Good morning everyone. I hope everyone had a good week

Today under Covid-19 News I start with the global death toll from Covid-19. Next to CDC approval of Pfizer vaccine for children aged 5-11. Next the UK granted approval of molnupiravir yesterday. Lastly is the WHO approval of the Indian vaccine.

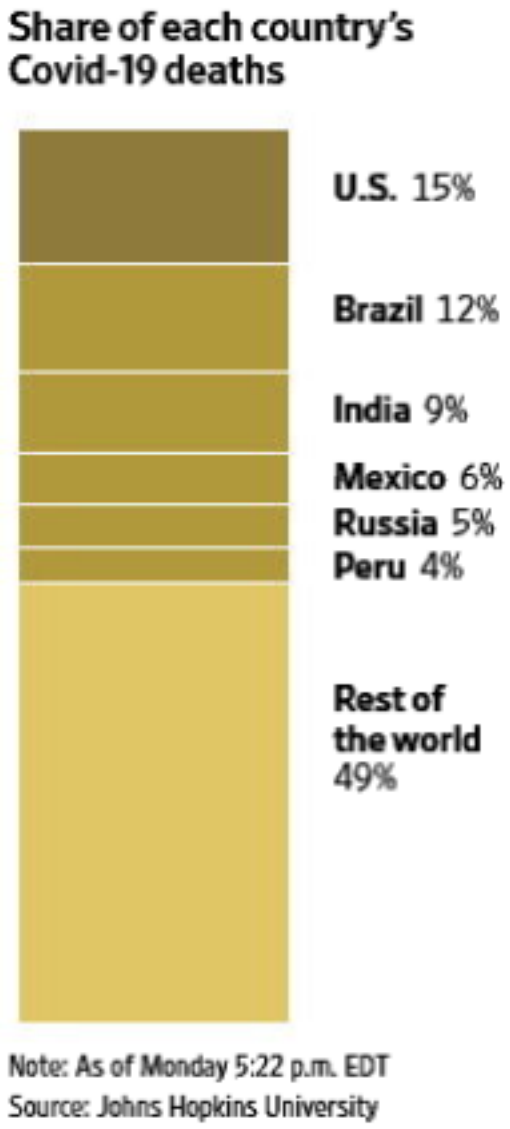
Under Journal Review I try to continue the discussion on the concept of hybrid immunity. The first article looks at primary and secondary immune responses. Next is an interesting article that found that a vaccine after the infection can set off the secondary memory B cell response, enhancing immune protection for those who already have had COVID-19. The next article reported that prior SARS-CoV-2 infection was associated with a statistically significantly lower risk for breakthrough infection among individuals receiving the Pfizer or Moderna vaccines. The next article examined the durability of antibody levels after vaccination with mRNA SARS-CoV-2 vaccine in individuals with or without prior infection. The last article suggest that a third dose of the Pfizer vaccine is highly effective in protecting individuals against severe COVID-19-related outcomes, compared with receiving only two doses at least 5 months ago supporting the concept of a booster dose.

Have a wonderful weekend

Ed

COVID-19 News

Global Covid-19 Death Toll
The reported global Covid-19 death toll surpassed five million Monday, according to data compiled by Johns Hopkins University. The US unfortunately has the highest number of total confirmed deaths from Covid-19, with nearly 746,000 recorded since the start of the pandemic. Brazil, India, and Mexico have the next highest reported death tolls.



Comment: For comparison, the 1918 pandemic killed 675,000 in the US and 50 million worldwide. The population was 1/3 what it is today.

