Given the FDA panel meeting today and several key publications I wanted to make sure you had this edition in your inboxes when you wake up tomorrow.

COVID-19 News

The big news- members of VRBPAC voted 17-4 in favor of the Pfizer vaccine, with one panelist abstaining. The agency is expected to quickly grant the special clearance to Pfizer's vaccine. There was a discussion about how Pfizer could address concerns about the potential for allergic reactions to the vaccine, given the news of two healthcare workers who experienced allergic reactions after having the vaccine but who have since recovered. Members of the panel urged the FDA and Pfizer to investigate any connection between reaction to the vaccine and known allergies. Canadian health regulators on December 9 announced their nation's conditional approval of Pfizer's vaccine for people ages 16 and older.

Literature Review

Today in this section I am putting my comments on the initial paper Clinical Outcomes of A COVID-19 Vaccine: Implementation Over Efficacy first which in many ways is more important than the publication in the NEJM published online today on the Pfizer vaccine. The third paper reminds us that delay in cancer diagnosis and treatment has impact on survival. We have seen how COVID has impacted screening and treatment. The last paper uses a very large database to report on COVID-19 complications.

Have a wonderful weekend

Ed

Clinical Outcomes of A COVID-19 Vaccine: Implementation Over Efficacy
Health Affairs published online November 2020
doi: 10.1377/ hlthaff.2020.02054

Comment: This is a very timely article. One of the authors is Dr. Rochelle Walensky who will be the next CDC director. The study found that the most important factor in a given vaccine's success is not necessarily how well that vaccine works. In fact, it is how quickly and strategically the vaccine is distributed across the country, how well received it is and whether people continue to abide by other recommendations, like mask wearing and physical distancing. Recent surveys indicate only ~50% of the population say they are willing to take the vaccine! The US has invested billions of dollars into vaccine development, but much less into actually getting people vaccinated. The Association of State and Territorial Health Officials has said that its members need at least $8.4 billion to develop and run a successful COVID vaccination program. So far, the federal government has allocated less than $1 billion. Moncef Slaoui, the head of Operation Warp Speed, has said that 100 million Americans could be immunized against COVID-19 in the next 100 days: 20 million in December 30 million in January and 50 million February. That timeline may indeed be possible, but I am skeptical. To complicate matters, nearly half do not even have data management programs comprehensive or reliable enough to keep track of who gets inoculated and when (especially given the Pfizer, Moderna and Astra Zeneca vaccines involve two doses). Less than half say they are prepared to identify and tally the number of people in their state

who will be eligible for the very first shots, and few — between half and one-third — have plans to combat vaccine misinformation or reach racial minorities and other vulnerable populations!

We must make clear that it will be crucial to wear face masks and practice physical distancing for some time to come. [~May 2021] We should also be clear about the difference between expected and fictional risks. While the vaccine appears to be safe in adults of any race or ethnicity, they have not yet been tested in children, pregnant women, or nursing mothers.

My last thought: While both Pfizer and Moderna vaccines have side effects like high fever and nausea, none of them can give a person Covid-19. The results from Pfizer and Moderna support significant public optimism regarding the potential value of these two vaccines in reducing the burden of COVID-19.

