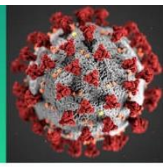
COVID-19 Science Update



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Section headings in the COVID-19 Science Update align with the CDC Science Agenda for COVID-19.

Detection, Burden, and Impact

PEER-REVIEWED

COVID-19 and Persistent Symptoms

Here we present 2 studies looking at persistence of significant symptoms up to a year after diagnosis with COVID-19.

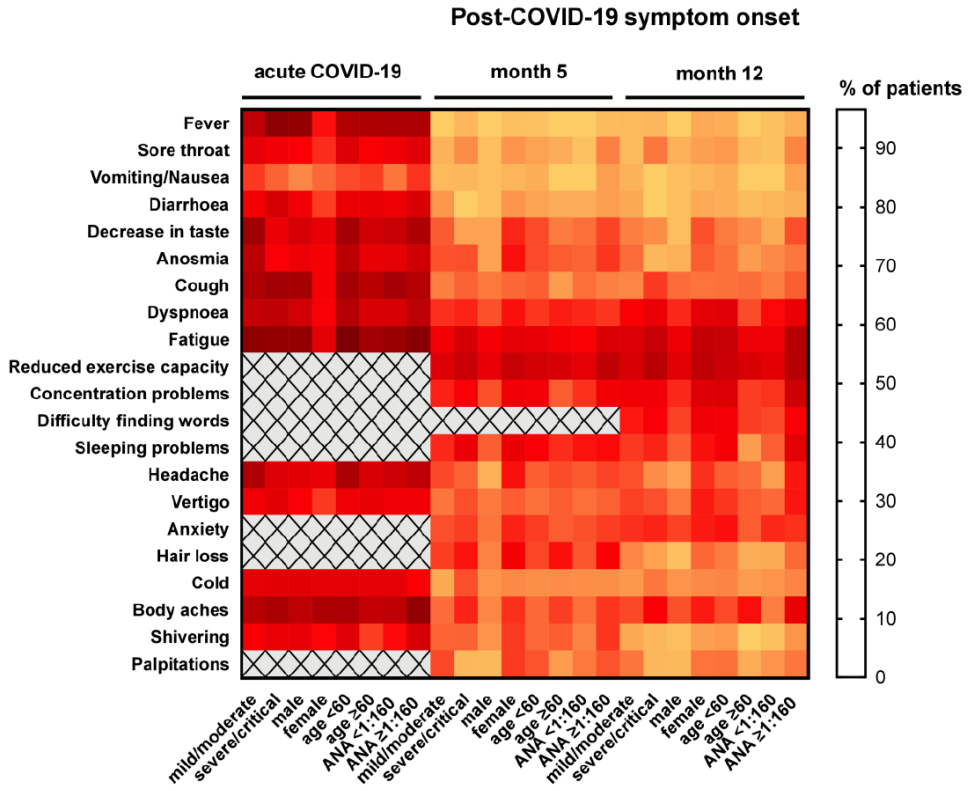
A. Persistent symptoms in adult patients one year after COVID-19: a prospective cohort study. Seeßle *et al.* Clinical Infectious Diseases. (July 5, 2021).

Key findings:

- 77.1% of patients reported 1 or more COVID-19 symptoms persisting up to 12 months post infection.
  - 56.3% reported reduced exercise capacity, 53.1% fatigue, 37.5% trouble breathing and 39.6% concentration problems (Figure).
- At 12 months post COVID-19 symptom onset, antinuclear antibody (ANA) titers were ≥1:160 in 43.6% of patients.
  - Women with ANA titers ≥1:160 had a higher frequency of problems concentrating compared with than those with lower titers (66.7% vs. 26.1%).

Methods: Prospective cohort study tracked symptoms, quality of life, and antibody levels in 96 patients in Germany treated for acute COVID-19 between February 22, 2020 and April 18, 2020. Both in- and outpatients were enrolled. *Limitations*: 50 patients of the original 146 were lost to follow-up after 5 months, which may lead to overestimation of symptom frequency at 12 months if those lost to follow-up had fewer symptoms.

Figure:



Note: Adapted from Seeßle *et al*. Heat map of symptom frequencies in 96 patients at time of acute infection, and 5- and 12-months post infection. **High** to low frequencies stratified by disease severity, gender, age, and ANA titer. X marks indicate parameter not analyzed at that time. Used per permission of Infectious Diseases Society of America via RightsLink.

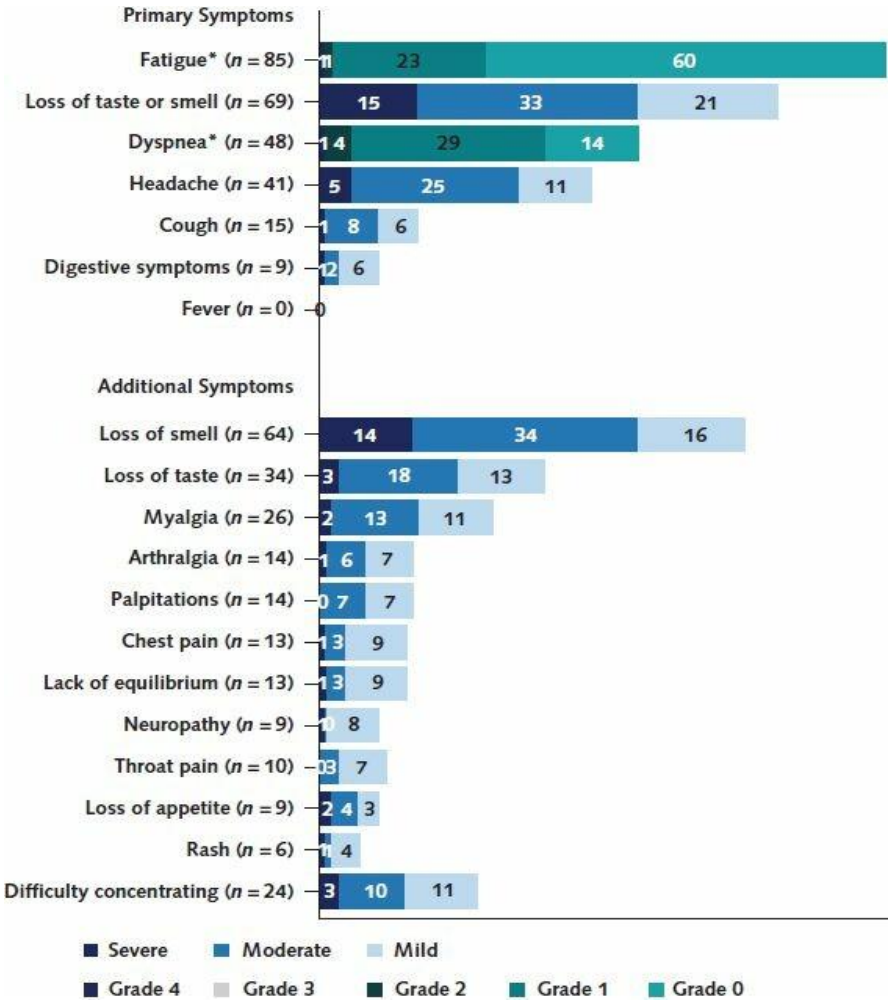
B. **Prevalence of symptoms more than seven months after diagnosis of symptomatic COVID-19 in an outpatient setting.** Nehme *et al.* Annals of Internal Medicine (July 6, 2021).

