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# Immunogenicity and reactogenicity of heterologous and homologous mRNA-1273 and BNT162b2 vaccination: A multicenter non-inferiority randomized trial

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## Summary

**Background** Although effective mRNA vaccines for SARS-CoV-2 infection have been deployed worldwide, their interchangeability could facilitate the scale-up of vaccination programs. The objective of the trial was to assess whether the immune response induced by a heterologous SARS-CoV-2 mRNA primo vaccination is non-inferior to that of a homologous mRNA vaccination.

**Methods** We conducted a multicenter, randomized, open-label trial in adults ≥18 years of age and older who received a first dose of SARS-CoV-2 mRNA vaccine. Participants were randomly assigned in a 1:1 ratio to receive a second

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dose of BNT162b2 or mRNA-1273, 28 to 49 days after the first dose. Randomization was stratified on the vaccine received at the first vaccination. The primary endpoint was the anti-spike IgG antibodies titer measured 28 days after the second vaccine dose. This study is registered with ClinicalTrials.gov, Trial, NCT04900467.

**Findings** Of the 414 randomized participants recruited from May 28 to July 2, 2021, 390 were included in the per protocol analysis: 94 participants in group 1 (BNT162b2/BNT162b2), 96 in group 2 (BNT162b2/mRNA-1273), 97 in group 3 (mRNA-1273/mRNA-1273), and 103 in group 4 (mRNA-1273/BNT162b2). The geometric mean titers ratios of anti-spike IgG antibodies for each heterologous regimen relative to the corresponding homologous regimen were 1.37 (two-sided 95% CI, 1.10 to 1.72) in the groups 1 and 2 and 0.67 (two-sided 95% CI, 0.55 to 0.82) in the groups 3 and 4. Levels of neutralizing antibodies to the main circulating SARS-CoV-2 viral strains were higher with the vaccine regimen containing mRNA-1273. Participants who received mRNA-1273 as a second dose experienced a higher rate of local adverse reactions and general symptoms than those who received BNT162b2 ( $p < 0.0001$ ).

**Interpretation** The two SARS-CoV-2 mRNA vaccines could be used with flexibility for the second dose of COVID-19 primo vaccination. Tolerance remains good regardless of vaccine sequence although mRNA-1273 was more reactogenic.

**Funding** French Ministries of Solidarity and Health and Research. BNT162b2 was provided by Pfizer/BioNTech. mRNA-1273 was provided by Moderna.

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### Research in context

#### *Evidence before this study*

We searched PubMed through November 26, 2021, for COVID-19 vaccine clinical trials using the search terms "SARS-CoV-2," "vaccine," "immunogenicity," and "clinical trial" without language restriction. Only peer-reviewed publications were included. A few studies comparing the immunogenicity of heterologous and homologous vaccine regimens combining ChAdOx1 nCoV-19 and SARS-CoV-2 mRNA vaccines were found. We did not find any randomized study to confirm the non-inferiority and good tolerance of heterologous vaccine regimens composed of mRNA vaccines in primary vaccination. However, the question needs to be addressed given the frequent use of these combinations.

#### *Added value of this study*

In this first open-label, multicenter, non-inferiority, randomized clinical trial, anti-spike IgG antibody titers for the heterologous BNT162b2/mRNA-1273 combination regimen were non-inferior to two doses of BNT162b2. Neutralizing antibodies tended to be higher in regimens including mRNA-1273. Reactogenicity was higher with mRNA-1273 for the second dose.

#### *Implications of all evidence available*

The results of this study will help streamline vaccination campaigns and schedules. Regardless of the availability of any of the SARS-CoV-2 mRNA vaccines, vaccination campaigns can continue and rapidly increase vaccination coverage in all countries that are still under-vaccinated.

### Introduction

To date, coronavirus disease 2019 (COVID-19), due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused over 270 million cases and eight million deaths worldwide.<sup>1</sup> To fight the pandemic, effective vaccines were rapidly developed and to date, over eight billion doses have been administered.<sup>1</sup> A large number of people in the world still need to be vaccinated. Indeed, a number of high-income countries have vaccine coverage of over 70% of the population, but many countries have low vaccine coverage.<sup>2-4</sup> Low- and middle-income countries will still need to vaccinate more than three-quarters of their population.<sup>5</sup>

As part of the COVID-19 vaccine campaign, the two available mRNA SARS-CoV-2 vaccines, BNT162b2 (COMIRNATY®)<sup>6</sup> and mRNA-1273 (SPIKEVAX®)<sup>7</sup>, administered in two doses have shown over 90% efficacy in preventing COVID-19 infection. Both vaccines are based on similar technologies but were developed independently.

In accordance with the vaccines licenses, the same vaccine has been recommended for both doses. However, supply and logistical constraints may make it difficult to use the same vaccine for both doses used for primo-vaccination. The WHO announced in April 2021<sup>8</sup> that, in the absence of available data, vaccine interchangeability could not be recommended. In France, the primo vaccination with two different SARS-CoV-2 mRNA vaccines was authorized by the health authorities<sup>9</sup> when it was not possible to administer the same mRNA vaccine for the second dose. However, data are still needed to demonstrate the non-inferiority of a heterologous vaccine schedule.

