

Supplementary Table 1. Characteristics of study participants included in the correlates of protection analysis at T9.

		N or Median (IQR)	
		T9 – T11 (1 year period)	T9 – T12 (1.5 year period)
Age		49 (15 IQR)	49 (14 IQR)
Sex	Female	116	100
	Male	22	15
Comorbidities	Yes	93	76
	No	45	39
Smoking	Yes	49	36
	No	89	79
Vaccine doses	0	0	0
	3	138	115
Number of previous infections	0	47	44
	1	68	50
	2	21	19
	3	2	2
First dose type	Pfizer	137	114
	Moderna	1	1
Second dose type	Pfizer	137	114
	Moderna	1	1
Third dose type	Pfizer	57	46
	Moderna	81	69

Supplementary Table 2. Characteristics of study participants at T11.

		N or Median (IQR)				
		Total	Infected only	First infected hyb	First vaccinated hyb	Vaccinated only
Age		52 (14)	51 (12.5)	53 (17)	50 (16)	55 (19)
Sex	Female	78	8	27	35	8
	Male	15	2	6	4	3
Comorbidities	Yes	61	7	26	20	8
	No	32	3	7	19	3
Smoking	Yes	30	2	10	15	3
	No	63	8	23	24	8
Vaccine doses	0	10	10	0	0	0
	3	58	0	22	29	7
	4	25	0	11	10	4
Number of previous infections	0	11	0	0	0	11
	1	37	0	8	29	0
	2	32	7	17	8	0
	3	11	3	6	2	0
	4	2	0	2	0	0
First dose type	Pfizer	81	-	31	39	11
	Moderna	2	-	2	0	0
Second dose type	Pfizer	81	-	31	39	11
	Moderna	2	-	2	0	0
Third dose type	Pfizer	36	-	18	15	3
	Moderna	47	-	15	24	8
Fourth dose type	Pfizer	25	-	11	10	4
	Moderna	0	-	0	0	0

Supplementary Table 3. Characteristics of study participants at T13.

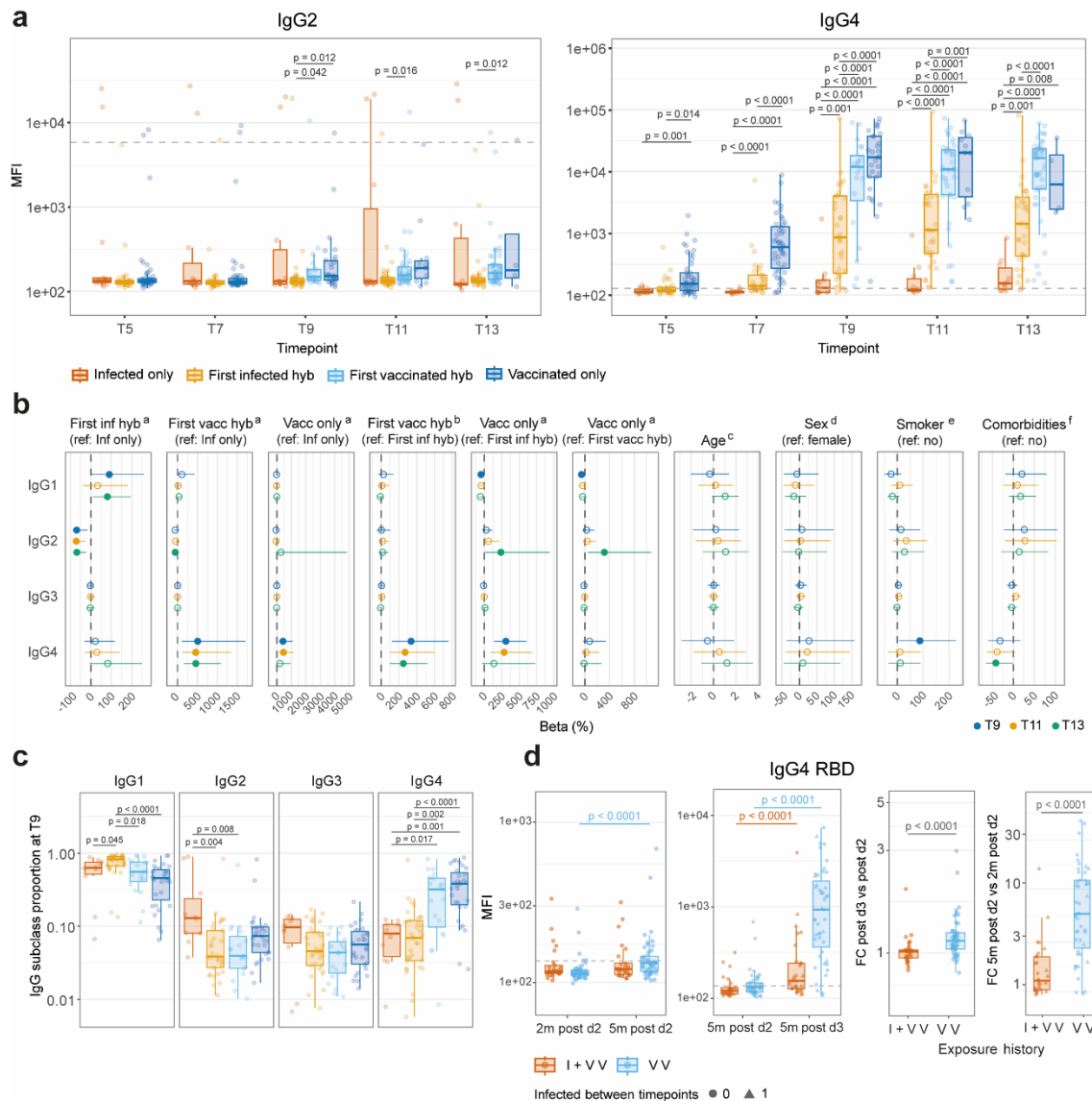
		N or Median (IQR)				
		Total	Infected only	First infected hyb	First vaccinated hyb	Vaccinated only
Age		52.5 (14)	49 (12.5)	52 (17)	50 (16.5)	48.5 (14,25)
Sex	Female	78	8	27	42	1
	Male	15	2	6	5	2
Comorbidities	Yes	61	7	26	25	3
	No	32	3	7	22	0
Smoking	Yes	32	2	10	19	1
	No	61	8	23	28	2
Vaccine doses	0	10	10	0	0	0
	3	54	0	21	21	2
	4	21	0	8	12	1
	5	8	0	4	4	0
Number of previous infections	0	3	0	0	0	3
	1	22	0	3	19	0
	2	41	3	12	26	0
	3	17	5	12	0	0
	4	7	1	4	1	0
	5	3	1	1	1	0
First dose type	Pfizer	81	-	31	47	3
	Moderna	2	-	2	0	0
Second dose type	Pfizer	81	-	31	47	3
	Moderna	2	-	2	0	0
Third dose type	Pfizer	36	-	18	17	1
	Moderna	47	-	15	30	2
Fourth dose type	Pfizer	29	-	12	16	1
	Moderna	0	-	0	0	0
Fifth dose type	Pfizer	8	-	4	4	0
	Moderna	0	-	0	0	0

