

1 **Robust spike antibody responses and increased reactivity in seropositive individuals after a**  
2 **single dose of SARS-CoV-2 mRNA vaccine**

3  
4 Florian Krammer<sup>1</sup>§, Komal Srivastava<sup>1</sup>, the PARIS team<sup>1\*</sup>, and Viviana Simon<sup>1,2,3</sup>§

5  
6 <sup>1</sup>Department of Microbiology, Icahn School of Medicine at Mount Sinai New York, NY, USA

7 <sup>2</sup>Department of Medicine, Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai New  
8 York, NY, USA

9 <sup>3</sup>Global Health and Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai New York, NY,  
10 USA

11  
12  
13 \*PARIS team (in alphabetical order): H. Alshammary, A. Amoako, M. Awawda, K. Beach, C. M.  
14 Bermúdez-González, D. Bialak, Dr. JM Carreño, R. Chernet, L. Eaker, E. Ferreri, D. Floda, C. Gleason, Dr.  
15 J. Hamburger, K. Jiang, Dr. G. Kleiner, Dr. D. Jurczynszak, J. Matthews, W. Mendez, Dr. LCF Mulder, Dr. I.  
16 Nabeel, A. Raskin, K. Russo, A. Salimbangon, Dr. M. Saksena, A. Shin, Dr. G. Singh, L. Sominsky, Dr. D.  
17 Stadlbauer and Dr. A. Wajnberg.

18  
19  
20 § Co-Corresponding Authors:

21 Florian Krammer, [florian.krammer@mssm.edu](mailto:florian.krammer@mssm.edu)

22 Viviana Simon, [viviana.simon@mssm.edu](mailto:viviana.simon@mssm.edu)

23

24

25

26

27

28 **Abstract**

29 An important question is arising as COVID-19 vaccines are getting rolled out: Should individuals  
30 who already had a SARS-CoV-2 infection receive one or two shots of the currently authorized mRNA  
31 vaccines. In this short report, we show that the antibody response to the first vaccine dose in individuals  
32 with pre-existing immunity is equal to or even exceeds the titers found in naïve individuals after the second  
33 dose. We also show that the reactogenicity is significantly higher in individuals who have been infected  
34 with SARS-CoV-2 in the past. Changing the policy to give these individuals only one dose of vaccine  
35 would not negatively impact on their antibody titers, spare them from unnecessary pain and free up many  
36 urgently needed vaccine doses.

37

38 **Manuscript**

39 Two SARS-CoV-2 spike mRNA vaccines received emergency use authorization by the FDA in  
40 December 2020 (BNT162b2/Pfizer; mRNA-1273/Moderna).<sup>1</sup> Both Phase 3 trials reported high efficacy in  
41 preventing symptomatic SARS-CoV-2 infections after two doses of the vaccine administered three to four  
42 weeks apart (BNT162b2: 21 days; mRNA-1273: 28 days) in participants without previous COVID-19.<sup>2,3</sup> For  
43 individuals with pre-existing immunity to SARS-CoV-2 the first vaccine dose likely immunologically  
44 resembles the booster dose in naïve individuals. Anecdotally, individuals with pre-existing immunity also  
45 experience more severe reactogenicity after the first doses compared to naïve individuals. This begs the  
46 question if individuals with pre-existing immunity should even receive a second dose of vaccine.

47

48 Here we describe the antibody responses in 109 individuals with and without documented pre-  
49 existing SARS-CoV-2 immunity (seronegative: 68, seropositive: 41) who received their first vaccine dose  
50 in 2020. Repeated sampling after the first dose indicates that the majority of seronegative individuals  
51 mount variable and relatively low SARS-CoV-2 IgG responses within 9-12 days after vaccination (median  
52 AUC pre-vaccination: 1 [N=68]; 9-12 days: 439 [N=13]; 13-16 days: 1037 [N=15], 17-20 days: 1,037  
53 [N=15], 21-24 days: 1,075 [N=11], and post 2<sup>nd</sup> dose 1,399 [N= 21]; Fig. 1A). In contrast, individuals with  
54 pre-existing SARS-CoV-2 immune responses (as evidenced by SARS-CoV-2 antibodies) rapidly develop  
55 uniform, high antibody titers within days of vaccination (median AUC pre vaccination: 91 [N=41]; 5-8 days:  
56 14,208 [N=15], 9-12 days: 20,783 [N=8]; 13-16 days: 25,927 [N=20], 17-20 days: 12,661 [N=5], 21-24  
57 days: 16,263 [N=4] and post 2<sup>nd</sup> dose: 22,509 [N=7], Fig. 1A). The antibody titers of vaccinees with pre-  
58 existing immunity are not only 10-20 times higher than those of naïve vaccines at the same time points ( $p$   
59  $<0.0001$ , two tailed Mann Whitney test), but also exceed the median antibody titers measured in naïve  
60 individuals after the second vaccine dose by more than 10-fold. Ongoing follow-up studies will show  
61 whether these early differences in immune responses are maintained over time.

