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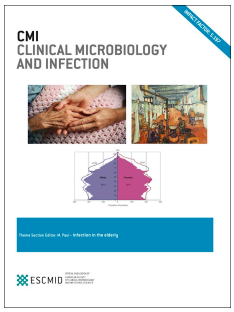

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Bivalent BNT162b2mRNA original/Omicron BA.4-5 booster vaccination: adverse reactions and inability to work compared to the monovalent COVID-19 booster

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To the Editor

Vaccination is a key prevention method against COVID-19 but emerging SARS-CoV-2 variants of concern (VOC), especially the Omicron VOC, have impaired the effectiveness of the original, wild-type SARS-CoV-2 based COVID-19 vaccines.(1, 2) Consequently, bivalent COVID-19 vaccines combining the wild-type spike mRNA with an Omicron VOC BA.1 or BA.4-5 spike mRNA became available. For the bivalent mRNA-1273.214 vaccine (Wuhan-Hu-1/BA.1) slightly higher rates of the predominant adverse reactions have been reported.(3) Due to approval without an additional clinical study, to date no evidence is available on adverse reactions and inability to work following a BA.4-5 adapted, bivalent COVID-19 vaccination.

This non-randomised controlled study examined adverse reactions, PRN (*pro re nata*) medication intake and inability to work after a fourth vaccination (i.e. second booster) among HCWs (healthcare workers) of the prospective CoVacSer study including follow-up participations until the 17th of November 2022. All enrolled individuals previously had been administered three COVID-19 vaccine doses. The second booster was performed with the monovalent BNT162b2mRNA vaccine or the bivalent BNT162b2mRNA original/Omicron BA.4-5 vaccine. Study participants administered with a different COVID-19 vaccine as second booster were excluded. As coadministration of COVID-19 and influenza vaccination might influence immunogenicity and side effects,(4) individuals receiving a simultaneous influenza vaccination were also excluded.

The study protocol was approved by the Ethics committee of the University of Wuerzburg (file no. 79/21). Data were collected by a questionnaire using REDCap (Research Electronic Data Capture, projectredcap.org). Data analysis was performed using GraphPad Prism 9.4.1 (GraphPad Software, San Diego CA, USA). Null-hypothesis testing was performed using Fisher's exact test (for gender, smoking, SARS-CoV-2 convalescence, side effects, PRN drug intake, and percentage inability to work) and Mann-Whitney U test (for BMI, age, and time intervals). The two-tailed significance level α was set to 0.05.

104 HCWs received a fourth dose of COVID-19 vaccination between the 13th of August 2021 and the 28th of October 2022 with either the original, monovalent BNT162b2mRNA (38.5%, 40/104) or the bivalent BNT162b2mRNA original/Omicron BA.4-5 vaccine (61.5%, 64/104). Individuals who received the bivalent vaccine showed no statistically significant differences to those who received the monovalent regarding gender (82.8% vs. 77.5% female), median age (51 [IQR: 40-66] vs. 47 [34-58] years), median BMI (24.1 [21.6-29.1] vs. 24.5 [22.1-29.7] kg/m²), smoking (15.6% vs. 15.0%), COVID-19 convalescence rate (31.3% vs. 17.5%) and time between infection and fourth dose (210 [198-235] vs. 156 [120-242] days). All infections except one occurred after the third vaccine dose. No participant reported having been infected more than once. The median interval between first and second COVID-19 booster vaccination was significantly longer among bivalent vaccinated participants compared to monovalent vaccinated participants (329 [320-335] vs. 199 [118-265] days, $p<0.0001$), the median interval between fourth vaccination dose and filling out the questionnaire shorter (18 [15-22] vs. 22 [15-50] days, $p=0.02$).

The rate of adverse reactions for the second booster dose was significantly higher among participants receiving the bivalent 87.5% (95% CI 77.2%-93.5%; 56/64) compared to the monovalent 52.5% (95% CI 37.5-67.1%; 21/40) vaccine ($p=0.0002$). Bivalent vaccinated participants further reported higher rates of adverse reactions in all subcategories (*Figure 1A*). Also, there were more frequent intake of PRN medication (*Figure 1B*), numerically higher rates of work ability restrictions (*Figure 1C*), and longer mean duration of the inability to work (2.1 ± 3.5 vs. 1.2 ± 0.4 days) in the bivalent vaccinated group.

In a multiple logistic regression including vaccine type, convalescence, gender, age, smoking, BMI, interval between third and fourth vaccination, and between fourth vaccination and filling out the questionnaire, significant effects of the bivalent vaccine ($p<0.0001$) and a shorter interval between third and fourth vaccine dose ($p=0.03$) on a higher rate of adverse reactions could be observed as well as non-significant effects of the bivalent vaccine on more frequent PRN medication intake ($p=0.27$) and work ability restrictions ($p=0.15$). SARS-CoV-2 convalescence showed a significant effect on more frequent work ability restrictions ($p=0.01$) and non-significant effects on a higher

rate of adverse reactions (p=0.23) and PRN medication intake (p=0.32) after the fourth vaccine dose.

