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HCFI Dr KK Aggarwal Research Fund

CORONAVIRUS UPDATES

Delta Variant Spreads by Cell-to-Cell Fusion

Compared to the spike protein on the previous versions of the coronavirus, the spike on the Delta variant has a better capability to break into lung cells and fuse them together, according to a preprint posted on BioRxiv.

Spread by cell-to-cell fusion enables the virus to spread faster in infected individuals and partially hide from the immune system. And by spreading through cell-to-cell fusion, the virus reduces its chances of encountering immune system cells that can attack and inactivate it, said Markus Hoffman of Georg-August-University Göttingen in Germany, co-author of the study. These "skills" might make the Delta variant more transmissible, and the resulting illness more severe. It was also found that although the Delta variant can evade antibodies, it is not completely resistant. (*Source: Medscape*)

Germany Strongly Recommends Mixing of COVID-19 Vaccines

Germany has become one of the first countries to make a strong recommendation for the mixing of coronavirus disease 2019 (COVID-19) vaccines on the basis of efficacy. The German Standing Committee on Vaccination (STIKO) said that people who receive a first dose of the Oxford-AstraZeneca vaccine *"should get an mRNA vaccine as their second dose, regardless of their age."* STIKO said that current study data suggest that the immune response generated after a mixed dose vaccination is superior. (*Source: CNN*)

Sickle Cell Disease Patients with History of Pain are at Risk of Severe COVID-19

Patients with sickle cell disease (SCD) having a history of disease-related comorbidities have been reported to have a greater risk for worse COVID-19 outcomes. A new study published in the journal *Blood Advances* has shown that children were more likely to require hospital admission for COVID-19, if they had frequent prior acute care visits for pain (relative risk [RR] 2.15, $p < 0.0001$), and had SCD-related heart and lung comorbidities (RR 1.61, $p = 0.0001$).

- Previous acute care visits for pain were the most common SCD-related comorbidity among children (55.5%) as well as adults (78.5%).
- History of pain was also a risk factor for hospital admission in adults (RR 1.78, $p = 0.002$).
- Children with a history of pain (RR 3.09, $p = 0.009$), SCD-related heart and lung comorbidities (RR 1.76, $p = 0.03$), and SCD-related renal comorbidities (RR 3.67, $p < 0.0001$) had a greater risk of developing serious COVID illness.

The researchers said, "SCD is a chronic inflammatory disease. An infection like COVID-19 that targets the lungs can lead to decreased oxygenation and blood hypoxia, which promotes sickling, vaso-occlusive episodes and pain." Patients at high risk should consider vaccination. (*Source: Medpage Today*)

Repurposing Hepatitis C Antiviral Drugs as Possible Treatment of COVID-19

An antiviral combination sofosbuvir/ledipasvir, used to treat hepatitis C infection, and an antiprotozoal drug nitazoxanide may eliminate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), according to preliminary results presented at the International Liver Congress 2021. Sofosbuvir/ledipasvir was particularly efficacious. Molecular docking studies that make use of computation to find ligands that bind to proteins, revealed that both sofosbuvir/ledipasvir and nitazoxanide might block key proteins in SARS-CoV-2.

The study grouped 190 patients with mild and moderate COVID-19 infections into three groups. One group was given sofosbuvir/ledipasvir, another group also received nitazoxanide. All the three groups also received standard care. The effect of sofosbuvir/ledipasvir appeared within 5 days and viral clearance was achieved in most patients within 2 weeks. Nitazoxanide had a weaker effect but still appeared to achieve a benefit. No serious adverse events or mortality was recorded. (*Source: Medscape*)

US FDA Cautions About Increased Risk of Guillain-Barré Syndrome with J&J COVID-19 Vaccine

The US Food and Drug Administration (FDA) has revised the Janssen COVID-19 vaccine fact sheet for healthcare providers administering vaccine (vaccination providers) and for recipients and caregivers to include a warning about increased risk of Guillain-Barré syndrome following vaccination.

The Fact Sheet for Recipients and Caregivers notes that vaccine recipients should seek medical attention right away if they develop any of the following symptoms after receiving the Janssen COVID-19 Vaccine: weakness or tingling sensations, especially in the legs or arms, that's worsening and spreading to other parts of the body; difficulty walking; difficulty with facial movements, including speaking, chewing or swallowing; double vision or inability to move eyes; or difficulty with bladder control or bowel function... (*Source: US FDA*)

Beta Variant may also be More Transmissible

The second wave of COVID-19 in South Africa, primarily driven by the Beta variant (B.1.351), recorded a dramatic increase in the number of cases compared to the first wave (240.4 per 1,00,000 people vs. 136 per 1,00,000, respectively), hospital admissions (27.9 per 1,00,000 vs. 16.1 per 1,00,000) and deaths (8.3 per 1,00,000 vs. 3.6 per 1,00,000), as per a study in *The Lancet Global Health*. A multivariable analysis of the second wave showed a 31% increased risk of in-hospital death (adjusted odds ratio [OR] 1.31, 95% confidence interval [CI] 1.28-1.35). Mortality was particularly high when the hospitals were stretched to their capacity. According to the authors, the Beta variant binds more strongly to the angiotensin-converting enzyme 2 (ACE2) receptors thereby increasing the risk of transmission. (*Source: Medpage Today*)

