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dicon DUKE INFECTION CONTROL OUTREACH NETWORK

COVID-19 Vaccine Update

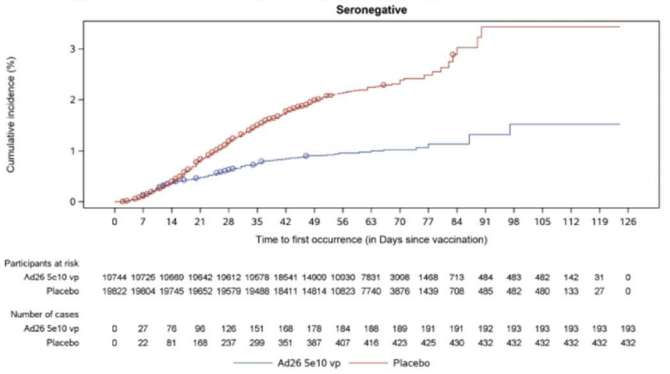
Vaccine rollout to date:

As of the end of February, over 72 million doses of COVID-19 vaccines have been administered in the United States.[1] More than 48 million Americans have received at least one dose, which represents roughly 15% of the population. [1] More importantly, due to the prioritization schema recommended by CDC and adopted by most states, over 25% of all Americans >65 years old have received their first dose of vaccine.[1] Advanced age is highly correlated with greater disease severity, so our vaccination prioritization will reduce hospitalizations and death disproportionately to the number of vaccines administered. Despite a relatively slow start to our national vaccination campaign, we're now administering roughly 1.5 million doses per day. Pfizer and Moderna have committed to increase the amount of vaccine delivered to the United States over the next 2 months, so we will likely reach 3 million doses administered per day by the end of April. Overall, the United States is behind only Israel, UAE, and the United Kingdom in terms of doses per capita and on track to vaccinate half the nation by summer.[2]

A new addition to the arsenal:

On February 27, 2021, the FDA issued Emergency Use Authorization (EUA) to Janssen Biotech's COVID-19 vaccine.[3] Janssen's COVID-19 vaccine is a replication-deficient human adenovirus vector vaccine that is stable at conventional freezer temperature for two years and refrigerator temperature for three months, negating many of the cold-chain storage issues related to Pfizer and Moderna's mRNA vaccines.[4] Janssen's vaccine prevents approximately 2/3 of moderately symptomatic cases within 2 weeks of administration and 85% of severe/critical cases within 28 days of administration.[4] Pertinently, **no patients who received Janssen vaccine required hospitalization or died if they had received vaccine at least 28 days from symptom onset**.[4] These findings are consistent with both Pfizer and Moderna's vaccines, which have demonstrated near complete protection from severe illness requiring hospitalization or resulting in death. Figure 1 below shows the incidence curve of confirmed moderate-severe/critical COVID-19 cases from the time of vaccine or placebo administration.

Figure 1. Cumulative Incidence Curve of Centrally Confirmed Moderate to Severe/Critical COVID-19 Cases With Onset at Least 1 Day After Vaccination, Full Analysis Set



Janssen's vaccine is unique among currently authorized and prospective vaccine candidates because **it is a single dose vaccine**. The implications of a single dose vaccine are significant; not needing to provide a second dose will effectively double the number of people that can be vaccinated compared to Pfizer and Moderna's mRNA vaccines. Additionally, populations that are unlikely to return for a second dose (e.g. those experiencing homelessness, dementia, mental health issues, or simple transportation issues) can receive full vaccination status with Janssen's product.

Much has been made in the lay press about the efficacy of Janssen's product compared to Pfizer and Moderna, but we're unable to draw direct comparisons between these products. Because Janssen studied a single dose vaccine, the outcome data is presented at 14 and 28 days after vaccine, which is earlier than Moderna's outcome assessment. Additionally, the Janssen's phase 3 trial occurred later in 2020 and 2021 than Pfizer or Moderna's trials and recruited 30% of their participants from South Africa and Brazil.[4] This is an important distinction because the variants in South Africa and Brazil (B.1.351 and P1) that concern many epidemiologists due to their ability to "escape" vaccine targets were predominant at the time of the Janssen trial. From a public health perspective, the most important aspect of Janssen's vaccine is that it appears

to prevent hospitalization and death just as well as Pfizer and Moderna's vaccines.[4] Any vaccine that can reduce COVID-19 to a mild illness is bound to have a profound impact on our medical infrastructure, preserving bed capacity and medical resources for other ailments.

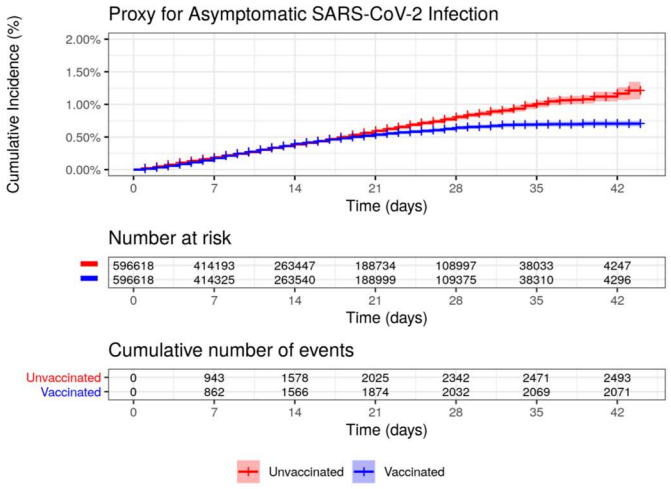
Evidence against transmissibility for the vaccinated:

