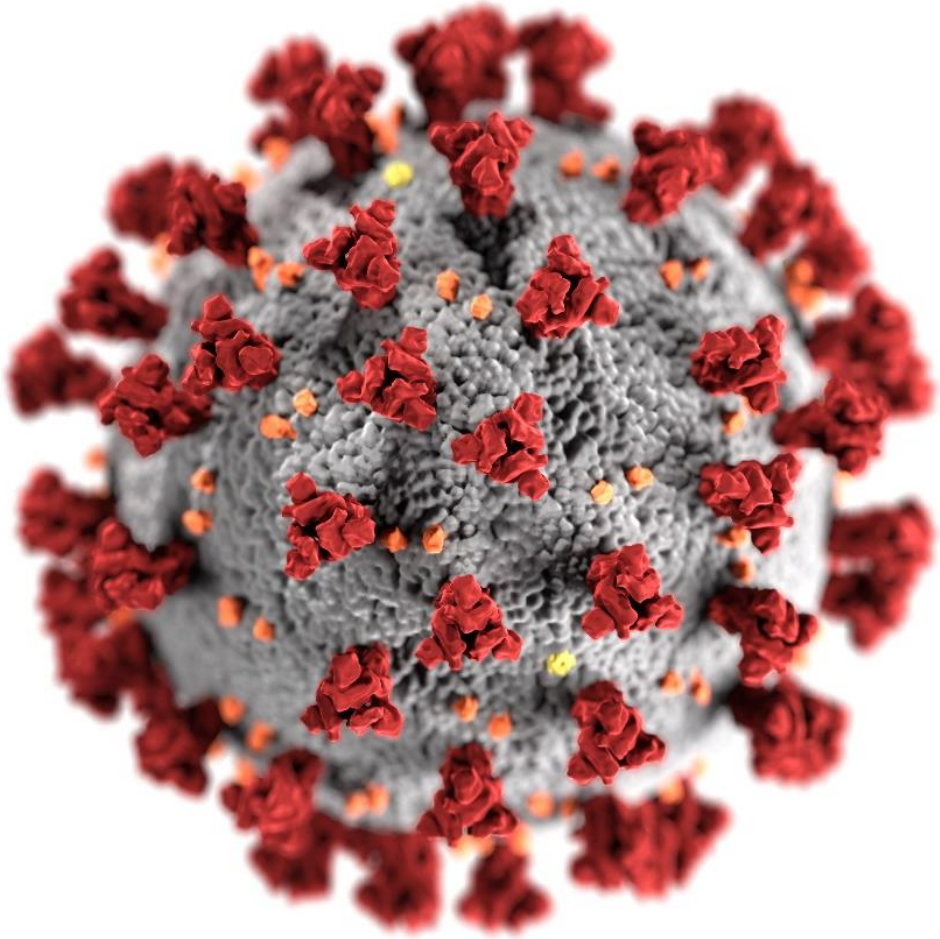
COVID-19 mRNA vaccines in adolescents and young adults: Benefit-risk discussion



Dr. Megan Wallace and Dr. Sara Oliver

ACIP Meeting

June 23, 2021

cdc.gov/coronavirus

Current COVID-19 mRNA vaccine policy

- COVID-19 vaccines are recommended for persons 12 years of age and older in the United States under FDA's Emergency Use Authorization

COVID-19 mRNA vaccines in adolescents and young adults

Risk after COVID-19 mRNA vaccines in adolescents and young adults

COVID-19 mRNA vaccines in adolescents and young adults

Risk after COVID-19 mRNA vaccines in adolescents and young adults

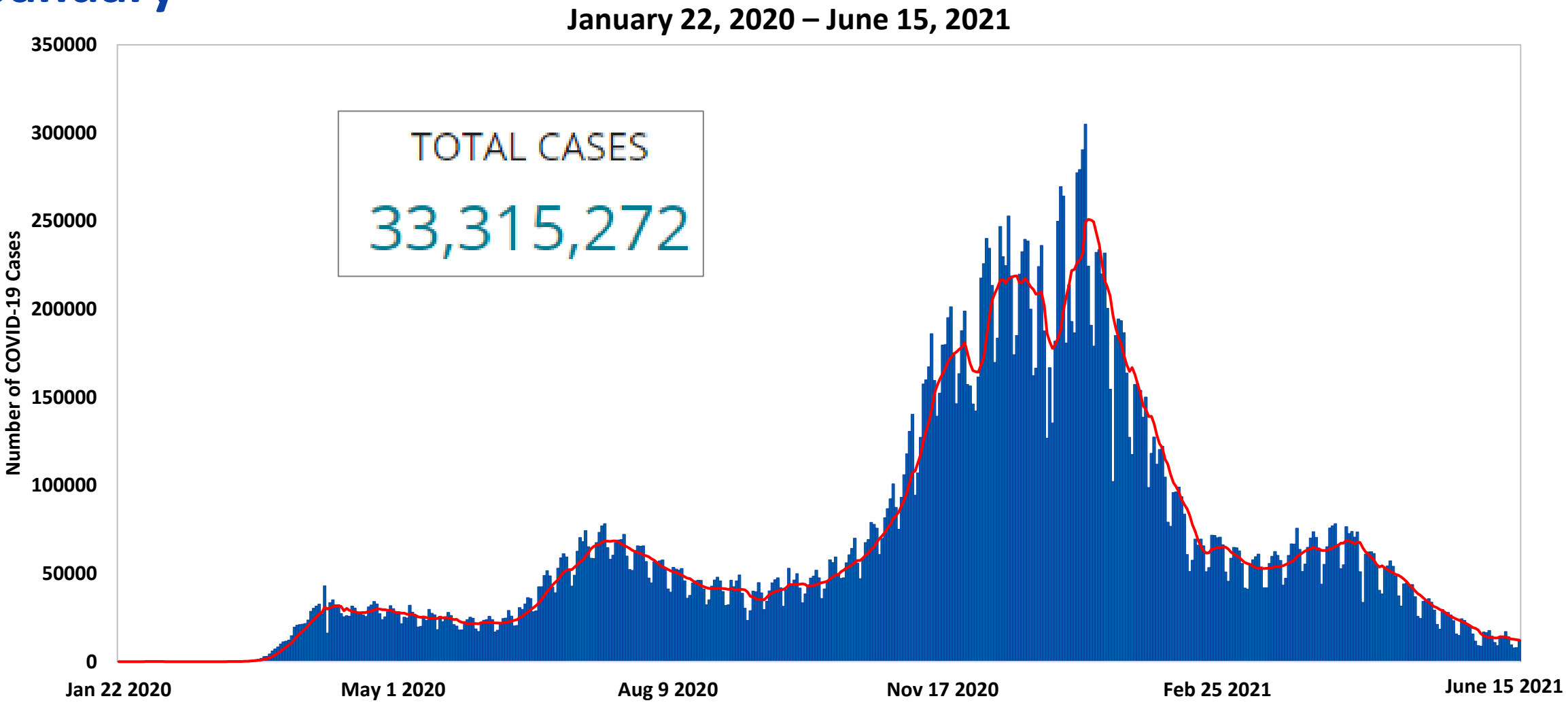
Benefits of COVID-19 mRNA vaccines in adolescents and young adults

COVID-19 mRNA vaccines in adolescents and young adults:
Benefit-risk discussion

- Public health problem
  - COVID-19 infections and complications in adolescents and young adults
    - Epidemiology in adolescents and young adults 12–29 years of age
  - Post-COVID conditions, including MIS-C and MIS-A
  - Myocarditis
- Benefit/Risk assessment
  - Benefits of mRNA vaccines
  - Risk of myocarditis after mRNA vaccines
- Work Group interpretation
- Questions for ACIP

