Heterologous ChAdOx1-S/BNT162b2 vaccination: neutralizing antibody response to SARS-CoV-2

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Dear Editor,

A recent report questioned whether one vaccine was better than another and how to evaluate this difference, but only homologous vaccination schedules were considered [1]. Concern about the safety of the ChAdOx1-S vaccine have prompted some European countries to recommend using a heterologous booster, as proposed for mRNA vaccines for people under 55 years old [2]. Immunogenicity and reactogenicity of a BNT162b2 booster in ChAdOx1-S-primed subjects was assessed in a multicenter, open-label, randomised, controled phase 2 trial [3], but included no homologous vaccination comparator. Few studies have compared the immune responses to homologous and heterologous vaccination schedules in humans [4].

We followed up the responses of 132 healthcare workers (HCWs) whose pre-vaccination Wantai SARS-CoV-2 Ab ELISA results were negative before their vaccination. We determined their neutralizing antibodies by end-point dilution using a live virus-based assay at the time of the second injection and one month later [5]. Those HCWs who were over 55 years old (y.o) could choose a homologous schedule, ChAdOx1-S/ChAdOx1-S or BNT162b2/BNT162b2, or the heterologous schedule, ChAdOx1-S/BNT162b2. The under 55s were given a ChAdOx1-S or BNT162b2 first injection followed by a BNT162b2 booster. We set up matched pairs (age and gender) of HCWs within each group: ChAdOx1-S/BNT162b2 and BNT162b2/BNT162b2, and ChAdOx1-S/ChAdOx1-S for the over 55 y.o group. This study was approved by the French Research Ethics Committee Est-III (COVID BioToul, ID-RCB 2020-A01292-37, ClinicalTrials.gov Identifier: NCT04385108).

The median age of the 66 HCWs under 55 (48 females, 74%) was 37 years (range: 20-55). The neutralizing antibody titers after the first injection of those given ChAdOx1-S and those

given BNT162b2 were not statistically different. There was also no significant difference after the second injection between the HCWs given ChAdOx1-S/BNT162b2 (75.7% had an increased titer $\geq$ 2 dilutions) and those given BNT162b2/BNT162b2 (87.8% had an increased titer $\geq$ 2 dilutions, p=0.33, Fisher's exact test, Figure 1A).

The median age of the 66 HCWs over 55 (44 females, 67%) was 59 years (range: 56-75). These HCWs all had not different neutralizing antibody titers after the first injection, regardless of the type of vaccine. The neutralizing antibody titers one month after the second injection of the HCWs given ChAdOx1-S/BNT162b2 were significantly more often higher (95.4% had an increased titer $\geq$ 2 dilutions) than of those given ChAdOx1-S/ChAdOx1-S (63.6%, p=0.02; Fisher exact test, Figure 1B) or of those given BNT162b2/BNT162b2 (68.2%, p=0.04, Fisher exact test, Figure 1B). There was no statistical difference in the neutralizing antibody titers of the HCWs given ChAdOx1-S/ChAdOx1-S and those given BNT162b2/BNT162b2.

These data indicate that a ChAdOx1-S/BNT162b2 heterologous regimen provided a stronger antibody response in the over 55 y.o HCWs than either of the homologous regimens. Although the correlation between this response and protection has not yet been defined, individuals with a high neutralizing antibody response could be better protected against SARS-CoV-2. Despite the small sample size, our findings could help optimize future vaccination strategies.