CDC Approved Pfizer vaccine for Children aged 5-11

The CDC on Tuesday formally endorsed the Pfizer vaccine for children 5-11. According to the CDC every million doses given to children ages 5 to 11 would prevent about 58,000 cases and 226 hospitalizations in that group. Immunizing these children is expected to prevent about 600,000 new cases from November 2021 to March 2022. In addition, increasing immunity may reduce the chances that young children will transmit the virus to vulnerable adults in their families and communities. Since the beginning of the pandemic, more than 8,300 children ages 5 to 11 have been hospitalized with Covid, and at least 94 have died. In addition, about 10 percent of children with mild symptoms may have lingering problems months after the infection has resolved. And at least 2,300 children ages 5 to 11 have developed MIS-C. The CDC's advisers also evaluated data on the vaccine's risks. They felt there was enough information to conclude that the benefits of the vaccine outweighed the risks, even without

more long-term safety data. To remind everyone the vaccine VE was 90 percent in children ages 5 through 11. Results from the Pfizer vaccine's trial in children under age 5 are not expected until the end of this year at the earliest.

Formulation and Dosing for Pfizer-BioNTech COVID-19 Vaccines

	Formulation for ≥12-year-olds (purple cap)	Formulation for 5–11-year-olds (orange cap)
Age group	12 years and older	5-11 years
Vial cap color		
Dose (mRNA concentration)	30 ug	10 ug
Injection volume	0.3 mL	0.2 mL
Fill Volume (before dilution)	0.45 mL	1.3 mL
Amount of Diluent* Needed per vial	1.8 mL	1.3 mL
Doses per Vial	6 (after dilution)	10 (after dilution)

*Diluent: 0.9% sterile Sodium Chloride Injection, USP (non-bacteriostatic; DO NOT USE OTHER DILUENTS)
Modified from https://www.cdc.gov/vaccines/covid-19/downloads/Pfizer-Pediatric-Reference-Planning.pdf

Comment: This is good news-the challenge will be how many children aged 5-11 will actually get vaccinated. As I reported in the November 1 Briefing**,** a recent Kaiser Foundation survey found only 27% of parents would immunize their children immediately, while 33% said they would wait and see and 30% they would definitely not vaccinate their children. In addition, about half of the parents in the Kaiser poll said they worried about mandates that would force them to inoculate their children. Over 15 million doses have already been shipped. Starting Thursday many sites have begun to vaccinate children aged 5-11.

Molnupiravir
The UK granted approval to molnupiravir Thursday. Merck has also applied to the FDA and EMA (European Medicines Agency). Molnupiravir works by introducing genetic errors that garble the coronavirus's genetic code and prevent it from making copies of itself.

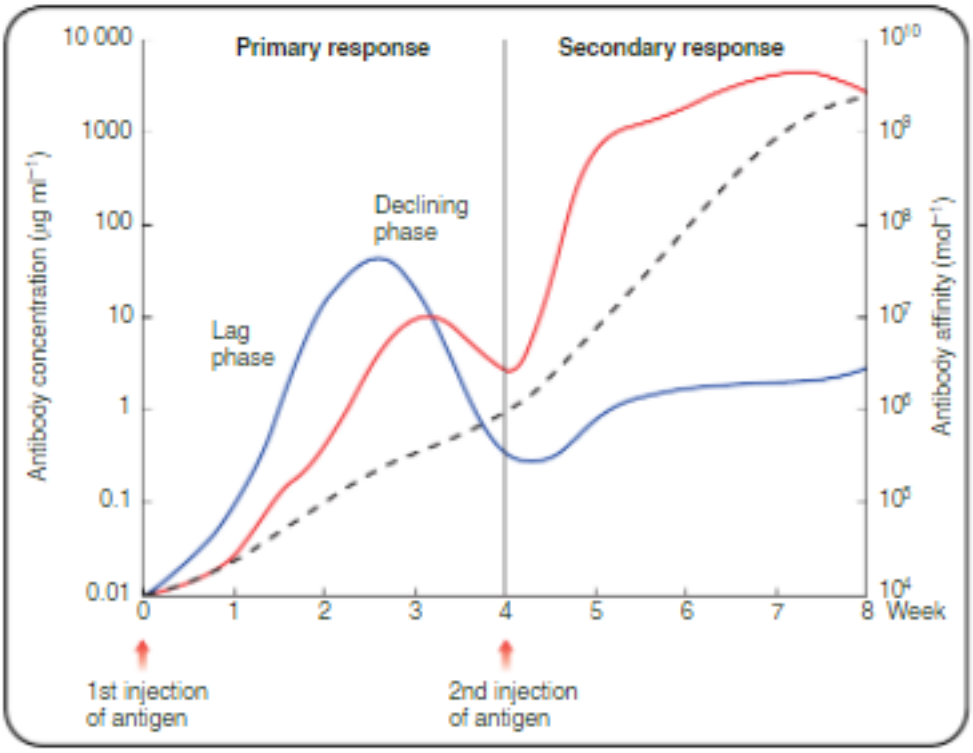
Comment: Investigators are hopeful that in addition to decreasing the risk of developing severe illness, the drug could help reduce transmission of the virus as well. The pill is notably easy to use compared to monoclonal antibodies, a costly treatment that is infused or injected. Molnupiravir was reviewed in the Briefing on October 5, 2021. Among 775 patients who were initially enrolled in the trial, molnupiravir reduced the risk of hospitalization or death through day 29 by approximately 50% (7.3% vs 14.1% with placebo). (P=0.0012). There were no deaths in the molnupiravir group compared to 8 deaths in the placebo group. The dosage of molnupiravir in the clinical trial was 800 mg twice daily for 5 days. Although molnupiravir is another therapeutics in our toolbox, vaccinations remain the principal tool in fighting this pandemic. Just announced Pfizer has an antiviral pill which reduces risk of hospitalization and death >85% to be reviewed next week.