Supplementary Table 4. Number of vaccinations and infections of study participants at T5

		N			
		Infected only	First infected hyb	First vaccinated hyb	Vaccinated only
Total		13	29	1	50
Vaccine doses	0	13	0	0	0
	1	0	1	0	0
	2	0	28	1	50
Number of previous infections	0	0	0	0	50
	1	12	28	1	0
	2	1	1	0	0

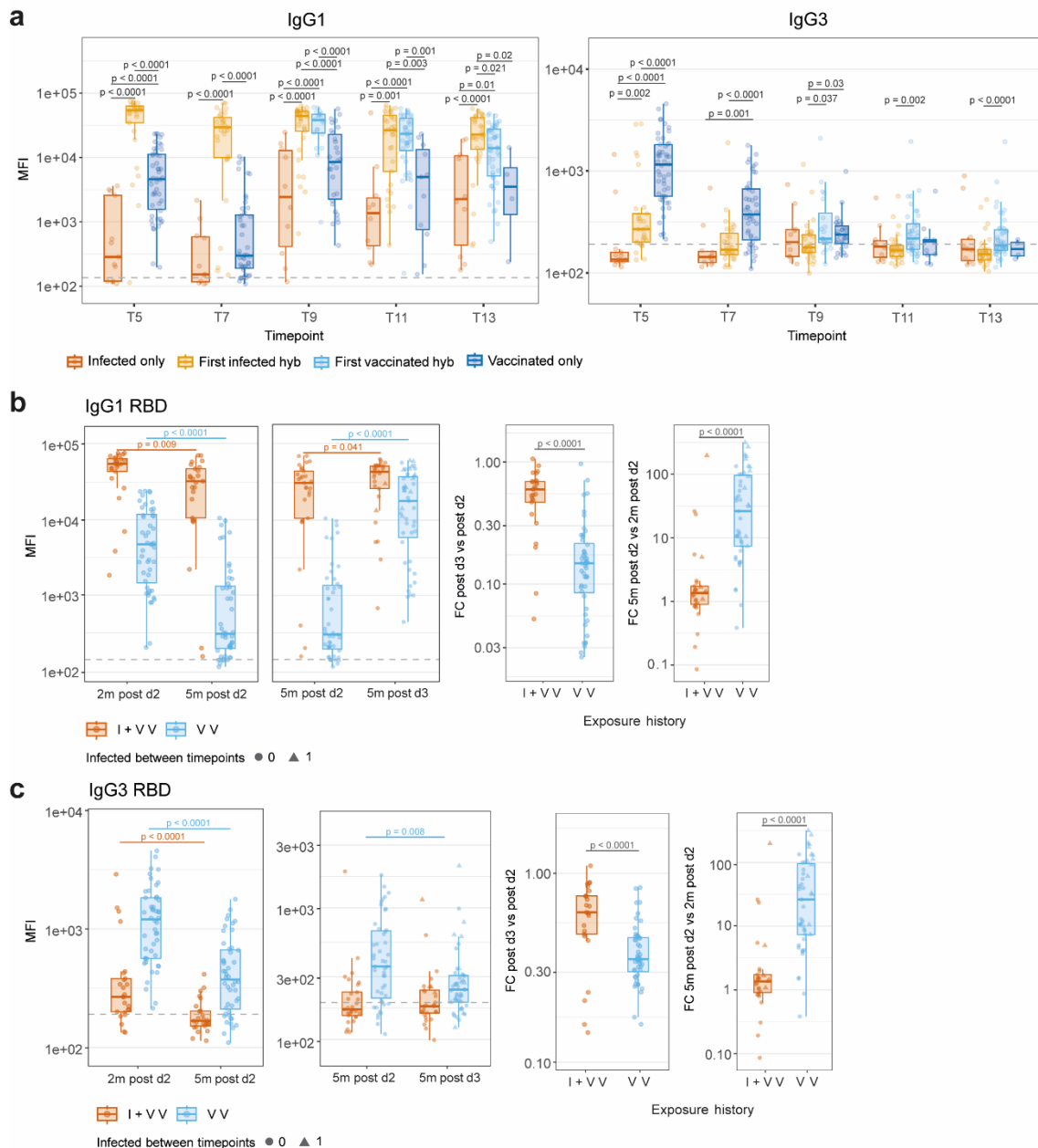
Supplementary Table 5. Number of vaccinations and infections of study participants at T7

