Summary of Major Literature Related to COVID-19 (September 29, 2021)

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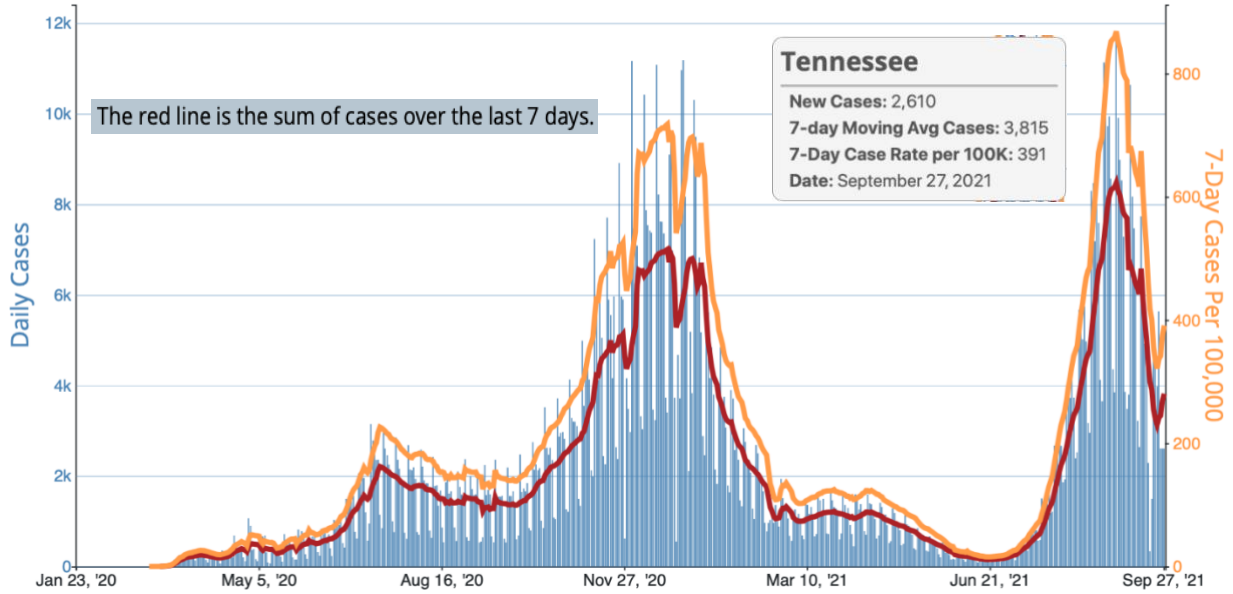
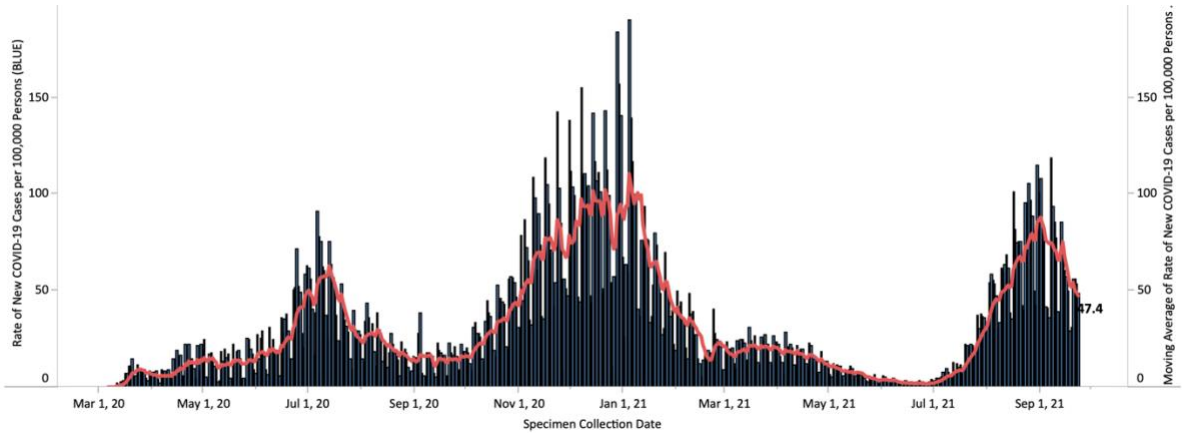
***This is informational and not intended to create variance from VUMC policies/guidance**