Covaxin
WHO approved for EUA the Indian developed vaccine. The panel said the vaccine was found to have 78 percent efficacy against covid-19 “of any severity,” 14 or more days after the second dose. The vaccine is given in two doses, four-weeks apart in all age groups 18 and older. Bharat Biotech, the India company says it has the capacity to produce 50 million to 55 million doses per month. Unlike mRNA vaccines, Covaxin uses an inactivated antigen of the virus to stimulate an immune response — an older, well-established technology for vaccines. This new addition and the manufacturing capacity this should boost vaccine availability.

Journal Review

Immune Responses: Primary and Secondary
Wiley Online Library September 30, 2020
https://doi.org/10.1002/9780470015902.a0029196
Key Concepts

- The innate immune system is the first line of defense against infectious agents. When this is breached, the adaptive immune system provides a more efficient response to clearing pathogens.
- The adaptive immune system has the capacity to ‘remember’ previous antigens; a process termed immunological memory.
- Antigen-specific T cells are selected during a primary immune response and expand to produce clones of T cells with high specificity for the activating antigen.
- In a B cell primary response to a thymus-dependent antigen, the immune system selects B cells with a high affinity and specificity for the antigen and these become memory cells.
- The selection of B cells with a high affinity for a given antigen occurs in the germinal centers of secondary lymphoid follicles and requires the enzyme activation-induced cytidine deaminase (AID) and interactions with other immune cells.
- The ability to change the isotype of antibody produced (class switching) by a B cell also occurs in germinal centers and requires AID.
- In a secondary response to the same antigen, memory cells are rapidly activated. This process is quicker and more effective than the primary response.



Blue IgM; Red IgG

Feature	Primary response	Secondary response
Antigen presentation	Mainly non-B cells, e.g. dendritic cells	B lymphocytes increasingly important
Antigens induced by	All antigens	Protein antigens
Antigen concentration required to induce response	Relatively high dose optimally with adjuvant	Relatively low dose usually without adjuvant
Lag or latent phase	Usually 5–10 days	Usually 2–5 days
Specific B-cell frequency	10^{-4}–10^{-6}	10^{-3}
Somatic hypermutation	Low	High
Peak concentration	Low	High
Class (isotype)	Predominantly immunoglobulin M (IgM)	Predominantly IgG or IgA depending on site
Affinity	Low	High

High-affinity memory B cells induced by SARS-CoV-2 infection produce more plasmablasts and atypical memory B cells than those primed by mRNA vaccines

