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Down To Earth

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THE WAR WITHIN

We barely understand the workings of our immune system

ILLUSTRATIONS: RITIKA BOHRA / CSE

IN SEARCH OF IMMUNITY

We constantly hear of pills and food supplements that we must consume or lifestyle changes we must inculcate to boost our immune system. Companies and even governments now sell or make recommendations about such products. The reality is that it has taken a pandemic for us to realise how little we know of immunity.

An analysis by

VIBHA VARSHNEY

IMMUNITY. Never before has this word been so bandied about as it is being now. It is said to have played a key role for most of the 28 million people worldwide who have made it through the novel coronavirus disease (covid-19) over the past 10 months. Even governments are pinning their hopes on this magic word as their economies limp back to action. But this belief in "immunity" has also made it the most abused word in recent months.

In July, just after the lockdown eased in India, Emami Agrotech launched its Healthy & Tasty Smart Balance Oil, with a tag line "*Ab banega har nivala,* immunity *wala*". The company based its claim on the fact that the oil contains vitamins A, C, D, E and omega 3 which can strengthen the immune system. In September, the Union Ministry of Chemicals and Fertilizers launched eight immunity-boosting products under the Pradhan Mantri Bhartiya Janaushadhi Priyojana (PMBJP), a campaign to provide medicines at affordable prices to the masses. Fortified with several vitamins and micronutrients, these products are now available for sale through PMBJP stores across the country. Speaking on the occasion, Minister of Chemicals & Fertilizers D V Sadananda Gowda said, "The launch of new nutraceuticals is significant in view of the COVID-19 pandemic. These products will help in boosting immunity of the people."

Since 2016, consumer goods company Hindustan Unilever has also been selling a immunity boosting hand sanitiser under its soap brand, Lifebuoy. The company claims that the product, prepared using a patented technology, not only kills germs and viruses instantly but also enhances the innate immunity of the skin by boosting its "antimicrobial peptides" (small proteins that act against a wide variety of microorganisms, from bacteria to fungi). The Drug Controller General of India has recently pulled up Hindustan Unilever for its claims calling it "misleading". The market, however, remains flooded with everything from pills and ayurvedic formulations to superfoods and wellness products that claim to boost one's immunity during the pandemic.

Immunity is not one thing. That's why it is hard to envisage being able to improve it. Even vaccine acts only against one particular infection and cannot improve immunity in any general sense

In June, barely four months after the first case of COVID-19 was diagnosed in India, Mumbai-based Pronto Consult analysed medical bills in eight cities and found that 92 per cent of the bills were against immunity-boosting products. The number historically has been below 40 per cent, says Pronto. Industry estimates show global market of immunity boosting food products is set to grow from US $16.31 billion in 2019 to $24.02 billion in 2023.

The trend exasperates immunologists. "There is no one thing called 'immunity' and it is hard to even envisage being 'able to improve' it," says immunologist Satyajit Rath, visiting professor at the Indian Institutes of Science Education and Research, Pune. Even vaccine, that works by changing the immune response, acts only against one particular infection and cannot "improve immunity" in any general sense. "I am yet to see any consistent body of evidence that any nutritional supplementation in an ordinarily healthy individual can 'improve' the immune response," he says.

It is irresponsible to make such claims and these should be monitored by law, says Shashank Tripathi, assistant professor at the Centre for Infectious Disease Research, Indian Institute of Science, Bengaluru. His fear is people might get overconfident because of such claims and expose themselves to the virus, believing that they are immune. These supplements can at best oil your engine, he says.

Their concerns stem from the fact that immune system is an extremely complex biological system and continues to confound scientists even over a century after scientists explained its workings; in 1908, the Nobel Prize in Physiology or Medicine was awarded to Ilya Ilyich Mechnikov and Paul Ehrlich for their contribution to explaining immune response.