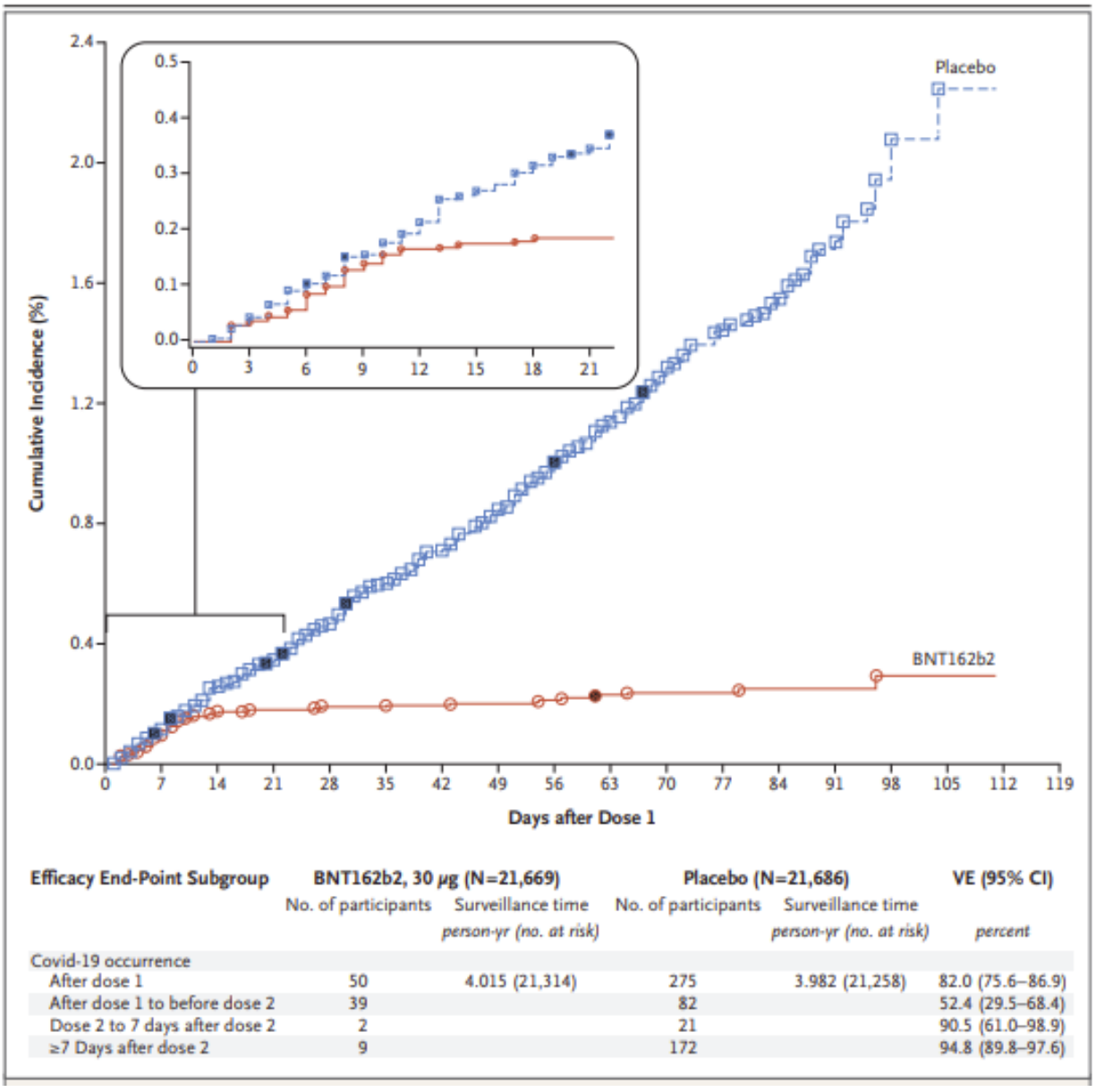
Review

The authors examined how different definitions and thresholds of vaccine efficacy, coupled with different levels of implementation effectiveness and background epidemic severity, translate into outcomes including cumulative infections, hospitalizations, and deaths. Using a mathematical simulation of vaccination they found that factors related to implementation will contribute more to the success of vaccination programs than a vaccine's efficacy as determined in clinical trials. The benefits of a vaccine will decline substantially in the event of manufacturing or deployment delays, significant vaccine hesitancy, or greater epidemic severity. An example, the effects of any COVID-19 vaccine will be highly dependent on the effective reproductive number of the virus (RO) at the time a vaccine is deployed. When RO is comparatively low (1.5)—indicating that viral circulation is being controlled through these non-pharmaceutical measures—vaccines with low efficacy as low as 25% are capable of producing larger reductions in the fraction of infections and deaths than vaccines with much higher efficacy (75%) introduced at times when RO is significantly higher (2.1). Their findings demonstrate the urgent need for health officials to invest greater financial resources and attention to vaccine production and distribution programs, to redouble efforts to promote public confidence in COVID-19 vaccines, and to encourage continued adherence to other mitigation approaches, even after a vaccine becomes available.