Tennessee

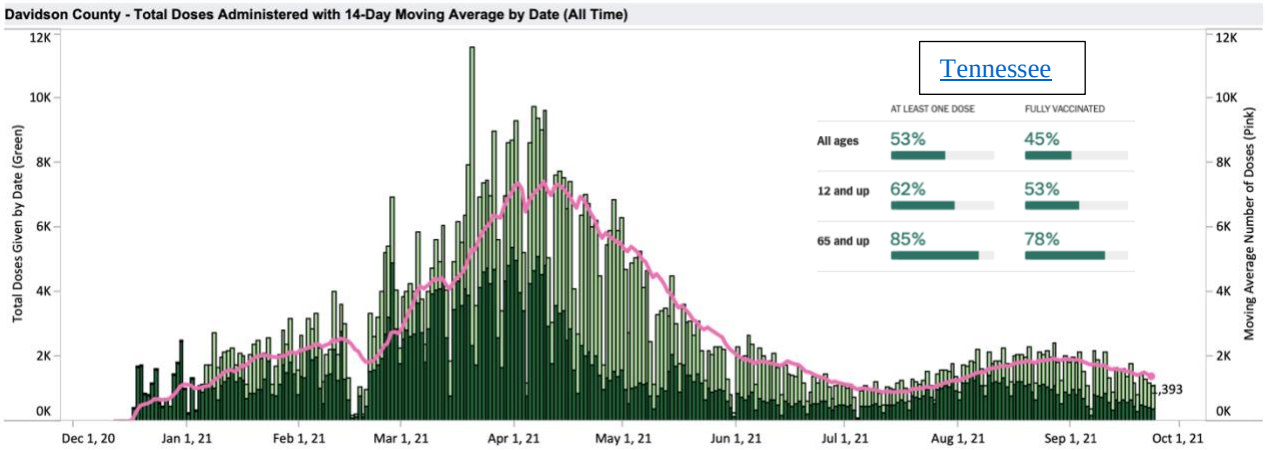
Daily Trends in Number of Cases and 7-Day Cumulative Incidence Rate of COVID-19 Cases in Tennessee Reported to CDC, per 100,000 population.



Davidson county



Davidson County Vaccination Curve



EPIDEMIOLOGY

1. **Outbreak of SARS-CoV-2 B.1.617.2 (Delta) Variant Infections Among Incarcerated Persons in a Federal Prison — Texas, July–August 2021.** Hagan et al. MMWR. 21 Sept 2021.

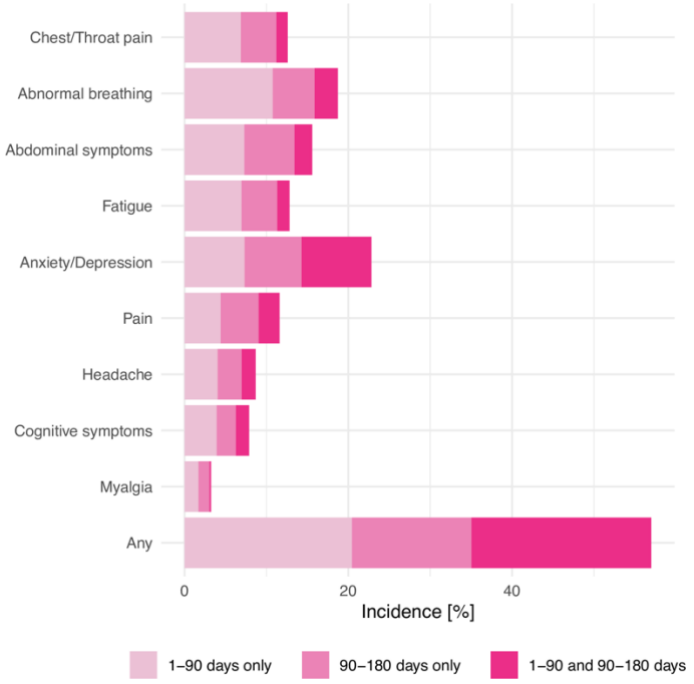
- Epidemiologic investigation of a COVID-19 outbreak in a Texas prison during a period of Delta variant predominance, infecting three-fourths (172/233) of incarcerated persons in 2 connected housing units
    - ~80% of the 233 were fully vaccinated, 66% of them with Pfizer-BioNTech vaccine
    - 76% of Pfizer-BioNTech recipients had been vaccinated ≥4 months before the outbreak, vs. none of the Moderna recipients
- 18 individuals received positive SARS-CoV-2 rapid antigen tests on July 12; 3 of them had reported symptoms on July 8 but were not tested at that time, introducing exposure into a high-contact setting
- Attack rate:
    - Significantly higher among unvaccinated (39/42, 93%) than fully vaccinated (129/185, 70%) (p=0.002)
    - Lowest (1/21, 5%) among those fully vaccinated *with* a prior SARS-CoV-2 infection
    - Significantly higher among those vaccinated ≥4 months earlier (83/93, 89%) compared to more recently (44% to 61%)
- 3 of 4 hospitalized patients were unvaccinated, one of whom died
- Among a subset of 70 symptomatic persons providing swabs for serial testing, median interval between reported symptom onset and last positive RT-PCR result was non-significantly shorter in vaccinated versus unvaccinated persons (9 versus 11 days; p=0.37)
- Limitations: Very small numbers for some estimates, particularly among those with prior infection; potential confounding by differences in characteristics between vaccinated and unvaccinated groups (and between Pfizer-BioNTech and Moderna groups) that were not accounted for in the comparisons of attack rates; no data presented on symptoms
- Implications: In a highly vaccinated population with high prevalence of obesity, smoking, diabetes, and hypertension and high-density congregate living, vaccination provided important protection against severe disease; protection against infection was significantly higher among vaccinated than unvaccinated, but those who had no prior infection and 2 doses of Pfizer-BioNTech vaccine ≥4 months earlier had little protection against infection