Key findings:

- 44% (95% CI 39.5-48.6%) of COVID-19 outpatients (n = 479) reported symptoms 30–45 days post-diagnosis; 39% (95% CI 34.3-43.9%) reported symptoms at 7–9 months (n = 410).
    - Fatigue was the most common symptom (20.7%, 95% CI 16.9-25.0%) 7-9 months after diagnosis.
- Most participants with symptoms 7–9 months post-diagnosis categorized them as mild to moderate in severity (Figure).

Methods: Between March 18 and May 15, 2020, 629 symptomatic SARS-Cov-2 positive outpatients in Geneva, Switzerland were enrolled in a follow-up program, reporting COVID-19 symptoms at the time of diagnosis, 30–45 days post-diagnosis and 7–9 months post-diagnosis using a Likert scale for intensity of symptoms. *Limitations*: Only 65.2% of the initial cohort completed the follow-up survey at 7–9 months post-diagnosis.

Figure:



Note: Adapted from Nehme *et al*. COVID-19 symptoms among outpatients 7–9 months following diagnosis. Total number of patients reporting symptoms is listed. Fatigue and dyspnea were stratified into Grade 0 through Grade 4, with 0 representing little impact of these symptoms to 4 representing disability. All other symptoms were defined as being Mild, Moderate, or Severe. Permission request in progress.

Implications for Seeßle *et al.* and Nehme *et al.*: Symptoms can remain for months after initial COVID-19 diagnosis. Healthcare systems may have increased burden from persistent symptoms in COVID-19 patients.

PREPRINTS (NOT PEER-REVIEWED)

REACT-1 round 13 interim report: acceleration of SARS-CoV-2 Delta epidemic in the community in England during late June and early July 2021. Riley *et al.* medRxiv (July 8, 2021).

Key findings:

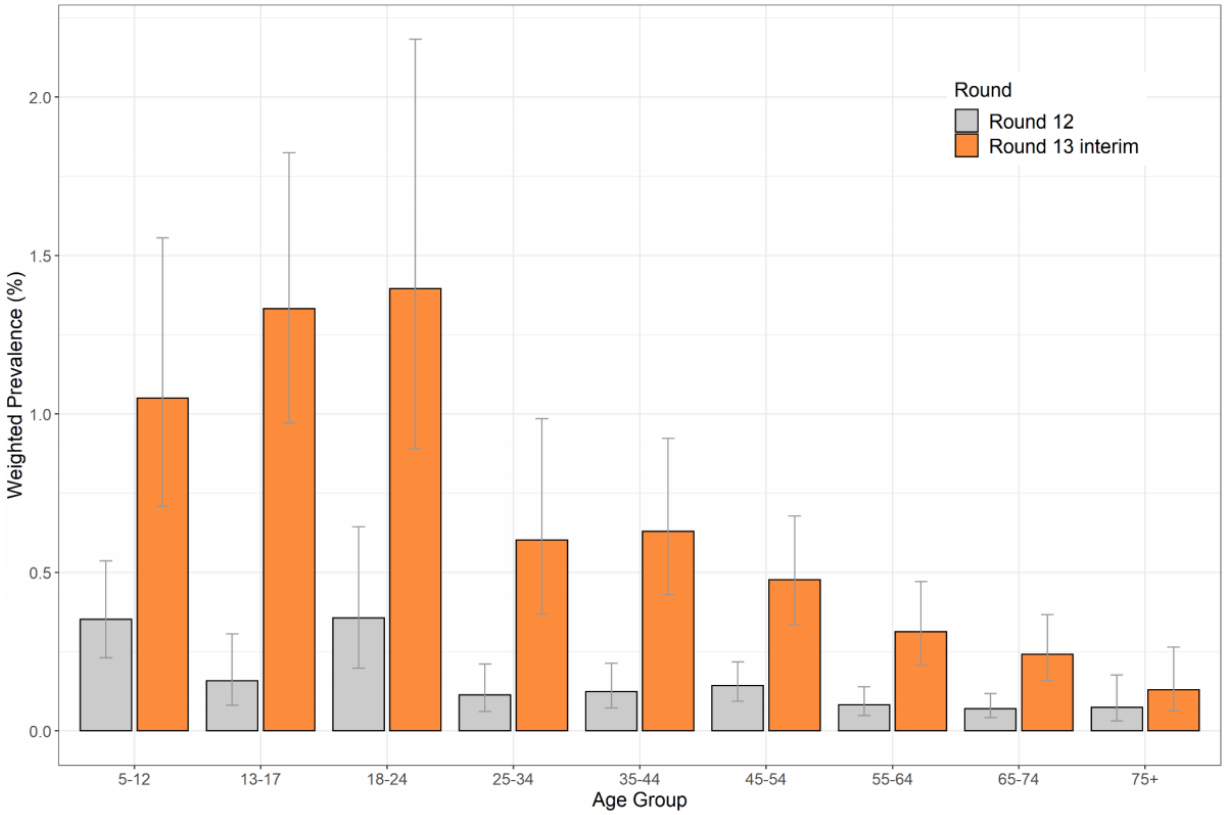
- The weighted prevalence of SARS-CoV-2-positive swabs increased nearly 4-fold from 0.15% (95% CI 0.12-0.18%) during Round 12 (May 20–June 7, 2021) to 0.59% (95% CI 0.51-0.68%) during Round 13 (interim) (June 24–July 5, 2021) (in England's REACT-1 surveillance study.
    - During round 13 (interim), among persons <65 years:
        - 1.15% (0.92-1.43%) of unvaccinated individuals tested positive

- 0.35% (95% CI 0.26-0.45%) of fully vaccinated individuals tested positive.
- Increased SARS-CoV-2 prevalence was detected across all age groups but was largest in those 13–17 and 18–24 years old (Figure).