The current trial was therefore designed to evaluate whether the immunogenicity of a regimen combining the two mRNA SARS-CoV-2 vaccines (i.e., either a second dose of vaccine with mRNA-1273 COVID-19 vaccine after a first dose of BNT162b2 COVID-19 vaccine, or a second dose of the BNT162b2 COVID-19 vaccine after a first dose of mRNA-1273 COVID-19 vaccine) is non-inferior to a standard vaccination regimen with two doses of the same mRNA SARS-CoV-2 vaccine.

## Methods

### Study design

We conducted an open-label, multicenter, non-inferiority, randomized clinical trial (NCT04900467) across 17 centers in France. Participants were recruited from May 28, 2021 to July 2, 2021. The protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the “CPP Ile-de-France III” Ethics Committee (Paris, France – Ref: 3859) on May 11, 2021 and the competent authority “ANSM” (Ref: MEDAECNAT-2021-05-0011) on May 19, 2021. This study was funded by the French Ministry of Solidarity and Health and the French Ministry of Research and sponsored by Assistance Publique Hôpitaux de Paris.

### Participants

Adult persons were eligible to participate if they had received a first dose of an mRNA SARS-CoV-2 vaccine (mRNA-1273 or BNT162b2) and were scheduled for receiving a second dose 28 to 49 days later. Main exclusion criteria were pregnancy or breastfeeding, history of SARS-CoV-2 infection, acute febrile infection within the previous 72 h, symptoms suggestive of COVID-19 or contact with a case within the last 14 days prior to the inclusion visit, use of immunosuppressive medications or any immunosuppression condition that may reduce the immune response, history of severe post-vaccination adverse events or severe allergic manifestations, having received another vaccine within four weeks prior to the first injection or who are scheduled to receive a licensed vaccine within the next four weeks.

Written informed consent was obtained from each participant before enrolment and randomization.

### Randomization

Participants were randomly assigned in a 1:1 ratio to receive one dose of mRNA-1273 or BNT162b2 vaccine stratified on the vaccine received at the first dose. The randomization was stratified by center and by the vaccine received at the first dose (BNT162b2 or mRNA-1273 vaccine). We used a web-based randomization system (CleanWeb e-CRF, Telemedicine Technologies, S. A.S), with a centralized block randomization list with

blocks of size four (not communicated to the investigating team). The randomization list was generated by an independent statistician from the trial clinical research unit (URC-EST). Participants were randomized by the investigator.

### Procedures

Vaccines were administered intramuscularly by appropriately trained staff. Blood samples were planned for quantification of anti-spike IgG antibodies, anti-N antibodies, and neutralizing antibodies at D0 and D28. Samples collected at each site were sent to a certified core laboratory (CRB APHP.SU) before being sent for virological analysis (Inserm-UMR190).

For serological analysis, we used the Euroimmun® Anti-SARS-CoV-2 QuantiVac ELISA kit (Lübeck, Germany) run on the EUROLabWorkstation instrument, to detect and quantify IgG antibodies titers directed against the S1 domain of the SARS-CoV-2 spike protein. We reported quantitative results as antibody unit (BAU)/mL according to the WHO international standard (NIBSC code 20/136). Antibodies neutralizing the SARS-CoV-2 were detected and quantified using a CPE (cytopathic effect)-based virus neutralization test (VNT) in a 96-well format, as previously described.<sup>10</sup> The test uses 100 TCID<sub>50</sub> per well of virus grown five days onto TMPRSS2-expressing Vero cells. A human isolate of the SARS-CoV-2 D614G European variant (strain BavPat1/2020, obtained from the European Virus Archive, reference 026V-03,883) or Alpha, Beta and Delta variants of SARS-CoV-2 provided by the French reference center for respiratory viruses were used in a VNT<sub>100</sub> (100% of wells lysed in quadruplicate) format. The test was automated in a NSB3 laboratory for all dilution and dispensing steps, and for CPE reading. Dilutions tested were 20, 40, 80, 160, 320, 640, 1280. The range was extended if a titer of 1280 was observed in the first instance. All sera were tested against the European variant strain. Measurement of neutralizing antibodies against the specific variants (Alpha, Beta, Delta) was performed on a representative population of 30 subjects randomly selected after stratification on vaccine schedule group, age (<40 years, ≥40 years, and <55 years, ≥55 years), and level of anti-spike IgG against the wild-type viral strains at D28 (<1000 BAU/mL, ≥1000 BAU/mL, and <5000 BAU/mL, ≥5000 BAU/mL).

### Outcomes

The primary outcome was the immune response (anti-spike IgG antibodies titer) 28 days after the second injection of mRNA vaccine. Secondary outcomes were (1) Adverse reaction, local and systemic reaction occurring up to 28 days after the second injection, (2) additional analysis of other pre-specified immunologic efficacy endpoints. These were: (1) increase in anti-spike

IgG titers between pre- and four weeks post second vaccine dose and (2) neutralizing antibodies levels against an early SARS-CoV-2 European strain (for all participants) and the Alpha, Beta, and Delta SARS-CoV-2 variants (for 30 participants), 28 days after the second vaccine dose.

Diary cards were provided to each participant to collect tolerance and safety data of local and general reactions previously reported during mRNA SARS-CoV-2 vaccine trials (i.e., fever, headache, asthenia, myalgia, arthralgia, sickness, chills, nausea, vomiting, insomnia, pain in the extremities, lymphadenopathy)<sup>6,7</sup> within one week after vaccination, as well as any unsolicited adverse events occurring within 28 days after injection.