Just like a country's military forces, the immune system's task is to distinguish

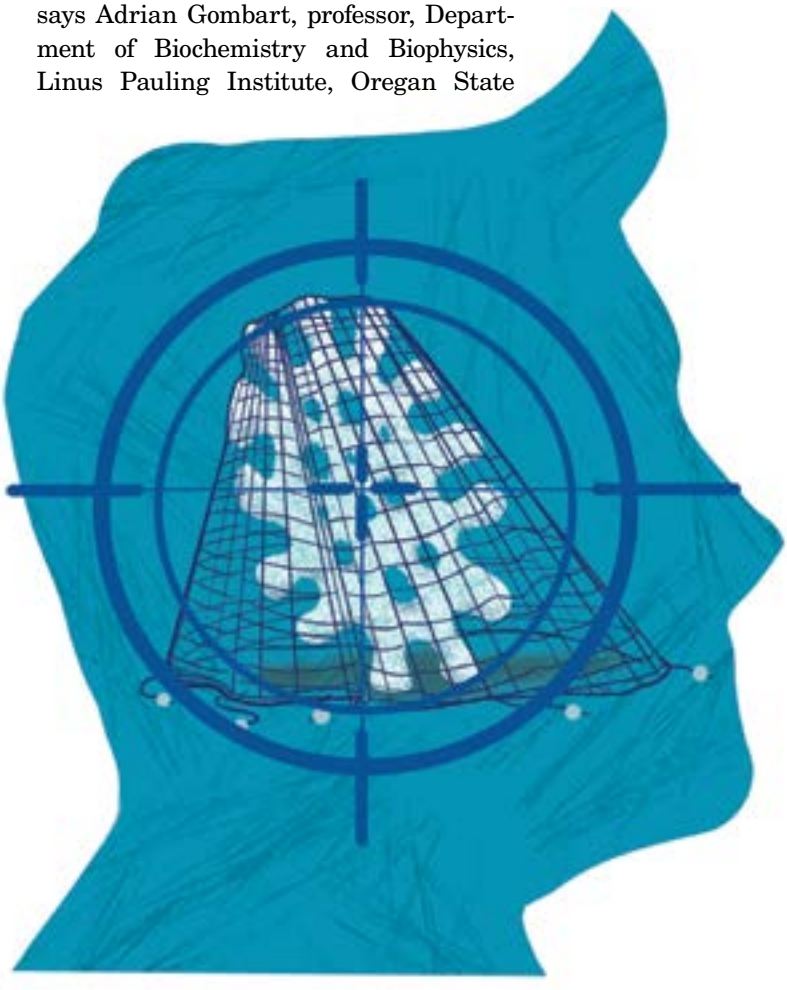
between "self" and "non-self" and defend the body by eliminating organisms that can cause infection. For this, it depends on a variety of organs, tissues, cells and proteins spread throughout the body and is continually in action. Broadly, it operates through its two arms: innate and adaptive. Innate immune system is the first line of defence against any incoming threat and consists of physical barriers like skin, airways and mucous layer of the digestive tract, and a cavalry of white blood cells that keeps circulating the body like a vigilant force. They are constantly on the lookout for foreign antigens, which are typically proteins on the surface of the invading bacteria or viruses. Some of its fierce personnel include phagocytes that simply swallow up the pathogens within minutes of getting alerted about an intrusion. Fever is the most common symptom of this war.

But most of the pathogens that cause serious infections in humans, particularly the ever mutating, microscopic viruses, have evolved strategies to circumvent or suppress the innate immune responses. Besides, a weak innate response is often observed in old people and those who have underlying health problems. For all such occasions, the innate immune system sends messengers to summon the adaptive immune system, which joins the war with its specialised forces—B cells and T cells. Over the next few days B cells tailor-make immunoglobulins (Ig), or antibodies specific for the antigen. These antibodies neutralise the pathogen by binding to its antigen and thus preventing it from attaching to host cell and entering it. For those pathogens that have already invaded the host cells, it calls upon T cells. The cytotoxic T cells—CD8+—neutralise the pathogen by directly destroying infected cells where the pathogen is multiplying, while helper T cells—CD4+—coordinate further attacks on the pathogen.

