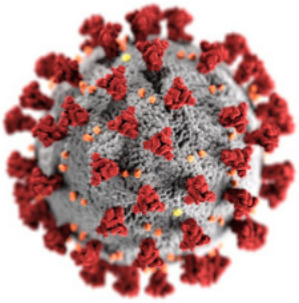

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
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The Situation: U.S. Cases 33,737,982; U.S. Deaths 605,799; U.S. Persons Fully Immunized 47.9%

In the world as of July 6, 2021, 184,394,772 cases and 3,988,239 deaths have been confirmed. In the United States, there have been 33,737,982 cases, the most in the world followed in order by India, Brazil, France and Russia. China is now 97th in the world with 103,891 cases. Deaths in the U.S. through July 6 have been estimated at 605,799.[1]

From March 10, 2020 through July 2, 2021, there have been 263,271 confirmed cases of Covid-19 reported from Dallas County with 4,135 deaths.[2] Seventy percent of hospitalized cases in Dallas County have been under 65 years of age. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men than women have died. The percentage of cases due to variant viruses is being determined. Of 166 cases in Dallas County due to a variant coronavirus, 131 cases were due to B.1.1.7 (U.K., Alpha), 2 cases due to B.1.351 (So. Africa, Beta), 15 cases due to P.1 (Brazil, Gamma), 9 cases due to B1.617.2 (India, Delta) and 9 cases due to B.1.429 (U.S., Epsilon). The Delta variant appears to be gaining in predominance in Dallas as elsewhere. With the relaxation of personal precautions, other common respiratory viruses are rebounding, with SARS-CoV-2 constituting only 3.2% of specimens submitted for diagnosis of respiratory viruses in the latest report on 6/25/21, down from a peak value of 30.5% a year earlier, obtained during the week ending 7/4/20. As of 6/25/21, the percentages of tests performed for the leading isolates are RSV (25%), rhinovirus/enterovirus (14%) and parainfluenza virus (19%). From 8/1/20 through 6/25/21, influenza A and B antigen tests on specimens from the respiratory tract have been negative.

References:

1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 7/6/2021)
2. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 7/6/21

Feature Article

Vaccine Hesitancy

Tara DuVal, MD, Division of Geriatrics

In 2019, the World Health Organization (WHO) listed vaccine hesitancy as a top 10 threat to global health. The WHO defines vaccine hesitancy as "the reluctance or refusal to vaccinate despite the availability of vaccines," and notes that it threatens to reverse progress made in tackling vaccine preventable diseases.[1] Recently, vaccine hesitancy has become an even more important topic as it threatens the development of herd immunity to COVID-19.

The reasons behind vaccine hesitancy are complex and multidimensional. A meta-synthesis study published in 2019 found 5 recurrent themes in those who are vaccine hesitant: (1) risk conceptualization; (2) mistrust; (3) alternative health beliefs; (4) philosophical view/responsibility; (5) parents' information. Risk

conceptualization refers to an overestimation of the risks of vaccines in relation to their benefit. Fear of side effects and "toxic" ingredients are often cited by those who are vaccine hesitant. In this regard, vaccines are felt to be a victim of their own success, since negative outcomes of vaccine preventable diseases are not commonly seen in a society with high vaccination rates. Secondly, mistrust refers to suspicion of institutions such as pharmaceutical companies, the media, and the government. Doubts of integrity of the research and concern for financial conflicts of interests are often voiced by the vaccine hesitant. Thirdly, alternative health beliefs encompass the idea that leading a healthy lifestyle can eliminate the need for vaccine. There is a belief that vaccination is "unnatural" and interferes with the body's "natural immunity." Philosophical view/responsibility refers to a belief that vaccine interferes with religious faith or divine intervention. Parents cite the right to vaccinate their children according to their own beliefs. Finally, parents' information refers to the perception of being inadequately informed about vaccination to decide. Some cite a lack of information from their healthcare provider; others cite contradictory information released by the media. There is also a tendency in those who are vaccine hesitant to rely on friends, family members, word of mouth, and the internet for information.

Social media and the internet have played a large role in vaccine hesitancy by widely circulating unproven myths, ideas, and conspiracy theories. Social media algorithms allow for anti-vaccine messages and disinformation to be amplified. Anti-vaccination messages are more likely to be "liked" and shared than pro-vaccine messages on social media sites such as YouTube, Facebook and Twitter.[3] These messages are often shared by computer automated systems known as "bots" and paid persons that seek to spread disinformation , known as "troll farms."[4] Additionally, in March 2021 the Center for Countering Digital Hate and the Anti-Vax Watch identified 12 individuals who are responsible for 65% of antivaccine misinformation shared to social media platforms. These individuals, known as the Disinformation Dozen, are: Joseph Mercola; Robert F. Kennedy Jr.; Ty and Charlene Bollinger; Sherry Tenpenny; Rizza Islam; Rashid Buttar; Erin Elizabeth; Sayer Ji; Kelly Brogan; Christiane Northrup; Ben Tapper; Kevin Jenkins.[5]