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine
N Engl J Med published online December 10, 2020
This is the Pfizer placebo-controlled, observer-blinded, pivotal efficacy trial. Participants were randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose). The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site,

fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

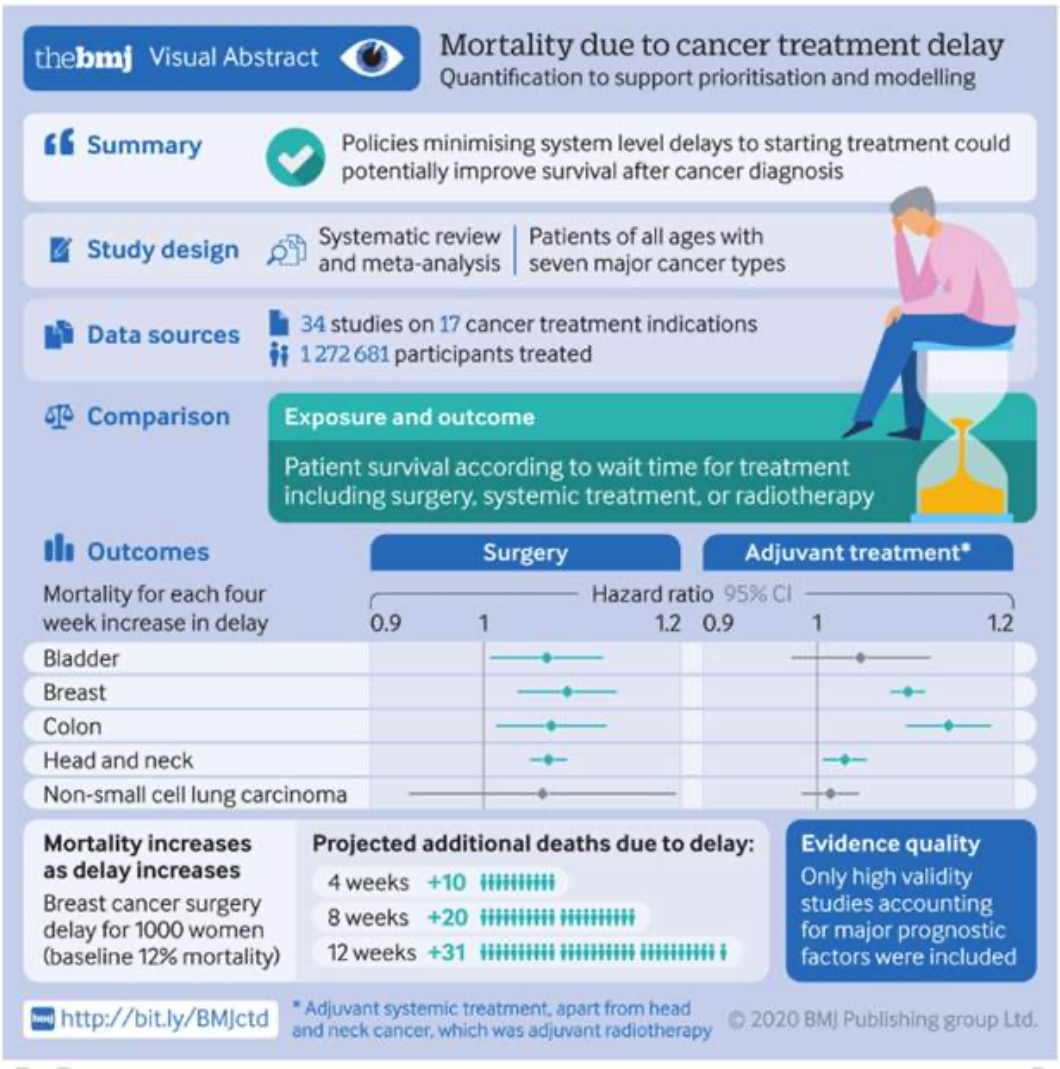


Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Comment: This publication does not address the prevention of COVID-19 in other populations, such as younger adolescents, children, and pregnant women. The cumulative incidence of COVID-19 cases over time among placebo and vaccine recipients begins to diverge by 12 days after the first dose, 7 days after the estimated median viral incubation period of 5 days, 10 indicating the early onset of a partially protective effect of immunization. The study, however, was not designed to assess the efficacy of a single-dose regimen. Although the vaccine can be stored for up to 5 days at standard refrigerator temperatures once ready for use, very cold temperatures are required for shipping and longer storage.

