TGIF! 😊

Today I focus on vaccine efficacy and variants in both the COVID-19 News and Journal Review.

Under News, Pfizer has applied to the FDA for full approval. The WHO has established threat levels for variants. Not reported, but Canada has approved the Pfizer vaccine in children ages 12-15 – vaccinations to start Monday. The US FDA should act on Pfizer's request hopefully this coming week.

Under Journal Review I start with an article on the efficacy on the Novavax vaccine against the South African variant B.1.351. The next article found vaccination was 87 to 89.5 percent effective at preventing infection with B.1.1.7 among people who were at least two weeks past their second shot. It was 72.1 percent to 75 percent effective at preventing infection with B.1.351. The next article found that the vaccine was more than 95 percent effective at protecting against SARS-CoV-2, hospitalization, and death among fully vaccinated people 16 and older. The last article looks at reinfection in patients who have recovered from natural infection with SARS-CoV-2.

In the United States, experts now believe that attaining herd immunity is unlikely because of the spread of variants and hesitancy among some people in the country to be vaccinated. On Monday I will comment on the potential on failing to achieve herd immunity.

Have a great weekend

Ed

COVID-19 News

Pfizer and BioNTech Apply for Full U.S. Approval for their Covid Vaccine
Pfizer has become the first company to apply to the FDA for full approval of their Covid-19 vaccine for use in people 16 and older. The vaccine is currently being administered to adults in America under an emergency use authorization granted in December 2020. The approval process is likely to take months. Pfizer has submitted clinical data, which includes six months of information on the vaccine's safety and efficacy, to the FDA.

CDC, WHO Establish New Threat Levels for COVID-19 Variants

Known genetic variants of SARS-CoV-2

Variant	First identified in	More contagious?	Ability to evade vaccine	CDC/WHO classification
B.1.1.7	United Kingdom	Yes	Minimal	Concern
B.1.351	South Africa	Yes	Moderate	Concern
P.1	Brazil	Yes	Moderate	Concern
B.1.526	New York	Unknown	Potentially	Interest
B.1.525	New York	Unknown	Potentially	Interest
P.2	Brazil	Unknown	Potentially	Interest
B.1.427	California	Yes	Moderate	Concern
B.1.429	California	Yes	Moderate	Concern
P.3	Philippines	Unknown	Unknown	Under investigation
A.23.1 with E484K	England	Unknown	Unknown	Under investigation
B.1.1.7 with E484K	England	Unknown	Unknown	Under investigation
B.1.525	England	Unknown	Unknown	Under investigation
B1.1.318	Unknown	Unknown	Unknown	Under investigation
B1.324.1 with E383K	Unknown	Unknown	Unknown	Under investigation
B.1.111 with E383K and 429S	Columbia	Unknown	Unknown	Unknown

Sources: Rappler.com, CDC.gov, Health.com, WHO Weekly Epidemiological Update, Public Health England

- A **variant of interest** has caused discrete clusters of infections in the United States or in other countries or seems to be driving a surge in cases. It also has gene changes that suggest it might be more contagious or that may help it to escape immunity conferred by natural infection or vaccination. Therapeutics and tests may not work as well against it. The CDC is watching three of these.
- A **variant of concern** has been proven through scientific research to be more contagious or to cause more severe disease. It may also reduce the effectiveness of therapeutics and vaccines. People who have previously had COVID-19 may become reinfected by the new strain. The CDC is tracking five of these.
- A **variant of high consequence** causes more severe disease and greater numbers of hospitalizations. It has also been shown to defeat medical countermeasures, such as vaccines, antiviral drugs, and monoclonal antibodies. So far, none of the variants meets this definition.

Comment: So far, the CDC is tracking five variants of concern: the B.1.1.7 variant, first identified in the United Kingdom; the P.1 variant, first detected in Japan and Brazil; the B.1.351 variant, first reported in South Africa; and the B.1.427 and B.1.429 variants, which have been spreading in California.

