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RA CAPITAL'S COVID–19 MAP:
Frequently Asked Questions

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HAVE A QUESTION WE HAVEN'T ANSWERED?

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SUBMIT A QUESTION

VIROLOGY

1. How does SARS–CoV–2 compare to other viruses?

Unlike many other viruses, SARS-CoV-2 is able to proofread its genetic code while it replicates, keeping the mutation rate low. However, mutations that cause the virus to behave differently than the original strain have already arisen, causing existing vaccines to provide varying degrees of protection. Therefore, we will need to adapt our SARS-CoV-2 vaccines to be effective against new strains and give booster shots to those already inoculated. In addition to the original strain, two variants, referred to as the UK strain and the South African strain due to their origin of identification, as well as a handful of others (Brazil, NY, California) are widely circulating. The UK variant (B.1.1.7) is more transmissible and more lethal than the original strain, demonstrating a 64% increase in mortality risk relative to the original SARS-CoV-2 strain in a community-based study in the UK.[1] While the efficacy of current vaccines against the B.1.1.7 strain is decreased, the mutation is such that they are still largely effective, especially at preventing severe disease and hospitalization. The bigger concern is the South African (SA) variant (B.1.351), as the E484K mutation in this strain changes the spike protein in a way that reduces antibody recognition,[2] which may reduce the immune protection provided by prior infection or vaccination. The Brazil and New York variants also have the E484K mutation in the spike protein, so we might expect them to behave similarly.

Because the virus will continue to acquire mutations, we will likely need to continuously monitor emergence of new strains and adapt our response accordingly with multivalent vaccines and updated therapeutics.

2. What is the origin of the virus?

- **SARS-CoV-2 is believed to likely have been naturally transmitted to humans from other animals, but there is still ongoing investigations into whether it was engineered in a lab.** The genetic evidence supports that SARS-CoV-2 is the result of natural selection in either humans or another animal expressing a human-like ACE2 protein.[3] SARS-CoV-2 likely resulted from recombination between a bat coronavirus and a "spike" protein that is very similar to one found in pangolins (scaly anteaters). Specifically, researchers have shown that:
- The genetic makeup of SARS-CoV-2 is very similar to that of a bat coronavirus
- The spike protein of SARS-CoV-2 is very similar to that of a spike protein circulating in pangolins
- The way the viral spike protein binds to ACE2 on host cells is consistent with natural mutations that are not easily predicted by computational models and are therefore unlikely the result of rational design. In other words, if humans had made the virus, they would have used tactics that made sense based on our understanding of how to make such a virus; in this case the virus appears to have serendipitously achieved its goal, thus we should credit nature with surprising us yet again with her creativity.
- The WHO confirmed these findings in February 2021 during their investigation into the origins of the strain that initiated in Wuhan, China.[4] Recent investigations into Fall 2019 illnesses of several Wuhan lab workers have re-ignited the lab leak theory, but nothing has been confirmed.

1. https://www.bmj.com/content/372/bmj.n579
2. https://www.the-scientist.com/news-opinion/south-african-sars-cov-2-variant-alarms-scientists-68317
3. "The proximal origin of SARS-CoV-2 | Nature Medicine." 17 Mar. 2020, https://www.nature.com/articles/s41591-020-0820-9. Accessed 12 May 2020.
4. https://www.cnbc.com/2021/02/09/who-outlines-wuhan-findings-on-origins-of-covid-pandemic.html

TRANSMISSION

3. What vaccines are approved? What vaccines are in development?

Three vaccines have received emergency use authorization (EUA) in the United States as of June 2nd, 2021. Moderna's mRNA vaccine (mRNA-1273), Pfizer/BioNTech's mRNA vaccine (BNT162b2), and Johnson and Johnson's adenoviral vector vaccine (Ad26.CoV2.S) have been authorized in the United States with an estimated >40% of the US population being fully vaccinated. All 3 vaccines have shown a 100% efficacy rate against death in their respective phase 3 clinical trials. While it is difficult to directly compare between trials that were run at different times and in different locations with differing levels of variants, the data have looked promising for all modalities. The two mRNA vaccines (PFE/BNTX and MRNA) have shown an overall vaccine efficacy (VE) of 95% and 100% efficacy against severe disease. JNJ's vaccine has shown an overall 66% VE and 85% efficacy against severe disease.