### Statistical analysis

The statistical plan is available in supplement 1.

Preliminary data from our department suggested that the geometric mean anti-spike antibody level measured by Elisa was 2.4 log<sub>10</sub> BAU/mL (253 BAU/mL) with a standard deviation of 0.54, 28 days after the second dose. The sample size calculation, i.e., 100 subjects per group and 400 in total, was based on a non-inferiority margin corresponding to a geometric mean ratio (GMR) of 0.61 between vaccination with a second dose of a heterologous vaccine regimen and a second dose of the homologous vaccine (i.e., -0.215 in absolute difference on a base ten logarithmic scale and a standard deviation of the geometric mean of 0.54 on a base ten logarithmic scale), with power of 80% and a one-sided alpha risk of 2.5%.

The primary endpoint was analyzed under the hypothesis of non-inferiority of vaccination with two doses of different vaccines (combined vaccination) compared to vaccination with two doses of the same vaccine (standard vaccination) (i.e., BNT162b2/mRNA-1273 versus BNT162b2/BNT162b2 and mRNA-1273/BNT162b2 versus mRNA-1273/mRNA-1273) separately. For each group, the anti-SARS-CoV-2 IgG antibody titers directed against the S1 domain of the spike protein measured at D0 and D28 were described as geometric means with two-sided 95% confidence intervals (95% CI). The geometric mean ratio (GMR) and its two-sided 95% CI were calculated. Since this was a non-inferiority study, the primary endpoint was assessed on the per protocol population with an additional sensitivity analysis on the as randomized population. The non-inferiority of vaccination with two doses of different vaccines compared to vaccination with two doses of the same vaccine was demonstrated if the two analyses were consistent. The as randomized population is all randomized subjects except those with positive, uncertain or missing NP antibody serology at inclusion. The per-protocol population is all randomized, vaccinated subjects without major protocol deviations (i.e., non-compliance with the selection criteria or with the allocated vaccine or the

time between the two doses, missing primary endpoint, or subjects with positive, doubtful or missing NP antibody serology at inclusion or day 28). Missing data for the primary endpoint was replaced by the geometric mean value of antibody levels observed in the group of the concerned subject. Other missing data were not replaced.

Safety assessment was analyzed among the safety population (i.e., all randomized subjects). Adverse reactions and events were described using frequencies and percentages.

SAS software (version 9.4, SAS Institute, Cary, NC) was used for the statistical analyses. R freeware (version 3.6.3) and GraphPad Prism software (version 9.2.0, San Diego, California USA) were used for the graphs. Statistical significance was considered when the lower bound of the two-sided 95% CI of the primary endpoint was above the pre-defined margin for non-inferiority analyses, and when the p-value of the other endpoints was below 0.05. In case of multiple comparisons, Bonferroni correction was performed. Supplemental statistical analysis methods are reported in supplement 2.

This study is registered with ClinicalTrials.gov, NCT04900467; N° EudraCT: 2021-002,174-52.

### Role of the funding source

This study was supported by the French Ministry of Solidarity and Health and the French Ministry of Research and sponsored by Assistance Publique Hôpitaux de Paris. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

### Study participants

A total of 414 adults were randomized from May 28 to July 2, 2021, of whom 203 had received BNT162b2 and 211 mRNA-1273 as their first injection. Of these, 101 subjects were allocated to the BNT162b2/BNT162b2 group, 102 to the BNT162b2/mRNA-1273 group, 105 to the mRNA-1273/mRNA-1273 group, and 106 to the mRNA-1273/BNT162b2 group. Details of exclusion causes and follow-up not performed are described in the flow diagram, [Figure 1](#). We did not observe differences for baseline characteristics across study arms ([Table 1](#)).

Overall, 390 (94%) participants were retained in the per-protocol analysis ([Figure 1](#)).

### Immunogenicity

Based on the non-inferiority margin of 0.61, a second dose of mRNA-1273 was non-inferior to a second dose of BNT162b2 after a first dose of BNT162b2. Moreover, a second dose of mRNA-1273 met criteria for superiority

