I hope everyone had a wonderful, joyous, and safe Christmas weekend.

Today I start with a very good article exploring how we evaluate investigational vaccines after EUA of two effective vaccines. The authors raise an important question: can we ethically continue placebo-controlled trials. The next article demonstrates that specific memory B cells, "remember" infection by the virus, and if challenged again, through re-exposure to the virus, triggers a protective immune response through rapid production of protective antibodies. These results are important because they show that patients infected with the COVID-19 virus do in fact retain immunity against the virus. The next article is a review from American College of Allergy, Asthma, and Immunology (ACAAI) Updated Guidance on Risk of Allergic Reactions to mRNA Vaccines. The next article confirms prior studies that use of monoclonals when coadministered with remdesivir, did not demonstrate efficacy among hospitalized patients who had COVID-19 without end-organ failure. The last article reviews variation in US hospital mortality rates for patients admitted with COVID-19 during the first 6 months of the pandemic.

Have a wonderful day

Ed

Evaluating SARS-CoV-2 Vaccines After Emergency Use Authorization or Licensing of Initial Candidate Vaccines

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doi:10.1001/jama.2020.25127

FDA in recent weeks has issued EUA for 2 vaccines against SARS-CoV-2. Both vaccines have shown approximately 95% efficacy in preventing symptomatic COVID-19 infections in phase 3 trials. Additional phase 3 trials of vaccines manufactured by Janssen (J&J) and AstraZeneca [vectored vaccines] are underway; with rapidly rising case counts in the US and elsewhere results from these trials should be available very soon. All of these trials compare the incidence of symptomatic infection among vaccine recipients with that among a placebo control group. [we await further results to see if they also prevent infection] The rapid and successful development of these vaccines represents a major scientific triumph. The question raised by this author now that we have two highly efficacious vaccines, is it ethical to continue placebo-controlled trials? They suggest a few strategies to address this important question.

One strategy depends on defining if there is an established immunologic association of efficacy such as levels of antibodies to vaccine antigens. In that case we could administer experimental vaccines to groups of participants and to then base decisions to authorize or approve those vaccines on surrogate measures. However, adequate evidence is not yet available to define what constitutes a validated surrogate marker of vaccine efficacy. In addition, evaluating efficacy alone would not adequately address determining safety.

A second strategy would be to conduct head-to-head randomized trials comparing a novel vaccine candidate with a vaccine that has previously received EUA or full licensure. Such trials could use noninferiority designs that could declare the novel vaccine effective if the incidence of symptomatic COVID-19 infection or other primary end point is not higher by some specified margin than incidence in the comparator group. These trials also could facilitate direct comparisons of safety between the novel vaccine and its established comparator; such comparisons are of particular importance given widespread public concerns about safety. Conducting such a trial would hinge on cooperation between the manufacturer of the novel vaccine and the manufacturer of the established vaccine, which poses both logistical and financial challenges.

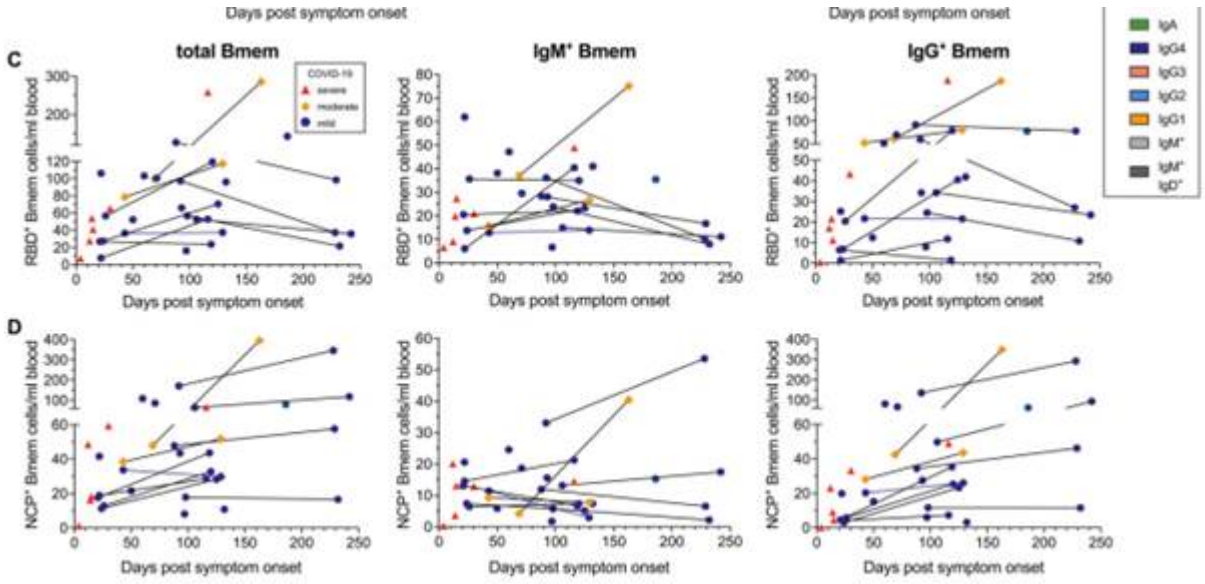
The third strategy would be to initiate a multigroup platform trial that tests authorized or approved vaccines alongside investigational vaccine candidates. This would allow for direct comparisons of efficacy and safety among established as well as investigational vaccines. Investigational vaccine groups would be added to the platform as soon as the candidate vaccines met safety and immunogenicity benchmarks in smaller, earlier phase 2 trials. [Operation Warp Speed could be that platform] Based on interim safety and efficacy analyses, candidate vaccines would be dropped from the platform and their development discontinued using an adaptive design if they proved to have inferior efficacy or significant safety concerns as measured against benchmark comparators. Conversely, once reassuring initial safety and efficacy data were available, enrollment in novel vaccine groups could be extended to children and other populations that have either been excluded or underrepresented from current phase 3 trials.