Methods: RT-PCR was used to detect SARS-CoV-2 from self-administered throat and nasal swabs in continuation of England's real-time assessment of community transmission-1 (REACT-1) cross-sectional study (methods described here). *Limitations*: No sequencing performed.

Implications: Coincident with rising prevalence and transmission of the SARS-CoV-2 Delta variant, positive cases continue to increase in England, with younger populations experiencing the largest increases.

Figure:



Note: Adapted from Riley *et al*. Weighted prevalence of SARS-CoV-2 swab positivity by age for **June 24–July 5, 2021** (n = 47,729) compared to **May 20–June 7, 2021** (n = 108,911) in England. Bars indicate 95% confidence interval. Licensed under CC-BY-NC-ND 4.0.

Natural History of SARS-CoV-2 Infection

PEER-REVIEWED

Williams *et al.* **COVID-19 outbreak associated with a SARS-CoV-2 P.1 lineage in a long-term care home after implementation of a vaccination program – Ontario, April-May 2021.** Clinical Infectious Diseases (July 8, 2021).

Key findings:

- Among fully vaccinated residents and staff, 39% (19/48) of residents and 9.3% (4/43) of staff tested positive for SARS-CoV-2 P.1 (Gamma).

  - Severe illness (hypoxemia, hospitalization, or death) was reported among residents only (12.5%).
- Estimated vaccine effectiveness (VE) was 52.5% (95% CI 26.9%-69.1%) among residents, and 66.2% (95% CI 2.3%-88.3%) among staff.
  - VE against severe illness among residents was 78.6% (95% CI 47.9%-91.2%).

Methods: Outbreak investigation among staff and residents at long-term care facility in late April 2021. As of March 2021, 54% (120/224) of staff and 81% (100/121) residents were fully vaccinated with BNT162b2 (Pfizer/BioNTech). Positive SARS-CoV-2 cases were confirmed by RT-PCR, and genomic sequencing was performed. *Limitations*: Small sample sizes resulting in estimates with wide confidence intervals; because not all facility residents were included, vaccine effectiveness rates may be underestimated.

Implications: Two doses of BNT162b2 provided reduced protection against transmission of the SARS-CoV-2 P.1 variant among residents in a long-term care facility outbreak.

COVID-19 Vaccines in Cancer Patients

COVID-19 mRNA vaccines have been shown to be effective in healthy individuals, but limited information is available for the protection and duration for persons with cancer or who may be undergoing immunocompromising therapies.

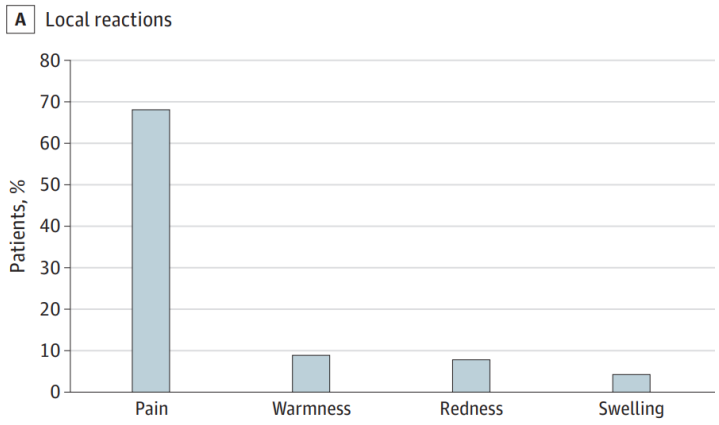
A. Goshen-Lago *et al*. **Serologic status and toxic effects of the SARS-CoV-2 BNT162b2 vaccine in patients undergoing treatment for cancer**. JAMA Oncology (July 8, 2021).

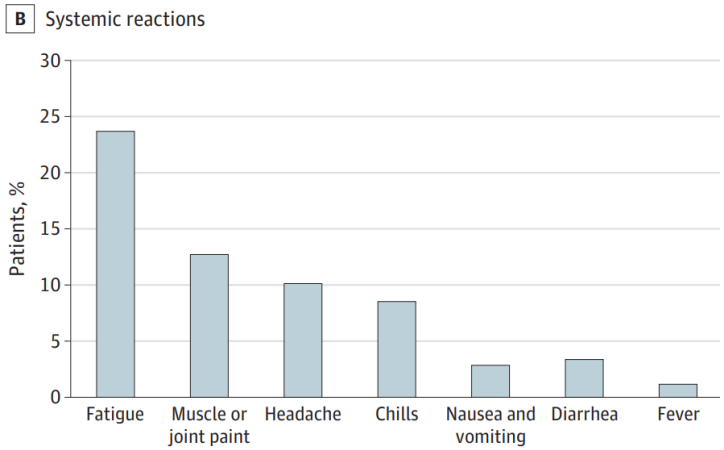
Key findings:

- Only 29% (25/86) of BNT162b2 (Pfizer/BioNTech) vaccinated patients undergoing cancer treatment seroconverted after 1st dose compared to 84% (220/261) of controls (P <.001).
  - After 2nd dose, seropositivity increased to 86% (187/218) in cancer patients with no difference by age, sex, or disease stage.
- Reported local and systemic reactions included pain: 69% (Figure A), and fatigue: 24% (Figure B).
  - Overall, adverse events resembled those of healthy individuals.