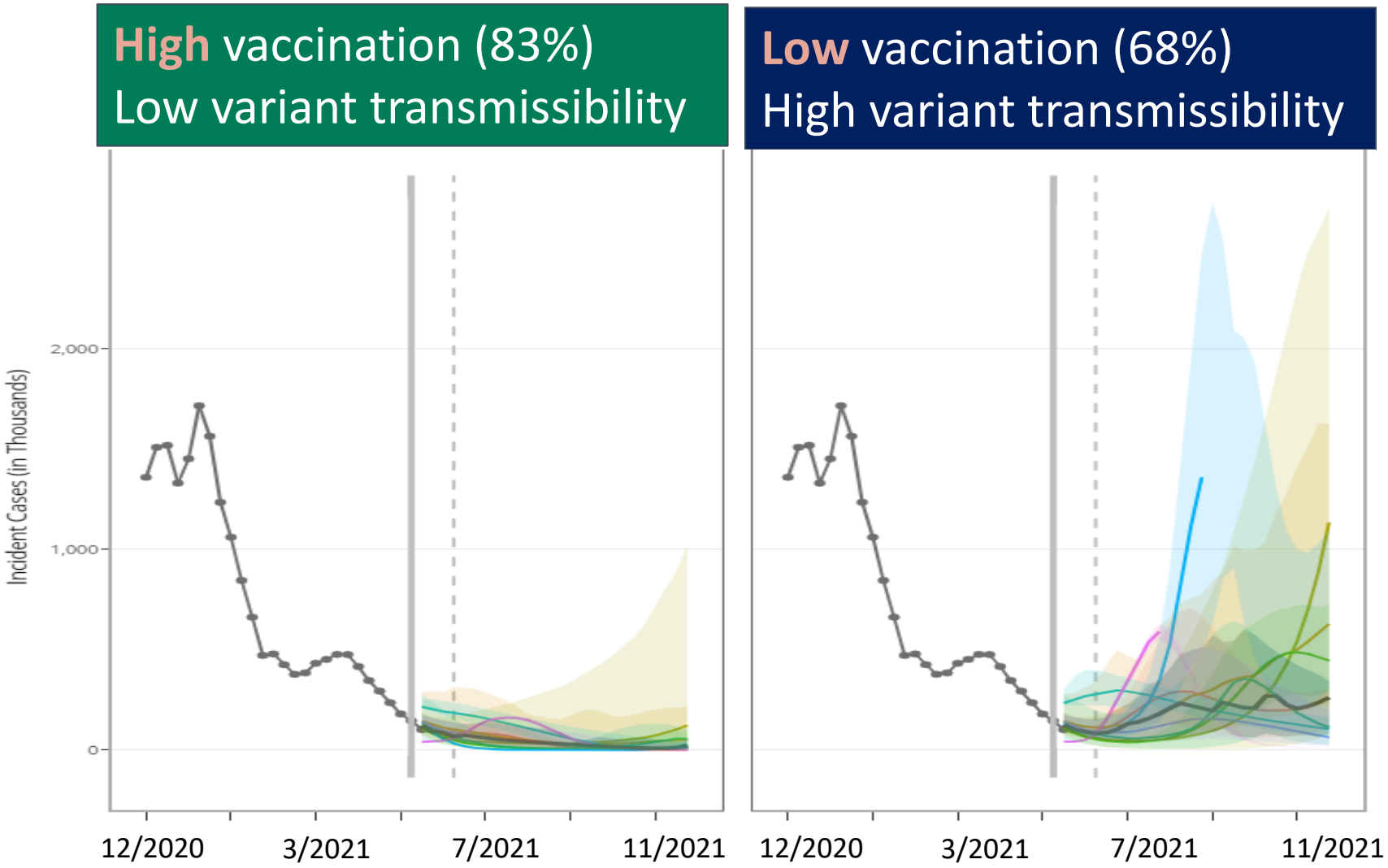
Public Health Problem

Overall COVID-19 cases in the US have been declining since January



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

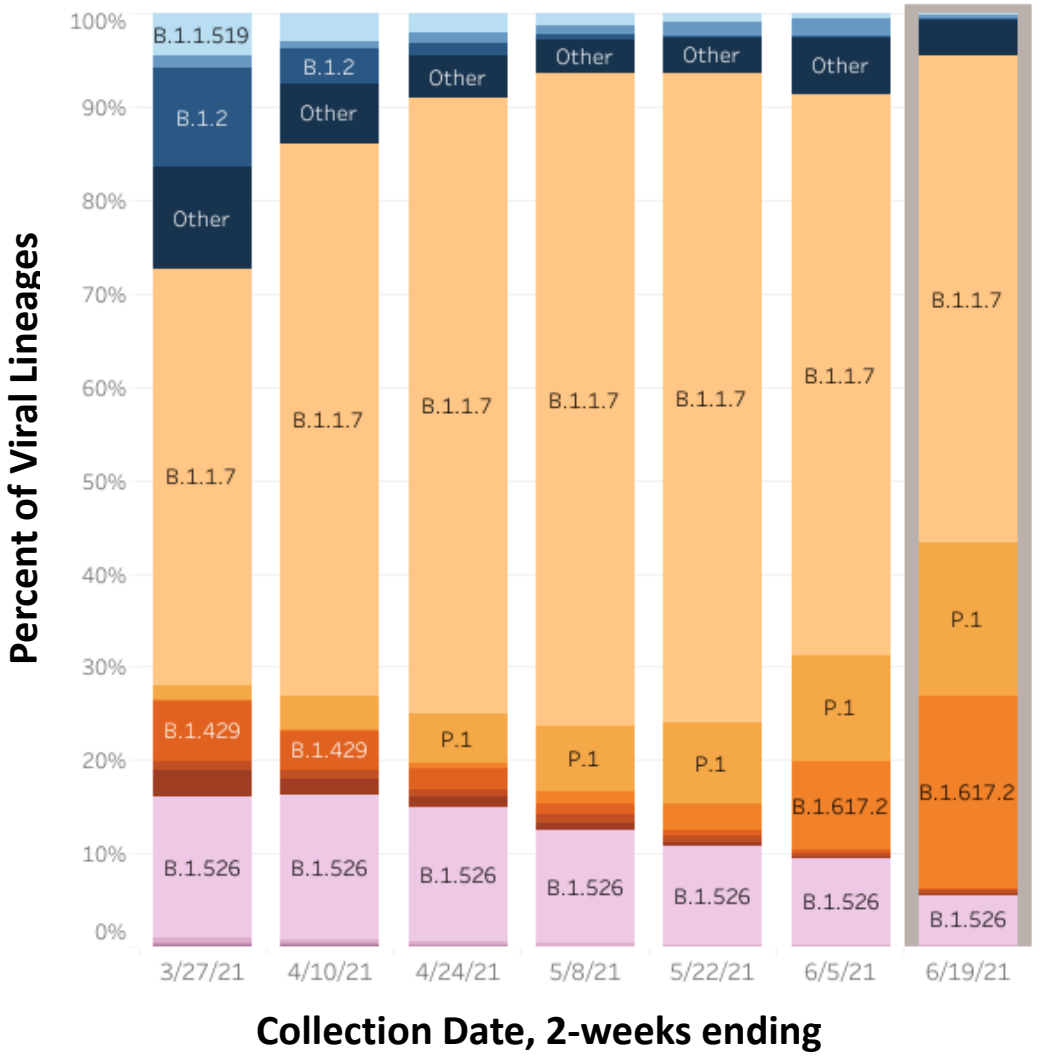
Based on projections, cases may increase substantially in the setting of low vaccination rates and high variant transmissibility