Comment: The authors make the point that the last approach (platform-trial approach) has several advantages compared to the other two approaches. First, it could provide an efficient mechanism for evaluating novel vaccines in the setting of available alternatives and ethical reservations about continuing RCTs. Second, it could allow for comparative safety and efficacy evaluation not only of investigational vaccines but also of those that already have EUA. Third, particularly while access to authorized vaccines is limited, offering priority access to individuals willing to enroll in the platform trial would contribute to the generation of critical public health data more rapidly. There clearly is a need to develop additional vaccines as alternatives to the current vaccines. I do believe the adaptive platform offers an opportunity to rapidly assess safety and efficacy while simultaneously allowing continued study of current vaccines against SARS-CoV-2.

Rapid Generation of Durable B Cell Memory to SARS-CoV-2 Spike and Nucleocapsid Proteins in COVID-19 and Convalescence

Science Immunol published online December 22, 2020
DOI: 10.1126/sciimmunol.abf8891

The investigators developed fluorescently labeled tetramers of the spike receptor binding domain (RBD) and nucleocapsid protein (NCP) to determine the longevity and immunophenotype of SARS-CoV-2-specific Bmem cells in COVID-19 patients. A total of 36 blood samples were obtained from 25 COVID-19 patients between 4- and 242-days post-symptom onset including 11 paired samples. While serum IgG to RBD and NCP was identified in all patients, antibody levels began declining at 20 days post-symptom onset. RBD- and NCP-specific Bmem cells predominantly expressed IgM+ or IgG1+ and continued to rise until 150 days. RBDspecific IgG+ Bmem were predominantly CD27+, and numbers significantly correlated with circulating follicular helper T cell numbers. Thus, the SARS-CoV-2 antibody response contracts in convalescence with persistence of RBD- and NCP-specific Bmem cells. Flow cytometric detection of SARS-CoV-2-specific Bmem cells enables detection of long-term immune memory following infection or vaccination for COVID-19.



Comment: This publication demonstrated that specific memory B cells, "remember" infection by the virus, and if challenged again, through re-exposure to the virus, triggers a protective immune response through rapid production of protective antibodies. As with other studies—looking only at the antibody response—the researchers found that antibodies against the virus started to drop off after 20 days post infection. More importantly all patients continued to have memory B cells that recognized one of two components of the SARS-CoV-2 virus, the spike and nucleocapsid proteins. These results are important because they show, definitively, that patients infected with the COVID-19 virus do in fact retain immunity against the virus. The question remains will we see the same effect from vaccination. Nonetheless this is an exciting development.

American College of Allergy, Asthma, and Immunology (ACAAI) Updated Guidance on Risk of Allergic Reactions to mRNA Vaccines
published online December 22, 2020

- Patients experiencing a severe allergic reaction after getting the first shot should not receive the second shot.
- The mRNA COVID-19 vaccines should be administered in a healthcare setting where anaphylaxis can be treated. All individuals must be observed for at least 15 to 30 minutes after injection to monitor for any adverse reaction. All anaphylactic reactions should be managed immediately with epinephrine as first-line treatment.
- The mRNA COVID-19 vaccines should not be administered to individuals with a known history of a severe allergic reaction to any component of the vaccine. Although the specific vaccine component causing the anaphylaxis has not been identified, polyethylene glycol is one of its ingredients and has been known to cause anaphylaxis.
- Data related to risk in individuals with a history of allergic reactions to previous vaccinations and/or mast cell activation syndrome/idiopathic anaphylaxis is very limited and evolving. A decision to receive either of the mRNA COVID-19 vaccines that are currently approved for Emergency Use Authorization by the FDA should be undertaken by the individual, along with their physician or other provider administering the vaccine using their professional judgment balancing the benefits and risks associated with taking the vaccine.