		N			
		Infected only	First infected hyb	First vaccinated hyb	Vaccinated only
Total		11	31	3	48
Vaccine doses	0	11	0	0	0
	2	0	31	3	48
Number of previous infections	0	0	0	0	48
	1	9	29	3	0
	2	2	2	0	0

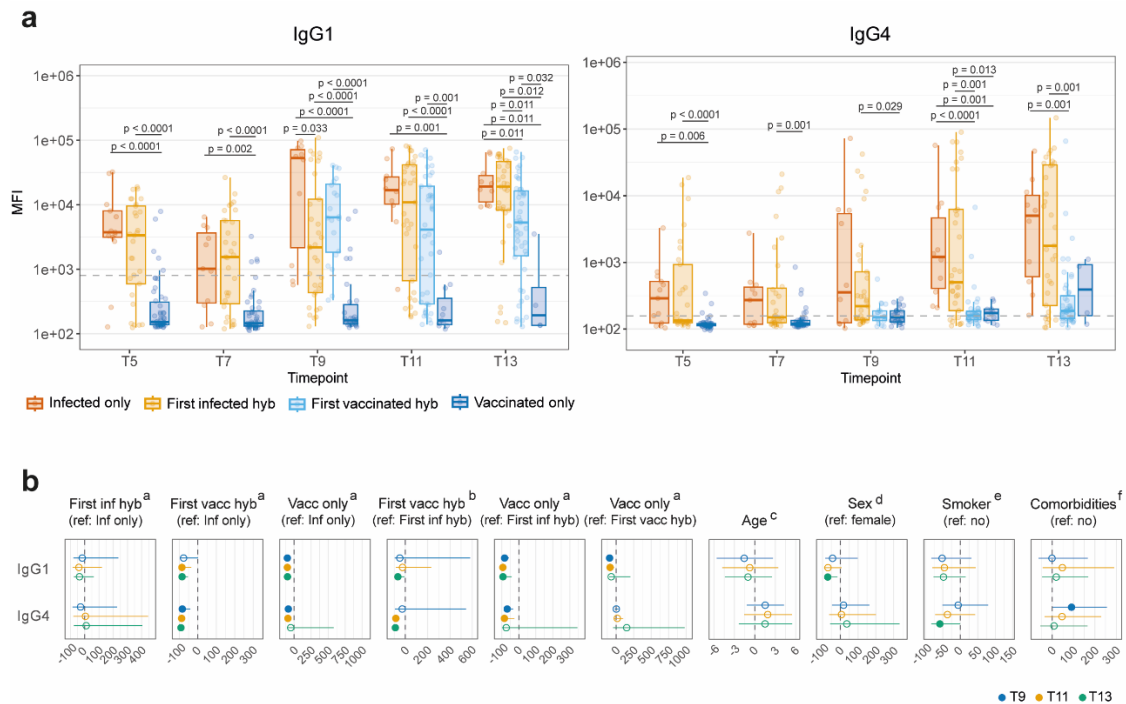


Supplementary Figure 1. Dynamics and determinants of IgG2 and IgG4 responses to RBD XBB following SARS-CoV-2 infection and vaccination. **a.** IgG2 and IgG4 levels across timepoints (T5, T7, T9, T11, T13) in four exposure groups: infected only, first infected then vaccinated (first-infected hybrid), first vaccinated then infected (first-vaccinated hybrid), and vaccinated only. Statistical significance was tested by Wilcoxon rank sum test and adjusted for multiple comparisons using Benjamini–Hochberg method. **b.** Associations between clinical and demographic factors and antibody levels (IgG1–4) at T9, T11, and T13, using multivariable linear regression models. Beta (β) and 95% confidence intervals (CI) are shown as percentage changes. Filled circles indicate $p < 0.05$, while unfilled circles indicate non-significant p -values after adjustment for multiple testing by Benjamini-Hochberg. Error bars represent the 95% CI. ^aAdjusted by age, sex, comorbidities, smoking, time since last exposure (natural spline, $df = 3$). ^bAdjusted by age, sex, comorbidities, smoking, time since last exposure (natural spline, $df = 3$), and number of exposures. ^cAdjusted by sex. ^dAdjusted by age. ^eAdjusted by age and sex. ^fAdjusted by age, sex, smoking. **c.** Proportion of each IgG subclass at T9 by exposure group. Proportions were derived from non-normalized MFI values; thus, absolute values are not directly interpretable. Comparisons should be restricted to relative differences among exposure groups within each subclass. **d.** IgG4 MFI levels and fold changes across key intervals: from 2 months post-2nd dose (T5) to 5 months post-2nd dose (T7), and from T7 to 5 months