With regard to the COVID-19 vaccine, as of May 2021, 62% of people in the U.S. surveyed have already received the vaccine, and 4% plan to get it as soon as possible. Of those who remain hesitant, 12% state they will "wait and see," 7% state they will obtain the vaccine only if required, and 13% state they will definitely not get the vaccine.[6] The group with the highest percentage that will "wait and see" are black adults (22%). Republicans have the highest group of those who will "definitely not" get the vaccine (27%). Those who say they will "definitely not" get the vaccine cited a range of reasons, including the vaccine being "too new"/uncertainty about long term effects, the belief that it is not effective against COVID-19, the belief they do not need it, concern about vaccine ingredients and side effects, disliking vaccines in general, lack of concern about getting sick from COVID-19, a general lack of trust, already having had COVID-19, and the belief that their own immune system will protect them. A systematic review of 126 studies found that those who are hesitant to receive the COVID-19 vaccine are more likely to be of lower income, lower level of education, lack health insurance, live in rural areas, have larger households, have a belief that vaccines are unnecessary, and have a general anti-vaccine stand.[7]

Addressing vaccine hesitancy with patients is vital for healthcare providers. A recommendation for vaccines from the doctor or other healthcare provider has been consistently shown to be the strongest predictor of vaccination uptake. It is important to keep in mind that vaccine hesitancy exists along a continuum, from those that accept vaccines without reservations, to those who are hesitant or questioning, to those who refuse all vaccinations. The greatest impact can be had on the middle, hesitant group. When talking with the patient, start with a statement that vaccines are due, to establish vaccination as the normative choice. For example, state, "you are due for your flu vaccine today", rather than "do you want a flu vaccine today?"[8] If the patient expresses hesitancy, motivational interviewing has been shown to improve vaccine acceptance. Motivational interviewing uses open ended questions to elicit concerns. For example, "what concerns do you about the COVID-19 vaccine?" The provider then should ask permission to share information; for example, ask "Would it be OK for me to share what I know about this with you?" Specific questions should then be answered with relevant facts. It is important to keep it conversational, and not a lecture. Personal anecdotes, including the provider's personal decision to get vaccinated, may be shared. It is important to be confident and knowledgeable about vaccines when talking with the patient.

Focusing on the positive has been shown to be helpful. Explain the benefits of receiving the vaccine, instead of focusing on the consequences of not taking it. When asked what they want most from a vaccine, respondents in one poll cited "a return to normal," followed by "safety" and "immunity".[10] Discuss returning to normal, reopening the economy, and appeal to altruism and the positive impact on the community. Promoting prosocial motivations has a stronger impact than promoting personal motivations.[11] Family is a powerful motivator for vaccine acceptance. Significantly more people noted that they would be willing to receive the vaccine for their "family" as opposed to "your country," "the economy," "your community," or "your friends."[10]

The following are specific statements about the COVID-19 vaccine, and the percent that stated they would be more likely to receive the vaccine after hearing the statement:[12]

1. The vaccines are nearly 100% effective at preventing hospitalization and death from COVID-19. 41%
2. Although the COVID-19 vaccines themselves are new, scientists have been working on the technology used in these vaccines for 20 years. 32%
3. There is no cost to get the COVID-19 vaccine. 27%
4. More than 100,000 people from diverse backgrounds and ethnicities participated in the COVID-19 vaccine clinical trials. 26%
5. The vast majority of doctors who have been offered the vaccine have taken it. 26%
6. While the long-term effects of the vaccine may be unknown, the long-term effects of getting COVID-19 could be even worse. 24%
7. Even though most people who die from COVID-19 are older or have other health conditions, some young and healthy people have also been hospitalized and died from COVID-19. 19%
8. The main reason the COVID-19 vaccines were approved so quickly is because red tape that is usually part of the development process was removed, not because corners were cut. 17%

There are some things to avoid when discussing vaccine hesitancy. Beware debunking myths; it is time consuming and ineffective.[13] Spending too much time debunking a myth makes it more memorable in the person's mind. If the truth seems complicated, the myth becomes easier to accept. Simply identify it as a myth and state it is false. Do not lecture, get bogged down in details, provide too much information, or focus only on science and statistics. Do not assume what people's concerns are, and instead, elicit them using the motivational interviewing style described above. Do not turn it into a moral issue. One poll showed that turning vaccination into a moral issue was less likely to have an impact on the decision to vaccinate. 62% of respondents chose "getting vaccinated will help keep you, your family, your community, the economy, and your country safe and healthy" over "taking the vaccine is the right thing to do for yourself, for your family, your community, the economy, and the country" (38%).[10] Finally, do not lose patience. These conversations can be time consuming, and it may take more than one interaction to change a person's mind.

