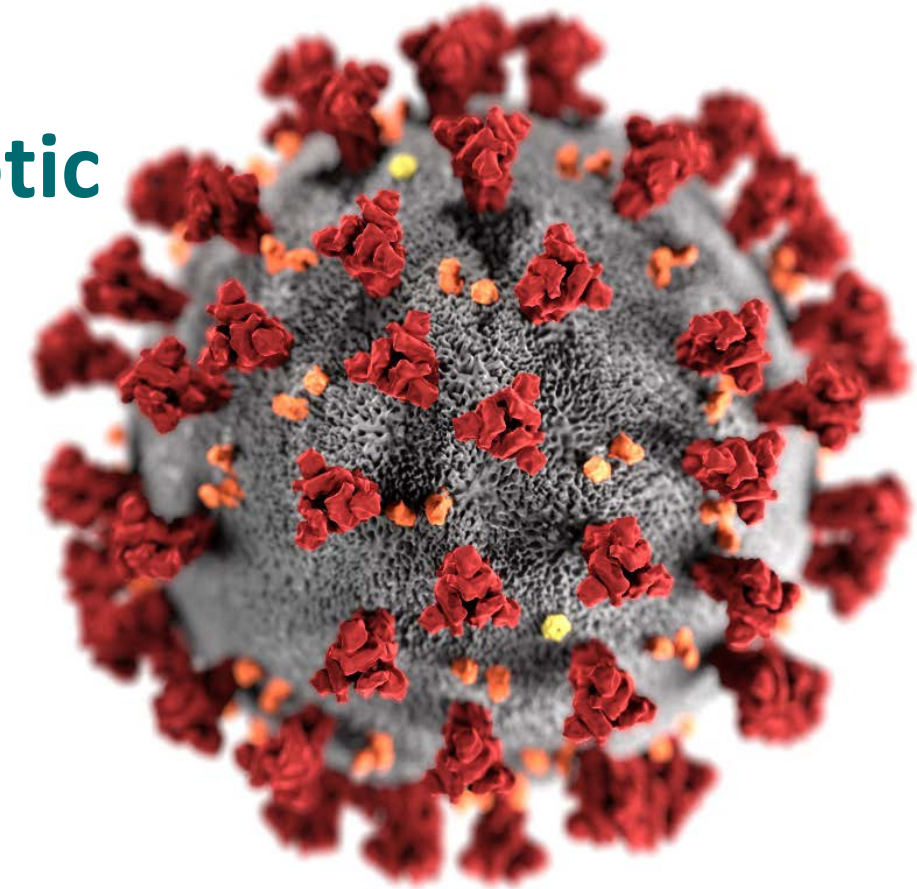
Risk/Benefit assessment of thrombotic thrombocytopenic events after Janssen COVID-19 vaccines:

Applying Evidence to Recommendation Framework



Sara Oliver MD, MSPH

ACIP Meeting

April 23, 2021

Evidence to Recommendations Framework

Evidence to Recommendations (EtR) Framework

- Structure to describe information considered in moving from **evidence** to ACIP vaccine **recommendations**

- Provide **transparency** around the impact of additional factors on deliberations when considering a recommendation

Evidence to Recommendations (EtR) Framework

Policy Question

- Should vaccination with the Janssen COVID-19 vaccine (1 dose) be recommended for persons 18 years of age and older under an Emergency Use Authorization?

Evidence to Recommendations (EtR) Framework:

Previous Janssen COVID-19 vaccine Recommendations

EtR Domain	Question
Public Health Problem	• Is the problem of public health importance?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?
Values	• Does the target population feel the desirable effects are large relative to the undesirable effects? • Is there important variability in how patients value the outcomes?
Acceptability	• Is the intervention acceptable to key stakeholders?
Feasibility	• Is the intervention feasible to implement?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?
Equity	• What would be the impact of the intervention on health equity?

Evidence to Recommendations (EtR) Framework:

Adaptation to Risk/Benefit assessment for Janssen COVID-19 vaccine recommendations

EtR Domain	Question
Public Health Problem	• Recent COVID-19 Epidemiology • Thrombosis after COVID-19 Disease • Cerebral Venous Sinus Thrombosis (CVST) • Heparin Induced Thrombocytopenia (HIT) • AstraZeneca COVID-19 vaccines: Available global data
Benefits and Harms	• Benefits of Janssen COVID-19 vaccine • Harms of Janssen COVID-19 vaccine: Estimated cases of TTS after Janssen COVID-19 vaccine • Benefit/Risk Assessment of COVID-19 vaccines

Evidence to Recommendations (EtR) Framework:

Adaptation to Risk/Benefit assessment for Janssen COVID-19 vaccine recommendations

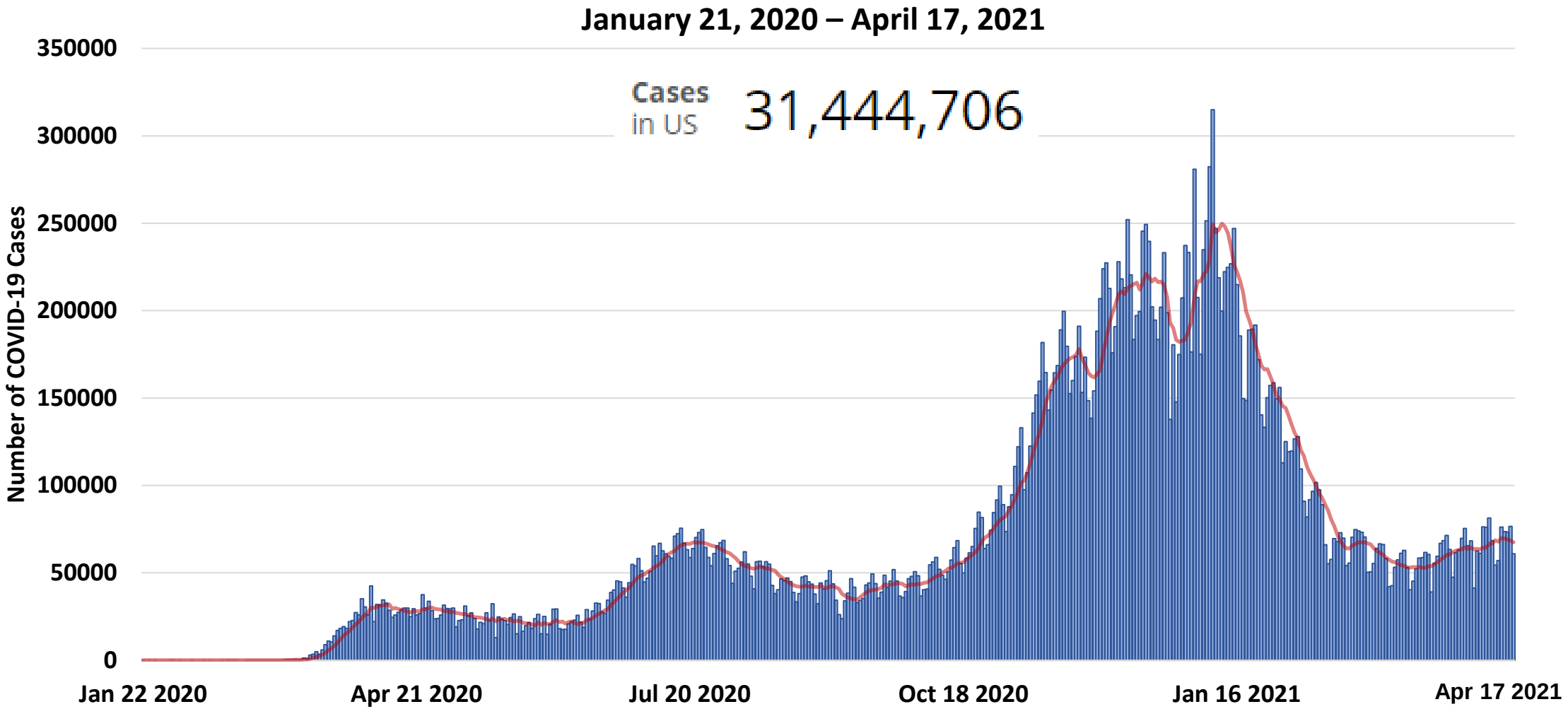
EtR Domain	Question
Values and Acceptability	• Intent to receive 1-dose COVID-19 vaccine • Intent to receive Janssen COVID-19 vaccine over time
Feasibility	• Jurisdictional use of Janssen COVID-19 vaccine Possible impact of Janssen COVID-19 vaccine policy options
Equity	• Possible impact of Janssen COVID-19 vaccine policy options in disproportionately affected populations
Resource Use	• No information available

EtR Domain: Public Health Problem

Public Health Problem:

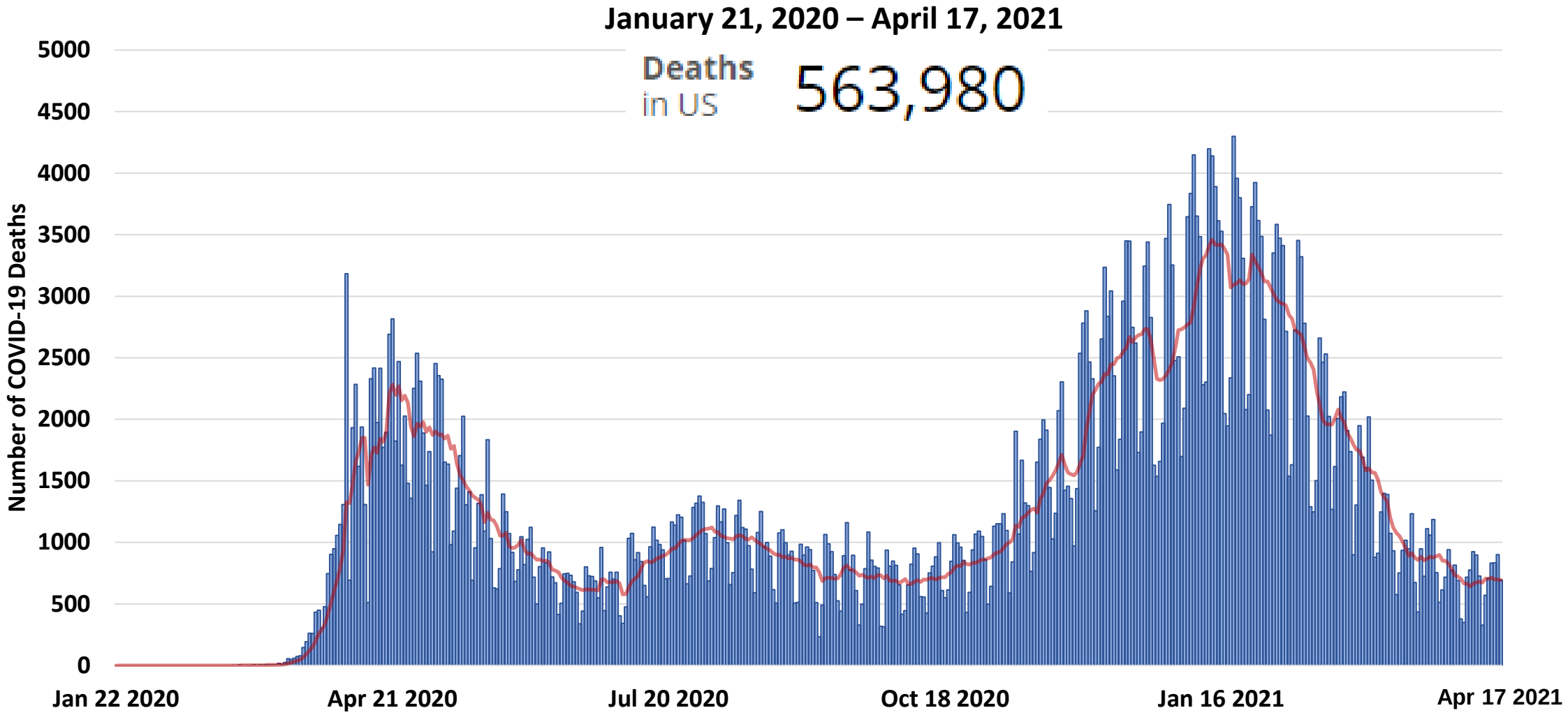
- Recent COVID-19 Epidemiology
  - COVID-19 cases, hospitalization and deaths, stratified by age, sex, race and ethnicity
- Cerebral Venous Sinus Thrombosis (CVST)
- Heparin Induced Thrombocytopenia (HIT)
- Thrombosis after COVID-19 Disease
- AstraZeneca COVID-19 vaccines
  - Review of available global data

Trends in Number of COVID-19 Cases in the US



https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases

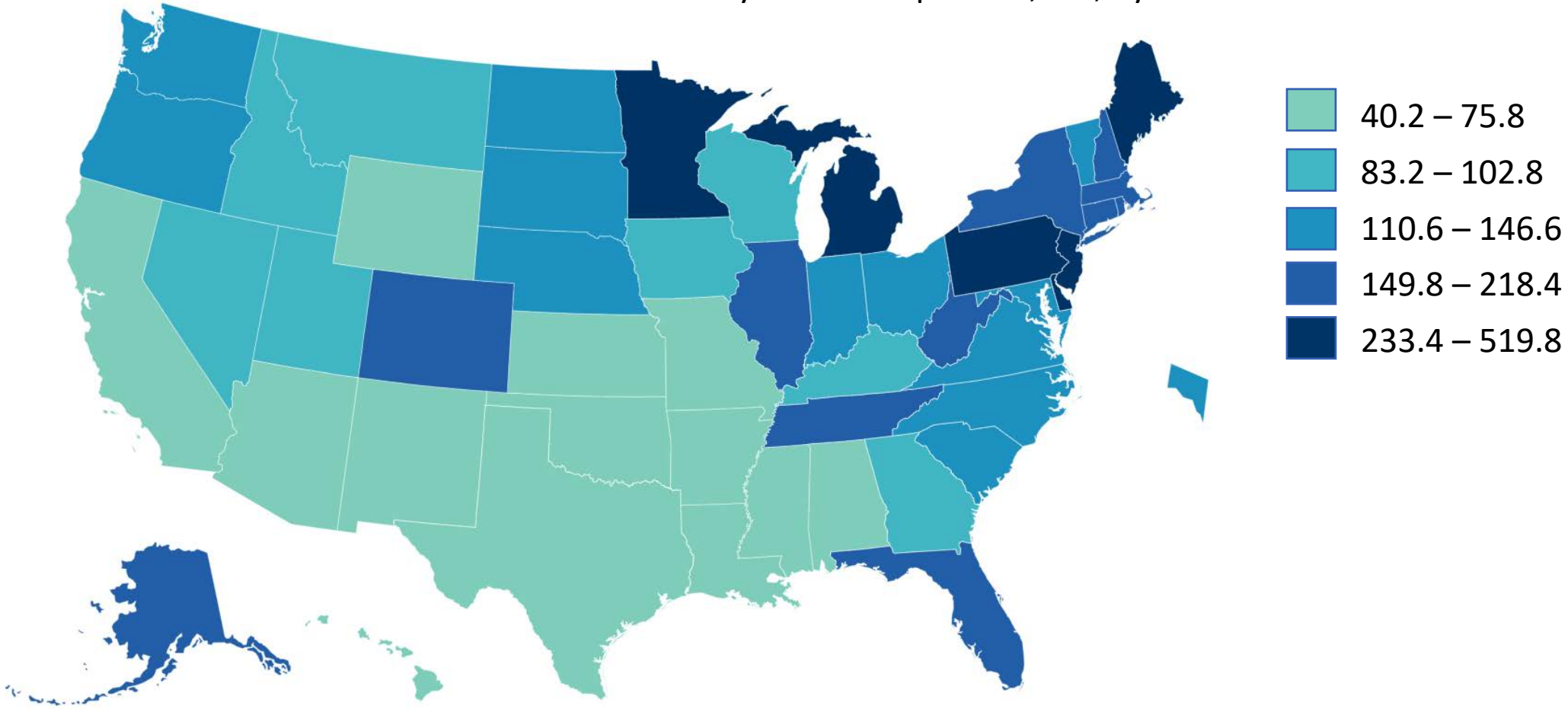
Trends in Number of COVID-19 Deaths in the US