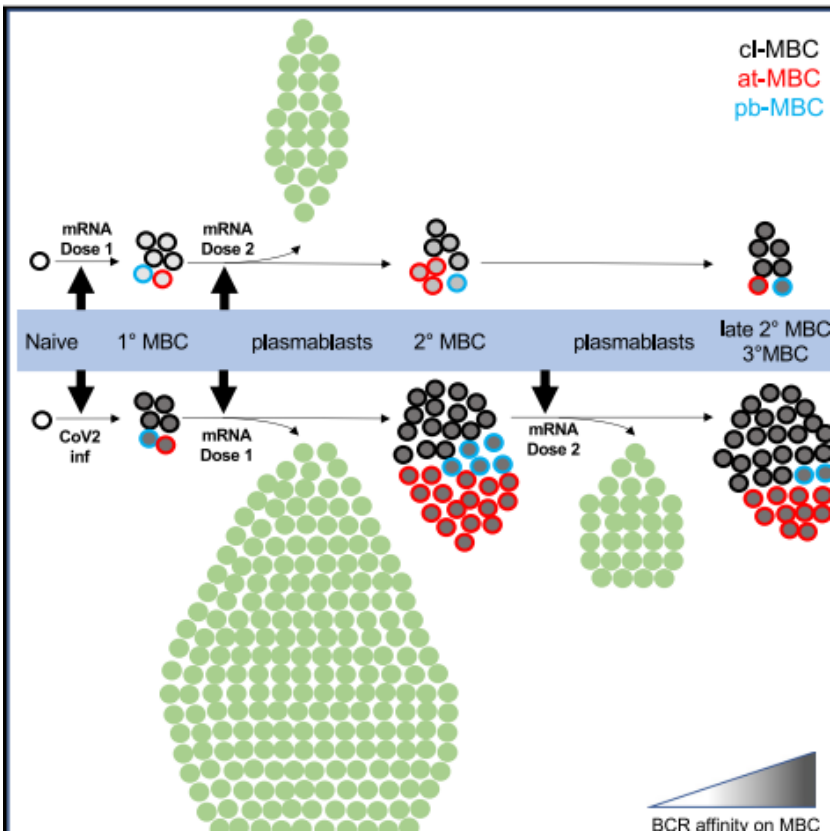
Cells Reports published October 12, 2021
doi.org/10.1016/j.celrep.2021.109823

Key Points:

- Primary MBCs(memory B cells) in SARS-CoV-2-infected and vaccinated people were similar in frequency
- SARS-CoV-2-induced primary MBCs were more affinity matured than vaccine-induced MBCs
- SARS-CoV-2-induced primary MBCs had better secondary responses than vaccine-induced MBCs
- Secondary MBCs in SARS-CoV-2-infected individuals had a poor tertiary response

The investigators compare SARS-CoV-2 spike receptor binding domain (S1-RBD)-specific primary MBCs that form in response to infection or a single mRNA vaccination. Both primary MBC populations have similar frequencies in the blood and respond to a second S1-RBD exposure by rapidly producing plasmablasts with an abundant immunoglobulin (Ig)A+ subset and secondary MBCs that are mostly IgG+

and cross-react with the B.1.351 variant. However, infection-induced primary MBCs have better antigen-binding capacity and generate more plasmablasts and secondary MBCs of the classical and atypical subsets than do vaccine-induced primary MBCs. Our results suggest that infection-induced primary MBCs have undergone more affinity maturation than vaccine induced primary MBCs and produce more robust secondary responses.



Comment: These new results show that a SARS-CoV-2 infection, like a first vaccine dose, will elicit the primary response, as expected. The investigators also found that a vaccine after the infection can set off the secondary memory B cell response, enhancing immune protection for those who already have had COVID-19. In fact, this secondary reaction exceeded responses after two vaccine doses in those with no history of SARS-CoV-2 infection. The findings suggest that vaccination is particularly valuable for people who have already had COVID-19, ensuring a robust immune reaction if the virus finds them again.

