# THE BEST OF THE WEEK (01 mag – 07 mag 2023)

Rosa Morello et al.

**Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study**

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**Abstract**

Adults and children can develop post-Covid-19 condition (PCC) (also referred to as Long Covid). However, existing evidence is scarce, partly due to a lack of a standardised case definition, short follow up duration, and heterogenous study designs, resulting in wide variation of reported outcomes. The primary aim of this study was to characterise risk factors for PCC and longitudinal rates of recovery in a cohort of children and young people using a standardised protocol.

Methods

We performed a prospective "disease-based" cohort study between 01/02/2020 to 31/10/2022 including children aged 0–18 years old, with a previous diagnosis of Covid-19. Children with microbiologically confirmed SARS-CoV-2 infection, were invited for an in-clinic follow-up assessment at a paediatric post-covid clinic in Rome, Italy, at serial intervals (3-, 6-, 12- and 18-months post-onset). PCC was defined as persistence of otherwise unexplained symptoms for at least three months after initial infection. The statistical association between categorical variables was obtained by Chi-squared tests or Fisher's exact tests. Multivariable logistic regressions are presented using odds ratios (OR) and 95% confidence interval (CI). Survival analysis was conducted using the Kaplan–Meier method.

Findings

1243 children were included, median age: 7.5 (4–10.3) years old; 575 (46.3%) were females. Of these, 23% (294/1243) were diagnosed with PCC at three months post-onset. Among the study population, 143 patients remained symptomatic at six months, 38 at 12 months, and 15 at 18 months follow up evaluation. The following risk factors were associated with PCC: >10 years of age (OR 1.23; 95% CI 1.18–1.28), comorbidities (OR 1.68; 95% CI 1.14–2.50), and hospitalisation during the acute phase (OR 4.80; 95%CI 1.91–12.1). Using multivariable logistic regression, compared to the Omicron variant, all other variants were significantly associated with PCC at 3 and 6 months. At least one dose of vaccine was associated with a reduced, but not statistically significant risk of developing PCC.

Interpretation

In our study, acute-phase hospitalisation, pre-existing comorbidity, being infected with pre-Omicron variants and older age were associated with a higher risk of developing PCC. Most children recovered over time, but one-in-twenty of those with PCC at three months reported persistent symptoms 18 months post-Sars-CoV-2 infection. Omicron infection was associated with shorter recovery times. We did not find a strong protective effect of vaccination on PCC development. Although our cohort cannot be translated to all Italian children with PCC as more nationwide studies are needed, our findings highlight the need of new strategies to prevent and treat pediatric PCC are needed.

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**Developing Mucosal Vaccines for Severe Acute Respiratory Syndrome Coronavirus 2: What Will It Take?**

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**Abstract**

Initial efficacy results from the randomized clinical trials of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger RNA vaccines were impressive. Vaccine efficacy against laboratory-confirmed coronavirus disease 2019 (COVID-19) approached 95% after 2 doses of vaccine [1, 2]. We were pleased by these findings and encouraged that the vaccines would also reduce infection and subsequent transmission. However, the outbreak of COVID-19 in a largely vaccinated group of adults in July 2021 in Barnstable County, Massachusetts, highlighted that prevention of infection and subsequent transmission with parenteral vaccines was a daunting task [3]. Subsequent population-based studies have confirmed the limitations of vaccines and prior infection in conferring sterilizing immunity. While binding and neutralizing antibody responses and systemic cellular responses have been standard measures of infection and vaccine-induced immunity, mucosal antibody or cellular responses in tissue-resident lymphocytes have been less well studied. Since SARS-CoV-2 infection is initiated at the mucosal surfaces in the respiratory tract, generation of robust adaptive immunity at respiratory mucosal sites has the potential to prevent infection and subsequent transmission, in addition to protecting against disease.