https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases

COVID-19 Incidence Rates, by State

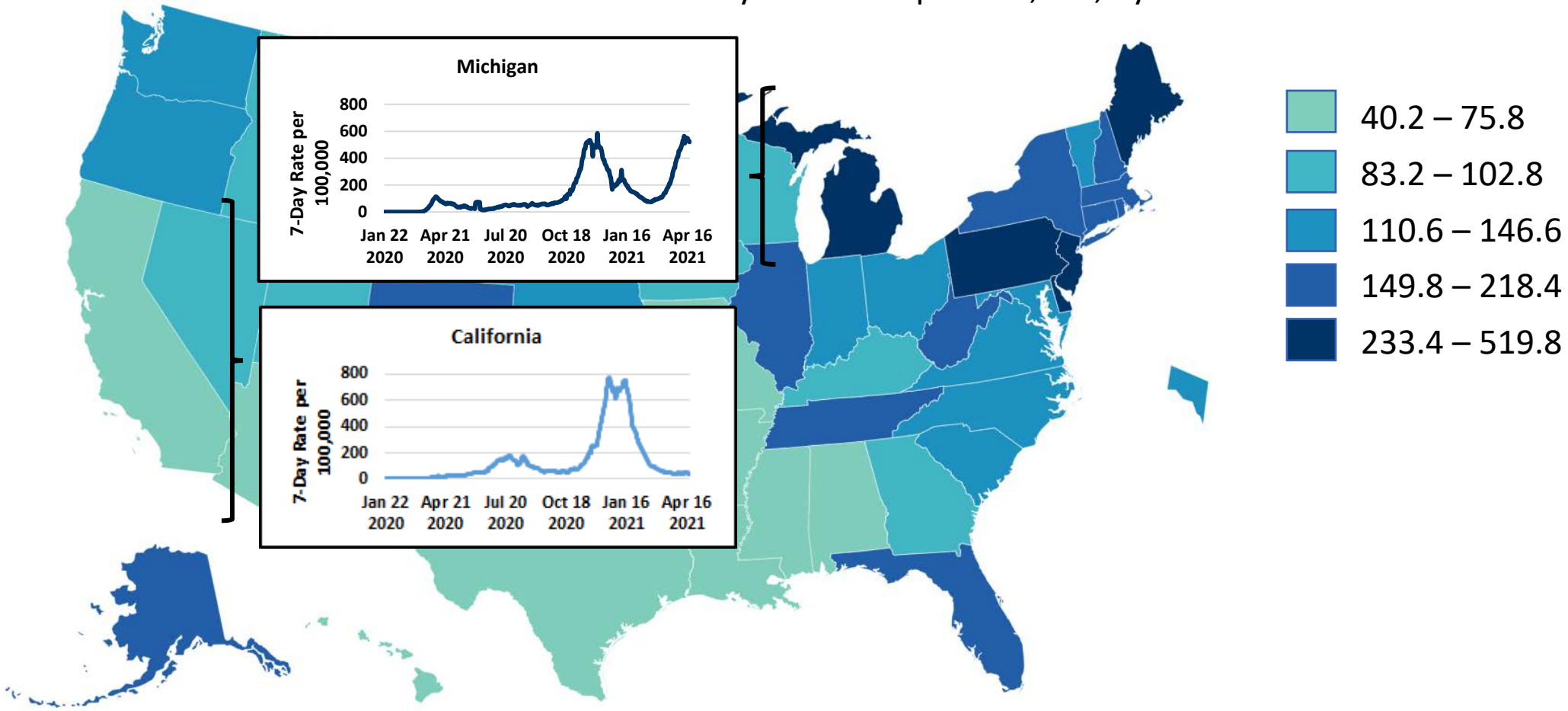
US COVID-19 7-Day Case Rate per 100,000, by State



https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days

COVID-19 Incidence by State

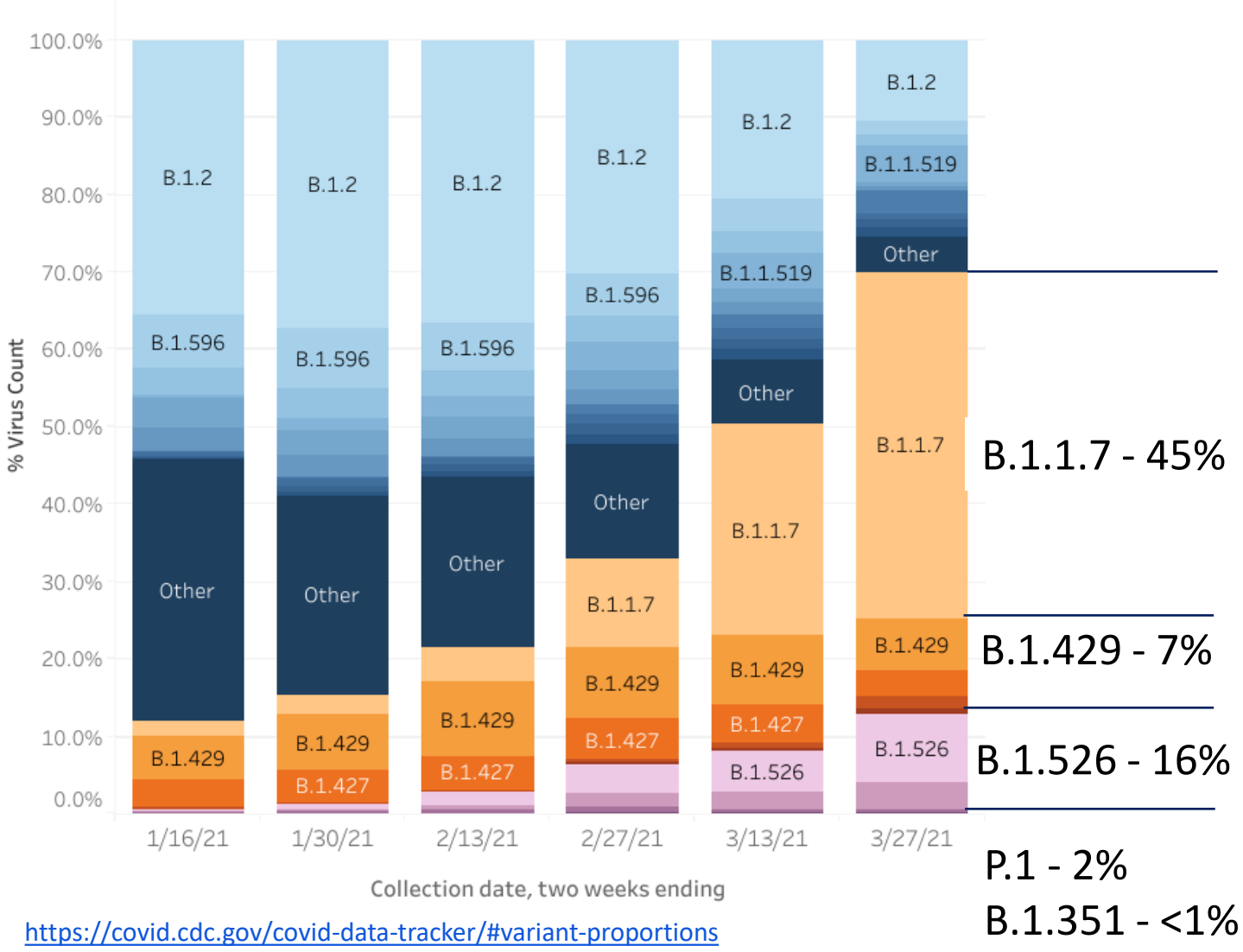
US COVID-19 7-Day Case Rate per 100,000, by State



https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days

SARS-CoV-2 Variants Circulating in the United States

Variant Proportions, January 3 - March 27, 2021



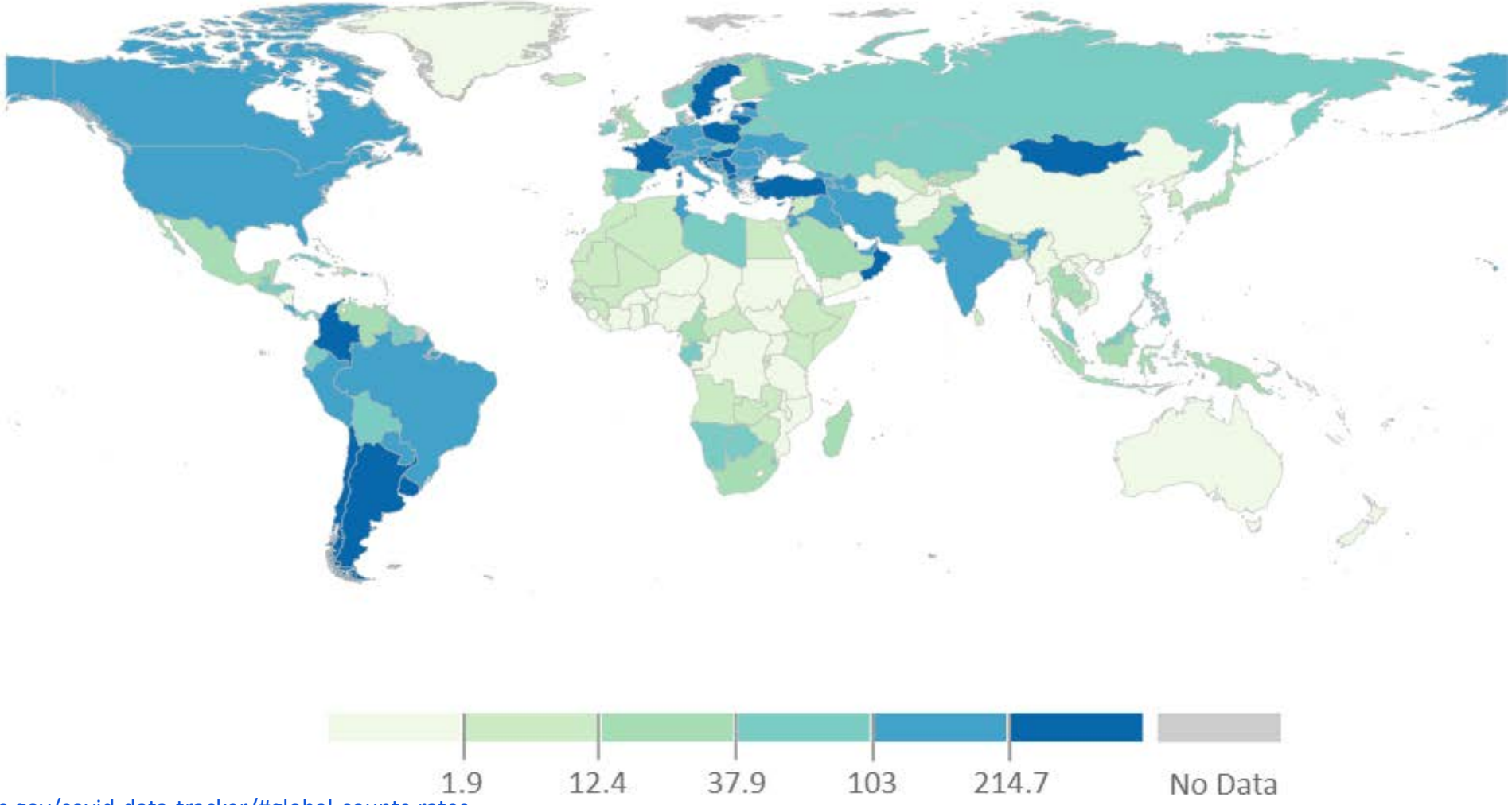
	Lineage	% Total	95%CI	Type
Most common lineages	B.1.1.7	44.7%	41.8-47.5%	VOC
	B.1.2	10.5%	9.5-11.6%	
	B.1.526	8.9%	6.9-11.4%	VOI
	B.1.429	6.9%	5.2-9.0%	VOC
	B.1.1.519	4.5%	3.8-5.3%	
	B.1.526.1	3.6%	3.0-4.2%	VOI
	B.1.526.2	3.2%	2.6-3.9%	
	B.1.427	3.1%	2.4-4.0%	VOC
	B.1	1.6%	1.4-1.9%	
	B.1.596	1.6%	1.3-2.0%	
	P.1	1.5%	1.1-2.1%	VOC
	R.1	1.1%	0.9-1.4%	
	B.1.575	1.1%	0.8-1.4%	
	B.1.243	0.7%	0.5-0.9%	
	B.1.1	0.7%	0.4-1.0%	
	B.1.234	0.5%	0.3-0.6%	
Additional VOI/VOC lineages	B.1.351	0.7%	0.5-1.1%	VOC
	P.2	0.3%	0.2-0.4%	VOI
	B.1.525	0.3%	0.2-0.4%	VOI
Other*	Other	4.7%	4.0-5.5%	

Summary data that appear in the table include specimen collection dates from March 14 through March 27, 2021.
* Other represents >200 additional lineages, which are each circulating at <1% of viruses
** Most recent data are subject to change as samples from that period are still being processed.

