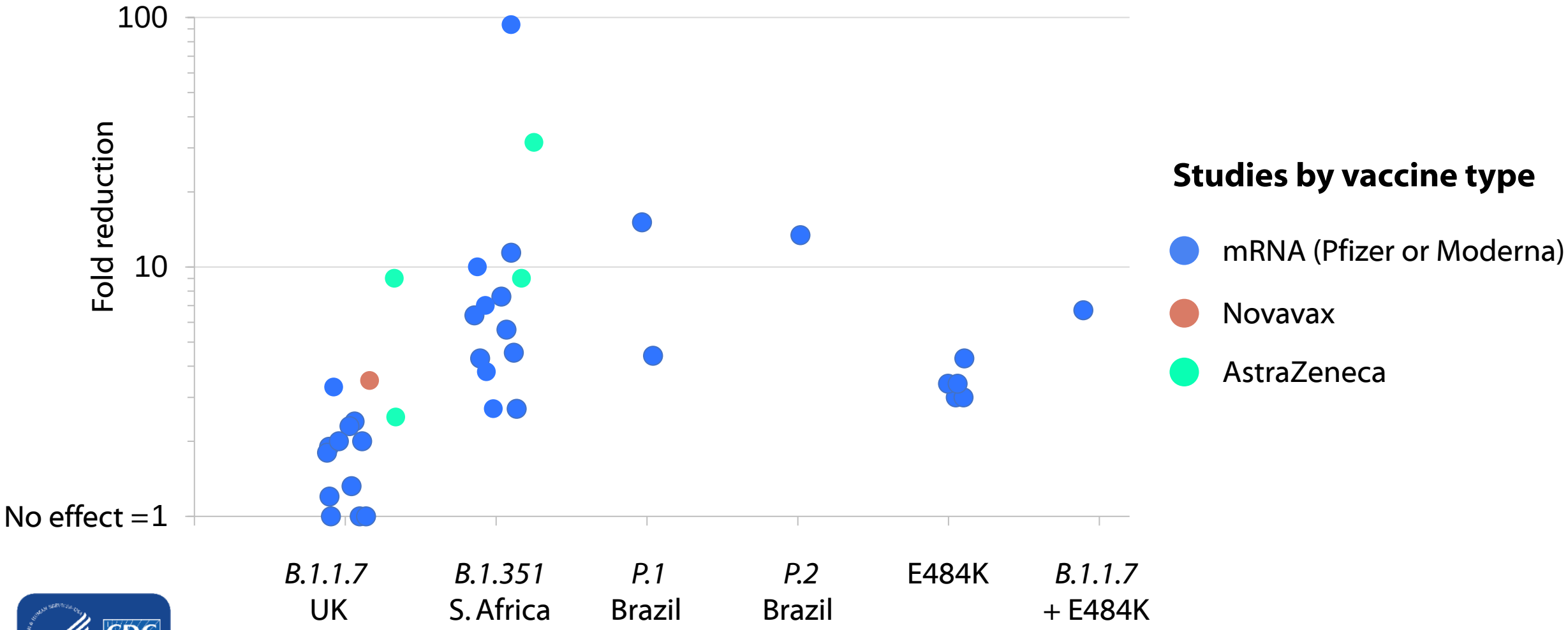
Review of 26 studies: Vaccine sera neutralization of SARS-CoV-2 variants

- 8 published studies and 18 preprint studies; all small sample sizes (n=5−50)
- 13 studies only Pfizer; 3 studies only Moderna; 2 studies on AstraZeneca; 7 studies on ≥1 vaccine; 1 study on unspecified mRNA vaccine
- 8 studies on single/limited sets of mutations – generally minimal impact
  - E484K and E484K-K417N-N501Y larger effects*
- Largest impacts: **B.1.351** (South Africa) > **P.1, P.2** (Brazil) > **B.1.1.7** (UK)
  - Most B.1.351 studies: 3−11-fold reduction, ranged up to 97-fold
  - Most B.1.1.7 studies: <3-fold reduction, ranged up to 9-fold