Methods: An Israeli prospective serologic study of 232 BNT162b2-vaccinated cancer patients with solid tumors receiving cancer treatment, and age-matched healthcare worker controls. Sero-immunogenicity (IgG) was determined >10 days after 1st dose, and at ~14 days after 2nd dose. *Limitations*: Median age of 68 years may limit generalizability; no information on corticosteroid use; fewer patients tested for immunogenicity after 1st dose compared with 2nd dose.

Figure:





Note: Adapted from Goshen-Lago *et al.* Reported local (A) and systemic (B) reactions following BNT162b2 vaccine by cancer patients undergoing treatment (January–March 2021). Licensed under CC BY.

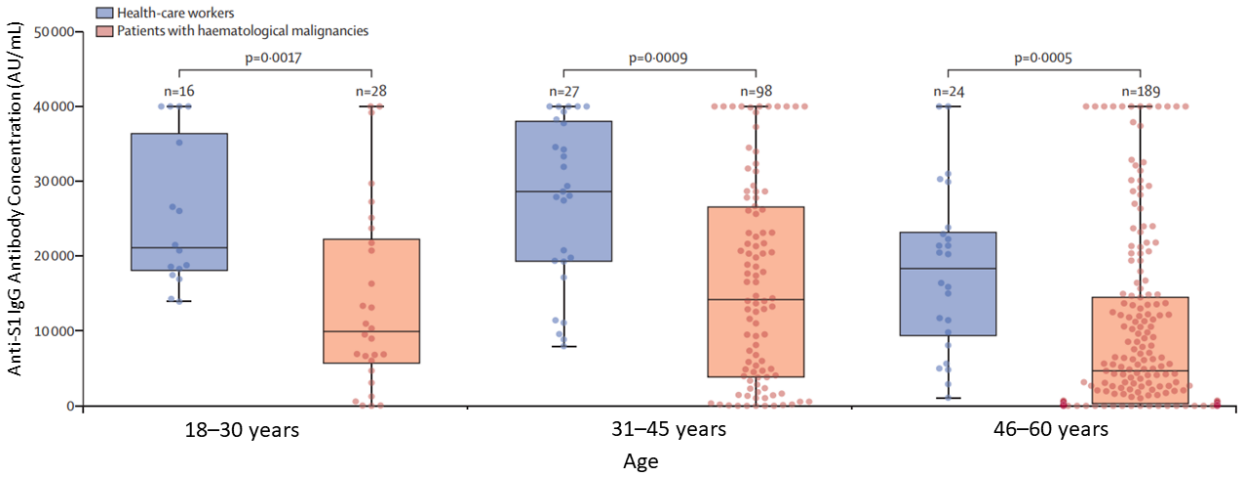
B. **Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study.** Maneikis *et al.* The Lancet Haematology (July 2, 2021).

Key findings:

- The neutralizing antibody (Ab) response of individuals receiving 2 doses of BNT162b2 (Comirnaty, Pfizer-BioNTech) while undergoing treatment for hematological malignancies was significantly lower than that of healthy controls (Figure).
- Active treatment with Bruton tyrosine kinase inhibitors, ruxolitinib, venetoclax, or anti-CD20 Ab therapy most inhibited vaccine response.
- Excepting anti-CD20 therapy, vaccination >6 months post-treatment matched controls; >12 months produced best response for anti-CD20.

Methods: A prospective cohort study of serologic response to BNT162b2 in 885 patients (age 18–60 years) with hematological malignancies; 67 healthcare worker controls were compared to a subgroup of 315 patients. Anti-S1 IgG antibodies were measured at least 10 days before 1st vaccine dose and 7–21 days following 2nd dose for all participants. *Limitations:* small number of participants in some subgroups; study did not account for the disease duration of patients.

Figure:



Note: Adapted from Maneikis *et al.* Serological response to 2 doses of BNT162b2 in **health-care workers** and in **individuals with hematological malignancies,** grouped by age. The boxes show IQR, center line shows the median, and whiskers show maximum and minimum values; the dots show individual participants. Permission request in progress.

Implications from Goshen-Lago *et al*. and Maneikis *et al*.: Among cancer patients, immunogenicity and seropositivity was low after a single dose of BNT162b2, higher seropositvity was achieved following a 2nd vaccine dose but immunogenicity remained lower than healthy controls and was even lower among those on certain treatments such as anti-CD20. Nonpharmaceutical interventions in addition to vaccination likely will play an important role in protecting immunocompromised populations.

PREPRINTS (NOT PEER-REVIEWED)

Effectiveness of SARS-CoV-2 mRNA vaccines for preventing COVID-19 hospitalizations in the United States. Tenforde *et al.* medRxiv (July 8, 2021).

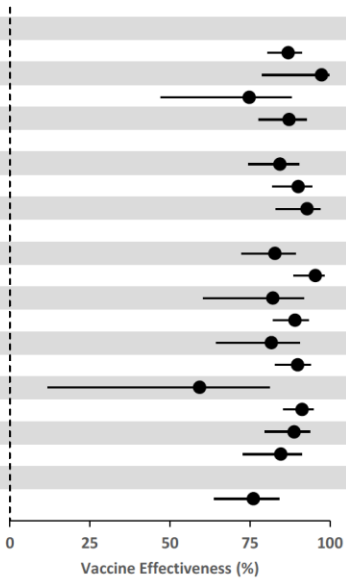
Key findings:

- Overall vaccine effectiveness (VE) for preventing hospitalization was 86.9% (95% CI 80.4-91.2%).
- Vaccine effectiveness was significantly lower for patients with immunocompromising conditions (59.2%, 95% CI 11.9-81.1%) compared to individuals without an immunocompromising condition (91.3%, 95% CI 85.5-94.7%).
- There were 45 vaccine breakthrough COVID-19 hospitalizations; 20 of whom had immunosuppression.

Methods: Multicenter case-control study of 1,210 US adults hospitalized March 11–May 5, 2021, comparing odds of antecedent SARS-CoV-2 vaccination among hospitalized cases and controls. Cases (n = 590) were PCR positive for SARS-CoV-2, controls were PCR negative for SARS-CoV-2. *Limitations:* Study was not adjusted for behavioral characteristics, such as mask wearing and social distancing; most sequencing results were B.1.1.7 (Alpha) variant not B.1.617.2 (Delta) that is widely circulating now.