The war ends. But the cells do not drop their guard. Some of the B and T cells develop memory—which can persist for decades or even for a lifetime—and settle inside the lymphatic organs and tissues, such as spleen and thymus. These do not prevent reinfection but remember every pathogen they have ever overcome. The next time a familiar pathogen attacks the body, they act swiftly, without the days-long delay, and in more numbers, stopping

it from spreading throughout the body. Antibodies, like IgG, which becomes detectable in the blood once the immune response gains an upper hand, also continues to circulate in the bloodstream for a couple of weeks or months after the pathogen is cleared.

A healthy individual naturally possesses all cells of the immune system. But they proliferate and get trained only upon encountering a pathogen. This is how vaccination works. It exposes an individual to a pathogen or an antigen in a controlled manner, without making them sick, and creates memory cells against it that fight the disease. "One can measure blood levels of various immune cells to determine if immunodeficiency issues exist, but a clinician cannot tell who will have a better response to an infection based on baseline measurements before a person is sick," says Adrian Gombart, professor, Department of Biochemistry and Biophysics, Linus Pauling Institute, Oregan State University, US. No amount of supplements can also train the cells how to fight off a pathogen. Rather, excessive consumption of supplements can make you sick, very sick. *More on this later.*



Now, let's analyse what happens to a person who survives an encounter with a pathogen. Does it guarantee him the much aspired long-term immunity? Not necessarily, say scientists. First, because pathogens, such as viruses that cause common cold, do not elicit a strong immune response, and thus do not leave behind much of a memory. This makes us vulnerable to reinfection. Even vaccines against such viruses require regular booster shots to maintain immunity. Viruses are also quick to mutate and this makes immune memory against them useless.

Even antibodies, which are mere proteins and thus degrade over time, do not guarantee long-term immunity. This is the reason serosurveys, or surveys to assess the presence of antibodies in a population during the current pandemic, should be used to understand only the epidemiology of the disease and not to ascertain immunity developed by a person, to issue immunity passport or to assess herd immunity. This is also the reason the use of antibodies as therapy makes them unreliable. The Indian Council of Medical Research (ICMR) has recently said that its plasma therapy study on COVID-19 patients—which essentially works by harvesting antibodies from recovered patients and then administering it on those with acute symptoms to help them fight off the infection—did not really help.

THEN WHAT HELPS?

COVID-19 has innovated research projects on immune response like never before. Contradictory results are still confusing our understanding

Hope is mostly pinned on B and T cells that provide long-term immunity. First, some good news. In August this year, researchers from the Karolinska COVID-19 Study Group, Sweden, published a study

in journal *Cell* that maps SARS-COV-2-specific T cell responses in unexposed individuals, exposed family members and those sick with COVID-19. They found that T cells even in the seronegative exposed family members and those with asymptomatic or mild COVID-19. The researchers say these SARS-COV-2 memory T cells can provide long-term immune protection against COVID-19. This is unexpected considering that immunity against other coronaviruses is short-lived; as per some estimates it is just about a year. Another study, published in *Nature Reviews Immunology* on July 29, 2020, has also found a significant level of CD8+ and CD4+ T-cells in hospitalised COVID-19 patients.

But this does not seem to be universal, and overdependence on T cells is not advised. Observations suggest that a bout of the disease leads to T cell exhaustion where the surviving T cells in COVID-19 patients are not able to function at full capacity and leave the patients more vulnerable to secondary infection. A study published on May 5 in journal *Frontiers in Immunology* reports that COVID-19 patients with severe symptoms had lower T cell counts. Nonetheless, this understanding is important as it suggests that instead of focusing on respiratory function, it would be better to base treatment on T cell counts and their function—patients with low T cell counts should receive care urgently. The researchers also proposed that COVID-19 virus may not be attacking T cells directly but trigger a cytokine storm, which then drives down T cell numbers.