Association of Prior SARS-CoV-2 Infection With Risk of Breakthrough Infection Following mRNA Vaccination in Qatar

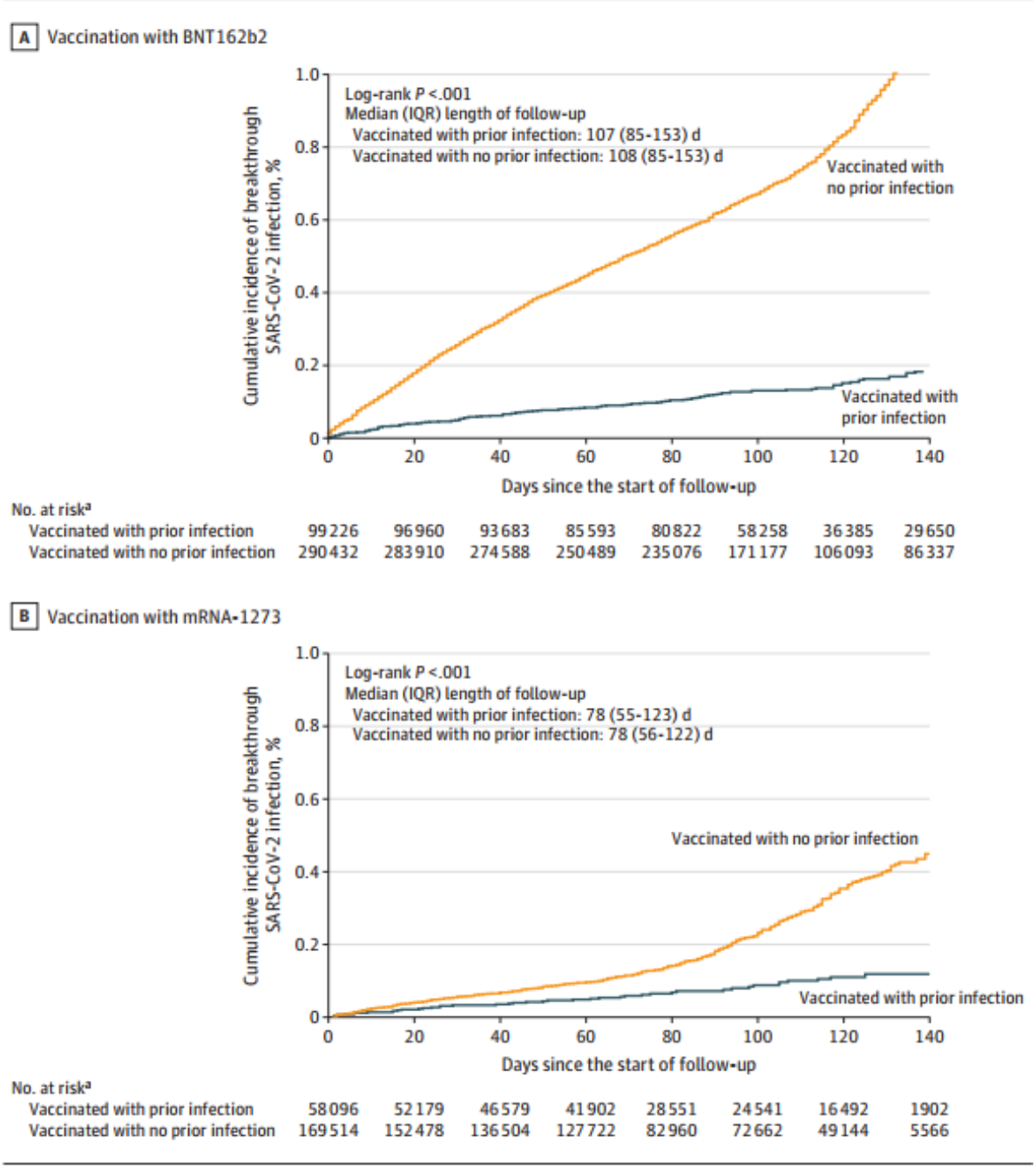
JAMA Netw Open published November 1 ,2021

