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Beta-variant recombinant SARS CoV-2 vaccine induces durable cross-reactive antibodies against Omicron BA variants

Check for updates

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Abstract

Background We previously reported the safety and immunogenicity data from a randomized trial comparing the booster responses of vaccinees who received monovalent (MV) recombinant protein Beta-variant (MVB.1.351) and MV ancestral protein (MVD614) vaccines with AS03 adjuvant (Sanofi/GSK) to booster response of vaccinees who received mRNA MV ancestral strain BNT162b2 vaccine (Pfizer-BioNTech).

Methods First booster of the vaccines was administered in adult participants previously primed with 2 doses of MV ancestral strain BNT162b2. A subset of these participants with available blood samples collected at Day 0 (D0), at 28 days (D28), and 3 months (M3) post-booster were contacted for additional testing (195/208 participants). The persistence of cross-neutralizing antibodies, including against Omicron BA.1 and BA.4/5, up to 3 months after boosting was evaluated using a validated pseudovirus neutralization assay.

Results Across the whole population, MVB.1.351 vaccine induces highest NAbs titers against Omicron BA.1 and BA.4/5 variants at D28 and M3 post-booster. In participants with SARS-CoV-2 infection between D28 and M3, both MVB.1.351 and BNT162b2 vaccine groups show an increase in GMTs against Omicron BA.1 and Omicron BA.4/5 following infection. Among uninfected participants, the ratio of M3 to D28 GMTs was higher for the MVB.1.351 group than the BNT162b2 group against Omicron BA.1 (0.64 [0.53; 0.77] versus 0.43 [0.35; 0.53]), Omicron BA.4/5 (0.61 [0.50; 0.75] versus 0.44 [0.34; 0.56]), and D614 (0.68 [0.58; 0.81] versus 0.46 [0.39; 0.55]).

Conclusions The MVB.1.351 vaccine induces higher and durable cross-neutralizing antibodies against Omicron subvariants up to 3 months after boosting compared to an MV ancestral and mRNA BNT162b2 booster vaccine.

Plain language summary

The SARS-CoV-2 virus has changed over time, resulting in new virus variants. It is important to understand how booster vaccines work against different virus variants and how long protection may last. We compared the impact of different COVID-19 vaccines on the immune response of people who had previously received an original licensed mRNA vaccine and then received a third dose (first booster) with either the same type of mRNA-based vaccine or with one of two protein-based vaccines. None of these vaccines contained the omicron variant. We saw differences in response depending on the different combinations of vaccine used. Our results suggest booster vaccination using different types of vaccines could enable people to have better protection against SARS-CoV-2 infection. This should be considered when considering which COVID-19 vaccines to use during booster vaccination programs.

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants led to the development and approval of the Omicron-containing bivalent messenger ribonucleic acid (mRNA) COVID-19 vaccines¹, and, approval of a Beta-variant containing recombinant protein-based booster vaccine with AS03 adjuvant (MVB.1.351) in Europe and the United Kingdom². The efficacy of monovalent ancestral Spike-based

vaccinations was substantial following their release in late 2020. Nonetheless, reductions in vaccination efficacy (VE) in the Omicron-dominant phase against infection and COVID-19-related hospitalization have been noted due to diminishing protection with time and discrepancies between the virus for which the original vaccines were formulated and the evolving circulating variations. The Omicron variation, which surfaced in November 2021, had