This finding is supported by research by Shiv Pillai, professor of medicine and health sciences and technology at Harvard Medical School, US, and his team who have found that COVID-19 patients with high levels of cytokines are less likely to develop long-term immunity against SARS-COV-2. Pillai's team found that the spleen and lymph nodes of deceased COVID-19 patients showed a distinct lack of germinal centres, which are integral in developing long-term immune response. These germinal centres are activated upon infection or vaccination and encourage B cells to mature into memory cells. The paper, published in *Cell* on August 19, also shows that helper T cells needed by germinal centres to develop are absent in severely ill COVID-19 patients. "The immune response we saw was likely because of a virus that could not be controlled in early stages. We suspect similar things happen with any severe viral infection (like Ebola or a novel flu virus like swine flu) but these other diseases have not been studied properly before," says Pillai. "What we have learnt could be applied to make vaccines produce better long-lived antibodies and we are working on that," he adds.

We know a lot about cells and the system of our immunity but know very little about how they respond to a stimulus. Our immune system is one of the most complex biological systems on this planet

But the fact is every research appears to have only deepened the mystery surrounding immune response. "We know a lot about the cells and system of our immunity but know very little about how they respond to a stimulus. Our immune system is one of the most complex biological systems on this planet. Millions of cells work together to counter a pathogen. Just imagine how much coordination is required. A small break in their coordination may result in disaster," says Rakesh Singh, associate professor at biochemistry department of the Institute of Science, Banaras Hindu University, Varanasi. "The probability of a non-specific response cannot be overruled as there is no accuracy even in a perfectly designed natural system."

What Singh means is that an immune cell primed for a specific pathogen or an antigen may provide partial protection against the second pathogen. When our immune cells are constantly exposed to various pathogens, they may acquire significant capability to cross protect. Take the example of BCG (Bacille Calmette-Guérin) vaccine used against tuberculosis. In this case, the immune cells are primed for specific bacterial antigens but they may have potential to protect from other pathogenic antigens. There are some indications that BCG vaccine protects against COVID-19. "Protection depends on

the quality of immune responses that have been developed in one's body against a pathogen," says Singh. Although, with the current level of knowledge it is difficult to quantify the quality of an effective immune response required for cross protection, measuring the numbers of antigen-specific memory B or T cells may help, he explains.

This is substantiated by the fact that SARS-COV-2 reactive CD4+ T cells were found in 20 to 50 per cent of the blood samples, collected before the virus was discovered in 2019. The researchers report in journal *Science* on August 4, 2020, that a range of pre-existing memory CD4+ T cells that can react to SARS-COV-2 and the four other common cold coronaviruses were present in the samples.

NATURE V NURTURE

The unknowns surrounding immune response do not end here. Have you ever tried to understand why cases of COVID-19 are low in African countries that have weak healthcare systems, crowding, lack of sanitation facilities and are poor?

Researchers from the Netherlands recently tried to find an answer for this. They analysed the impact of early and extensive testing, lockdown stringency, demography and environmental exposure to pathogens on the incidence of the disease. They narrowed down the reason for fewer than expected cases in Africa to be constant exposures to pathogens. Unlike the much talked about link between non-communicable diseases and COVID-19, there is little research on how infectious diseases such as HIV/AIDS, tuberculosis, and other respiratory infections or those caused by helminths affect COVID-19, they said in the August 7, 2020 issue of *Science*. The authors say such an exposure to microbes and parasites educates the immune system to guard against invading pathogens not only specifically but also non-specifically through "trained immunity", which involves reprogramming of innate cells. These cells on secondary encounter with a pathogen can show a stronger response or "virtual memory" in which virtual T cells expand in response to cytokines, rather than through antigens.

