

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

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4 Florian Krammer¹§, Komal Srivastava¹, the PARIS team^{1*}, and Viviana Simon^{1,2,3}§

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6 ¹Department of Microbiology, Icahn School of Medicine at Mount Sinai New York, NY, USA

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

9 ³Global 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.

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20 § Co-Corresponding Authors:

21 Florian Krammer, florian.krammer@mssm.edu

22 Viviana Simon, viviana.simon@mssm.edu

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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.

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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).¹ 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.^{2,3} 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.

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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 2nd 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 2nd 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.

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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^{2,3}. 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.^{4,5} Such policies would allow not only
83 expanding limited vaccine supply but also limit the reactogenicity experienced by COVID-19 survivors.

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85 **Acknowledgment**

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

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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.

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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.

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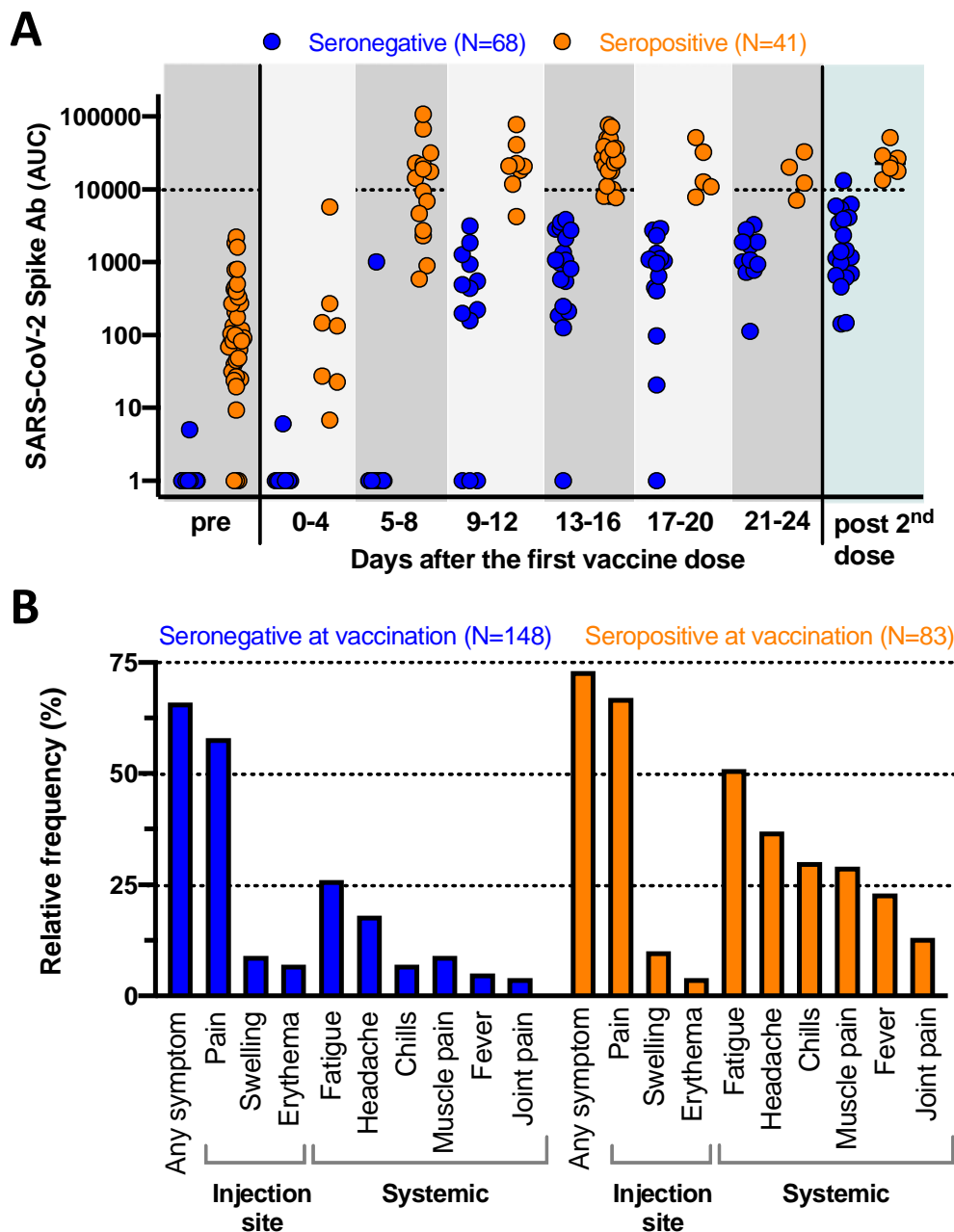
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Fig. 1: Immunogenicity and reactogenicity of SARS-CoV-2 RNA vaccines. A: Quantitative SARS-CoV-2 spike antibody titers (ELISA, expressed as area under the curve, AUC) for 109 individuals. “Pre” represents the antibody response prior to vaccination while “post 2nd 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.