COVID-19 Scenario Modeling Hub Round 5: https://covid19scenariomodelinghub.org/viz.html

Variants of concern (VOC) are an increasing proportion of SARS-CoV-2 lineages circulating in the US

March 13 – June 19, 2021 with NOWCAST



Variants of Concern

B.1.1.7 (Alpha) 52%

P.1 (Gamma) 16%

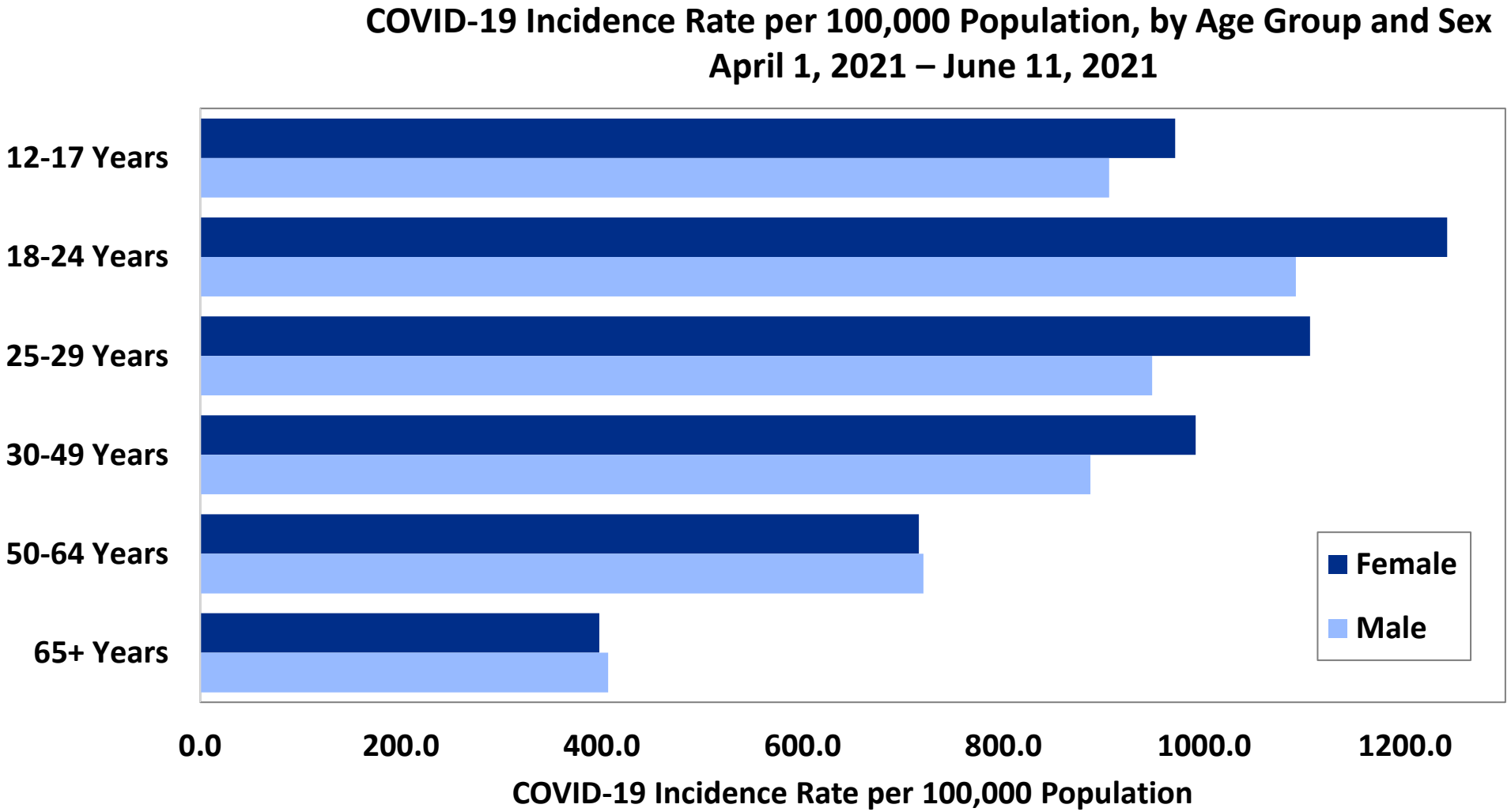
B.1.617.2 (Delta) 21%

B.1.351 (Beta) <1%

B.1.427/B.1.429 (Epsilon) <1%

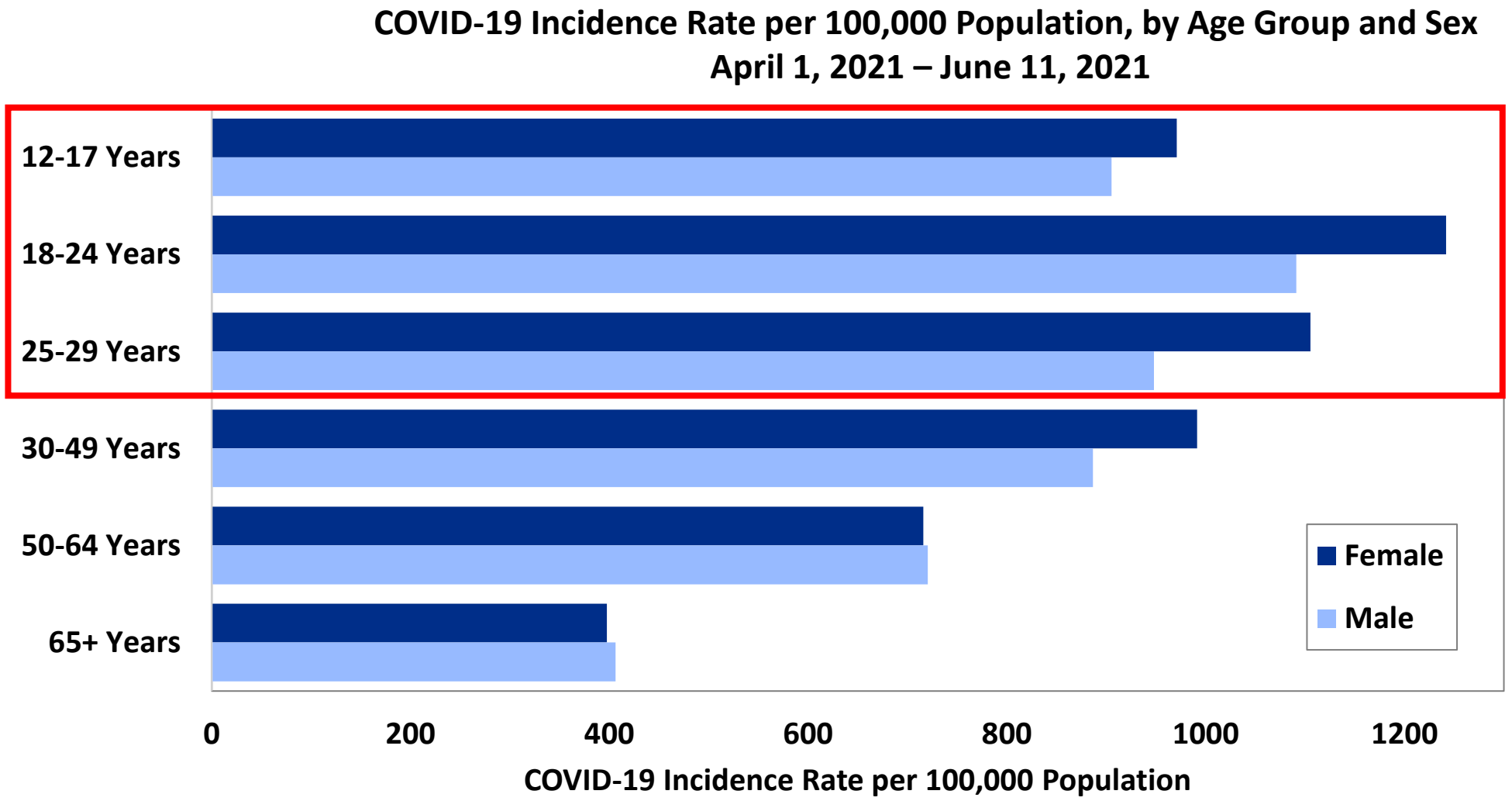
CDC COVID Data Tracker As of 6/14/21; VOC=Variant of Concern; VOI=Variant of Interest