Mortality Due to Cancer Treatment Delay: Systematic Review and Meta-Analysis
BMJ published online November 4, 2020
doi.org/10.1136/bmj.m4087
This review included 34 studies for 17 indications (n=1 272 681 patients). No high validity data were found for five of the radiotherapy indications or for cervical cancer surgery. The association between delay and increased mortality was significant (P<0.05) for 13 of 17 indications. Surgery findings were consistent, with a mortality risk for each four-week delay of 1.06-1.08 (e.g., colectomy 1.06, 95% confidence interval 1.01 to 1.12; breast surgery 1.08, 1.03 to 1.13). Estimates for systemic treatment varied (hazard ratio range 1.01-1.28). Radiotherapy estimates were for radical radiotherapy for head and neck cancer (hazard ratio 1.09, 95% confidence interval 1.05 to 1.14), adjuvant radiotherapy after breast conserving surgery (0.98, 0.88 to 1.09), and cervix cancer adjuvant radiotherapy (1.23, 1.00 to 1.50).

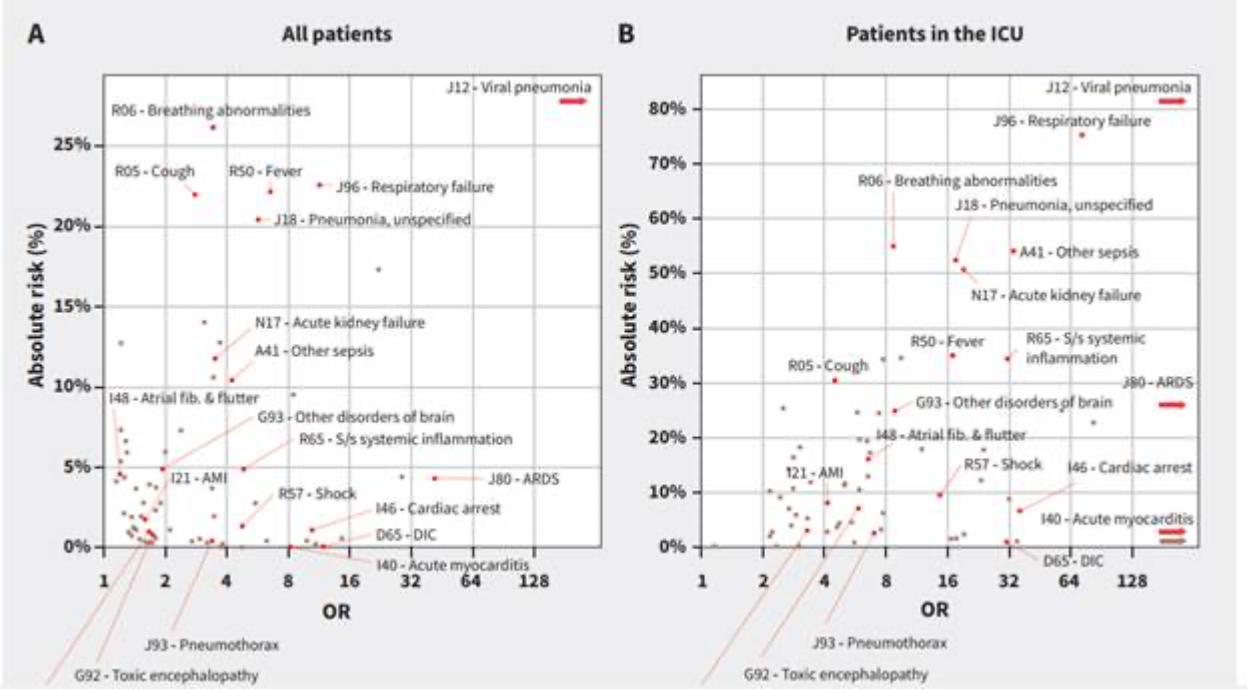
Cancer treatment delay is a problem in health systems worldwide. The impact of delay on mortality can now be quantified for prioritization and modelling. Even a four-week delay of cancer treatment is associated with increased mortality across surgical, systemic treatment, and radiotherapy indications for seven cancers.



