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Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth

Possible Mental Health Pandemic

Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID) and a top White House COVID-19 advisor, is concerned how Americans will react once the pandemic is controlled. An American Psychological Association survey has noted high stress levels among people because of the pandemic. Hence, there are concerns about a possible mental health pandemic.

The survey has revealed the following:

- 61% of respondents reported experiencing undesired weight changes since the pandemic started.
- 67% reported changes in their sleep habits, with 35% reporting that they slept more while 31% slept less.
- 23% of the respondents reported drinking more alcohol to tackle stress.
- 47% reported that they delayed or canceled healthcare services because of the pandemic.
- 48% reported that their stress levels had increased. (*WebMD*)

UK COVID Variant More Deadly

The B.1.1.7 strain, first identified in Britain, is 30-100% more deadly than previous dominant variants. The strain is now found in over 100 other countries. Scientists have stated that it is about 40-70% more transmissible than previous dominant variants. In a UK study, published in *The BMJ*, infection with the new variant resulted in 227 deaths among 54,906 COVID-19 patients, compared to 141 deaths among the same number of patients matched for age, sex, sociodemographic background, date of infection, etc., who were infected with other variants. (*Mint*)

Data Suggest Vaccine 94% Effective in Preventing Asymptomatic Infection, Say Pfizer and BioNTech

Pfizer Inc and BioNTech SE stated that real-world data from Israel suggests that their COVID-19 vaccine is 94% effective in preventing asymptomatic infections. This would mean that the vaccine could significantly reduce transmission. The latest analysis of the data from Israel shows that the vaccine was 97% effective in preventing symptomatic disease, severe disease and death. This is in accordance with the 95% efficacy reported by the companies from the late-stage clinical trial in December. (*Reuters*)

Molnupiravir for Treatment of COVID-19

Interim phase 2 results from the oral experimental COVID-19 drug molnupiravir were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2021 Annual Meeting. The drug led to significant reduction in the infectious virus in symptomatic patients who had tested positive for COVID-19 during the previous 4 days but were not hospitalized. After 5 days of treatment, none of the subjects who received molnupiravir had detectable virus, while 24% who received placebo did. (*Medscape*)

Mental Health Impact of COVID-19

A new survey looked at the mental health impact of COVID-19 globally. The findings revealed high rates of trauma and clinical mood disorders related to the pandemic. The survey was conducted by Sapien Labs in eight English-speaking countries and included 49,000 adults. About 57% of respondents reported having experienced some COVID-19–related adversity or trauma. About a quarter had clinical signs of or had a risk for a mood disorder. Just 40% of the respondents described themselves as succeeding or thriving. (*Medscape*)

Is One mRNA Vaccine Dose Enough for People Who have had COVID-19?

Individuals who have had COVID-19 may need only one dose of the Pfizer/BioNTech or Moderna vaccine to get the effect of two doses. The disease seems to prime the body to produce antibodies seen with the two-dose vaccine regimen, reported an exploratory study presented at the virtual Conference on Retroviruses and Opportunistic Infections. The study looked into the titer

levels of antibodies among patients who had COVID-19 and those who did not… (*Medpage Today*)

Is Pollen Driving COVID-19 Infection?

Some scientists have identified a pattern to the recurring waves of COVID-19 infection across the globe. They noted that as pollen levels increased in outdoor air across 31 countries, cases of COVID-19 increased. However, certain other studies point to the contrary, indicating that peaks in pollen seasons correspond to a decline in the spread of some respiratory viruses, such as COVID-19 and influenza. There's even some evidence that pollen may compete with the virus known to cause COVID-19 and may help prevent infection. (*Medscape*)

COVID-19 Vaccination in Immunocompromised

In a study with 436 COVID-naïve subjects who received a first dose of mRNA vaccine, a mere 17% attained detectable antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On the contrary, among immunocompetent individuals who were vaccinated, 100% attained detectable antibody levels. It was noted that individuals taking antimetabolites, **such as mycophenolate or azathioprine,** had about five times lesser odds of developing antibody responses (8.75% detectable antibody in those taking antimetabolites compared to 41.4% in those not taking them).

Considering these findings, the Centers for Disease Control and Prevention (CDC) guidelines for vaccinated individuals should be updated, warning immunosuppressed people that they still may be prone to COVID-19 following vaccination.

