

HCFI Dr KK Aggarwal Research Fund

HCFI Round Table Expert Zoom Meeting on “Breakthrough Infection after COVID Vaccination”

6th November, 2021 (11 am-12 noon)

Key points

- Coronavirus disease 2019 (COVID-19) vaccines are effective at preventing infection, serious illness and death. Vaccinated persons are 8 times less likely to be infected and 25 times less likely to experience hospitalizations and death.
- Vaccines are not 100% effective; therefore, some people may still get COVID-19 even if they are fully vaccinated.
- Immunocompromised persons may not have adequate levels of protection after the 2-dose primary vaccine series. They should continue to take all precautions. The Centers for Disease Control and Prevention (CDC) has recommended an additional dose of the vaccine for moderately to severely immunocompromised persons.
- The CDC has defined breakthrough infection as when a person tests positive for COVID-19 at least 2 weeks after becoming fully vaccinated.
- Breakthrough infections are related to vaccine efficacy and immune evasion.
- A study in Washington state of more than 4 million fully vaccinated individuals showed breakthrough infection rate of about 1 in 5,000 between January 17 and August 21, 2021. But more recent studies have shown breakthrough infection rates of around 1 in 100 fully vaccinated people.
- It is not easy to track every case of breakthrough infection. Most studies give different figures and are not truly representative of a population. According to the CDC, breakthrough cases are underreported as many such infections are asymptomatic or mild and therefore not reported.
- The rate of fully vaccinated Americans who have experienced a breakthrough case resulting in hospitalization or death has remained below 0.01% (CDC).
- As per media reports, over 25% of healthcare workers (HCWs) were infected with the Delta variant despite full vaccination.
- As per a German study reported in the media, the suspected breakthrough infections among symptomatic COVID-19 cases in the 18 to 59 years age group were 8.2%.
- As per government data, 2.6 lakh people have tested positive for COVID-19 after being vaccinated in India till August 3 after administration of around 53 crore vaccine doses. While 1.71 lakh breakthrough infections were reported in people who had taken one dose of the vaccine, the number of breakthrough infections among the fully vaccinated population was 87,049. Kerala alone has recorded 40,000 breakthrough infections.
- Breakthrough infection is seen more in the elderly population.
- A study of HCWs has found symptomatic breakthrough infections occurring in 15 persons (13.3%), out of which one required hospitalization (*Diabetes Metab Syndr.* 2021 May 3).
- A meta-analysis of 18 studies involving 2,28,873 HCWs found the risk of COVID-19 infection to be very low in both partially and fully vaccinated HCWs; 1.3% for fully vaccinated, 3.7% for partially vaccinated and 10.1% for unvaccinated HCWs.
- The immunocompromised persons are more at risk of developing a breakthrough infection. The CDC recommends that persons with weakened immune system receive a third dose of the vaccine 28 days after the second dose.
- It has also been suggested that being vaccinated reduces the chances of long COVID.
- Breakthrough infections can be prevented by following all safety precautions. Indoor gatherings where there is overcrowding or poor adherence to masks or are ill-ventilated should be avoided.
- The course of action after a breakthrough infection is similar to that after a COVID-19 infection. Isolation is still needed.
- There are no restrictions for travelers in the US and Dubai if they are fully vaccinated and they test negative for COVID. In Dubai, 200 or less people were allowed in a hall.
- The incidence of breakthrough infections remains the same, whether they are HCWs, who get the

infection in a healthcare facility or those who get the infection outside the healthcare facility.