For the last several months, public health officials have warned that while vaccination is critically important to end this pandemic, individuals who have been vaccinated still need to practice all of the risk mitigation strategies that we have been promoting for the past year (e.g. masking, distancing, hand hygiene). In part, this is because vaccination does not completely eliminate the risk of infection, but another legitimate concern is whether or not COVID-19 vaccination induces sterilizing immunity, meaning that it prevents transmission to others. The current narrative in the public discourse regarding sterilizing immunity belies the fact that most epidemiologists would agree that the appropriate question has never been whether or not vaccination will reduce transmission, but rather *how much* it will reduce transmission.

In order to truly determine whether or not vaccination reduces transmission, we need population level infection data interfaced with well-resourced contact tracing data and serial surveillance testing on representative samples of the population. These data are unlikely to exist or be analyzed for months or years to come. Within the last several weeks, studies out of Israel (the country with the greatest per capita vaccination rate to date) and the United Kingdom have assessed the "asymptomatic infection" rate among vaccinated individuals, which, when taken in conjunction with the known symptomatic infection rates, is a reasonable surrogate for potential transmissibility. After all, if you have no detectable viral genetic material on respiratory sampling, your likelihood of transmitting infection is essentially zero.

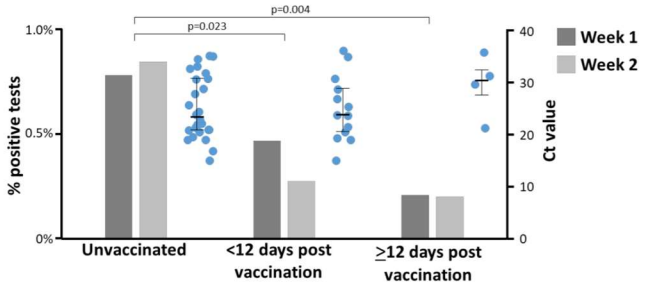
The Israeli study, recently published in the New England Journal of Medicine, analyzed data from the largest integrated health system in Israel, which cares for over half the population.[5] The authors confirmed the phase 3 clinical trial data for symptomatic infection with Pfizer's vaccine, finding a 94% reduction in symptomatic illness when assessing patients at least one week after their second dose, but they also found a 90% reduction in "asymptomatic infection" (defined as positive PCR with no reported symptoms) at this timepoint (see figure 2 below).[5] Indeed, the authors identified that protection from asymptomatic infection began around 14 days after the first dose, which is consistent with when some degree of protection is conferred against symptomatic infection.[5,6]

Figure 2. Asymptomatic infection in matched population sample.



A preprint publication from the United Kingdom demonstrated a four-fold reduction in asymptomatic infection for individuals who are at least 12 days from first dose of Pfizer vaccine, and pertinently, also demonstrated that individuals who did become infected despite being >12 days from vaccine administration had significantly higher cycle thresholds (Cts), which is a marker of lower viral burden (see figure 3 on the next page).[7] Increased viral load correlates with increased transmissibility, so even if vaccinated individuals get infected, they will be less likely to infect others.[8,9]

Figure 3. Cycle threshold (Ct) and % positive tests after Pfizer vaccine.



These reductions in asymptomatic cases are not unique to mRNA vaccines such as Pfizer or Moderna. A recent preprint publication for the AstraZeneca vaccine, a chimpanzee adenovirus vector vaccine, demonstrated a 67% reduction in PCR positivity among patients vaccinated ≥14 days previously.[10] It is important to note that this vaccine is not yet authorized by the FDA. The data that Janssen submitted to the FDA included an analysis of asymptomatic infection as well. Enrolled trial participants had PCR and serology performed on or after day 29 from their single dose vaccine. If patients had a positive PCR or a non-S protein positive serology (indicating a serologic response to a protein unrelated to the protein encoded within the vaccine) and reported no history of symptoms, they were deemed to have had asymptomatic infection. Using these definitions, Janssen vaccine led to a 74% reduction in asymptomatic infection.[4]

So can vaccinated individuals take off their masks?

No! Even though case counts and hospitalizations have dropped dramatically in the last 6 weeks, community transmission is still high throughout the United States. Even though vaccinated individuals will be less likely to get infected and less likely to transmit infection to others, the protection is not complete and the possibility that new escape variants may arise still exists. Risk mitigation strategies such as masking, distancing, and hand hygiene should continue until community transmission is negligible. To explain this to lay persons, I try to reason that if you're driving a car, you wouldn't take your seat belt (masks) off until the car has stopped moving (community transmission ceases) just because you added brakes (vaccines) to the car.

In summary, while no vaccine will completely eliminate the possibility of transmission, there's good reason to believe that all available vaccines will lead to both a substantial reduction in symptomatic illness and use of medical resources, but also a substantial reduction in transmission. The available data corroborates this hypothesis and as vaccine administration increases across the United States, we remain cautiously optimistic that our current trend of declining cases and hospitalizations will continue.

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