Post-acute COVID-19 syndrome (Long-COVID)

2. **Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19.** Taquet et al. PLoS Medicine. 28 Sept 2021.

- Large retrospective EHR network cohort study of the incidence and co-occurrence of 9 common long-COVID features and their relationship to age, sex and severity of infection among 273,618 COVID-19 survivors through 16 Dec 2020
    - Mean age 46.3y, 56% female; 58% White, 18% Black/AA; 16% Hispanic/Latino
- Outcomes: Breathing difficulties/breathlessness, fatigue/malaise, chest/throat pain, headache, abdominal symptoms, myalgia, other pain, cognitive symptoms, and anxiety/depression
    - Defined using all ICD-10 codes considered to be encompassed by each particular feature
    - Two follow up time windows post-COVID diagnosis: 1 to 180 days, and 90-180 days ("long" phase)
- 57% had one or more features of long-COVID recorded in the entire 6-month period after COVID-19 diagnosis
    - the incidence of individual features ranged from 3.24% (including 1.54% in the "long" phase) for myalgia, to 22.8% (including 15.49% in the "long" phase) for anxiety/depression

    - incidence of all features except pain was lower in the "long" phase than in the 1 to 90-day period
- 37% had a long-COVID feature recorded in the "long phase" (either incident or recurrent)
    - among these, 40% had no record of any long-COVID feature during the first 3 months after COVID-19 diagnosis (see Figure)
- Cognitive symptoms were observed in ~8% of patients after COVID-19, with higher incidence in the elderly and in those requiring hospitalization/ICU
- Additional analyses were done using a propensity-matched (1:1) cohort of 106,578 patients diagnosed with influenza during the same time period who did not have a diagnosis or positive test for COVID-19
    - 42.8% of influenza patients had one of the same 9 features recorded (including 29.7% during the "long" phase)
    - All 9 features were more frequent after COVID-19 than after influenza, with an overall excess incidence of 16.60% and overall HRs of 1.65 for the 1 to 180-day period and 1.56 for the "long" phase



- Some differences in long-COVID clinical profiles were observed based on age, sex and illness severity
- Limitations: Focus on only 9 features may underestimate incidence of post-acute sequelae; No data on prevalence of the studied symptoms prior to COVID-19 or on long-COVID symptoms by vaccination status; Findings are only generalizable to those who sought medical attention for the 9 symptoms after COVID-19/influenza, and biased reporting or recording of diagnoses after COVID-19 vs after influenza cannot be ruled out (although atopic dermatitis as a negative control was diagnosed at similar rate in the two cohorts); Follow-up for symptom persistence beyond 6 months is needed; Reliance on EHR diagnoses for ascertainment of symptoms; Unknown impact of high prevalence of pre-existing comorbidities or of characteristics of the acute infection on long-COVID
- Implications: In one of the largest studies to address post-acute COVID-19 outcomes to date, long-term sequelae of COVID-19 are common, diverse and interconnected, with features involving pain (headache, myalgia and pain combined) having the highest incidence and persisting; more data are needed
- **See also: 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records.** Taquet et al. Lancet Psychiatry. 1 May 2021.

