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PANDEMIC IN SOUTH ASIA

Covid-19: The significance of India's emerging "hybrid immunity"

The pandemic has revealed a form of "super-immune" response among some who have been both infected with the virus and vaccinated against it. This has particular consequences for India, writes **Kamala Thiagarajan**

Kamala Thiagarajan *freelance journalist*

In January 2021, shortly after India rolled out its plans for nationwide vaccination coverage, a team of researchers led by the Kerala based rheumatologist Padmanabha Shenoy, medical director of CARE Hospital in Kochi, began a study into patients' covid-19 immunity.¹

Shenoy and his team examined the immune response from serum and plasma samples of 1500 patients with rheumatic diseases who had registered at CARE. Eventually, four groups were formed of 30 patients each.

The first group consisted of patients who had been infected with covid-19 in the 12 months before August 2021 and who had received a single dose of the vaccine after they'd recovered. The second included patients who had been infected with covid-19 in the six months before August 2021 but who had not received any vaccine; while the last two groups followed those who had no prior infection but had been vaccinated with either their first or both doses.

Their initial results were published in *The Lancet* in November 2021.² Of the four groups, the first had more antibodies and a stronger immune reaction compared with the other three (box 1). This is because the antibodies seem to evolve and become stronger.

Box 1: Study details

The vaccine used in the study was Covishield, the AstraZeneca vaccine manufactured by the Serum Institute of India. The average age of the patients in each of the four groups was 55.8 years, and 106 participants of the 120 (88%) were female.

In the first group, the gap between being infected with SARS-CoV-2 and receiving their first dose was 4-5 months, mirroring the Indian government recommendation to vaccinate at least three months after a covid-19 infection. Overall, 23 of 30 participants (77%) from the first group registered a mild disease (as per World Health Organization classification), five (17%) a moderate disease, and two (7%) a severe disease. Of the patients in this first group, 87% had a 30% neutralising antibody response (the capacity to quell the infection), the highest of all the groups.

"At the time, it was widely believed that vaccine coverage would induce a higher immune response [than natural exposure]," says Shenoy, "However, we found that if someone were to contract SARS-CoV-2 first, and then receive a single dose of the vaccine, this mounted a hybrid immune response that is 20-30 times stronger than [in] those who have

been vaccinated, even with two doses (without contracting the virus)."

"Hybrid immunity" refers to a kind of "super" immune response gained from the combination of being exposed to natural infection as well as a single dose of vaccination. The term was first coined in the context of covid-19.³ "A similar phenomenon is likely to be present for other organisms, but hasn't been examined yet," says Sakir Ahmed, consultant rheumatologist at Pradyumna Bal Memorial Hospital in Bhubaneswar and a coauthor of the study with Shenoy.

Scientists worldwide are researching the phenomenon. Initial studies found that serum samples taken from vaccinated individuals who had been infected with the virus did a far better job of neutralising immunity evading strains such as the beta and delta variants, compared with samples from those who were vaccinated but had never been infected.⁴

Studies of hybrid immunity are especially important in the Indian context, says Swapneil Parikh, a clinical researcher at Kasturba Hospital for Infectious Diseases in Mumbai and co-author of the book *The Coronavirus*.

From January 2020 to 22 November 2021, over two waves of covid-19, India recorded 34.5 million positive cases of SARS-CoV-2, with 33.9 million people recovering. India accelerated its vaccination rollout as a result: to date 354.5 million people (around 46% of the population) have received the first of the two required doses.

"The number of people who have been infected and have had at least one dose is quite high. These individuals have robust hybrid immunity," says Parikh. He says that whether they were infected first and were then vaccinated or contracted a breakthrough infection after being vaccinated doesn't matter—both offer robust protection against severe disease. That said, Ahmed says their initial data indicate the stronger immune response comes from infection followed by the vaccine.

Knowns and unknowns

The questions that researchers are now grappling with are how long hybrid immunity lasts compared with standard vaccine induced or natural immunity; the effect, if any, on population level herd immunity; and, as the world deals with the new threat of

omicron, what this may mean for new emerging variants.

Studies into all these are ongoing, says Shenoy, but the immediate findings can influence national vaccination policy. “We know that some people have a weaker immune response than others. Instead of giving everyone booster shots, we have recommended identifying the vulnerable population—the elderly and the immunocompromised for administering boosters,” he says.

The idea of herd immunity depends on a large fraction being highly resistant to infection and transmission, says Anurag Agrawal, director of the CSIR Institute of Genomics and Integrative Biology in New Delhi. “In India, the 2021 Delta wave infected over half the population. Most of our vaccination is after that, implying that the majority have hybrid immunity. This is good in terms of lowering our risk for further waves of infection.”

The herd immunity India is seeing now is due to the mix of both natural infections plus vaccination, thinks Ahmed. “Hybrid immunity contributes to herd immunity and we believe that it has a major role in limiting spread of infections,” he says. “There is a high likelihood that hybrid immunity has played a definite part in the decline of the second wave and delay of the third. We still need to test more.”

Even in individuals with hybrid immunity, it’s still not clear how long mucosal immunity (in the nose and upper respiratory tract, where the virus replicates) will exist. “Mucosal immunity may wane and individuals with hybrid immunity, while protected themselves, may still play a role in transmission,” points out Parikh.

But while hybrid immunity after the delta fuelled second wave seems to have had an effect, it may not hold against omicron, warns Agrawal. “The major changes to the spike protein may yet break past such immunity.⁵ Only time will tell, but I don’t expect the herd effect to be very strong or long lasting against an evolving virus.”

Omicron makes it clear that SARS-CoV-2 hasn’t hit an evolutionary endpoint, says Parikh. “India has all the conditions to breed super variants and a much poorer capacity to detect them in real time. That is very concerning.”

Increasing India’s capacity for genomic sequencing—to help detect new variants and trigger isolation measures and contact tracing—will help. The government has recently sought the help of private laboratories across the country to detect new variants, to assist the network of 28 government run laboratories that are currently involved in genomic sequencing. According to media reports, an increase in capacity from the current sequencing of over 7000 samples a month to around 80 000 samples a month is in the pipeline.⁶

But India still has a sizeable population that hasn’t been either infected or vaccinated. Based on serosurvey data, Parikh estimates that is around 100-150 million adults (around 10-15% of 940 million people).⁷ There is a need to prioritise people who are unvaccinated or partly vaccinated and urge them to complete vaccination quickly, he says. “We need to maximise two dose vaccine coverage worldwide, especially ensuring the highest possible coverage in vulnerable and highly exposed populations.”

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