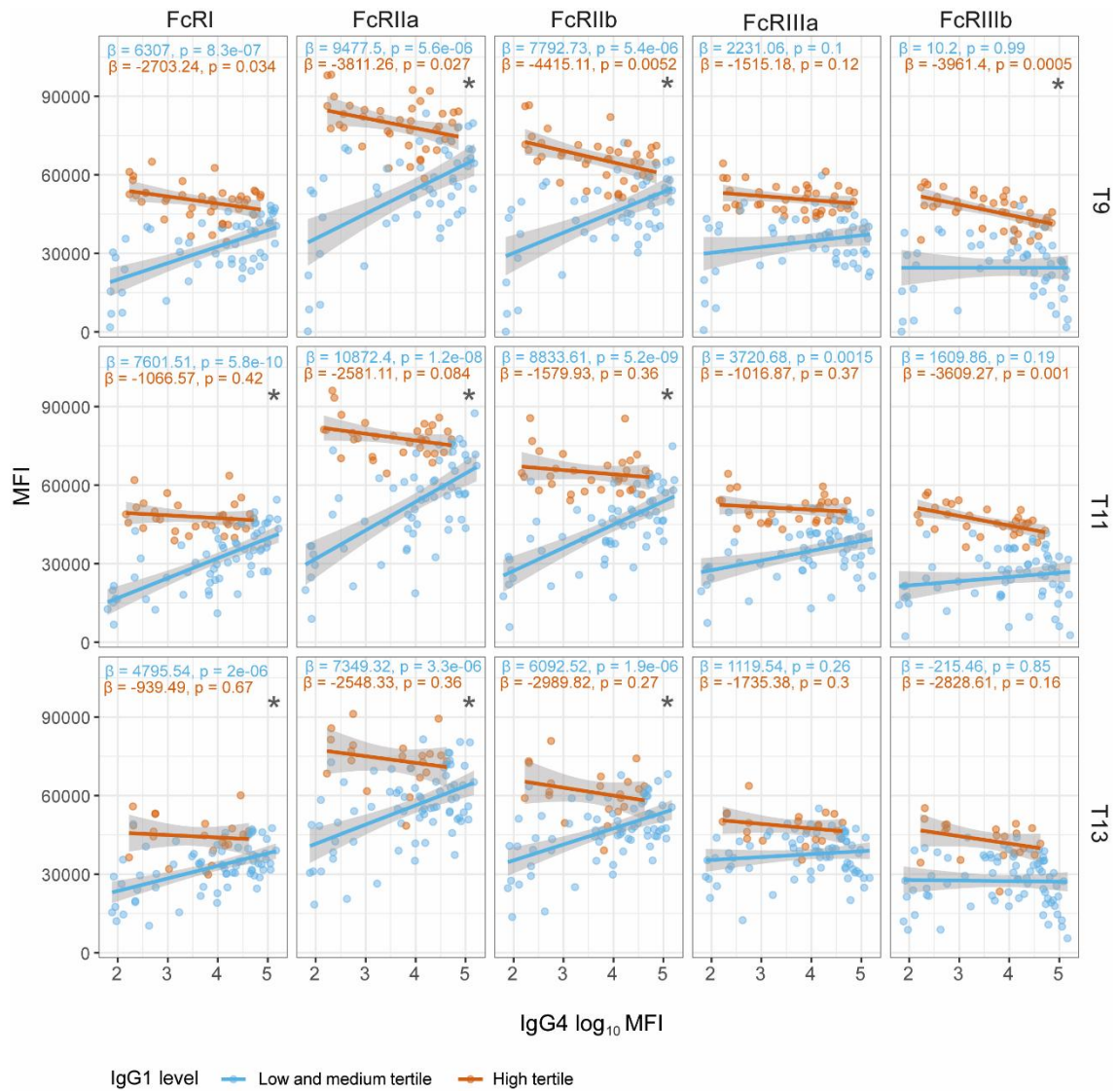
post-3rd dose (T9), in individuals with two vaccine doses with a previous infection (I + VV) versus those with two doses and no infection (VV only). The rightmost panels display the fold-change comparisons across timepoints. Grey dashed line depicts the positivity cutoff for the given antibody. Receptor-binding domain (RBD). T: timepoint. MFI: median fluorescence intensity. FC: fold-change.



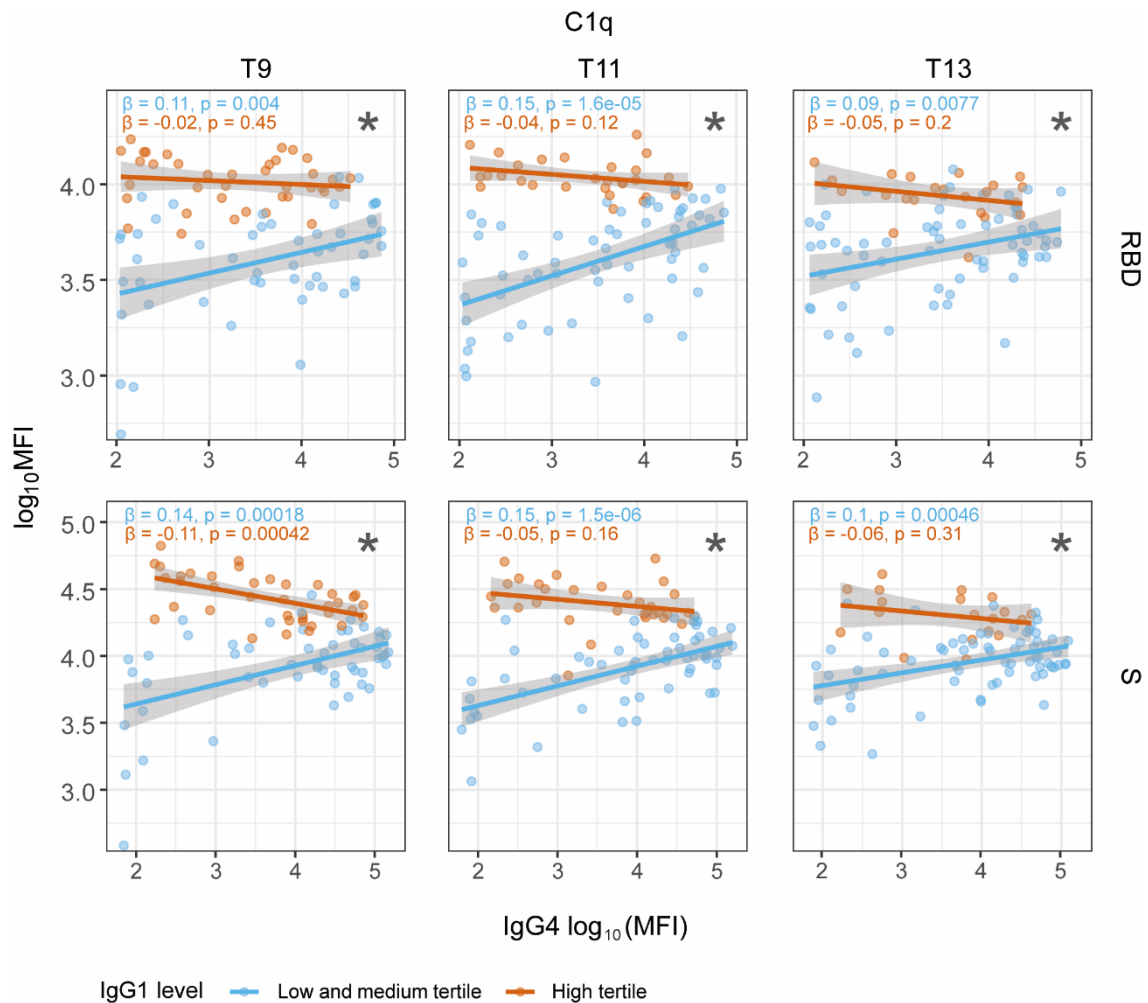
Supplementary Figure 2. Dynamics and determinants of IgG1 and IgG3 responses to RBD Wuhan following SARS-CoV-2 infection and vaccination. **a.** IgG1 and IgG3 levels to RBD Wuhan across timepoints (T5, T7, T9, T11, T13) in four exposure groups: infected only, first infected then vaccinated (first-infected hybrid), first vaccinated then infected (first-vaccinated hybrid), and vaccinated only. Statistical significance was tested by Wilcoxon rank sum test and adjusted for multiple comparisons using Benjamini–Hochberg method. **b, c.** IgG1 (**b**), and IgG3 (**c**) MFI levels and fold changes across key intervals: from 2 months post-2nd dose (T5) to 5 months post-2nd dose (T7), and from T7 to 5 months post-3rd dose (T9), in individuals with two vaccine doses with a previous infection (I + VV) versus those with two doses and no infection (VV only). The rightmost panels display the fold-change comparisons across timepoints. Grey dashed line depicts the positivity cutoff for the given antibody. Receptor-binding domain (RBD). T: timepoint. MFI: median fluorescence intensity.