* Mutations found in South Africa (B.1.351) and Brazil (P.1, P.2)

References in Appendix

Reduced neutralization activity of vaccine sera relative to wildtype/dominant strain, by study (n=22)



References in Appendix

Neutralization of variants after 1 & 2 vaccine doses

- Postponing 2nd mRNA dose may leave some less protected against variants
- Minimal/no neutralization of B.1.351 after one dose
  - History of COVID-19 + 1 dose → moderate protection against B.1.351
- Improved neutralization of B.1.1.7 and B.1.351 after 2nd dose
- Delayed antibody response against variants

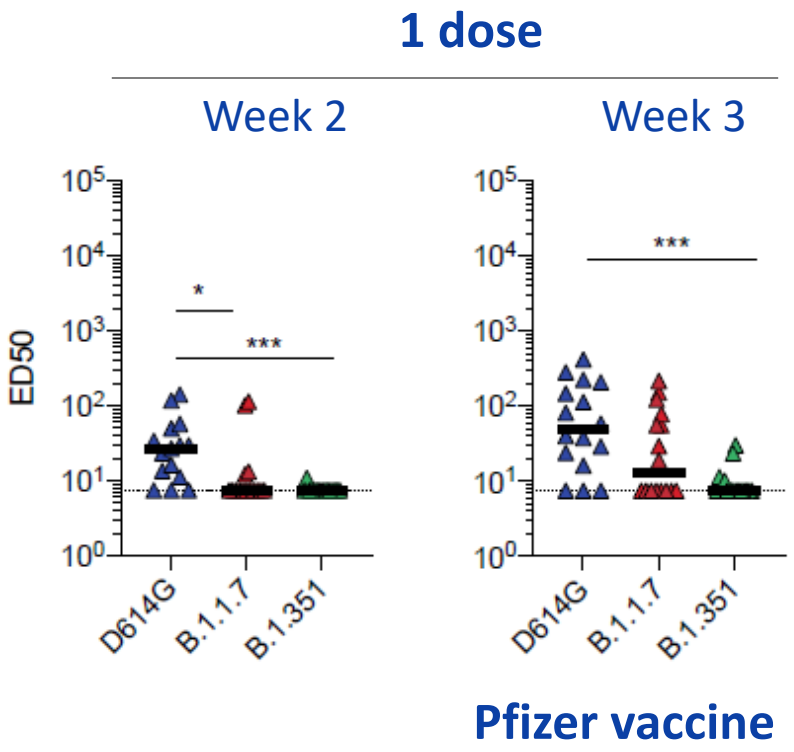


Figure Source: Planas et al. bioRxiv preprint (Feb 12 2021: https://doi.org/10.1101/2021.02.12.430472
Skelly et al. Res square preprint (Feb 9 2021); https://www.researchsquare.com/article/rs-226857/v1
Garcia-Beltran et al. medRxiv preprint (Feb 14 2021): https://doi.org/10.1101/2021.02.14.21251704
Shen et al. bioRxiv preprint (Jan 28 2021); https://doi.org/10.1101/2021.01.27.428516
Collier et al. medRxiv preprint (Feb 15 2021): https://doi.org/10.1101/2021.01.19.21249840
Stamatatos et al. medRxiv preprint (Feb 5 2021): https://doi.org/10.1101/2021.02.05.21251182
Supasa et al.Cell (2021): https://doi.org/10.1016/j.cell.2021.02.033