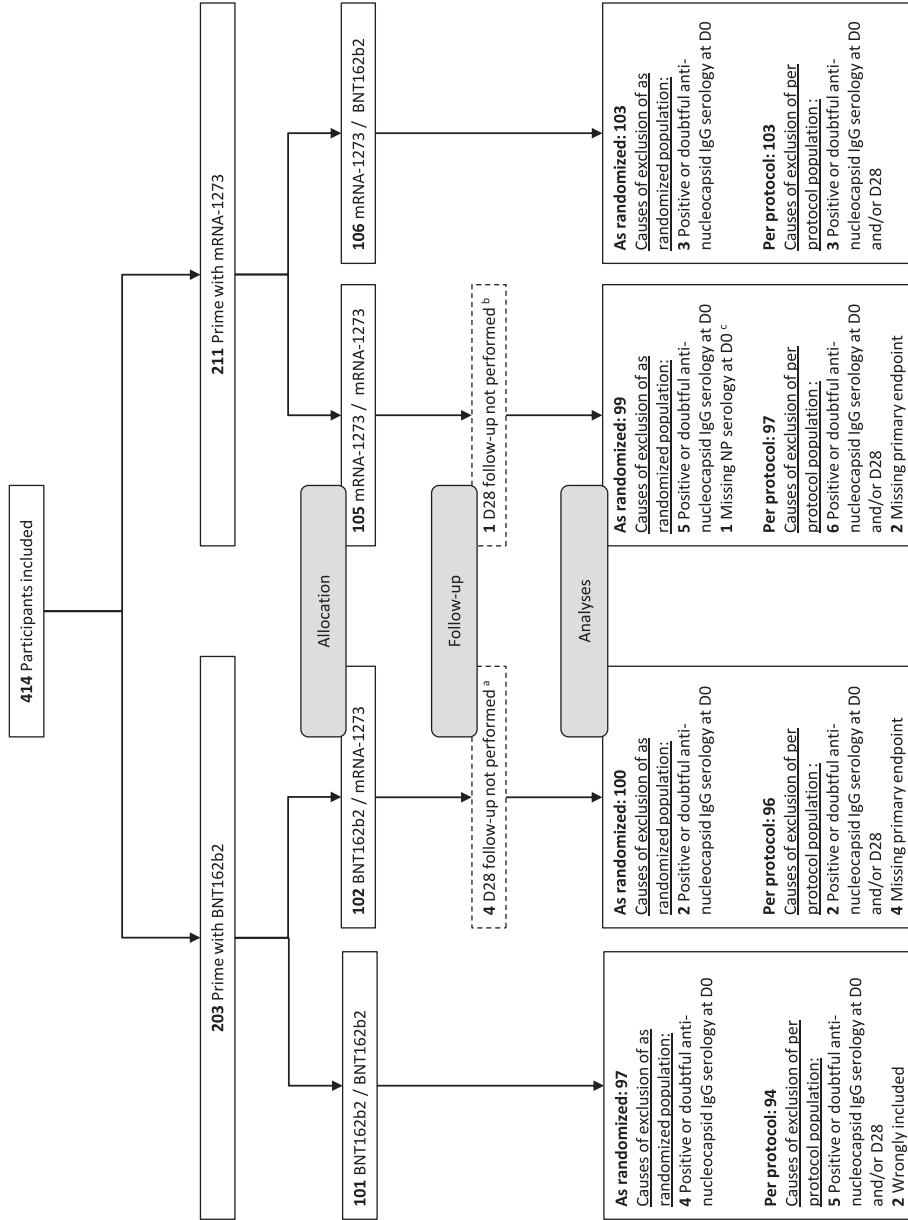


Figure 1. Study flow diagram.



	Per protocol population (n = 390)	BNT162b2/ BNT162b2 (n = 94)	BNT162b2/mRNA-1273 (n = 96)	mRNA-1273/mRNA-1273 (n = 97)	mRNA-1273/BNT162b2 (n = 103)
Age at inclusion, y					
Mean (SD)	40.3 (13.0)	40.2 (11.7)	37.6 (12.7)	42.0 (13.4)	41.4 (13.6)
Range	18.2–78.9	19.5–64.4	18.4–69.0	18.2–76.8	18.6–78.9
Female gender, n (%)	163 (41.8)	37 (39.4)	39 (40.6)	49 (50.5)	38 (36.9)
BMI, kg/m <sup>2</sup>					
Mean (SD)	25.0 (4.4)	25.1 (4.5)	24.3 (4.2)	24.5 (4.5)	26.0 (4.4)
Range	14.2–44.1	17.3–43.9	16.7–38.8	14.2–43.5	18.7–44.1
Current smoker, n (%)	90 (23.1)	17 (18.1)	25 (26.0)	25 (25.8)	23 (22.3)
Comorbidity, n (%)					
Diabetes	7 (1.8)	3 (3.2)	0 (0)	1 (1.0)	3 (2.9)
Hypertension	18 (4.6)	3 (3.2)	4 (4.2)	4 (4.1)	7 (6.8)
Obesity <sup>a</sup>	37 (9.5)	9 (9.6)	6 (6.3)	5 (5.2)	17 (16.5)
Time between 1st and 2nd dose, n (%)					
≤ 35 days	185 (47.4)	42 (44.7)	50 (52.1)	45 (46.4)	48 (46.6)
> 35 days	205 (52.6)	52 (55.3)	46 (47.9)	52 (53.6)	55 (53.4)

**Table 1: Per protocol population description.**  
 BMI, body mass index.  
<sup>a</sup> BMI ≥ 30 kg/m<sup>2</sup>.

compared with a second dose of BNT162b2 after a first dose of BNT162b2 (lower bound of 95% CI >1.00). The GMT ratio of anti-spike IgG at 28 days for the combined BNT162b2/mRNA-1273 regimen relative to the BNT162b2/BNT162b2 regimen was 1.37 (95% CI, 1.10 to 1.72) (Figure 2 and Supplementary Figure 1). In contrast, the non-inferiority of a second dose of BNT162b2 to a second dose of mRNA-1273 after a first dose of mRNA-1273 was not demonstrated. The GMT ratio of anti-spike IgG antibody at 28 days for the combined mRNA-1273/BNT162b2 regimen relative to the mRNA-1273/mRNA-1273 regimen was 0.67 (95% CI, 0.55 to 0.82). Similar findings were observed in the as randomized population.