It is clear that immunosuppressed people need their second vaccine dose. Additionally, it is important for immunosuppressed people to understand that they are not necessarily immune after receiving the vaccine, and should consult with their providers about antibody testing. (*Medpage Today*)

Blood Type A Linked to COVID-19 risks

Blood type A has been found to be linked with a greater risk of severe COVID-19 in one recent study and with a higher risk of contracting the disease in another study. Dr James Szymanski of Montefiore Medical Center and Albert Einstein College of Medicine in New York City, co-author of one of the studies, stated that their study indicates that blood Group A may be associated with a greater risk, while the second study gives one possibility on the 'how' part. That study suggests that the receptor-binding domain (RBD) of the SARS-CoV-2 virus interacts with respiratory cells via the blood Group A antigen. (*Medscape*)

Child Vaccinations Required for Herd Immunity

Anthony Fauci, Director of the NIAID, stated that while it is not known what the magical point of herd immunity is, but if a major proportion of the population is vaccinated, it will be good. He added that children will have to be in that mix. He estimated that 70-85% of the population would need to be vaccinated or immune in order to attain herd immunity. (*WebMD*)

Changes to the Sebum Lipidome with COVID-19 Infection

In a study published by *Lancet EClinicalMedicine*, sebum samples were obtained from 67 hospitalized patients, 30 of whom were COVID-19 positive and 37 were negative. Lipidomics analysis detected 998 reproducible features. Lipid levels were depressed in COVID-19-positive individuals, suggesting dyslipidemia. (https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00066-3/fulltext)

Variants may Escape Vaccines

Antibodies induced by the Moderna and Pfizer vaccines appear to be considerably less effective when it comes to neutralizing certain variants. A new study collected blood samples from 99 people who had been given one or two doses of either vaccine and evaluated the vaccine-induced antibodies against engineered virus that mimic 10 variants circulating across the globe. Five out of the 10 variants were highly resistant to neutralization, even when the study participants had received both doses of the vaccines, reported researchers in *Cell*. All of the five highly resistant variants had mutations in the spike [K417N/T, E484K and N501Y]. The proportion of neutralizing antibodies was found to decline 5- to 6-times against the variants discovered in Brazil. Neutralization declined 20- to 44-fold against the variant discovered in South Africa. It appears that vaccine-induced antibodies may find it harder to neutralize variants with E484K. (*Reuters*)

Older Individuals More Likely to Catch COVID Again

A new study suggests that older individuals who have recovered from COVID-19 cannot assume that they have immunity against a second attack. The study suggests that those below the age of 65 are less prone to reinfection. The study, conducted in Denmark, noted that those below 65 had nearly 80% protection for at least 6 months against contracting COVID a second

time. Contrary to that, those above 65 had only 47% protection. Authors of the study, published in the *Lance*t, say that it is important to take measures to protect elderly people, who also have an increased likelihood of death from COVID-19. The study confirms previous findings that reinfection is rare in younger, healthy people, but the elderly have a higher risk of catching the infection again. (*The Guardian*)

Women in 40s, 50s Who Survive COVID have Higher Odds of having Persistent Problems

Women in their 40s and 50s seem to have a higher risk of long-term problems following discharge from hospital after COVID-19. Several of them may suffer from months of lingering symptoms like fatigue, breathlessness and brain fog, noted two UK studies. In one study, 5 months following discharge, COVID-19 patients who were also middle-aged, white, female, and had other health problems including diabetes, lung or heart disease, had a higher likelihood of reporting long-COVID symptoms. A second study by the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) revealed that women below 50 years of age were more likely to have worse long-term health outcomes compared to men as well as older participants, even in the absence of any underlying health conditions. (*Reuters*)

Kaleido Biosciences Says Its Experimental Oral Drug Reduces COVID-19 Recovery Time, Hospitalizations

Kaleido Biosciences has stated that in an early trial, its experimental oral treatment reduced recovery time and hospitalizations as well as emergency room visits among patients with mild-to-moderate COVID-19. KB109, the experimental treatment, decreased the number of hospitalizations, emergency room visits and urgent care visits by 51% in the study that included 350 patients, and by 62% among patients who had one or more comorbidities. This treatment is a targeted, synthetic glycan that works by changing the composition and metabolic output of gut microbes. (*Reuters*)

Pfizer and Moderna Vaccines Effective for Healthcare Workers

Data from healthcare workers in the United States and Israel have confirmed the effectiveness of the Pfizer and Moderna vaccines against COVID-19. The data are published in *The New England Journal of Medicine*.