Transmission to endemicity

3. Transition to endemicity: Understanding COVID-19. Antia and Halloran. Immunity 24 Sept 2021.

- Discussion of the transition of COVID-19 from an epidemic to an endemic state and how the number of infections and disease severity might change during this transition
- Epidemics require the basic reproductive number of the virus R_0 to be >1; world-wide spread defines a pandemic
- If the epidemic is isolated (i.e., islands) the epidemic can fade out completely; if not, the virus can likely persist at a lower but relatively stable prevalence for a long time - entering the endemic phase

- The transition to the endemic phase is significantly impacted by immune efficacy (IE); IE can be generated by infection or vaccination; IE has three components that are given values of 0 to 1
    - Immunity impacts susceptibility to infection (IE_S) - 0 no protection to 1 the response leads to sterilizing immunity
    - Immunity impacts infectiousness (IE_I) - again 0 represents no reduction in infectiousness and 1 represents completely block in transmission
    - Immunity reduces pathology (IE_P) - 0 represents no reduction in pathology and 1 is mild/asymptomatic disease
- With SARS-CoV2 immunity, there are waning in levels of Ab and insufficient immunity to prevent infection, but also more rapid control of infection with immunity and consequently, immunity should lower transmission and pathology. The expectation with CoV2 is that IE_S is waning faster than IE_I and IE_P.
- Endemic hCoV in adults gives rise to transient protection from infection (initially high IE_S which wanes); hCoV reinfections result in substantial virus transmission from infected individuals (intermediate levels of IE_I); Less is understood about IE_P
    - OC43, one of the currently circulating hCoVs, probably caused the so-called Russian Flu epidemic in 1889-1890
    - Disease severity with OC43 was then reduced over time; unknown if development of immunity in the population or virus evolution impacted disease severity
- The prevalence and, thus, the transition to the endemic phase is impacted by 1. the waves of infection (influenced by non-pharmaceutical interventions & policy & virus evolution) and 2. Vaccination rates and 3. how fast immunity wanes
- During the endemic phase, most primary infections happen in children - these infections may not contribute to severity and disease burden if mild; reinfections may also be mild if IE_P is high and long-lasting -outlasting the waning of IE_S
- Limitations*:* there is not a complete understanding as to the breadth of protection against new virus variants after vaccination vs natural infection. It is not known if multiple infections or boosters are needed to generate long-lasting protection against pathology, and whether this depends on the age of the individual.
- Implications*:* Since vaccination against SARS-CoV-2, like natural infections, is not likely to produce long-lasting transmission-blocking immunity, vaccination can generate transient herd immunity. This makes CoV-2 eradication unlikely, and endemicity the likely long-term outcome.

COVID-19 AND PREGNANCY

4. **High antibody levels in cord blood from pregnant women vaccinated against COVID-19.** Trustle et al. Am J Obstet Gynecol. 21 Sept 2021.

- Umbilical cord blood was collected at delivery and analyzed for both anti-N (nucleocapsid protein) and anti-S (spike) to determine the presence and levels of transplacental antibody transmission in cord blood of women (36) vaccinated against COVID-19 during pregnancy
- All but one of the women recruited for the study had received 2 doses of mRNA vaccine; none had a history of COVID-19 infection; 72% received Pfizer/BioNTech; 83% initiated vaccine series in the 2nd trimester; study performed at NYU Langone Health
- 36/36 neonates were positive for anti-S IgG (34 had IgG titers >250U/mL)
- 30/31 neonates tested for anti-N IgG were negative
- Limitations: Small study; no positive control or analysis of antibody responses after natural infection of women; most women in the study received vaccination in their second trimester

5. **Titers of SARS CoV-2 antibodies in cord blood of neonates whose mothers contracted SARS CoV-2 (COVID-19) during pregnancy and in those whose mothers were vaccinated with mRNA to SARS CoV-2 during pregnancy.** Kashani-Ligumsky et al. J Perinatology. 25 Sept 2021.