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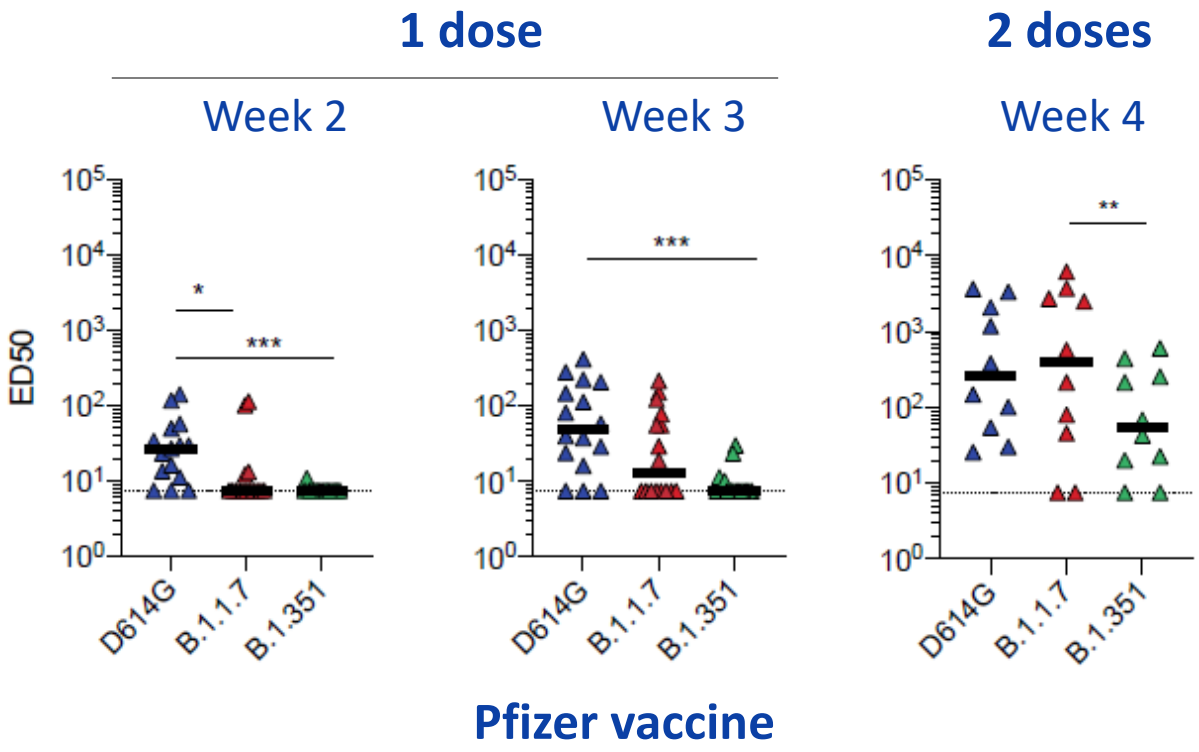

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Supasa et al.Cell (2021): https://doi.org/10.1016/j.cell.2021.02.033

Discussion of lab studies

- Difficult to estimate how laboratory results might translate to clinical protection
  - No immunological correlate of protection for SARS-CoV-2
- Neutralization antibodies in sera from mRNA vaccine recipients generally shown to be higher than COVID-19 convalescent sera
- Variation in results may be explained by differences in experimental conditions
  - Neutralization assays — replicating & nonreplicating pseudovirus vs. SARS-CoV-2
  - Sera — time post-vaccination, or population (e.g., age, COVID-19 history)
  - Use of limited or full sets of spike mutations vs. clinical isolates of variants
- AstraZeneca — not prefusion stabilized spike, limited generalizability to other vaccines
- Limitation for all studies — small sample sizes and lack generalizability
  - Many studies are preprints not yet peer-reviewed

Vaccine efficacy or effectiveness (VE) against variants

Vaccine	Study type	VE
Pfizer	Post-licensure	• 86% in UK (predominate B.1.1.7 circulation)* • 94% in Israel (up to 80% of cases from B.1.1.7)
Janssen	Pre-licensure	• 74% in U.S. • 66% in Brazil (69% of cases from P.2) • 52% in S. Africa (95% of cases from B.1.351)
Novavax	Pre-licensure Pre-licensure	• 96% against non-B.1.1.7 in UK • 86% against B.1.1.7 in UK • 60% in S. Africa (93% of cases from B.1.351)
AstraZeneca	Pre-licensure Pre-licensure	• 84% against non-B.1.1.7 in UK • 75% against B.1.1.7 in UK • 10% against B.1.351 in South Africa