Vaccine hesitancy is a threat to global health and to efforts to end the COVID-19 pandemic. Physicians and healthcare providers can have a significant impact on vaccine uptake in their patients. Patients look to their healthcare provider for trusted information and recommendations. We must take back the narrative on vaccines and work to overcome vaccine hesitancy in our patients and in our community.

References:

1. https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019, Accessed June 4, 2021
2. Diaz Crescitelli ME, et al. A meta-synthesis study of the key elements involved in childhood vaccine hesitancy. Public Health. 2020; 180,38-45
3. Wawrzuta D, Jaworski M, Gotlib J, Panczyk M. Characteristics of Antivaccine Messages on Social Media: Systematic Review. J Med Internet Res 2021; 23(6):e24564
4. Wilson S and Wiysonage C, BMJ Global Health 2020.
5. https://www.counterhate.com/disinformationdozen; Accessed June 4, 2021

6. https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-may-2021/; Accessed June 4, 2021
7. Lin C, Tu P, Beitsch LM. Confidence and Receptivity for COVID-19 Vaccines: A Rapid Systematic Review. *Vaccines*. 2021; 9(1):16
8. Hofstetter AM, Robinson JD, Lepere K, Cunningham M, Etsekson N, Opel DJ. Clinician-parent discussions about influenza vaccination of children and their association with vaccine acceptance. Vaccine. 2017 May 9;35(20):2709-2715
9. Reno JE, O'Leary S, Garrett K, Pyrzanowski J, Lockhart S, Campagna E, Barnard J, Dempsey AF. Improving Provider Communication about HPV Vaccines for Vaccine-Hesitant Parents Through the Use of Motivational Interviewing. J Health Commun. 2018;23(4):313-320
10. https://debeaumont.org/changing-the-covid-conversation/vaccineacceptance/; Accessed June 4, 2021
11. Jordan, Jillian & Yoeli, Erez & Rand, David. (2020). Don't get it or don't spread it? Comparing self-interested versus prosocially framed COVID-19 prevention messaging. 10.31234/osf.io/yuq7x.
12. https://files.kff.org/attachment/Topline-KFF-COVID-19-Vaccine-Monitor-March-2021.pdf; Accessed June 4, 2021
13. Lewandowsky S, Ecker UKH, Seifert CM, Schwarz N, Cook J. Misinformation and Its Correction: Continued Influence and Successful Debiasing. *Psychological Science in the Public Interest*. 2012;13(3):106-131

Clinical Advance

SARS-CoV-2 Predominates in Airways and Lung and Secondarily Involves Vascular Tissue Diffusely in Fatal Covid-19

A recent CDC study measuring SARS-CoV-2 virus quantitation and localization in patients dying from Covid-19 has been published in the *Journal of Infectious Diseases*. Airways and lung involvement predominated with lesser diffuse endothelial virus being a secondary finding. The investigators studied postmortem tissue from 64 patients who had lived throughout the U.S., 32 of whom had documented Covid-19. Twenty-one of these Covid-19 patients had a positive pharyngeal swab test by RT-PCR for Covid-19. An additional 11 patients had tissue samples obtained at autopsy that were positive for SARS-CoV-19, making a total of 32 patients who were either positive for virus by pharyngeal swab or by study of tissue samples or both. The remaining 32 patients were negative for virus and could be considered as a control population. They included patients with negative pharyngeal swab tests corroborated by analysis of tissue by RT-PCR. These last 32 patients showed no evidence of Covid-19 and were of particular interest in studying supra-infection with other viruses or bacteria.

The tissues obtained were formalin-fixed and paraffin-embedded (FFPE). They were processed in the usual manner for pathological analysis. They extracted RNA from the tissue samples by standard techniques and the following tests were performed on the patients' specimens:

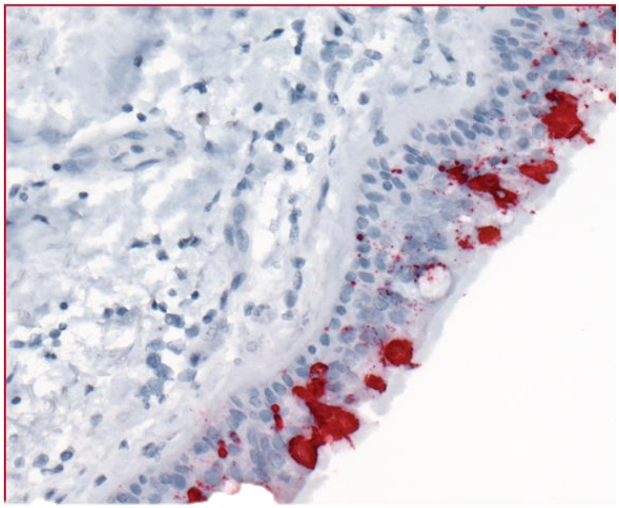
1. Conventional RT-PCR
2. Real time RT-PCR
3. Subgenomic RT-PCR
4. In situ hybridization (ISH)
5. Whole gene sequencing (WGS)

Reagents for RT-PCR were derived from the spike (S) and nucleocapsid (N) genes of SARS-CoV-19. The quantity of virus in each sample was estimated from the RT-PCR cycle thresholds (Ct). A low Ct means a larger amount of virus since it takes fewer cycles to show positivity exceeding the background level. Conversely, a high Ct value means a smaller amount of virus.