- Umbilical cord blood was collected at delivery and the titers of anti-N and anti-S antibodies were determined from women infected with SARS-CoV-2 during pregnancy (n = 29) or vaccinated during pregnancy (n = 29, all third trimester, 2 doses of Pfizer/BioNTech BNT162b2 vaccine) and from women not infected and not vaccinated (n = 21)
- The cohort of women were recruited between in early March 2021, Bnei Brak, Israel
- Of the 29 women infected with SARS-CoV-2 during pregnancy, 17 were asymptomatic and put into this group based on positive serology at the time of admission; 25 of the cord blood samples from these 29 were positive for SARS-CoV2-N antibodies; 3 of the negative cord blood samples from this group were from mothers who were asymptomatic
- All umbilical cord samples from previously infected and vaccinated were seropositive for the SARS-CoV-2 IgG S protein; The mean antibody titer of women previously infected was 83.7 ± 91.6 u/ml compared with 224.7 ± 64.3 U/ml in women who were vaccinated (*p*,0.05)
- When available (30 samples) maternal Ab titers at delivery strongly correlated with titers in cord blood
- Limitations*:* small cohort; secondary outcomes clinical disease in neonates was not measurable; lack of correlation to the presence of antibodies in breastmilk; timing of SARS-CoV-2 infection was not available from women who had asymptomatic infection

Implications*:*

- Cord blood levels observed in this population suggests a high degree of vertical transmission of these antibodies after vaccination
- Neonates born to mothers vaccinated during pregnancy have higher antibody titers than those born to women who had SARS-CoV2 infection
- Taken together with safety of vaccination during pregnancy and the increased risk of severe COVID-19 in women who are pregnant, these results support the current recommendation for SARS-CoV2 vaccination during pregnancy

VACCINE SAFETY/EFFICACY

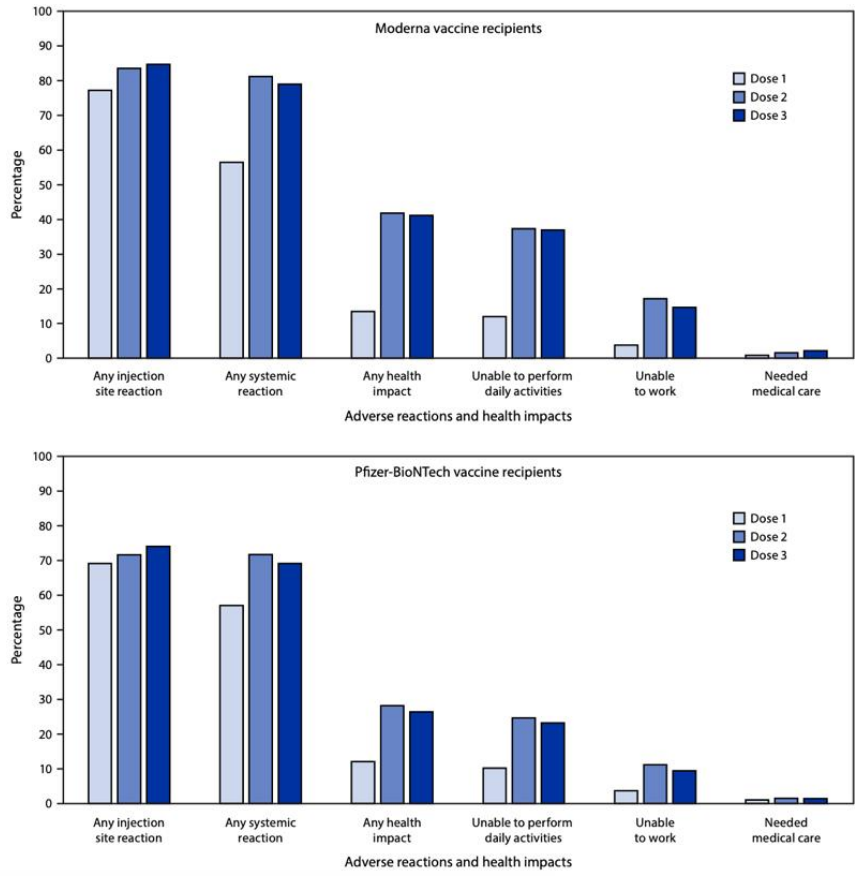
6. **Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021**. Self et al (IVY Network, **VUMC authors**). MMWR. 17 Sept 2021.

