Check for updates

Cross-reactive adaptive immunity against coronaviruses in young children

Coronavirus-specific antibody and T cell responses were characterized in young children who had been naturally infected with SARS-CoV-2. Immune responses were focused against the spike protein, strong and stable in magnitude, and showed notable cross-reactivity with other human coronaviruses.

This is a summary of:
Dowell, A. C. et al. Children develop robust and sustained cross-reactive spike-specific immune responses to SARS-CoV-2 infection. *Nat. Immunol.* https://doi.org/10.1038/s41590-021-01089-8 (2021).

Published online:
22 December 2021

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

The question

Age is the most important risk factor for severe COVID-19 but it is unclear how the immune response controls SARS-CoV-2 infection so effectively in young children. SARS-CoV-2 viral load within the upper airways is similar in children and adults, and the innate immune system is thought to be most effective against this virus early in life[1]. However, the relative magnitude, specificity and quality of the adaptive immune response to SARS-CoV-2 at different ages, as assessed by antibody and cellular immune responses, is unclear. Understanding how age effects the adaptive immune response to SARS-CoV-2 is important as it might provide insight into how protective immune responses are mediated. This information is also needed to guide the introduction of COVID-19 vaccines in children.

The solution

We looked for evidence of SARS-CoV-2-specific adaptive antibody and cellular immune responses in 91 children of primary school age with a median age of 7 years. This evidence was compared with findings in 151 adults who were teachers in the same schools. 47% and 59% of these two groups, respectively, were found to have been previously infected with SARS-CoV-2. All of the infections had been mild and no one had been admitted to hospital. We went on to measure the strength, specificity, quality and longevity of the immune responses of the participants in each group over the next 12 months.

We found that virus-specific immune responses in children were focused strongly against the SARS-CoV-2 spike protein, which is present on the viral envelope and enables the virus to enter host cells to cause infection. Furthermore, antibody levels against the spike protein were higher in children than in adults and T cell responses were also twofold higher in children (Fig. 1a). Interestingly, a proportion of antibody and T cell responses in children cross-reacted with the spike protein of other human coronaviruses. The SARS-CoV-2 spike protein is composed of S1 and S2 subunits, and we found that these cross-reacting antibodies were specific for the conserved S2 subunit (which mediates fusion of the viral and host-cell membranes) of the spike protein in Beta-coronaviruses. The functional quality of antibody responses, as assessed by their ability to neutralize SARS-CoV-2, was similar across ages. However, the immune responses were broadly stable for 6–12 months after infection in children, but they declined in adults.

Finally, even in children that had never been infected with SARS-CoV-2, we detected spike-specific immune responses[2] (Fig. 1b). These responses are likely to result from recent infections with other human coronaviruses and may help to protect children against severe COVID-19.

The implications

Both the antibody and cellular arms of the adaptive immune response against SARS-CoV-2 display unique features in young children in that they are strong, sustained and more cross-reactive against other coronaviruses than these immune responses in adults. This fact could support superior SARS-CoV-2 clearance in children and suggests that immune memory will be longer lasting in children of primary school age. Furthermore, the immune system seems to be more cross-reactive in early life and this reactivity might play an important part in broadening immune responses against pathogens as the immune system evolves[3].

A limitation of our work is that we were not able to collect blood samples from individuals before and after SARS-CoV-2 infection. This sampling would be interesting as it would allow us to see whether antibodies and T cells that were developed against other human coronaviruses could be 'recruited' into the immune response against SARS-CoV-2[4].

There is now considerable interest in extending the COVID-19 vaccine rollout to young children. This work suggests that the immunogenicity of natural infection is robust in children. As such, vaccine-induced immunity in young children could be profound and the vaccine dose might need to be titrated before it is administered to this age group. Understanding the level and durability of immunity generated in response to vaccination in all demographic groups is crucial.

Paul Moss[1] and Shamez Ladhani[2]
[1]University of Birmingham, Birmingham,UK. [2]Public Health England, London, UK.

EXPERT OPINION

"The authors have produced some very insightful results about the adaptive immune response to SARS-CoV-2 infection in children. The study cohort in particular is a very nicely controlled group of samples in which to compare the adult and pediatric response to SARS-CoV-2 infection. For that reason in particular, I think these findings are high impact." **Jason Lavinder, The University of Texas at Austin, Austin, TX, USA**

