PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	RECAST: An observational study for the understanding of the increased REsilience of Children compared to Adults in SARS-CoV-2 infection
AUTHORS	Stricker, Sebastian; Ziegahn, Niklas; Karsten, Martin; Boeckel, Thomas; Stich-Boeckel, Heike; Maske, Jakob; Rugo, Evelyn; Balazs, Anita; Millar Büchner, Pamela; Dang-Heine, Chantip; Schriever, Valentin; Eils, Roland; Lehmann, Irina; Sander, Leif Erik; Ralser, Markus; Corman, Victor; Mall, Marcus; Sawitzki, Birgit; Roehmel, Jobst

VERSION 1 – REVIEW

REVIEWER	Rita Carsetti Bambino Gesù Children's Hospital, Rome, Diagnostic Immunology Unit
REVIEW RETURNED	18-Sep-2022

GENERAL COMMENTS	This is an interesting and long-needed study protocol. The proposed experiments will be useful to understand and compare the immune systems of children and adults, hopefully explaining the different susceptibility to severe disease after SARS-CoV-2 infection. The protocol is clear, the proposed experiments are appropriate, and sample collection and banking are organized. It will be important to have a sufficient number of children of different ages, especially those in the very young age groups.

REVIEWER	Mona Aldabbagh King Abdulaziz Medical City - Jeddah, Department of Pediatrics
REVIEW RETURNED	07-Feb-2023

GENERAL COMMENTS	This is a very well-written study protocol with very promising expectations that address crucial questions related to childhood immune response to infections and compare it to adults' immune responses. The study specifically aims to investigate the age-dependent differences in immune response post-primary SARS-CoV-2 infections in children and compares it with adults using a multi-omics approach. The study is registered at the German Clinical Trials Register and recruitment is ongoing since October 2020. The data is part of another study (Pa-COVID-19). The target sample size is around 720 subjects including 6 prespecified age categories including the two extremes of age. Infected subjects will be followed up for up to 6 months and their follow-up investigation will be done during three visits. It was unclear which tests will be done at each visit. The authors need to clarify if all the tests will be done in all visits or otherwise, specify which test will be done each visit and when they

	will take place. The study included children of all ages, and their workup will include lung function testing and testing of smell and taste. However, it is unclear how will these two elements be assessed in young infants. Note: There is a spelling mistake on Page 16, line 54 “Nasal swaps” Thank you and kind regards

VERSION 1 – AUTHOR RESPONSE

1. “Please update the ‘Ethics and dissemination’ section of your Abstract to include details of your dissemination plan. See published articles for examples.”

Implementation:

Results originating from nasal epithelial culture and functional in-vitro analyses, mass cytometry, mass spectrometry-based proteomics, single-cell sequencing and lung function testing and multiple breath washout as well as clinical data will be will be disseminated separately or in context in a variety of ways including abstracts, posters and presentations at conferences and published manuscripts in peer-reviewed journals. As soon as all analyses are completed, a comprehensive review will be published to put the findings in context of each other.

2. “Please revise the ‘Strengths and limitations of this study’ section of your manuscript (after the abstract). This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. The novelty, aims, results or expected impact of the study should not be summarised here.”

Implementation:

• Sample collection from children and adults with primary SARS-CoV-2 infection at multiple time points, however samples from severely ill patients are not included

• Mass cytometry, single-cell RNA sequencing and mass spectrometry-based serum and plasma proteomics display the local and systemic immune response

• Air-liquid interface cultures reproduce in-vivo conditions and will be used for functional studies

• Analysis of clinical data and lung function testing complement the multi-omics approach

3. Please include the planned start and end dates for the study in the methods section.

Implementation:

Recruitment started in October 2020 and is planned to end in October 2023.

4. It was unclear which tests will be done at each visit. The authors need to clarify if all the tests will be done in all visits or otherwise, specify which test will be done each visit and when they will take place.

Implementation:

Medical history, clinical assessment and functional testing

[…]

Data are collected at first contact and during the follow-up visits.

Functional testing, including lung function testing and multiple breath washout, will be conducted at the follow-up visits after two weeks and four to six months.

Sample collection

Samples will be collected from SARS-CoV-2 positive participants at each of three time points, directly after the diagnosis and at follow-up visits after two weeks and four to six months, and once from healthy age-matched controls.

5. The study included children of all ages, and their workup will include lung function testing and testing of smell and taste. However, it is unclear how will these two elements be assessed in young infants.

Implementation:

Loss of smell and taste are assessed with the “U-Sniff” test, a 12-item odor identification, the “Sniffin' Sticks” olfactory threshold test and taste samples for sweet, sour, salty, and bitter tastes in children aged six years or older.

[…]

[MBW] is already feasible without sedation in children from 2 years of age. Spirometry depends on the cooperation of the participant and may usually be conducted with children aged six years or older

6. Note: There is a spelling mistake on Page 16, line 54 “Nasal swaps”

Implementation:

Nasal swabs