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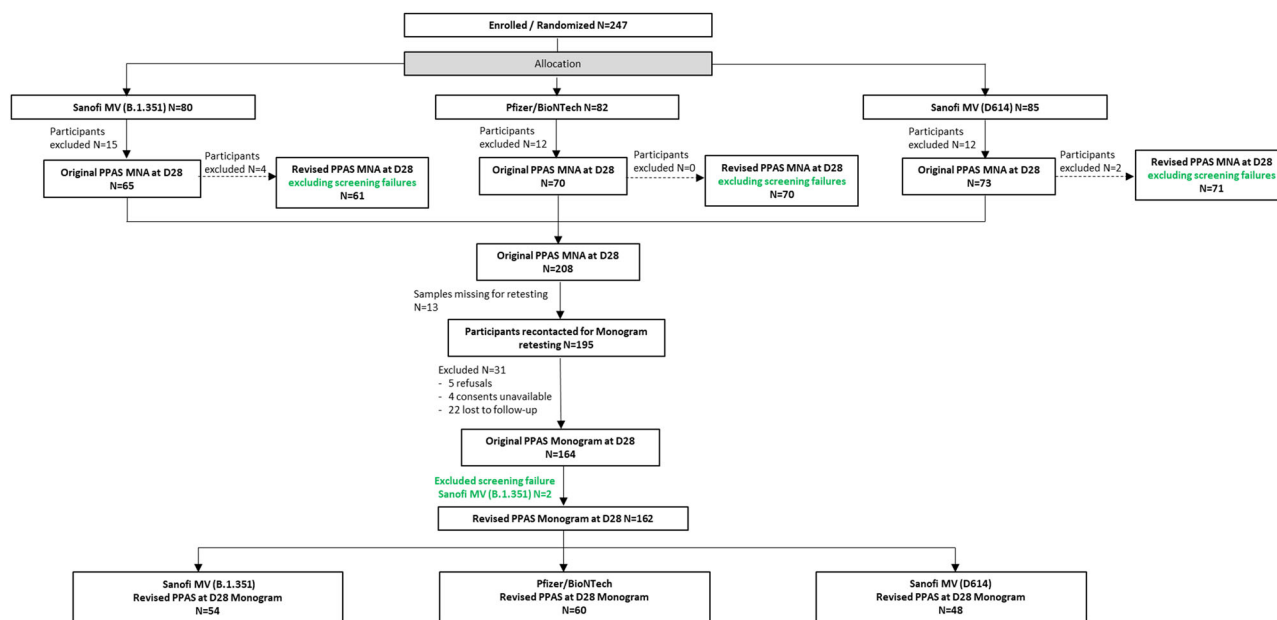


Fig. 1 | Summary of participant disposition in the study and per protocol analysis sets. N: number of participants in the Revised Per-Protocol Analysis Set Monogram; MV: Monovalent, PPAS: per protocol population, MNA: micro-neutralization assay. The Revised Per-Protocol Analysis Set Monogram was used for statistical analysis and comprised all randomized participants who received the booster, did not have prespecified major protocol deviations, those who consented for sending their samples for pseudovirus neutralization antibody testing, who were

not screen failures and excluded participants with a positive anti-nucleocapsid serology at D0, D14, or D28 or lost to follow-up. Evaluation of the subset of selected participants based on availability of samples for this re-analysis indicated comparability in baseline characteristics of sex and age (assessed both categorically and continuously) and no systematic bias in the definition or composition of these participants.

heightened immune evasion relative to prior variants. A third monovalent booster dose conferred enhanced protection against infection and severe disease during the Omicron predominance; however, the vaccine efficacy of monovalent booster doses against COVID-19-associated hospitalization has diminished over time since administration, particularly during the recent periods dominated by the BA.2/BA.2.12.1 and BA.4/BA.5 sublineages. We previously reported safety and immunogenicity data measured at 15 days after booster from a head-to-head randomized trial comparing monovalent (MV) ancestral and MVB.1.351 adjuvanted vaccines (Sanofi) to the mRNA BNT162b2 MV ancestral strain vaccine (Pfizer-BioNTech)³. Our study showed that the MVB.1.351 induced higher neutralizing antibodies (NABs) against a broad panel of variants (i.e., ancestral strain, Beta, Delta, Omicron BA.1) than homologous boosting with BNT162b2 vaccine.

Here, we report the persistence of cross-neutralizing antibodies, including against Omicron BA.4/5, extended up to 1 and 3 months after booster from the same study. Results from this study show that MVB.1.351 vaccination as a third dose following two-dose primary vaccination produces superior and long-lasting cross-neutralizing antibodies, up to 3 months after boosting as compared to an MV ancestral BNT162b2 mRNA vaccine or the MVD614 vaccine.