NOTES

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Conflict of Interest

The authors declare no conflict of interest

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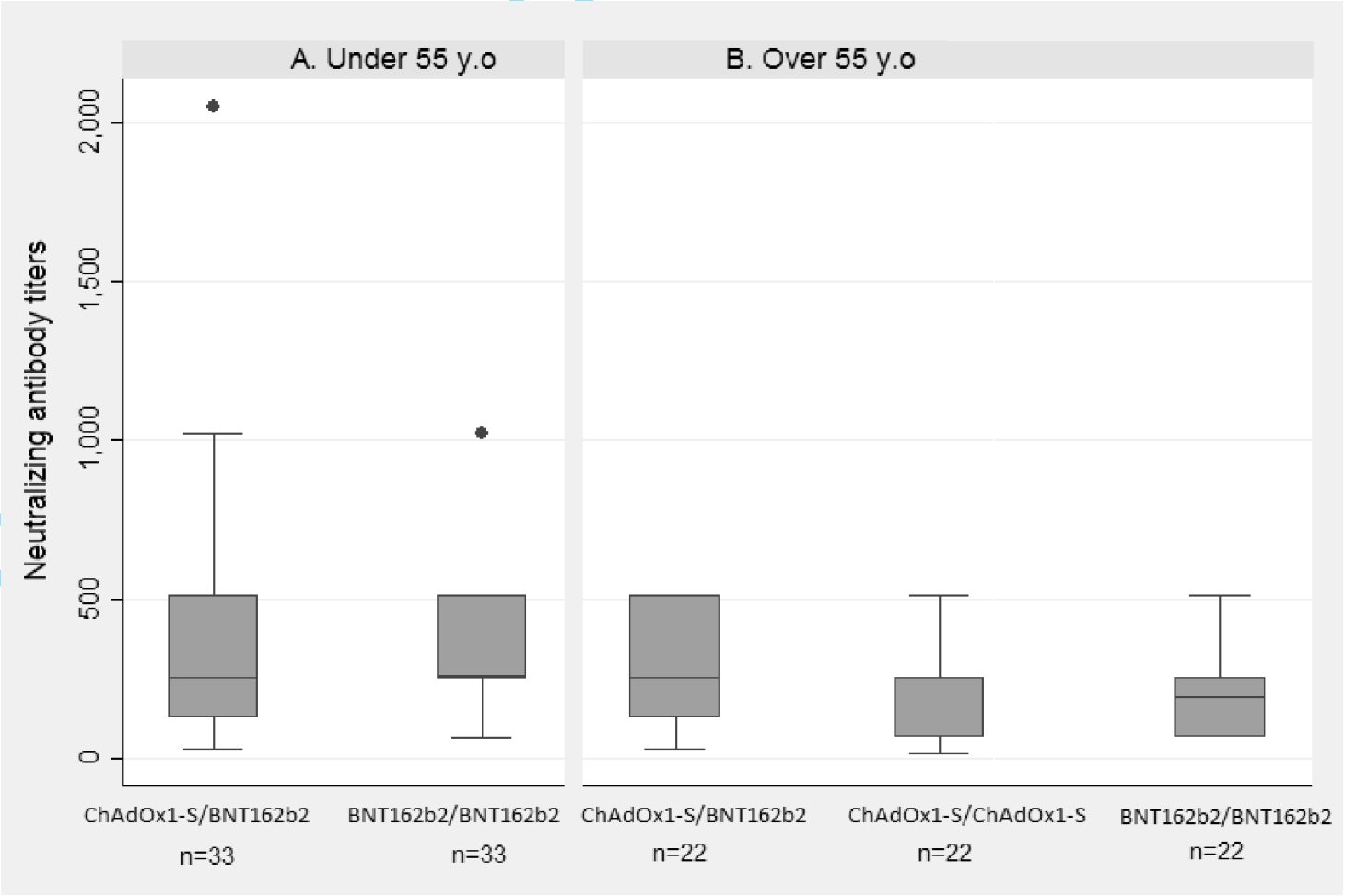
FIGURE LEGEND

Figure 1: Distribution of neutralizing antibody titers according to vaccination schedule: homologous schedules (ChAdOx1-S/ChAdOx1-S; median delay between injections: 84 days, IQR [79;84]; or BNT162b2/BNT162b2; median delay: 28 days, IQR [27;28]), and heterologous schedule (ChAdOx1-S/BNT162b2; median delay: 83 days, IQR [77;84])

A: among the HWCs under 55 years old,

B: among the HCWs over 55 years old.

Figure 1


A. Under 55 y.o
B. Over 55 y.o
Neutralizing antibody titers
0
500
1,000
1,500
2,000
ChAdOx1-S/BNT162b2
n=33
BNT162b2/BNT162b2
n=33
ChAdOx1-S/BNT162b2
n=22
ChAdOx1-S/ChAdOx1-S
n=22
BNT162b2/BNT162b2
n=22