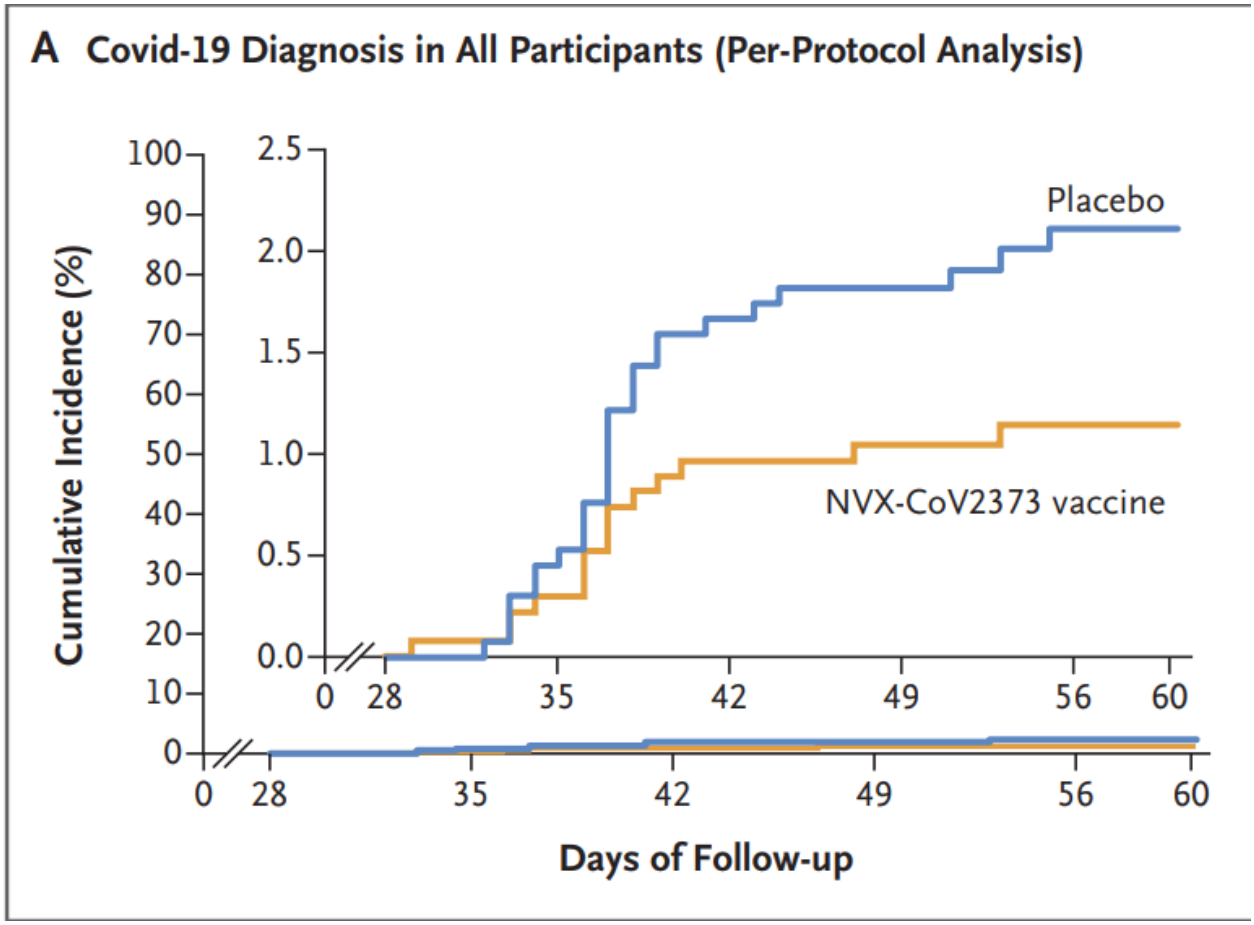
Surveillance of these variants is currently limited. The United States surveillance of the virus is lower compared with other countries, like the United Kingdom, but funding and capacity are increasing. The B.1.1.7 variant is at least 50% more contagious than the wild type. It has caused major COVID-19 surges in the United Kingdom, Israel, US, and Europe. Labs have detected 142 cases of the B.1.351 variant. These come from 25 states. There have been at least 27 cases of the P.1 variant in at least 12 states.

Studies have shown that the current vaccines are less effective against these two variants. They are also not as vulnerable to some of the monoclonal antibody therapies that have been developed. B.1.1.7, B.1.351 appear to be about 50% more contagious. The B.1.427 and B.1.429 variants appear to be about 20% more contagious than earlier versions of the virus. They may also slightly reduce the effectiveness of vaccines and therapeutics. The immunity generated by the vaccines is so strong, though, that this reduction is not expected to keep them from being effective at preventing severe infections or reducing transmission of the virus.

Journal Review

Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant
N Engl J Med published online May 5, 2021
DOI: 10.1056/NEJMoa2103055
This is a phase 2a-b trial in South Africa. They randomly assigned HIV-negative adults between the ages of 18 and 84 years or medically stable HIV-positive participants between the ages of 18 and 64 years in a 1:1 ratio to receive two doses of either the NVX-CoV2373 nanoparticle vaccine (5 µg of recombinant spike protein with 50 µg of Matrix-M1 adjuvant) or placebo. The primary end points were safety and vaccine efficacy against laboratory-confirmed symptomatic Covid-19 at 7 days or more after the second dose among participant without previous SARS-CoV-2 infection.