Methods

Study design

The design of this multicenter, randomized, single-blind trial (ClinicalTrials.gov NCT05124171; EudraCT number 2021004550-33) has been previously described³. Briefly, between December 8, 2021 (first participant first visit) and January 14, 2022 (last participant first visit), adult participants who had received primary vaccination with two doses of ancestral strain based BNT162b2 (second administration received between 3 and 7 months earlier) and who had given informed consent to take part in the study were recruited and randomly assigned to receive one of 3 vaccines as a third administration (first booster): MVB.1.351, MV ancestral recombinant protein (MVD614), or BNT162b2. This study was approved by Research Ethics Committee “Ile de France III” and French Health Products Safety Agency (ANSM).

The primary endpoint of rise in neutralizing antibodies between Day 0 and Day 15 as measured by microneutralization assay (MNA) against the ancestral D614 strain, B.1.351 (beta), Delta, and omicron BA.1 variants in the per protocol population analysis set was previously reported³. The sample size was designed to obtain an appropriate level of precision around the primary endpoint estimate. At enrollment, the time interval from the 2nd vaccine dose to participants receiving the study booster vaccine showed no major differences in median days (Interquartile range; IQR) between the randomized groups: 176 (IQR: 167.5; 188), 171 (IQR: 164; 184), and 174.5 (IQR: 160; 188) for Sanofi MV D614 group, Sanofi MVB.1.351 group, and Pfizer BNT162b2 group, respectively, as in the original publication³. In addition, the neutralizing antibodies against D614 and additional variants tested using a microneutralization assay were similar at baseline for the three randomized groups, as shown in the original publication³.

To generate data using a validated assay for regulatory submission, the protocol was appended with an associated Statistical Analysis Plan (SAP) that prespecified the analyses and success criteria based on formal hypothesis testing to undertake the testing of samples with a validated assay (i.e., the Monogram pseudovirus neutralization assay). The analyses reported in this manuscript are prespecified with formal hypothesis testing in the post-hoc SAP finalized prior to the release of the Monogram assay results (data not shown). The purpose of this post hoc supplementary analysis was: 1) to confirm the findings from the original study using a validated assay; 2) to compare the cross-neutralizing antibody titers against evolving clinically relevant omicron subvariants like BA.4/5 between the groups receiving the Sanofi B.1.351 and BNT162b2 vaccines using a validated assay 3) to assess the durability of the immune response beyond the D15 timepoint (secondary objective of the original protocol).

The analysis plan prespecified the subset of the participants population from the original per protocol population (PPAS) with available blood samples collected at Day 0 (D0, before vaccine administration), at 28 days (D28), and 3 months (M3) post-booster were contacted to reobtain their informed consent for additional testing (195/208 participants). This revised PPAS included 162 naive participants (54 in MVB.1.351, 60 in BNT162b2, and 48 in

Table 1 | Baseline characteristics between the revised population tested by MNA and revised re-tested population by Monogram PsVN assay - revised PPAS MNA at D28 / Revised PPAS monogram at D28

	SANOFI D614- Revised tested with MNA (N = 71)	SANOFI D614- Revised retested with PsVN (N = 48)	Differences Revised retested minus revised ^a	SANOFI B.1.351- Revised tested with MNA (N = 61)	SANOFI B.1.351- Revised retested with PsVN (N = 54)	Differences Revised retested minus revised ^b	PFIZER BNT162b2- Revised tested with MNA (N = 70)	PFIZER BNT162b2- Revised retested with PsVN (N = 60)	Differences Retested minus Revised ^c
Sex: n (%)									
Male	43 (60.6)	29 (60.4)	-0.15 (-17.76; 16.97)	39 (63.9)	34 (63.0)	-0.97 (-18.19; 16.12)	35 (50.0)	31 (51.7)	1.67 (-15.15; 18.34)
Female	28 (39.4)	19 (39.6)	0.15 (-16.97; 17.76)	22 (36.1)	20 (37.0)	0.97 (-16.12; 18.19)	35 (50.0)	29 (48.3)	-1.67 (-18.34; 15.15)
Age category: n (%)									
18-55 years	61 (85.9)	44 (91.7)	5.15 (-7.09; 16.90)	52 (85.2)	46 (85.2)	-0.06 (-13.66; 13.01)	59 (84.3)	52 (86.7)	2.38 (-10.36; 14.50)
56-64 years	8 (11.3)	4 (8.3)	-2.93 (-13.62; 9.54)	8 (13.1)	7 (13.0)	-0.15 (-12.68; 12.93)	8 (11.4)	7 (11.7)	0.24 (-10.97; 12.11)
≥65 years	2 (2.8)	0	-2.82 (-9.70; 4.87)	1 (1.6)	1 (1.9)	0.21 (-7.03; 8.25)	3 (4.3)	1 (1.7)	-2.62 (-10.32; 5.10)
Age (year)									
M	71	48		61	54		70	60	
Mean (SD)	41.1 (13.2)	41.9 (10.7)	0.811 (-3.73; 5.35)	41.8 (11.2)	42.2 (10.8)	(-3.70; 0.384, 4.47)	40.9 (14.0)	40.7 (13.3)	-0.248 (-5.01; 4.51)
Min;Max	19.0;73.0	19.0;64.0		22.0;68.0	23.0;68.0		20.0;69.0	20.0;68.0	

