Antiviral humoral immunity against SARS-CoV-2 Omicron subvariants induced by XBB.1.5 monovalent vaccine in infection-naïve and XBB-infected individuals

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Abstract

To control infection with SARS-CoV-2 Omicron XBB subvariants, the XBB.1.5 monovalent mRNA vaccine has been available since September 2023. However, we have found that natural infection with XBB subvariants, including XBB.1.5, does not efficiently induce humoral immunity against the infecting XBB subvariants. These observations raise the possibility that the XBB.1.5 monovalent vaccine may not be able to efficiently induce humoral immunity against emerging SARS-CoV-2 variants, including a variety of XBB subvariants (XBB.1.5, XBB.1.16, XBB.2.3, EG.5.1 and HK.3) as well as BA.2.86. To address this possibility, we collected two types of sera from individuals vaccinated with the XBB.1.5 vaccine; those who had not been previously infected with SARS-CoV-2 and those who had been infected with XBB subvariants prior to XBB.1.5 vaccination. We collected sera before and 3-4 weeks after vaccination, and then performed a neutralization assay using these sera and pseudoviruses.

Text

To control infection with SARS-CoV-2 Omicron XBB subvariants, the XBB.1.5 monovalent mRNA vaccine has been available since September 2023. However, we have found that natural infection with XBB subvariants, including XBB.1.5, does not efficiently induce humoral immunity against the infecting XBB subvariants.[1-3] These observations raise the possibility that the XBB.1.5 monovalent vaccine may not be able to efficiently induce humoral immunity against emerging SARS-CoV-2 variants, including a variety of XBB subvariants (XBB.1.5, XBB.1.16, XBB.2.3, EG.5.1 and HK.3) as well as BA.2.86. To address this possibility, we collected two types of sera from individuals vaccinated with the XBB.1.5 vaccine; those who had not been previously infected with SARS-CoV-2 (N=9; **Figure A**) and those who had been infected with XBB subvariants prior to XBB.1.5 vaccination (N=10; **Figure B**). We collected sera before and 3-4 weeks after vaccination, and then performed a neutralization assay using these sera and pseudoviruses. As expected, XBB.1.5 vaccine sera with prior XBB infection efficiently (1.8- to 3.6-fold) boosted antiviral humoral immunity against all variants tested with statistical significance (**Figure B**). Importantly, in the case of the XBB.1.5 vaccine sera without prior infection, XBB.1.5 vaccine also induced efficiently antiviral activity (2.1- to 3.9-fold) against all variants tested with statistical significance (**Figure A**). These observations suggest that a single dose of XBB.1.5 monovalent vaccine potentially induces antiviral humoral immunity against XBB subvariants as well as BA.2.86 without prior infection.

The induction efficiency of neutralizing activity was comparable between the infection-naïve cohort (**Figure A**) and the XBB-infected cohort (**Figure B**). However, in sera collected prior to XBB.1.5 vaccination, the 50% neutralization titer of sera from the XBB-infected cohort was 5.7- to 10.4-fold higher than that of sera from the infection-naïve cohort (**Figure**). In addition, although all pre-vaccination sera of XBB-infected cohort exhibited antiviral activity against all variants tested, some individuals vaccinated with XBB.1.5 vaccine without natural infection showed no antiviral activity against XBB.1.5 (N=2), XBB.1.16 (N=1), XBB.2.3 (N=3), EG.5.1 (N=3), HK.3 (N=3) and BA.2.86 (N=2). Taken together, these results suggest that a single dose of XBB.1.5 monovalent vaccine may not be sufficient to induce effective antiviral humoral immunity in infection-naïve individuals and that a booster dose of XBB.1.5 monovalent

vaccine may be required in some cases.

