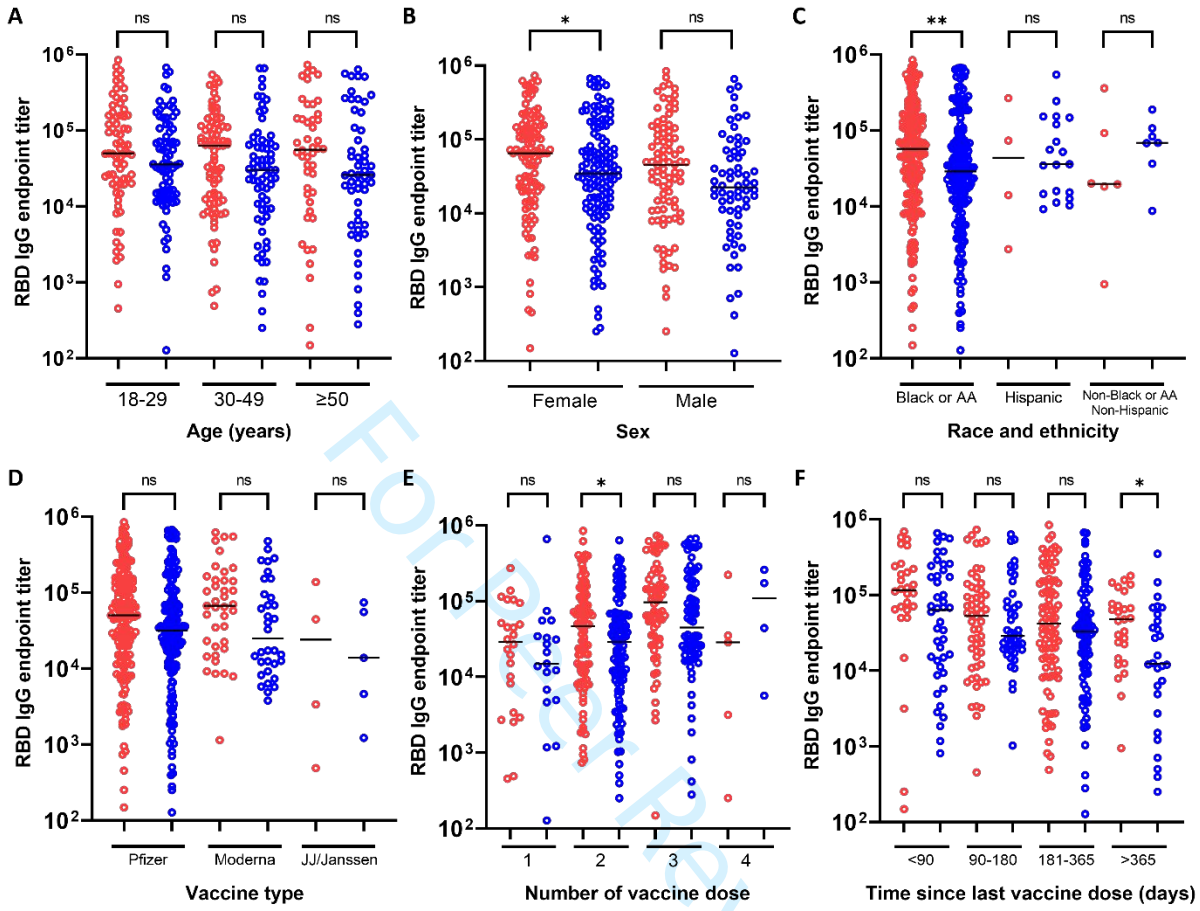
Supplementary Data

Detection of SARS-CoV-2 neutralizing antibodies by blockade of ACE-2 binding (BoAb) assay.