Hall et al. Lancet preprint (Feb 22 2021): https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3790399; *VE for symptomatic & asymptomatic infection
Dagan et al. NEJM (2021). https://www.nejm.org/doi/full/10.1056/NEJMoa2101765?query=TOC
https://www.fda.gov/media/146217/download
Novavax.: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3
Madhi et al. medRxiv preprint (Feb 12 2021): https://doi.org/10.1101/2021.02.10.21251247
Emary et al. Lancet preprint (Feb 4 2021): https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160

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73-82% for severe/critical disease in each country

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Dagan et al. NEJM (2021). https://www.nejm.org/doi/full/10.1056/NEJMoa2101765?query=TOC
https://www.fda.gov/media/146217/download
Novavax.: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3
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Emary et al. Lancet preprint (Feb 4 2021): https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160

Summary of preliminary data: Implications of SARS-CoV-2 variants of concern on vaccine effectiveness

- **B.1.1.7** (first detected in the United Kingdom)
  - Exponential increase in prevalence in United States
  - Minimal impact on vaccine effectiveness, but attention needed for variants with additional substitutions in RBD, such as E484K
- **B.1.351** (first detected in South Africa)
  - Currently low prevalence in United States
  - Moderate impact on vaccine effectiveness, suggests it's prudent to start evaluating variant vaccines in case prevalence substantially increases
- **P.1** (first detected in Brazil/Japan)
  - Very low prevalence in United States, but same three RBD mutations as B.1.351
  - Additional data needed on potential impact on vaccine effectiveness

Modifying vaccines to target SARS-CoV-2 variants

- Current prevention measures and licensed vaccines offer protection against SARS-CoV-2 variants
  - Efforts needed to increase speed and degree of uptake
- Periodic update of SARS-CoV-2 vaccines likely needed
- Modeling study predicts changing COVID-19 vaccines to target faster spreading viral variants more effective than targeting the slower dominant strain, despite initial prevalence [1]

1. Bedwick et al. medRxiv preprint (Feb 8 2021); doi: https://doi.org/10.1101/2021.01.05.21249255

Response to variants

SARS-CoV-2 Interagency Group (SIG)

- Established by Dept. of Health & Human Services to improve coordination
  - CDC
  - National Institutes of Health (NIH)
  - Food and Drug Administration (FDA)
  - Biomedical Advanced Research and Development Authority (BARDA)
  - US Department of Agriculture (USDA)
  - Department of Defense (DoD)
- Focuses on rapid characterization of emerging variants and monitors potential impact on SARS-CoV-2 diagnostics, therapeutics, and vaccines

Walensky, Walke and Fauci. JAMA (2021): https://jamanetwork.com/journals/jama/fullarticle/2776739