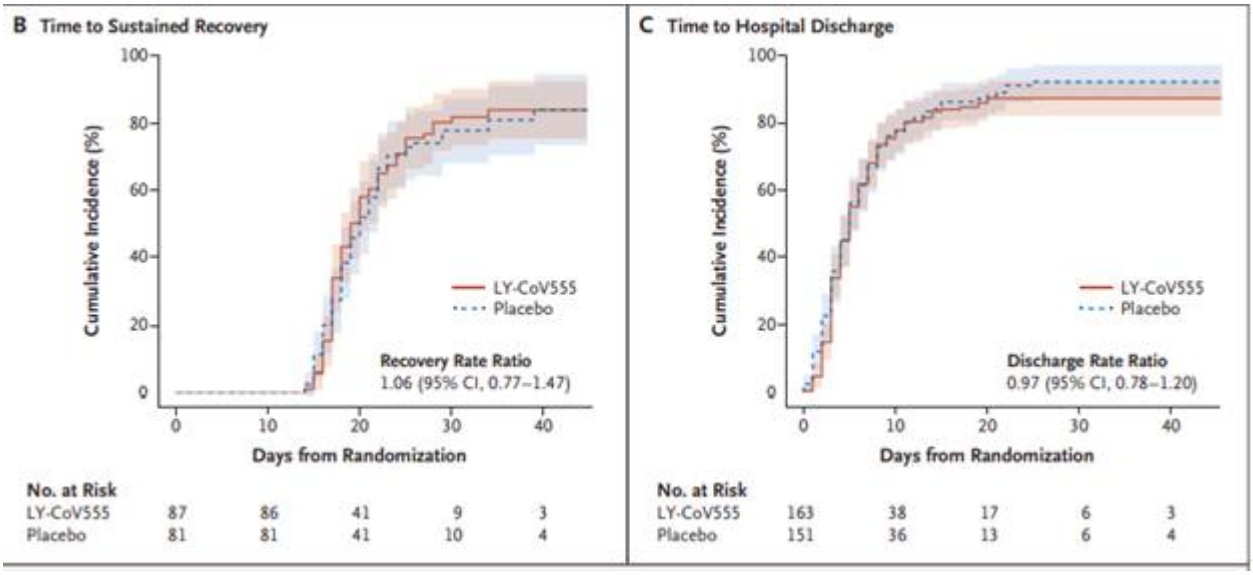
- People with common allergies to medications, foods, inhalants, insects and latex are no more likely than the general public to have an allergic reaction to the mRNA COVID-19 vaccines. Those patients should be informed of the benefits of the vaccine versus its risks.
- The mRNA COVID-19 vaccines are not live vaccines and can be administered to immunocompromised patients. Physicians and other providers should inform such immunocompromised patients of the possibility of a diminished immune response to the vaccines.

Comment: ACAAI's recommendations are in line with guidance issued by the CDC. Scientists are looking at PEG as the likely culprit.

A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19
N Engl J Med published online December 22, 2020
DOI: 10.1056/NEJMoa2033130
The investigators randomly assigned hospitalized patients who had Covid-19 without end-organ failure in a 1:1 ratio to receive either LY-CoV555 or matching placebo. In addition, all the patients received high-quality supportive care as background therapy, including the antiviral drug remdesivir and, when indicated, supplemental oxygen and steroids. LY-CoV555 (at a dose of 7000 mg) or placebo was administered as a single intravenous infusion over a 1-hour period. The primary outcome was a sustained recovery during a 90-day period, as assessed in a time-to-event analysis. An interim futility assessment was performed on the basis of a seven-category ordinal scale for pulmonary function on day 5.