This could well be happening in India too. "Challenging day-to-day life with tuberculosis, malaria, dengue, chikungunya and many more pathogens likely made Indians more immune compared to several other nations. Hot weather and spicy, plant-based food habits might add Indians some degree of resistance to infection," says Rajalingam Raja, director, Immunogenetics and Transplantation Laboratory, University of California San Francisco.

But not everyone agrees with the theory. According to Rath, the low number of cases seen in India may simply be an accident of a late onset and inadequate diagnosis. Speculating about possible explanations for a phenomenon that may or may not be real is somewhat premature, he says. Tripathi elaborates further. "The logic that Indians have a better immune response because we live in an environment that has a lot of microbes is flawed. We are the number one country in infectious disease. We have the highest load of dengue, malaria and tuberculosis. It does not seem that living with a lot of microbes is protecting us from infections," he says.

This suggests that the "hygiene hypothesis", which postulates that early and chronic exposure to pathogens can activate immune cells and induce a strong immune response to counteract inflammation, fails to fully explain why some have better immune response than others.

As the world tries to understand this, the answer could be in their genetic makeup, the lifestyle they lead or the environment they live in. Studies show that Asian Indians have gained more genes that protect them from viral infections during evolution. "Two families of genes play in this protective function—one is KIR (killer Ig-like receptor) genes and the other is HLA (human leukocyte antigen) genes. Indians have more KIR genes compared to the Chinese and

Know thy immunity

From gestational age to gene and lifestyle, all regulate one's immunity response

Individual specifics

- Age
- Sex
- Genetics
- Co-morbidies

Exposure to microbes

- Infection
- Parasites
- Antibiotics
- Probotics & prebiotics
- Microbiota
- Preexisting immunity