doi:10.1001/jama.2021.19623

The study involved following 1,531,736 Qataris starting 14 days after receipt of the second dose of Pfizer or Moderna COVID-19 vaccine from Dec 21, 2020, to Sep 19, 2021. The country had experienced two COVID-19 surges with the Alpha and Beta variants from January to June 2021. Community transmission of the SARS-CoV-2 Delta variant was identified at the end of March, and the strain became dominant by summer. The Pfizer group was made up of 99,226 COVID-19 survivors and 290,432 matched SARS-CoV-2–naïve controls; median age was 37 years, and 68% were men. The Moderna group consisted of 58,096 COVID-19 survivors and 169,514 never-infected controls; median age was 36 years, and 73% were men.

Among the Pfizer group, 159 (0.16%) breakthrough COVID-19 infections were reported in COVID-19 survivors, 1 of whom was severely ill with the new infection, while 2,509 (0.86%) occurred in those without previous infection. Of those, 26 had severe disease and 2 were in critical condition. In the Moderna group, 43 breakthrough infections (0.07%) occurred in COVID-19 survivors, but with none of them severe, compared with 368 (0.22%) breakthrough infections in coronavirus-naïve participants, 1 of whom became seriously ill. None of the Pfizer or Moderna vaccine recipients died.

Cumulative incidence of breakthrough infections among Pfizer vaccinees was estimated at 0.15% (95% confidence interval [CI], 0.12% to 0.18%) in COVID-19 survivors and 0.83% (95% CI, 0.79% to 0.87%) in those without previous infection at 120 days of follow-up (adjusted hazard ratio [aHR] for infection in coronavirus-naïve vaccinees, 0.18 [95% CI, 0.15 to 0.21]). Among Moderna vaccinees, cumulative infection incidence was estimated at 0.11% (95% CI, 0.08% to 0.15%) in those with previous infection and 0.35% (95% CI, 0.32% to 0.40%) in those without at 120 days of follow-up (aHR, 0.35 [95% CI, 0.25 to 0.48]. In other words, those who were infected with SARS-CoV-2 before getting vaccinated had a 65% to 82% lower rate of breakthrough infection compared with those who were vaccinated but never infected.



Comment: Prior SARS-CoV-2 infection was associated with a statistically significantly lower risk for breakthrough infection among individuals receiving the Pfizer or Moderna vaccines in Qatar between December 21, 2020, and September 19, 2021. Although both vaccines were found to be highly effective against the Alpha, Beta, and Delta variants, prior infection among those vaccinated—so called hybrid natural and vaccine immunity—appeared to be associated with additional reduction in breakthrough infection.

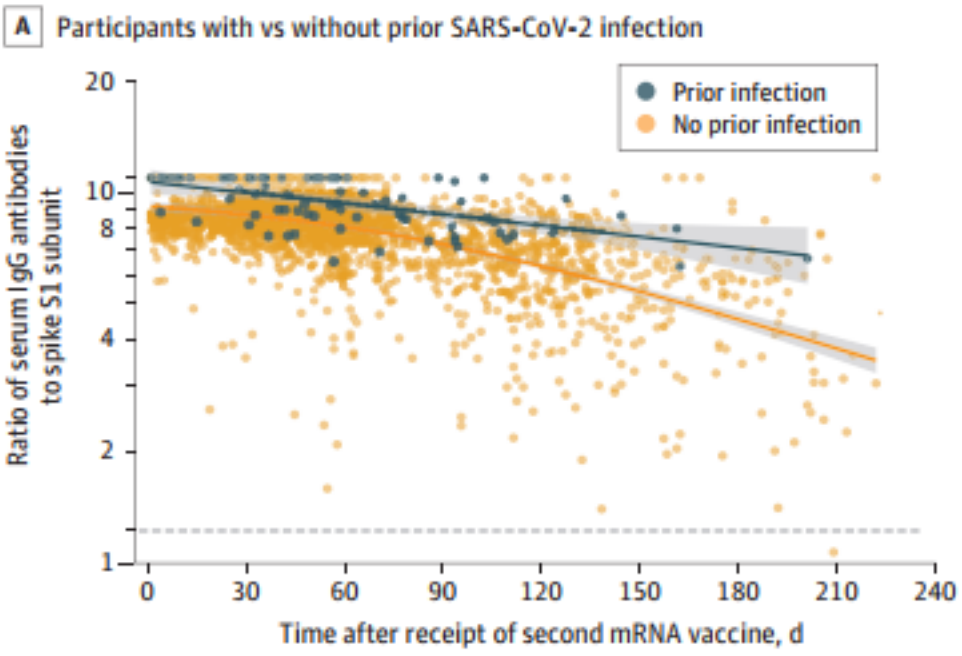
Durability of Antibody Levels After Vaccination With mRNA SARS-CoV-2 Vaccine in Individuals With or Without Prior Infection