Adolescents and young adults have the highest COVID-19 incidence rates



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

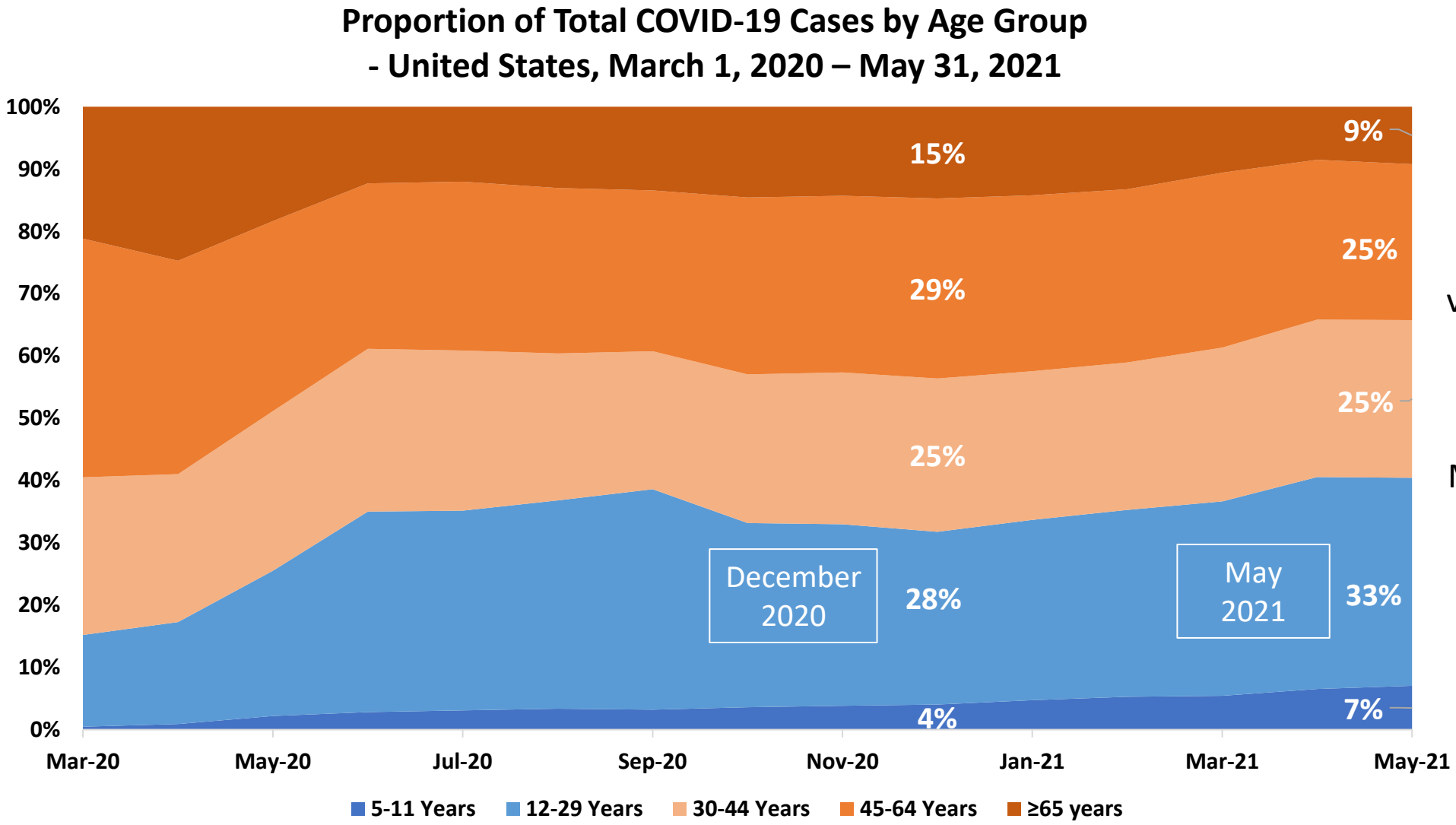
Adolescents and young adults have the highest COVID-19 incidence rates



Since beginning of pandemic **at least 7.7 million** COVID-19 cases have been reported among persons aged 12–29 years

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

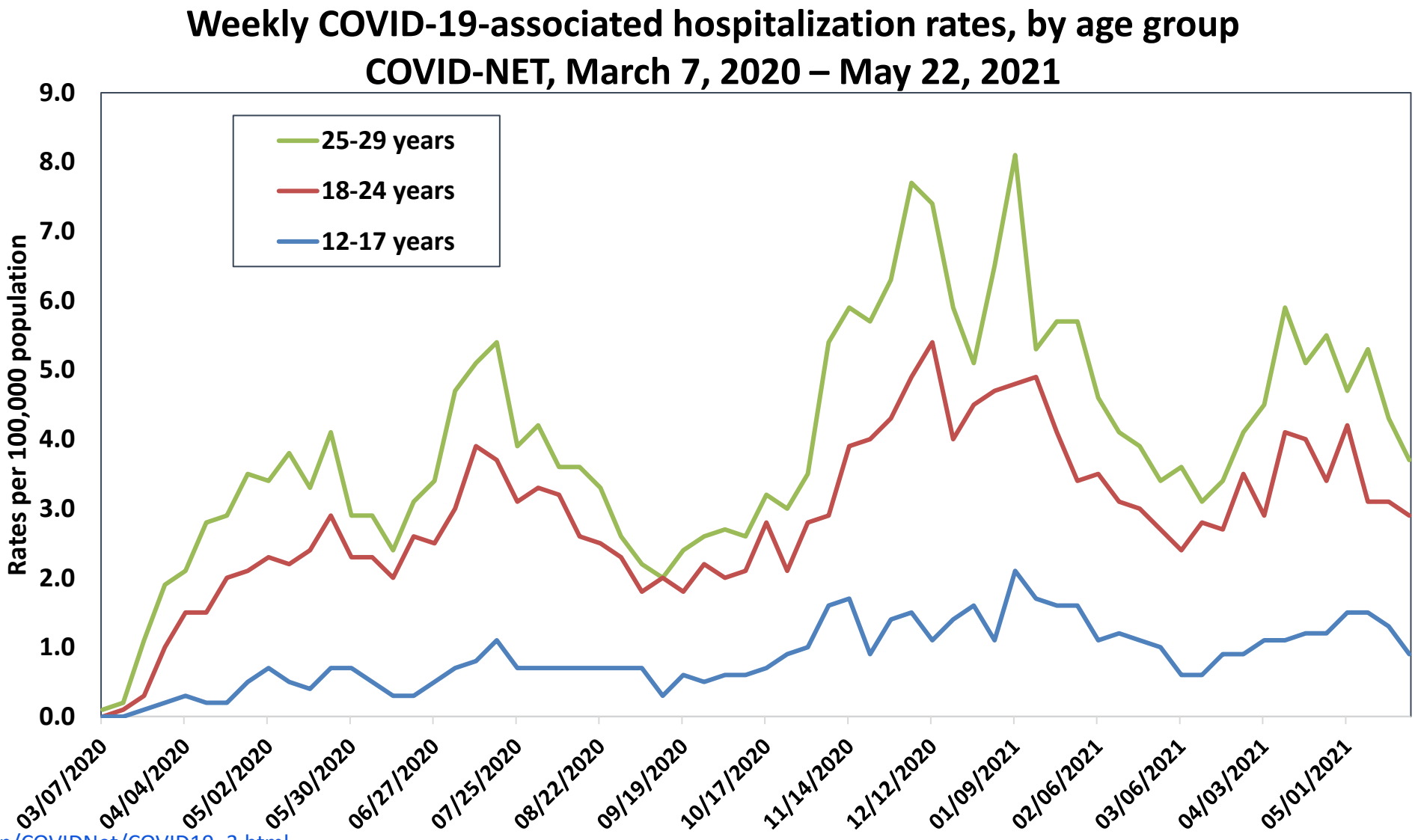
Adolescents and young adults are an increasing proportion of COVID-19 cases reported