In a complementary analysis, the titers of anti-spike antibodies were higher after the first injection of mRNA-1273 (geometric mean, 474.1; 95% CI, 400.3 to 561.6) than the titers after the first injection of BNT162b2 (geometric mean, 137.3; 95% CI, 113.5 to 166.0; p-value <0.001) (Not shown). This difference was persistent 28 days after the second injection between BNT162b2/BNT162b2 (geometric mean, 2697.9; 95% CI, 2277.6 to 3195.7) and mRNA-1273/mRNA-1273 (geometric mean, 3995.0; 95% CI, 3510.9 to 4545.8) regimens (p-value <0.001) (Supplementary Table 1).

The titers of anti-spike antibodies were higher in the groups receiving mRNA-1273 as a second dose compared to those receiving BNT162b2. The titers of the anti-spike antibodies were higher (p = 0.002) in the BNT162b2/mRNA-1273 group (geometric mean, 3706.1; 95% CI, 3201.5 to 4290.3) versus 2697.9 (95% CI, 2277.6 to 3195.7) for BNT162b2/BNT162b2. No

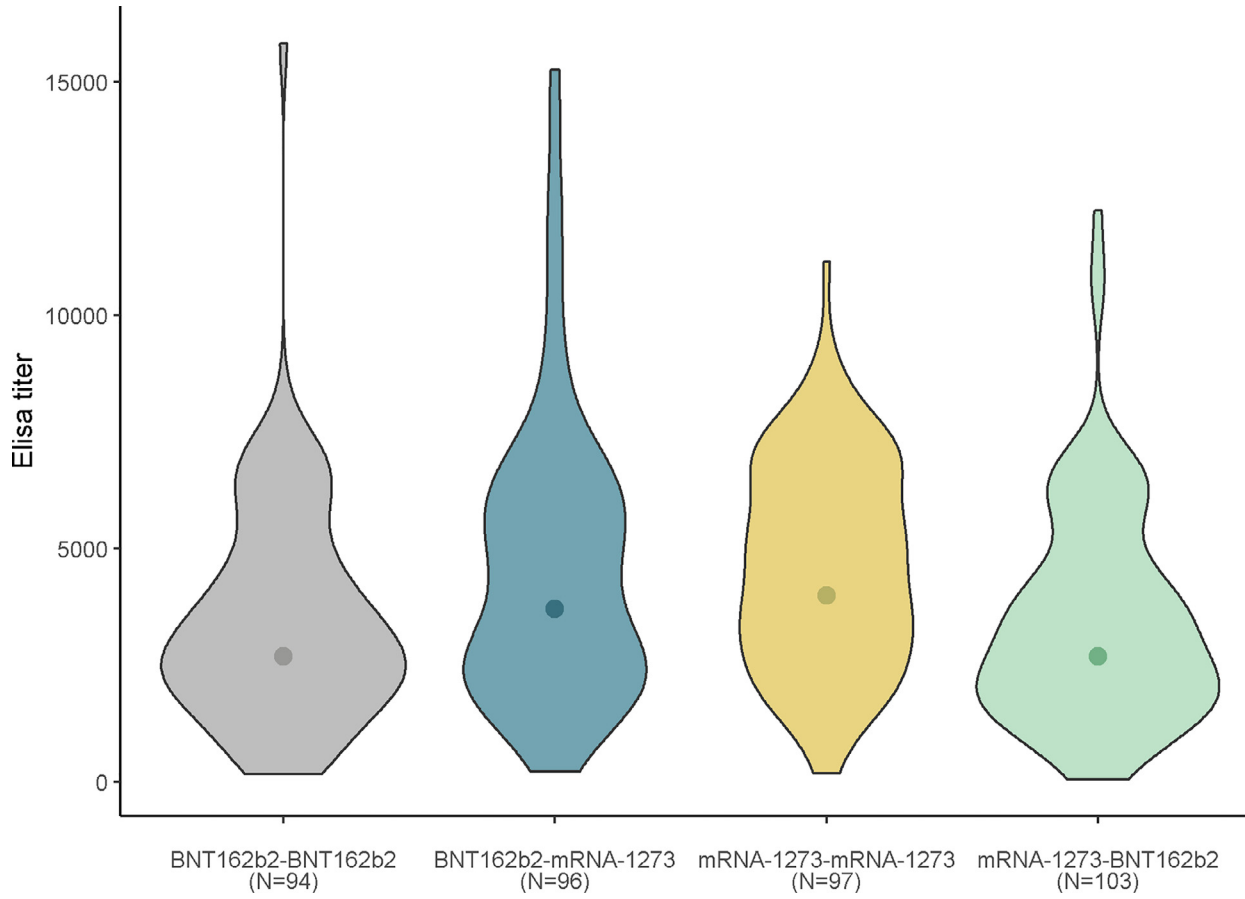
difference was demonstrated on anti-spike antibodies between the BNT162b2/mRNA-1273 group (geometric mean, 3706.1; 95% CI, 3201.5 to 4290.3) and mRNA-1273/BNT162b2 group (geometric mean, 2689.9; 95% CI, 2296.2 to 3151.1) groups (Supplementary Table 1).