Figure:

Subgroup	Vaccinated case patients / total case patients (%)	Vaccinated control patients / total control patients (%)	Vaccine effectiveness (95% confidence interval)
Full vaccination			
Overall	45/499 (9.0)	215/489 (44.0)	86.9 (80.4 to 91.2)
18 to 49 yr	1/186 (0.5)	25/140 (17.9)	97.3 (78.9 to 99.7)
50 to 64 yr	14/185 (7.6)	39/136 (28.7)	74.7 (47.2 to 87.9)
≥65 yr	30/128 (23.4)	151/213 (70.9)	87.2 (77.6 to 92.7)
Covid-19 vaccine product			
Pfizer-BioNTech	28/482 (5.8)	122/396 (30.8)	84.3 (74.6 to 90.3)
Moderna	17/471 (3.6)	93/367 (25.3)	90.0 (82.0 to 94.4)
B.1.1.7 variant lineage	7/116 (6.0)	215/489 (44.0)	92.8 (83.0 to 96.9)
Underlying medical condition			
Chronic cardiovascular disease	38/263 (14.5)	150/311 (48.2)	82.8 (72.3 to 89.3)
No chronic cardiovascular disease	7/236 (3.0)	65/178 (36.5)	95.4 (88.5 to 98.1)
Chronic lung disease	14/98 (14.3)	72/158 (45.6)	82.1 (60.3 to 91.9)
No chronic lung disease	31/398 (7.8)	143/331 (43.2)	89.0 (82.1 to 93.2)
Diabetes mellitus	19/151 (12.6)	73/162 (45.1)	81.6 (64.5 to 90.5)
No diabetes mellitus	26/347 (7.5)	142/327 (43.4)	89.8 (82.8 to 94.0)
Immunocompromising condition	20/79 (25.3)	56/116 (48.3)	59.2 (11.9 to 81.1)
No immunocompromising condition	25/417 (6.0)	159/373 (42.6)	91.3 (85.5 to 94.7)
Obesity	21/289 (7.3)	95/215 (44.2)	88.7 (79.7 to 93.8)
No obesity	24/203 (11.8)	120/273 (44.0)	84.6 (72.8 to 91.3)
Partial vaccination			
Overall	45/499 (9.0)	103/377 (27.3)	76.0 (63.7 to 84.1)



Note: Adapted from Tenforde *et al.* Vaccine effectiveness of BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) vaccines by subgroup. Licensed under CC-BY-NC-ND 4.0.

Implications: Vaccine effectiveness of mRNA vaccines in the general population is estimated to be around 87%, however, VE is lower in immunosuppressed groups.

Prevention, Mitigation, and Intervention Strategies

PREPRINTS (NOT PEER-REVIEWED)

Effectiveness of COVID-19 vaccines against variants of concern, Canada. Nasreen *et al.* medRxiv (July 3, 2021).

Key findings:

- Across all vaccines evaluated, single doses generally were more protective against hospitalization and death than symptoms.
    - Against Delta, vaccine effectiveness (VE) for preventing hospitalization or death was ≥78% after 1 dose of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), or ChAdOx1 (Oxford/AstraZeneca) (Table).

Methods: 69,533 symptomatic SARS-CoV-2 positive individuals and 351,540 non-infected controls were identified in Ontario, Canada between December 14, 2020, and May 30, 2021; vaccination status was determined in both groups to calculate VE. Most variants were classified by screening for N501Y and E484K mutations with some confirmed by whole genome sequencing. *Limitations*: Probabilistic methods used to identify most Delta cases could lead to overestimation.

Implications: Full and partial vaccination against SARS-CoV-2 provides protection from symptomatic or severe disease in the face of circulating Alpha, Beta/Gamma, and Delta variants.

Figure:

Outcome	Adjusted VE* (95% CI)			
	Non-VOC	Alpha	Beta/Gamma†	Delta‡
Symptomatic infection				
BNT162b2 (Pfizer-BioNTech)				
≥14 days after dose 1 only§	61 (54, 68)	66 (64, 68)	60 (52, 67)	56 (45, 64)
≥7 days after dose 2	93 (88, 96)	89 (86, 91)	84 (69, 92)	87 (64, 95)
mRNA-1273 (Moderna)				
≥14 days after dose 1 only§	54 (28, 70)	83 (80, 86)	77 (63, 86)	72 (57, 82)
≥7 days after dose 2	89 (65, 96)	92 (86, 96)	-¶	-¶
ChAdOx1 (AstraZeneca)				
≥14 days after dose 1 only§	67 (38, 82)	64 (60, 68)	48 (28, 63)	67 (44, 80)
≥7 days after dose 2	-**	-**	-¶	-¶
Hospitalization or death				
BNT162b2 (Pfizer-BioNTech)				
≥14 days after dose 1 only§	68 (54, 78)	80 (78, 82)	77 (69, 83)	78 (65, 86)
≥7 days after dose 2	96 (82, 99)	95 (92, 97)	95 (81, 99)	-¶
mRNA-1273 (Moderna)				
≥14 days after dose 1 only§	57 (28, 75)	79 (74, 83)	89 (73, 95)	96 (72, 99)
≥7 days after dose 2	96 (70, 99)	94 (89, 97)	-¶	-¶
ChAdOx1 (AstraZeneca)				
≥14 days after dose 1 only§	-¶	85 (81, 88)	83 (66, 92)	88 (60, 96)
≥7 days after dose 2	-¶	-**	-¶	-¶

Note: Adapted from Nasreen *et al*. Vaccine effectiveness against Alpha (B.1.1.7), Beta (B.1.351)/Gamma (P.1), and Delta (B.1.617.2) variants of concern (VOC) by outcome, vaccine product, and number of doses received for those tested for SARS-CoV-2 between 14 December 2020 and 30 May 2021 in Ontario, Canada. Sample size was not adequate to evaluate VE against ChAdOx1 at ≥7 days after the 2nd dose. Licensed under CC-BY-NC 4.0.