62 In addition, we compared frequency of local, injection side-related as well as systemic reactions  
63 after the first dose of vaccination in 231 individuals (148 seronegative and 83 seropositive; Fig. 1B).  
64 Overall both vaccines are well tolerated without any side effects requiring additional medical attention.  
65 159/231 of the participants completing the survey after the first dose experienced any kind of side effect  
66 (66% seronegative and 73% seropositive). Most common were localized injection site symptoms (e.g.,  
67 pain, swelling and erythema), which occurred with equal frequency independent of the serostatus at the  
68 time of vaccination and resolved spontaneously within days of vaccination. Vaccine recipients with pre-  
69 existing immunity experience systemic side effects with a significantly higher frequency than antibody  
70 naïve vaccines (e.g., fatigue, headache, chills, fever, muscle or joint pains, in order of decreasing  
71 frequency,  $P < 0.001$  for all listed symptoms, Fisher's exact test, two-sided). Most of the participants for  
72 whom antibody results are presented above also completed the vaccine side-effect survey.

73

74 These findings suggest that a single dose of mRNA vaccine elicits very rapid immune responses in  
75 seropositive individuals with post-vaccine antibody titers that are comparable to or exceed titers found in  
76 naïve individuals who received two vaccinations. We also noted that vaccine reactogenicity after the first  
77 dose is substantially more pronounced in individuals with pre-existing immunity akin to side-effects  
78 reported for the second dose in the phase III vaccine trials<sup>2,3</sup>. These observations are in line with the first  
79 vaccine dose serving as boost in naturally infected individuals providing a rationale for updating vaccine  
80 recommendations to considering a single vaccine dose to be sufficient to reach immunity. Using  
81 quantitative serological assays that measure antibodies to the spike protein could be used to screen  
82 individuals prior to vaccination if the infection history is unknown.<sup>4,5</sup> Such policies would allow not only  
83 expanding limited vaccine supply but also limit the reactogenicity experienced by COVID-19 survivors.

84

#### 85 **Acknowledgment**

86 We thank the study participants for their generosity and continued support of COVID19 research.

87

#### 88 **Ethics statement**

89 The study protocols for the collection of clinical specimens from individuals with and without SARS-CoV-2  
90 infection by the Personalized Virology Initiative were reviewed and approved by the Mount Sinai Hospital  
91 Institutional Review Board (IRB-16-00791; IRB-20-03374). All participants provided informed consent prior  
92 to collection of specimen and clinical information. All specimens were coded prior to processing.

93

#### 94 **Conflict of interest statement**

95 The Icahn School of Medicine at Mount Sinai has filed patent applications relating to SARS-CoV-2  
96 serological assays and NDV-based SARS-CoV-2 vaccines which list Florian Krammer as co-inventor.

97 Daniel Stadlbauer and Viviana Simon are also listed on the serological assay patent application as co-  
98 inventors. Mount Sinai has spun out a company, Kantaro, to market serological tests for SARS-CoV-2.  
99 Florian Krammer has consulted for Merck and Pfizer (before 2020), and is currently consulting for Seqirus  
100 and Avimex. The Krammer laboratory is also collaborating with Pfizer on animal models of SARS-CoV-2.