Pooled data from employees from the University of California, San Diego and the University of California Los Angeles health systems suggest that during a system of aggressive testing, carried out during a spike in COVID-19 cases in the general population, **there was a dramatic decline in the rate of new infections among the staff, beginning the second week after the first dose of the vaccine was given.**

Testing revealed **new cases in 2.5% of those tested within the first week following the first dose, 1.2% in the second week, 0.7% in the third week, 0.4% during the week following the second dose and less than 0.2% during the second week following the second dose.**

In North Texas, workers were also vaccinated amid the largest COVID-19 surge in the region. Here, 2.61% of unvaccinated employees developed the infection compared to 1.82% of partially-vaccinated workers and 0.05% of fully-vaccinated employees. There was more than 90% reduction in the number of employees either in isolation or quarantine, thus preserving the workforce when it was needed the most during the surge. (*Medscape*)

SARS-CoV-2 Variants Detected in Animals

Veterinarians in Texas and the UK have identified infections with B.1.1.7 among dogs and cats. Animals in the UK study were also found to have heart damage. However, it is not clear if the damage was caused by the virus or was already there and was detected because of their infections.

Researchers at the Institut Pasteur, Paris noted that the B.1.351 and P.1 variants of concern, first detected in South Africa and Brazil, respectively, can infect mice. Thus, the virus seems to have a potential new host. Older versions of the virus couldn't infect mice as they could not bind to receptors on their cells. However, these two variants can.

Good: This will assist scientists conduct experiments in mice easily. Earlier, conducting an experiment with SARS-CoV-2 in mice needed the use of a special strain of mouse that was bred to carry human angiotensin-converting enzyme 2 (ACE2) receptors on their lung cells. Now, since the mice can contract the infection naturally, any breed can be used.

Bad: Virus could now have more and varied ways to spread. (*Medscape*)

Rituximab therapy has been found to be tied to more severe COVID-19 among patients with inflammatory rheumatic and musculoskeletal diseases in a study published in *The Lancet Rheumatology*.

From April 15 till November 20, 2020, investigators looked at data from 1,090 patients who had

inflammatory rheumatic and musculoskeletal diseases and suspected or confirmed COVID-19 from the French RMD COVID-19 cohort. Sixty three of these patients were treated with rituximab, particularly for rheumatoid arthritis (49%), antineutrophil cytoplasmic antibody-associated vasculitis (17%) and systemic sclerosis (11%). Of the 1,027 patients who were not given rituximab, a subgroup of 495 patients had diseases for which rituximab is a known treatment option. (*Lancet Rheumatology*)

Moderna and Pfizer-BioNTech Vaccines Effective in Real-world Settings at Preventing COVID Infections

The Moderna and Pfizer-BioNTech COVID-19 vaccines are proving to be highly effective for the prevention of symptomatic and asymptomatic infections under real-world settings. There has been a discussion whether vaccinated people can get asymptomatic infections and transmit the virus and the findings suggest that transmission may be highly unlikely. Virus variants were in circulation when the study by researchers at the CDC was conducted, but the vaccines still provided robust protection. In line with the clinical trial data, a two-dose regimen prevented 90% of infections by 2 weeks following the second dose. Following one dose, 80% of infections were prevented by 2 weeks. (*NY Times*)

COVID-19 Risk in Adult Congenital Heart Disease

Most adults with congenital heart disease (CHD) do not appear to have an increased risk of COVID-19 mortality; however, certain subgroups may have a high risk, reports an international study. Fever, dry cough and malaise seem to be the most common presenting symptoms. Sixty patients had no presenting symptoms but underwent testing on the basis of known exposure or an upcoming procedure. A total of 179 patients (17%) were hospitalized and 67 patients (6.4%) needed ICU admission, 36 of whom had to be intubated.

There were 24 COVID-19–related deaths, with a case/fatality rate of 2.3% (95% confidence interval [CI], 1.4-3.2%). This is in line with a reported cumulative world fatality rate of 2.2%. Mortality rates and severe course varied by CHD diagnosis and were found to be the highest in patients with Eisenmenger physiology (13%), cyanosis (12%) and pulmonary arterial hypertension (10%). The findings are published in the *Journal of the American College of Cardiology*. (*Medscape*)

New COVID Vaccines Needed within a Year

Around two-thirds of epidemiologists from across the globe state that we will need new or modified vaccines for COVID-19 within a year. A survey of 77 epidemiologists from 28 countries by the People's Vaccine Alliance, reported that about 66.2% predicted that the world has a year or even less before the available vaccines become ineffective against the variants.

Around one-third (32.5%) of the surveyed epidemiologists said that ineffectiveness would be seen in 9 months or less while 18.2% said it will be seen within 6 months or less. Around 88% of those surveyed said that persistently low vaccine coverage in many countries would increase the likelihood of emergence of vaccine-resistant mutations. (*Medscape*)

When variants of SARS-CoV-2 started surfacing in late 2020, there were concerns that they might elude the immune responses generated by previous infection or vaccination, thus making reinfection more likely or vaccination less effective.