N: number of participants in Revised rPAS MNA at D28 or Revised PPAS Monogram at D28.

M: number of participants available for the endpoint.

2-sided 95% CI for the difference between proportions was based on the Wilson score method without continuity correction.

The number of participants from the Revised PPAS Monogram at D28 (N) may differ from the number of available results (M) as some sample testing may generate nonvalid results (i.e., testing not meeting quality control, ZNG40-liter does not exceed specificity control parameter). The baseline demographics of participants whose samples were retested with the validated monogram PsVN assay are comparable to those tested with the MNA (Revised PPAS MNA at D28). Selection of participants based on availability of samples for this re-analysis and resulting comparability based on sex and age (assessed both categorically and continuously) indicate no systematic bias in the definition or composition of the subset of participants in this re-analysis.

^a2-sided 95% CI for difference of mean age was based on the student t-distribution.

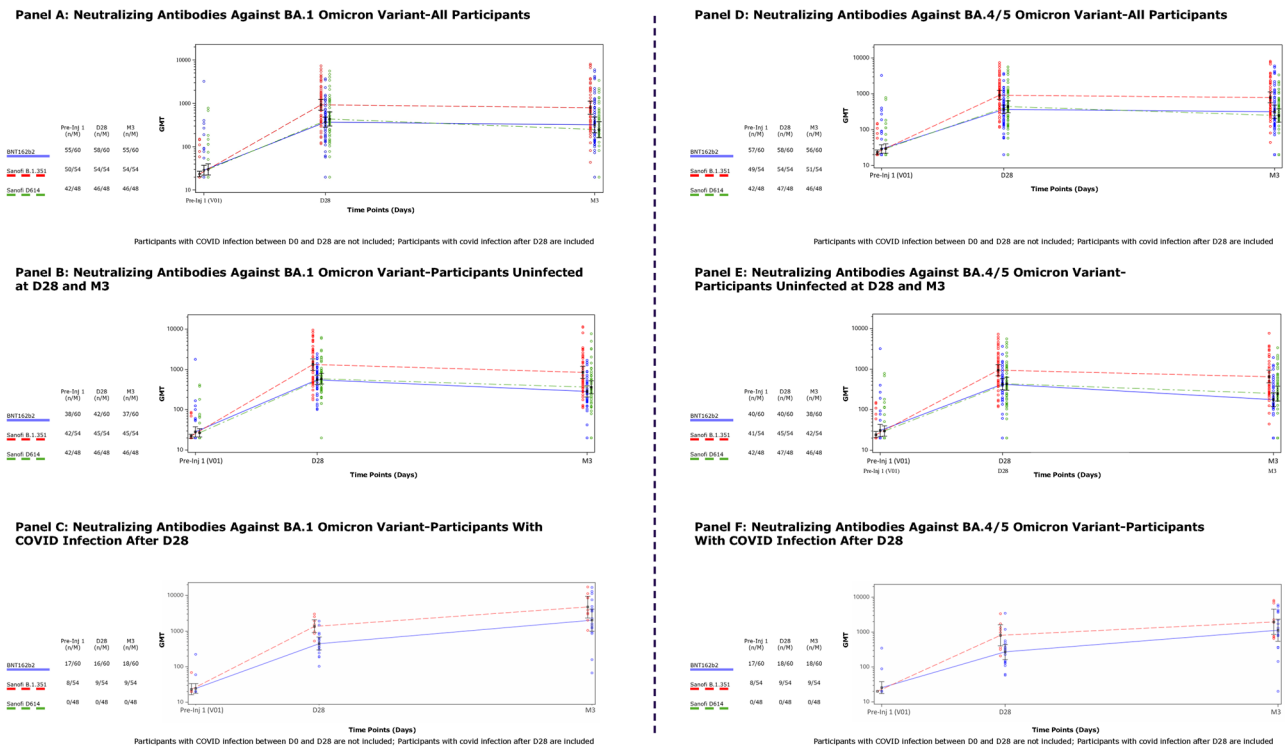


Fig. 2 | Kinetics of post-booster neutralization antibody responses against Omicron BA.1 and BA.4/5 variant strains assessed prior to, at 28 days and 3 months after receipt of a third vaccine dose (Revised Per-Protocol analysis set Monogram). Shown are geometric mean titers of neutralizing antibodies against the Omicron BA.1 (A–C) and BA.4/5 (D–F) variant strains of SARS-CoV-2. The blue line, red even dashes, and green uneven dashes indicate BNT162b2, Sanofi B.1.351, and Sanofi D614 vaccines, respectively. Circles represent the GMT values at 0, 28 days and 3 months after receipt of a third vaccine dose. Error bars indicate 95% confidence intervals for the GMTs. A and D depict all participants, B and E show GMTs for subgroup of participants without SARS-CoV-2 infection up to 3 months