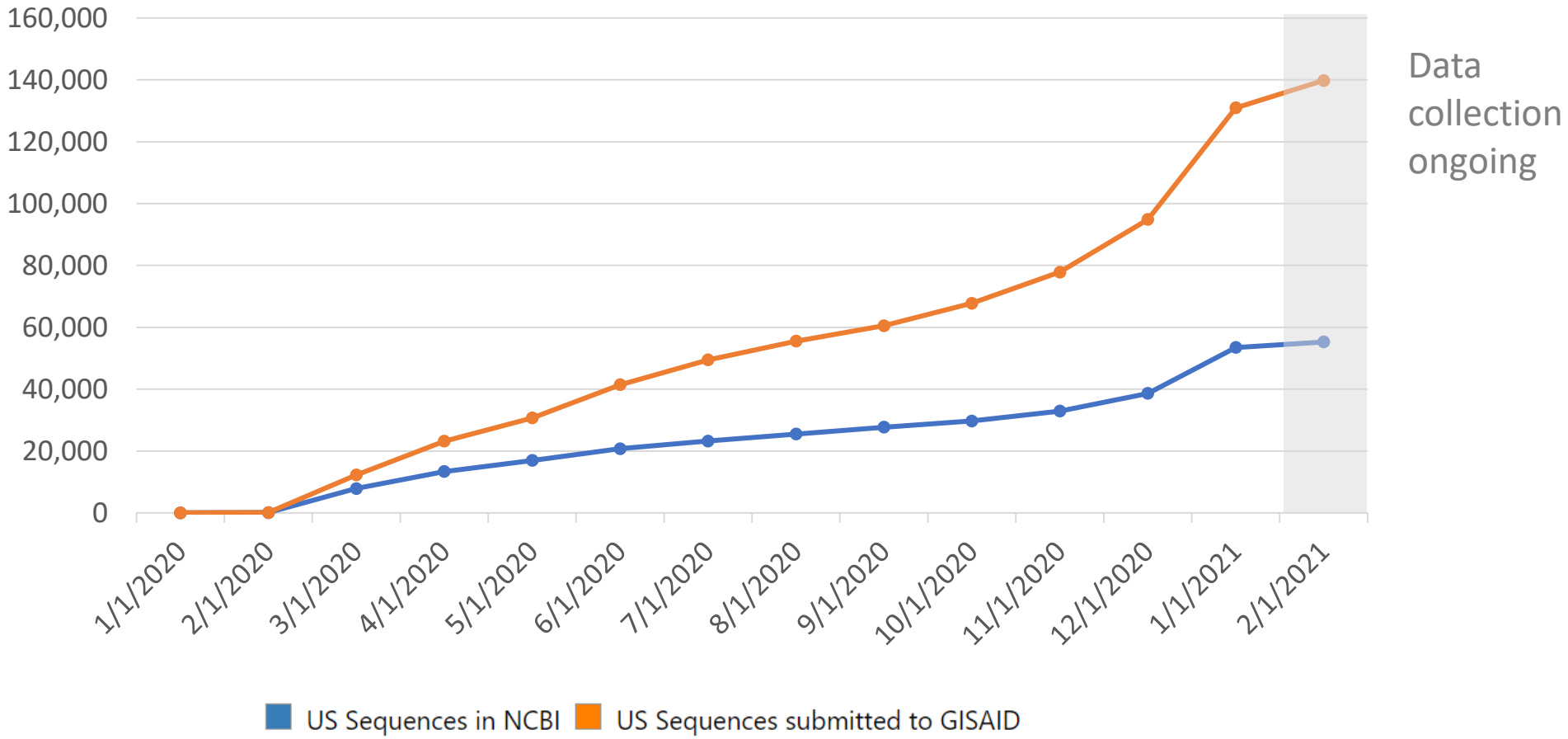
CDC approaches to genomic surveillance and epidemiology

- National SARS-CoV-2 Strain Surveillance (NS3)
  - Approximately 3,000 random specimens/month regularly submitted from public health laboratories across U.S.
- Partnership with commercial diagnostic laboratories
  - Scaling to 6,000 sequences/week
- Contracts and partnerships with state and local health departments and universities
- SPHERES* Consortium of ~170 domestic partners — open sharing of sequencing data
- Focused molecular epidemiologic studies

* SPHERES= SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance.html
https://www.aphl.org/programs/preparedness/Crisis-Management/COVID-19-Response/Pages/Sequence-Based-Surveillance-Submission.aspx
https://www.cdc.gov/coronavirus/2019-ncov/covid-data/spheres.html

U.S. sequences available in public repositories



https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/genomic-surveillance-dashboard.html as of 2/28/21

National Center for Biotechnology Information (NCBI); GISAID, a global initiative maintaining a repository of viral sequencing data

Investigating COVID-19 vaccine breakthrough cases

- Despite high vaccine efficacy, vaccine breakthrough cases expected
  - Some will be caused by variants, even if vaccine has similar effectiveness against variants
- *Vaccine breakthrough case:* person with SARS-CoV-2 RNA or antigen detected in respiratory specimen collected ≥14 days after completing primary series of an FDA-authorized COVID-19 vaccine
- Cases identified from national case-based surveillance, Vaccine Adverse Events Reporting System (VAERS), health departments, healthcare providers
  - Working with state health departments on case investigation
  - Respiratory specimens used for whole genome sequencing to identify variants
- Data from investigations will be posted or published when available