https://covid.cdc.gov/covid-data-tracker/#variant-proportions

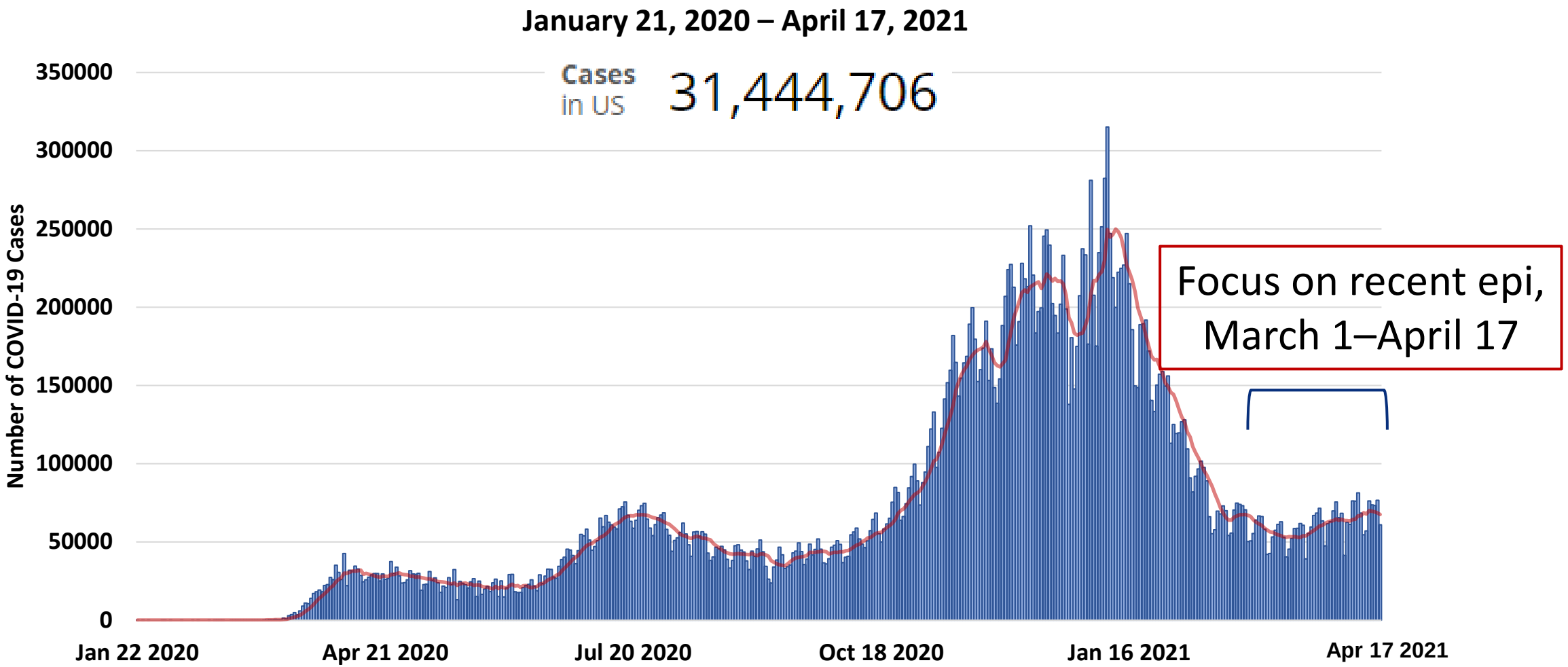
Global COVID-19 Incidence Rates

Global cases of COVID-19 reported per 100,000 population in the past 7 days



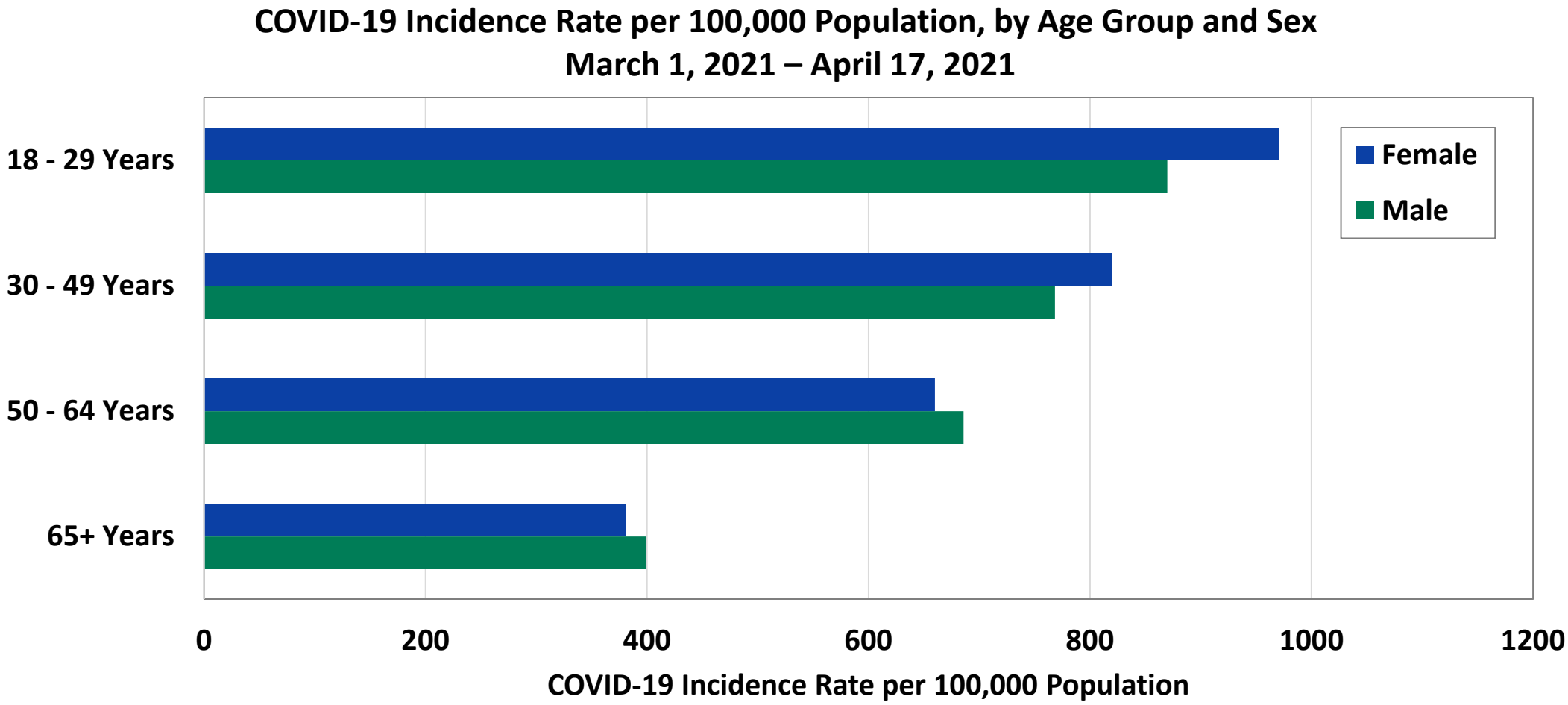
https://covid.cdc.gov/covid-data-tracker/#global-counts-rates

Trends in Number of COVID-19 Cases in the US



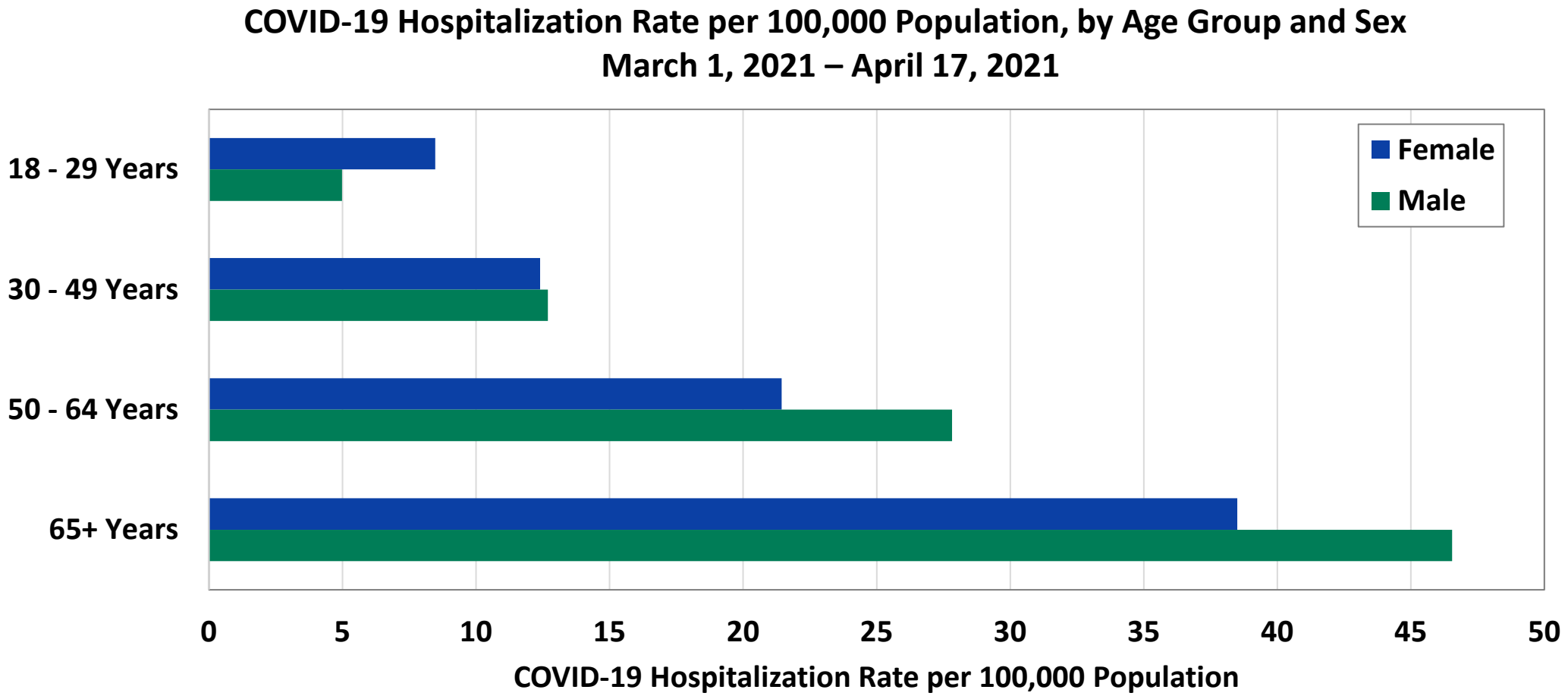
https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases

COVID-19 Incidence Rates, by Age Group and Sex



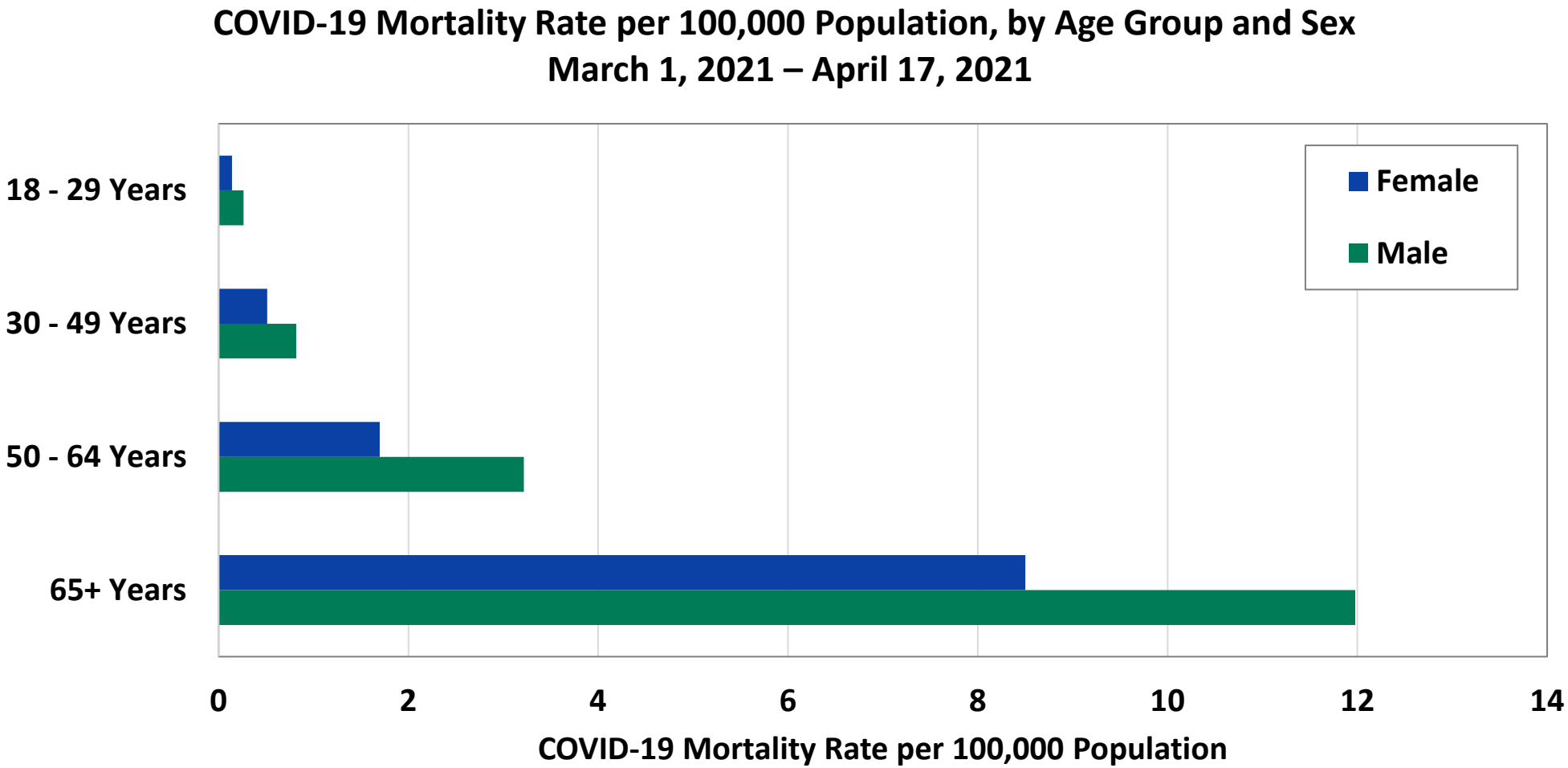
https://covid.cdc.gov/covid-data-tracker/#demographics

COVID-19 Hospitalization Rates, by Age Group and Sex



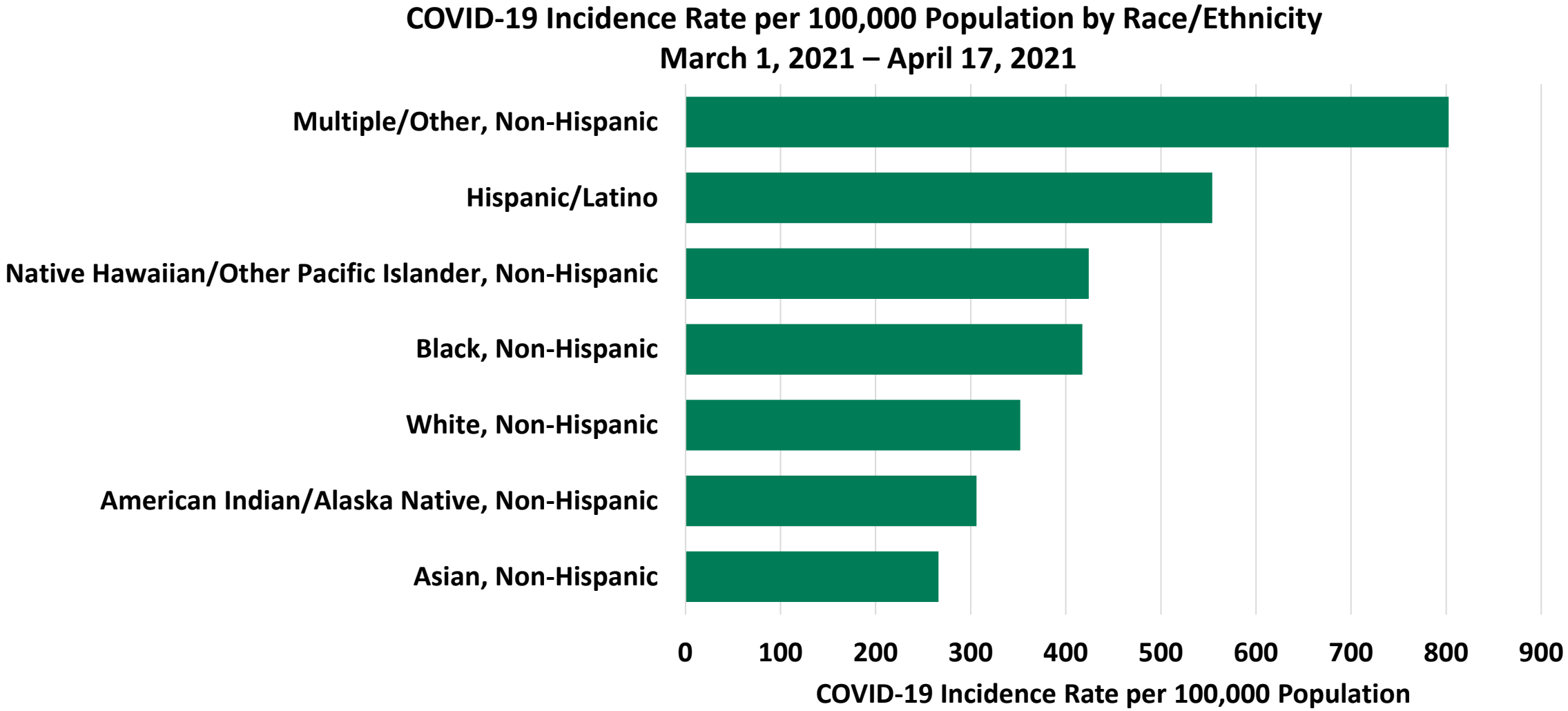
https://covid.cdc.gov/covid-data-tracker/#demographics