post-booster, and C and F show GMTs for subgroup of participants with SARS-CoV-2 infection identified between D28 and M3. Please refer to Table 4 for the number of participants at each time point. Infected participants were defined with either a positive anti-nucleocapsid serology at M3 or who developed clinical symptoms with confirmatory testing for SARS-CoV-2 between D28 and M3. SARS-CoV-2 neutralizing antibody responses were measured using a lentivirus-based pseudovirus neutralization (PsVN) assay expressing the full-length S protein of the SARS-CoV-2 D614G or Omicron (BA.1 or BA.4/5) variants. Laboratory testing was performed by staff who were blinded to group allocation and time points. The figure was created using SAS® 9.4.

Table 2 | Comparison of post-booster geometric mean titer (GMT) and geometric mean titer ratio (GMTR) and associated 95% CI between MVB.1.351 and BNT162b2 by variant at Day 28, Month 3 for all participants

Strain	Time Point	MVB.1.351 (N = 54)			BNT162b2 (N = 60)			MVB.1.351/BNT 162b2		
		M	GMT	95% CI	M	GMT	95% CI	GMTR	95% CI ^a	Non-Inferiority ^b
Omicron BA.1	D28	54	1327	(1005;1753)	58	524	(423;649)	2.53	(1.80; 3.57)	Y
	Month 3	54	1120	(788;1593)	55	544	(366;808)	2.06	(1.22; 3.48)	Y
Omicron BA.4/5	Day28	54	925	(698;1227)	58	370	(283;483)	2.50	(1.70;3.67)	Y
	Month 3	51	796	(564;1124)	56	321	(211;488)	2.48	(1.44; 4.27)	Y
D614G	Day 28	54	6459	(5103;8174)	60	4507	(3695;5498)	1.43	(1.06;1.94)	Y
	Month 3	54	5432	(3985;7403)	60	3428	(2520;4662)	1.58	(1.03;2.44)	Y

M: number of participants available for the endpoint.
 N: number of participants in the Revised Per-Protocol Analysis Set Monogram.
^a2-sided 95% CI was based on the student t-distribution of logarithmic transformation of the individual titers.
^bNon-inferiority (NI) was concluded as Yes (Y) if the lower limit of the two-sided 95% CI for the ratio was greater than 1/2.
 The NI margin was set to 2. The NI was assessed based on a lower bound of the 95% CI > 0.5 (1/NI margin). The NI margin was defined as a clinically relevant criterion. A nominal significance level of 0.025 one-sided was used for hypothesis testing defined for primary objective. No multiplicity adjustment was done.