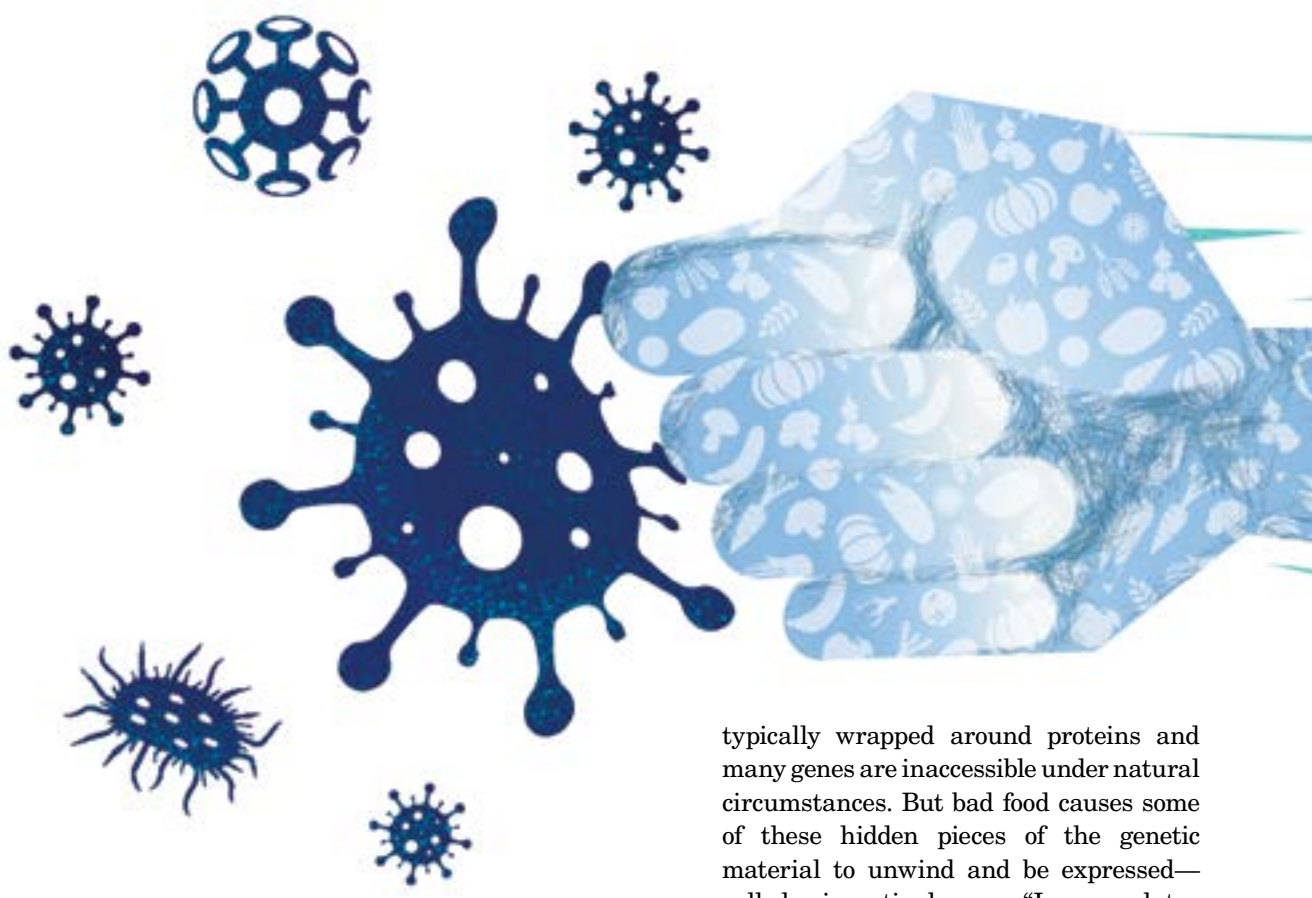
Perinatal life

- Gestational age
- Birth weight
- Breastfeeding
- Maternal antibodies
- Maternal infection during pregnancy
- Other maternal factors

Caucasians. These genes enable Natural Killer cells (usually classified as part of the innate immunity but also displays memory, just like the cells of adaptive immunity) and in case of COVID-19 pandemic, the Indian-specific immune genes are clearly playing a role in low spread of SARS-COV-2," says Raja. He explains that as humans migrated from Africa to India, they gained newer genes to help them adapt to the changing environment. People who reached the coastal areas, retained these genes as the environment there was variable too. On the other hand, those who reached the plains of China, where the environment is stable, lost the genes.

A similar advantage is also seen in people of African descent. In September 2014, the ImmVar Project published their initial findings in the *Science* on how ancestry affected T cell responses. The scientists analysed blood samples from 348 healthy volunteers representing African, Asian or European ancestry, isolated the CD4+ T cells and activated them in a cell culture to model their response to antigens. They then used computational analysis to measure which genes were turned on or off in the cells from each person. They found that there is stronger activation of some genes in people of African ancestry. They observed this specifically for a type of response in T "helper 17" cells that protect from microbes that enter airways or the intestinal tract.

But observations on incidence of COVID-19 in Africa and USA negate the possibility of genes providing protection against the disease. African in America have been found susceptible to the disease unlike those in Africa. Armed with such results, the COVID Human Genetic Effort, an international consortium that aims to discover inborn errors of immunity, plans to study hundreds of COVID-19 patients



from around the globe to understand the role of genes in the disease.

This is likely to be difficult as environmental factors and diet also play important roles in manifestation of a disease by leading to the expression of certain genes. Factors such as diet, exposure to toxins, lack of sleep, stress, lack of physical activity can regulate such expression.