As more older adults are vaccinated, adolescents & young adults make up greater % of total cases: **33%** of cases reported in May 2021 among persons aged 12–29 years

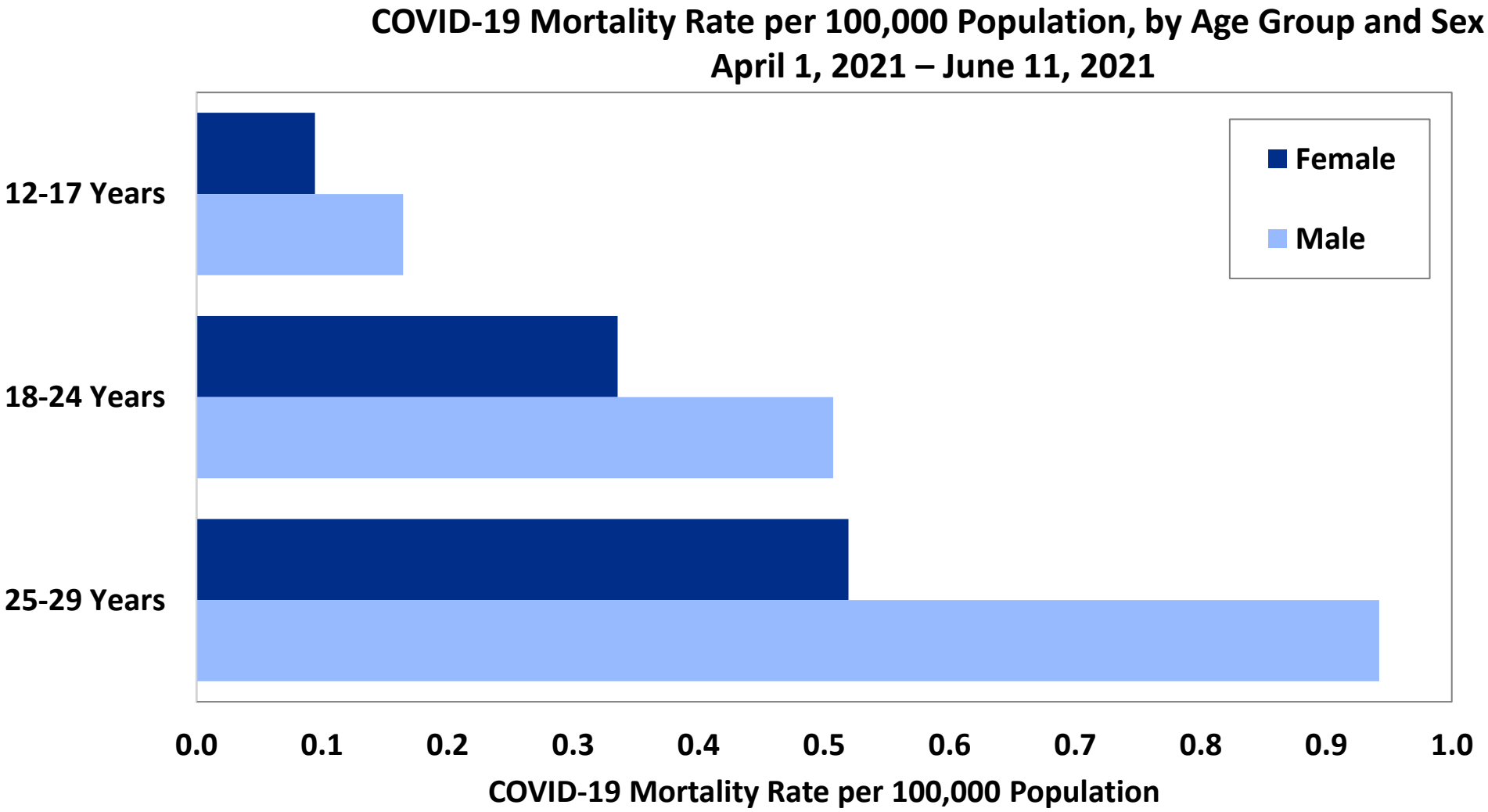
https://covid.cdc.gov/covid-data-tracker/#demographicsovertime

COVID-19-associated hospitalization rates have remained stable in adolescents and young adults



https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

COVID-19-associated deaths continue to occur in adolescents and young adults



Since beginning of pandemic, **2,767** COVID-19 deaths have been reported among persons aged 12-29 years; **316** deaths reported since April 1, 2021

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

Post-COVID conditions can occur after COVID-19

- No standardized definition, but generally **new** or **persisting symptoms** from acute infection or exacerbation of a chronic condition **≥4 weeks after SARS-CoV-2 infection**
- Reported after infections ranging from asymptomatic to severe
- Limited data in adolescents/young adults, but recent cross-sectional studies have shown evidence of new or persisting COVID symptoms in this age group[1,2]
  - Up to one-half of study participants had symptoms 1 month post-diagnosis
  - Symptoms reported include fatigue, insomnia, rhinorrhea, muscle pain, headache, lack of concentration, exercise intolerance, dyspnea, chest pain

[1]Buonsenso et al, Acta Paediatrica (2021)
[2]Walsh-Messinger et al, medRXiv (2020)

Multisystem Inflammatory Syndrome in Children (MIS-C)

- Severe hyperinflammatory syndrome occurring 2–6 weeks after acute SARS-CoV-2 infection among persons <21 years old, resulting in a wide range of manifestations and complications
  - 60%–70% of patients are admitted to intensive care, 1%–2% die[1,2]
- **4,018 MIS-C** cases have been reported to national surveillance as of June 2, 2021[3]
  - Estimated incidence of 1 MIS-C case in 3,200 SARS-CoV-2 infections[4]
  - 36% of cases in persons aged 12–20 years
  - 62% of reported cases have occurred in children who are Hispanic/Latino or Black, Non-Hispanic