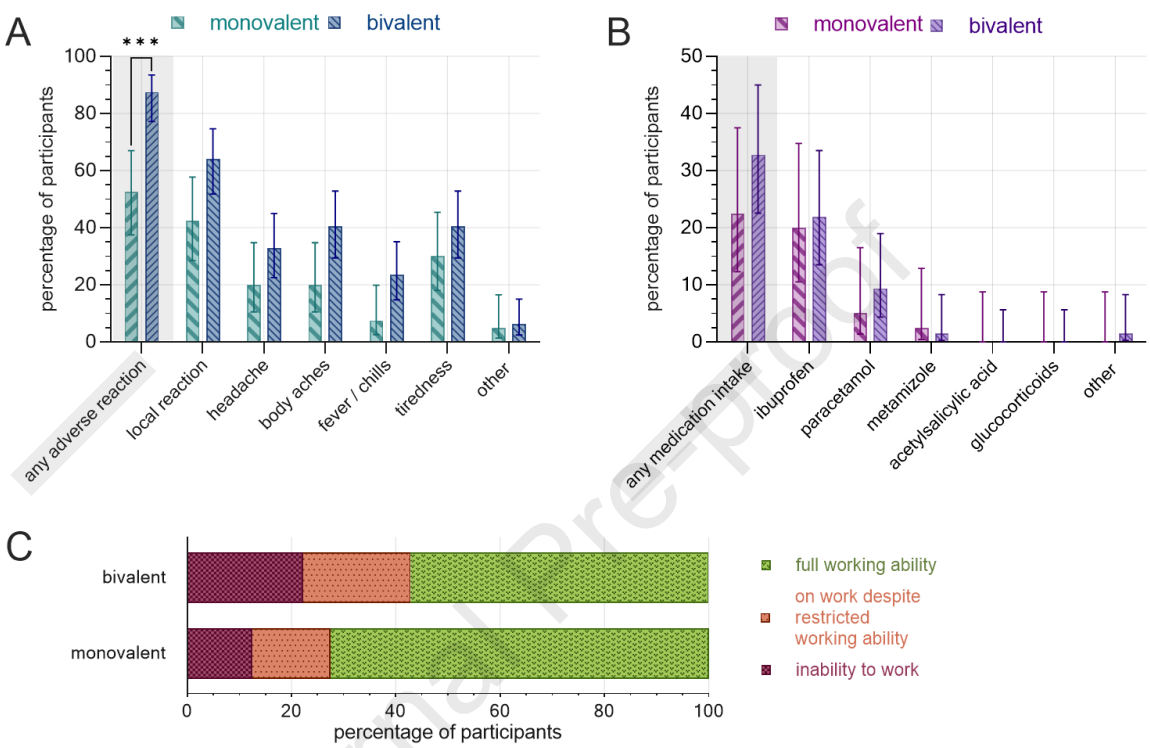

***Figure 1**: Post-vaccination adverse reactions, PRN medication and inability to work following the second COVID-19 booster administration, separated by vaccine. **A)** Rate of adverse reactions by subcategory and **B)** rate of PRN medication, **C)** work ability restrictions. Monovalent: BNT162b2mRNA (n=40), bivalent: BNT162b2mRNA original/Omicron BA.4-5 (n=64). Error bars indicate 95% CI. ***: p<0.001*

Individuals receiving a second COVID-19 booster vaccination with the bivalent BNT162b2mRNA original/Omicron BA.4-5 vaccine reported adverse reactions more frequently compared to those receiving the monovalent vaccine. There was a trend towards an increased rate of inability to work and intake of PRN medication following bivalent vaccination. Limitations of this study are the retrospective questionnaire-based assessment, the lack of randomisation

and blinding as well as the difference in the interval between both booster vaccinations between the two groups. Due to underdetection of asymptomatic SARS-CoV-2 infections, the convalescent rate might be underestimated. Our study focused on a direct comparison between the monovalent BNT162b2mRNA and the corresponding bivalent vaccine. In the light of preprints reporting inconclusive results in neutralising antibody levels between the compared vaccines,(5-7) our results and further studies on safety and reactogenicity of bivalent COVID-19 booster vaccines are highly important to aid clinical decision making in the choice between bivalent and monovalent vaccinations.

Transparency declaration

Manuel Krone receives honoraria from GSK and Pfizer outside the submitted work. All other authors declare no potential conflicts of interest.

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Role of funding source

This study was initiated by the investigators. The sponsoring institutions had no function in study design, data collection, analysis, and interpretation of data as well as in the writing of the manuscript. All authors had unlimited access to all data. Isabell Wagenhäuser, Julia Reusch, Alexander Gabel, Nils Petri, and Manuel Krone had the final responsibility for the decision to submit for publication.

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Data sharing statement

Additional data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) as well as the study protocol, statistical analysis plan, and analytic code is made available to researchers who provide a methodologically sound proposal to achieve aims in the approved proposal on request to the corresponding author.

Author contributions

All authors had unlimited access to all data. Isabell Wagenhäuser and Manuel Krone take responsibility for the integrity of the data and the accuracy of the data analysis.

Conception and design: Oliver Kurzai, Nils Petri, Manuel Krone.

Trial management: Isabell Wagenhäuser, Julia Reusch, Nils Petri, Manuel Krone.

Statistical analysis: Isabell Wagenhäuser, Julia Reusch, Alexander Gabel, Lukas Krone, Manuel Krone.

Obtained funding: Oliver Kurzai.

First draft of the manuscript: Isabell Wagenhäuser, Lukas Krone, Manuel Krone.

The manuscript was reviewed and approved by all authors.

Previous presentation of the information reported in the manuscript

The preliminary analysis of the study has been published as preprint on medRxiv (https://www.medrxiv.org/content/10.1101/2022.11.07.22281982v1).

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