Among 2684 baseline seronegative participants (94% HIV-negative and 6% HIV-positive), predominantly mild-to-moderate Covid-19 developed in 15 participants in the vaccine group and in 29 in the placebo group (vaccine efficacy, 49.4%; 95% confidence interval [CI], 6.1 to 72.8). Vaccine efficacy among HIV-negative participants was 60.1% (95% CI, 19.9 to 80.1). Of 41 sequenced isolates, 38 (92.7%) were the B.1.351 variant. Post hoc vaccine efficacy against B.1.351 was 51.0% (95% CI, -0.6 to 76.2) among the HIV-negative participants. Preliminary local and systemic reactogenicity events were more common in the vaccine group; serious adverse events were rare in both groups. The found that previous infection with first-wave prototype-like, pre-B.1.351 viruses did not appear to reduce the risk of Covid-19 due to subsequent infection with B.1.351 variants among placebo recipients during the initial 2 months of follow-up.



Comment: A significant weakness of this trial was at the time of analysis, trial investigators had captured almost exclusively mild-to-moderate Covid-19 end points in a predominantly young, healthy population; consequently, but they have not yet been able to report on vaccine efficacy against severe Covid-19. Most large trials of vaccine efficacy against Covid-19 have reported notably higher vaccine efficacy against severe disease than against mild-to-moderate disease. [See next article]

Effectiveness of the BNT162b2 Covid-19 Vaccine Against the B.1.1.7 and B.1.351 Variants
N Engl J Med published online May 5, 2021
DOI: 10.1056/NEJMc2104974
Qatar launched a mass immunization campaign with the Pfizer vaccine on December 21, 2020. As of March 31, 2021, a total of 385,853 persons had received at least one vaccine dose and 265,410 had completed the two doses. Vaccination rollout occurred as Qatar was undergoing its second and third waves of SARS-CoV-2 infection, which were triggered by expansion of the B.1.1.7 variant (starting in mid-January 2021) and the B.1.351 variant (starting in mid-February 2021). The B.1.1.7 wave peaked during the first week of March, and the rapid expansion of B.1.351 started in mid-March and continues to the present day. Viral genome sequencing conducted from February 23 through March 18 indicated that 50.0% of cases of Covid-19 in Qatar were caused by B.1.351 and 44.5% were caused by B.1.1.7. Nearly all cases in which virus was sequenced after March 7 were caused by either B.1.351 or B.1.1.7.

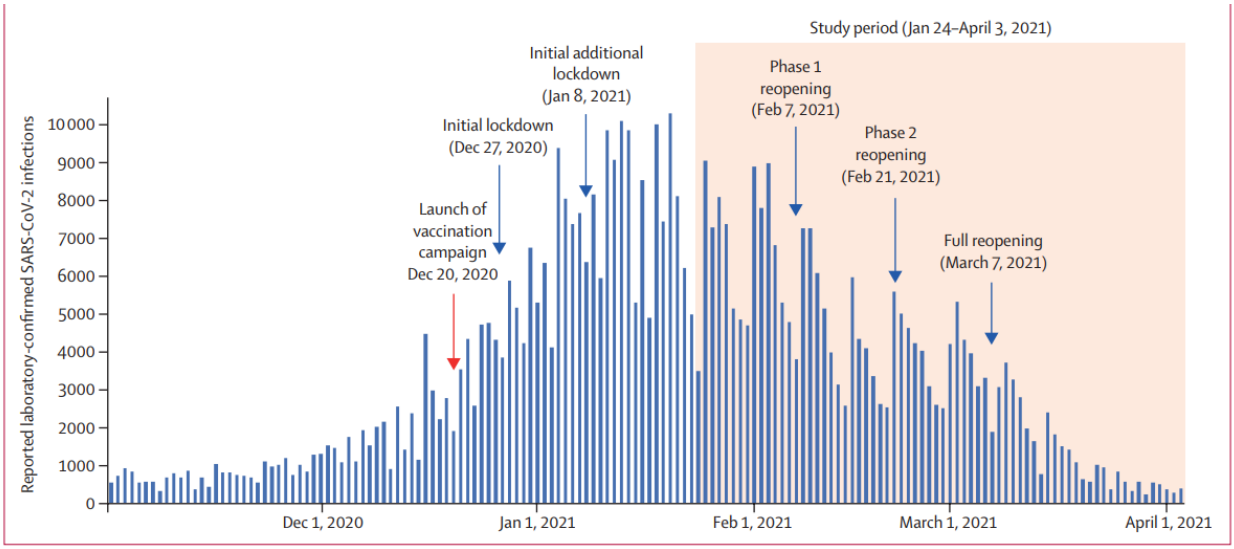
The estimated effectiveness of the vaccine against any documented infection with the B.1.1.7 variant was 89.5% (95% confidence interval [CI], 85.9 to 92.3) at 14 or more days after the second dose. The