Accordingly, the authors estimated the amount of virus resent in the sample, what cells were infected, whether the quantity of virus could be related to inflammatory changes occurring in the tissue, whether the amount of virus correlated with the viability of the virus as determined by subgenomic RT-PCR, and whether the pathological results could be attributed to a particular variant identified by WGS. Subgenomic RT-PCR measurements, which detect short-lived RNA fragments involved in active replication, relies on technology that

has not been accepted by all investigators. In situ hybridization involves the binding of tissue RNA to complementary nucleic acid tagged with a visible dye. Whole genome sequencing determinations identified the viral variant causing the infection.

The figure on the next page, which was featured on the cover of the *Journal of Infectious Diseases*, shows an ISH assay directed against the spike protein of SARS-CoV-19 (shown in red) in tracheal tissue from an autopsied patient.[1] A mononuclear infiltrate is present in the submucosa. Lower amounts of virus were found in involved vascular tissue. SARS-CoV-2 was found in airways and lungs of 17 of the 32 patients with proven disease. Tests for subgenomic viral RNA were positive in these tissues, implying the presence of viable active virus at these sites.[2] The virus was present in airway epithelial cells, macrophages, hyaline membranes and at the sites of active inflammation, inferring a relationship between inflammatory changes and viral replication. Virus quantity, reflected in Ct values, was higher in airways early in the course of the disease and in the lungs later. ISH studies demonstrated "importantly" the presence of virus in endothelial cells and in the tunica media of blood vessels in a variety of tissues including the lung, heart, liver, spleen, kidneys, pancreas and the leptomeninges. Virus was always higher in the airways and lungs suggesting a lower viral load in non-respiratory tissues. Thrombi were found around the sites of vessel involvement. The authors suggested that these findings may be explained by direct viral infection of endothelial cells, leading to vascular dysfunction, hypercoagulability, and thrombosis.



Identification of SARS-CoV-19 spike protein (red color) in postmortem tracheal tissue by in-situ hybridization.

The authors studied the presence of other respiratory pathogens in Covid-19 and non-Covid-19 cases. In Covid-19, 1 of 10 patients' specimens were positive for *Streptococcus pneumonia*e, 4 of 10 were positive for *Streptococcus spp.* and 1 of 1 for *Staphylococcus aureus*. Respective values for these bacteria in non-Covid patients were 0 of 3, 1 of 3, and 5 of 6. They concluded that bacterial supra-infection constitutes only a small component of disease in these patients. WGS sequencing, performed retrospectively in 26 patients, identified clusters of cases caused by distinct virus variants. The capacity to detect these viral variants could have epidemiological implications in the further study of future epidemics.

The conclusions of this study are that viral replication in the lungs and its attendant inflammation suggest an ongoing disease process that can last for 2 weeks and longer in immunosuppressed patients and that there is a relatively long potential window for therapy in these patients. Tracheal and lung involvement predominate. Endothelial cells are diffusely involved. Under certain circumstances, endothelial cell involvement can lead to vascular thrombosis. Only a small component of the illness is related to bacterial supra-infection. WGS sequencing of conventionally processed autopsied tissue samples could have epidemiological significance in determining the virus variants involved in the epidemic.

References:

1. Bhatnagar j, Gary J, Reagan-Steiner S et al. Evidence of severe acute respiratory syndrome coronavirus 2 replication and tropism in the lungs, airways, and vascular endothelium of patients with fatal coronavirus disease 2019: an autopsy case series. *J Infect Dis* 2021:223 (1 March). DOI.1093/infdis/jiab039.
2. Milewska A, Kula-Pacurar A, Wadas, J, et al. Replication of severe acute respiratory syndrome coronavirus 2 in human respiratory epithelium. *J Virol* 2020; 94e00957-20.

From the Editors

The editors thank Dr. DuVal for her feature article on Vaccine Hesitancy.

The aim of this weekly newsletter is to serve as a source of information for the UT Southwestern community which can lead to better understanding and control of a new disease (Covid-19) caused by the pandemic spread of an emerging viral pathogen (SARS-CoV-2). We welcome questions, comments, and suggestions for topics and authors.