- Case-control analysis of effectiveness of the approved vaccines in preventing COVID-19 hospitalization
- N=3,989 adults ≥18y, without immune compromising conditions, who were hospitalized at 21 hospitals across 18 states from March 11-August 15, 2021
    - 1,682 cases with confirmed COVID-19, 2,007 controls with a negative SARS-CoV-2 PCR test
    - Overall, 64% unvaccinated, and 12.9%, 20.0% and 3.1% were fully vaccinated with Moderna, Pfizer-BioNTech, and Janssen (J&J), respectively
    - Overall median age 58y, 48% female, 23% non-Hispanic Black, 18% Hispanic
    - Some differences, including age, prevalence of underlying comorbidities, and geographic distributions, were observed between vaccine groups
- Vaccine efficacy (VE) after full vaccination:
    - Significantly higher for Moderna (93%) than Pfizer-BioNTech (88%); both mRNA vaccines were significantly higher than Janssen (71%)
    - At >120 days after second vaccine, Moderna VE remained at 92% (median=141 days), while Pfizer-BioNTech decreased to 77% (median=143 days)

- Also conducted antibody analysis 2-6 weeks after vaccination among 100 healthy individuals with no prior SARS-CoV-2 infection
    - 32 Moderna, 51 Pfizer-BioNTech, 17 Janssen (median age 31, 27 and 31y, respectively)
    - Anti-RBD IgG levels were significantly higher in participants vaccinated with the Moderna vaccine (geometric mean = 4,274; 95% CI = 3,393–5,384 BAU/mL) than Pfizer-BioNTech (geometric mean = 2,950; 95% CI = 2,325–3,742) or Janssen (geometric mean = 51; 95% CI = 30–90)
    - Anti-spike IgG levels were similar among those vaccinated with Moderna (geometric mean = 3,059; 95% CI = 2,479–3,774) and Pfizer-BioNTech (geometric mean = 2,444; 95% CI = 1,936–3,085), but were significantly lower in participants who received Janssen vaccine (geometric mean = 56; 95% CI = 32–97)
- Limitations: Antibody titers at a single time point and with no data on cell-mediated immune response may not translate into long-term protection; despite adjustment for date of hospital admission, region of hospital, age, sex and race/ethnicity, there remains potential for confounding by differences between groups receiving the different vaccines; very small number of Janssen vaccine recipients hamper interpretation of data for that vaccine
- Implications: All three vaccines provided a high level of protection against COVID-19 hospitalizations, with two-dose mRNA vaccines having higher efficacy compared to the single-dose Janssen vaccine; protection for the Pfizer-BioNTech vaccine declined 4 months after vaccination

7. Safety Monitoring of an Additional Dose of COVID-19 Vaccine — United States, August 12–September 19, 2021. Hause et al. MMWR. 28 Sept 2021**.**

FIGURE. Adverse reactions and health impacts reported by persons who received 3 doses* of Moderna (N = 6,283) or Pfizer-BioNTech (N = 6,308) COVID-19 vaccine and completed at least one v-safe health check-in survey on days 0–7 after each dose, by dose number — United States, August 12–September 19, 2021



- Earlier Pfizer-BioNTech phase 3 clinical trial of 306 persons aged 18–55y who received a third dose 5-8 months after completion of their 2-dose primary vaccination series showed that adverse reactions were similar to those reported after dose 2
- This surveillance study was based on voluntary, self-reported v-safe data for 22,191 individuals who received an additional COVID-19 vaccine dose from Aug 12-Sept 19, 2021 after primary series completion
    - 63.3% female, 30% each aged 18-49, 50-64, 65-74y; 97.6% reported a primary 2-dose mRNA vaccination series followed by a third dose of the same vaccine
    - Local (74.9%) and systemic (69.9%) reactions were frequently reported during the week after an additional dose
- Among 12,591 who completed at least one health check-in survey on days 0-7 after all 3 doses, 79.4% and 74.1% reported local or systemic reactions, respectively, after

dose 3, compared with 77.6% and 76.5% who reported local or systemic reactions, respectively, after dose 2
    - For both Pfizer-BioNTech and Moderna, local reactions were somewhat more common and systemic reactions were less common after dose 3 than dose 2
- Limitations: unknown generalizability of survey population; low representation of racial/ethnic minorities; no information about immune status of participants; safety data not presented by age
- Implications: In this population of individuals, presumably primarily with moderate to severe immune compromising conditions, no unexpected patterns of adverse reactions were observed after a booster vaccine dose, and reported local and systemic reactions were mild to moderate and transient