- There is no perfect methodology to establish how the T cells respond.
- The human leukocyte antigen (HLA) system responds differently in different individuals to infections as well as vaccine challenges. This is an area that needs to be studied; it may then be possible to identify persons who actually need a booster dose of the vaccine.
- Cellular protection is variable in comorbidities.
- Reverse transcription-polymerase chain reaction (RT-PCR) is 87% to 93% specific for COVID with different methods.
- Studies have shown that after 3 months, the antibody levels start to decline and by 6 months, they decline significantly. People who are immunocompromised or have risk factors should be considered for a third dose. This is the right time for the Expert Committee to recommend a booster dose for HCWs, in particular those who are in direct contact with COVID patients and the immunocompromised persons as well.
- We must find out what is the half-life of immunity after vaccination.
- C-reactive protein (CRP) has excellent sensitivity for COVID but it is not specific to COVID.
- About 25% HCWs have been affected with the Delta variant.
- The currently available vaccines have been shown to be effective against the Delta variant, although work is ongoing to modify the vaccine as per the variants.
- Booster dose should be the same as the primary vaccination. The body should not be re-challenged.

Participants: Dr KK Kalra, Dr Ashok Gupta, Dr DP Lokwani, Dr Arun Jamkar, Dr DR Rai, Ms Balbir Verma, Ms Ira Gupta, Mr Saurabh Aggarwal, Dr S Sharma

HCFI Round Table Expert Zoom Meeting on “Monoclonal Antibodies in COVID-19”

Speaker: Prof Dr Arun Jamkar, Ex-Vice Chancellor, Maharashtra University of Health Sciences, Nashik; Technical Consultant, Persistent Systems Ltd; Chief Medical Officer, Indx Technology, Distinguished Professor, SIU Pune

13th November, 2021 (11 am-12 noon)

Key points

- Where epitopes and receptor interactions are known and valid, monoclonal antibodies work. In COVID, the exact pathogenesis is still not well-understood.
- Kohler and Milstein provided the most outstanding proof of clonal selection theory by fusion of normal and malignant cells (Hybridoma technology) for which they were awarded the Nobel Prize in 1984.
- Transplant rejections were improved after the introduction of the first monoclonal antibody OKT3 in 1986. It was US Food and Drug Administration (FDA) approved for preventing kidney transplant rejection.
- The steps of preparation of antibodies are immunize animal, isolate spleen cells (containing antibody producing B-cell), fuse spleen cells with myeloma cells (using PEG), allow unfused B cells to die, add aminopterin to culture and kill unfused myeloma cells, clone remaining cells, screen supernatant of each clone for presence of desired antibody, grow chosen clone of cells in tissue culture indefinitely and harvest antibody from the culture.
- Nomenclature of monoclonal antibodies: If it is murine, it is called “omab”; if it is chimeric but still human, it is called “ximab” and once it is humanized (>60%), it is called “zumab”. When it is fully humanized, it is called “umab”.
- Monoclonal antibodies prevent viral binding and/or fusion with host cell. They bind to the spike protein, prevent the virus from attaching to human cells and tag it for destruction preventing the development of severe COVID-19.
- Tocilizumab was one of the most successful drugs in managing cytokine storm, which is a lethal event in COVID-19 and is mediated through interleukin (IL)-6 and tumor necrosis factor (TNF)- α .
- In a meta-analysis of 16 randomized controlled trials, tocilizumab reduced mortality risk in severe to critical disease and lowered mechanical ventilation requirements. It also facilitated hospital discharge.
- If monoclonal antibodies are given within 7 days of getting the infection, they are most successful. It does not allow the virus to attach to the cell. Hence, it can be a game changer in the treatment of COVID. Only symptomatic patients – mild or moderate - can be given monoclonal antibodies.
- Casirivimab and imdevimab antibody cocktail was used in India for the first time in Medanta hospital.