Do not Ignore Atypical Symptoms in Older Adults with Severe COVID-19

A study reported in the *Journals of Gerontology: Series A* stated that over a third of older adults who were hospitalized with COVID-19 during the early months of the pandemic had an atypical presentation, with a mix of typical and atypical symptoms. Almost a quarter of patients ages 65 and older presented with functional decline, while 11.3% presented with altered mental status and around 9% had gastrointestinal symptom. Among those with an atypical presentation, 49% presented with atypical symptoms only. But, patients with typical symptoms were 1.39 times more likely to be admitted to the ICU than those with atypical symptoms.

Study author, Allison Marziliano, PhD, from the Feinstein Institutes for Medical Research in Manhasset, New York said, *"While we found that atypical presentation in older adults does not necessitate the same need for ICU-level care as typical presentation (often characterized by respiratory distress), it must not be dismissed, as those presenting atypically have just as poor short-term outcomes of hospital length of stay, 30-day readmission and hospital mortality as those older adults presenting typically"... (Source: Medpage Today)*

Some Countries are Adopting the Mix-and-Match COVID Vaccines Strategy

Despite the data being preliminary, certain countries are going ahead with mixing and matching mRNA and adenoviral vector COVID-19. Germany has recommended to mix-and-match, encouraging citizens to follow AstraZeneca vaccine dose with a dose of an mRNA vaccine. Chancellor Angela Merkel followed her initial AstraZeneca dose with a shot of Moderna in June. Canada and Thailand have also started administering vaccines on a heterologous schedule.

The European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) have not issued any specific recommendations, but say in a press release that the approach "may allow populations to be protected more quickly and make better use of available vaccine supplies."Neither the World Health Organization (WHO) nor the CDC endorse the approach. (*Source: Medpage Today*)

Journal Retracts Study on Masks in Children

JAMA Pediatrics has retracted a research letter *"Experimental assessment of carbon dioxide content in inhaled air with or without face masks in healthy children: a randomized clinical trial"* published online June 30, 2021, which suggested that children should not be forced to wear face masks as masks may harm them by exposing them to high carbon dioxide levels. The research letter had reported unacceptably high levels of carbon dioxide as per German standards in air inside masks worn by children in a laboratory environment. In the retraction notice, the editors cited "numerous scientific issues", also including questions over the applicability of the CO_2 measurement device and the validity of the study conclusions.

CDC does not outline any known risk to children from wearing face masks, and has recently recommended that unvaccinated children should wear masks when school reopens in the fall... (*Source: Medpage Today*)

A Different Approach to Reach the Unvaccinated

Ozarks Healthcare, based in the city of West Plains, Missouri in the United States adopted a unique approach to encourage people to come forward to take the vaccine. They recently issued an impassioned plea for people to get vaccinated, even if it is done in secret.

They offered to answer any questions about the vaccine and help with scheduling in a recent statement. The health system said in a statement: "If you are afraid of walking into a public area where you might be seen getting your vaccine, we will work to accommodate even more of a private setting for you to receive your vaccine."

Amid misinformation and vaccination status largely divided by political lines, making a public appeal to offer the COVID vaccine in private seems to be a unique approach... (*Medpage Today*)

With inputs from Dr Monica Vasudev

HCFI Round Table Expert Zoom Meeting on "Delta Plus Variant and Third Wave of COVID"

3rd July, 2021 (11 am-12 noon)

