# Infants with severe COVID-19 show unique dual immune activation unlike older children and adults



Infants admitted to hospitals with severe COVID-19 are displaying immune responses markedly distinct from those of older children and adults, according to a study published in *Nature Communications*. Researchers from various prestigious institutions, including St. Jude Children’s Research Hospital and Yale University, uncovered evidence that suggests a unique operation of the infant immune system during viral infections, necessitating tailored approaches in both treatment and prevention for this vulnerable population.

The study highlighted a phenomenon never observed in typical viral infections: infants with severe COVID-19 exhibited both elevated interferon responses and heightened levels of inflammation simultaneously. This dual activation of immune systems marks a significant deviation from the standard understanding that usually sees interferon and inflammatory responses in equilibrium. In most cases, an upregulation of one occurs at the expense of the other, providing a pivotal insight for medical professionals who are now called to reconsider existing paradigms about immune function in young children.

Infants participating in the research, aged between a few weeks to 16 months, presented T and B cells that, despite being largely naïve, were highly activated and some even generated robust antibody responses against SARS-CoV-2. This activation in infants, many of whom have not yet developed their antibodies independently from maternal transmission, raises questions regarding their immune adaptability. Co-corresponding author Dr. Octavio Ramilo emphasised the necessity for dedicated studies on infant immunology, stating, “We found that the infant immune system’s response to SARS-CoV-2 looks nothing like the immune response at any other age.”

The researchers applied single-cell RNA sequencing techniques to precisely map the immune response of these infants across varying levels of disease severity. Notably, they found that those with more severe manifestations had markedly higher levels of interferon-stimulated genes and inflammatory cytokines. The ambiguous role of these responses—whether they serve as protective mechanisms or exacerbate disease—calls for further investigation.

Interestingly, this developmental discrepancy is echoed in related studies which indicate that children generally display a quicker and more potent innate immune response to new pathogens compared to adults. For instance, young children have been observed to maintain robust antibody levels longer than adults, who tend to show a quick spike followed by a decline. It appears that infants and young children are particularly adept at establishing a barrier against SARS-CoV-2, likely aided by higher baseline levels of immune cells crucial for an early antiviral response, such as neutrophils in the nasal passages.

Moreover, research illustrates that younger children's innate immune advantages may include a more diverse repertoire of T cell receptors (TCRs). These characteristics facilitate a broader recognition of viral antigens, enhancing their ability to combat infections. As children age and their immune systems mature, they naturally transition from a predominance of naïve T cells to memory T cells, diminishing their initial response capabilities against new pathogens, such as SARS-CoV-2.

The findings regarding infants' immune responses underscore a critical need for age-specific consideration in treating COVID-19 and other viral infections. Current insights challenge previously held beliefs about infant immune disorders and highlight the potential for innovative therapeutic strategies aimed specifically at this demographic as the virus becomes endemic. As Ramilo aptly put it, “As COVID-19 is now an endemic disease, we need to understand the unique features of the infant immune system better so we can find ways to help these babies through such infections during their first months of life."

Understanding the nuanced characteristics of infant immunity not only holds promise for immediate clinical applications but also paves the way for long-term strategies to enhance health outcomes in one of society's most defenseless groups.

### Reference Map

1. Core findings about infant immune responses and implications for treatment.
2. Insights on childhood immune responses to pathogens and implications for infection severity.
3. Discussion of the sustained antibody response in children compared to adults.
4. Advantages of children’s innate immunity in combatting infections.
5. Information on the naïve T cell populations in children versus adults.
6. Examination of innate immune differences and their impact on younger children.
7. Summary of the unique innate immune responses in children.

Source: [Noah Wire Services](https://www.noahwire.com)

## Bibliography

1. <https://neurosciencenews.com/infant-covid-immune-system-28957/> - Please view link - unable to able to access data
2. <https://www.axios.com/2020/09/28/coronavirus-kids-infection-severity> - A study led by Betsy Herold, a pediatric infectious disease expert, suggests that children have a quicker and stronger innate immune response when encountering unfamiliar pathogens, which may contribute to less severe coronavirus infections compared to adults. However, some experts note that many studies, including this one, enroll patients too late in the infection to fully understand the immediate response of the innate immune system. It is also possible that children may develop long-term defenses against the virus, potentially preventing them from experiencing severe infections in the future, should the virus become endemic.
3. <https://www.nih.gov/news-events/news-releases/study-reveals-how-young-children-s-immune-systems-tame-sars-cov-2/> - A study revealed that young children's antibody response to SARS-CoV-2 differs from that of adults. Typically, adults produce antibodies to the virus at levels that spike for a few weeks, then decline. In contrast, infants and young children produced protective antibodies at levels that spiked and remained high for up to the full 300-day observation period. The study also found that the blood of adults with SARS-CoV-2 infection typically had high levels of inflammatory cytokines, which are associated with severe COVID-19 and death, while the blood of babies and children did not. However, the children's noses had high levels of inflammatory cytokines and a potent antiviral cytokine, suggesting that cytokines snuffed out SARS-CoV-2 infection right at the site where the virus entered the children's bodies, potentially explaining the mildness of their COVID-19 disease.
4. <https://www.frontiersin.org/articles/10.3389/fimmu.2025.1440169/full> - This article discusses the differences in immune responses between children and adults during SARS-CoV-2 infection. It highlights that children possess several distinct innate immune advantages, such as higher baseline levels of immune cells critical for early antiviral responses in their nasal passages. The enhanced presence of neutrophils in children's nasal cavities facilitates rapid accumulation at infection sites and subsequent recruitment and activation of additional immune cell populations. The article also notes that children exhibit a more diverse T cell receptor (TCR) repertoire, allowing for potentially broader recognition of viral antigens, while adults often display a more focused but potentially less flexible TCR repertoire.
5. <https://www.uhhospitals.org/blog/articles/2022/04/why-do-children-tend-to-fight-off-covid-19-better-than-adults> - This article explains that children have more 'naive' versions of T cells, which are abundant in young children and decrease with age. By the time a person reaches their thirties, many of their naive T cells will have encountered specific pathogens and changed into 'memory' T cells, which can respond rapidly when the same pathogen or a structurally similar pathogen enters the body. As people age and more of their naive T cells change into memory T cells, the body decreases its production of naive T cells. Consequently, adults have fewer naive T cells to recognize and fight new pathogens like SARS-CoV-2.
6. <https://www.frontiersin.org/articles/10.3389/fimmu.2021.741639/full> - This study suggests that SARS-CoV-2-positive children show more pronounced changes in innate immune cell populations compared to infected adults. These results may, in part, provide a mechanistic explanation for the reduced susceptibility and severity of SARS-CoV-2 infection in children compared to adults. Recent data suggests further reduced severity and transmission of SARS-CoV-2 in younger children compared to adolescents. The study also notes that children under five years old showed significantly lower proportions of circulating monocytes and dendritic cells during infection compared to children over the age of five.
7. <https://www.mdpi.com/2076-393X/11/2/418> - This article discusses various studies explaining that children have a milder infection due to strong innate responses, including higher levels of IFN-gamma and IL-17A, and lower levels of TNF-alpha and IL-6 in serum. SARS-CoV-2 infected children also have a lower adaptive immune response, as shown by lower memory T cells, Fc gamma receptor levels, lesser antibody-dependent cellular phagocytosis reactions, and reductions in neutralizing antibody responses than adults. The innate immune response in the nasal mucosa of children is also stronger and more vigorous than adults, with children displaying higher gene expression related to IFN and NLRP3 inflammasome signaling.