MVD614 groups) while 33 participants were excluded (reasons detailed in Fig. 1, more than 84% of the participants did re-consent). The re-consent and retesting has been done according to Good Clinical Practices (GCP).

Statistics and reproducibility

Descriptive statistics on demographics for both the original and revised PPAS are provided in Table 1. Samples for the analysis presented here were tested using a validated pseudovirus neutralization assay (Monogram Biosciences,

South San Francisco, CA, USA)⁴. Statistical analyses were performed to evaluate the non-inferiority of NAb responses against Omicron BA.1, BA.4/5, and D614G over time after a booster dose of MVB.1.351 compared to BNT162b2 vaccine. The non-inferiority approach was performed as follows with no multiplicity adjustment. H0: $GMT_{SANOFI\ B.1.351} / GMT_{PFIZER\ BNT162b2} \leq 1/\delta$; H1: $GMT_{SANOFI\ B.1.351} / GMT_{PFIZER\ BNT162b2} > 1/\delta$, where GMT meant geometric mean titer, and δ , the non-inferiority margin was set to 2. All analyses were performed using SAS® 9.4.

Ethics

Authors affirm that this study adheres to all relevant ethical regulations specified in the Declaration of Helsinki and GCP.

Reporting summary

Further information on research design is available in Nature Portfolio Reporting Summary linked to this article.

Results and discussion

For the overall population, the MVB.1.351 vaccine induced the highest NAb titers against Omicron BA.1 and BA.4/5 variants (Fig. 2A, D) at both D28 and M3 post-booster. At D28, the geometric mean titer ratio (GMTR) of MVB.1.351 booster relative to BNT162b2 was 2.53 (1.80;3.57) and 2.50 (1.70;3.67) against BA.1 and BA.4/5 strains, respectively, which met the noninferiority criterion of the lower limit of the two-sided 95% CI of GMTR > 0.5 (Table 2). At M3, the GMTR of MVB.1.351 relative to BNT162b2 was 2.06 (1.22;3.48) and 2.48 (1.44;4.27) against BA.1 and BA.4/5, respectively, meeting the noninferiority criterion. Antibody titers elicited by MVD614 and BNT162b2 vaccines were comparable to each other (Fig. 2A, D).

To further understand the persistence of NAb at M3 and potential impact of differentiated post-D28 infections between vaccine groups, a subgroup analysis was performed in individuals infected or not infected between D28 and M3. This analysis should be interpreted as supplemental to the main analysis acknowledging the post-randomization nature of the strata definition with potential unknown confounders impacting the interpretation. Infected participants were defined with either a positive anti-nucleocapsid serology at M3 or who developed clinical symptoms with confirmatory testing for SARS CoV-2 between D28 and M3. Nine of 54 participants (17%) from MVB.1.351 group, 18 of 60 participants (30%) from BNT162b2 group and 0 of 48 (0%) participants in the MVD614 were identified as infected between D28 and M3 in the revised PPAS monogram at D28. In the intent-to-treat (ITT) population, 17 of 78 participants (22%) from MVB.1.351 group, 30 of 80 participants (38%) from BNT162b2 group, and 18 of 84 participants (21%) in the MVD614 were identified as infected between D28 and M3 (Table 3).

Among uninfected participants (Fig. 2B, E), the ratio of M3 to D28 GMTs (Table 4) was higher for the MVB.1.351 group than the BNT162b2 group against Omicron BA.1 (0.64 [0.53;0.77] versus 0.43 [0.35;0.53]), against Omicron BA.4/5 (0.61 [0.50; 0.75] versus 0.44 [0.34; 0.56]), and against D614 (0.68 [0.58,0.81] versus 0.46 [0.39,0.55]) indicating better persistence of NAb over three months for the MVB.1.351 group. The beta containing variant booster MVB.1.351 elicited higher NAb titers against the original D614 virus strain compared to the two D614-containing booster groups BNT162b2 and MVD614 groups at both D28 and M3 (Table 2).