effectiveness against any documented infection with the B.1.351 variant was 75.0% (95% CI, 70.5 to 78.9). Vaccine effectiveness against severe, critical, or fatal disease due to infection with any SARS-CoV-2 (B.1.1.7 and B.1.351 variants being predominant) was very high, at 97.4% (95% CI, 92.2 to 99.5).

Comment: Consistent with other studies, vaccine effectiveness against the B.1.351 variant was approximately 20 percentage points lower than the effectiveness (>90%) reported against wild type or B.1.1.7, however, vaccine effectiveness is still quite high against severe disease and death. In Qatar, as of March 31, breakthrough infections have been recorded in 6689 persons who had received one dose of the vaccine and in 1616 persons who had received two doses. Seven deaths from Covid-19 have been also recorded among vaccinated persons. Despite reduced effectiveness against infection with the B.1.351 variant, protection against the most severe forms of infection (i.e., those resulting in hospitalization or death), was still very robust, at greater than 90%.

Impact and Effectiveness of mRNA BNT162b2 Vaccine Against SARS-CoV-2 Infections and COVID-19 Cases, Hospitalisations, and Deaths Following a Nationwide Vaccination Campaign in Israel: An Observational Study Using National Surveillance Data
Lancet published online May 5, 2021
doi.org/10.1016/ S0140-6736(21)00947-8
The investigators used national surveillance data from the first 4 months of the nationwide vaccination campaign to ascertain incident cases of laboratory-confirmed SARS-CoV-2 infections and outcomes, as well as vaccine uptake in residents of Israel aged 16 years and older. Vaccine effectiveness against SARS-CoV-2 outcomes (asymptomatic infection, symptomatic infection, and COVID-19-related hospitalization, severe or critical hospitalization, and death) was calculated on the basis of incidence rates in fully vaccinated individuals (defined as those for whom 7 days had passed since receiving the second dose of vaccine) compared with rates in unvaccinated individuals (who had not received any doses of the vaccine). The proportion of spike gene target failures on PCR test among a nationwide convenience-sample of SARS-CoV-2-positive specimens was used to estimate the prevalence of the B.1.1.7 variant.

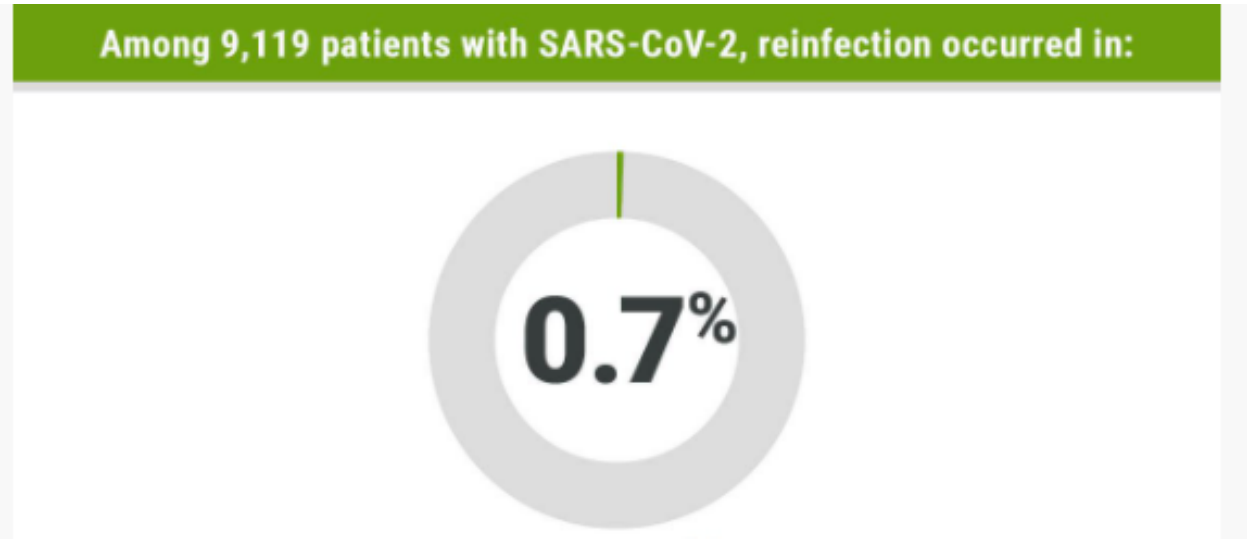
By April 3, 2021, 4,714,932 (72·1%) of 6,538,911 people aged 16 years and older were fully vaccinated with two doses of BNT162b2. Adjusted estimates of vaccine effectiveness at 7 days or longer after the second dose were 95·3% (95% CI 94·9–95·7; incidence rate 91·5 per 100,000 person-days in unvaccinated vs 3·1 per 100,000 person-days in fully vaccinated individuals) against SARS-CoV-2 infection, 91·5% (90·7–92·2; 40·9 vs 1·8 per 100,000 person-days) against asymptomatic SARS-CoV-2 infection, 97·0% (96·7–97·2; 32·5 vs 0·8 per 100,000 person-days) against symptomatic COVID-19, 97·2% (96·8–97·5; 4·6 vs 0·3 per 100,000 person-days) against COVID-19-related hospitalization, 97·5% (97·1–97·8; 2·7 vs 0·2 per 100,000 person-days) against severe or critical COVID-19-related hospitalization, and 96·7% (96·0–97·3; 0·6 vs 0·1 per 100,000 person-days) against COVID-19-related death. In all age groups, as vaccine coverage increased, the incidence of SARS-CoV-2 outcomes declined. Estimated prevalence of the B.1.1.7 variant was 94·5% among SARS-CoV-2 infections.