COVID-19 Mortality Rates, by Age Group and Sex



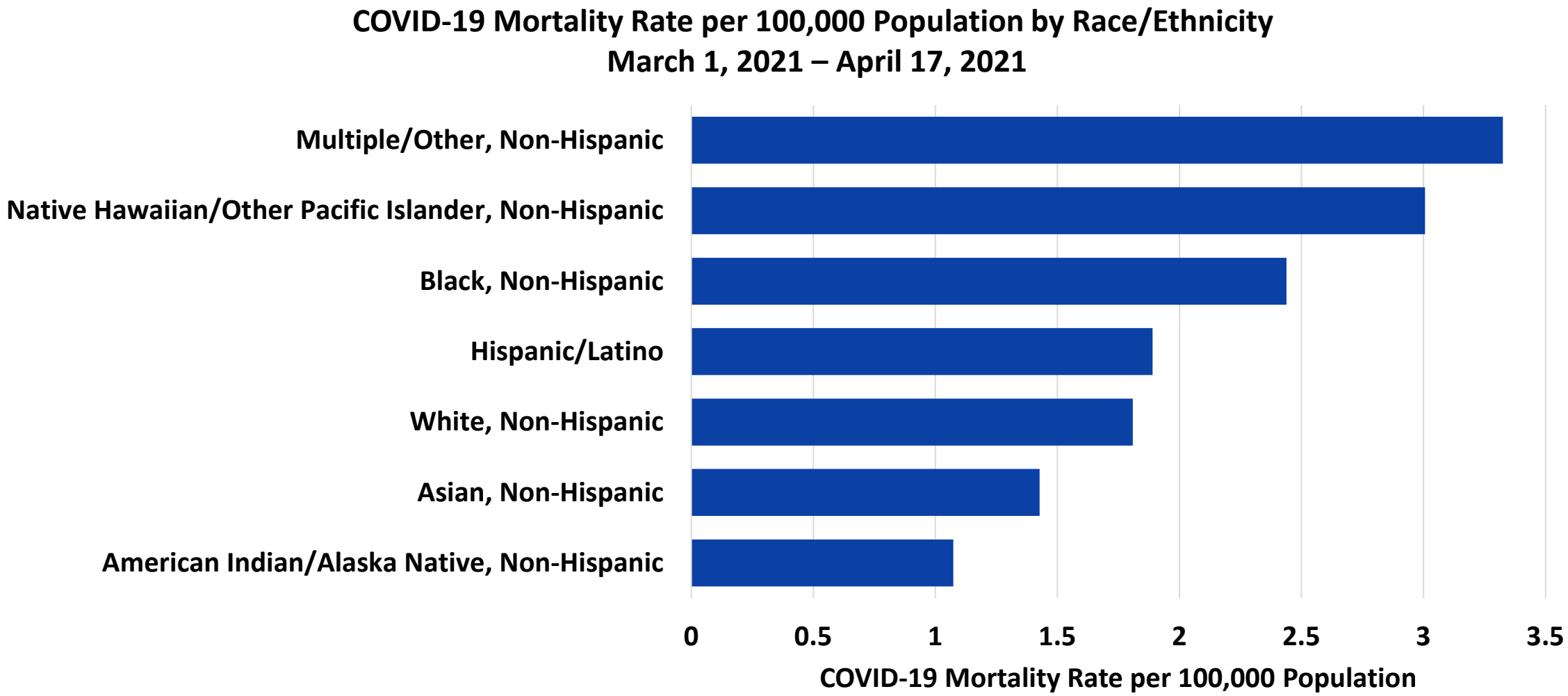
https://covid.cdc.gov/covid-data-tracker/#demographics

COVID-19 Incidence Rates, by Race/Ethnicity



https://covid.cdc.gov/covid-data-tracker/#demographics

COVID-19 Mortality Rate, by Race/Ethnicity



https://covid.cdc.gov/covid-data-tracker/#demographics

Summary of the COVID-19 Epidemiology

March 1–April 17, 2021

- **Incidence**
  - Cumulative incidence rate for adults: **710.9** per 100,000 population
  - Younger females (18-29 years) have the highest incidence of new infections
- **Hospitalization**
  - Cumulative hospitalization rate for adults: **20.6** per 100,000 population
  - Most hospitalizations still occur in persons aged ≥ 65 years
    - Proportion of hospitalizations occurring in persons aged ≥65 years declining
- **Mortality**
  - Cumulative mortality rate: **3.0** per 100,000 population
  - Most COVID-19 deaths still occur in persons aged ≥ 65 years
    - Proportion of deaths occurring in persons aged ≥65 years declining

https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html . https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html . https://covid.cdc.gov/covid-data-tracker/#trends_totalandratedeathssevendayrate

Epidemiology of Cerebral Venous Sinus Thrombosis (CVST) and Splanchnic Vein Thrombosis (SVT)

- Cerebral Venous Sinus Thrombosis (CVST) incidence: **14.5–28.5** per million U.S population
  - Incidence increasing in recent years (4% annually)
  - Higher in women aged 18–49 years
  - Risk factors (e.g. hereditary thrombophilia, oral contraceptives, obesity) identified in up to 85% of cases
  - Mortality ~5-10%
- Splanchnic Vein Thrombosis (SVT) incidence: **84–179** per million U.S. population
  - Incidence higher among men
  - Risk increases with age
- Incidence with thrombocytopenia much lower than without thrombocytopenia
  - CVST with thrombocytopenia: **0.7–1.6** per million U.S. population

Data source: Health Care Utilization Project (HCUP) National Inpatient Sample (NIS) for 2018 and Marketscan Treatment Pathways (Continuously-enrolled Commercial Insurance and Medicaid) for 2019

Otite et al. Neurology 2020; 95: e2200-e2213. 2020; Silvis et al. *Nat Rev Neurol* 13, 555–565 (2017). Silvis et al. *Semin Thromb Hemost* 2016;42:622–631.;

Heparin-Induced Thrombocytopenia with Thrombosis (HITT)

- Heparin-induced thrombocytopenia (HIT) occurs in 0.5% to 1% of patients exposed to unfractionated heparin for medical and surgical indications
  - Incidence: **23–45** per million total U.S. population*
- Of patients with HIT, thrombosis occurs in about 20%−64% (called HITT)
- Immune mediated — antibodies against platelet factor 4 (PF4) & heparin
- Risk factors for developing thrombosis
  - Genetic polymorphisms
  - Lower platelet count (and earlier fall in count)
  - Higher titer of anti-heparin/PF4 antibodies
  - Prior surgery (cardiac, orthopedic, trauma)
  - Cardiovascular disease
- Limited case series published on HIT occurring after COVID-19

* Source: HCUP NIS 2018 and Marketscan (Continuously-enrolled Commercial Insurance and Medicaid) for 2019, unable to distinguish autoimmune HIT vs heparin-induced HIT Arepally et al. 2021. https://www.ahajournals.org/doi/epub/10.1161/ATVBAHA.120.315445; Nand et al. 1998 https://doi.org/10.1002/(SICI)1096-8652(199709)56:1<12::AID-AJH3>3.0.CO;2-5; Fabris et al 2002. https://onlinelibrary.wiley.com/doi/epdf/10.1046/j.1365-2796.2002.01021.x ; Greinacher et al. 2005. https://www.thieme-connect.com/products/ejournals/abstract/10.1160/TH04-12-0825

CVST associated with COVID-19

- Systematic review, meta-analysis of CVST among patients hospitalized for COVID-19
  - Estimates between **0.03%** and **0.08%** of hospitalized COVID-19 patients
- Estimated risk of **5–6** cases of CVST per million SARS-COV-2 infections*
- CVST + thrombocytopenia in COVID-19 patients is extremely rare
- Pathology appears different than TTS after COVID-19 vaccines
  - PF4/heparin specific antibodies negative by ELISA or platelet functional assay for confirmed COVID-19 patients (n=222), including 10 with thromboembolic complications

* Data source: Premier Healthcare Database, January 2020-January 2021

Acronyms: Cerebral Venous Sinus Thrombosis (CVST), Thrombosis with Thrombocytopenia Syndrome (TTS)

Katsanos et al. (2020) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7753413/ ; Baldini et al. (2021) https://doi.org/10.1111/ene.14727; Mowla et al. (2020) https://doi.org/10.1016/j.jns.2020.117183; Greinacher et al. Research Square preprint (Apr 9, 2021): https://www.researchsquare.com/article/rs-404769/v1

CVST associated with COVID-19

- Recent study using electronic health records (81m patients, mostly U.S.) to estimate CVST & portal vein thrombosis (PVT) incidence in 513,284 COVID-19 cases
  - Highest baseline CVST incidence observed over any 2-week period: **0.41** per million people
  - CVST incidence 2 weeks after COVID-19 diagnosis (among hospitalized): **39** per million
  - CVST incidence higher after COVID-19 diagnosis than after mRNA vaccines (**4.1** per million) or after influenza disease (**0.0** per million)
  - Mortality was 20% for CVST and 19% for PVT

<u>Limitations</u>

- Unable to assess incidence of CVST after adenovirus vector vaccines (Janssen, AstraZeneca)
- Did not provide rates of CVST + thrombocytopenia
  - Limited ability to directly compare to rates of CVST + thrombocytopenia after vaccines reported in US or Europe

Acronyms: Cerebral Venous Sinus Thrombosis (CVST), Portal Vein Thrombosis (PVT)

Taquet et al. Open Science preprint (April 15 2021): https://osf.io/a9jdq/

Thrombosis with Thrombocytopenia Syndrome (TTS) after AstraZeneca vaccine in Europe

- As of 4 April 2021, **169** cases of CVST & **53** cases of splanchnic vein thrombosis reported to EudraVigilance. ~34 million people vaccinated in EEA & UK by this date.
  - EU ~**10 cases per million** (1 case per 100,000) vaccinated adults
    - Higher in younger adults compared to older adults
  - Most of cases in women aged <60 years within 2 weeks of receiving 1st vaccine dose

- European Medicines Agency concluded benefit/risk ratio still favorable to use vaccine
  - Causal association plausible
  - Unable to identify definitive cause, but possibly similar to heparin-induced thrombocytopenia
  - No specific risk factors to date (epidemiology may be related to vaccine delivery)
  - Added unusual blood clots with low platelets to the label as very rare side effect

https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield)

https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood

https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant_en.pdf

UK decision on use of AstraZeneca vaccine — April 14, 2021

- Through April 14: **168 reports** of blood clotting with low platelets
  - 77 CVST with thrombocytopenia; 91 in other major veins with thrombocytopenia
  - 93 women, 75 men, aged 18–93 years
  - 32 deaths
  - Most cases occurred after first vaccine dose; one case occurred after second dose
- Rate: **7.9 per million** (21.2 million AZ doses given)
- **Benefits continue to outweigh risks** — stronger evidence for a link of vaccine to extremely rare blood clots with lower platelets, but more work needed
  - Careful consideration be given to those at higher risk of blood clots because of medical conditions or pregnancy
  - Continue to give second doses, except to those with blood clots and low platelets after first dose
- Recommended **ages 18–29** years at low risk of infections be offered other vaccines

https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting
https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots
https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement/jcvi-statement-on-use-of-the-astrazeneca-covid-19-vaccine-7-april-2021

EMA's safety committee (PRAC) meeting on U.S. TTS cases after Janssen vaccine, April 20, 2021

- Reviewed evidence on 8 U.S. reports of serious cases of unusual blood clots with low levels of blood platelets, one of which had a fatal outcome. Over 7 million U.S. people had received Janssen vaccine, as of 13 April 2021
- Cases reviewed **very similar** to cases occurring with AstraZeneca COVID-19 vaccine
- Concluded that a **warning** about unusual blood clots with low blood platelets should be added to the product information for Janssen COVID-19 vaccine
- Very rare event, and the overall benefits of Janssen COVID-19 vaccine in preventing COVID-19 outweigh the risks of side effects
- Emphasized importance of healthcare provider awareness

https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood

Public Health Problem:

COVID-19

Hospitalization:
200 per million population

Death:
30 per million population

HIT

23–45 per million population

CVST

14.5–28.5 per million population

CVST + Thrombocytopenia

0.7–1.6 per million population

CVST after COVID-19

5-6 per million SARS-COV-2 infections

TTS after AZ vaccine

EU:
10 per million vaccinated population

UK:
7.9 per million vaccinated population

Acronyms: Cerebral Venous Sinus Thrombosis (CVST), Heparin-Induced Thrombocytopenia (HIT), Thrombosis with Thrombocytopenia Syndrome (TTS)

EtR Domain: Benefits and Harms

Benefits and Harms:

- Benefits of Janssen COVID-19 vaccine
  - Prevention of COVID-19 cases, hospitalizations and deaths
- Harms of Janssen COVID-19 vaccine
  - Estimated cases of TTS after Janssen COVID-19 vaccine, by age and gender
- Benefit and Risk summary

Benefits of the Janssen COVID-19 vaccine

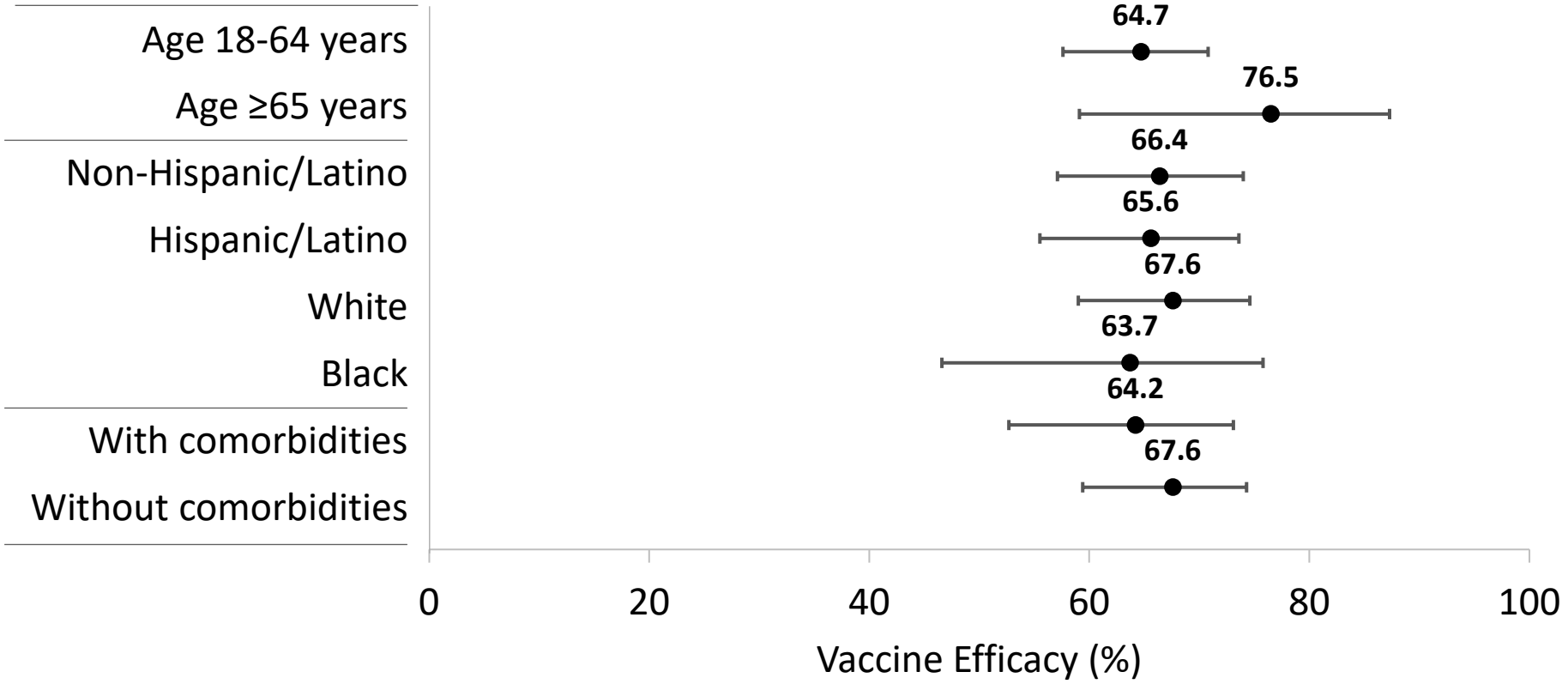
- The clinical trial demonstrated efficacy against symptomatic, laboratory-confirmed COVID-19. The overall efficacy was **66.3%** (95% CI: 59.9%, 71.8%)
- Vaccine efficacy against COVID-19 associated hospitalization was **93%** (95% CI: 71%, 98%)
- **Higher** efficacy against **severe** outcomes than for any symptomatic COVID-19
  - VE against **deaths** due to COVID-19**: 100%**
- Efficacy against severe disease[†] remained high across world regions (**73-82%**[*]), suggesting protection against severe illness with variant strains