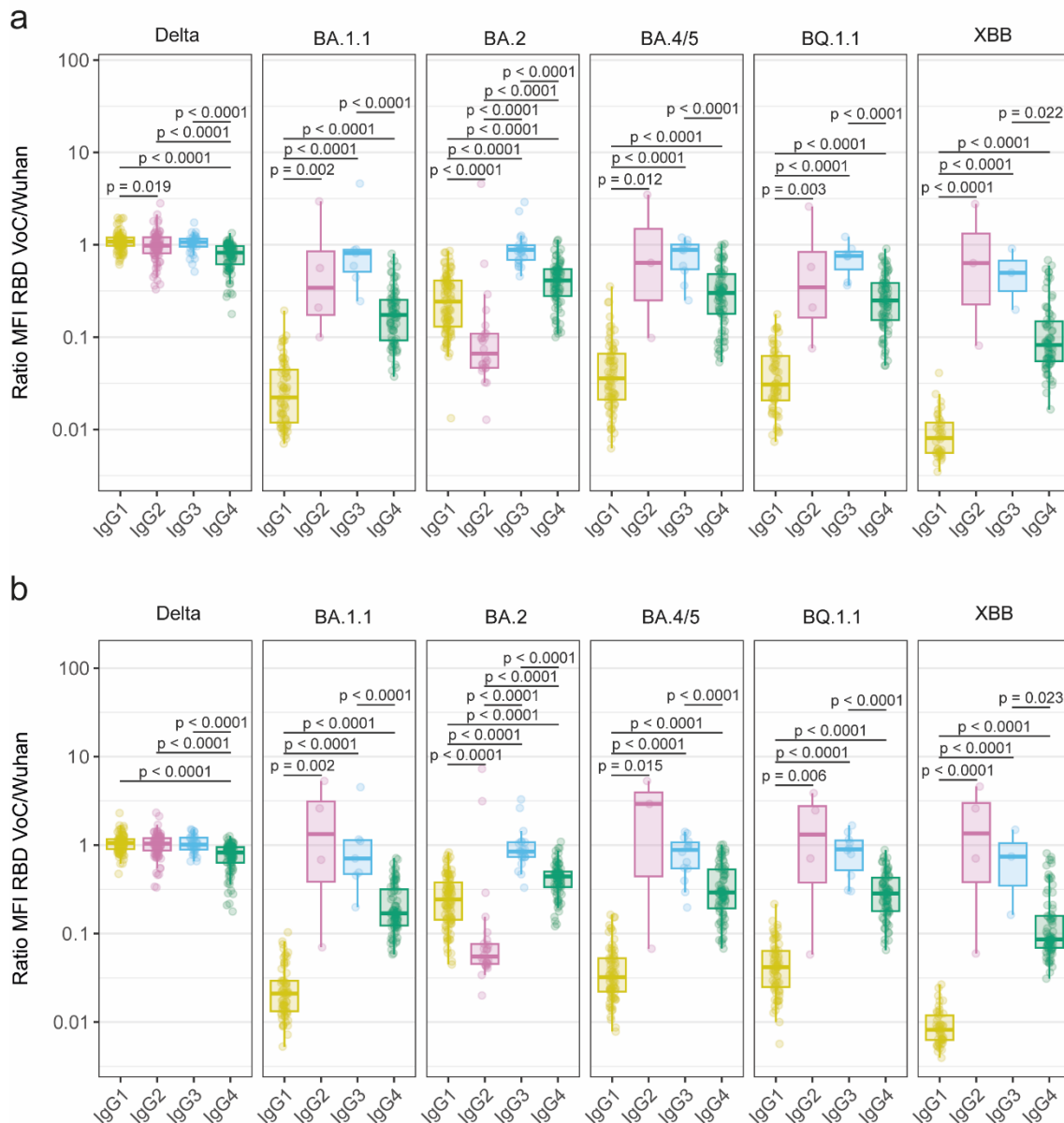
Supplementary Figure 3. Dynamics and determinants of IgG1 and IgG4 responses to nucleocapsid (N) following SARS-CoV-2 infection and vaccination. **a.** IgG1 and IgG4 levels across timepoints (T5, T7, T9, T11, T13) in four exposure groups: infected only, first infected then vaccinated (first-infected hybrid), first vaccinated then infected (first-vaccinated hybrid), and vaccinated only. Statistical significance was tested by Wilcoxon rank sum test and adjusted for multiple comparisons using Benjamini–Hochberg method. **b.** Associations between clinical and demographic factors and antibody levels (IgG1, IgG4) at T9, T11, and T13, using multivariable linear regression models. Beta (β) and 95% confidence intervals (CI) are shown as percentage changes. Filled circles indicate $p < 0.05$, while unfilled circles indicate non-significant p -values after adjustment for multiple testing by Benjamini-Hochberg. Error bars represent the 95% CI. ^aAdjusted by age, sex, comorbidities, smoking, time since last exposure (natural spline, $df = 3$). ^bAdjusted by age, sex, comorbidities, smoking, time since last exposure (natural spline, $df = 3$), and number of exposures. ^cAdjusted by sex. ^dAdjusted by age. ^eAdjusted by age and sex. ^fAdjusted by age, sex, smoking.