In participants with SARS-CoV-2 infection between D28 and M3 (Fig. 2C, F), both the MVB.1.351 (n = 9) and BNT162b2 (n = 18) vaccine groups showed an increase in GMTs against Omicron BA.1 and Omicron BA.4/5 following infection (Table 4). Among the limited number of participants, the MVB.1.351 group maintained a higher magnitude of NAb titers than the BNT162b2 group, both at D28 and M3.

The limitations of this study included a lack of data on currently circulating and emerging variants with a consequence of no direct comparative data with the newer Omicron sublineages. Although such data are not available, this ongoing study will generate additional information about

Table 3 | Participant disposition

	Sanofi B.1.351	Pfizer BNT162b2	Sanofi D614
ITT # Participants	78	80	84
Non-Naïve at any timepoint	23	28	22
Non-Naïve between D28-M3 ^(a)	11 (14.10%)	19 (23.75%)	12 (14.29%)
Covid infection cases D28-M3 ^(b)	6 (7.69%)	11 (13.75%)	6 (7.14%)
Infected ^(a + b)	17 (21.79%)	30 (37.50%)	18 (21.43%)

ITT intent to treat, D day, M month.

^aA participant anti-NP positive at Month 3 was considered as non-naïve in the D28-M3 time window unless participant had Covid before D28 (re-infection not considered).

^bA participant reporting Covid infection and testing positive with at least one diagnostic test.

Table 4 | Summary of post-booster Geometric Mean Titers (GMT) and Geometric Mean Titer ratio (GMTR) and associated 95% CI in Sanofi MVB.1.351, BNT162b2 and Sanofi MVD614 vaccine booster groups by SARS-CoV-2 infection status subgroup and by variant strain

Subgroup: SARS CoV-2 Status	Strain	Time Point	Sanofi MVB.1.351 (N = 54)			BNT162b2 (N = 60)			Sanofi MVD614 (N = 48)		
			M	GMT/ GMTR	(95%CI) ^a	M	GMT/ GMTR	(95%CI)	M	GMT/ GMTR	(95%CI)
SARS CoV- 2 Uninfected up to 3 months post-booster	Omicron BA.1	D28	45	1320	(950;1834)	42	557	(431;721)	46	587	(434;794)
		M3	45	840	(593;1191)	37	287	(208;398)	46	362	(248;529)
		M3/D28	45	0.64	(0.53;0.77)	37	0.43	(0.35;0.53)	44	0.67	(0.55;0.81)
	Omicron BA.4/5	D28	45	949	(689;1307)	40	426	(309;587)	47	438	(301;637)
		M3	42	656	(454;946)	38	177	(117;266)	46	250	(163;381)
		M3/D28	42	0.61	(0.50;0.75)	36	0.44	(0.34;0.56)	45	0.57	(0.46;0.72)
	D614	D28	45	6241	(4760;8183)	42	4900	(3887;6177)	48	5163	(3927;6788)
		M3	45	4257	(3146;5761)	42	2260	(1702;3002)	48	3370	(2468;4601)
		M3/D28	45	0.68	(0.58;0.81)	42	0.46	(0.37;0.55)	48	0.65	(0.55;0.78)
SARS CoV-2 Infection between Day 28 and Month 3	Omicron BA.1	D28	9	1365	(894;2085)	16	446	(296;674)	0	NC	
		M3	9	4722	(2351;9484)	18	2016	(983;4137)	0	NC	
		M3/D28	9	3.46	(1.51;7.93)	16	4.60	(2.06;10.3)	0	NC	
	Omicron BA.4/5	D28	9	814	(408;1624)	18	270	(163;446)	0	NC	
		M3	9	1972	(857;4534)	18	1128	(550;2313)	0	NC	
		M3/D28	9	2.42	(1.21;4.86)	18	4.18	(2.15;8.12)	0	NC	
	D614	D28	9	7665	(4654;12623)	18	3710	(2474;5562)	0	NC	
		M3	9	18367	(8700;38772)	18	9057	(4940;16607)	0	NC	
		M3/D28	9	2.40	(1.17;4.92)	18	2.44	(1.38;4.31)	0	NC	

N: number of participants in the Revised Per-Protocol Analysis Set Monogram.

