COVID-19: younger patients develop fewer neutralising antibodies, study finds

But older patients who had more neutralising antibodies did not recover faster

R. PRASAD

Analysis of blood samples from 175 patients with mild COVID-19 disease who were discharged from the Shanghai Public Health Clinical Centre as on February 26 revealed that about 30% of patients had unexpectedly low levels of antibodies against novel coronavirus (SARS-CoV-2). Ten patients had such low levels of neutralising antibodies that these could not be detected, while two patients showed very high levels.

The study threw up another surprise – the plasma of elderly and middle-age patients had significantly higher amount of neutralising antibodies and spike-binding antibodies than young patients. The median age of the patients was 50 years and the median length of hospital stay was 16 days and median disease duration was 21 days.

The study was posted on *medRxiv* preprint server on April 6. Preprints are yet to be peer-reviewed and published in scientific journals.

Age a factor: The higher amounts of antibodies found in older patients may be due to a "strong immune response" in aged people. ▪ GETTY IMAGES

Disease duration

Though about 30% of patients failed to develop high amounts of neutralising antibodies even after recovering from COVID-19 disease, the disease duration was not longer than older patients. Likewise, older patients who had more neutralising antibodies did not recover faster. So immaterial of the amount of neutralising antibodies found, both young and old patients took the same time to recover.

The amount of neutralising antibodies generated in response to vaccination determines the efficacy of the vaccine in protecting against the virus. In this case, if infection with actual virus has not resulted in eliciting strong antibody response and hence elevated neutralising antibodies, it is not clear if the vaccine which had killed or weakened viruses would be able to produce high amounts of antibodies.

But the researchers were not able to detect viral DNA in the blood samples collected, and information about viral load was not available for all the patients. So it is not known if the young patients had lower viral load thus resulting in lower amount of neutralising antibodies. "This study is preliminary," the authors caution.

The team led by Jinghe Huang was able to detect coronavirus-specific neutralising antibodies 10-15 days after onset of the disease, and the level remained stable thereafter.

Mild symptoms

All the 175 patients included in the study had only mild symptoms. The researchers excluded patients who had been admitted to intensive care units because many of them already had antibodies from donated blood plasma.

The efficacy of passive antibody therapy, otherwise called as convalescent plasma therapy, relies on the concentration of neutralising antibodies in the plasma. The low levels of neutralising antibodies in younger patients who have recovered from the disease strongly suggest that convalescent plasma should be titrated before being used for therapy.

The authors wonder if the low levels of neutralising antibodies in about 30% of patients would put them at risk of infection rebound or reinfection and suggest that further studies are undertaken to understand this.

Immune response

The higher amounts of neutralising antibodies found in older patients may be due to "strong immune response" in aged people, the study suggests. But whether the elevated neutralising antibodies found in older people protect them from progression to severe and critical conditions is not known. But the world over, it has become clear that older COVID-19 patients are at higher risk of adverse disease outcomes. Studies carried out earlier using the SARS virus infection in aged macaques resulted in elevated immune responses, resulting in more severe pathology than younger adult macaques.

The researchers also found that antibodies generated in response to novel coronavirus (SARS-CoV-2) could bind with 2003 SARS strains. However, the binding was not able to stop the SARS virus from replicating. This raises the possibility of developing a vaccine that might be effective against both novel coronavirus and the 2003 SARS virus.

When should we blow the shofar?

With COVID-19, we are fighting an invisible enemy

PARTHA P. MAJUMDER

The novel coronavirus (SARS-CoV-2) has already left a large footprint; it has spread itself far and wide. And it is spreading even further. It has killed in thousands. A wartime situation prevails. Strangely, we are fighting an invisible enemy. And yet our ability to return victorious is not obvious. Especially, when we may be able to blow the shofar.

An infected person can transmit the virus directly to many uninfected persons. The larger this number - called the Basic Reproductive Ratio, R_0, pronounced R-nought - the more contagious is the disease caused by the virus. The faster it will spread in the community. R-nought can be viewed as the product of three numbers: (1) the number of days an infected person remains infective (that is, can infect others), (2) the number of susceptible persons available to infect and (3) the chance that a susceptible person gets infected. The easiest way to keep R-nought low is to keep ourselves distanced from every other person. That way, the chance that a susceptible person gets infected remains low. It is not sufficient to distance ourselves only from those who show symptoms of infection. We have to continue to distance ourselves from every other person. Many apparently normal persons may actually be infected without showing symptoms of infection. Therefore, just as R-nought influences the spread of COVID-19, our behaviour also influences R-nought.