Several candidates in development are nearing approval, but all vaccines are less protective against novel variants relative to the original SARS-CoV-2 strain. Novavax's protein vaccine candidate (NVX-CoV2373) has recently shown the best efficacy data to date (96% VE against the original strain) and will likely receive EUA authorization in 3Q21. NVX-CoV2373 achieved 100% efficacy against mortality and severe disease, 86% VE against the UK strain, and 60% VE against the SA strain. AstraZeneca is also nearing the final stages of development having recently reported phase 3 data for its adenoviral vector vaccine, AZD-1222. This vaccine has already received EUA in Europe and published efficacy data are likely sufficient for US approval (70.4% overall VE, 100% efficacy against severe disease, 75% VE against UK strain, 10% VE against SA strain), but general concerns over their methods of reporting and reports in Europe of an associated risk of blood clot might impact its use in the US.

While all vaccines have shown 100% prevention of mortality in clinical studies, the efficacy has been reduced against the mutant strains. Pfizer/BioNTech's vaccine and Moderna's vaccine were developed prior to the discovery of the new strains, so we do not have much clinical trial data to show their efficacy against variant strains, and while both showed 95% VE against the original strain we can expect that estimate to decrease based on the results of other vaccines against the newer strains. PFE/BNTX reported 100% VE against the SA strain, but the numbers were so small that this is not very meaningful (only 6 detected cases, all in the placebo group). Both Pfizer/BioNTech and Moderna have begun development/testing of booster vaccine candidates.[5] Novavax's vaccine candidate achieved 96% VE against the original strain, but this efficacy was decreased against the variant strains (86% VE against the UK strain, and 60% VE against the SA strain). Similarly, JNJ's vaccine showed 72% VE against the original strain, 72% VE against the UK strain, and 57% VE against the SA strain. Concerningly, AZN/Oxford's vaccine candidate achieved 84% VE against the original strain, 75% VE against the UK strain, but only 10% VE against the SA strain.

Also in development are booster vaccines for variant strains against which the original vaccine showed reduced efficacy. PFE/BNTX are administering a third dose of their vaccine to understand effects against the new variants, as well as preparing to test a modified version that is specifically designed to protect against the SA variant. A modified version would be tested as both a booster dose in those already vaccinated and as a first vaccine in those who are unvaccinated.[6] Moderna began testing its booster shots in early March 2021 with a booster shot targeting the SA variant at different doses and in combination with the original vaccine.

5. https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-it-has-shipped-variant-specific-vaccine
6. https://www.cnbc.com/2021/02/25/pfizer-biontech-are-testing-a-booster-shot-of-their-covid-vaccine-in-a-new-trial.html

The timeline of vaccination has progressed rapidly in the US. Healthcare workers and nursing home residents were vaccinated first, starting in December 2020 when PFE/BNTX received EUA, shortly followed by MRNA. In an effort to protect the most vulnerable and exposed populations first, the elderly and other frontline workers besides healthcare workers were next in line. President Biden fulfilled his promise that adults over 16 years old in all 50 states become eligible to receive a vaccine as of April 19, 2021. Adolescents (age 12-15) are also now able to receive a vaccine after PFE/BNTX's vaccine was approved for this age group on May 10, 2021. Although it will take some time for the majority of the population to receive their vaccine shots, and full protection does not set in until 2 weeks after the final dose, this timeline suggests that we could be approaching herd immunity by 4Q21, and possibly sooner.

4. Can SARS–CoV–2 be spread via surfaces?

While transmission through surfaces cannot be ruled out, it is probably very rare. A study out of Tufts University estimates that the risk of infection from touching a contaminated surface is less than 5 in 10,000, which is lower than the risk of SARS-CoV-2 infection through aerosols and lower than surface transmission risk for the flu or norovirus.[7]

5. Can a vaccinated person transmit SARS–CoV–2?

The risk of a vaccinated person transmitting SARS-CoV-2 is likely low. For transmission to occur, the virus needs to be able to replicate in the upper or lower respiratory tracts. We know from studies in Rhesus macaques (that were challenged with the virus after being vaccinated with PFE/BNTX, MRNA, or JNJ's vaccines) that viral replication in the respiratory tracts after vaccination is prevented or greatly limited. Therefore, people vaccinated against COVID-19 that are infected are unlikely to be able to transmit virus to others.[8,9] A preprint of a study from epidemiologists at the Harvard School of Public Health has estimated that one dose of Moderna's vaccine reduces the potential for transmission by at least 61%, and possibly much more.[10] The endpoints of the RCTs from the Moderna, AstraZeneca, and JNJ vaccines were designed to test for protection against infection and therefore do not provide sufficient information on the magnitude of protection that the vaccines could offer against transmission.