On October 26, 2020, the data and safety monitoring board recommended stopping enrollment for futility after 314 patients (163 in the LY-CoV555 group and 151 in the placebo group) had undergone randomization and infusion. The sample size of more than 300 patients for the early futility assessment provided high statistical power for determining whether recruitment should continue to the full sample size of 1000 patients. At day 5, a total of 81 patients (50%) in the LY-CoV555 group and 81 (54%) in the placebo group were in one of the two most favorable categories of the pulmonary outcome. Across the seven categories, the odds ratio of being in a more favorable category in the LY-CoV555 group than in the placebo group was 0.85 (95% confidence interval [CI], 0.56 to 1.29; *P* = 0.45). Meanwhile, 90 patients (55%) who received LY-CoV555 and 85 patients (56%) who received placebo had been discharged from the hospital by day 5. Most of the patients (95%) were also receiving remdesivir. The majority of patients had hypoxemia and were placed on steroids.

Among 167 patients who were followed for at least 28 days or who died within this time frame, 71 of 87 patients (82%) in the LY-CoV555 group and 64 of 81 patients (79%) in the placebo group had a sustained recovery (rate ratio, 1.06; 95% CI, 0.77-1.47). In the overall cohort, hospital discharge occurred in 143 (88%) patients in the LY-CoV555 group and 136 patients (90%) in the placebo group (rate ratio, 0.97; 95% CI, 0.78-1.20). Through day 5, the percentage of patients with the primary safety outcome (a composite of death, serious adverse events, or clinical grade 3 or 4 adverse events) was similar in the LY-CoV555 group and the placebo group (19% and 14%, respectively; odds ratio, 1.56; 95% CI, 0.78-3.10; *P* = 0.20).



Comment: Bottom line, monoclonal antibody LY-CoV555, when coadministered with remdesivir, did not demonstrate efficacy among hospitalized patients who had COVID-19 without end-organ failure. Although the trial was not adequately powered for robust subgroup analyses, they identified no evidence that the effect of LY-CoV555 on the ordinal outcomes at day 5 differed according to any subgroup, including the baseline pulmonary ordinal category and the duration of symptoms before enrollment. This design was under the assumption that the greatest effect of an antiviral agent would be observed in patients with less severe illness. [this has been true for RDV] The authors state the reasons for the lack of benefit for LY-CoV555 in this trial are unknown and may include slow or ineffective penetration of the antibody into infected tissue, minimal intrinsic potency, rapid selection of escape mutants no longer neutralized by the agent, and harmful effects of the antibody. It has been hypothesized that such harmful effects (which have been described as “antibody-dependent enhancement”) could theoretically be associated with increased viral replication or exaggerated inflammation. The results in this trial appear different from the outpatient trials where monoclonals are given early in high-risk patients with minimum symptoms decrease progression and hospitalization in preliminary studies. Another explanation may be that given earlier before initiation of the inflammatory response may be the optimal time to administer. Additional research will be needed to help sort out some of these questions.

Variation in US Hospital Mortality Rates for Patients Admitted With COVID-19 During the First 6 Months of the Pandemic

