# Airway immune responses to COVID-19 vaccination in COPD patients and healthy subjects



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*To the Editor*:

COPD patients have a higher risk of developing severe illness and mortality following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. Vaccination protects against coronavirus disease 2019 (COVID-19) through the development of systemic and airway immune responses. Patients with COPD display altered humoral immunity, with reduced antibody responses compared to healthy controls [2, 3]. We studied SARS-CoV-2 vaccine-specific immune responses in COPD patients *versus* healthy controls, using systemic, nasal and sputum samples.

Samples were analysed from three subject groups: 27 vaccinated subjects (11 COPD and 16 healthy controls), 43 pre-vaccine subjects (24 COPD and 19 controls) and nine healthy controls with a history of COVID-19 infection. Vaccinated subjects donated samples >2 weeks after completing two doses of either Vaxzevria (Oxford/AstraZeneca; five COPD patients and nine healthy controls) or Comirnaty (Pfizer; six COPD patients and seven controls); all subjects provided blood and nasal samples, while 10 COPD patients and nine healthy controls also provided sputum. All subjects were aged >40 years, COPD patients were older than controls (mean 66.1 *versus* 58.8 years, respectively; p=0.04), with a similar gender mix (55% *versus* 50% males, respectively). COPD patients were either Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 2 (n=9) or grade 3 (n=2), with 10 being ex-smokers. All subjects reported no history of COVID-19, supported by a negative result for plasma antibodies against SARS-CoV-2 nucleocapsid protein [4]. Pre-vaccination samples were obtained from two populations: 1) sputum from COPD patients (n=22) and healthy controls (n=10), and plasma from COPD patients (n=13) and healthy controls (n=12), with some subjects donating both samples (these were collected and frozen before the pandemic); and 2) blood and nasal samples collected during the pandemic from six unvaccinated subjects (COPD: n=2; healthy controls: n=4) for cellular immunity and immunoglobulin analysis. Healthy controls (n=9) with a PCR-proven history of COVID-19 prior to vaccination donated blood (n=6) and nasal samples (n=9); at sampling; eight had received a single dose of vaccine (four Vaxzevria and four Comirnaty). Subjects reported no acute respiratory illness within 2 weeks of sample collection. COPD patients had smoking history >10 pack-years and forced expiratory volume in 1 s ($FEV_1$) <80% predicted, with $FEV_1$ to forced vital capacity ratio <0.7. Healthy controls had normal lung function, no respiratory diseases, smoking history <1 pack-year and were not current smokers.

Heparinised blood was collected for cellular immunity assessment and plasma for immunoglobulin assessments. Nasal absorption, for nasal epithelial lining fluid (NELF), was collected and processed as previously described to measure immunoglobulins post-COVID-19 [5]. Sputum supernatants were processed without dithiothreitol, as described previously [6]. Anti-SARS-CoV-2 spike IgA and IgG levels in plasma, NELF and sputum supernatants were measured by quantitative ELISA (AESKU, Wendelsheim, Germany). For plasma, the standards supplied, prepared in a plasma-like matrix, were used, while recombinant anti-spike IgA and IgG antibodies (Native Antigen Company, Oxford, UK) prepared in PBS containing 1% bovine serum albumin and 0.05% Tween-20 (Sigma-Aldridge, Poole, UK) were used for NELF and sputum supernatant. The presence of anti-SARS-CoV-2 nucleocapsid protein antibodies in plasma was examined by Roche Elecsys qualitative assay, reported as positive or negative (The Doctors Laboratory, London, UK). Spike protein-induced interferon-γ from blood T-cells (cellular immunity)

Shareable abstract (@ERSpublications)
**Airway and blood immune responses to COVID-19 vaccination were examined in COPD patients and healthy subjects. Anti-spike IgG, but not IgA, levels were higher in airways post-vaccination, with similar responses in COPD patients and healthy subjects.** https://bit.ly/3zt6D6v

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was assessed using Euroimmun's Quan-T-Cell assay (Lübeck, Germany). Results were analysed using Mann–Whitney and Spearman's rank tests, using GraphPad Prism version 9.2.0.

Vaccinated COPD patients and healthy controls had higher anti-spike IgA and IgG levels in plasma and anti-spike IgG levels in sputum compared to unvaccinated COPD patients and controls (figure 1a and b). Sputum anti-spike IgA levels were not higher following vaccination.

For cellular immunity and nasal analysis, we combined COPD patient and healthy control results due to limited pre-vaccine samples (n=6); vaccinated subjects had higher blood cellular immunity spike-protein responses and nasal anti-spike IgG levels, but not nasal anti-spike IgA levels, compared to unvaccinated subjects (figure 1b and c). Similar vaccine-induced immune responses were observed in COPD patients compared to healthy controls. For combined COPD and healthy control results, plasma (27 530 *versus* 2391 U·mL$^{-1}$; p=0.005) and nasal (11.0 *versus* 2.6 ng·mL$^{-1}$; p=0.03) IgG levels were higher following vaccination with Comirnaty compared to Vaxzevria, with similar trends (non-significant) for plasma IgA (231.5 *versus* 73.4 U·mL$^{-1}$; p=0.056) and sputum IgG (17.9 *versus* 3.6 ng·mL$^{-1}$; p=0.052). The time between vaccination and sample collection was similar for Comirnaty and Vaxzevria (means of 97 and 100 days, respectively; p=0.9). Immune responses were similar between COPD and healthy controls for each vaccine, when analysed independently.