†Definition: Respiratory Rate ≥ 30, Heart Rate ≥125, SpO2≤ 93% on room air at sea level or PaO2/FIO2< 300 mm Hg; OR respiratory failure or Acute Respiratory Distress Syndrome (ARDS), defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO; OR evidence of shock (systolic blood pressure <90mmHg, diastolic BP<60mmHg or requiring vasopressors); OR significant acute renal, hepatic or neurologic dysfunction; OR admission to an intensive care unit or death

*Assessed ≥ 14 days post vaccination

Benefits of the Janssen COVID-19 vaccine

- **Similar** efficacy for across age, sex, race, and ethnicity categories, and those with underlying medical conditions at ≥14 days post-vaccination



Benefits of the Janssen COVID-19 vaccine

- Vaccine shipment and storage (3 months) at **refrigerator** temperatures (2-8°C)*
  - Refrigerator-stable vaccine could facilitate the availability of the Janssen COVID-19 vaccine in many community settings and mobile sites
- **Single-dose** series
- Easier to reach some disproportionately affected groups such as: homeless, rural residents, justice-involved, disabled, homebound, or with no/limited access to healthcare

* Long-term storage at standard freezer temperatures (-20°C)

Potential Harms of the Janssen COVID-19 vaccine

- 7.98 million vaccine doses administered* and 15 confirmed TTS cases as of April 21, 2021
  - Additional potential TTS cases under review, including potential male cases

	Females			Males		
Age group	**Cases**	**Doses admin**	**Reporting rate†**	**Cases***	**Doses admin**	**Reporting rate†**
18-49 years old	13	1,866,294	**7.0** per million	0	1,977,330	**0** per million
50+ years old	2	2,125,239	**0.9** per million	0	2,010,144	**0** per million

* Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations; Some age- and sex-specific doses administered data were imputed

† Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

* One TTS case occurred in the Phase 3 trial in a male aged 18-49 years.

Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Summary of Different Risk-Benefit Analyses

Population Level Risk-Benefit Analysis

Type of analysis	Objective
1. Population (6-month period)	• Quantify COVID-19 infections, hospitalizations, and deaths averted under different assumptions about resumption of Janssen vaccination • Quantify population-level, age-specific benefits and harms of resuming vaccination with Janssen COVID-19 vaccine

Individual Level Risk-Benefit Analysis

Type of analysis	Objective
2. Direct (1-month period)	• Quantify direct age and sex-specific benefits and harms, per million Janssen vaccine doses

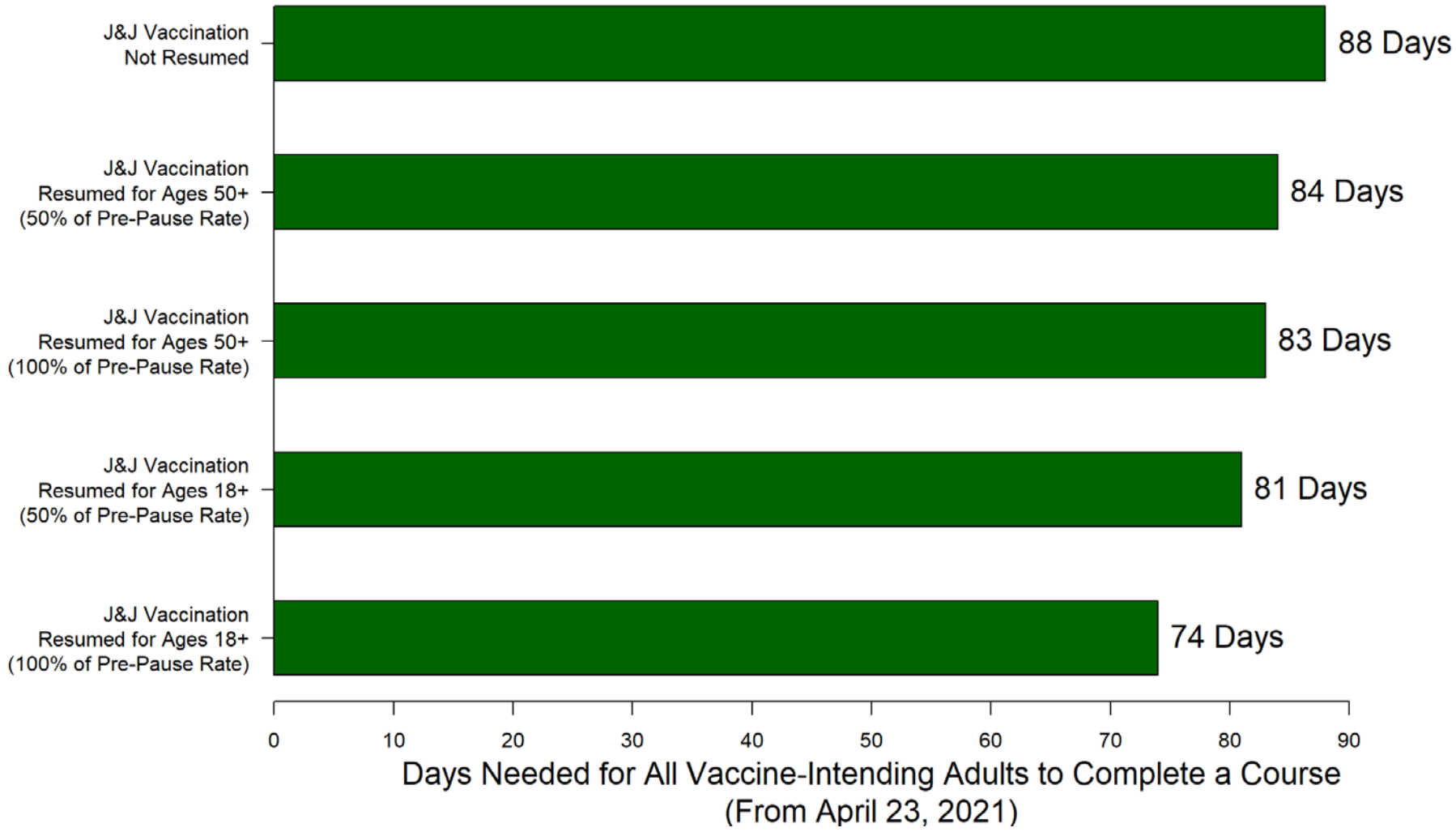
Modeled Janssen COVID-19 Vaccine Scenarios

- Objective: Quantify COVID-19 infections, hospitalizations, and deaths under different assumptions about resumption of Janssen vaccination
- In all scenarios we assume continued use of mRNA vaccines
- Evaluated the following scenarios:
  - Janssen vaccination **not resumed**
  - Janssen vaccination resumed on April 24th for all adults aged **18+ years**
    - **50%** of pre-pause J&J administration rate (in 18+ age group)
    - **100%** of pre-pause J&J administration rate (in 18+ age group)
  - Janssen vaccination resumed on April 24th in adults aged **50+ years only**
    - **50%** of pre-pause J&J administration rate (in 50+ age group)
    - **100%** of pre-pause J&J administration rate (in 50+ age group)

Model Overview & Assumptions

- Compartmental model used to simulate incident infections, hospitalizations, and deaths over the course of the epidemic in the US
  - Stratified by age, essential-worker status, and underlying conditions
  - Calibrated to observations through Spring 2021. Future activity based on external scenarios.
- Two vaccine types: mRNA and Janssen (VE informed by RCTs)
  - Immunity develops 14 days after administration
  - 28 days between mRNA doses
- No loss to follow-up or delays in administration
- No waning of immunity over time

Modeled Time to Complete Vaccination for All Intending Adults

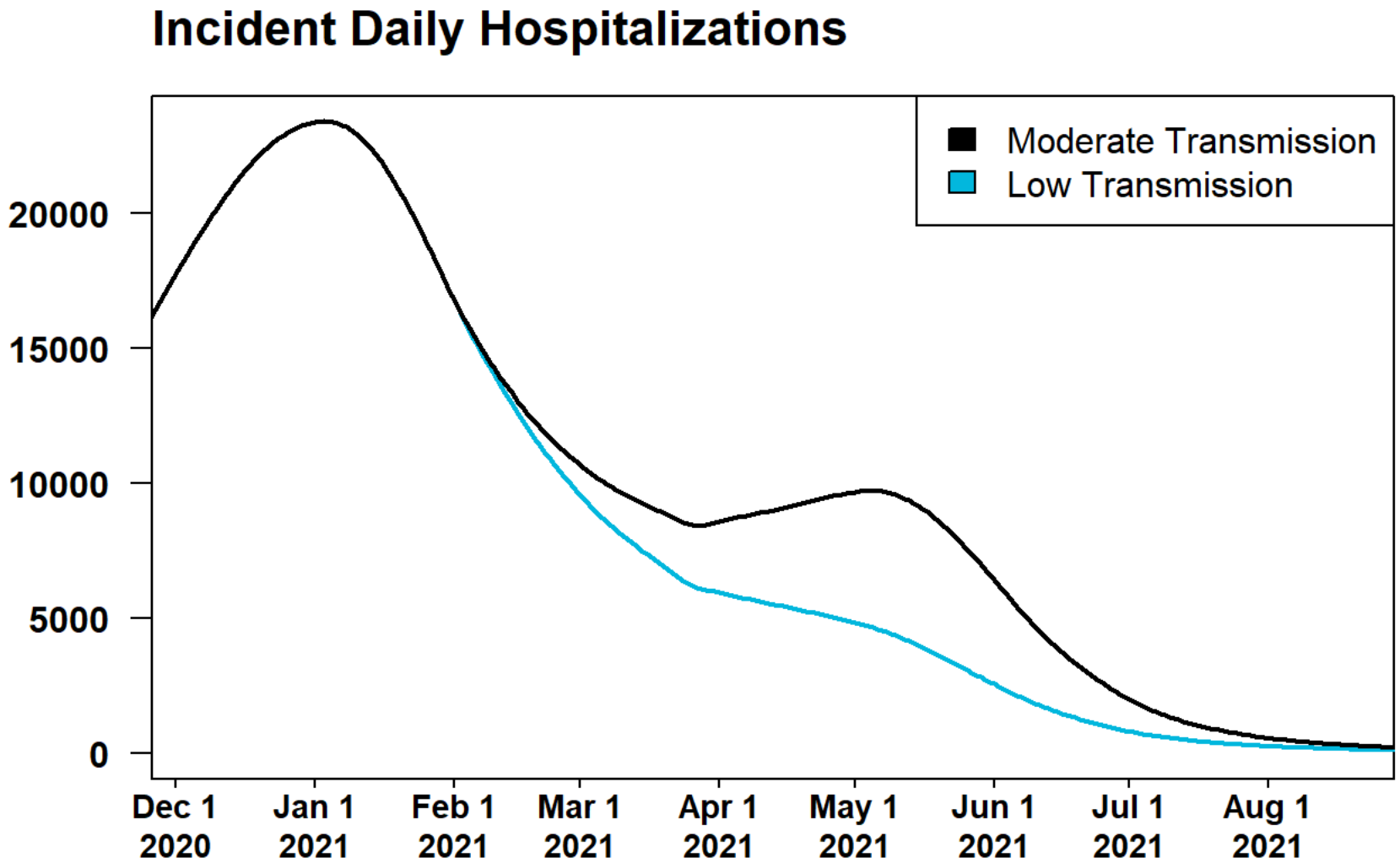


Multiple assumptions:

- Vaccine intent in each age group remains same
- Administration of mRNA vaccines continues at the same rate as before pause
- In practice, pace of administration may slow as those experiencing barriers to access and/or greater hesitancy comprise a greater share of the unvaccinated

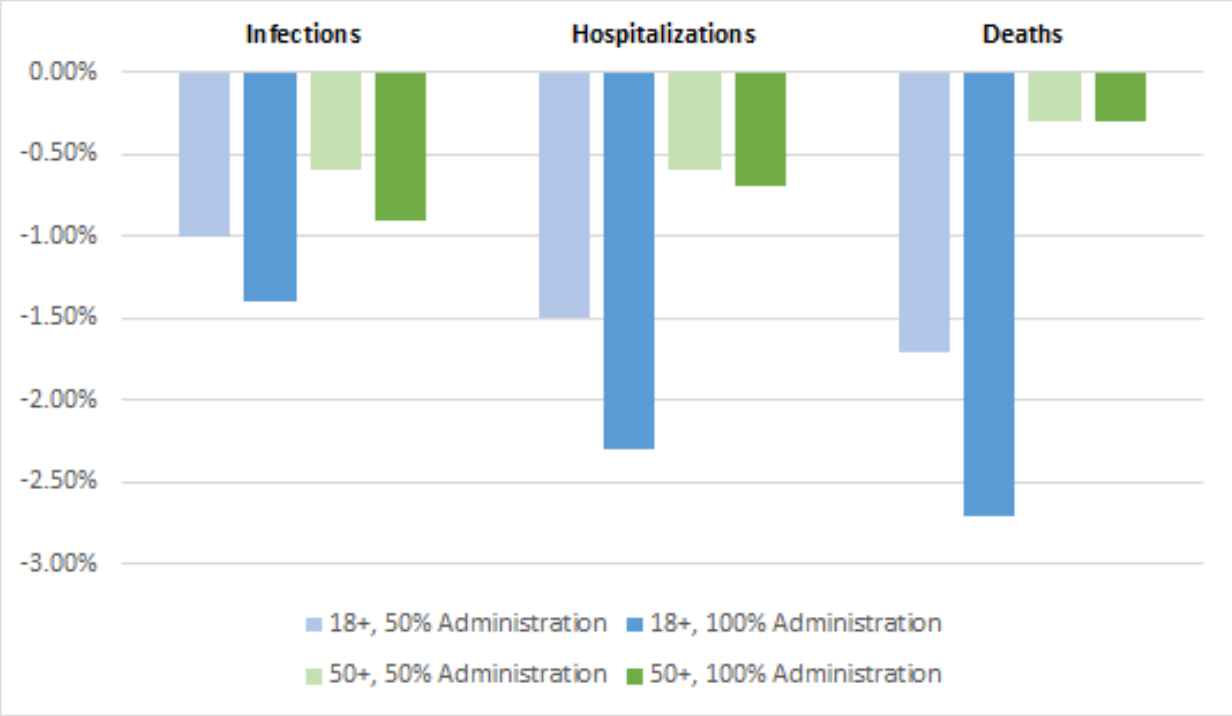
Modeling Transmission Scenarios

- Calibrated assuming no interruption of Janssen vaccination under two scenarios reflecting continued level of non-pharmaceutical interventions (i.e., low transmission and moderate transmission)
- Calibrated to Round 4 of the COVID-19 Scenario Hub