Neutralizing activity is measured by inhibition of interaction between SARS-CoV-2 spike conjugated bead and biotinylated ACE-2 by the presence of neutralizing antibody. The ACE-2 binding signal is amplified by streptavidin-beta-galactosidase and a fluorescent RGB-substrate which is readout as average enzymes per bead (AEB) using single molecule array (SIMOA) technology on the Quanterix HD-X platform. AEB signal and neutralizing activity are inversely correlated; 100% AEB signal is generated if 0% neutralizing activity is present, and 0% AEB signal is generated if 100% neutralizing activity is present. Half maximal AEB signal (50%) corresponds to 50% neutralizing activity, which is also the IC_{50} (50% inhibitory concentration) titer. For the two-point dilution approach, patient samples were tested at two dilutions (1:50 and 1:200), and their AEB signal was compared to the 50% maximal AEB signal generated by dilution series of monoclonal SARS-CoV-2 neutralizing antibody. The two dilutions were selected based on previous observation that IC_{50} titer for COVID-19 vaccinated patient samples measured by the BoAb assay clustered into three groups separated approximately at 1:50 and 1:200 dilution. Thus, neutralizing activity was binned into three groups as follows: “strong” if the 1:200 dilution showed greater than 50% neutralizing activity, “average” if the 1:200 dilution showed less than 50% neutralizing activity but the 1:50 dilution showed greater than 50% neutralizing activity, and “weak” if the 1:50 dilution showed less than 50% neutralizing activity.

Supplemental Figure S1



Supplemental Figure S1. Subgroup comparison of COVID-19 vaccine immune response in SCD (red) and matched non-SCD controls (blue) using SARS-CoV-2 RBD-specific IgG endpoint titer. Lines indicate median. Comparison by (A) age, (B) sex, (C) race and ethnicity, (D) COVID-19 vaccine type, (E) number of vaccine dose, and (F) time since last vaccine dose. Statistical difference measured by Mann-Whitney test. * = $P \leq 0.05$, ** = $P \leq 0.005$, ns = $P > 0.05$. AA, African American; RBD, receptor binding domain; SCD, sickle cell disease.

Supplemental Table S1. Analysis of P-values from subgroup comparison of RBD vaccine response in SCD vs controls

	P values	q value, FDR = 5%	Discovery
Age, years			
18-29	0.2157	0.3436	No
30-49	0.0563	0.1512	No
≥50	0.1641	0.2976	No
Sex			
Female	0.0478*	0.1512	No
Male	0.0682	0.1512	No
Race and Ethnicity			
Black or African American	0.004**	0.0798	No
Hispanic	0.8449	0.9364	No
Non-Black or African American, Non-Hispanic	0.4452	0.5551	No
Vaccine Type			
Pfizer-BioNTech	0.0585	0.1512	No
Moderna	0.0591	0.1512	No
Janssen (Johnson & Johnson)	0.9048	0.9500	No
Number of vaccine dose			
1	0.3892	0.5176	No
2	0.0408*	0.1512	No
3	0.0629	0.1512	No
4	0.2857	0.4071	No
Time since last vaccine dose, days			
<90	0.0953	0.1901	No
90-180	0.681	0.7992	No
181-365	0.2239	0.3436	No
>365	0.0198*	0.1512	No