Comment: Two doses of BNT162b2 are highly effective across all age groups (≥16 years, including older adults aged ≥85 years) in preventing symptomatic and asymptomatic SARS-CoV-2 infections and COVID-19-related hospitalizations, severe disease, and death, including those caused by the B.1.1.7 SARS-CoV-2 variant. These articles from Israel and Qatar offers hope that COVID-19 vaccination will eventually control the pandemic. These findings are of international importance as vaccination programs ramp up across the rest of the world, suggesting that other countries can similarly achieve marked and sustained declines in SARS-CoV-2 incidence if they can get enough vaccines and achieve high vaccine uptake.

Re-Infection with SARS-CoV-2 in Patients Undergoing Serial Laboratory Testing
Clin Infect Dis published online April 25, 2021
doi/10.1093/cid/ciab345/6251701
The investigators analyzed 9,119 patients with SARS-CoV-2 infection who received serial tests in a total of 62 healthcare facilities in United States between December 1, 2019, and November 13, 2020. Re-infection was defined by two positive tests separated by interval of greater than 90 days after resolution of first infection was confirmed by two or more consecutive negative tests.

Re-infection was identified in only 0.7% (n=63, 95% confidence interval [CI] 0.5%-0.9%) during follow up of 9,119 patients with SARS-CoV-2 infection. The mean period (±standard deviation [SD]) between two positive tests was 116 ± 21 days. A logistic regression analysis identified that asthma (odds ratio [OR] 1.9, 95% CI 1.1-3.2) and nicotine dependence/tobacco use (OR 2.7, 95% CI 1.6-4.5) were associated with re-infection. There was a significantly lower rate of pneumonia, heart failure, and acute kidney injury observed with re-infection compared with primary infection among the 63 patients with reinfection There were two deaths (3.2%) associated with re-infection.



Comment: This study demonstrated an extremely low rate of re-infection confirmed by laboratory tests in a large cohort of patients with SARS-CoV-2 infection. Re-infection appeared to be milder than primary infection, but there were two deaths. The exact prevalence of re-infection may be confounded by the selection criteria of our analysis which only included those with serial laboratory tests. This approach eliminates those patients who may have undetected SARS-CoV-2 re-infection because follow up laboratory tests were not performed. These observations suggest that survivors from SARS-CoV-2 infection cannot totally relax compliance with proven interventions in prevention of SARS-CoV-2 transmission such as social distancing and universal face mask use unless they are vaccinated. It has recently been shown that vaccines produce a more robust antibody and T-cell response compared to natural infection and better efficacy, so even if you have recovered from natural infection, you should receive at least one dose of an approved vaccine. The CDC recently reported on so-called breakthrough cases of person who were fully vaccinated, which they defined as positive Covid-19 test results received at least two weeks after patients receive their final vaccine dose. They found breakthrough cases represent 0.008% of the fully vaccinated population. [5800 cases among 77 million fully vaccinated] The CDC found that 29% of breakthrough infections were asymptomatic and only 7% of patients experiencing a breakthrough infection were hospitalized. So far, 74 people have died after experiencing breakthrough infections. [Daily Briefing April 16, 2021]