Percent Change* in Outcomes 6 Months Post-Pause, by Janssen Resumption Strategy

Moderate Transmission



* compared to a scenario in which administration of the J&J vaccine does not resume

Percent Change* in Outcomes 6 Months Post-Pause, by Janssen Resumption Strategy

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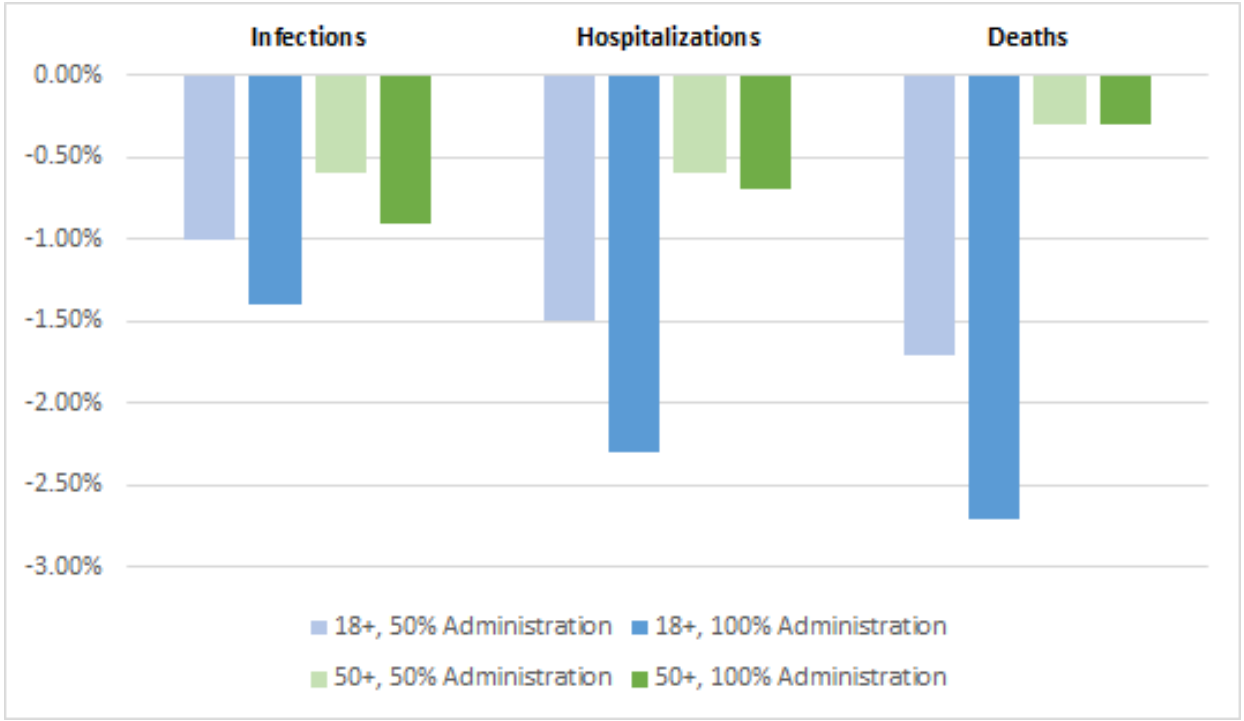
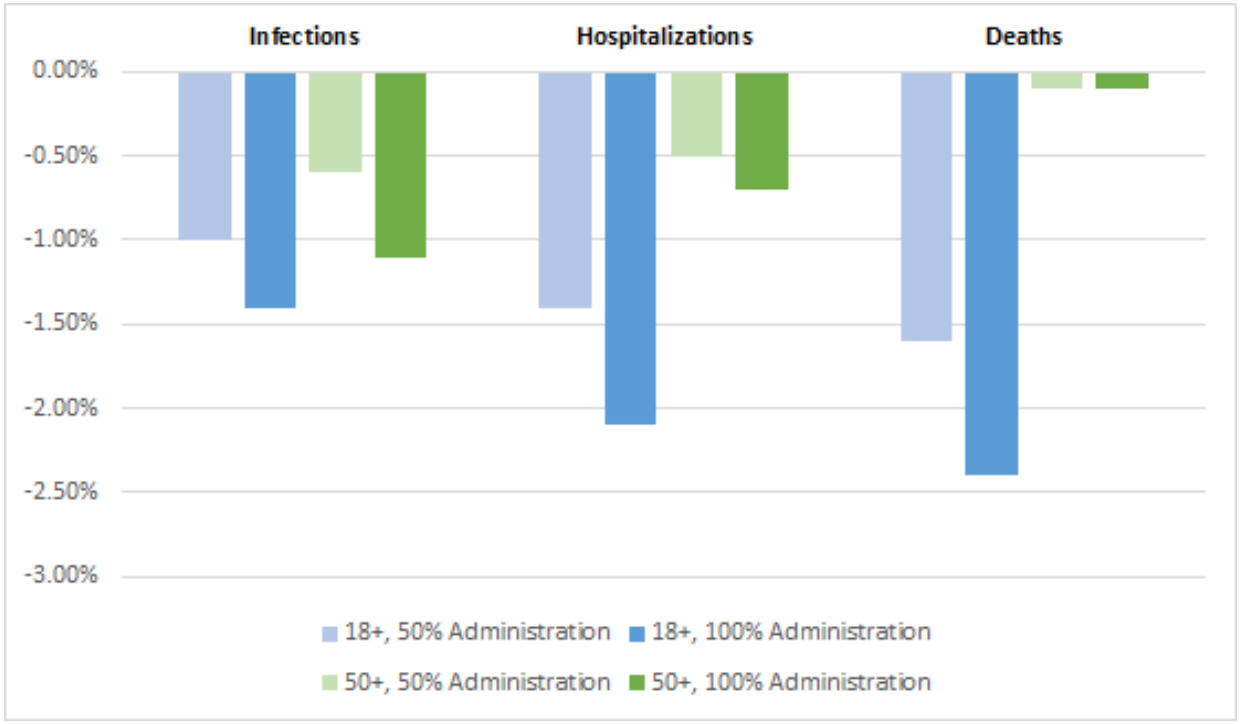


Low Transmission



There is a benefit of resuming Janssen vaccination in terms of infections, hospitalizations and deaths prevented under different epidemiologic assumptions

* Compared to a scenario in which administration of the J&J vaccine does not resume

Population Risk-benefit assessment

- Quantify age-specific risks and benefits of resuming vaccination with Janssen COVID-19 vaccine
  - Risks: Number of TTS
  - Benefits: Prevention of COVID-19-related hospitalizations, ICU admissions, and deaths

Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

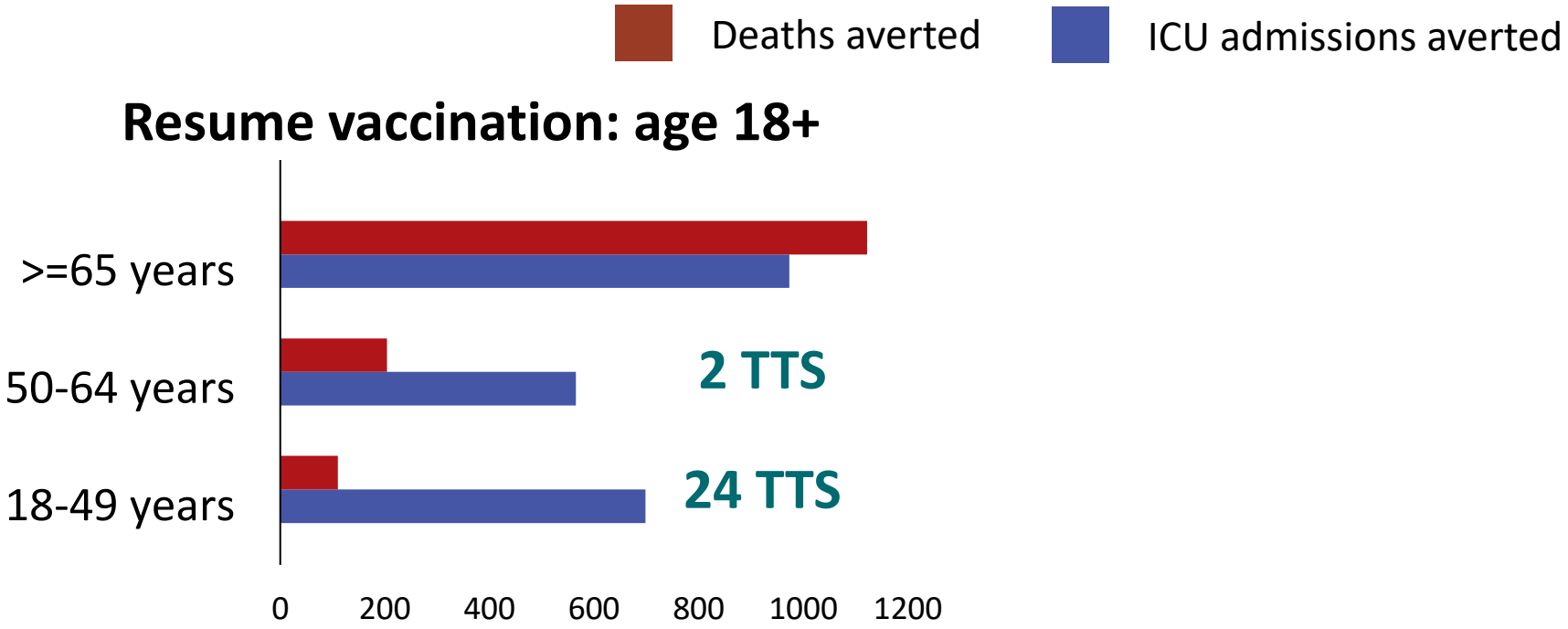
Population Risk-Benefit Inputs

- Estimates from compartmental model
  - Numbers of hospitalizations and deaths due to COVID-19
  - Number of persons estimated to receive Janssen COVID-19 vaccine after pause
  - Conditions: Low and moderate transmission; 50% and 100% of prior vaccination rate; Resuming in ages 18+ and 50+, vs no resumption
  - 6-month time horizon
- ICU admissions per hospitalization (CDC Pandemic Planning Scenarios)
- Counts of TTS cases by age (CDC data)
- Numbers vaccinated with Janssen COVID-19 vaccine, by age, before pause (CDC data)

Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Benefits and harms of resuming vaccination for ages ≥18 years vs. ≥50 years over 6-month period

Moderate transmission; Vaccination resumed at 50% of rate before pause



26 TTS in 9.8M vaccinations
Prevent 1,435 deaths, 2,236 ICU admissions

[1] Based on observed cases adjudicated as of 4/21/2021
NOTE: in Phase III RCT, one male in 18-49 year age group experienced TTS; not included in this analysis
Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

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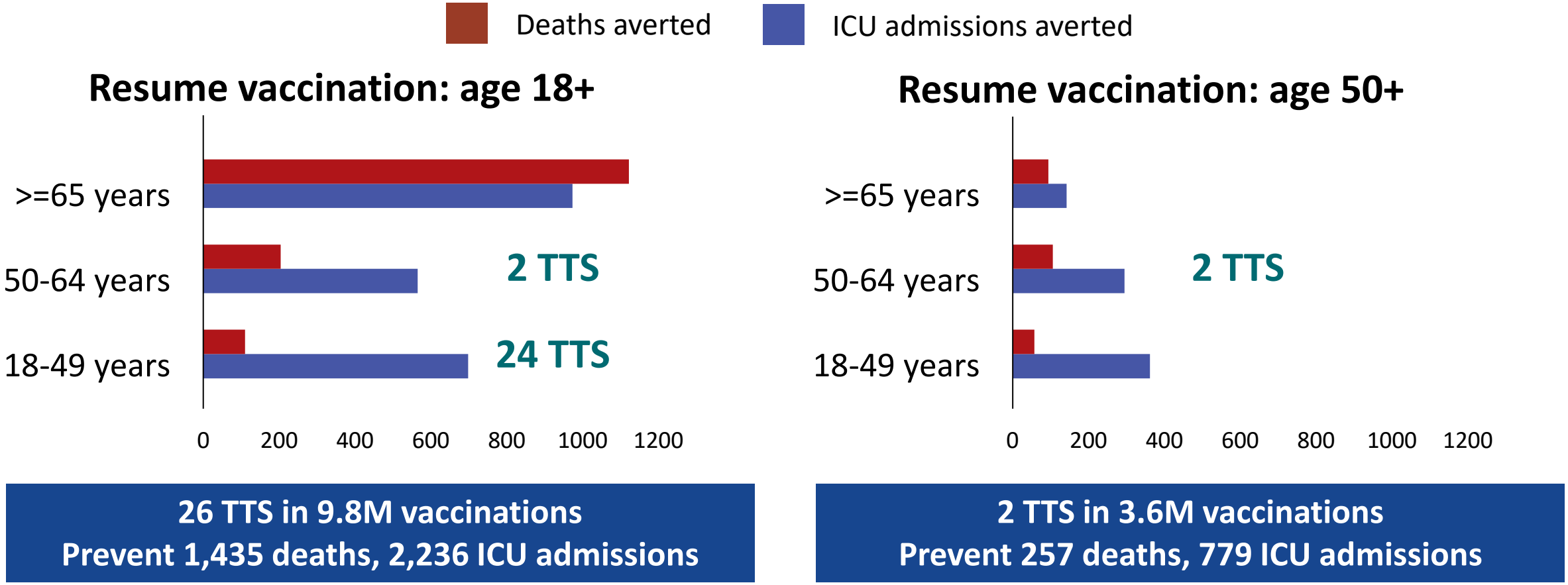


26 TTS in 9.8M vaccinations
Prevent 1,435 deaths, 2,236 ICU admissions

2 TTS in 3.6M vaccinations
Prevent 257 deaths, 779 ICU admissions

[1] Based on observed cases adjudicated as of 4/21/2021
NOTE: in Phase III RCT, one male in 18-49 year age group experienced TTS; not included in this analysis
Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Summary of population-level risks and benefits by recommendation, all scenarios

Recommendation for all persons aged 18+

- **Risks:** Expect **26–45 TTS** cases, depending on uptake
- **Benefits:** Depend on uptake, amount of transmission
  - **800–3,500 fewer ICU** admissions
  - **600–1,400 fewer deaths**

Recommendation for all persons aged 50+

Risks: Expect **2–3 TTS** cases, depending on uptake

Benefits: Depend on uptake, amount of transmission

300–1000 fewer ICU admissions

40–250 fewer deaths

Note: Benefits of vaccination apply to the whole population over a 6-month period, and result from direct and indirect effects.