Higher neutralizing antibodies titers were observed after mRNA-1273 first dose (geometric mean, 82.9; 95% CI, 72.7 to 94.4) compared with BNT162b2 (geometric mean, 47.3; 95% CI, 40.1 to 55.8; p-value <0.001) (Not shown). After 28 days, the geometric mean of neutralizing antibodies was higher with BNT162b2/mRNA-1273 (522.9; 95% CI, 435.8 to 627.3) than with BNT162b2/BNT162b2 (396.3; 95% CI, 333.3 to 471.1) regimen (p-value = 0.02). There was no difference between BNT162b2/mRNA-1273 (522.9; 95% CI, 435.8 to 627.3) and mRNA-1273/BNT162b2 (439.0; 95% CI, 372.6 to 517.3) regimen (p-value = 0.28) (Supplementary Table 2).

Neutralizing antibodies titers against SARS-CoV-2 variants were not different between the homologous and heterologous vaccine groups (Figure 3).

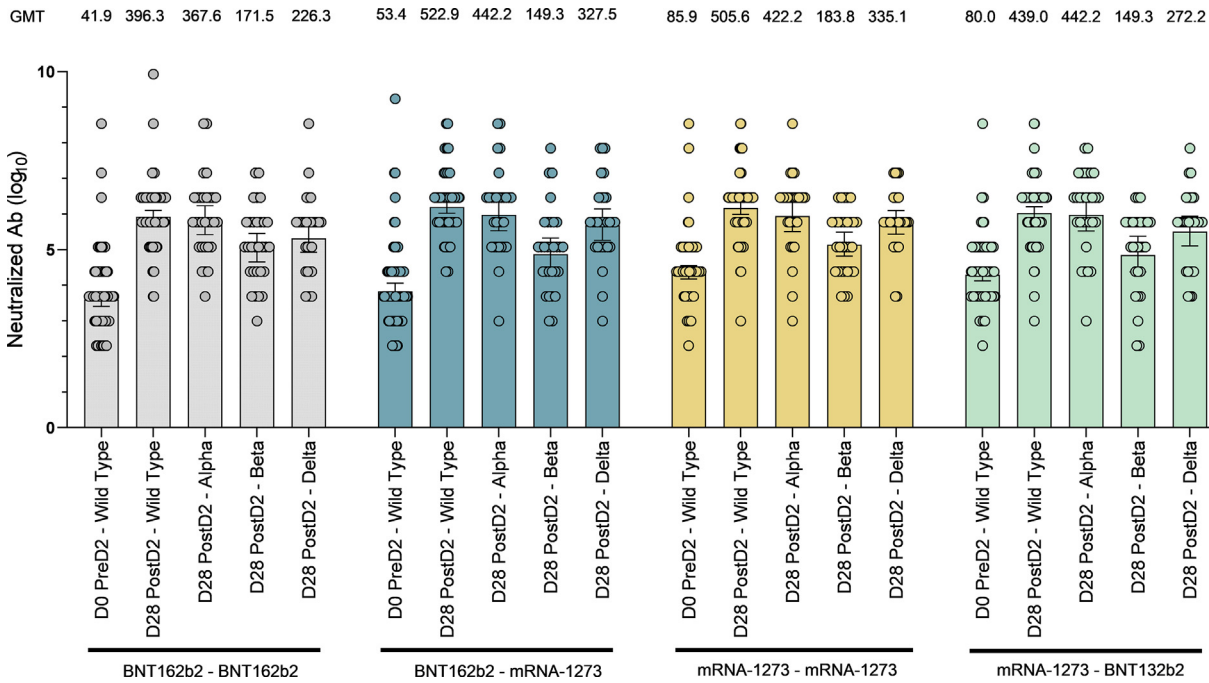
### Reactogenicity

Participants who received mRNA-1273 as a second dose experienced a higher rate of local adverse reactions and general symptoms than those who received BNT162b2 (p < 0.0001) (Figure 4). Three hundred twelve (76.3%) participants reported local adverse events and 302 (73.8%) reported general adverse events. Among the local adverse events, pain at the injection site was reported by nearly 100% of respondents, local edema was described by 27.8% of subjects after the double



**Figure 2.** Violin plots of anti-spike antibody titers determined by Elisa 28 days post dose 2 of vaccine.  
Legend: Within each diagram, the geometric mean is represented by a point.