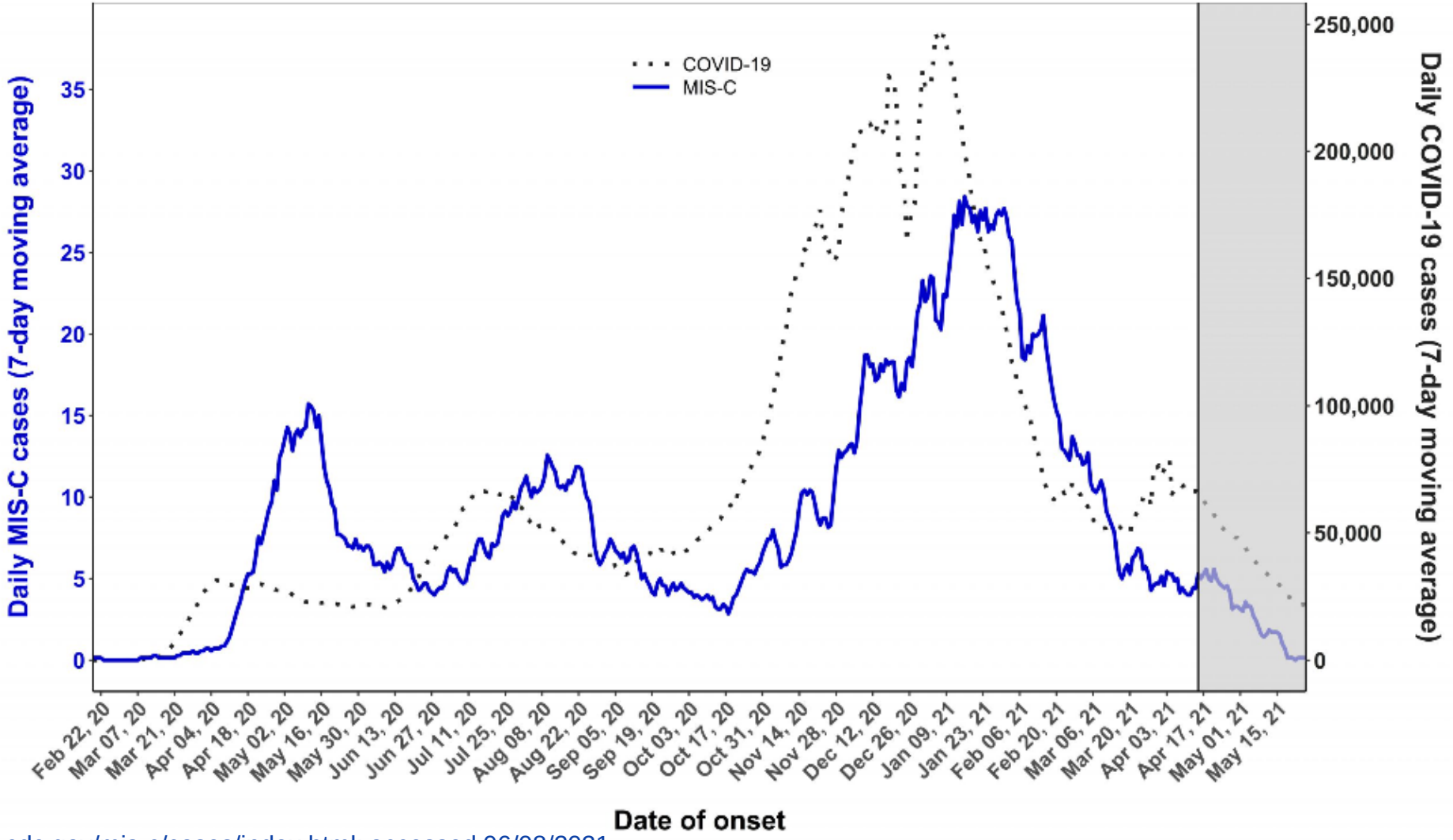
1. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. JAMA. 2021;325(11):1074-1087. doi:10.1001/jama.2021.2091

2. Belay ED, Abrams J, Oster ME, et al. Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic [published online ahead of print, 2021 Apr 6]. JAMA Pediatr. 2021;e210630. doi:10.1001/jamapediatrics.2021.0630

3. Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States. https://www.cdc.gov/mis-c/cases/index.html

4. Payne et al, *JAMA Netw Open.* 2021;4(6):e2116420. doi:10.1001/jamanetworkopen.2021.16420

Daily MIS-C cases and COVID-19 cases reported to CDC (7-day moving average)



https://www.cdc.gov/mis-c/cases/index.html; accessed 06/08/2021

Characteristics associated with Multisystem Inflammatory Syndrome in Adults (MIS-A)

- Single-center, retrospective cohort study identified 15 adults with MIS-A from those hospitalized with a positive SARS-CoV-2 test result[1]
  - 15 (**1.7%**) of 839 hospitalized patients
  - Patients with MIS-A were **younger** and more likely to have positive serologic test (SARS-CoV-2 antibodies) compared to acute COVID-19 patients.
    - Other demographic characteristics and comorbidities did not differ between MIS-A patients and patients with acute COVID-19
  - 8 of 15 MIS-A patients had cardiovascular involvement
- Case series of 27 MIS-A patients[2]
  - Antibody testing required to identify SARS-CoV-2 infection in approximately one third of cases
  - Age range: 21 – 50 years
  - 26 (96%) patients belonged to racial or ethnic minority groups
  - Three patients died

1. Davogustto et al, JAMA Netw Open. 2021;4(5):e2110323. doi:10.1001/jamanetworkopen.2021.10323
2. Morris SB et al, MMWR Morb Mortal Wkly Rep 2020;69:1450–1456. DOI: http://dx.doi.org/10.15585/mmwr.mm6940e

Epidemiology of myocarditis and pericarditis

- **Myocarditis** is inflammation of the heart muscle, and **pericarditis** is inflammation of the outer lining of the heart
- Myocarditis and pericarditis generally occur more frequently in:
  - Young adults
  - Men
  - Persons with certain medical conditions or recent medical procedure
- Can occur after SARS-CoV-2 infection
  - Data to estimate frequency after COVID-19 is limited
- There is a spectrum of disease but for the purpose of the benefit-risk discussion we will refer to both myocarditis and pericarditis as myocarditis

Gubernot D, Vaccine. https://doi.org/10.1016/j.vaccine.2021.05.016
https://www.nhlbi.nih.gov/health-topics/heart-inflammation

Myocarditis and COVID-19

- 1597 young athletes with recent SARS-CoV-2 infection had cardiac MRI[1]
  - 37 (**2.3**%) with abnormal MRI findings
  - However, **24** (65%) of 37 had **normal** lab findings and **no symptoms**
  - Another study suggested some MRI findings may be related to remodeling from athletic training[2]
- Retrospective study — children with acute myocarditis treated at a single center from 2018–2020[3]
  - 27 children <18 years of age identified
  - 7/27 (**26**%) had evidence of prior SAR-CoV-2 infection or exposure
    - 6 ultimately diagnosed with MIS-C
  - Individuals with myocarditis/MIS-C related to SARS-CoV-2 had better clinical course
    - None diagnosed with acute fulminant myocarditis
    - Shorter duration of inotropic drug support and ICU stay
    - Did not require mechanical respiratory support

[1]Daniels CJ, et al. *JAMA Cardiol.* Pub online May 27, 2021. doi:10.1001/jamacardio.2021.2065; [2]Clark DE, et al. Circulation; 2021:143(6): [3]Vukomanovic et al. PIDJ;2021:40(5):e173-e178

Myocarditis after mRNA vaccines:
Summary of clinical features

- Most commonly in males <30 years of age
- Symptom onset clusters in the week following vaccination
- Early data of acute outcomes have been good
  - Many cases hospitalized, usually for short duration
- No long-term data available yet
  - Continued monitoring ongoing

Marshall et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID- 19 vaccination. Pediatrics. 2021
Larson et al. Myocarditis after BNT162b2 and mRNA-1273 Vaccination.
Mouch et al. Myocarditis following COVID-19 mRNA vaccination. Vaccine. 2021 May 28;S0264-410X(21)00682-4.