- There are around 75 monoclonal antibodies available today in various stages of development. Many of them are in phase III trial.
- Bamlanivimab + etesevimab and casirivimab + imdevimab reduce viral load when given early on in the course of the infection and favorably impact clinical outcomes in patients with mild-to-moderate disease.
- Bamlanivimab + etesevimab bind to different but overlapping epitopes in the spike protein receptor-binding domain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Their distribution was paused in the US because both the Gamma and Beta variants have reduced susceptibility to bamlanivimab + etesevimab. But distribution has been reinstated in states with low rates of these variants.
- The FDA issued emergency use authorization (EUA) for treatment of mild-to-moderate COVID-19 in adults and children ≥ 12 years weighing ≥ 40 kg and who are at high risk for progressing to severe disease and/or hospitalization. It is given as IV infusion (casirivimab 600 mg + imdevimab 600 mg). Subcutaneous injection is an alternative route. It is to be administered as soon as possible after a positive RT-PCR and within 10 days of symptom onset in high-risk patients.
- Bamlanivimab + etesevimab is not yet available in India.
- According to an observational study from Pune, combination therapy of tocilizumab and steroids is likely to be safe and effective in the management of COVID-19-associated cytokine release syndrome.
- The 2018 Nobel Prize in Physiology or Medicine was awarded to James Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation. Inhibition of these molecules by immune checkpoint inhibitors can successfully activate the immune system to fight cancer.
- The immune checkpoint inhibitors act by blocking checkpoint proteins (cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) from binding with their partner proteins. This prevents the “off” signal from being sent, allowing the T cells to kill cancer cells.
- Anti-CTLA-4 opened a new field called immune checkpoint therapy.
- Ipilimumab blocks the CTLA-4 checkpoint protein. Pembrolizumab and nivolumab target the programmed cell death protein 1 (PD-1), while atezolizumab target the PD-L1 protein.
- Cancer is a disease of genome. In a survey of oncologists from the US, overall, 75% reported using next-generation sequencing (NGS) tests to guide treatment decisions.
- Monoclonal antibodies can be used not only in cancer, but also in rheumatoid arthritis.
- Challenges to the use of monoclonal antibodies are diversity of the virus, bioavailability in the lungs (most commonly affected organ).
- A larger clinical trial needs to be done with the support of the government.
- We need to find out which receptors are being used for monoclonal antibodies and which action has to be stopped. We are studying the results of the pathogenesis and not the origin and trigger of the pathogenesis.
- Monoclonal antibodies are costly and have to be administered under supervision. Infectious disease specialists at the tertiary center can supervise doctors at the periphery (community health center).

Participants: Dr KK Kalra, Dr Ashok Gupta, Dr Suneela Garg, Dr DP Lokwani, Dr Arun Jamkar, Dr Milind Deshpande, Ms Ira Gupta, Dr S Sharma

Moderator: Mr Saurabh Aggarwal

Coronavirus Updates

Interim results show 77.8% effectiveness of covaxin against symptomatic COVID

Interim results from a phase III trial show that Covaxin (BBV152) was highly effective against laboratory-confirmed symptomatic COVID-19 in adults. In the final per-protocol analysis, measured 14 days after the second dose, the overall vaccine efficacy was 77.8% against symptomatic COVID-19 and a higher efficacy against severe COVID-19 of 93.4%. It was well-tolerated with no safety concerns. Covaxin is an inactivated whole virus vaccine formulated with a novel adjuvant and has a two-dose regime given at a gap of 28 days... (Source: *The Lancet*)

France recommends against Moderna vaccine for people younger than 30 years

The Haute Autorite de Sante (HAS) or the French National Authority for Health has recommended that people younger than 30 years should be given the Pfizer COVID-19 vaccine in place of the Moderna vaccine citing “very rare” risks linked to myocarditis with the

Moderna vaccine. According to HAS, this risk appears to be around five times lesser with Pfizer's jab compared to Moderna's jab... (Source: Reuters)

ECG findings in COVID-19 patients

A review of the ECG findings in COVID-19 patients reported in the journal *Cardiac Electrophysiology Clinics* has described QRS axis changes, conduction abnormalities, arrhythmias (most commonly atrial fibrillation) and ST-segment and T-wave changes. The study authors write, "Clinicians should be cognizant of some of the reported ECG changes, such as abnormal QRS axis in nearly 20% of patients, conduction abnormalities in approximately 20%, atrioventricular block in about 2.5%, and premature beats in nearly 10% of patients." ST- and T-wave changes can be due to myocardial infarction or myocardial injury secondary to myocarditis, or microthrombi and so should be clinically correlated... (Source: *Cardiac Electrophysiology Clinics*).

