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BRIEF REPORT

Escape of SARS-CoV-2 Variant Omicron to Mucosal Immunity in Vaccinated Subjects

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Since it was first reported on November 24, 2021, and classified as a variant of concern 2 days later [1], the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant Omicron (B.1.1.529) has spread throughout the world [1, 2], rapidly replacing other circulating variants including Delta. The growth advantage of Omicron over Delta was observed not only in countries with low vaccination coverage such as South Africa, but also in those in which >90% of individuals were vaccinated such as Norway [3]. In keeping with the higher transmissibility of Omicron, 2 recent studies in English and Norwegian households have shown that the secondary attack rate was higher when the variant of the index case was Omicron compared with Delta [4, 5].

Compared to the ancestral reference strain, Omicron harbors 60 mutations among which 32 mutations in its spike protein in the N-terminal domain (NTD), receptor-binding domain (RBD) in vicinity of the furin cleavage site. Some of these mutations result in a higher affinity of spike for its human angiotensin-converting enzyme 2 (ACE2) receptor, a phenomenon that explains at least in part why Omicron multiplies in the upper airways 70 times faster than Delta [6]. Mutations in spike also account for the ability of Omicron to escape systemic antibody responses, as demonstrated by the reduced ability of plasma antibodies from both coronavirus disease 2019 (COVID-19)–convalescent and –vaccinated subjects to bind to the Omicron spike protein and to inhibit the binding of spike to ACE [7, 8].

While protection from severe forms of COVID-19 in vaccinated adults is mediated at least in part by SARS-CoV-2-specific antibodies, lessons drawn from other mucosal pathogens suggest that mucosal antibodies and especially secretory immunoglobulin A (sIgA) are those that efficiently block transmission of respiratory viruses such as SARS-CoV-2 [9]. Therefore, we hypothesize that Omicron disseminates more rapidly than Delta in vaccinated subjects because it escapes vaccine-induced mucosal immune responses.

To test this hypothesis, we prospectively collected nasal epithelial lining fluid (NELF) in a cohort of 84 otherwise healthy health care workers (Centre Hospitalier Universitaire de Nice) who had never exhibited polymerase chain reaction–documented COVID-19 and had received 3 doses of the Pfizer-BioNTech COVID-19 mRNA vaccine 10 to 131 days before NELF collection. In all subjects, NELF was collected before Omicron detection in the geographical area of inclusion, that is, between December 14 and 31, 2021. All subjects signed an informed consent to participate in this work. This study was approved by the CPP Sud Méditerranée V ethics committee (ClinicalTrial.gov identifier: NCT04418206).

NELF was gently collected with hydroxylated polyvinyl acetate (PVA) sponges (Merocel Standard Dressing, ref 400400, Medtronic, Minneapolis, MN, USA), inserted between the nasal septum and the inferior turbinate, left in place for 15 minutes until the sponges swelled, gently retrieved and placed in a 50-mL Falcon tube (Dustcher, Bernolsheim, France) containing 2 mL of saline solution. The fluid contained in the sponge (saline + nasal secretions) was then extracted by simple pressure, aliquoted, and frozen at −70°C until further analysis. The serum albumin concentration in NELF was >100-fold lower in NELF compared with serum, ruling out the possibility that collecting nasal fluids using swabs could have irritated the epithelia, eventually increasing exudation of tissue fluids. IgA and immunoglobulin G (IgG) to spike of the SARS-CoV-2 ancestral strain and of its Delta and Omicron variants were measured using the V-PLEX SARS-CoV-2 Panel (Meso Scale Discovery, Inc., Rockville MD, USA), as previously described [10]. Total IgA and IgG levels were measured using the V-PLEX Isotyping Panel 1 Human/NHP Kit. Nasal fluids were diluted 10-fold before being assessed for spike-specific and total IgA and IgG. Data were acquired on the V-PLEX Sector Imager 2400 plate reader and analyzed using Discovery Workbench 3.0 software. NELF antibodies were assessed for their ability to inhibit the binding of a soluble ACE2 to spike of the ancestral SARS-CoV-2 strain and its Delta and Omicron variants using the multiplex V-PLEX SARS-CoV-2 Panel 13 ACE2 Kit, as previously described [10]. NELF was diluted 10-fold before being

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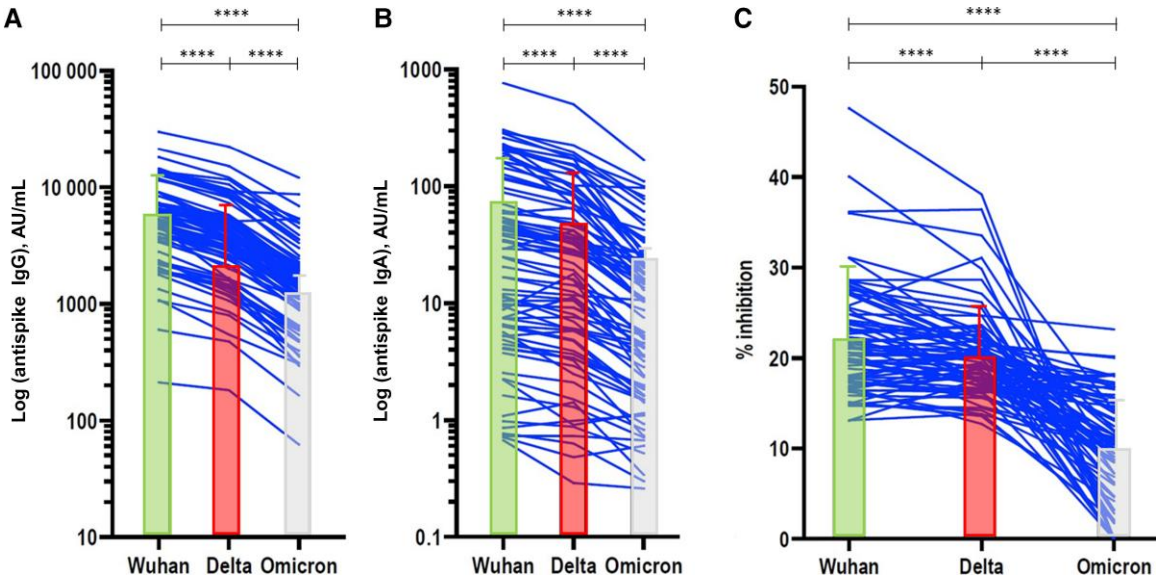