NIAID researchers evaluated blood cell samples from 30 people who had recovered from COVID-19 before the virus variants emerged. It was noted that **CD8+ T-cell continued to remain active against the virus.**

The investigators explored if CD8+ T cells in the blood of recovered COVID-19 patients, who had been infected with the initial virus, could recognize the three key variants: B.1.1.7, B.1.351 and B.1.1.248.

Investigators noted that the SARS-CoV-2-specific CD8+ T-cell responses were largely intact and recognized virtually all mutations in the variants that were studied.

The T-cell response in convalescent individuals, and in individuals who have been vaccinated, do not seem to be affected by the mutations in these three variants, and should protect against emerging variants.

Optimal immunity to the virus needs strong multivalent T-cell responses besides neutralizing antibodies and other responses to protect against current SARS-CoV-2 strains as well as the emerging variants. (*NIH*)

Measles Vaccine as Base for Experimental COVID-19 Vaccine

Measles vaccine is among the safest and most effective vaccines. The vaccine has been shown to be safe in both children and adults, and provides long-term protection against the measles virus. It uses a live, weakened strain of the measles virus.

Researchers have used it to develop an experimental vaccine against SARS-CoV-2. They created and evaluated a series of measles-based vaccine candidates. The vaccines were developed by inserting genes for

different forms of the coronavirus spike protein into the measles vaccine genome.

The modified measles virus serves as a vehicle and carries the gene for the spike protein into the body. The cells are instructed to produce the coronavirus spike protein, thus prompting the immune system to produce antibodies. This guides the immune system to neutralize the virus when encountered.

The study findings have been published in the *Proceedings of the National Academy of Sciences*.

Researchers found the most promising vaccine candidate, which produced the highest levels of neutralizing antibodies against SARS-CoV-2 in rodents. The vaccine carried the gene for the stabilized prefusion version of the spike protein, which forms the basis for the available vaccines.

The new vaccine, named rMeV-preS, yielded neutralizing antibody levels in rodents higher than those seen in patients who have recovered from COVID-19. The vaccine also evoked a robust T-cell response.

Researchers also assessed if the vaccine would protect against SARS-CoV-2 infection. Using golden Syrian hamsters, they noted that the vaccine protected them from infection and also prevented viral replication in the lungs and nasal passages.

This new candidate may offer several advantages. The measles vaccine is known to be safe, effective, and long-lasting. Several experimental measles-based vaccines against other viruses are also being evaluated in clinical trials. The new vaccine could protect against both COVID-19 and measles. (*NIH*)

Super-spreader Events Driving Variants

Super-spreader events are pivotal to the survival and predominance of new variants.

If the transmission of the virus only occurs one person at a time, a new variant cannot gain dominance and will die out in the population by chance.

Even strong variants can die out if they are not by chance transmitted in a super-spreader event.

Early super-spreader events that infect over five people are critical to the survival of a variant, while super-spreader events that infect over 20 people are critical to its dominance.

Even a highly infectious new variant will need a super-spreader event to help it overtake a current variant. (*Reuters*)

Vaccines Effective Against New York Variant

Antibodies induced by the Pfizer/BioNTech and Moderna vaccines as well as the antibody therapy from Regeneron, can neutralize a coronavirus variant currently surging in New York.

The New York variant contains mutations E484K, S477N and D235G. Experts were concerned that the variant might diminish antibody efficacy. However, new results suggest that this potential problem is not a problem.

The mutations cause changes to the spike protein. The researchers exposed copies of the New York variant to blood obtained from individuals who had received either the vaccines or the antibody combination from Regeneron. Vaccine-induced antibodies were found to be highly effective at binding to the altered spike protein, and the Regeneron therapy was also a potent blocker of the virus, reported researchers. (*Reuters*)

Immune Response could Explain Rare Clots After AstraZeneca COVID-19 Vaccine

Rare but serious blood clots have been reported among some individuals who have received AstraZeneca COVID-19 vaccine. They appear to be similar to heparin-induced thrombocytopenia (HIT). Here, heparin incites the immune system to produce antibodies that activate platelets. Drugs apart from heparin can lead to clotting disorders resembling HIT, and it is suspected that in rare cases, this vaccine may act as another such trigger.

Four healthy individuals who got the AstraZeneca vaccine and developed clots appeared to have the same kind of antibodies that activate platelets and initiate clotting in HIT, noted researchers in a paper posted on Research Square.