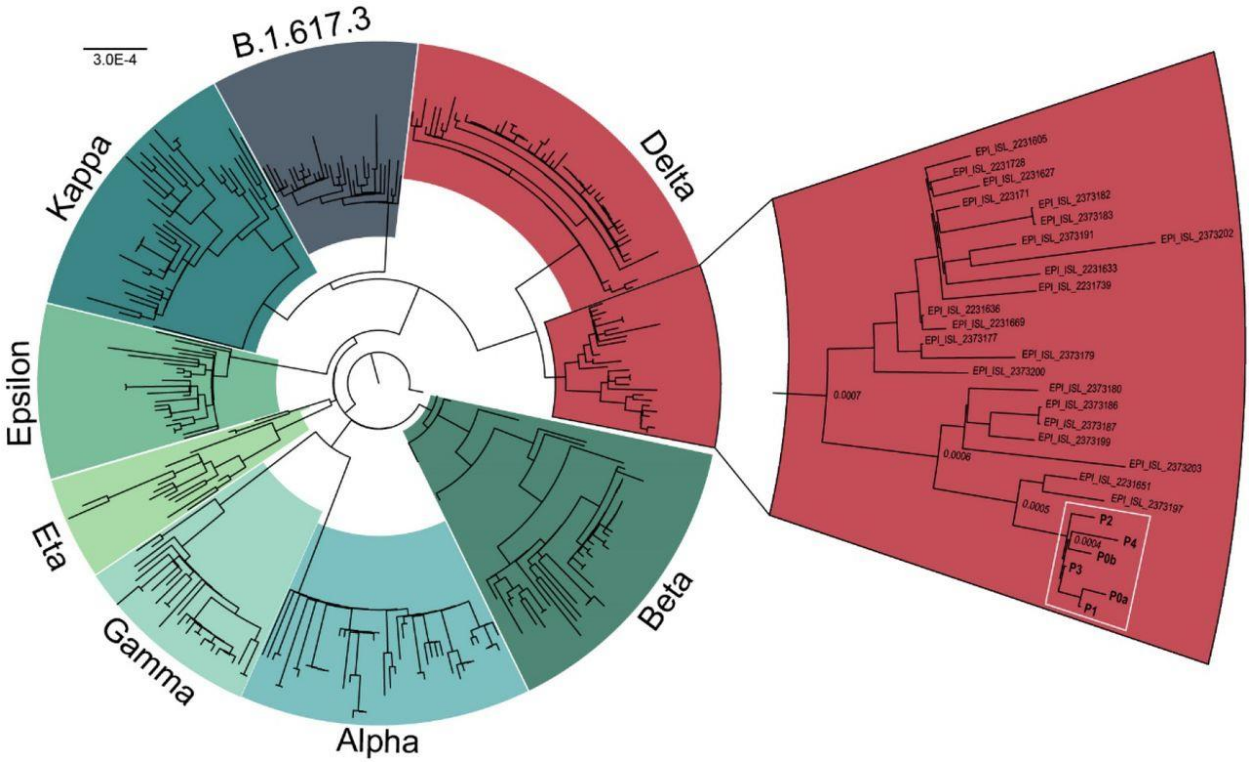
In Brief

Detection, Burden, and Impact

- Fu *et al*. **COVID-19 outcomes in hospitalized patients with active cancer: Experiences from a major New York City health care system**. Cancer (June 7, 2021). Among 4,184 hospitalized patients with SARS-CoV-2 at a single NYC hospital (March–May 2020), patients with active cancer (n = 233) had increased odds of mortality (adjusted OR 1.89; 95% CI 1.34-2.67). Among those with active cancer, hematologic malignancy had higher mortality compared to other cancers (47.8% vs. 28.7%, p<0.01).

Transmission of SARS-CoV-2

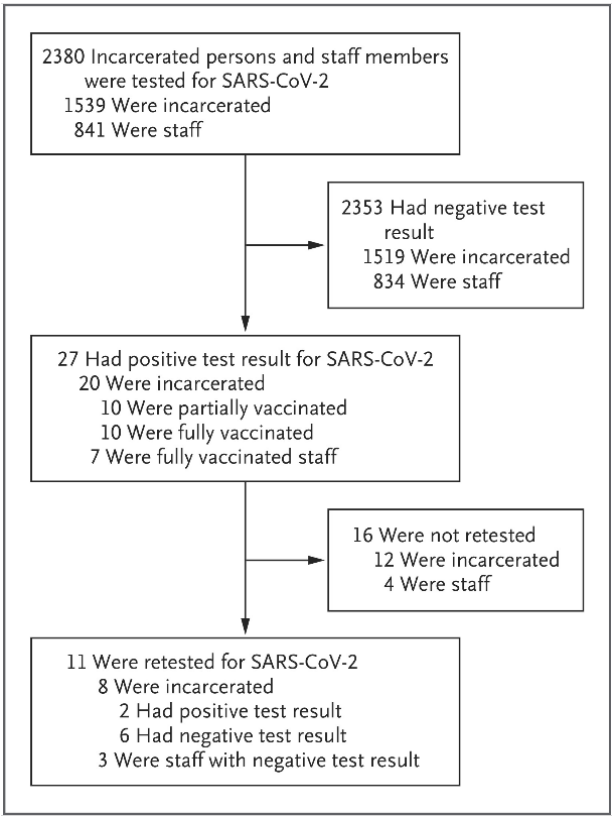
- Farinholt. **Transmission event of SARS-CoV-2 Delta variant reveals multiple vaccine breakthrough infections**. medRxiv (Preprint; July 12, 2021). Six symptomatic individuals (aged 51–70 years) were diagnosed with SARS-CoV-2 following their attendance at a wedding in Texas. The 2 presumed index cases, visiting from India, had been vaccinated with Covaxin BBV152; the other 4 positives had each received 2 doses of BNT162b2 (Pfizer/BioNTech, n = 2) or mRNA-1273 (Moderna, n = 2). All 6 virus sequences clustered in the Delta clade. One patient required hospitalization, and another died.



Note: Phylogenetic analysis of SARS-CoV-2 variants. All patients (white box) cluster in a sub-clade of the Delta variant (red). Sequences obtained from GISAID. Licensed under CC-BY-NC-ND 4.0.