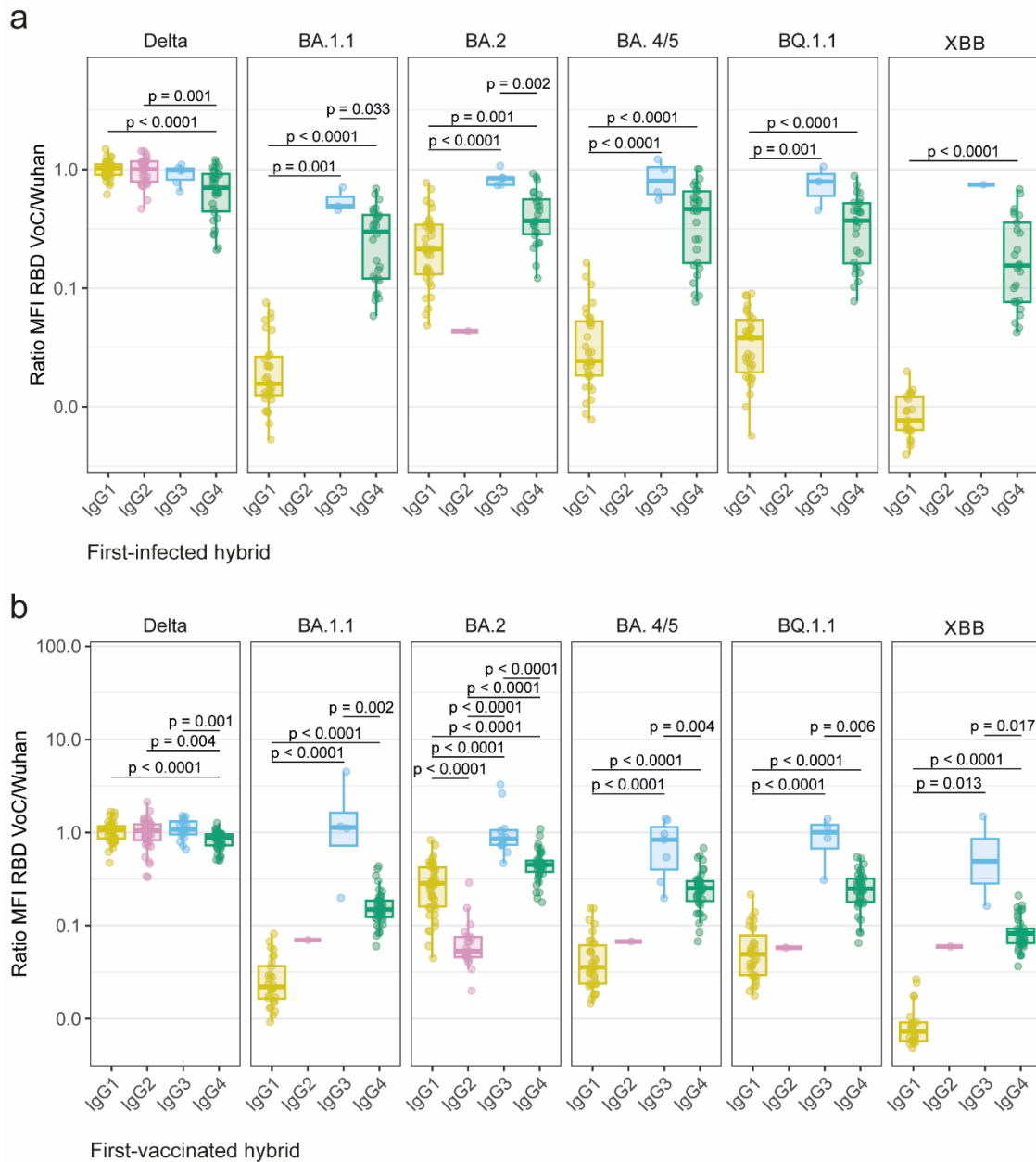
Supplementary Figure 4. Association between FcγR-binding antibodies and IgG4 levels to Spike according to IgG1 level at T9, T11, and T13. Linear regression analysis of Fcγ receptor (FcγR)-binding antibody levels versus IgG4 levels at timepoints T9, T11, and T13, stratified by IgG1 level (high vs. low/medium tertile). Each panel shows the regression line and 95% confidence interval for the two IgG1 groups. Regression coefficients (β) and p-values are displayed above each line. An asterisk (*) indicates a statistically significant interaction between IgG4 and IgG1 levels (p for interaction < 0.05). The sample size for the high IgG1 tertile group was 40 at T9, 29 at T11, and 24 at T13, while the low/medium tertile group included 53 participants at T9, 64 at T11, and 69 at T13. T: timepoint. MFI: median fluorescence intensity.