Twenty individuals who were administered the vaccine but did not develop clots were found not to have these antibodies. (*Reuters*)

SARS-CoV-2 Neutralizing Antibody Responses and Duration of Immunity

Antibodies against SARS-CoV-2 may die out at different rates based on the severity of the infection. The researchers in a new study, followed 164 COVID-19 patients for up to 9 months following infection. Five distinct groups were identified based on patterns of neutralizing antibodies:

- Negative group - did not develop neutralizing antibodies at the 30% inhibition level. They comprised 12% of patients in the study.

- Rapid waning group comprised 27% of the study patients. They had varying early levels of antibodies from around 20 days of symptom onset, but they sero-reverted in less than 180 days.
- Slow waning group - 29% of the study subjects; they remained antibody-positive at 180 days following symptom onset.
- Persistent group comprising 32% of the study subjects. They had minimal antibody decline up to 180 days.
- Delayed response group comprising 2% of the subjects in the study. They had a marked increase in neutralizing antibodies during late convalescence (at 90 or 180 days after symptom onset).

In the study published in *Lancet Microbe*, the researchers stated that persistence of neutralizing antibodies had a link with disease severity and sustained levels of pro-inflammatory cytokines, chemokines and growth factors. T-cell responses did not have a clear link with the different patterns of neutralizing antibodies.

(*The Lancet Microbe*)

With input from Dr Monica Vasudev

The CDC and the WHO have Determined New Criteria for the Classification of Variants of SARS-CoV-2

The new designations include "variant of interest"; "variant of concern" and "variant of high consequence".

- *A variant of interest* is the one that has led to discrete clusters of infections in the United States or in other countries, or appears to be guiding a rise in cases. It carries gene changes indicating that it might be more transmissible or that may help it to evade immunity conferred by natural infection or vaccination. Treatments and tests may not work as well against it. The CDC is looking at three of these.
- *A variant of concern*, as proven through scientific research, is more contagious or leads to more severe disease. It may also diminish the effectiveness of treatments and vaccines. People, who had previously been infected with COVID-19, may become reinfected by the new strain. The CDC is looking at five of these.
- *A variant of high consequence* is the one that leads to more severe disease and increased hospitalizations. It leads to failure of medical countermeasures, such as vaccines, antiviral drugs, and monoclonal antibodies. None of the variants thus far fulfil this criteria. (*Medscape*)

How Much Physical Distance is Required to Safely Reopen Schools?

- A study, conducted in Massachusetts, published in the journal *Clinical Infectious Diseases*, noted that it did not make a difference to keep children 6 feet apart compared to half of that.
- Data over the last year have revealed that schools do not seem to be super-spreading environments.
- Any outbreaks that may have happened in schools were associated with exposures in the community or happened in schools in the absence of protective protocols.
- The nonrandomized study compared COVID-19 rates in 242 Massachusetts school districts. Some of them kept students 6 feet apart while others maintained 3-foot distance over a 16-week period between September 2020 and January 2021. Student case rates were found to be similar in districts with ≥3 feet versus ≥6 feet of distance between students after adjusting for rates of SARS-CoV-2 in the community.
- Among school staff, there were similar case rates in districts with ≥3 feet versus ≥6 feet of physical distancing.
- Study authors thus concluded that lower physical distancing policies can be adopted in schools with masking mandates.
- The CDC also now recommends that a 3-foot distance can be used in situations, where teachers are fully vaccinated with two doses of a COVID-19 vaccine.
- Physical distancing continues to be a part of the recommendations for schools, besides universal masking, hand hygiene, cohorting of students and teachers, and use of outdoor space when possible.
- How to achieve herd immunity to COVID when children are excluded from vaccination? At least 70% of the population is required to have immunity, either through vaccination or natural infection, in order to reach herd immunity.
- In the US, about 25% of the population is below 18 years of age. Considering the number of adults refusing vaccination, it would be difficult to attain herd immunity through vaccination unless children and teens are included.
- Pfizer has completed enrollment for a clinical trial for older children (age 12 and up) and Moderna is having a trial underway in adolescents. (*Medpage Today*)

HCFI Round Table Expert Zoom Meeting on "Covishield Vaccine Halted in Some European Countries: Evidence-based or Knee Jerk Reaction?"