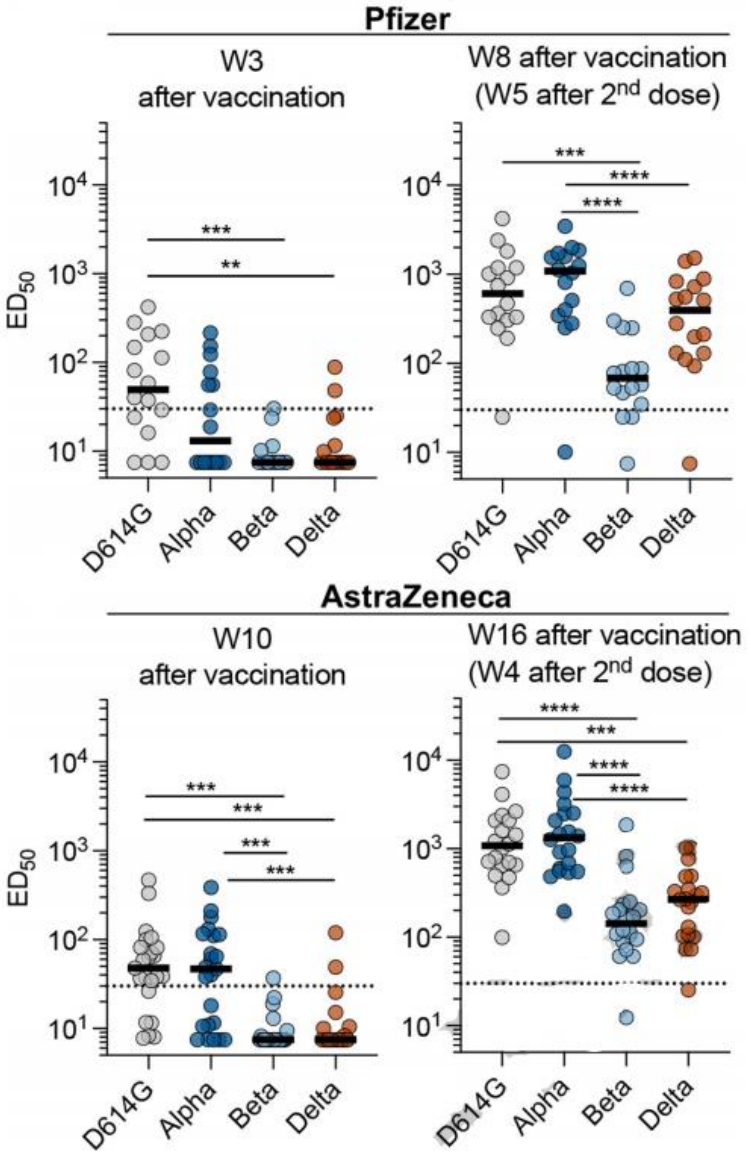
Natural History of SARS-CoV-2 Infection

- Brinkley-Rubinstein *et al.* **Breakthrough SARS-CoV-2 infections in prison after vaccination**. NEJM (July 7, 2021). Among 2,380 vaccinated individuals in the Rhode Island prison system, breakthrough infections were rare, and all cases were asymptomatic.



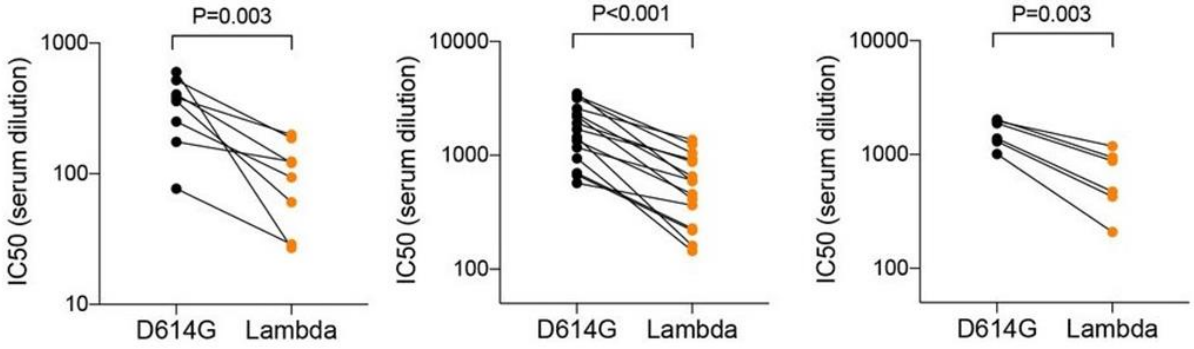
Note: Adapted from Brinkley-Rubenstein *et al*. Testing and breakthrough SARS-CoV-2 infections among vaccinated persons in a prison complex. Of the 27 vaccinated persons with a positive test, 8 (30%) had also tested positive for SARS-CoV-2 more than 3 months earlier. From the New England Journal of Medicine, Brinkley-Rubinstein *et al.*, Breakthrough SARS-CoV-2 infections in prison after vaccination. July 7, 2021, online ahead of print. Copyright © 2021 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

- Planas *et al*. **Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization**. Nature (July 8, 2021). B.1.617.2 (Delta) was weakly neutralized by some monoclonal antibodies, including bamlanivimab. Sera from convalescents up to 12 months post symptoms (n = 26) were 4-fold less potent against B.1.617.2 compared to B.1.1.7 (Alpha). Sera from recipients of 1 dose of Pfizer or AstraZeneca vaccines barely inhibited B.1.617.2; 2 doses led to a neutralization response in 95% of samples but titers were 3- to 5-fold lower than against B.1.1.7.



Note: Adapted from Planas *et al*. Top panels: neutralizing activity of SARS-CoV-2 D614G, **B.1.1.7** (Alpha), **B.1.351** (Beta) and **B.1.617.2** (Delta) variants to sera from Pfizer-vaccinated recipients sampled at week 3 (W3; n = 16) and week 8 post-vaccination/week 5 after 2nd dose (W8; n = 16). Bottom panels: neutralizing activity of sera from AstraZeneca-vaccinated recipients sampled at week 10 (W10; n = 23) and week 16 post-vaccination/week 4 post-2nd dose (W16; n = 20). The dotted line indicates the limit of detection (ED50 = 30). Thick horizontal lines are means. **p <0.02, ***p <0.001, ****p <0.0001. Permission request in progress.

