# Evidence mounts that MMR and TDAP vaccines strengthen protection against severe COVID-19

August 31 2021

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Vaccines are designed to induce a strong and long-lasting immune response through the creation of memory T cells and B cells. The

Measles-Mumps-Rubella (MMR) vaccine, given during early childhood, and Tetanus-Diphtheria-Pertussis (Tdap) vaccine, given every 10 years, are known to elicit a protective response against the diseases from which the vaccines get their names. But these vaccines may have an unexpected bonus: It's possible that they also elicit cross-reactive memory T cells capable of responding to protein targets called antigens that are present in other microbes that cause diseases—including the viral antigens in SARS-CoV-2. The concept is that pre-existing memory T cells generated by prior MMR or Tdap vaccination and activated by SARS-CoV-2 infection give the immune system a head start in responding to SARS-CoV-2, thereby lowering the risk of severe COVID-19.

To investigate whether the MMR and Tdap vaccines provide additional protection against COVID-19, researchers at Brigham and Women's Hospital conducted laboratory-based analyses using sensitive, new techniques to detect and characterize T cell responses to antigens. They applied these techniques to measure the response of T cells isolated from the blood of COVID-19 convalescent patients and patients vaccinated against COVID-19 to antigens from SARS-CoV-2 and the MMR and Tdap vaccines. Teaming up with collaborators at Cleveland Clinic, they also leveraged a large, well-annotated cohort of COVID-19 patients and found that prior MMR or Tdap vaccination was associated with decreased disease severity. Their results are published in *Med*.

"Our Cleveland Clinic colleagues observed an association where individuals with COVID-19 who had either MMR or Tdap vaccines had a much lower frequency of going to the intensive care unit or dying," said co-author Andrew Lichtman, MD, Ph.D., an immunologist and senior investigator in the Brigham's Department of Pathology and professor of Pathology at Harvard Medical School. "Although previous smaller studies suggested a similar link, our in-depth epidemiological analyses, together with our basic research results, suggest that these commonly given vaccines may protect against severe disease."

"During the COVID-19 pandemic, we know that there was a marked decline in routine vaccinations for children and adolescents," said corresponding author Tanya Mayadas, Ph.D., a senior scientist in the Brigham's Department of Pathology and professor of Pathology at Harvard Medical School. "Our findings emphasize the importance of routine vaccination for children and adults. We know vaccines protect against devastating diseases, and we're now seeing growing evidence that some of them provide a degree of protection against severe COVID-19 disease."

The team's investigation was jumpstarted by an unexpected observation. Mayadas, her postdoctoral fellow Vijaya Mysore, Ph.D., and colleagues noted in laboratory experiments using COVID-19 convalescent blood that whenever they observed a heightened T cell response to SARS-CoV-2 proteins, they also saw a heightened response to proteins from MMR and Tdap, which they had been using as controls. This was observed with both COVID-19 convalescent and uninfected individuals vaccinated against SARS-CoV-2.

This connection was made by the team's use of highly efficient antigen-presenting cells (described in a recently published *Nature Communications* paper) derived from blood, loaded with SARS-CoV-2, MMR or Tdap antigens, and co-cultured with T cells from the same individual. Using single-cell RNA sequencing and analysis of T cell antigen receptors, the team observed that the antigen receptors on many of the T cells from individuals who had recovered from COVID-19 that responded to proteins from SARS-CoV-2 (Spike-S1 and Nucleocapsid) were identical to the antigen receptors on T cells that responded to MMR and Tdap proteins. This discovery indicated the presence of T cell clones that can respond to both SARS-CoV-2 antigens and the MMR and Tdap vaccine antigens.

In a second analysis, Mayadas and colleagues teamed up with

investigators at Cleveland Clinic to examine the epidemiological evidence. The Cleveland Clinic team performed a retrospective cohort study using data from more than 75,000 patients seen at the Cleveland Clinic Health System in Ohio or Florida who had tested positive for COVID-19 between March 8, 2020, and March 31, 2021. The team used a statistical method known as overlap propensity score weighting to compare two disease severity outcomes (COVID-related hospitalization and COVID-related admission to the intensive care unit or death) for patients who had been vaccinated against MMR or Tdap and those who had not. They found that patients who had previously been vaccinated for MMR had a 38 percent decrease in hospitalization and a 32 percent decrease in ICU admission/death. Similarly, patients previously vaccinated for Tdap had 23 percent and 20 percent decreased rates, respectively, of these outcomes.

"Beyond learning about the potential benefits of the MMR and Tdap vaccines in the context of COVID-19, this study provides a blueprint for accelerating research," said co-author Lara Jehi, MD, MHCDS, Chief Research Information Officer of the Cleveland Clinic Health System. "Biomedical hypotheses generated in the laboratory can be explored through robust clinical and epidemiological research in well-curated, real-world data such as the Cleveland Clinic COVID Registry. Knowledge learned through this collaboration is much more than the sum of our individual parts."

The authors note that while their laboratory-based findings are strengthened by the epidemiological observations, further work is needed to assess the association between the MMR and Tdap vaccinations and severity of COVID-19 disease to determine if the relationship is a causal one. Prospective studies of vaccination and patient outcomes may help distinguish correlation from causation.

"With regards to COVID-19 vaccines, our findings predict that although

MMR and Tdap are not a substitute for COVID-19 vaccines they may afford greater and more durable protection, possibly against emerging spike variants than the COVID-19 vaccine alone," said Mayadas. "And in areas where the COVID-19 vaccines are not available, they could protect infected individuals from developing severe disease."

**More information:** Vijayashree Mysore et al, Protective heterologous T cell immunity in COVID-19 induced by the trivalent Measles-Mumps-Rubella and Tetanus-Diptheria-Pertussis vaccine antigens, *Med* (2021). DOI: 10.1016/j.medj.2021.08.004

Provided by Brigham and Women's Hospital