It has been observed that consumption of junk food over long periods of time reprograms the genetic makeup of immune cells and their precursors in mice, as per a study published in *Cell* in January 2018. The mice fed with the Western diet—high in salt, sugar and fat—had higher number of immune cells like granulocytes and monocytes (part of the innate immune system). When the mice went back to low-fat diets, their inflammation l evels w ent down, but the genetic reprogramming of their immune cells continued. This is called trained innate immunity. It has been postulated that the Western diet changes the way in which genetic information is packaged. The genetic material is typically wrapped around proteins and many genes are inaccessible under natural circumstances. But bad food causes some of these hidden pieces of the genetic material to unwind and be expressed—called epigenetic changes. "In general, too much refined and processed carbohydrates and certain unsaturated fats are pro-inflammatory and can drive obesity. Individuals who make higher levels of certain inflammatory cytokines early in disease have a worse outcome. It is likely that diet linked to pre-existing conditions contribute to eventual cytokine storms when the virus hits hard," says Pillai.

Several lifestyle diseases are believed to be the result of a deranged immune system. In his recent book *The 21-day Immunity Plan*, Aseem Malhotra, a cardiologist in UK, writes excess body fat in the abdomen that surrounds the liver, pancreas and even fat underneath the skin release too much of pro-inflammatory cytokines. He says metabolic disorders can be treated by improving immunity through consumption of good food.

A diet rich in fibre can improve immunity by improving the gut microbiota. A high-fibre diet improves gut microbiota which in turn increases the production of short-chain fatty acids which can then dampen the innate immune response that is typically associated with tissue damage,

and also enhance the adaptive immune response that is charged with eliminating pathogens in mice. The study was published in journal *Immunity* in 2019. In vitro studies show processed, simple sugars reduce white blood cell phagocytosis and possibly increase inflammatory cytokine markers in the blood. Meanwhile, complex carbohydrate fibre, such as that found in fruits and vegetables, appear to reduce inflammation in both humans and mice.

But good food does not involve supplements, which are being promoted as immunity boosters. Studies suggest over consumption of vitamins can be detrimental. A study published in the *Journal of Leukocyte Biology* in 2015 says although vitamin A supplementation can have health benefits when someone is deficient, too much it shuts down the body's adaptive immunity and makes the person more vulnerable to infections. "Vitamin A supplementation should only be done with clear biological and clinical arguments," writes Mihai G Netea, Radboud University Medical Center in Nijmegen, the Netherlands, who was part of the study. "The interface of nutrition and immunity is an area of considerable importance, especially in an age when dietary supplements and vitamins are quite common," notes John Wherry, deputy editor of the *Journal of Leukocyte Biology* in a press

Lifestyle

- Smoking
- Alcohol consumption
- Exercise
- Acute psychological stress
- Chronic psychological stress

Vaccine

- Vaccine type
- Vaccine product
- Vaccine strain
- Adjuvants
- Vaccine dose

Nutrition

- Body mass index
- Nutritional status
- Micronutrients (vitamin A,D,E & Zn)
- Enteropathy

Environment

- Rural or urban
- Geographic location
- Season
- Family size
- Toxins

note issued at that time. But impact of food on immunity too is not linear.

"Balanced use of some vitamin supplements help the immune system," says Adrian Gombart, professor, Department of Biochemistry and Biophysics, Linus Pauling Institute, Oregon State University, US. For example, vitamin C is important for both innate and adaptive immune systems. It accumulates in phagocytic cells like neutrophils and enhances chemotaxis (the movement of cells toward chemical signals), phagocytosis (the eating of bacterial cells), generation of oxygen-based pathogen killing activity, and ultimately killing of pathogens. It also helps macrophages clear debris from the immune response to reduce tissue damage. It enhances differentiation and proliferation of B and T cells. Vitamin D is important for the expression of genes by macrophages, involved in killing pathogens through phagocytosis. It induces the expression of antimicrobial peptides that kill bacteria. It is important for regulating T cell responses and reducing inflammation. "Junk food does not have adequate levels of the micronutrients that we are discussing," says Gombart.