- Tada *et al*. **SARS-CoV-2 Lambda variant remains susceptible to neutralization by mRNA vaccine-elicited antibodies and convalescent serum**. bioRxiv (Preprint; July 3, 2021). SARS-CoV-2 Lambda had a 3-fold reduction in neutralization compared to wild-type by sera from convalescents (n = 8) and BNT162b2 (Pfizer/BioNTech, n = 15) or mRNA-1273 (Moderna, n = 6) vaccinees. While Lambda was about 3.6-fold resistant to neutralization by REGN10987, it was neutralized well by REGN10933.



Note: Adapted from Tada *et al*. Neutralization (IC50) of Lambda variant spike protein, compared to wild-type (D614G), by sera from convalescents, BNT162b2 vaccinees, and mRNA-1273 vaccinees. Statistical significance of decreases shown on horizontal bars. Used by permission of author.

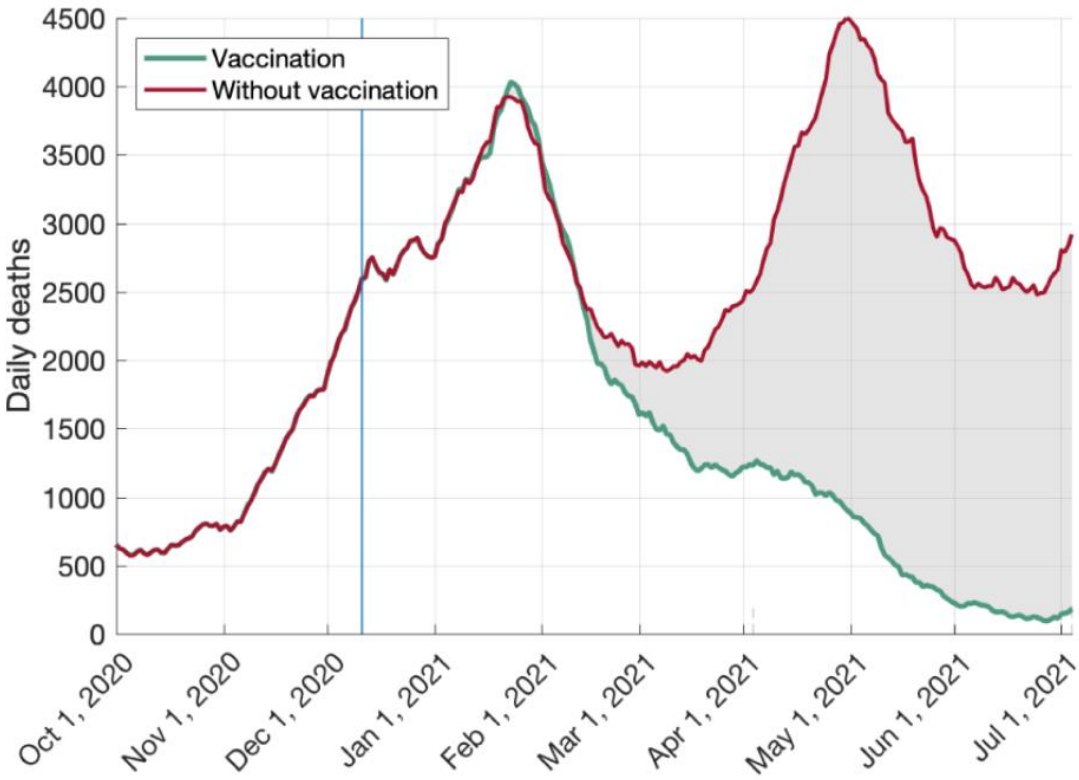
- Mostafa *et al*. **SARS-CoV-2 infections in mRNA vaccinated individuals are biased for viruses encoding spike E484K and associated with reduced infectious virus loads that correlate with respiratory antiviral IgG levels**. medRxiv (Preprint; July 7, 2021). Among 133 SARS-CoV-2 breakthrough infections in individuals fully vaccinated with mRNA vaccines, 68 were symptomatic and 2 required ICU admission. Compared to controls, breakthrough cases were significantly associated with the S: E484K mutation. In an analysis of samples with Ct<25, 80.2% (77/96) of the control group were positive on cell culture compared to 34.7% (17/49) of the vaccinated group, suggesting that SARS-CoV-2 transmission from vaccinated individuals might be reduced.

- Wei *et al*. **Anti-spike antibody response to natural SARS-CoV-2 infection in the general population**. medRxiv (Preprint; July 5, 2021). 24% of 7,256 individuals in the UK testing swab SARS-CoV-2 positive by PCR did not develop anti-spike IgG antibodies. Non-responders tended to be older and not report symptoms. Among those who did seroconvert, estimated anti-spike IgG half-life was 184 days and estimated protection against reinfection was an average of 1.5–2 years.

Prevention, Mitigation, and Intervention Strategies

- Jara *et al*. **Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile**. NEJM (July 7, 2021). Among 4.2 million Chilean adults receiving 2 doses of CoronaVac, the sex and age adjusted vaccine effectiveness was 61.2% (95% CI 60.3-62.0) against infection, 86.0% (95% CI 85.1-86.8) against hospitalization, and 84.4% (95% CI 82.4-86.2) against COVID-related deaths.

- Galvani *et al*. **Deaths and hospitalizations averted by rapid U.S. vaccination rollout**. The Commonwealth Fund (July 7, 2021). A model, accounting for Alpha, Gamma, and Delta variants, compared the observed epidemiologic trajectory in the U.S. to 2 counterfactual scenarios. At a daily vaccination rate 50% of actual, by June 2021 there would have been 121,000 additional deaths and >450,000 hospitalizations. Had there not been a vaccine program, an additional 279,000 deaths and 1.25 million hospitalizations were predicted.



Note: Adapted from Galvani *et al*. Estimated U.S. 7-day rolling average of daily deaths with and without vaccination. Permission request in process.

cdc.gov/coronavirus