Is ipsilateral administration of COVID-19 vaccine boosters the optimal approach?

Laura Ziegler,[a] Verena Klemis,[a] Tina Schmidt,[a] Sophie Schneitler,[b] Christina Baum,[c] Jürgen Neumann,[d] Sören L. Becker,[b] Barbara C. Gärtner,[b] Urban Sester,[e] and Martina Sester[a,*]

[a]Department of Transplant and Infection Immunology, Saarland University, Germany
[b]Department of Medical Microbiology and Hygiene, Saarland University, Germany
[c]Occupational Health Care Center, Saarland University, 66421, Homburg, Germany
[d]Department of Occupational Health, Robert Bosch GmbH, 66424, Homburg, Germany
[e]Department of Nephrology, SHG-Klinikum Völklingen, 66333, Völklingen, Germany

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We recently examined the effects of ipsilateral versus contralateral administration of a double-dose homologous mRNA-based vaccination regimen in a SARS-CoV-2 naive population.[1] In their correspondence, Iro and Buckland acknowledge that ipsilateral vaccination was associated with a more favourable immune response, and have made a valuable contribution to extend our discussion regarding the underlying mechanisms and relevance of our findings for further COVID-19 immunization events and other vaccines. While ipsilateral vaccination may benefit from the use of the same draining lymph node for priming and boosting, the colleagues speculated that contralateral vaccination may de novo mobilize B-cell clones not previously utilized. Similar to a broader B-cell response following a third dose after a longer time interval,[2] this may increase the breadth of the antibody response already after the second dose, which may improve protection towards a wider spectrum of viral variants. However, based on real-world observations from Israel, it appears that ipsilateral vaccination is associated with better effectiveness towards the parental strain that was circulating at the time of study, as individuals after ipsilateral vaccination had a lower risk of infection.[3]

We have studied the impact of ipsilateral and contralateral vaccination after a homologous dual dose COVID-19 vaccine regimen that was administered in a narrow time frame.[1] Based on the proposed underlying mechanism, our findings may also be relevant to other dual dose regimen of inactivated vaccines, where the same antigen is used. Even when two related influenza antigens were used for priming and boosting in an animal study, ipsilateral administration led to a more pronounced expansion of antibodies with both specificities which was based on cross-reactive germinal center B cells.[4] Upon repeated COVID-19 booster vaccinations in a real-world setting in humans, differences between ipsilateral and contralateral groups may become less pronounced due to other confounders known to influence immunogenicity such as longer intervals between the doses, heterologous sequence of different vaccine principles (including differences in dosages and adjuvants), or use of variant-adapted vaccines. In addition, systemic infections with SARS-CoV-2 will result in broader involvement of additional secondary lymphoid organs,[5] likely making the immunogenicity of subsequent booster vaccinations less dependent on the sides used for the first series. In this regard, further studies should also address whether the differences between ipsilateral and contralateral vaccinations are less pronounced for live vaccines, as they are presumably more prone to spread systemically and involve multiple lymphoid organs for priming. The Dengue vaccine, that was recently licensed in Europe[6] and is likely to be administered soon to larger cohorts of immunologically naïve individuals, will be an attractive candidate to study the role of the vaccination side in the context of a live attenuated vaccine. In any case, documentation of the vaccine side may be easily implemented in future vaccine studies to broaden our understanding on its role for vaccine efficacy and effectiveness.

Contributors

L.Z. and M.S. wrote the letter. All authors have provided further input and approved the final version.

Declaration of interests

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*Corresponding author. Center for Infectious Diseases, Department of Transplant and Infection Immunology, Saarland University, Building 77, Kirrberger Straße, D-66421, Homburg, Germany.
E-mail address: martina.sester@uks.eu (M. Sester).

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