Comment: The pandemic forced shutdowns and slowdowns throughout the country, another major risk to human health is delay in diagnosis and treatment of many cancers. In the early months of the pandemic, millions of people heeded warnings and fears about contracting SARS-CoV-2 and avoided, or could not even get, in-person medical visits and cancer screenings, allowing newly developed cancers to escape detection and perhaps progress. Cancers cannot be treated unless they are detected. The BMJ reviewed above found for every four-week delay in cancer detection and treatment, the risk of death from cancer rises nearly 10 percent, on average. The study found increased mortality following delays in treatment for 13 of 17 cancer types. Following a four-week delay in surgery for breast cancer, the death rate increased by 8 percent; for colorectal cancer, it rose 6 percent. Now with the COVID surging again around the country, many medical centers may be forced to again limit elective procedures, those not deemed urgent. I believe cancer treatment is not elective — it is urgent and should not be delayed. Last April in the Daily Briefing during the pause in elective surgery here in Houston, I shared my story. A year prior in April 2019 I was diagnosed with prostate cancer (one area with a high Gleason score) and scheduled for a radical prostatectomy on May 2, 2019. If it were April 2020, my surgery would have been delayed. I personally know of cases just like mine that were postponed in April/May 2020. Learning that I had cancer was stressful enough. Imagine getting the diagnosis during the pandemic or worse yet postponing diagnostic studies, when if caught early could be potentially curable. This is just another medical consequence of the pandemic which impacts mortality and quality of life.

Diagnosis-Wide Analysis of COVID-19 Complications: An Exposure-Crossover Study
CMAJ published online December 8, 2020
doi: 10.1503/cmaj.201686
The authors set out to study all possible complications of COVID-19 to confirm previously reported complications and to identify potential complications not yet known. Using United States health claims data, we compared the frequency of all International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis codes occurring before and after the onset of the COVID-19 pandemic in an exposure crossover design. We included patients who received a diagnosis of COVID-19 between Mar. 1, 2020, and Apr. 30, 2020, and computed risk estimates and odds ratios (ORs) of association with COVID-19 for every ICD-10-CM diagnosis code.

Disorders showing both strong association with COVID-19 and high absolute risk included viral pneumonia (OR 177.63, 95% confidence interval [CI] 147.19– 214.37, absolute risk 27.6%), respiratory failure (OR 11.36, 95% CI 10.74–12.02, absolute risk 22.6%), acute kidney failure (OR 3.50, 95% CI 3.34–3.68, absolute risk 11.8%) and sepsis (OR 4.23, 95% CI 4.01–4.46, absolute risk 10.4%). Disorders showing strong associations with COVID-19, but low absolute risk included myocarditis (OR 8.17, 95% CI 3.58–18.62, absolute risk 0.1%), disseminated intravascular coagulation (OR 11.83, 95% CI 5.26–26.62, absolute risk 0.1%) and pneumothorax (OR 3.38, 95% CI 2.68– 4.26, absolute risk 0.4%).



Comments: In this study of more than 70,000 individuals who received a diagnosis of COVID-19, the authors found that COVID-19 was associated with a broad range of complications. [not unexpected] The more common complications that they identified — including viral pneumonia, respiratory failure, acute kidney failure and sepsis — were expected. They also identified fewer common complications, previously described in case series or small studies, such as DIC, pneumothorax, myocarditis and rhabdomyolysis. Although COVID-19 has been widely reported to increase the risk of stroke, this was not observed in this study. Multisystem inflammatory syndrome in children could not be directly assessed because it has no specific ICD-10-CM code, although no association was noted for the similar condition Kawasaki disease, as evaluated under the code M30.3. During the initial stages of COVID-19 treatment, many chronic conditions and less severe conditions may not have been considered priorities for care and were therefore less likely to be captured in a claim or persons did not seek care at all. This likely explains the fact that, although they observed strong associations with COVID-19 for complications such as cough and disturbances of smell or taste, their overall risk estimates (22.0% and 0.6%, respectively, in the overall population) were substantially lower than has been reported (79% and 65%, respectively). In contrast, risk estimates for severe, overt disorders are more likely to reflect actual risk, as they are more likely to be treated or brought to the attention of a care provider, and thus are more consistently captured in a medical claim. They estimated only the risk of newly diagnosed disease and did not estimate the risk of events where a pre-existing condition existed. Moreover, their estimates reflect only the risk among patients who seek medical care for COVID-19. A limitation of claims data is that they identified COVID-19 cases using diagnosis codes and depends on documentation. Although the codes we used to identify patients are intended for confirmed cases of COVID, it is possible that some patients were misclassified. The care settings reflected in this database were not exclusively academic medical centers, where more severe cases of COVID-19 may be treated; as such, their results may have missed some of the more severe cases.