* = P ≤ 0.05

** = P ≤ 0.005

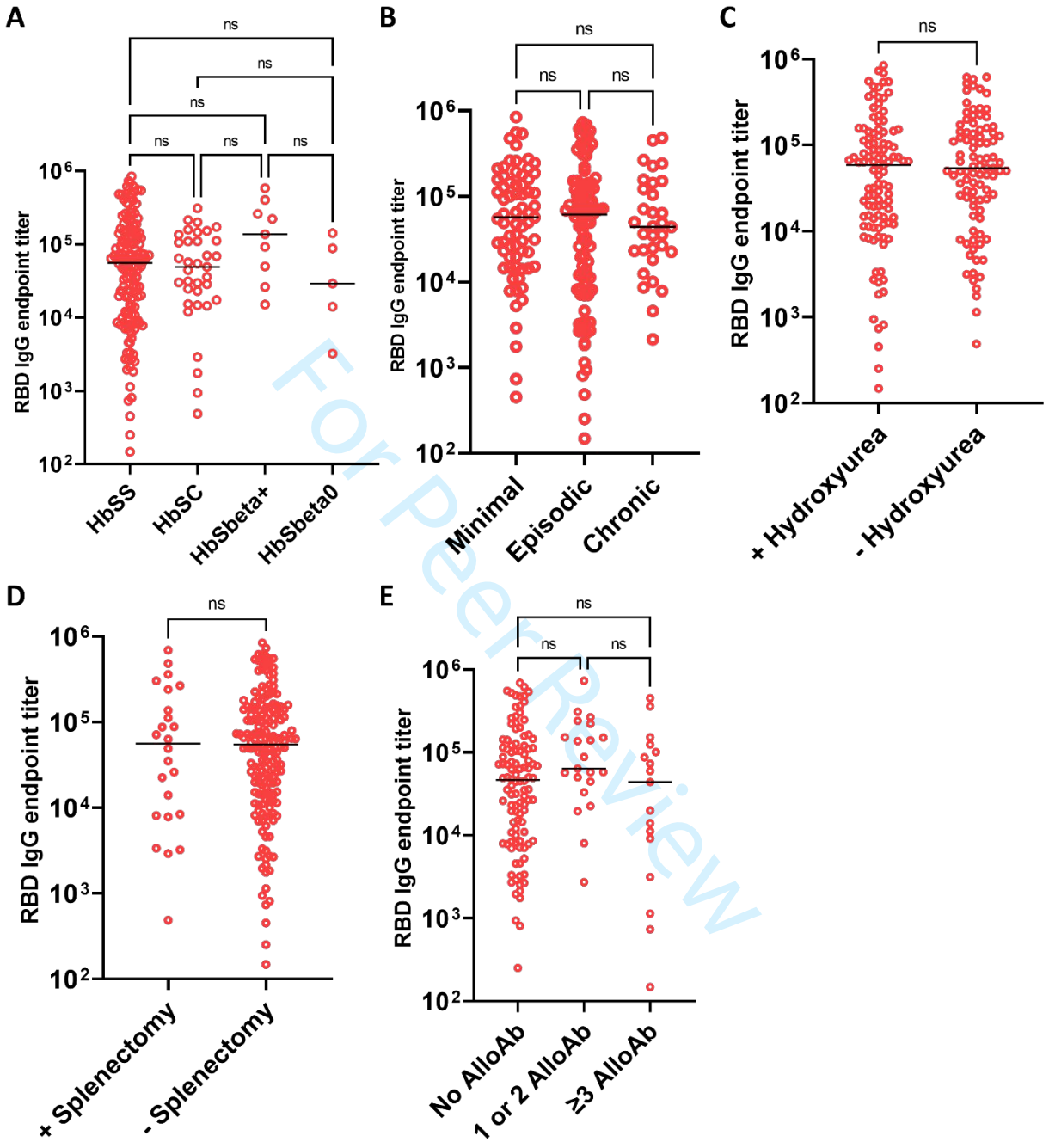
FDR, false discovery rate

Supplemental Table S2. Descriptive Statistics of SCD Study Cohort Characteristics

Hemoglobin genotype	**n = 201**
SS	75.6% (n = 152)
SC	17.4% (n = 35)
S/β^{+}-thalassemia	4.5% (n = 9)
S/β^{0}-thalassemia	2.5% (n = 5)
RBC transfusion burden[a]	
Minimal	35.3% (n = 71)
Episodic	48.8% (n = 98)
Chronic	15.9% (n = 32)
Hydroxyurea at time of vaccination	
Yes	53.7% (n = 108)
No	46.3% (n = 93)
Total Surgical Splenectomy	
Yes	11.9% (n = 24)
No	88.1% (n = 177)
Historic RBC alloantibody, n (%)	**Total Records Available (n = 146)**
No alloantibody	74.0% (n = 108)
1 alloantibody	8.2% (n = 12)
2 alloantibody	6.2% (n = 9)
3 or more alloantibody	11.6% (n = 17)

[a]See Materials and Methods for RBC transfusion burden categories

Supplemental Figure S2



Supplemental Figure S2. Subgroup comparison of COVID-19 vaccine immune response within SCD cohort using SARS-CoV-2 RBD-specific IgG endpoint titer. Lines indicate median. Comparison by (A) sickle genotype, (B) RBC transfusion burden, (C) hydroxyurea at time of first vaccine dose, (D) history of total surgical splenectomy, and (E) number of RBC alloantibodies. Statistical difference measured by Mann-Whitney test for pairwise comparisons and Kruskal-

Wallis test followed by Dunn's test for multiple comparisons. ns = P > 0.05. RBD, receptor binding domain.