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LETTER TO THE EDITOR

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Letter: is pneumococcal vaccination safe during the COVID-19 pandemic?

Dear Editors,

We read with interest the review article by Al-Ani et al about the management of COVID-19 in inflammatory bowel disease patients, in which the authors strongly encouraged patients to receive pneumococcus and influenza virus vaccines for reducing preventable co-infections.[1] Worse prognosis of COVID-19 is associated with the development of acute respiratory distress syndrome (ARDS) and sepsis, and bacterial co-infections, mainly caused by *Streptococcus pneumonia* and *Haemophilus influenza* type b may contribute to the morbidity and increased mortality.[2] However, considering the immunopathogenesis of COVID-19 and potential immunologic effects of pneumococcal vaccines, we have concerns about the safety of protective vaccinations, especially for those against pneumococcal infections, during the pandemic.

NLRP3, an important innate immunity receptor, recognises several intracellular pathogen- and danger-associated molecular patterns and induces the formation of multiprotein inflammasome complex, which results in proteolytic activation of IL-1β and IL-18 by activated caspase-1. Triggering of NLRP3-inflammasome by intracellular viral pathogens results in development of immune responses and helps their eradication. However, uncontrolled or overactivation of inflammasome complexes cause a hyperinflammatory response by excessive production of IL-1β with pathological consequences rather than improved host immunity.[3] Cytokine storm and hyperinflammatory response observed in SARS-CoV-2-associated COVID-19 represents an example of IL-1β-driven pathologies.[4] Previous studies documented that SARS-CoV, the coronavirus with very high sequence homology to SARS-CoV-2 and causing SARS, activates NLRP3-inflammasome in several ways, particularly via its envelope (E) and ion channel proteins (ORF3a and ORF8b) and induces IL-1β production.[5-7] In the same line, dampened NLRP3-inflammasome-associated immune response in bats has been implicated as one of the mechanisms responsible for its unique viral reservoir status.[8]

Pneumococcal polysaccharide vaccines induce humoral pathways to develop protective immunity. However, pneumococcal antigens are also recognised by the innate immune system via different pathogen recognition receptors including TLRs, NLRs and DNA sensors and induce production of proinflammatory mediators, including TNF, IL-1β and IL-6, with stimulation of the transcription factors NF-κB and/or IRF3/7.[9]

Local and systemic hyperinflammatory responses after the administration of conjugated or polysaccharide pneumococcal vaccines were observed in patients with monogenic autoinflammatory disease of cryopyrin-associated periodic syndrome (CAPS).[10] CAPS is caused by gain-of-function mutations in the *NLRP3* gene, which result in constitutive activation of inflammasome complex and pathologically enhanced activation of IL-1β in response to different triggers. The aberrant local and systemic inflammatory responses observed in vaccinated patients seem directly related to the activation of NLRP3 by polysaccharide antigens themselves, since the polysaccharide vaccine lacks Alum or other inflammasome triggers in contrast to the conjugated pneumococcal vaccine.

Although immunisation of especially vulnerable populations has been shown to be protective for fatal bacterial complications in elective conditions, pneumococcal vaccination of a patient with a probable or existing COVID-19 during pandemic could cause a hyperinflammatory response by further activating the NLRP3-inflammasome and progression to the cytokine storm, ARDS and death. Therefore, because of the safety concerns, we consider that vaccination decisions, especially for pneumococcal vaccines, should be given very carefully during the pandemic until further data become available.

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LINKED CONTENT

This article is linked to Al-Ani et al papers. To view these articles, visit https://doi.org/10.1111/apt.15779 and https://doi.org/10.1111/apt.15940

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REFERENCES

1. Al-Ani AH, Prentice RE, Rentsch CA, et al. Review article: prevention, diagnosis and management of COVID-19 in the IBD patient. *Aliment Pharmacol Ther*. 2020;52:54-72.
2. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020;80:639-645.
3. Zhao C, Zhao W. NLRP3 inflammasome - a key player in antiviral responses. *Front Immunol*. 2020;11:211.
4. Wan S, Yi Q, Fan S, et al. Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients. *Br J Haematol*. 2020;189:428-437.
5. Chen IY, Moriyama M, Chang MF, Ichinohe T. Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. *Front Microbiol*. 2019;10:50.
6. Nieto-Torres JL, Verdiá-Báguena C, Jimenez-Guardeño JM, et al. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. *Virology*. 2015;485:330-339.
7. Siu K-L, Yuen K-S, Castano-Rodriguez C, et al. Severe acute respiratory syndrome coronavirus ORF3a protein activates the NLRP3 inflammasome by promoting TRAF3-dependent ubiquitination of ASC. *FASEB J*. 2019;33:8865-8877.
8. Ahn M, Anderson DE, Zhang Q, et al. Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host. *Nat Microbiol*. 2019;4:789-799.
9. Koppe U, Suttorp N, Opitz B. Recognition of *Streptococcus pneumoniae* by the innate immune system. *Cell Microbiol*. 2012;14:460-466.
10. Jaeger VK, Hoffman HM, van der Poll T, et al. Safety of vaccinations in patients with cryopyrin-associated periodic syndromes: a prospective registry based study. *Rheumatology (Oxford)*. 2017;56:1484-1491.