JAMA Netw Open Published online November 1 ,2021
doi:10.1001/jama.2021.19996
Investigators set out to compared durability of SARS-CoV-2 spike IgG antibodies in fully vaccinated HCWs with and without previous COVID-19 infection from June 2020 to Sep 3, 2021. Participants provided serum samples 14 days after receipt of the second dose of Pfizer or Moderna vaccine and then again at least 90 days later.

Among the 1,960 HCWs who gave serum samples, 73 (3.7%) had evidence of previous SARS-CoV-2 infection, 41 of whom tested positive for COVID-19 in the 90 days before vaccination and 32 of whom tested positive more than 90 days before vaccination. Of this group, 80% were women, 95% were non-Hispanic, and 80% were White; median age was 40.4 years.

Of the Covid-19 naïve participants, adjusted median antibody concentrations were 8.69 at 1 month, 7.28 at 3 months, and 4.55 at 6 months after vaccination (possible range was 1.23 to 11.00). Relative to never-infected participants, COVID-19 survivors maintained higher adjusted antibody levels after vaccination by an absolute difference of 1.25 (relative difference, 14%) at 1 month, 1.42 (19%) at 3 months, and 2.56 (56%) at 6 months.

Participants infected with COVID-19 more than 90 days before vaccination had higher adjusted antibody concentrations after vaccination than those infected within 90 days before vaccination, at 1 month (absolute difference, 0.86; relative difference, 9%) and 9.31 at 3 months (absolute difference, 1.09; relative difference, 13%).



Comment: Consistent with work comparing extended vaccine dosing intervals, this study showed that a longer interval between infection and first vaccine dose actually may enhance the antibody response. Further studies on whether increased antibody durability in COVID-19 survivors can be attributed to number of exposures, interval between exposures, or the interaction of natural and vaccine-induced