Key points of HCFI Expert Round Table

- India is currently in between waves. In North India, the second wave is almost over. A potential third wave looms large.
- The coronavirus is a medium sized virus, but has the largest mRNA genome. The virus has 4 or 5 structural proteins (S, M, N, E and HE). Each of these structural proteins has a function to perform and is better understood today. The spike protein is crucial for receptor binding.
- The SARS-CoV-2 binds 10-20 times more strongly to ACE2 receptors than the SARS-CoV. The concentration of ACE2 receptors is highest in type 2 alveolar cells followed by the bronchial epithelium, buccal epithelium, upper gastrointestinal (GI) epithelium, myocardial cells, proximal tubule cells of the kidneys and bladder urothelial cells. It is now known that it also binds to the pancreatic β cells.
- Antibody-dependent enhancement, i.e., antibodies can create a backdoor enhancement for viral replication.
- The Delta variant is B.1.617.2, which is predominantly seen as a mutation in the spike protein.
- Large number of cases in the UK and USA are Delta variant.
- The second wave in India had a geometric spike. As per the prediction susceptible-infected-removed (SIR) model, the wave should have continued for much longer, but there is a sudden decline in the number of cases, i.e., a higher peak and a very sharp and precipitous decline. The reasons for this sudden fall in the cases are being explored. The second wave was predominantly driven by the Delta variant.
- New symptoms to watch out for in the second wave are nausea, abdominal pain, hearing impairment, vomiting, diarrhea, GI complications, joint pain, weakness, loss of appetite, skin rash, discoloration of finger and toes.
- The second wave has not yet ended in the country; around 40,000 new daily cases are still being reported. Of these, around 10,000 are from Maharashtra, another 10,000 are from Kerala and the remaining 20,000 are from the North East, West Bengal, Odisha, Telangana, Andhra Pradesh and Tamil Nadu (at the time of the meeting).
- The three strains that emerged from genomic sequencing and which predominantly led the second wave are 617.1 (Kappa variant), 617.2 (Delta variant) and 617.3. The Alpha variant was still present in Delhi, Punjab and Haryana.
- A new variant, Delta plus, has become a cause for concern and has been red flagged. Delta plus or AY.1 has a new K417N mutation, similar to the Beta variant (first found in South Africa). This mutation was mainly seen in UK and Nepal prior to being detected in India.
- The first Delta plus was in the UK, where it was found that it was more transmissible, had a tighter binding to the ACE2 receptor and escaped the monoclonal antibodies; it also caused immune escape.
- Genomic sequencing labs in India documented around 41 cases of Delta plus (at the time of the meeting). Genomic sequencing is still ongoing. There were two deaths: one was not vaccinated, the second was >80 years with comorbidities.
- These genomic samples were taken at the end of May, so the patients have survived for at least 4 weeks with mild-to-moderate disease; so far this variant does not appear to be sinister in nature.
- No connection has been found between AY.1 strain found in Nepal and AY.1 strain found in Ratnagiri in Maharashtra (Mango belt).
- The features of Delta variant are cluster spreading, faster spreading and faster recovery with low case mortality.
- Delta is a cause for concern as it is rapidly transmissible and cluster spreading. It may be faster recovering but virulence is not known. Delta has immune escape mainly to Covishield.

- Delta is now the predominant strain in the country; in Mumbai, Kappa strain is still present and in Punjab, the Alpha strain is still found.
- Early observation shows that Delta plus is also fast spreading but probably not as fast as the Delta variant.
- Three challenges when unlocking: Keep the test positivity rate by reverse transcription polymerase chain reaction (RT-PCR) <5%, try to saturate 70% of population with vaccination and have zero tolerance for nonadherence to COVID-appropriate behavior and follow COVID-appropriate protocol.
- The second wave is not abating in some parts of the country because of the rapid unlocking.
- Earlier we vaccinate, lesser will be the intensity of the next wave, if and when it comes.
- The factors which may cause an outbreak are immune escape and lack of adherence to COVID-appropriate behavior.
- To prevent this, make sure to double mask whenever in public, follow COVID-appropriate protocols, take both vaccine doses at the earliest, aggressive vaccination and have better ventilated environments. Avoid crowded and poorly ventilated spaces.
- The third wave may come faster and the second wave may merge into the third wave, which is expected somewhere between September and November.
- It appears that the disease is becoming endemic in Maharashtra and Kerala; hence, testing, tracking and treating strategy needs to be ramped up regularly.
- Five states are contributing to 36% of cases in the country, with Kerala contributing the maximum.
- Any modeling will take into consideration factors like how we unlock, how much is our susceptible pool (though serosurveys show 60-70% seroconversion; we do not know how long these antibodies will last for), how much of the population is following COVID-appropriate behavior, how much percentage of population is immunized and the efficacy of the vaccines. How we manage the second wave will be the most important.
- COVID-appropriate behavior and immunization coverage will ultimately decide about the susceptible pool of the population.
- Efforts are ongoing to educate about the management of children. IAP is closely involved in this.
- Probably the third wave will not be as ferocious as the second wave, but we have to closely monitor the genetic variations. Genomic sequencing therefore becomes very important.
- There is a need to be more transparent in sharing data between organizations.
- Some punitive measure for nonadherence to COVID-appropriate behavior is required.
- Issues such as the need for a booster dose and mixing of two vaccines are being discussed at the National Technical Advisory Group meetings.
- Vaccination can prevent development of new variants.
- The gold standard to detect neutralizing antibodies is the plaque reduction neutralization test (PRNT). It is done in special (BSL3) labs. N serology test is an indirect test; it is expensive and cannot be done as a routine. A test for T-cell response is not yet available in routine practice.
- Hybrid immunity is immunity due to natural infection, immunity due to vaccine and a combination of both.
- Vaccines are protective; antibody tests may be misleading; antibody tests may not be sufficient; continue to wear the mask.
- How we unlock and how strictly we follow COVID-appropriate behavior will decide about the next wave.

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