Boosters and second-generation vaccines against SARS-CoV-2 variants

- Moderna and Pfizer launching booster studies of current vaccines in U.S. and developing second-generation vaccines against B.1.351
  - Moderna: Variant-specific vaccine (mRNA-1273.351) and multivalent vaccine with original authorized vaccine and variant vaccine (mRNA-1273.21)
- Yet to be defined:
  - Evidence indicating need for a modified vaccine
  - Process for evaluating, deciding and recommending whether a modified vaccine is needed
- World Health Organization (WHO) has likely role in global coordination — developing framework for risk assessment

https://investors.modernatx.com/news-releases/news-release-details/moderna-covid-19-vaccine-retains-neutralizing-activity-against
https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-it-has-shipped-variant-specific-vaccine
https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-part-broad-development

FDA: Data needed to support EUA amendment for a vaccine addressing emerging SARS-CoV-2 variants

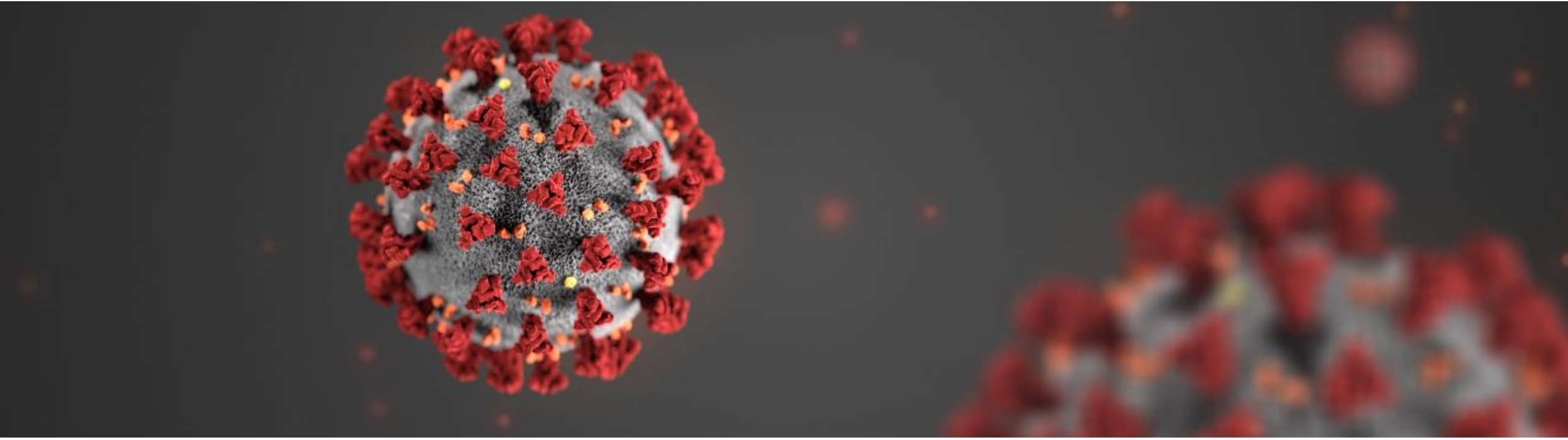
1. Good manufacturing practices and controls
2. Nonclinical data, e.g., laboratory studies, animal models
3. Clinical data from immunogenicity studies — noninferiority with licensed vaccine
   - Primary series or booster dose
   - Could be single age group with extrapolation to other age groups
   - Safety data from during the immunogenicity evaluation period
4. Laboratory assays and immunogenicity endpoints
   - Correlates of protection not yet established

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19

Variants: Implications for vaccine policy

- Continue to monitor evidence:
  - Emergence and spread of SARS-CoV-2 variants
  - Vaccine effectiveness
  - Breakthrough infections in vaccinated or previously infected persons
  - Ability of postvaccination serum to neutralize emerging variant viruses

- Work Group and ACIP will review evidence submitted for any next generation vaccines



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.