13th March, 2021 (11 am-12 pm)

Participants: Dr KK Aggarwal, Dr Shashank Joshi, Dr Suneela Garg, Dr DR Rai, Mrs Upasana Arora, Ms Balbir Verma, Dr KK Kalra, Dr Ashok Gupta, Dr Anil Kumar, Ms Ira Gupta, Dr S Sharma

Consensus Statement of HCFI Expert Round Table

- If the reactogenicity is uncontrolled, inflammation is likely.
- Delayed local injection site reaction to vaccine is uncommon; they are likely due to T-cell–mediated hypersensitivity.
- Mantra: In susceptible high-risk (proinflammatory and/or procoagulative) individuals, reactogenic vaccines can trigger transient thromboinflammation, lasting for first few (up to 4) days.
- Muscle COVID vs. COVID disease: Vaccine-induced disease is nonpulmonary. In muscle COVID, nonreplicable dose of the gene is injected, whereas in COVID disease, the gene is replicable. Vaccine is a fixed-dose, whereas in the disease, the dose is variable. In vaccine, the acute inflammation lasts for up to 4 days, whereas in the disease, the inflammation lasts for 10 days or more.
- Individuals with microalbumin in urine, C-reactive protein (CRP) >1 and 6-minute walk text (MWT) <200 m are high risk.
- Acanthosis nigricans is procoagulative or prothrombotic state.
- This vaccine is going to be more reactogenic than mRNA vaccine.
- Reactogenicity is different from allergenicity and immunogenicity.
- Cases of disease enhancement are being seen. If vaccine is given in the presence of non-neutralizing antibodies, these patients may develop some degree of nonpulmonary disease enhancement presenting with high-grade fever and high CRP.
- Considering the large coverage of Covishield, the reported adverse drug reactions (ADRs) seem to be reasonably less. Direct cause-effect relationship has not been established.
- The Indian vaccination program perhaps has the largest pharmacovigilance database, but there is a need to simplify the system and make it single point reporting, harmonize the ADR reporting and make it hassle-free and digital.
- Maharashtra is in the second surge. In Maharashtra, the Vidharbha and Marathwada regions were less exposed during the first surge. There were gatherings, no masking and no physical distancing and total lack of adherence to COVID appropriate behavior protocol. In Amravati, Akola, clusters of cases were seen. Whole buildings were affected.
- There is an unusual strain, which is spreading rapidly, but it has good recovery and case fatality rate is very low. Testing frequency had dramatically come down. In Mumbai local trains, physical distancing is not possible and masking was scanty. Hence, double masking is being recommended.
- About 80% of cases in Maharashtra are asymptomatic. They do not home isolate despite stamp. In some districts, institutional quarantine is being done even for asymptomatic cases otherwise they become spreading points.
- Gut COVID is seen more; patients are coming with diarrhea. Sewage may be a source of infection.
- Contact tracing has been increased to 1:30.
- The positive signals are asymptomatic infection, faster recovery, younger age and lower death rates.
- Usually Maharashtra precedes the country; what is happening here, it is likely to happen in the rest of the country. Maharashtra is in the same stage as Europe was 2-3 months back. Rapid vaccination is the answer. Citizens have to take responsibility.
- Dissemination of findings of investigation of death after vaccine is important, whether related to the vaccine or not. Precautions to be taken by susceptible persons should be more widely disseminated.

Viral Vector Vaccines Don't Seem to Alter DNA

- Adenoviral vector vaccines have been in development for decades. However, only a few of them have been approved for use in humans.
- Adenoviruses are common cold viruses known to cause illnesses that range from cold-like symptoms to bronchitis, gastroenteritis and conjunctivitis.
- Most serotypes of adenovirus cause mild illness, while serotype 7 is linked with more severe illness. Older adults and immunocompromised individuals or those having pre-existing respiratory or cardiac disease may have worse illness.
- Since adenoviruses are so common, one problem with using them in vaccines is that people may

already have antibodies against them, which might overwhelm them before they can do their work.