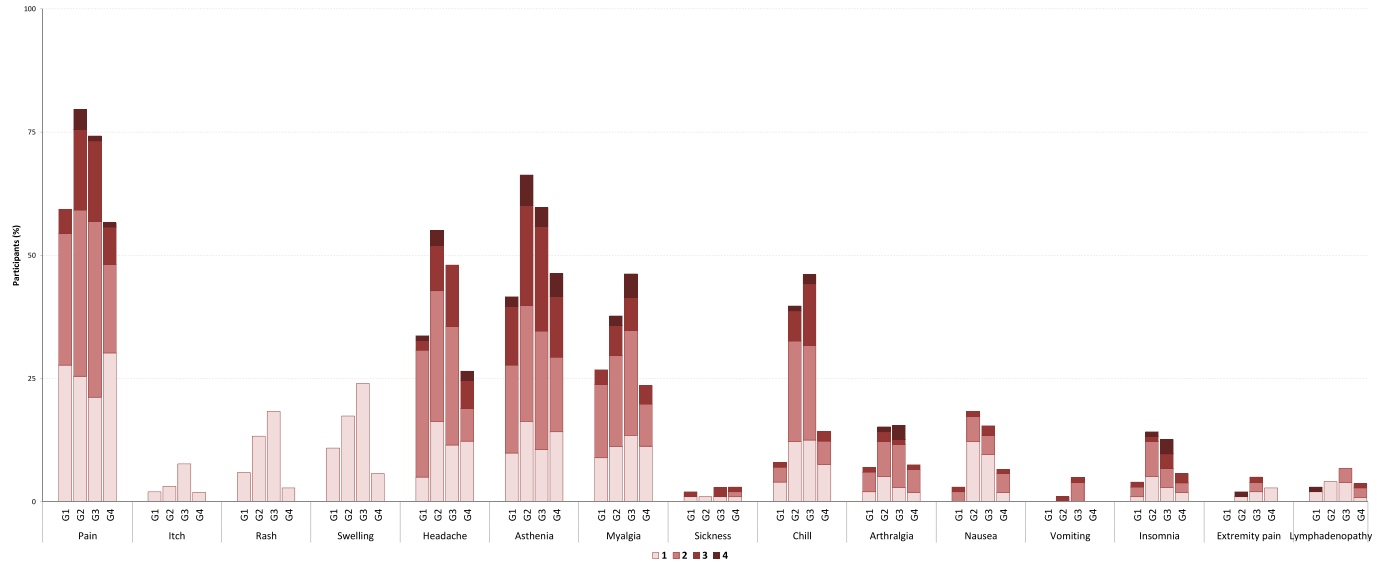


**Figure 3.** Bar graphs of neutralizing antibodies against wild type SARS-COV-2 (Pre-dose 2, 28 days post dose 2) and against Alpha, Beta and Delta variants (28 days post dose 2), per protocol population.

Legend: Measurement of neutralizing antibodies against specific variants (alpha, beta, delta) was performed on a population of 30 subjects randomly selected from participants after stratification on vaccine schedule group, age (< 40 y, ≥ 40 y and < 55 y, ≥ 55 y), and level of anti-spike IgG against wild-type viral strains at D28 (< 1000 BAU/ml, ≥ 1000 BAU/ml and < 5000 BAU/ml, ≥ 5000 BAU/ml).

\*PreD2: Pre-dose 2

\*\*PostD2: Post dose 2.



**Figure 4.** Adverse events reported by healthy volunteers after the second COVID-19 mRNA vaccines injection between D0 and D7.  
 Legend: G1 BNT162b2/ BNT162b2 ( $n = 101$ ), G2 BNT162b2/mRNA-1273 ( $n = 102$ ), G3 mRNA-1273/mRNA-1273 ( $n = 103$ ), G4 mRNA-1273/BNT162b2 ( $n = 106$ )  
 Colors to grade adverse reactions from 1 to 4.

dose of mRNA-1273 versus 8.6% in the mRNA-1273/BNT162b2 group, and erythema by 4.3% of subjects for the mRNA-1273/BNT162b2 group versus 21.1% for double dose mRNA-1273. Regarding systemic effects, asthenia was reported in 73% of cases, headache in 57%, myalgia in 46% and chills in 37%. The difference between the groups was mainly due to more frequent shivering in the mRNA-1273 vaccine groups at the second injection (55.6% with BNT162b2/mRNA-1273, 48.8% with two injections of mRNA-1273 vs. 21.4% with mRNA-1273/BNT162b2, 12.9% with two injections of BNT162b2). No serious adverse events were reported.

### Discussion

In this multicenter, non-inferiority, randomized, open-label trial, the heterologous BNT162b2/mRNA-1273 vaccination for SARS-CoV-2 was non-inferior to the homologous scheme based on either BNT162b2 or mRNA-1273 vaccine regimen. BNT162b2/mRNA-1273 was even superior to BNT162b2/BNT162b2. We could not conclude for the heterologous regimen with mRNA-1273 vaccine as the first injection. The regimen based on a second injection of mRNA-1273 induced a higher rate of neutralizing antibodies against wild-type SARS-CoV-2, Alpha, Beta, and Delta variants, than those with BNT162b2. Although all vaccine regimens were well tolerated, those with a second injection of mRNA-1273 resulted in a higher rate of systemic adverse events. As the expected minimum immunogenicity threshold is reached by both vaccines and the tolerance is satisfactory for both, we consider that they can be used indifferently. Although the statistical data do not formally conclude this from a clinical point of view, our results argue for flexibility in the use of mRNA-1273 or BNT162b2 as a second dose of the primary vaccination, which could facilitate the deployment of the vaccination.

Many studies<sup>11–14</sup> have analyzed combination regimens between mRNA and viral vector vaccines against SARS-CoV-2. However, to our knowledge, none compared the combined regimens of mRNA vaccines. Moreover, there was no large-scale evidence supporting the use of heterologous vaccination with prime-boost mRNA vaccines against SARS-CoV-2 infection. Pozzetto et al.<sup>15</sup> showed that a scheme combining the ChAdOx1-S adenoviral vector vaccine to the BNT162b2 mRNA vaccine was an acceptable alternative to the BNT162b2/BNT162b2 regimen. They demonstrated that such heterologous alternative combination conferred better protection than the homologous combination by inducing a strong anti-spike antibody response with higher neutralizing activity, regardless of SARS-CoV-2 variants. Our study sheds light on the acceptability of heterologous scheme based on mRNA vaccines, especially those based on mRNA-1273 for the second

injection, yet without assessing its superiority to the ChAdOx1-S/BNT162b2 combination.