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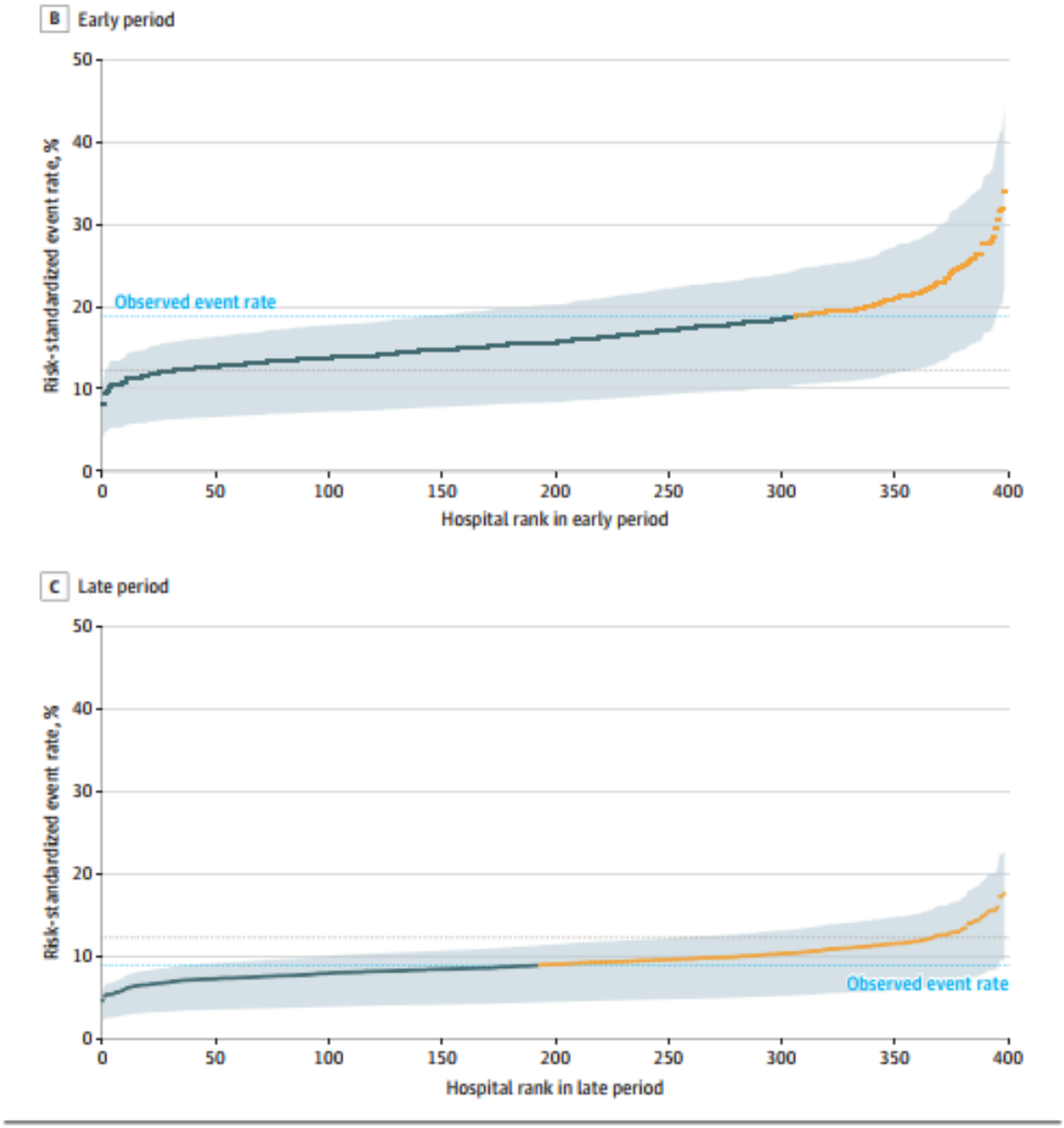
Doi:10.1001/jamainternmed.2020.81933

The authors assessed 38,517 adults who were admitted with COVID-19 to 955 US hospitals from January 1, 2020, to June 30, 2020, and a subset of 27,801 adults (72.2%) who were admitted to 398 of these hospitals that treated at least 10 patients with COVID-19 during 2 periods (January 1 to April 30, 2020, and May 1 to June 30, 2020). The goal was to identify variation in COVID-19 mortality rates and how those rates have changed after the first months of the pandemic using administrative claims.

They found that a hospital’s risk-standardized event rate (a composite of hospital mortality or referral to hospice) because of COVID-19 had significantly decreased. Specifically, the risk-adjusted mortality decreased from 16.56% to 9.29% in the early period of this study (January through April 2020) compared

with the later period (May through June 2020). The authors found that mortality rates were higher when the community prevalence of COVID-19 was higher. One likely reason for this finding is that hospitals may not perform as well when they are overwhelmed.



Comment: Since the first wave, physicians have learned a great deal about the best ways to treat this infection. Steroids have been shown to decrease mortality in patients with respiratory failure. Remdesivir may shorten hospitalizations of patients with serious illness especially if given early. Anticoagulation and prone positioning have helped certain patients. Using noninvasive ventilation and high-flow oxygen therapy have spared a subset of patients from the harms of intubation, such as ventilator induced lung injury. Although the care of patients with COVID-19 has undoubtedly improved,

there may be other factors of why mortality improvement. Patients who were admitted to the hospital during the earlier period likely had greater illness severity in ways that cannot easily be adjusted for. Patients with frailty, especially those in nursing homes, were disproportionately represented during the first wave of the epidemic. They were much better protected from infection in later months and represented a smaller proportion of patients entering the hospital during the second wave. While COVID-19 cases have also tended to occur among younger persons in the second wave, the mortality models did adjust for age. Another possibility of why mortality has decreased is the possibility that larger infective doses of COVID-19 may lead to more severe illness than smaller inoculums. In the beginning of the first wave, there was very limited use of masks and social distancing. As 2020 progressed, more people wore masks and observed social distancing, which may have decreased the infecting inoculum. However, the hypothesis between the inoculum and severity needs to be confirmed. The finding by the authors that a risk factor for a hospital's standardized event rate was community prevalence of COVID-19 and subsequent increased hospitalization is an important observation. As hospitals were stress adequate staffing and converting units to COVID-19 units including ICUs need to be examined further. Staffing ratios and percent agency nurses should be examined. There is reason, however, to celebrate this medical progress, especially as we rollout vaccines and monoclonal antibodies, as well as maintaining increased masking and social distancing.