Summary

- COVID-19 incidence, hospitalization, and mortality rates are decreasing overall
  - Variants continue to spread and scenarios exist in which cases increase in fall
  - Adolescents are growing proportion of cases given vaccine coverage among adults
- Post COVID-19 conditions also impact adolescents and young adults
  - 4,018 MIS-C cases have been reported to national surveillance
- Myocarditis is a disease marked by inflammation of the heart muscle
  - Risk factors include younger age and male sex
  - Can occur with SARS-CoV-2 infection
- Myocarditis after mRNA vaccines noted with highest frequency in males aged 12–29 years following 2nd dose
  - Early outcomes have been encouraging, but no long-term data available yet

Benefits and Harms

COVID-19 mRNA vaccines in adolescents and young adults

Benefit and Risk Summary

Benefits

Estimated COVID-19 cases and hospitalizations prevented by mRNA COVID-19 vaccines, by age and gender

Potential harms

Estimated cases of myocarditis after mRNA COVID-19 vaccines, by age and gender

Benefits of the Pfizer-BioNTech COVID-19 vaccine

- Clinical trial data demonstrated efficacy against symptomatic, laboratory-confirmed COVID-19 among individuals ≥16 years of age
  - Overall efficacy was **95%** (95% CI: 90.3%, 97.6%)
- Vaccine efficacy against COVID-19 associated hospitalization was **100%** (95% CI: -9.9%, 100%)
- Also demonstrated high efficacy against symptomatic, laboratory-confirmed COVID-19 in adolescents aged 12–15 years
  - Overall efficacy was **100%**, immunogenicity non-inferior to 16–25 year old population

Polack FP et al. N Engl J Med 2020; DOI: 10.1056/NEJMoa2034577
Frenck RW et al. N Engl J Med 2021; DOI: 10.1056/NEJMoa2107456

Benefits of the Moderna COVID-19 vaccine

- Clinical trial data demonstrated efficacy against symptomatic, laboratory-confirmed COVID-19 among individuals ≥18 years of age
  - Overall efficacy was **94.1%** (95% CI: 89.3%, 96.8%)
- Vaccine efficacy against COVID-19 associated hospitalization was **89%** (95% CI: 13%, 99%)

Baden LR et al. N Engl J Med 2021; DOI: 10.1056/NEJMoa2035389

Real-world effectiveness of mRNA COVID-19 vaccines

- Multiple real-world effectiveness studies from the United States and other countries demonstrate that a two-dose mRNA COVID-19 vaccination series in age groups for which the vaccine is recommended is effective
  - Against SARS-CoV-2 infection: **64–99%** estimate range
  - Against COVID-19-associated hospitalization: **87–97%** estimate range

https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

Potential harms of the mRNA COVID-19 vaccines:

After dose 2

- 133 million vaccine 2nd doses administered* and 636 reported myocarditis cases as of June 11, 2021
  - Additional potential myocarditis cases under review

	Females			Males		
Age group	**Cases§**	**Doses admin**	**Reporting rate†**	**Cases§**	**Doses admin**	**Reporting rate†**
12-17 years old	19	2,189,726	8.68	128	2,039,871	62.75
18-24 years old	23	5,237,262	4.39	219	4,337,287	50.49
25-29 years old	7	4,151,975	1.69	59	3,625,574	16.27
30-39 years old	11	9,356,296	1.18	61	8,311,301	7.34
40-49 years old	18	9,927,773	1.81	34	8,577,766	3.96
50-64 years old	18	18,696,450	0.96	18	16,255,927	1.11
65+ years old	10	21,708,975	0.46	11	18,041,547	0.61

§ Cases reported through VAERS using a 7-day risk window

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

†Reporting rate = myocarditis cases per 1 million mRNA COVID-19 vaccine doses administered

Summary of benefit-risk analyses

Individual Level Benefit-Risk Analysis

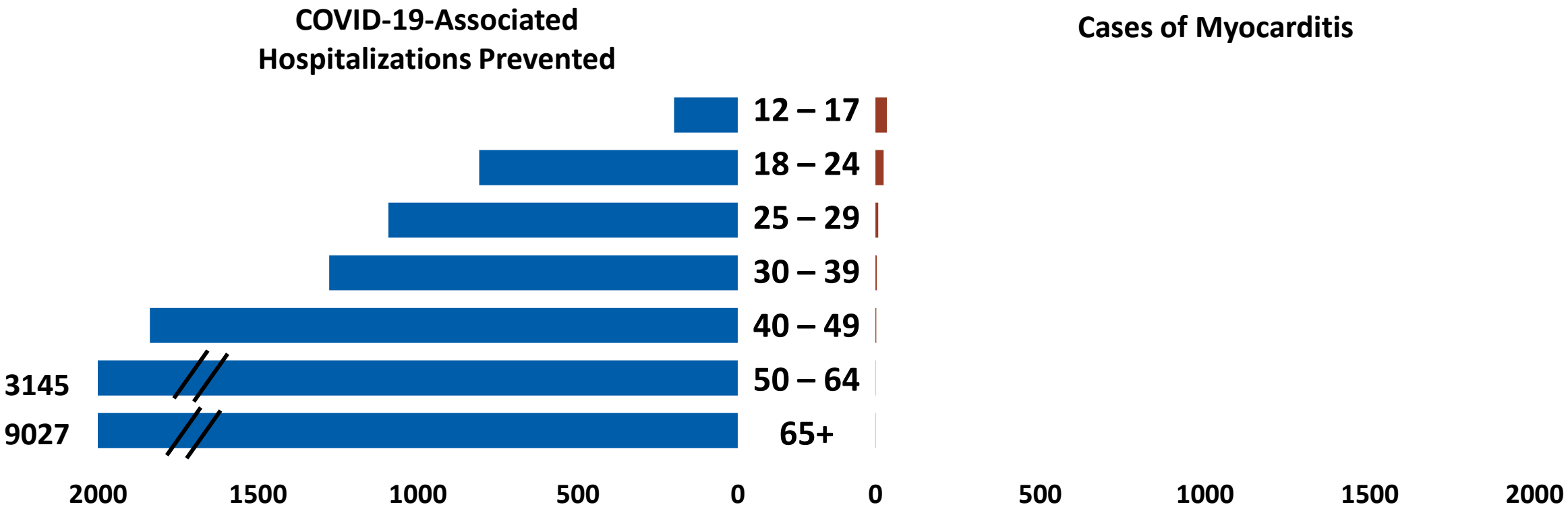
- Evaluate direct benefits and risk, per million mRNA COVID-19 vaccine doses
- Examine sex and age differences in risk and benefits
- Calculations based on:
  - Recent COVID-19 case and hospitalization incidence
  - mRNA vaccine efficacy
  - mRNA vaccinations to date
  - Number of persons already vaccinated
  - Myocarditis risk within 7 days after dose 2
  - 120-day risk period