- Researchers try to overcome this issue by using adenoviruses that humans are not likely to have encountered before.
- Five adenovirus vector vaccines for COVID-19 are in use across the globe.
- Each of them works on the same basic principle, while delivery platforms may differ. The AstraZeneca/Oxford vaccine uses the ChAdOx1 platform, which is based on a modified chimpanzee adenovirus.
- The Johnson & Johnson vaccine makes use of a proprietary AdVac platform, which constitutes a recombinant human adenovirus (adv26). It's the same platform that the company uses in its Ebola virus vaccine (approved in Europe) and its investigational Zika, respiratory syncytial virus (RSV) and human immunodeficiency virus (HIV) vaccines.
- Sputnik V uses recombinant human adenoviruses Ad26 and Ad5 for the first and second doses, respectively.
- China's CanSino vaccine uses recombinant human adenovirus Ad5.
- In the 1990s, study on adenoviruses for use in gene transfer therapy to treat diseases like cystic fibrosis began.
- Adenoviruses induced robust T- and B-cell immune responses, leading to quick viral clearance but this limited their purpose in gene therapy. But as adenoviral vectors induced a strong immune response, it made them key candidates for developing vaccines against infectious diseases.
- Scientists have therefore been working on adenoviral vector vaccines against several viruses, including Zika, RSV, HIV, influenza, dengue and Middle East respiratory syndrome (MERS). During the Ebola outbreaks in West Africa and the Democratic Republic of the Congo (DRC), two adenoviral vector vaccines were developed and deployed. Adenoviruses can also be genetically modified for targeting and eliminating cancer cells.
- The platform that is being used in the AstraZeneca/Oxford vaccine had been in clinical trials in humans for over a decade for several other diseases.
- Adenoviruses can be used almost like a plug-and-play system. The platform doesn't need to be changed but we may switch out the gene of interest for a particular disease.
- Earlier work has provided data on dosage and safety of adenoviral vector vaccines in humans.
- Safety data from several trials in humans showed that they are safe and incite good immune responses.
- Adenoviral vector vaccines seem to have similar side effects as other types of vaccines like flu shots, such as pain at the injection site, headache or mild fever.
- Adenoviruses deliver DNA that enters the cell nucleus.
- Unlike retroviruses such as HIV or lentiviruses, wild-type adenoviruses do not have the enzymatic machinery which is required for integration into the host cell's DNA. This makes them good vaccine platforms for infectious diseases.
- Engineered adenoviruses used in vaccines have been further debilitated by deleting chunks of their genome. Therefore, they are not able to replicate, further increasing their safety.
- The cell lines that are used for adenovirus vaccines are well characterized cell lines. They are nonintegrating, which means that there is no evidence in humans and multiple animal models of vector-borne DNA integrating into a host.

(*Medpage Today*)

Women and COVID vs. Women and Vaccine

- CDC: Side effects from the vaccines appear to be worse in women. For example, 63 out of 66 reported cases of anaphylaxis occurred in women.
- Men in acute disease suffer worse outcomes. Men appear to have three times greater likelihood of being admitted into the ICU compared to women.
- Men appear to be more vulnerable to severe outcomes from viral infections, as evidenced in severe acute respiratory syndrome (SARS) epidemic in 2003 and in MERS epidemic.
- Immune response seems to be stronger in women as compared to men. Is it related to the two X chromosomes with the hormones that women have more of? The answer is both.
- X chromosome is enriched for immune response genes.
- Before menopause, every immune cell in our bodies has receptors for estrogen and progesterone hormones. These hormones regulate the functioning of immune cells. They can turn the

responses on and off. This holds true for androgens as well, like testosterone in men. Testosterone is anti-inflammatory and turns off several initial antiviral, inflammatory types of immune responses that trigger and let the body detect that there is something foreign you need to mount a protective response.

- So, women have two X chromosomes allowing additional activation to protect against immune function and response, and they also have the hormones that turn on response to target the virus; and men have the hormone that turns off the ability to target the virus?
- In women, the responses that get turned on and help protect against a virus, **can become dangerous when they mount against one-self, as in** autoimmune diseases.
- In systemic lupus erythematosus (SLE), there are 9-to-1 women to men. That's where one starts attacking own DNA. In multiple sclerosis, one is attacking the lining of one's nerve fibers. About 80% of all autoimmune disease patients are women.
- Significantly more women suffer from long COVID compared to men.
- Anecdotal reports suggest that women with COVID-19 have reported changes to their menstrual cycles. The parts of the brain that are associated with induction of fever are also the parts that control the hormonal regulation of menstrual cycle. So, it is feasible to see a connection. The connection between the immune system and reproductive function is known.
- Many vaccine adverse events are mediated by inflammation. If women have more of the inflammatory responses which are required to protect you against infection, that could be accountable for the development of these types of adverse reactions.
- In 1993, Revitalization Act required inclusion of women in all clinical trials.
- In 1977, it was determined that women of reproductive ages should not be included in clinical trials. This was meant to protect pregnant women and their developing fetuses from any potential toxicological effects of drugs or in the case of vaccines, biologics. But eventually, women were completely excluded from clinical trials and we were not given autonomy to make a decision for themselves, to claim that they wanted or didn't want to be included.
- Government Accounting Office audit in 2016 of all NIH uncovered that now more women than men enroll in clinical trials.
- But what's not happening is that there is no separation of the outcome data from men and women and comparison of those data.
- So, publication of data from clinical trials often don't tell us whether a drug or whether a vaccine or an intervention worked equally well in men and women. Or if there were differences in adverse events. Usually that becomes known only after a drug or a vaccine or an intervention has come out in to the market.
- In COVID vaccines, women weren't really given the choice to participate. Pregnant women were not subjected to the vaccines by their own choice. And now, women are going to get the vaccine who are pregnant and have a higher risk of COVID and severe outcomes from COVID; they don't really know how the vaccine works in pregnancy. (*Medpage Today*)