Our finding of higher immunogenicity induced by a regimen including a second dose of mRNA-1273 supports the results of Steensels et al.<sup>16</sup> demonstrating higher humoral immunogenicity with double dose of mRNA-1273 compared to the BNT162b2 vaccine. In addition, we found higher serum neutralization with the BNT162b2/mRNA-1273 and homologous mRNA-1273 regimen than with the homologous BNT162b2 regimen. Noteworthy, the preliminary report of data on heterologous boost vaccinations also found a greater increase in seroneutralization with heterologous regimens (6.2- to 76-fold) compared to homologous ones (4.2 to 20-fold).<sup>17</sup> A longer interval between priming and enhancement for mRNA-1273 (28 days) versus BNT162b2 (21 days) may explain this difference,<sup>18</sup> but we did not find any difference in response when adjusting immunogenicity on timing between the two-vaccine injection. Another explanation might be the higher mRNA level in mRNA-1273 (100 µg)<sup>19</sup> compared to BNT162b2 (30 µg). Results of trial with half-dose vaccine will be essential to solve this issue. Finally, work on nanoparticles structure and composition should clarify their impact on the immunogenicity and reactogenicity of mRNA vaccines.

### Strengths

Our study is the first randomized study to compare in primovaccination heterologous versus homologous regimens of mRNA vaccines. We have demonstrated that, in the primary vaccination setting, interchangeability of SARS-CoV-2 mRNA vaccines is possible from an immunological perspective and with respect to reactogenicity. Although all homo and heterologous mRNA vaccine regimens elicit a good immune response, the composition of the mRNA-1273 vaccine allows for a higher immunological response at the expense of greater reactogenicity. These results are crucial, considering the need to simplify vaccination campaigns and schedules to allow a rapid increase in vaccination coverage in all countries that are still under-vaccinated.

### Limitations

First, the population of the current study was younger and had a lower rate of high blood pressure and/or obesity than the population at risk of severe forms of SARS-CoV-2 infection. Second, the age distribution did not allow to study the impact of immunosenescence on immunological vaccine efficacy according to hetero or homologous vaccine regimens. Third, we report the 28-days results after the second mRNA vaccine injection, but late immunogenicity assessment beyond six months is planned. We were unable to study the clinical efficacy of the vaccine regimens. We are thereby not able to

assess whether waning immunity is different according to the different regimens. However, one may suggest that higher early immunogenicity will result in lower waning immunity.

The two mRNA SARS-CoV-2 vaccines (BNT162b2 and mRNA-1273) could be used flexibly for COVID-19 primo vaccination. Second injection of mRNA-1273 results in higher immunogenicity and reactogenicity than BNT162b2-based regimen, although tolerance remains good regardless of the vaccine sequence.

### Contributors

OL, CJ, AR, XDL, LB and TS designed the study. AT, CP, OL, CJ, ML, JM, OE, ZMV, CC, BL, HA, AA, KL, CSM, EBN, MB, TB, PL, BB, OB and MM acquired, analyzed or interpreted the study. CJ, OL, MC, CP, AR, LN, ML, JM, OE, ZMV, CC, BL, HA, AA, KL, CSM, EBN, MB, TB, PL, BB, OB drafted the manuscript. OL, TS, CJ, AR and XDL critically reviewed the manuscript for important intellectual content. MC and AR did the statistical analysis. OL obtained funding. CP, AT, FD were in charge of administrative, technical and material support. OL, CJ and TS supervised the study. CJ and OL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

### Data sharing

The individual participant-level data that underlie the results reported in this article will be shared after de-identification (text, tables, figures, and appendices). This clinical trial is ongoing, and all individual participant-level data will not be available until after the immune persistence assessments have been done. The data will be made available immediately after publication and finalization of the complete clinical study report, for at least 6 months. Researchers who provide a scientifically sound proposal will be allowed to access the de-identified individual participant data. Proposals should be sent to the corresponding authors. These proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit. To gain access, data requesters will need to sign a data access agreement.

### Declaration of interests

OL reports grant from French ministry of health and grants or contracts from Pfizer, Sanofi-Pasteur, GSK, MSD, AstraZeneca and Janssen. CJ reports fees for boardmembership from AstraZeneca, Pfizer and MSD. TS reports grant from DGOS (French Ministry of health), AstraZeneca, Bayer, Novartis, Sanofi, Boehringer, Daiichi Sankyo, Eli Lilly, GSK and personal fees for boardmembership and consulting from various pharmaceutical companies, including AstraZeneca, Sanofi, Bayer, Ablative Solutions and 4 Living Biotech.

KL reports personal fees from Gilead, MSD, Janssen, ViiV, Spikimm and fees for development of educational presentations from Janssen, Gilead, MSD, Sobi, and Chiesi. PL reports personal fees for board membership from Pfizer, Janssen, AstraZeneca, MSD, Viiv, GSK, consultancy and travel accommodation from Pfizer. EBN has received grant pending from Sanofi Pasteur and fees for board membership from Pfizer, and Janssen. MB reports travels grants from various pharmaceutical companies, including Pfizer, Novex, Janssen. XDL reports research grant from INSERM.

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### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101444.

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