Figure 1. Levels of NELF IgG and IgA to spike and ability of NELF antibodies to inhibit the binding of spike to ACE-2. NELF was analyzed for IgG (A) and IgA (B) to spike of the ancestral Wuhan strain and its B.1.617.2 (Delta) and B.1.1.529 (Omicron) variants. Data are expressed in arbitrary units per mL (AU/mL) in individual subjects after normalization total IgG and IgA, respectively. Medians with interquartile ranges are shown. C, NELF was analyzed for inhibiting the binding of spike of the Wuhan strain and of its variants to ACE-2. Percentages of inhibition in individual subjects are shown. Samples from the same subject are connected by lines. The Wilcoxon matched paired signed-rank *t* test was used to compare the binding inhibition of IgG and IgA to spike of the indicated strain to ACE-2. ****$P < .0001$. Abbreviations: ACE-2, angiotensin-converting enzyme 2; IgA, immunoglobulin A; IgG, immunoglobulin G; NELF, nasal epithelial lining fluid.

assessed for binding inhibition. Data were acquired on the V-PLEX Sector Imager 2400 plate reader and analyzed using Discovery Workbench 3.0 (MSD). Diluent alone was used as a blank. The percent inhibition was calculated according to the manufacturer's instructions. This assay has been shown to correlate with assays for viral neutralization.

We found that mucosal IgG and IgA bound less efficiently to the Omicron spike protein compared with those of the Delta or Wuhan ancestral strains (Figure 1*A*–*B*). NELF antibodies from vaccinated individuals were also less efficient at inhibiting the binding of the Omicron spike protein to ACE-2 compared with those of the Delta or ancestral strains (Figure 1*C*).

Our results show that Omicron escapes vaccine-induced mucosal antibody response more efficiently than Delta. This may explain the increased risk of onward transmission of Omicron, consistent with its successful global displacement of Delta in countries with high vaccination coverage.

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Potential conflicts of interest. The authors declare no competing interests. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References

1. Callaway E. Heavily mutated Omicron variant puts scientists on alert. Nature **2021**; 600:21.
2. Barnard RC, Davies NG, Pearson CAB, Jit M, Edmunds WJ. Projected epidemiological consequences of the Omicron SARS-CoV-2 variant in England, December 2021 to April 2022. MedRxiv 2021.12.15.21267858 [Preprint]. December 16, **2021.** Available at: https://doi.org/10.1101/2021.12.15.21267858. Accessed 3 August 2022.
3. Venetin L, Bøåsn H, Bråthen Kristoffersen A, et al. Reduced risk of hospitalisation among reported COVID-19 cases infected with the SARS-CoV-2 Omicron BA.1 variant compared with the Delta variant, Norway, December 2021 to January 2022. Euro Surveill **2022**; 27:2200077.
4. Allen H, Tessier E, Turner C, et al. Comparative transmission of SARS-CoV-2 Omicron (B.1.1.529) and Delta (B.1.617.2) variants and the impact of vaccination: national cohort study, England. MedRxiv 2022.02.15.22271001 [Preprint]. February 17, **2022**. Available at: https://doi.org/10.1101/2022.02.15.22271001. Accessed 3 August 2022.
5. Jorgensen SB, Nygard K, Kacelnik O, Telle K. Secondary attack rates for Omicron and Delta variants of SARS-CoV-2 in Norwegian households. JAMA **2022**; 327:1610–1.
6. Kumar S, Thambiraja TS, Karuppanan K, Subramaniam G. Omicron and Delta variant of SARS-CoV-2: a comparative computational study of spike protein. J Med Virol **2022**; 94:1641–9.
7. Wolter N, Tempia S, von Gottberg A, et al. Seroprevalence of SARS-CoV-2 after the second wave in South Africa in HIV-infected and uninfected persons: a cross-sectional household survey. Clin Infect Dis **2022**:ciac198. doi:10.1093/cid/ciac198.
8. Planas D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. Nature **2022**; 602:671–5.
9. Russell MW, Moldoveanu Z, Ogra PL, Mestecky J. Mucosal immunity in COVID-19: a neglected but critical aspect of SARS-CoV-2 infection. Front Immunol **2020**; 11:611337.
10. Martinuzzi E, Benzaquen J, Guerin O, et al. A single dose of the Pfizer-BioNTech COVID-19 mRNA vaccine induces airway immunity in SARS-CoV-2 naive and COVID-19 convalescent subjects. Clin Infect Dis **2022**:ciac378. doi:10.1093/cid/ciac378.