6. Will the weather affect spread? Does air humidity affect spread?

Warmer months have shown reduced transmission, which may be due in part to SARS-CoV-2 being less stable in humid, warm temperatures as well as the ability to spend more time outside distanced during warmer weather. For instance, during the Summer of 2020, transmission was reduced compared to the Fall of 2020. Although the effect is small, there is likely some seasonal variation to the infectivity of SARS-CoV-2, driven both by people's behavior and properties of the virus. From lab experiments, we know that SARS-CoV-2 favors dark, cold, and dry conditions and that it degrades faster in warmer and more humid environments and/or when exposed to UV light.[11] During the first 4 months of the pandemic, when there were limited control measures in place, infection rates were higher in places with less UV light.[12]

7. "Environ. Sci. Technol. Lett. 2021, 8, 2, 168–175 Publication Date:December 14, 2020 https://doi.org/10.1021/acs.estlett.0c00875 https://pubs.acs.org/doi/10.1021/acs.estlett.0c00875
8. https://www.biorxiv.org/content/10.1101/2020.12.11.421008v1.full
9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7581548/
10. https://www.medrxiv.org/content/10.1101/2021.02.25.21252415v1.full
11. https://www.nature.com/articles/d41586-020-02972-4
12. https://www.nature.com/articles/d41586-020-02972-4

7. I have been diagnosed with COVID–19; when am I "all clear"? Can I be reinfected?

If you were infected with the virus and have recovered at home, the CDC currently recommends isolating at minimum 10 days after symptoms first appeared, including at least three isolation days after recovery[13] though it could be prudent to wait longer, perhaps a week or longer. Recovery is defined as the resolution of fever without the use of fever-reducing medicine and improvement in respiratory symptoms.

Reinfection is possible but rare, and when someone is reinfected it's likely that their symptoms are milder. People who become reinfected may not even notice, but they could still spread the virus to others. This is one reason why it's important that people who have recovered still abide by social distancing.

Research has shown that those who recover from COVID-19 have immunity to the virus that can last at least 8 months, and maybe longer.[14]

8. What is herd immunity?

Herd immunity is a form of indirect protection against a pathogen that arises when enough people in a population are immune (either by prior infection or vaccination). Because in this scenario so many people are immune, the infectious agent has difficulty spreading to new hosts and therefore even those who are not immune are given some level of protection.

9. What drugs are approved or have an EUA?

The RNA polymerase inhibitor remdesivir is modestly effective in speeding up recovery and reducing the chance of death for hospitalized COVID-19 patients. This drug is given by IV administration for five to ten days (for patients not requiring invasive mechanical ventilation and/or ECMO, 5 days is recommended, but if a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days [15]) and has toxicity, so it is not one that is going to be used widely to treat mild disease. Remdesivir received EUA for hospitalized COVID-19 patients on May 1, 2020[16] and was fully approved by the FDA for the treatment of COVID-19 on October 22, 2020[17].

Monoclonal antibodies that inhibit the virus from entering cells and induce the immune system to destroy infected cells are a second promising class of COVID-19 drugs. In 4Q20, the FDA granted EUA for antibody therapies targeting SARS-CoV-2 from Regeneron and Eli Lilly in the outpatient setting. Clinical efficacy data for antibody therapies from Regeneron and Eli Lilly are limited by the small trial sizes, but nonetheless the data support the conclusion that these antibodies can reduce the risk of hospitalization if given 1) early in the disease course and 2) to patients who have not yet mounted a sufficient immune response (known as 'seronegative').

Eli Lilly's immunomodulatory Jak1/2 inhibitor baricitinib (previously approved for rheumatoid arthritis) was granted EUA in combination with remdesivir in hospitalized patients.

13. "Disposition of Non-Hospitalized Patients with COVID-19 | CDC." https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html. Accessed 28 March 2021.

14. https://science.sciencemag.org/content/371/6529/eabf4063

15. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf

16. https://www.fda.gov/media/137564/download Accessed 12 May 2020.

17. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19

In the first half of 2021, we are expecting oral antiviral clinical data from Merck/Ridgeback's molnupiravir and Atea/Roche's AT-527, which have the same mechanism of action as Gilead's IV remdesivir. A broadly available and effective oral antiviral would be a huge step forward in the outpatient and prophylaxis settings and, if proven to be effective, such therapies might be stockpiled by governments to protect their citizens in the event of future coronavirus outbreaks.