A person infected with SARS-CoV-2 can remain infective for 10-to-14 days. During the initial phases of spread, there will be a large number of uninfected persons to infect. For SARS-CoV-2, R-nought has been estimated to be between 2 and 3. Let us take the best case scenario. Assume R-nought to be 2 and the infective period to be 10 days. Then, the first person will infect two others, each of whom will infect two others (22), each of these four persons will infect two others (23) and so on. In 10 days, this one infected person will have infected 2,046 persons. A person who is infected or has recovered cannot be infected again. At least not in the next several months or even years. An infection activates the immune system which learns to recognize the virus and remembers it. The next time the virus tries to infect him, his immune defenses are able to recognise and protect him against further infection. Therefore, as the infection spreads, there will be less and less number of uninfected persons to infect. An increasing number of persons in the community will have gained immunity from having been infected earlier. This is called herd immunity. (If there was a vaccine for SARS-CoV-2, it would have helped achieve herd immunity without a large number of persons being infected. A vaccine simulates the effect of an infection and builds immune resistance to the virus. We have eradicated polio in this way.) As herd immunity increases in the community, many infected persons will not find another person to infect during the entire infective period. R-nought will then be less than one, on average. Consequently, there will be few new cases arising and existing cases will recover or die. Spread of the disease will slow down and the pandemic will end.

COVID-19 may be long-lasting

There is also a related issue to consider. When there is an outbreak, persons in the community get symptomatically infected one after another. The length of time between appearance of two successive persons with symptoms of infection is called the Series Interval. This interval informs us about the spreadability of the virus. The shorter this interval, the greater the speed of spread through the community. For SARS-CoV-2, the Series Interval is between 5 and 7 days. For influenza, this interval is 1.3 days. Therefore, influenza spreads four to six times faster than COVID-19. Is this good news for us? The answer is no. COVID-19 is spreading through the community slowly. Herd immunity will therefore arise slowly. This means that the COVID-19 pandemic is going to last for a long time.

The current lockdown cannot go on forever. Is there a scientific basis to determine when the lockdown may be lifted? Will the lockdown be lifted only after everyone in the country becomes immune to the virus? No; we can never be sure that everyone has gained immunity. However, if the chance that an infected person finds a person to infect is sufficiently low, then the virus will stop spreading. Then the lockdown can safely be lifted. This will happen if a certain proportion of individuals in the country is immune. This proportion is called the "herd immunity threshold." It is calculated as $1-(1/R_0)$. For SARS-CoV-2, R_0 is 2 or 3. An R_0 of 2 would mean a herd immunity threshold of 1-(1/2) or 50%. An R_0 of 3 would mean a herd immunity threshold of 1-(1/3) or 67%. We should play safe. Therefore, lockdown can be safely lifted if about two-thirds of our population attains immunity to the virus. But how would we know that two-third of our citizens has gained immunity. We need to estimate this proportion by testing our citizens selected randomly and in large numbers. Surveillance testing in communities has now been initiated in India. We hope that the results of these tests will be used to determine when to blow the shofar.

A policy is immediately required

Daily wage earners are now unable to earn their daily bread. Families are going hungry. Enforcement of the lockdown is leading to clashes – of citizens with the police, between groups of villagers and so on. Yet lifting the lockdown before herd immunity threshold is achieved will be disastrous. However, a hungry person does not have the luxury of being mindful about personal and public health arising from this virus. Either food has to be provided by the Government and by those of us who can afford, or we will have to soften the lockdown and allow them to work. Certainly, all large gatherings – including religious and political gatherings – must continue to be banned. If distancing can be maintained and the net of symptom-monitoring and community-testing can be cast more widely, then allowing a minority of our citizens to work even during the period of lockdown may be a socially viable option. A policy is immediately required.

A compromise

It may be extremely difficult for us to ensure, as science dictates, that two-third of all our citizens have gained immunity. We may identify geographical regions where COVID-19 appears to be affecting people in large numbers. In these regions, lockdown may be extended, surveillance-testing intensified and spread of the infection more strictly monitored. Infected persons should be isolated. Further, contract tracing – identification and listing of persons in close contact with an infected person, testing to identify infected persons among contacts and isolating them or, if testing of all contacts is infeasible, isolating all contacts and following them up for signs of infection – will serve to reduce the likelihood of infection. Thereby R-nought will be reduced in that region. If the spread of the infection from these high-intensity regions can be arrested, then there will be an overall reduction of infection in the country. Of course, surveillance-testing and deep monitoring should continue at some level throughout our country to identify new pockets of high-intensity that may arise whether or not the general lockdown is lifted on April 14th. .

(The writer is currently an emeritus professor at the Indian Statistical Institute, Kolkata.)