Thrice-Weekly Antigen Test or Once-Weekly RT-PCR

Amount of virus: When an individual is initially infected with SARS-CoV-2 (Day 0), a minute amount of the virus starts replicating inside them until it becomes so abundant that it cannot be contained. The infected individual thus becomes infectious and can spread the virus to others. This transition to becoming infectious usually **occurs around Day 3. By about the 5th day,** infected individuals usually reach peak contagiousness. The person's immune system starts containing the situation, and from Day 5 onward, the amount of virus starts declining. After nearly a week of contagiousness, by about Day 9, the virus is repressed. Viral particles continue to remain for weeks or months but are no longer a threat to others.

Polymerase chain reaction (PCR) is a better test. It can potentially detect virus very slightly earlier, and for much longer. However, what is important is detecting contagious virus.

- In order to detect **contagious virus, antigen tests appear to work just** as well and do not detect virus that does not pose a threat.
- One may consider two screening strategies: once-weekly PCR or thrice-weekly antigen testing.
- Let us imagine Day 0 is Sunday. If a student gets infected at a weekend playdate, the virus starts replicating, but the level is lesser than the threshold

for detection if a PCR test is done on Wednesday. If the test results are received on Friday, they will be negative. This is true for how the student was on Wednesday; but false for Friday.

- The infectious student has a false reassurance; so do the classmates, teachers, parents, etc. The student stays in school. When the infected student is again tested on Wednesday, the results on Friday show it as positive. This time, it is true for Wednesday but false for Friday (considering contagiousness). After a week of being contagious in school, the student is now sent home to self-isolate and the classroom is quarantined.
- Now, due to false positives, another classroom ends up shutting down. The teacher had a distant infection from which she has recovered and is no longer a threat. But considering several classrooms now with positive tests, the school has an outbreak and shuts down.
- If the infected student had been assessed with thrice a week antigen testing, it would have been identified on Friday. The results would have come out immediately, say within 15 minutes. The student would have been advised to self-isolate at home, and close contacts would have been sent home to quarantine. The PCR-positive teacher would have tested negative with an antigen test. The class would not have had to quarantine, and there would not have been an impression of outbreak at the school.
- Daily antigen screening would be even better. If everyone is screened every day, positive cases can be detected (and isolated) before anyone gets exposed. But even in the absence of daily screening, antigen testing several times a week would allow early detection. (*Medscape*)

COVID-19 Vaccination for Patients with Rheumatic and Musculoskeletal Diseases

The American College of Rheumatology: Guidance on COVID-19 vaccination for patients with rheumatic and musculoskeletal diseases (RMDs)

- Decisions to be individualized, with regard to disease severity, comorbidities and treatments.
- Patients with underlying diseases should be given priority for vaccination.
- A patient with rheumatoid arthritis whose disease is controlled with hydroxychloroquine will probably have lesser risk than someone with severe vasculitis under treatment with intravenous cyclophosphamide or rituximab.
- Vaccination should be done when the underlying disease is well controlled, if possible. However, a theoretical risk for disease flare or worsening after vaccination still exists.
- No one vaccine preferred over another; patients should be given whatever is easily available.
- No need to delay vaccination for patients on hydroxychloroquine, sulfasalazine, leflunomide, apremilast or intravenous immune globulin.
- For patients treated with rituximab, vaccination should be scheduled to be started 4 weeks prior to the next rituximab dose. This recommendation is based on a study that demonstrated differences in response to influenza vaccination on the basis of timing of rituximab dose.
- Methotrexate should be withheld for a week after each dose of the vaccine. This recommendation was based on studies of pneumococcal and influenza vaccines.
- A similar recommendation has been made for JAK inhibitors, owing to concern about the effects of this drug class on interferon signaling that may lead to decreased vaccine response.
- Abatacept must be withheld for a week prior to and after the first dose of the vaccine. This recommendation was based on findings of a possible negative effect of this drug on the immunogenicity of the vaccine. Furthermore, the first dose tends to prime naive T cells; CTLA4 inhibits naive T-cell priming; and abatacept is a CTLA4-Ig construct.
- Intravenous cyclophosphamide is usually given at intervals of 2 or 4 weeks. The recommendation in this case was to give cyclophosphamide dosing a week after the vaccine doses, if possible.
- It was recommended that rituximab be administered 2-4 weeks following the second vaccine dose if possible, but only if the disease is controlled enough to allow such a delay. This recommendation was based on immune responses to other vaccines, and it may not be possible to fully generalize this to the COVID-19 vaccine. (*Medpage Today*)

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