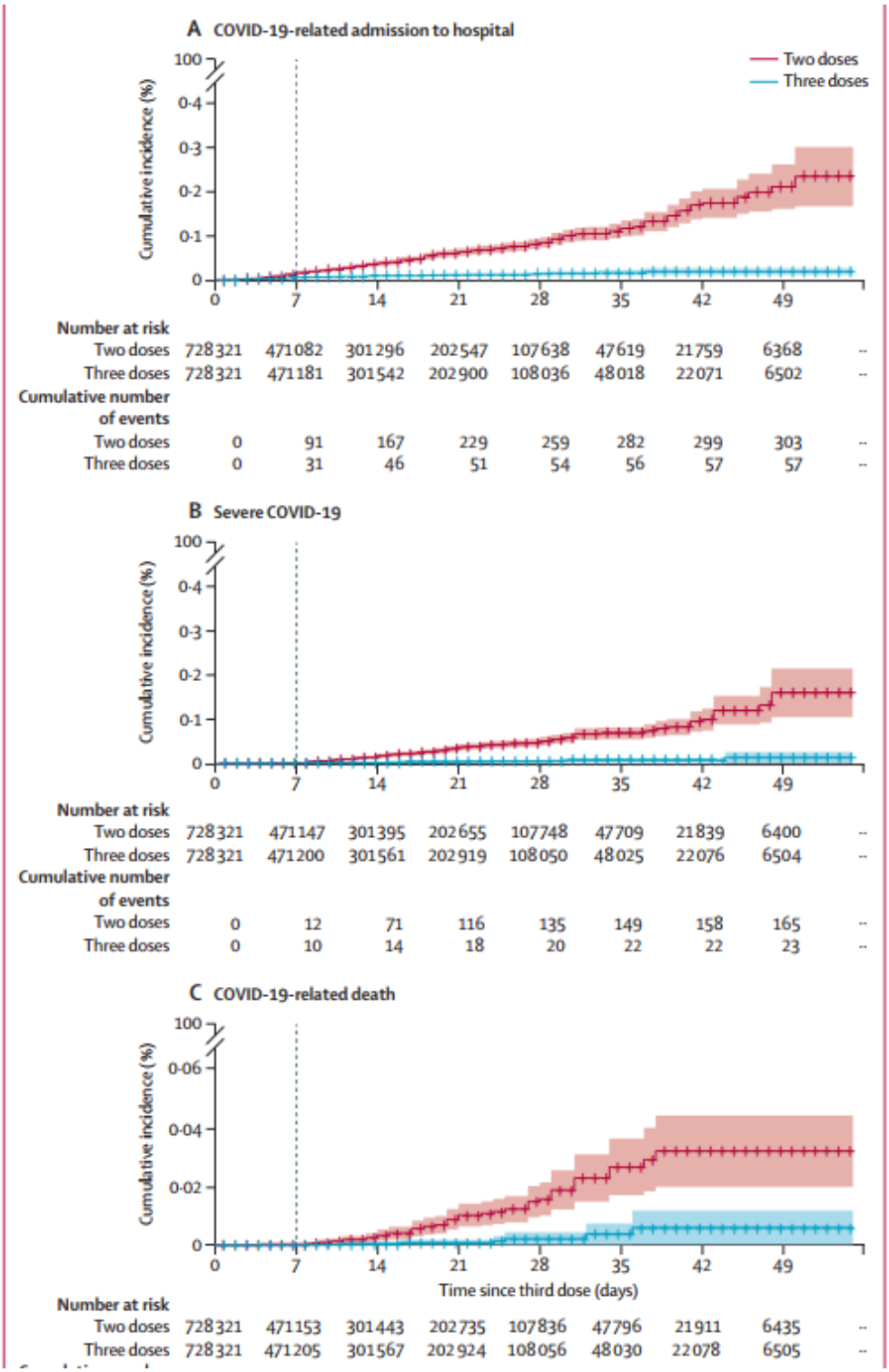
immunity need to be performed. Further studies are also needed to elucidate how serological testing can inform optimal vaccine timing and need for booster doses.

Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study

Lancet published online October 29, 2021
doi.org/10.1016/ S0140-6736(21)02249-2

Investigators studied the effectiveness of a third dose of the Pfizer vaccine in preventing severe COVID-19 outcomes using the data repositories of Israel's largest healthcare organization.

- For inclusion in the third dose group, researchers identified 1,158,269 individuals as eligible.
- Following matching, 728,321 individuals were included in both the third dose and control groups.
- Compared with receiving only two doses at least 5 months ago, receipt of the third dose was linked with vaccine effectiveness (evaluated at least 7 days after the receipt) of 93% (231 events for two doses vs 29 events for three doses; 95% CI 88–97) for admission to hospital, 92% (157 vs 17 events; 82–97) for severe disease, and 81% (44 vs seven events; 59–97) for COVID-19-related death.



Comment: The findings in this study suggest that a third dose of the Pfizer vaccine is highly effective in protecting individuals against severe COVID-19-related outcomes, compared with receiving only two doses at least 5 months ago. These findings were review earlier in the Briefing when posted on medRxiv. Many countries are experiencing a surge of Covid-19 despite vaccination campaigns. This situation in part has been caused by the more transmissible Delta variant, the relaxation of NPIs, and by waning

immunity as time passes from earlier vaccination. As a result several countries are planning to administer a third booster dose of mRNA COVID-19 vaccine after 6 months from the second dose.