Study indicates sex-specific differences in immune system

SHUBASHREE DESIKAN

A study led by researchers from Australia finds crucial differences in the way the immune system acting in the body fat of male and female mice operates. Studying the visceral adipose tissue (VAT) in the mice, they find key differences. Visceral adipose tissue is fat tissue that is found in the abdominal region, surrounding various organs. This includes perigonadal VAT which surrounds the ovaries in females and testes in males, which is what the researchers studied.

Controlling immune response

The perigonadal VAT taken from male mice had many more regulatory T cells (Treg) than that of female mice. These cells play a role in controlling immune response to the self and external cells, thereby protecting the body from autoimmune diseases such as rheumatoid arthritis or lupus. The Treg cells in the male VAT also showed a distinct phenotype, functional parameters and gene expression pattern compared to Treg cells in female VAT. "We found elevated expression of inflammatory genes in male VAT. A special population of stromal cells that made the cytokine IL-33 was exclusive to male VAT," says Ajith Vasanthakumar, from Department of Microbiology and Immunology, Peter Doherty Institute for Infection and Immunity, University of Melbourne, Australia. He is the first author of the paper published in *Nature*. "Historically, visceral adipose tissue was simply regarded as an energy storage [organ]. Many studies, however, have highlighted its endocrine function. Visceral adipose tissue has an endocrine function, meaning it secretes adipokines and hormones that play key roles in energy balance and metabolism," says Dr. Vasanthakumar.

It is known that men (in a similar manner to male mice) are more susceptible to metabolic diseases such as type 2 diabetes. "This is linked to higher adipose tissue inflammation in men compared to women, again similar to mice," says Dr Vasanthakumar. "Finally, we have previously shown that human adipose tissue (omental) harbours Treg cells of a phenotype similar to the one found in mice." Thus, it is likely that the difference in Treg cell distribution seen in the visceral adipose tissue of male and female mice would hold true in humans.

The study has implications for the way trials are conducted with animal models when carrying out research on diseases. For instance when studying metabolic disease, mostly male mice are used. This study implies that findings of such a test will not hold equally good for males and females.

"Until the recent past, for clinical trials mostly men were recruited although it is clear that disease susceptibility and response to drugs are different," he says. "In this context tailoring drugs to gender is a possibility in the future. We will continue to explore the role of sex hormones in metabolism and other inflammatory and autoimmune diseases."

Coronavirus: two vaccines enter human trials, 60 in pre-clinical stage

Include non-replicating viral vector and messenger RNA vaccines

ASWATHI PACHA

With the genetic information of the novel coronavirus (SARS-CoV-2) available online, governments across the globe, top private players, academics and not-for-profit organisations are working at a breakneck pace to find a COVID-19 vaccine.

According to the "DRAFT landscape of COVID-19 candidate vaccines" released by the World Health Organization (WHO) on April 4, two vaccines are currently being tested on humans.

This includes a non-replicating viral vector vaccine developed by CanSino Biological Inc. along with the Beijing Institute of Biotechnology. A non-replicating vector vaccine can be developed either using a virus that is killed or a part of the virus. Since it is not a complete virus, it cannot replicate inside the host; but the antigens trigger our immune system to produce antibodies, which help fight the disease in case we contract it in the future.

RNA vaccine

According to the Chinese Clinical Trial Registry, men and women between the ages of 18 and 60 were recruited and tests are being conducted on three groups of 36 participants each. Three dosages are being tested – low, medium and high.

Clinical trials: Forty-five subjects, 18 to 55 years of age, of both sexes, will enrol in tests. ▪ AP

The second is a messenger RNA vaccine developed by Moderna and National Institute of Allergy and Infectious Diseases. In RNA vaccines, the messenger RNA from the pathogen is used. The messenger RNA gets translated into antigenic protein recognised by our immune cells and antibodies are produced. But mRNA is a highly unstable molecule making it difficult to handle. So the mRNA is encapsulated in a small ball of fat or lipid nanoparticle (LNP). This LNP acts as a delivery vehicle that helps the mRNA cross the host cell membrane and once inside the mRNA is released.

According to the website clinicaltrials.gov, forty-five subjects (18 to 55 years of age of both sexes) will be enrolled and divided into three groups. They will receive an intramuscular injection on days 1 and 29 in the deltoid muscle.

An analysis published on April 9 in *Nature Reviews Drug Discovery* by the Coalition for Epidemic Preparedness Innovations (CEPI) notes that "the global COVID-19 vaccine R&D landscape includes 115 vaccine candidates, of which 78 are confirmed as active and 37 are unconfirmed (development status cannot be determined from publicly available or proprietary information sources)." Along with the two vaccines mentioned by WHO, the list includes one vaccine developed by Inovio Pharmaceuticals and two from Shenzhen Geno-Immune Medical Institute.