Just like food, exposure to toxins in the environment too affect the immune response. For instance, exposure to pesticide can reduce proliferation of T cells and increase cell death which in turn reduces adaptive immunity. Pesticides can also affect innate immunity by reducing the binding capacity of N K cells. In macrophages, pesticides can reduce cytokine production and phagocytosis. Triggers like pesticides and heavy metals are not very easy to manage. The impact of toxins on the immune system can also be gauged from a study published in *International journal of Environmental Research and Public Health* in August 2019. It says children with blood lead concentrations between 1 and 5 µg/dL (micrograms per decilitre) had 11 per cent lower anti-measles and a 6 per cent lower anti-mumps antibody level compared to children with

blood lead concentrations less than 1 µg/dL after vaccination.

Ubiquitous air pollutants are also detrimental to immunity as they stimulate pro-inflammatory responses across multiple classes of immune cell and can enhance certain T helper cells, leading to allergy and asthma which further damage the organs. Air pollutants can also dysregulate anti-viral immune responses, notes a paper published in *Free Radical Biology and Medicine* in May 2020.

The adverse impact of toxins persist for a long time, even through generations. There seems to be a strong association between prenatal arsenic exposure and subsequent childhood respiratory infections, as well as morbidity from respiratory diseases in adulthood through changes in innate immunity. This adverse effect would persist even if the person shifts to cleaner environment, suggests an experiment on mice that were exposed to 100 ppb (parts per billion) sodium arsenite in the uterus, and infected with H1N1 upon reaching adulthood. Assessment of lung tissue and fluid after infection showed there was more lung damage and inflammation in arsenic-exposed mice.

Similarly, maternal exposure to dioxin, a common industrial pollutant, can harm the immune system of child by altering the cellular machinery by which genes are expressed. This alterations are then passed along to subsequent generations. Researchers exposed pregnant mice to dioxin and observed that the production and function of cytotoxic T cells was impaired when the mice were infected with influenza A virus.

TIME TO CRACK THE CODE

Our understanding of the immune system is still in a nascent stage. There is a need to speed up the pace if we want to benefit from it

New science keeps emerging every day. For example, it has been observed that vaccinated children are more resistant to COVID-19. But the impact was more pronounced in children who received adjuvants (pharmacological agent added to a vaccine to boost the immune response to produce more antibodies and longer-lasting immunity). Researchers are now trying to find if a similar effect can be seen in elderly who have received flu vaccines with or without adjuvants.

Similarly, Adam Cunningham, professor of functional immunity at the University of Birmingham, UK, and his team found that mothers exposed to a disease before pregnancy can transfer long lasting immunity to their children through breast milk. The study, published in *Science Advances* on May 29, 2019, may help design maternal vaccine strategies that provide longer-term protection to children.

Till we fully understand immunity, we can support the system by eating balanced healthy food and by exercising. This will provide multiple other benefits

The understanding will also help harness immunotherapies. They have already been found useful in treatment of cancer and autoimmune diseases like rheumatoid arthritis. In case of cancer, the immune system is ramped up to attack the cancer cells while in case of rheumatoid arthritis, it is ramped down to ensure that immune cells do not attack joint tissue and lead to chronic pain and joint damage. Basic understanding of immune cells has been found useful for treating COVID-19 too. In September, the Infectious Disease Research Institute in Seattle, US, used placenta-derived Natural Killer (NK) cells on 14 patients hospitalised with moderate COVID-19 symptoms over one week at eight testing sites followed by a second phase to measure results against a control group receiving care. The treatment differs from COVID-19 vaccines—while vaccines are preventive treatment, NK-cells would be used for treating those who have COVID-19.

What's clear is that there are too many unknowns around immune response. Till we have better understanding, we can support the immune system by eating balanced healthy food and by exercising. It will provide multiple benefits. As Tripathi explains, balanced diet and regular exercise help improve the immune response not just against COVID-19 but against all kinds of communicable and non-communicable diseases. DTE

@vibhavarshney