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Declaration of interest

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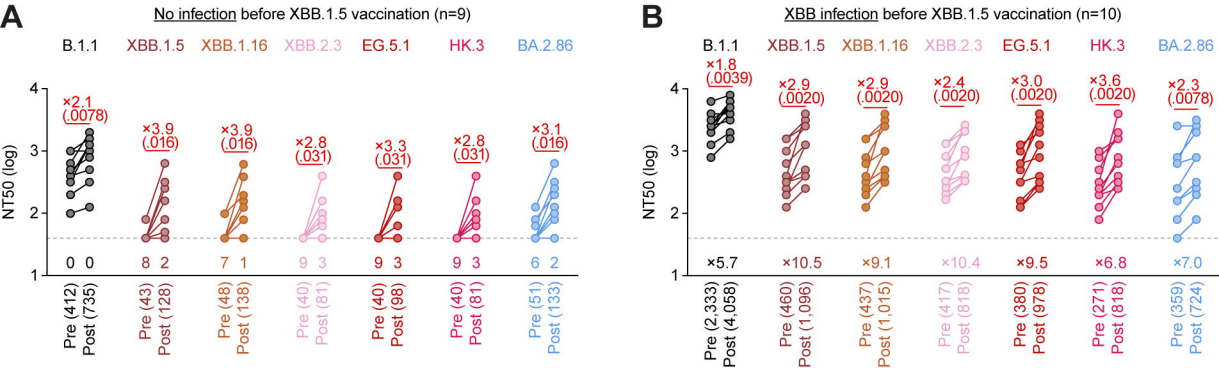
Figure. The neutralization activity induced by XBB.1.5 monovalent vaccine

Assays were performed with pseudoviruses harboring the S proteins of B.1.1, XBB.1.5, XBB.1.16, XBB.2.3, EG.5.1, HK.3 and BA.2.86. The following two sera were used: (**A**) vaccinated sera from fully vaccinated individuals who had not been infected ('no infection before XBB.1.5 vaccination', 9 donors), (**B**) vaccinated sera from fully vaccinated individuals who had been infected with XBB subvariants (after June 2023) ('XBB infection before XBB.1.5 vaccination', 10 donors). Sera were collected before vaccination ('Pre') and 3-4 weeks after XBB.1.5 monovalent vaccination ('Post').

Assays for each serum sample were performed in triplicate to determine the 50% neutralization titer (NT_{50}). Each dot represents the NT_{50} value for each donor, and the NT_{50} values for the same donor between pre- and post-vaccination are connected by a line. The number in parenthesis below the graph indicates the geometric mean of the NT_{50} value. The horizontal dashed line indicates the detection limit (40-fold dilution). In **A**, the number of the serum donors with the NT_{50} values below the detection limit is shown in the figure (below the horizontal dashed line). In **B**, the number with "X" (below the horizontal dashed line) indicates the fold change of the NT_{50} value of the pre-vaccination of the XBB-infected cohort samples (**B**) compared to that of the infection-naïve cohort samples (**A**).

Statistically significant differences between pre- and post-vaccination were determined by two-sided Wilcoxon signed-rank tests and are shown in red parentheses. The fold change of the reciprocal NT_{50} is calculated between pre- and post-vaccination and is shown in red. Background information on the vaccinated donors is summarized in **Table S1**.


A
No infection before XBB.1.5 vaccination (n=9)
B.1.1
XBB.1.5
XBB.1.16
XBB.2.3
EG.5.1
HK.3
BA.2.86
NT50 (log)
×2.1 (.0078)
×3.9 (.016)
×3.9 (.016)
×2.8 (.031)
×3.3 (.031)
×2.8 (.031)
×3.1 (.016)
0 0
8 2
7 1
9 3
9 3
9 3
6 2
Pre (412) Post (735)
Pre (43) Post (128)
Pre (48) Post (138)
Pre (40) Post (81)
Pre (40) Post (98)
Pre (40) Post (81)
Pre (51) Post (133)
B
XBB infection before XBB.1.5 vaccination (n=10)
B.1.1
XBB.1.5
XBB.1.16
XBB.2.3
EG.5.1
HK.3
BA.2.86
NT50 (log)
×1.8 (.0039)
×2.9 (.0020)
×2.9 (.0020)
×2.4 (.0020)
×3.0 (.0020)
×3.6 (.0020)
×2.3 (.0078)
×5.7
×10.5
×9.1
×10.4
×9.5
×6.8
×7.0
Pre (2,333) Post (4,058)
Pre (460) Post (1,096)
Pre (437) Post (1,015)
Pre (417) Post (818)
Pre (380) Post (978)
Pre (271) Post (818)
Pre (359) Post (724)