Population Level Considerations

- Describe benefits of vaccination at population level

Benefits and risks after dose 2, by age group

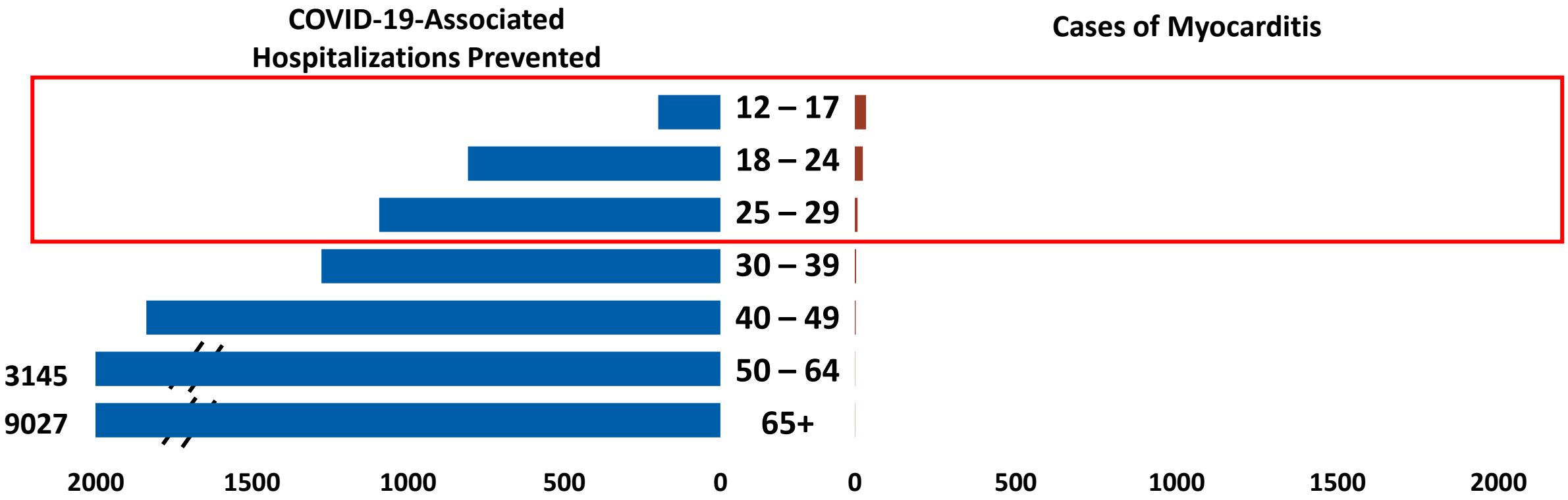
For every **million** doses of mRNA vaccine given with current US exposure risk[1]



[1] Based on hospitalization rates from COVID-NET as of May 22nd. Benefit/Risk calculated over 120 days.

Benefits and risks after dose 2, by age group

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



[1] Based on hospitalization rates from COVID-NET as of May 22nd. Benefit/Risk calculated over 120 days.

Predicted cases prevented vs. myocarditis cases for every million second dose vaccinations over 120 days

Females 12–17 Years

8,500 COVID-19 cases prevented

183 hospitalizations prevented

38 ICU admissions prevented

1 death prevented

8–10 myocarditis cases

Males 12–17 Years

5,700 COVID-19 cases prevented

215 hospitalizations prevented

71 ICU admissions prevented

2 deaths prevented

56–69 myocarditis cases

Hospitalizations, ICU admissions and deaths based on data for week of May 22, 2021.

Predicted cases prevented vs. myocarditis cases for every million second dose vaccinations over 120 days

Females 18–24 Years

14,000 COVID-19 cases prevented

1,127 hospitalizations prevented

93 ICU admissions prevented

13 deaths prevented

4–5 myocarditis cases

Males 18–24 Years

12,000 COVID-19 cases prevented

530 hospitalizations prevented

127 ICU admissions prevented

3 deaths prevented

45–56 myocarditis cases

Hospitalizations, ICU admissions and deaths based on data for week of May 22, 2021.

Predicted cases prevented vs. myocarditis cases for every million second dose vaccinations over 120 days

Females 24–29 Years

15,000 COVID-19 cases prevented

1,459 hospitalizations prevented

87 ICU admissions prevented

4 deaths prevented

2 myocarditis cases

Males 24–29 Years

15,000 COVID-19 cases prevented

936 hospitalizations prevented

215 ICU admissions prevented

13 deaths prevented

15–18 myocarditis cases

Hospitalizations, ICU admissions and deaths based on data for week of May 22, 2021.

Additional considerations for direct benefit and risk

Males 12–17 Years

5,700 COVID-19 cases prevented

215 hospitalizations prevented

71 ICU admissions prevented

2 deaths prevented

56–69 myocarditis cases 

Additional benefits to prevent post-COVID conditions

Prevention of MIS-C

Prevention of prolonged symptoms

Protection against variants

Benefit-risk analyses

Population Level Considerations

- No alternatives to mRNA vaccines for the foreseeable future in adolescents
- Vaccination of students offers an added layer of protection against COVID-19 and can be an important tool to return to 'normal'
- Higher levels of vaccination coverage can lead to less community transmission, which can protect against development and circulation of emerging variants
- Racial and ethnic minority groups have higher rates of COVID-19 and severe disease[1]
  - Potential changes in vaccine policy, or anything that would impact vaccination coverage for adolescents/young adults may disproportionately impact those groups with highest rates of poor COVID-19 outcomes

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

Benefit-risk interpretations and limitations

- Direct benefit-risk assessment shows **positive balance** for all age and sex groups
  - Considers individual benefits of vaccination vs. individual risks
  - Benefits are likely an underestimate
    - Analysis was performed using reported rates of cases and hospitalizations
    - Likely represent only a fraction of the true cases that have occurred in the population
  - Still uncertainty in rates of myocarditis after mRNA vaccines
    - Not all cases are verified and crude rates were used
- Balance of risks and benefits **varies** by age and sex
  - Balance could change with increasing or decreasing incidence
- Limited data currently on risk of myocarditis in 12–15 year old population
  - Due to timing of recommendations, limited number of 2nd doses given

Clinical Considerations

Vaccine considerations in people with a history of myocarditis or pericarditis

Scenario	Recommendation
Pericarditis prior to COVID-19 vaccination	Receive any FDA-authorized COVID-19 vaccine
Pericarditis after 1st dose of an mRNA COVID-19 vaccine but prior to 2nd dose	Proceed with a 2nd dose of mRNA COVID-19 vaccine after resolution of symptoms. Discuss with patient, guardian, and clinical team
Myocarditis prior to COVID-19 vaccination	Receive any FDA-authorized COVID-19 vaccine if heart has recovered
Myocarditis after 1st dose of an mRNA COVID-19 vaccine but prior to 2nd dose	Defer 2nd dose of mRNA COVID-19 vaccine until more information is known However, if heart has recovered, could consider proceeding with 2nd dose under certain circumstances. Discuss with patient, guardian, and clinical team

Work Group Interpretation

COVID-19 mRNA vaccines in adolescents and young adults: Benefit-risk discussion

Work Group Interpretation

- Initial presentations are reassuring; however, continued monitoring of cases, clinical course, and long-term outcomes of myocarditis after mRNA vaccines will be important
- Need to follow the benefit-risk balance as we learn more around myocarditis, as well as updates to epidemiology (cases, variants, etc)
- Currently, the **benefits** still clearly **outweigh** the risks for COVID-19 vaccination in adolescents and young adults

COVID-19 mRNA vaccines in adolescents and young adults

Current COVID-19 vaccine policy

- COVID-19 vaccines are recommended for persons 12 years of age and older in the United States under FDA's Emergency Use Authorization

Questions for ACIP

1. What does ACIP think about the benefit-risk balance of COVID-19 vaccines in adolescents and young adults, in the setting of reports of myocarditis?

2. What additional information or analyses could inform these discussions as we continue to closely monitor this situation?

Acknowledgements

- Stephen Hadler
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- Vaccine Safety Team
- Immunization team
- Epi Task Force
  - MIS-C unit
  - COVID-NET
- Data, Analytics and Visualization Task Force
- Division of Healthcare Quality Promotion
- Respiratory Viruses Branch