FIGURE

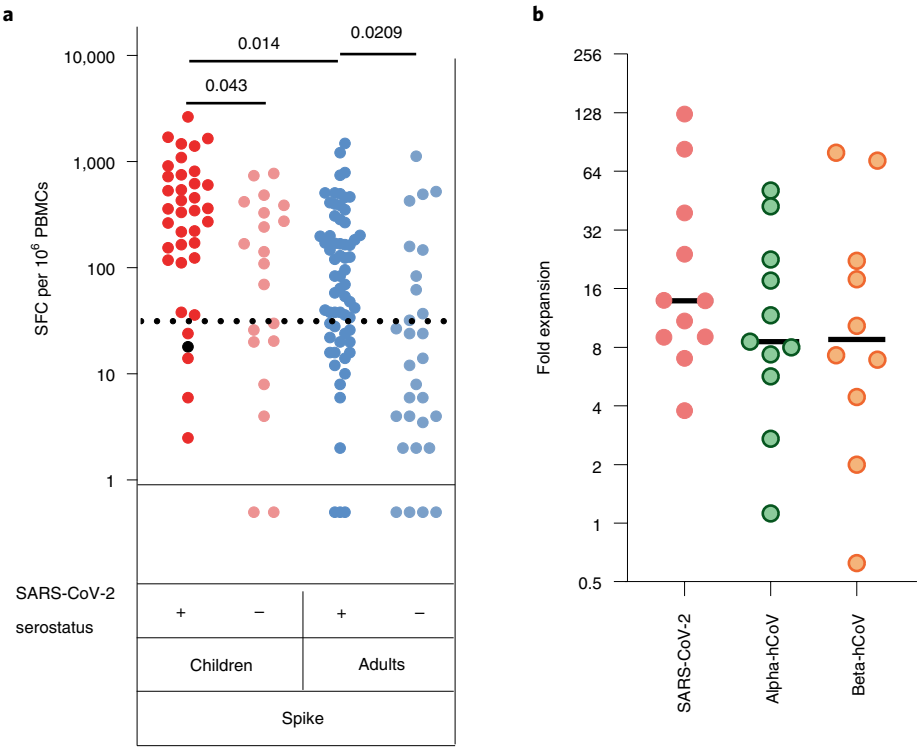

Fig. 1 | Spike-specific T cell responses to SARS-CoV-2 infection in children. a, Children develop stronger spike (S)-specific T cell responses after infection with SARS-CoV-2 than adults, with cross-reactive responses present in SARS-CoV-2 seronegative donors. **b**, Cellular responses specific to different human coronaviruses (HCoVs) expanded equivalently after stimulation of peripheral blood mononuclear cells (PBMCs) from children seronegative for SARS-CoV-2 with SARS-CoV-2 S2 peptides. SFC, spot forming cell. Credit: © 2021, Dowell, A. C., CC BY 4.0.

BEHIND THE PAPER

This project brings together a pediatric team with expertise in school infection surveillance and an immunology laboratory working on virus-specific immune responses. It was challenging to obtain blood samples from children and the team became adept at minimizing assay volumes. Logistics, communication and hard work were key! The team has also discussed the implications that this work might have for understanding the pathogenesis of the rare inflammatory disorder seen in some children after acute SARS-CoV-2 infection. This condition includes the development of autoimmune responses and is most common in children around 9 years of age, developing approximately 4–6 weeks after infection[5]. Given our finding that SARS-CoV-2 infection can boost antibody responses against even evolutionarily distant coronaviruses, it is possible that the enhanced 'cross-reactivity' of adaptive immune responses at a young age might sometimes 'spill over' into autoimmunity. **P.M. & S.L.**

REFERENCES

1. Madera, S. et al. Nasopharyngeal SARS-CoV-2 viral loads in young children do not differ significantly from those in older children and adults. *Sci. Rep.* **11**, 3044 (2021).
Analysis of 5,544 patients indicates that initial viral load is unlikely to underlie the mild clinical symptoms of COVID-19 seen in young people.

2. Ng, K. W. et al. Pre-existing and de novo humoral immunity to SARS-CoV-2 in humans. *Science* **370**, 1339–1343 (2020).
Study showing that some children and young people had antibodies before the pandemic that could bind SARS-CoV-2 with neutralizing potential.

3. Meade, P. et al. Influenza virus infection induces a narrow antibody response in children but a broad recall response in adults. *mBio* **11**, e03243–03219 (2020).
Study showing that children can respond to an H1 infection with a boost in the antibody response to H3 hemagglutinins following H3N2 infection early in life.

4. Consiglio, C. R. et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. *Cell* **183**, 968–981 (2020).
Analysis of COVID-19-associated multisystem inflammatory syndrome in children shows that patients lacked IgG antibodies to common coronaviruses, indicating that the absence of previous cross-reactive immunity is a risk factor for this syndrome.

5. Saletti, G. et al. Older adults lack SARS CoV-2 cross-reactive T lymphocytes directed to human coronaviruses OC43 and NL63. *Sci. Rep.* **10**, 21447 (2020).
Study showing that T cell immunity against human Alpha- and Beta-coronaviruses is virtually absent in older adults, and that cross-reactive T cells against SARS-CoV-2 are minimal in older people and might contribute to the clinical severity of COVID-19.

FROM THE EDITOR

"Characterizing how the immune response to SARS-CoV-2 differs in children and adults is crucial to understanding why children generally cope better with COVID-19 than adults or, from the other perspective, why adults do not cope as well. In this study, the authors do just that with a direct comparison over the course of 1 year. Other pediatric studies have either not been so longitudinal or not had that direct comparison." **Nick Bernard, Senior Editor, *Nature Immunology***