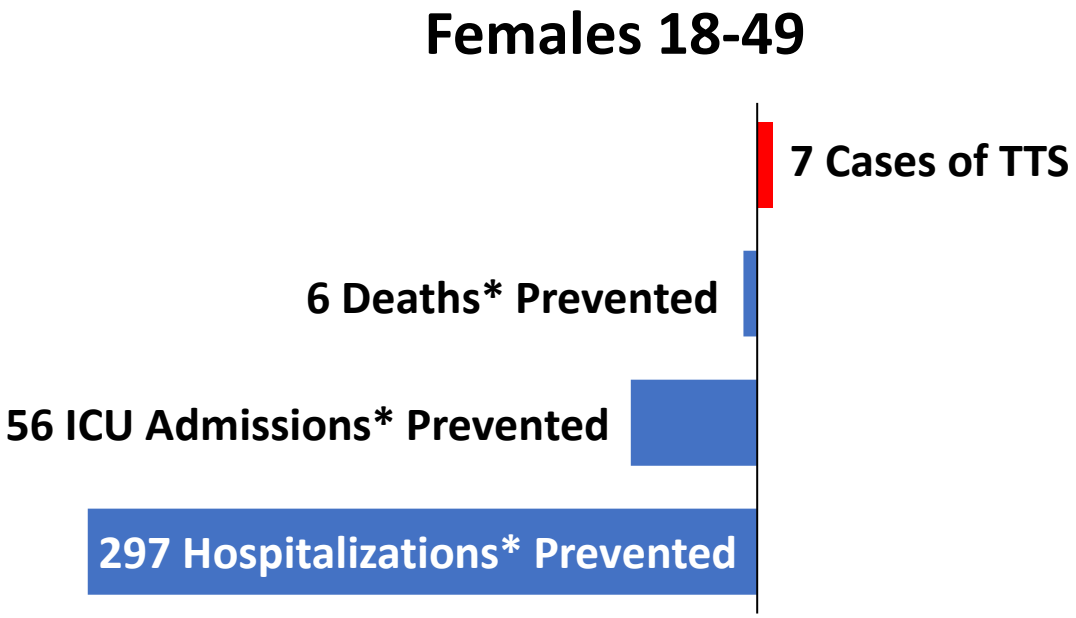
Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Estimation of direct benefits and risks to vaccinated persons

- Evaluate direct benefits and risk, per million Janssen vaccine doses
- Used to visualize sex differences in risk and benefits
- Calculations based on recent hospitalization incidence, VE, Janssen vaccinations to date, number of persons already vaccinated
- 30-day period

Risks and benefits by for females, by age group

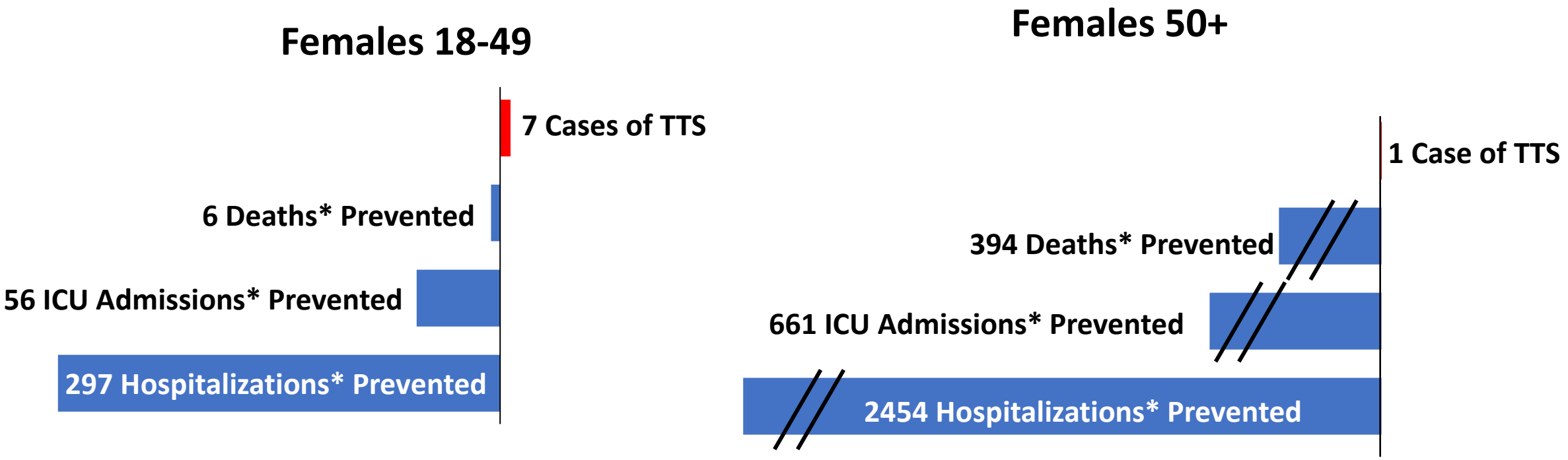
For every **1 million** doses of vaccine given with current US exposure risk[1]



* Deaths, ICU admissions, and deaths due to COVID-19
Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Risks and benefits females, by age group

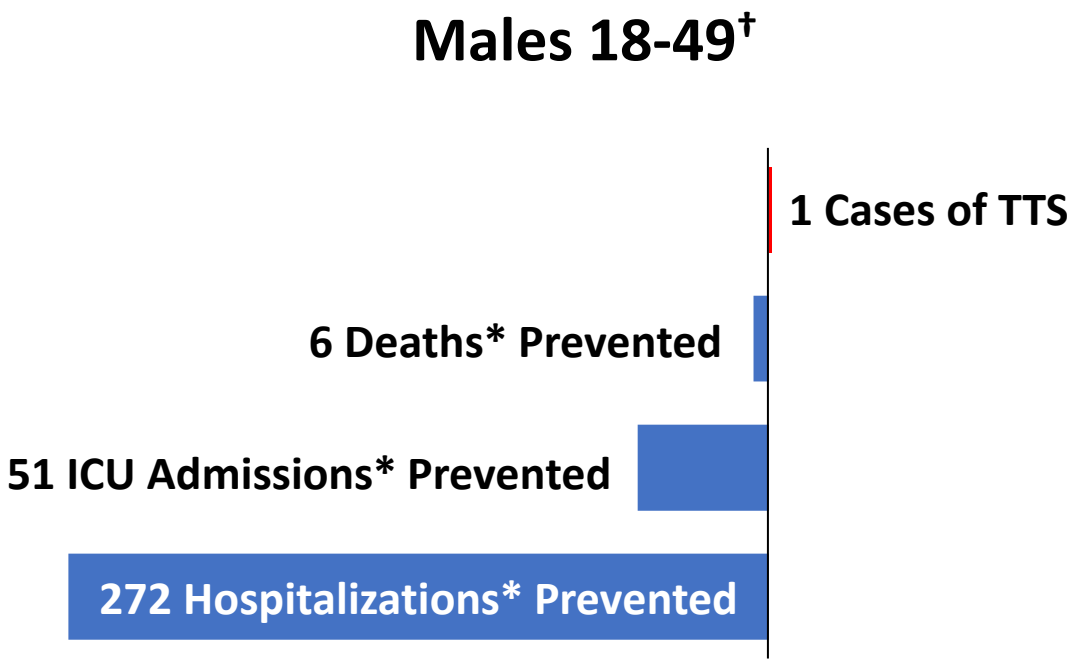
For every **1 million** doses of vaccine given with current US exposure risk[1]



* Deaths, ICU admissions, and deaths due to COVID-19
Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Risks and benefits males, by age group

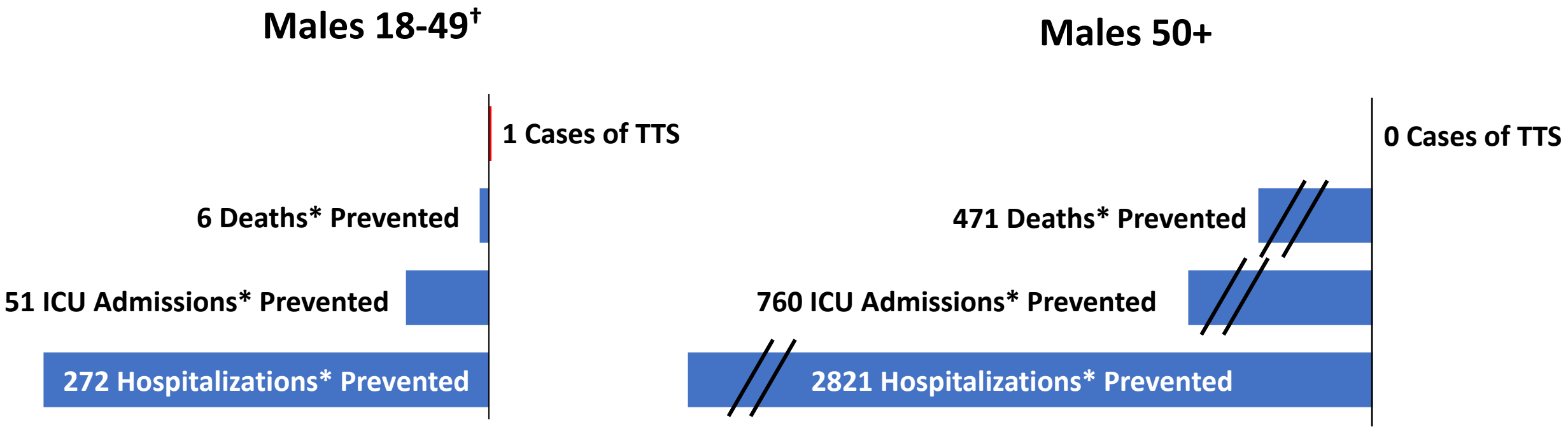
For every **1 million** doses of vaccine given with current US exposure risk[1]



†Analyses incorporated one TTS case that occurred in the Phase 3 trial in a male aged 18-49 years.
*Deaths, ICU admissions, and deaths due to COVID-19
Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Risks and benefits males, by age group

For every **1 million** doses of vaccine given with current US exposure risk[1]



†Analyses incorporated one TTS case that occurred in the Phase 3 trial in a male aged 18-49 years.
*Deaths, ICU admissions, and deaths due to COVID-19
Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Risk-benefit interpretations

- Population
  - Takes into account direct and indirect (herd) effects of vaccination
  - Incorporates availability of different vaccines
  - Simulates incidence, hospitalizations, and deaths over course of pandemic
  - 6-month time horizon
- Shows large population benefit of vaccination relative to rare TTS

- Direct
  - Considers individual benefits of vaccination vs. individual risks
  - Only considers getting Janssen vaccine vs. not getting a vaccine
  - Short, 1-month time horizon
- Shows positive balance for benefits vs. risks for all age and sex groups
- Balance of risks and benefits varies by age and sex

Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

EtR Domains: Values and Acceptability

Values and Acceptability:

- Intent to receive 1-dose COVID-19 vaccine
  - Data stratified by age, sex, race/ethnicity and income
- Intent to receive Janssen COVID-19 vaccine over time
- Effect on overall vaccine confidence

Values and Acceptability:

Intent to receive 1-dose COVID-19 vaccine

- Among unvaccinated respondents, if both a 2-dose and 1-dose COVID-19 vaccine were available, which would you choose? Assume that both types of vaccines are safe.
  - Respondents could choose 1-dose, 2-dose, either, neither
  - Data collected **February** 2021

- Examined by age, sex, race/ethnicity, and income
  - Overall, **6**% exclusively preferred 1-dose vaccine
  - No differences in proportion that preferred 1-dose by age, sex, or income
  - Significantly more Hispanic than White respondents (11%) preferred 1-dose

Source: Combined Data from IPSOS and NORC, February 2021 (3 waves)

Values and Acceptability:

Intent to receive Janssen COVID-19 vaccine over time

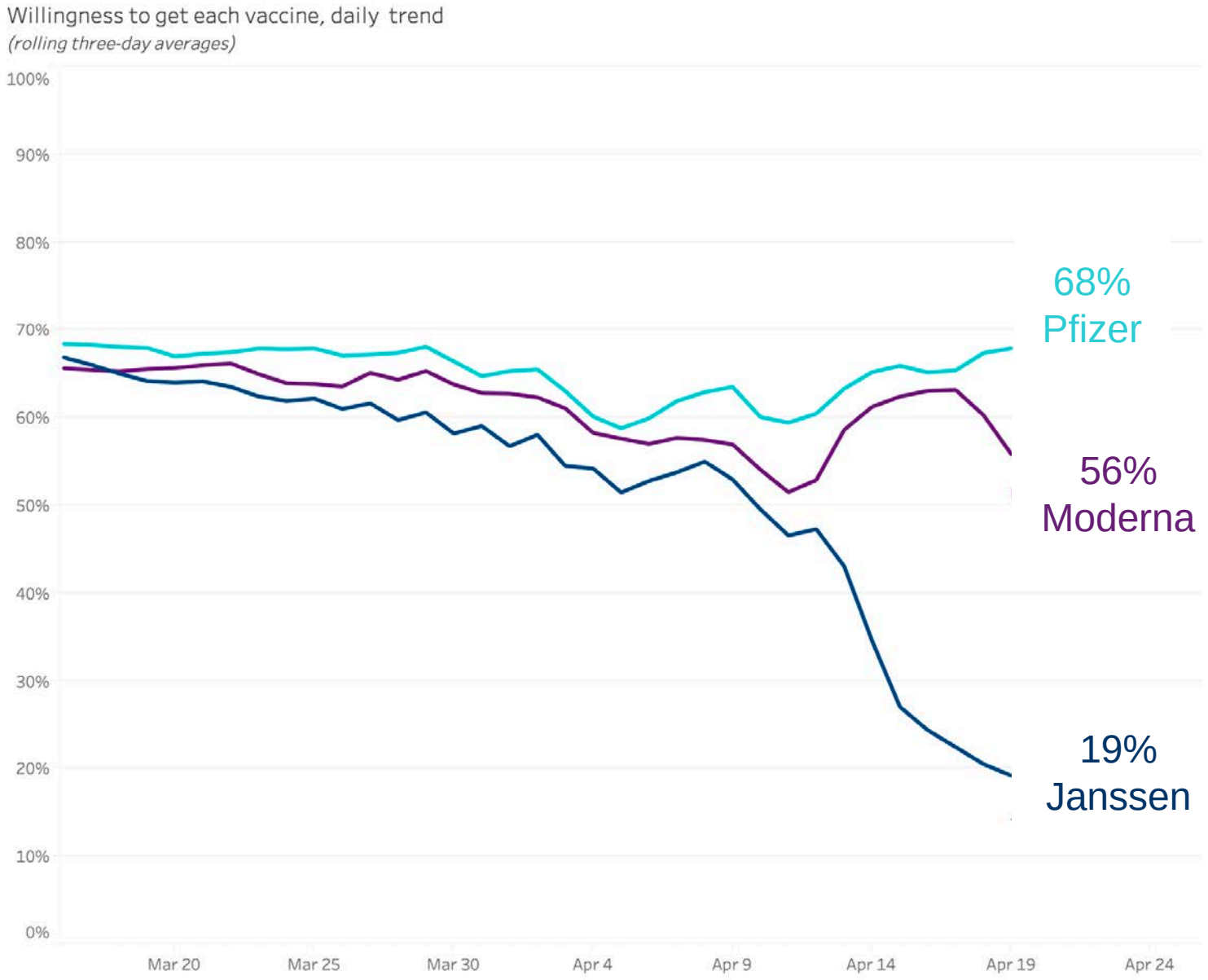
- Only 37% of respondents called the Janssen COVID-19 vaccine safe after the pause was announced[1]
  - Drop of 15% in two to three days

- Americans now much less likely to prefer the Janssen COVID-19 vaccine[2]
  - 13% decline in preference for the Janssen COVID-19 vaccine
  - Declined 9% to 25% across age and race categories

1. https://today.yougov.com/topics/politics/articles-reports/2021/04/15/johnson-johnson-vaccine-confidence
2. CVS Health Survey- COVID-19 Vaccine Brand Preferences and Hesitancy Post J&J Pause

Willingness to receive the J&J vaccine dropped immediately as a result of the pause

(Results among those who say "yes" they plan to get vaccinated but haven't yet)



Outbreaks Near Me

Boston Children's Hospital

Values and Acceptability:

Effect on overall vaccine confidence

- Drop in vaccine confidence does not appear to extend to the Pfizer-BioNTech and Moderna COVID-19 vaccines[1]
  - 59% consider them safe
  - 19% feel they are unsafe

- Recent poll did not suggest reduction in intent to be vaccinated[2]
  - 40% more likely to receive COVID-19 vaccine compared to one month ago
  - 36% report no change in intent

- A different survey found half of the unvaccinated are less inclined to receive COVID-19 vaccine after the pause, regardless of brand[3]