M: number of participants available for the endpoint.

D28: 28 days post booster.

M3: 3 months post-booster.

NC not computed.

^a2-sided 95% CI was based on the Student t-distribution of logarithmic transformation of the individual titers.

later time points and immunogenicity against subvariants like BQ.1.1 and XBB.1. Our findings for the MVB.1.351 vaccine offer an alternative to the conventional variant chasing approach, providing a valuable option for heterologous boosting.

In conclusion, these data show that the MVB.1.351 vaccine induced higher and durable cross-neutralizing antibodies against Omicron subvariants, up to 3 months after boosting compared to an MV ancestral BNT162b2 mRNA vaccine or to the MVD614 vaccine. Bivalent mRNA COVID-19 booster doses containing an Omicron BA.4/BA.5 sublineage were recommended due to the Omicron variant spreading and more recently recommendations moved to MV booster dose containing an Omicron XBB.1 sublineage. New sublineages of SARS-CoV-2 Omicron continue to emerge. The effectiveness of the updated vaccines against the new variants continues to be studied, acknowledging the degree to which this higher NAb response against Omicron subvariants, as compared to a licensed mRNA vaccine, translates into greater clinical protection is not yet quantified. Overall, bivalent vaccines have demonstrated higher relative effectiveness relative to MV ancestral booster vaccines⁵. Data with currently deployed bivalent BA.4/5-containing mRNA booster vaccines suggest that antibody responses against BA.4/5 may be similar following MV ancestral and bivalent mRNA boosters^{6,7}. A new comparative study demonstrated that the bivalent BA.4/5 vaccine was more immunogenic than the original MV BNT162b2 vaccine against circulating Omicron sublineages after a 4th dose in individuals >55 years of age⁸. Another study evaluating the effectiveness of a bivalent COVID-19 vaccine elicited modest protection (30%) against COVID-19⁹. Recent preliminary data comparing immune responses following administration of a 5th dose of a Monovalent XBB.1.5 booster to Bivalent BA.4/5 and XBB.1.5 booster vaccines did not show a strong advantage of the bivalent formulation¹⁰. In general, variant-chasing vaccines may only add value when the window between variant introduction and vaccine deployment is very short (<3 weeks). Hence, it is crucial to develop next-generation cross-neutralizing and durable vaccines^{11,12}.

Data availability

All data supporting the findings of this study are available within the paper. The numerical data (source data) underlying Fig. 2 can be found in Table 4.

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Author contributions

A.R., B.C., C.V., F.B., M.C., R.M.C., S.S., and T.M. contributed to data analysis or interpretation. A.T., B.D., C.C., C.M.-R., D.D., E.K., F.L., I.B.G., K.L., M.L., O.L., C.-S.M., and T.S. contributed to the concept or design of the study, data acquisition and data analysis or interpretation. M-PT and PP contributed to the concept or design of the study and data acquisition. L.B.L.N. contributed to the contributed to concept or design of the study. E.T. contributed to the concept or design of the study and to data analysis or interpretation. L.D. contributed to data acquisition and data analysis or interpretation. R.G. contributed to data analysis or interpretation and drafting the manuscript. E.B.-N. contributed to data acquisition. All authors contributed to critical review and final approval of the manuscript as well as are accountable for the accuracy and integrity of the manuscript.

Competing interests

The authors declare the following competing interests: R.G., T.M., C.V., F.B., L.D., R.M.C., B.C. and S.S. are Sanofi employees and may hold stocks/shares in the company. O.L. reports grant from French Ministry of Health and grants or contracts from Pfizer, Sanofi-Pasteur, GSK, MSD, MD, AstraZeneca, and Johnson & Johnson. T.S. reports grant from AstraZeneca, Novartis, Sanofi, Bayer and personal fees for board membership and consulting. K.L. reports personal fees and fees for development of educational presentations from Gilead, MSD, Janssen, ViiV, Spikimm, Janssen, Sobi, and Chiesi. EBN has received grant pending from Sanofi Pasteur and fees for board membership from Pfizer, and Janssen. L.B.L.N. received personal fees for advisory experts and participation to conference from Pfizer. All other authors have no competing interests to declare.

Additional information

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