Acta Biomed 2025; Vol. 96, N. 5: 18083 DOI: 10.23750/abm.v96i5.18083

Response to the Comment on Letter: "Impact of the COVID-19 pandemic on pediatric bacterial infection rates: a population-based study"

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To the Editor,

In response to the letter by Mehwish Amjad, we do appreciate the Authors' positive critical overview of the article, "Impact of COVID-19 pandemic on pediatric bacterial infection rates: a population-based study" published in Acta Biomedica 2025; 96(3) (1). However, we would like to clarify some criticisms raised by this letter.

"*First, the study has been conducted in a single center, in a third-level pediatric hospital in Italy. Therefore, there is a lack of generalizability. It may not reflect the pattern of infections in the entire population. If a multi-center approach had been followed, it would yield more generalized results indicative of the entire population*."

Of course, we agree to recognize this as a possible limitation of our study design, as also stated in the original manuscript "Our study is limited by the retrospective methodology and relatively small numbers of patients."

However, several similar reports, conducted in single-center settings, have been recently published supporting our results and that children were at higher risk for invasive bacterial infections post-pandemically (2-4).

Therefore, we also stated in the discussion: "Our experience may be representative of the Italian setting."

"*The study compares the infection rates of two groups,the first one comprising the patients from October to April of pre-COVID era (2018-19) and the second one from October to April of post-COVID era (2022-23) and includes 879 children. It fails to provide the trends of infections for all the seasons in a year and doesn't cover the entire pediatric population because of its limited sample size. This would have been overcome by observing the trends of the entire year and using a large sample size depictive of the whole population*."

Thank you for this valuable observation. We chose to focus only on the Autumn-Winter periods to trace the typical "respiratory" seasonal trend of some common infectious agents, as co-infections may have a role in the impact of invasive bacterial strains as observed in other larger reports (5).

"*The study highlights that delayed immune development in children might have occurred because of the reduced exposure to infections during the pandemic owing to non-pharmacological measures. However, it remains a hypothesis because of the lack of substantial evidence provided by immunological investigations. Therefore, the claim should have been more speculative rather than being stated as a fact."*

This is a hanfy point. It should be very interesting to demonstrate which is the effective immunological mechanism underlying the immune debt hypothesis. For example, there are also several studies focusing on the surge of some allergic manifestations following the pandemic period (6,7). Therefore, a complex of factors may be implied, and experimental studies should be

advocated to clarify the specific cytokine profile that may be altered. However, as most of these observations on the impact of COVID pandemic on the clinical aspects of bacterial infections in the post-pandemic years have been only retrospectively demonstrated, it is likely difficult to obtain more detailed data on specific cytokines or immune cells.

"*Also, the study does not provide the resistance profile of the organisms responsible for causing infections. This information would have been helpful for establishing empirical antibiotic treatment and formulating a public health policy*."

Thank you for raising this issue. However, all germs were to considered fully susceptible, unless further specified. For instance, MRSA infection rates were specifically reported: "*Escherichia coli* and Methicillin-resistant *Staphylococcus aureus* were found in both the time observation periods although in different rates (17% vs 29% for *E. coli* and 17% vs 14% for MRSA in 2022-2023 vs 2018-2019, respectively)".

"*Similarly, the paper also doesn't provide the comparison of different demographic and clinical features (age, nutritional status, immunization etc.). These factors would have affected the results of the study markedly*."

Thank you for raising this issue. Indeed, some clinical characteristics have been compared between the two groups of patients, as reported in the Results section and Table 1: gender, mean age, presence of chronic disease, mean duration of hospitalization (not statistically significant); concomitant acute viral illness and complete antipneumococcal vaccination (statistically significant). Further secondary subgroup analysis have been limited by the small sample-size.

"*Finally, the paper has mentioned the retrospective bias. But it does not provide any information about selection bias and the bias of missing data*."

Thank you for raising this issue. Due to the retrospective design, possible selection bias in the collection data phase should have been taken into account.

"*In the end, I would like to highlight that, despite the above-mentioned limitations, it is a very valuable study that provides an insight into the increased incidence of post-pandemic bacterial infections in the pediatric population. However, future studies should follow a multi-centered approach considering the data from the entire year and using a broad sample size. They should also provide immunologic evidence of immunity gap in the post-COVID era and the resistance profile of the organisms involved. They should consider the comparison between demographic and clinical factors as they can affect the results. Also, the important biases should be acknowledged*.

We do appreciate this insightful analysis of our work, and we agree that some minimal points could be improved. Multi-center studies should be desirable as a larger sample size and a prospective design may strengthen these observations. Still, the choice of a retrospective structure was also based on the need to rapidly disseminate preliminary evidence to highlight the interest in a concurrent phenomenon. Moreover, it is unlikely to objectively demonstrate the existence of an immunity gap by identifying the specific underlying immunological mechanisms, as 1) this appears to be the result of complex in-host and host-germ interactions, 2) a similar experimental design may imply the need to analyze data from a pre-pandemic period that could not be retrieved.

Conflict of Interest: Each author declares that he or she has no commercial associations that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: I.L and C.P. wrote this response.

Declaration on the use of AI: None.

Funding: None.

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Received: 11 August 2025
Accepted: 21 October 2025
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