EPIDEMIOLOGY

10. Why have elderly individuals been prioritized for vaccine distribution and children <12 years old left to wait?

Yes, the virus affects children (<12 years old), adolescents (13-17 years old), and young adults (18-25 years old), but the infection rate and risk of hospitalization and ICU admission among these younger people is significantly lower than that of older people.[18, 19] Because the majority (>78%) of deaths have been in individuals >65 years old, vaccine distribution was prioritized for this demographic because it's important that this population receives vaccine protection first in order to reduce overall mortality.[20]

Children are not yet eligible to receive vaccines because clinical trials have been conducted in adults and adolescents. The FDA granted EAU to PFE/BNTX's COVID vaccine for adolescents aged 12-15 years on May 10th, 2021. The first trials run in children <12 years old have only recently begun, so until the vaccine is proven safe for these children they cannot receive it. The anticipated timeline for vaccine eligibility in children is YE21/1H22 for children aged 6 months to 12 years.

11. Will COVID–19 continue to circulate after we have a vaccine?

Although is not yet absolutely clear whether SARS-CoV-2 will continue to circulate on a yearly basis (like the flu), or if widespread vaccination and herd immunity will be able to wipe it out, **the odds are high that SARS-CoV-2 will become the 5th endemic human coronavirus circulating globally forever,** in which case we may need to bundle the SARS-CoV-2 vaccine with the seasonal flu vaccine to boost everyone's immunity each year.

18. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf

19. https://www.fda.gov/media/137564/download Accessed 12 May 2020.

20. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19

PREVENTION

12. Should I wear a mask? Will it prevent me from getting infected? Can masks be used over multiple days?

If you are not vaccinated, you should wear a mask. Masks played an important role in reducing transmission of COVID-19. The major uses of masks are to:

I. Protect the wearer from getting infected. This is especially relevant for frontline healthcare workers (most data on protective equipment generated thus far have evaluated this group).

II. Prevent a potentially infected person from transmitting the virus to others. Current recommendations for the public focus on this use case.

Surgical masks and N95 respirators are designed for one-time use whereas homemade masks can be washed with soap and reused. SARS-CoV-2 can survive for days on the surface of the mask, potentially creating a reservoir if the mask is not cleaned properly.

Due to the success of vaccines at protecting individuals from both contracting COVID-19 and transmitting it, the CDC has delivered new guidelines that vaccinated individuals can resume activities without wearing a mask or staying 6 feet apart, except when required by local guidelines. If you are fully vaccinated, and the local rules do not require masking, you no longer need to wear a mask.

TYPES OF MASKS AND WHEN TO USE THEM

There are several different face masks that can help prevent transmission of SARS–CoV–2:

SURGICAL MASKS are loose–fitting masks that protect the wearer from large droplets that could contain viral particles; their main role is to prevent contamination of the surrounding area when a person coughs, sneezes, or even just talks. Healthy people can help reduce their exposure to SARS-CoV-2 by wearing a surgical mask, particularly if they are participating in activities that increase their risk of infection (e.g., caring for an infected person, visiting a crowded area, etc).

N95 RESPIRATORS are tight–fitting protective masks that filter out ≥ 95% of very small (0.3 micron) particles from the air, which includes bacteria and viruses, and therefore protect the wearer by reducing inhalation of viral particles. These specialized masks are in short supply and should currently be worn only by healthcare personnel due to their increased risk of exposure.

HOMEMADE CLOTH MASKS are a surrogate for surgical masks (which are still in short supply and may need to be prioritized for healthcare workers) if they fit snugly over the nose and mouth, allow for unrestricted breathing, and can be secured with ties or ear loops. The CDC recommends the use of a facemask, including homemade cloth masks, to help prevent the spread of SARS-CoV-2 when people must go into public settings (e.g., grocery stores or pharmacies).

FIGURE 1: TYPES OF MASKS

13. How might our approach to pandemic preparedness change?

There will likely be greater interest from society in discovering and developing new antivirals against a variety of viruses that could cause pandemics. Therefore, funding for this work, possibly from government sources, should likewise increase. There will also likely be more interest in scaling up the manufacturing capacity of vaccine platforms that could allow rapid responses to new pathogens. Of particular interest will be vaccine technologies that are effective with a single dose (e.g. adenoviral vectors, provided they are effective even when people have antibodies against the vector).

Also, we will likely do a better job of stockpiling masks and other PPE, as well as the materials we need to ramp up millions of easy-to-use diagnostic tests, both molecular/PCR tests that detect virus and serology tests that detect antibodies against a virus. Ideally, we will have validated and scaled up technologies to allow testing for viruses using saliva instead of invasive nasal/throat swabs. Ideal tests will allow rapid turnaround, on the scale of minutes, even at home or on-site so that people don't have to congregate in clinics or hospitals.

The next time there is news of a novel virus, our best chance of preventing another COVID-19 crisis is to immediately begin social distancing and use contact tracing to stamp out the infection within our borders and hope that other countries do the same. Two-to-three intense weeks of properly conducted social distancing early on could avert over a year of global pain.