Vaccines from India

The WHO draft adds that 60 candidate vaccines are in preclinical trials. This list contains the DNA plasmid vaccine developed by Gujarat based Zydus Cadila and Live Attenuated Virus vaccine developed by the Serum Institute of India.

DNA vaccines are made by taking genes from the pathogen and inserting it into the host's body with a vector. The host cells produce the protein of the viral gene and this is recognised as a foreign antigenic protein by the host's immune system.

DNA vaccines are comparatively easy to make, transport, store and are cheaper. Live attenuated virus vaccine is created by reducing the virulence of a pathogen or weakening it, but still keeping it alive.

Why hospitals are hotbeds of coronavirus transmission

Once in contact with the virus on objects and surfaces, there is high risk of infection

R. PRASAD

Across the world, hospitals have become hotspots for novel coronavirus (SARS-CoV-2) infection. And hundreds of healthcare workers have been infected in many countries, and some have died too. While the availability and quality of personal protective equipment (PPE) and the duration of exposure with severe and critical patients have been a factor in determining if healthcare workers were safe or not, a study posted on March 16 in a preprint repository *medRxiv* reveals how certain areas in the hospitals and certain objects had more viruses.

In another study posted on March 16 in a preprint repository *medRxiv,* a team of researchers collected 626 samples from 13 hospital function zones, five major objects, and three major PPE from the Zhongnan Medical Center in Wuhan during the period February 7-27, 2020. Preprints are yet to be peer-reviewed and published in scientific journals.

The study was carried out as 1,688 healthcare workers had become infected with novel coronavirus in China, including 1,080 healthcare workers in Wuhan, the epicentre of the epidemic in China. Widespread hospital contamination could have resulted in occupational exposure for healthcare workers in the hospital on a daily basis.

Paradox: At 31.9%, the intensive care unit specialised for taking care of COVID-19 patients was the most contaminated in the hospital, the study found. ▪ GETTY IMAGES

Routes of transmission

The primary routes of transmission of the virus are through large respiratory droplets and close contact, and contact with surfaces and objects contaminated with the virus. Once in contact with the virus on objects and surfaces, there is high risk of infection.

The study led by Xinghuan Wang from the Zhongnan Hospital of Wuhan University found at 31.9%, the intensive care unit specialised for taking care of COVID-19 patients was the most contaminated in the hospital followed by obstetric isolation ward for COVID-19 pregnant women (28.1%), and isolation ward for COVID-19 patients (19.6%).

They found nearly 14% of all commonly used hospital objects and medical equipment had the virus on them. Among the most contaminated objects in the hospital were the self-service printers (20.0%), desktop/keyboard (16.8%), doorknob (16.0%), telephones (12.5%) and medical equipment (12.5%). In China, the self-service printers are commonly used by patients themselves to print out examination or test reports in a hospital.

At 20.3%, hand sanitiser dispensers were the most contaminated objects followed by hand gloves (15.4%).

Survival duration

Earlier, a team led by Vincent J. Munster from the National Institute of Allergy and Infectious Diseases found that the novel coronavirus survived up to one day on cardboard and three days on plastic. Now, another team of researchers led by Leo L. M. Poon from The University of Hong Kong found shorter survival time of the virus on different surfaces. Dr. Poon's team did not find any virus on printing and tissue papers after three hours, while infectious virus could be found on treated wood and cloth on the second day.

Both the teams published their results in a letter. While Dr. Munster's team published the results on March 17 in *The New England Journal of Medicine,* Dr. Poon's team published it in *The Lancet* on April 2.

Much like the NIAID team, the researchers from The University of Hong Kong found that the virus could persist longer on smooth surfaces – infectious virus could be found on glass and banknotes even on day three, while they could find viable, infectious virus on stainless steel and plastic up to day six.

The NIAID team had found that the virus survived the least time – four hours – on copper, while they could find virus for relatively longer time on plastic (three days) and stainless steel (two days). The virus survived for a day on cardboard.

The most interesting but disturbing finding published by Dr. Poon's team is the presence of infectious virus on the outer layer of the surgical mask even on day seven. But the amount of virus found on mask on day seven was only 0.1% of the original number.

Temperature and pH

The University of Hong Kong researchers also found that at room temperature, the virus could survive in a broad range of pH conditions – pH 3-10.

They also studied the ability of different disinfectants to kill the virus. Compared with hand soap, no infectious virus could be found five minutes after the virus culture was added to various disinfectants. The study thus shows that surfaces can be made free of the virus using regular disinfectants.

"The SARS-CoV-2 can be highly stable in a favourable environment but is also susceptible to standard disinfection methods," they write. They also caution that method they used to recover virus from different surface that were tested does "not necessarily reflect the potential to pick the virus from casual contact".