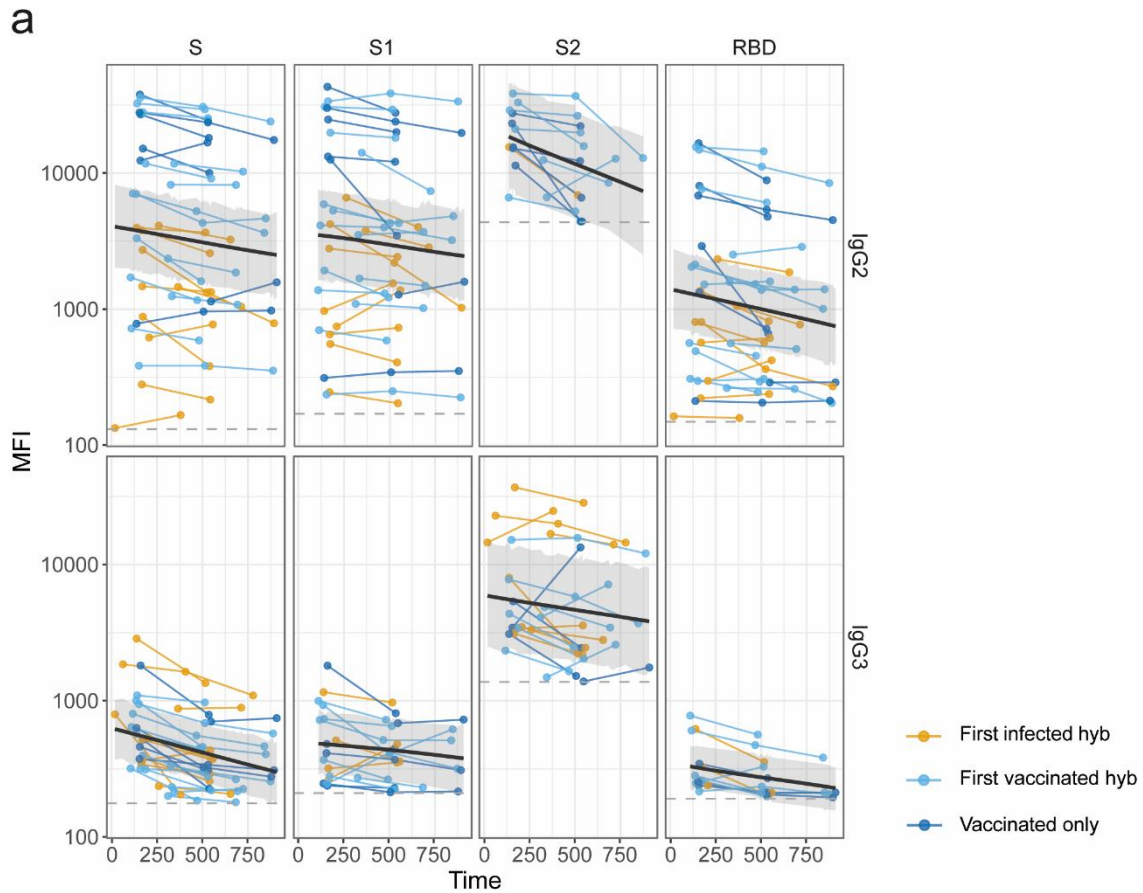
Supplementary Figure 5. Association between C1q-binding antibodies and IgG4 levels to RBD and Spike according to IgG1 level at T9, T11, and T13. Linear regression analysis of C1q-binding antibody levels versus $\log_{10}$ -transformed IgG4 levels at timepoints T9, T11, and T13, stratified by IgG1 level (high vs. low/medium tertile) to RBD and to full-length Spike. Each panel shows the regression line and 95% confidence interval for the two IgG1 groups. Regression coefficients (β) and p-values are displayed above each line. An asterisk (*) indicates a statistically significant interaction between IgG4 and IgG1 levels (p for interaction < 0.05). The sample size for the high IgG1 tertile group was 40 at T9, 29 at T11, and 24 at T13, while the low/medium tertile group included 53 participants at T9, 64 at T11, and 69 at T13. T: timepoint. MFI: median fluorescence intensity. Receptor-binding domain (RBD). Full-length spike (S).



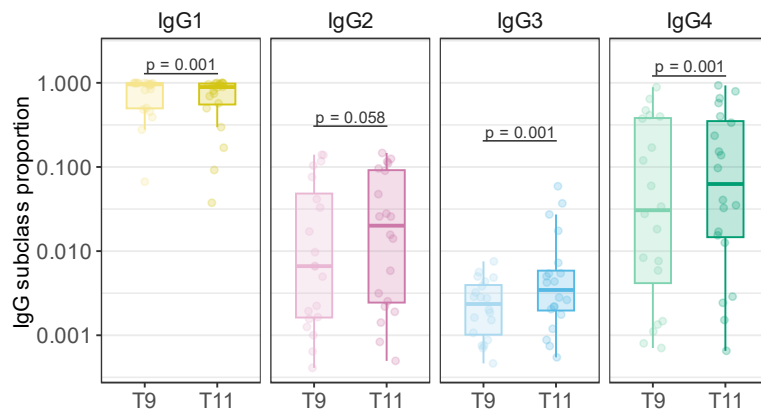
Supplementary Figure 6. IgG subclass cross-reactivity to SARS-CoV-2 variants of concern at T11 and T13. Ratio of IgG subclass binding to the receptor-binding domain (RBD) of SARS-CoV-2 variants of concern (VoCs)—Delta, BA.1.1, BA.2, BA.4/5, BQ.1.1, and XBB—relative to binding to the ancestral Wuhan RBD at T11 (**a**) and T13 (**b**). Data are shown for IgG1, IgG2, IgG3, and IgG4. Statistical significance was assessed using Wilcoxon rank sum test and adjusted for multiple comparisons using Benjamini–Hochberg method. Only samples with MFI values above the seropositivity cutoff for both the variant and Wuhan RBD were included in the analysis. Ratios were derived from non-normalized MFI values; thus, absolute values are not directly interpretable. Comparisons should be restricted to relative differences among IgG subclasses within each variant. MFI: median fluorescence intensity.