The work presented by Cohen and his colleagues at the National Institutes of Health (NIH) in this issue of Clinical Infectious Diseases provides some understanding of the challenges of using parenteral vaccines to stimulate mucosal immunity [4]. They measured antibody levels to the SAR-CoV-2 spike and nucleocapsid proteins in the plasma, nose, and saliva of vaccine recipients and infected persons who were employees at the NIH in Bethesda, Maryland. After vaccination, anti-spike antibody levels in the plasma were higher and declined more slowly than antibody levels in the nose and saliva. In addition, vaccination of previously infected persons boosted anti-spike antibody levels more in the plasma than in the nose or saliva. Both nasal and saliva anti-spike antibody levels correlated significantly with plasma antibody, suggesting that mucosal antibodies were derived from transudation from the blood rather than local production. The authors concluded, “these observations indicate the need for development of mucosal vaccines to induce potent immune responses at sites where SARS-CoV-2 infection occurs.”

Mucosal vaccines with the potential to generate effective local immunity to SARS-CoV-2 in the respiratory tract would be attractive options, although historically mucosal vaccines have posed unique challenges. Currently, there are 5 prototype mucosal vaccines licensed for human use, with 4 administered orally and only 1 vaccine licensed for intranasal administration, live attenuated influenza vaccine (LAIV). As another example of the challenges with intranasal vaccines, the first licensed mucosal vaccine in Europe, an intranasal inactivated influenza vaccine with a unique adjuvant, was associated with Bell's palsy in a significant number of vaccine recipients and led to the removal of that mucosal vaccine from the European market [8]. Thus, live mucosal vaccines represent a delicate balance between “overattenuation,” generating poorly immunogenic

responses, and “underattenuation,” leading to increased rates of local and systemic adverse events after vaccine receipt. In addition, as shown with the intranasal inactivated vaccine with the adjuvant, such vaccines may pose unique risks associated with their route of administration.

Despite the previous challenges with mucosal vaccines for respiratory infections, there are many mucosal vaccines in preclinical studies for SAR-CoV-2.

Few human studies have been conducted with mucosal vaccines.

How will these mucosal vaccines be evaluated to determine their efficacy? One approach used in the human studies thus far is to simply compare the immune responses both locally and systemically between the mucosal and the parenteral vaccines. However, this poses challenges because the level of antibody needed to prevent infection or disease has not been precisely determined. Another approach would be to conduct large efficacy studies, such as the study being conducted by Codagenix and the Serum Institute of India where the efficacy will be determined by comparing the number of laboratory-confirmed cases in the vaccine and the placebo groups, like the pivotal trials of the parenteral vaccines. However, this approach poses challenges as well since many people are already vaccinated, and thus the population is not generalizable. The selection of an appropriate and generalizable vaccinated population may likewise be difficult. The ethics of a placebo-controlled trial in susceptible individuals when effective vaccines exist raises additional concerns. One potential option to study the impact of the vaccines on infectivity would be to use human challenge models; some of these studies are ongoing. Like the animal studies, the challenge model could more precisely determine the impact of the vaccine on infectivity. However, human challenge studies have only been performed with the original Wuhan strain; how earlier findings would extrapolate to the evolving variants has not been determined.

Overall, we agree with Cohen et al that mucosal vaccines for SARS-CoV-2 need to be pursued. However, there are significant hurdles to mucosal vaccine development, including incomplete knowledge of the nature of protective mucosal immune response, ensuring the safety and efficacy of new mucosal adjuvants that might be needed to provide a robust immune response, and the most effective ways to test the effectiveness of the vaccines for prevention of infection in a largely vaccinated and/or previously infected population.This is further complicated by the continued circulation of evolved SARS-CoV-2 viruses that cause human infections. We propose that the best path to success is the coordinated, multidisciplinary effort that was used to accelerate the development of the initial parenteral SARS-CoV-2 vaccines. Such an approach will require a public investment of funds to ensure the best scientific and strategic path forward for development of mucosal vaccines.