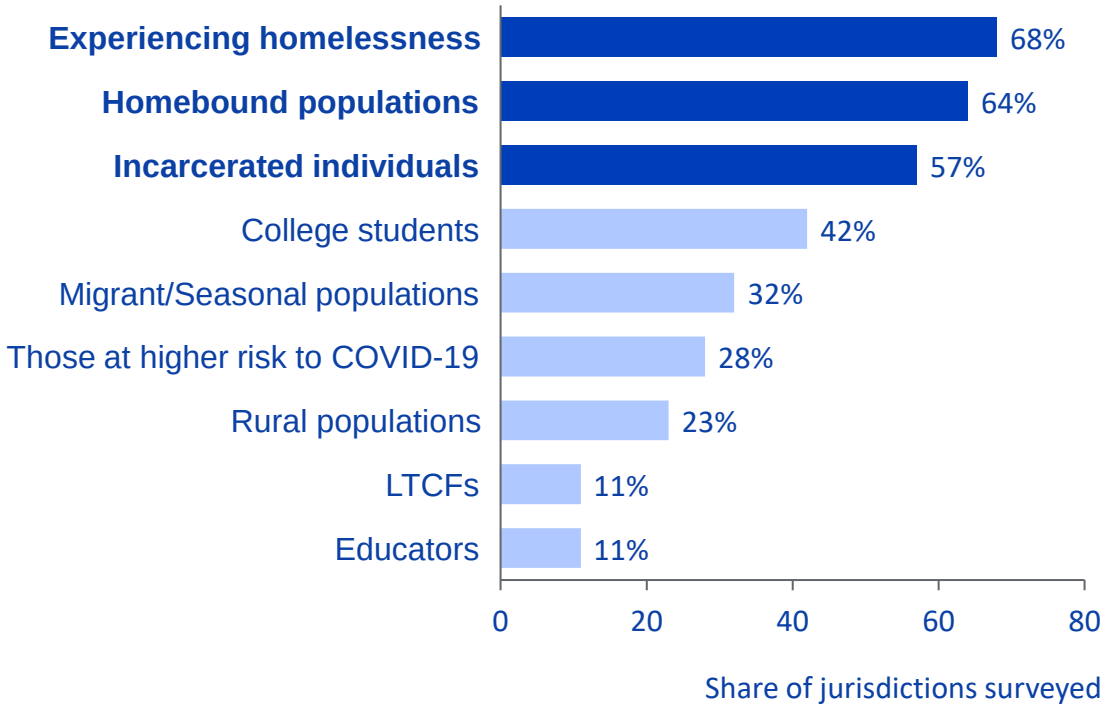
1. https://today.yougov.com/topics/politics/articles-reports/2021/04/15/johnson-johnson-vaccine-confidence
2. deBeaumont Foundation Poll, April 15-16, 2021. Vaccine Confidence Grows Despite J&J Pause
3. CVS Health Survey- COVID-19 Vaccine Brand Preferences and Hesitancy Post J&J Pause

EtR Domain: Feasibility

Feasibility: Jurisdictions' pre-pause use of Janssen vaccine

Populations: Focus on reaching those experiencing homelessness, homebound or currently incarcerated

Q: Prior to the pause in administration of the Janssen vaccine, which populations had you focused on vaccinating with this product?

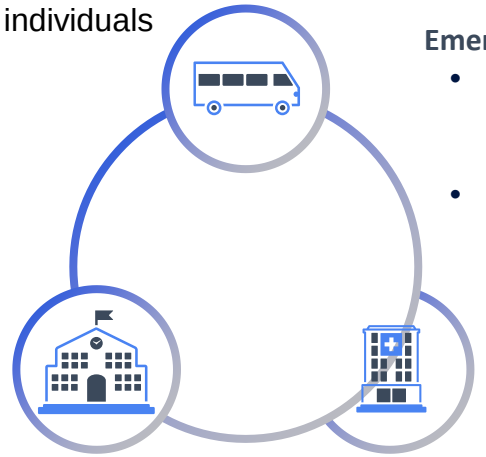


Jurisdictional survey on impacts of Janssen pause, April 18th- 21st, 2021 (n=53)

Vaccination settings: Three core settings used by jurisdictions to administer Janssen vaccine

Mobile vaccination

- Temporary PODs and mobile vans able to reach transient, rural and homebound individuals



Emergency departments

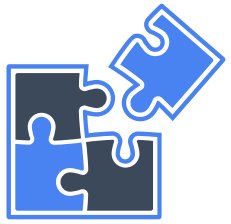
- Provided at discharge from urgent care or ER departments
- Particularly for 'safety-net' hospitals reaching transient groups

Student health centers

- On-campus vaccination centers with ambition to vaccinate students unable or less likely to return for second dose at end of semester

Feasibility: Impact if Janssen recommended for specific populations

Jurisdictions may need to reconfigure some vaccination sites, update scheduling tool, and have difficulty serving disproportionately affected populations

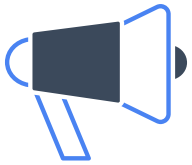


Changes to vaccination sites and schedulers might include…

Providers may need to carry multiple vaccines, if recommendation is restricted by sex.

Challenging to set-up dedicated community PODs if Janssen recommended for specific groups.

Would require IT systems update to internal scheduling and pre-screening tools.



Health depts. expressed concern about communicating change

Concerns about difficulty of communicating rationale for specific groups to public

Potential need to revise public-facing comms materials, provider training collateral, alongside re-training staff.

Expect low uptake on Janssen vaccine given negative publicity.

Greater difficulty serving disproportionately affected populations

Likely to see drop in completed series for those "at risk of loss to follow-up" e.g., experiencing homelessness, seasonal workers.

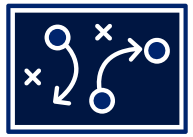
More challenging to reduce gap in vaccine disparities for racial and ethnic minorities through mobile vaccination.

Would increase barriers to access in rural and hard-to-reach areas.

Jurisdictional survey on impacts of Janssen pause, April 18th- 21st, 2021 (n=53)

Feasibility: Impact if Janssen were no longer recommended

Jurisdictions are particularly concerned about 2nd dose management and equity



Janssen provided flexibility to jurisdictions to…

Avoid additional second dose management, particularly for transient and hard-to-reach populations

Run mobile vaccination clinics without need for return visits

Reduce administrative burden on providers

Fully vaccinate college students before end of school year

Many individuals expressed a preference for Janssen

Convenience of single dose appeals to many recipients

Some individuals hesitant about receiving an mRNA vaccine

Possibility of second dose side effects causes some to favor Janssen

Some providers with lower volumes of patients have preference for single dose vaccine

Greater difficulty serving disproportionately affected populations

Increased challenge to reach homebound, transient, and rural populations because of need to administer second dose

Less flexibility to use mobile vaccination units

Reduced ability to vaccinate upon ED/hospital discharge

Decreased vaccine supply from loss of Janssen could harm vaccine access

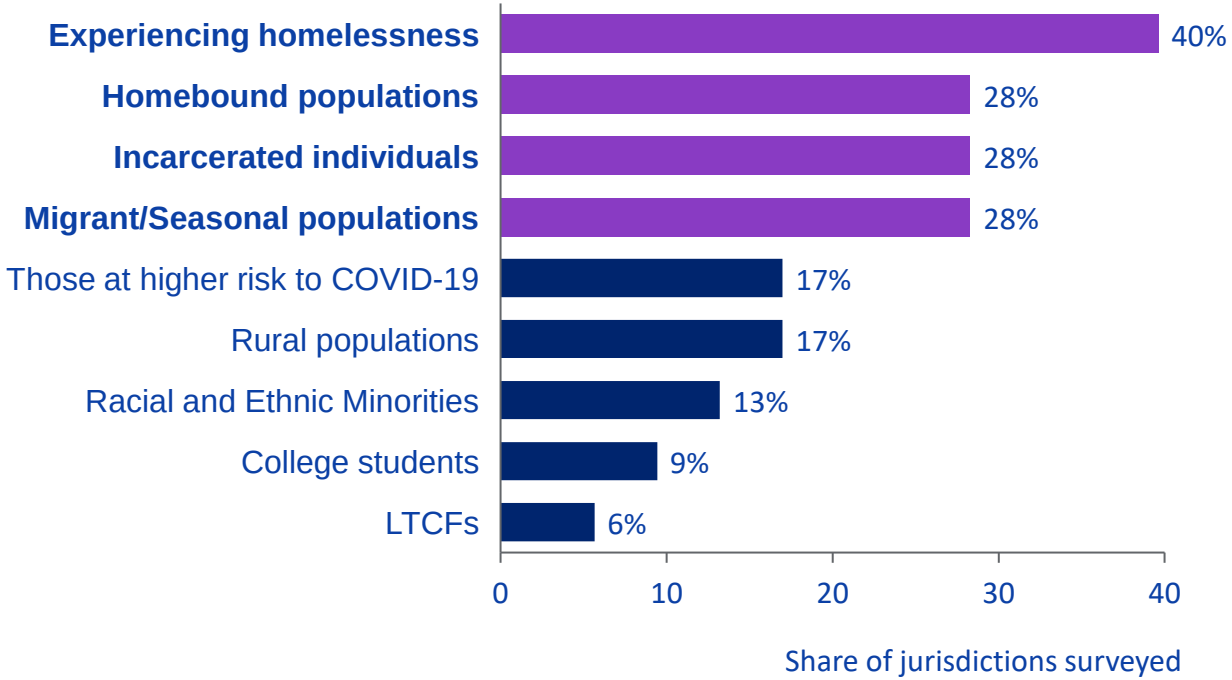
Jurisdictional survey on impacts of Janssen pause, April 18th- 21st, 2021 (n=53)

EtR Domain: Equity

Equity: Jurisdictions concerned revised recommendations would disproportionately affect several populations

Jurisdictions frequently raised four populations at risk of disproportionate impact

Q: Which, if any, populations would be disproportionally impacted if Janssen vaccine was no longer recommended or recommended for only a subset of the population?



Examples raised

Region 6 jurisdiction: "Most concerned about sub-populations that are difficult to reach e.g., people exp. homelessness, people who are working, as well as difficult geographic areas."

Region 2 jurisdiction: "The hardest to reach transient populations such as the homeless and those moving through substance use treatment programs, mental health treatment programs, etc. would be most impacted, given that they are among the most difficult individuals with whom to connect to provide second dose vaccination"

Region 10 jurisdiction: "…not having this vaccine would have an impact on trying to reduce the gap in vaccine disparities. We have community partners lined up to host events using the Janssen vaccine that are working with vulnerable populations in the state."

Jurisdictional survey on impacts of Janssen pause, April 18th- 21st, 2021 (n=53)

Policy Options

Policy Options for Janssen Policy Recommendations

Do **not** recommend use of Janssen vaccine

Recommend use of Janssen vaccine in **all adults** ≥18 years of age

Recommend use of Janssen/J&J COVID-19 vaccine in **some** populations

Policy Options for Janssen Policy Recommendations

- Recommend **against** use for all persons
- Reaffirm recommendations for **all** age and sex
  - FDA to include warning statement with EUA
- Recommend vaccination only for adults **≥50 years of age**
- Reaffirm recommendations for use; women aged <50 years should **be aware** of the increased risk of TTS, and **may choose** another COVID-19 vaccine (i.e. mRNA vaccines)

	Pros	Cons
Recommend **against use** in all persons	• No further cases of CVST/TTS after Janssen vaccine	• Would remove choice from individuals • Could lead to excess COVID-19 cases & deaths • Could disproportionately impact at-risk populations with barriers to access or difficulty returning for 2nd dose
Reaffirm recommendation for **all** ages/sex *Setting of FDA warning	• Allow for flexibility/choice • Allow for use of the vaccine in harder to reach populations	• Burden on individual to understand risk; health dept/providers to convey risk • May lead to more cases of TTS • At-risk populations for COVID-19 likely at risk for barriers to TTS identification and treatment

	Pros	Cons
Recommend vaccination only for **adults ≥50 years** of age	• Would remove vaccine from most at-risk population (reduce TTS cases) • Clear to communicate	• Difficult to implement (vaccination sites could need stock two vaccines) • Would remove an option in a population with lower risk (young men) • Could disproportionately impact at-risk populations
Reaffirm recommendations for use; women <50 should **be aware** of increased risk, and **may choose** another COVID-19 vaccine	• Allow for flexibility/choice • Allow for use of the vaccine in harder to reach populations, while still acknowledging risk in young women	• Could be difficult to implement (vaccination sites could need stock two vaccines) • Could be difficult to communicate

Policy Options for Janssen Policy Recommendations
Work Group Summary

- Detailed discussion of risk/benefit balance difficult in many current vaccination settings
- Recommendations that require vaccination sites to require two types of vaccines would be difficult to implement
- Access to vaccines for hard-to-reach populations remains important
- Risk/benefit balance may change as the pandemic evolves and risk of COVID-19 disease changes

Policy Options for Janssen Policy Recommendations

Work Group Summary

- Work Group discussed benefits and concerns with all policy options for Janssen COVID-19 vaccine
- No single policy option as clear choice by Work Group
- However, many on Work Group appreciated flexibility of a broader recommendation for use, but acknowledgement of elevated risk in women <50 years of age

Previous Janssen vote:

> The Janssen COVID-19 vaccine is recommended for persons 18 years of age and older in the U.S. population under the FDA's Emergency Use Authorization

Question for ACIP to discuss:

- Given the review of the benefits and risks, what recommendation does ACIP feel is appropriate for use of the Janssen COVID-19 vaccine?

Policy Options for Janssen Policy Recommendations

- Recommend **against** use for all persons
- Reaffirm recommendations for **all** age and sex
  - FDA to include warning statement with EUA
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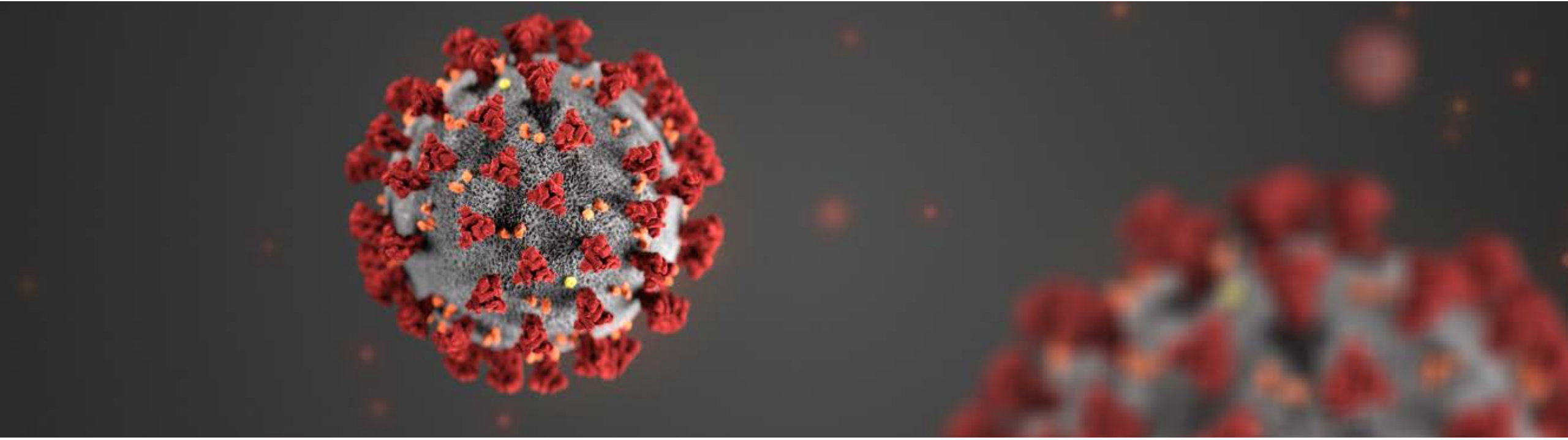

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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.