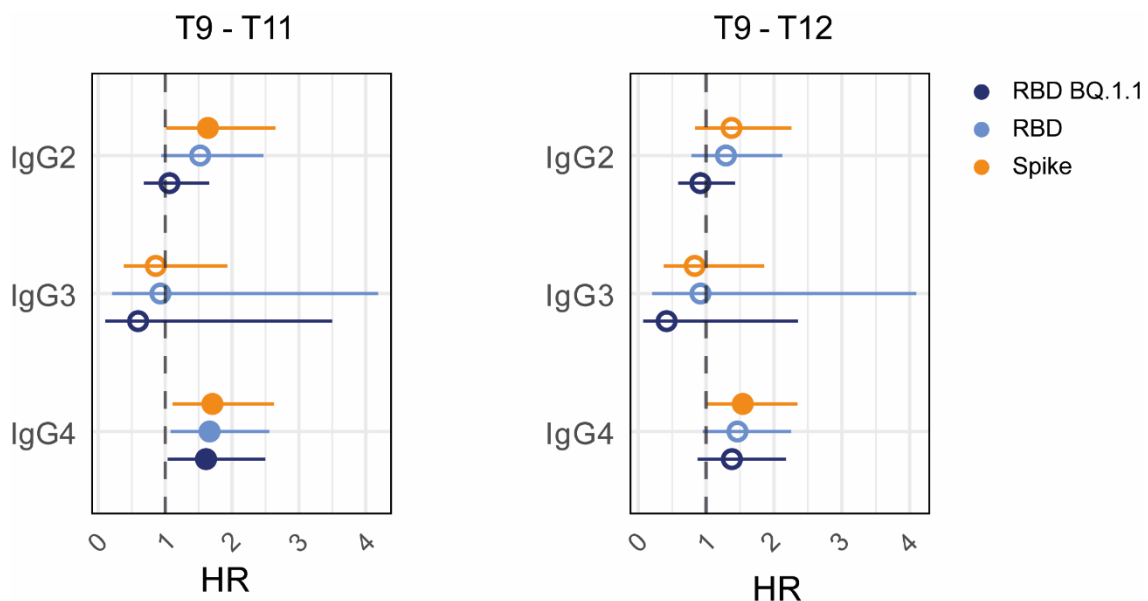
Supplementary Figure 7. IgG subclass cross-reactivity to SARS-CoV-2 variants of concern in first-infected and first-vaccinated hybrid at T9. Ratio of IgG subclass binding to the receptor-binding domain (RBD) of SARS-CoV-2 variants of concern (VoCs)—Delta, BA.1.1, BA.4/5, BQ.1.1, and XBB—relative to binding to the ancestral Wuhan RBD for first-infected (**a**) and first-vaccinated (**b**). Data are shown for IgG1, IgG2, IgG3, and IgG4. Statistical significance was assessed using Wilcoxon rank sum test and adjusted for multiple comparisons using Benjamini–Hochberg method. Only samples with MFI values above the seropositivity cutoff for both the variant and Wuhan RBD were included in the analysis. Ratios were derived from non-normalized MFI values; thus, absolute values are not directly interpretable. Comparisons should be restricted to relative differences among IgG subclasses within each variant. MFI: median fluorescence intensity.



Supplementary Figure 8. Longitudinal kinetics and estimated half-lives of IgG2 and IgG3 antibodies against SARS-CoV-2 spike and RBD variants. **a.** Longitudinal trajectories of IgG2 and IgG3 levels against SARS-CoV-2 Spike protein subunits (S, S1, S2), ancestral RBD, and RBDs from Delta, BA.1.1, BA.2, BA.4/5, BQ.1.1, and XBB variants. Lines represent exponential decay fits from a mixed-effects model with a random intercept for participant ($n = 32$), shown separately for IgG2 and IgG3. The shaded grey area indicates the 95% confidence interval around the fixed-effect prediction. Grey dashed lines denote the seropositivity cutoff for each subclass-antigen pair. **b.** Estimated antibody half-lives (in days) with 95% confidence intervals (CI) derived from the mixed-effects exponential decay model. Results are reported separately for IgG2 and IgG3 across all antigens. MFI: median fluorescence intensity. Receptor-binding domain (RBD). Full-length spike (S).



Supplementary Figure 9. Proportion of each IgG subclass to RBD at T9 and T11 in participants included in the decay analysis (n = 20). Proportions were derived from non-normalized MFI values, thus, absolute values are not directly interpretable. Comparisons should be restricted to relative differences between timepoints within each subclass. P-values were calculated using paired Wilcoxon signed-rank tests.



Supplementary Figure 10. Forest plot of Cox proportional hazard models for IgG2, IgG3, and IgG4 subclasses to RBD Wuhan, RBD BQ.1.1, and to S Wuhan adjusted by IgG1 over a 1-year (n=138, T9-T11) or 1.5-year follow-up (n=115, T9-T12). Hazard ratio (HR) represents the change in the relative hazard associated with a 10-fold increase in MFI. Models were adjusted by age, comorbidities, number of infections, sex, smoking, time since last exposure, first exposure type, and IgG1 levels. Filled circles indicate $p < 0.05$, while unfilled circles indicate non-significant p-values. RBD: Receptor-binding domain. S: Spike.