Unvaccinated persons have 20 times higher mortality risk

A study from Texas Department of State Health Services, US has concluded that compared to fully vaccinated people, unvaccinated persons were 13 times more likely to become infected with COVID-19. They were also 20 times more likely to die from COVID-19-related complications. The risk of death was 23 times higher in unvaccinated people in their 30s and 55 times higher for unvaccinated people in their 40s... (Source: *Texas Department of State Health Services*)

COVID-19 generates 8 million tons of plastic waste

COVID-19 has resulted in over 8 million tons of mismanaged plastic waste globally as of August reports the *Proceedings of the National Academy of Sciences*. And, more than 25,000 tons has entered the global ocean. Nearly 90% of the excess plastic waste generated during the pandemic were the medical waste from hospitals; individual personal protective equipment (PPE) contributed to just 7.6% of the plastic waste, while 4.7% came from packaging. Almost half of all the mismanaged plastic waste was produced in Asia... (Source: *PNAS*)

LZTFL1 gene predisposes South Asians to high risk of severe COVID-19

Researchers from Oxford University have identified a gene "leucine zipper transcription factor-like 1 (LZTFL1)" leads to a twofold increase in the risk of respiratory failure and death from COVID-19. The high-risk form of this gene is present in 60% of South Asians, 15% of Europeans and just 2% of persons with

African-Caribbean ancestry and 1.8% of people of East Asian descent. This gene does not affect the immune system, but affects the lungs. The study published in the journal *Nature Genetics* attempts to explain why some ethnic groups are at higher risk from COVID... (Source: *Medscape*)

More than 28 million excess years of life lost in 2020 during pandemic

A *BMJ* study has reported that more than 28 million excess years of life were lost in 2020 in 31 countries, with a higher rate in men than women (except New Zealand, Taiwan and Norway, where there was a gain in life expectancy in 2020). Excess years of life lost linked with the COVID-19 pandemic in 2020 were over fivefold higher compared to those linked to the seasonal influenza epidemic in 2015. The study evaluated the changes in life expectancy and years of life lost in 2020 associated with the COVID-19 pandemic in 37 upper-middle and high-income countries. The highest reduction in life expectancy was observed in Russia, the United States, Bulgaria, Lithuania, Chile and Spain... (Source: *BMJ*)

Single dose J&J COVID-19 vaccine is 74% effective in preventing COVID-19

A retrospective analysis of electronic health records of nearly 9,000 adults from the multistate Mayo Clinic Health System who received the single dose J&J shot during the first 5 months of its authorization reported in *JAMA Network Open* showed an actual effectiveness of 74%, which is in accordance with the 66.9% effectiveness reported in the phase III clinical trial of the vaccine. COVID-19 cases declined by 3.73-fold after the vaccination. The vaccinated group had 60 cases of COVID-19 compared to 2,236 cases in the unvaccinated group ... (Source: *Medscape*)

"When to test": A free online tool from NIH to decide if you need a COVID test

The National Institutes of Health (NIH)'s Rapid Acceleration of Diagnostics (RADx) initiative has launched the "When to Test Calculator for Individuals", a companion to the version for organizations introduced last winter. It is available at <https://whentotest.org/>. The new individual impact calculator helps to decide when should a person get tested for COVID-19—now or soon. It was developed and tested by computer modelers to help people determine if they are at risk of getting or transmitting COVID-19 based on a few variables, including vaccination status, transmission rates in the geographic area, and mitigation behaviors... (Source: *NIH*)