101

## 102 **Funding statement**

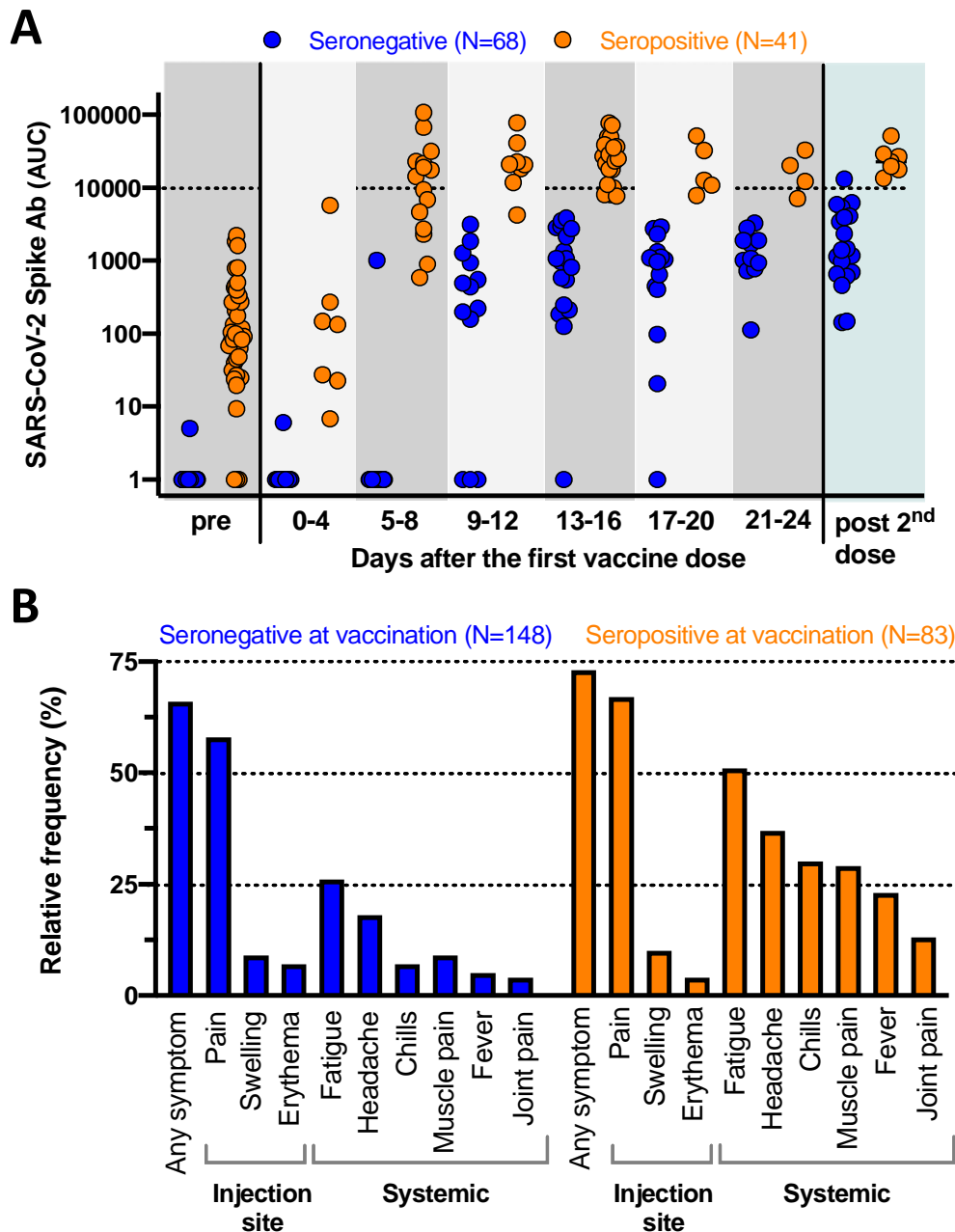
103 This work was partially funded by the NIAID Collaborative Influenza Vaccine Innovation Centers (CIVIC)  
104 contract 75N93019C00051, NIAID Center of Excellence for Influenza Research and Surveillance (CEIRS,  
105 contract # HHSN272201400008C), by the generous support of the JPB Foundation and the Open  
106 Philanthropy Project (research grant 2020-215611 (5384); and by anonymous donors.

107

## 108 **References**

- 109 1. Krammer F. SARS-CoV-2 vaccines in development. *Nature* 2020;586(7830):516-527. DOI:  
110 10.1038/s41586-020-2798-3.
- 111 2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2  
112 Vaccine. *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2035389.
- 113 3. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19  
114 Vaccine. *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2034577.
- 115 4. Krammer F, Simon V. Serology assays to manage COVID-19. *Science* 2020;368(6495):1060-1061.  
116 DOI: 10.1126/science.abc1227.
- 117 5. Amanat F, Stadlbauer D, Strohmeier S, et al. A serological assay to detect SARS-CoV-2  
118 seroconversion in humans. *Nat Med* 2020. DOI: 10.1038/s41591-020-0913-5.

119



120

121

122

123

124

125

126

127

128

**Fig. 1:** Immunogenicity and reactogenicity of SARS-CoV-2 RNA vaccines. A: Quantitative SARS-CoV-2 spike antibody titers (ELISA, expressed as area under the curve, AUC) for 109 individuals. “Pre” represents the antibody response prior to vaccination while “post 2<sup>nd</sup> dose” indicates the immune responses mounted after the second vaccine dose. Note that some of the individuals with pre-existing immunity had antibody titers below detection (AUC of 1) at the time point prior to vaccination. B: Vaccine associated side effects experienced after the first dose (N= 231 individuals). The local side effects occur with comparable frequency while the systemic symptoms are significantly more common in the individuals with pre-existing immunity.