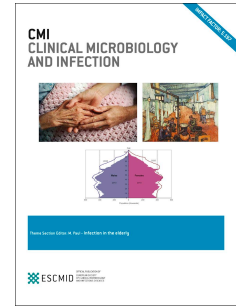


# Journal Pre-proof

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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1 *Research Note CLM-22-24730*

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

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20 To the Editor

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

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

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

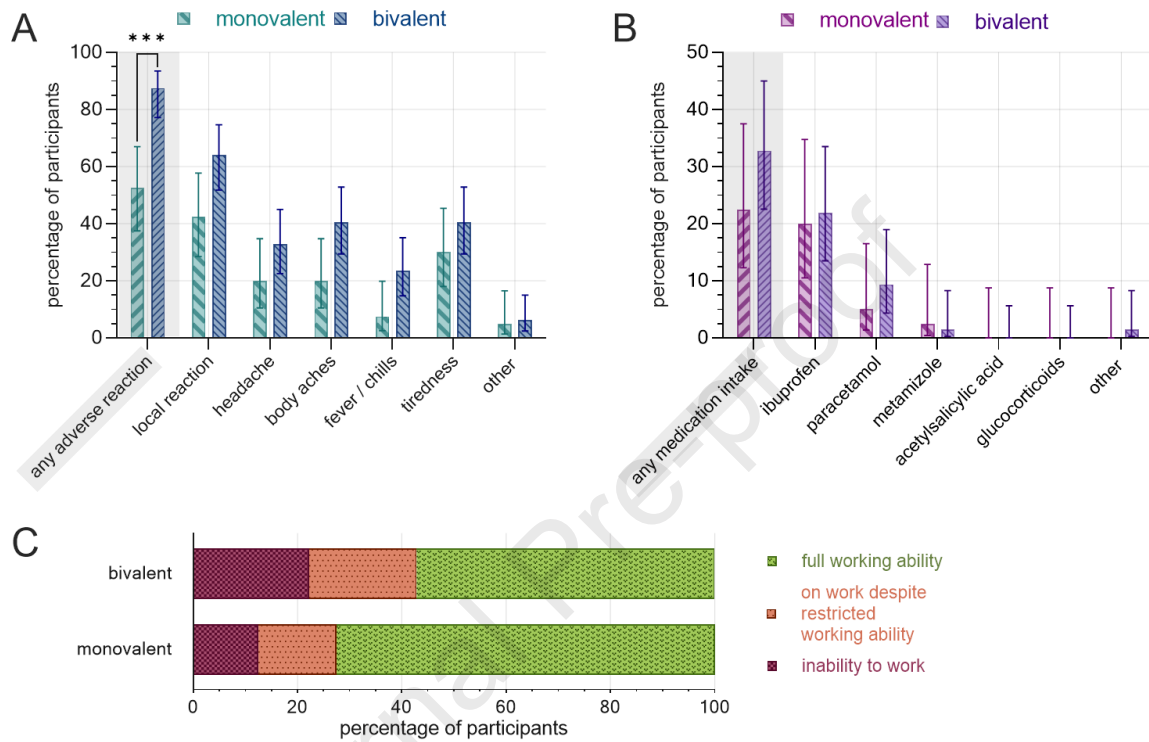
46 104 HCWs received a fourth dose of COVID-19 vaccination between the 13<sup>th</sup> of August 2021  
47 and the 28<sup>th</sup> of October 2022 with either the original, monovalent BNT162b2mRNA (38.5%,  
48 40/104) or the bivalent BNT162b2mRNA original/Omicron BA.4-5 vaccine (61.5%, 64/104).  
49 Individuals who received the bivalent vaccine showed no statistically significant differences to  
50 those who received the monovalent regarding gender (82.8% vs. 77.5% female), median age  
51 (51 [IQR: 40-66] vs. 47 [34-58] years), median BMI (24.1 [21.6-29.1] vs. 24.5 [22.1-29.7]  
52 kg/m<sup>2</sup>), smoking (15.6% vs. 15.0%), COVID-19 convalescence rate (31.3% vs. 17.5%) and  
53 time between infection and fourth dose (210 [198-235] vs. 156 [120-242] days). All infections  
54 except one occurred after the third vaccine dose. No participant reported having been infected  
55 more than once. The median interval between first and second COVID-19 booster vaccination  
56 was significantly longer among bivalent vaccinated participants compared to monovalent  
57 vaccinated participants (329 [320-335] vs. 199 [118-265] days,  $p < 0.0001$ ), the median interval  
58 between fourth vaccination dose and filling out the questionnaire shorter (18 [15-22] vs. 22  
59 [15-50] days,  $p = 0.02$ ).

60 The rate of adverse reactions for the second booster dose was significantly higher among  
61 participants receiving the bivalent 87.5% (95% CI 77.2%-93.5%; 56/64) compared to the  
62 monovalent 52.5% (95% CI 37.5-67.1%; 21/40) vaccine ( $p = 0.0002$ ). Bivalent vaccinated  
63 participants further reported higher rates of adverse reactions in all subcategories (*Figure 1A*). Also,  
64 there were more frequent intake of PRN medication (*Figure 1B*), numerically higher rates of work  
65 ability restrictions (*Figure 1C*), and longer mean duration of the inability to work ( $2.1 \pm 3.5$  vs.  $1.2 \pm$   
66  $0.4$  days) in the bivalent vaccinated group.

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

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

76



77

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

83

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

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

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## 99 Transparency declaration

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

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## 108 Role of funding source

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

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118 manuscript version as he died on the 4<sup>th</sup> of October 2022. We miss him as an enthusiastic  
119 college and friend who showed a great dedication to his work, family, and friends.

## 120 Data sharing statement

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

## 125 Author contributions

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

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

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

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

132 *Obtained funding:* Oliver Kurzai.

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

134 The manuscript was reviewed and approved by all authors.

## 135 Previous presentation of the information reported in the manuscript

136 The preliminary analysis of the study has been published as preprint on medRxiv

137 (<https://www.medrxiv.org/content/10.1101/2022.11.07.22281982v1>).

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