Post-vaccine nasal and sputum anti-spike IgG levels correlated with plasma IgG levels (figure 1d). Induced-IgG and cellular immunity levels negatively correlated with numbers of days between vaccination and sample collection (range 17–168 days) (Rho, plasma IgG: −0.58; nasal IgG: −0.50; sputum IgG: −0.60; and cellular immunity: −0.52; all p⩽0.01). A similar (non-significant) trend was seen for plasma IgA (Rho, −0.34; p=0.08). There were no significant correlations between any immune response and age for COPD patients or healthy controls.

In healthy controls with a history of COVID-19, and a single vaccination dose, anti-spike IgA levels were higher in plasma (1719 *versus* 138.6 U·mL$^{-1}$; p=0.006) and nasal samples (25.5 *versus* 7.2 ng·mL$^{-1}$;

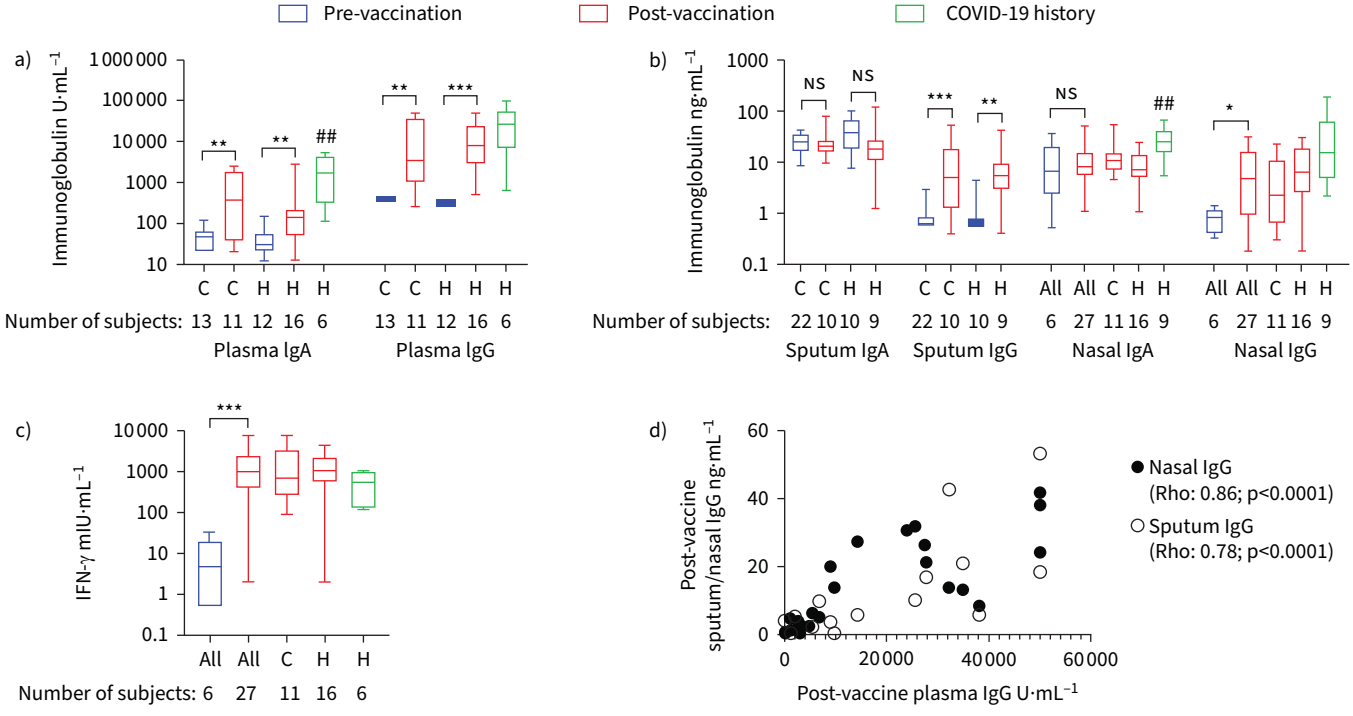


**FIGURE 1** Immune responses in COPD patients and healthy controls following SARS-CoV-2 vaccination or COVID-19 infection. Anti-spike IgA and IgG levels were measured in a) plasma and b) sputum and nasal samples by ELISA. c) Cellular immunity in blood was assessed by measuring spike protein-induced interferon-γ (IFN-γ) by ELISA. Pre-vaccination results are coloured in blue, post-vaccination in red and subjects with a history of COVID-19 in green. Pre- and post-vaccination levels were compared by Mann–Whitney test. *: p<0.05; **: p<0.01; ***: p<0.001; NS: non-significant. Comparisons between post-vaccination and post-COVID-19 infection levels were by Mann–Whitney test: ##: p<0.01. d) Correlations between post-vaccine plasma anti-spike IgG levels and post-vaccine sputum and nasal IgG levels were assessed by Spearman's rank test, with Rho and p-values reported. C: COPD samples; H: healthy control samples; All: combined COPD and healthy control samples.

p=0.003) compared to healthy controls post-vaccination, while plasma and nasal anti-spike IgG levels and cellular immunity responses were similar.

We provide novel results concerning pulmonary immune responses post-COVID-19 vaccination, including responses in COPD patients. Vaccination caused pulmonary IgG responses that were associated with systemic IgG responses. COPD humoral and cellular immune responses were similar to those from healthy controls, providing reassurance that current vaccines cause the desired immune responses in COPD, despite the presence of immune dysregulation [7].

We report strong correlations between systemic and both nasal and sputum IgG levels following vaccination. This suggests that airway IgG is derived from the plasma following transduction, as also reported for systemic influenza vaccine-induced nasal IgG [8]. While systemic anti-spike IgA levels were higher in post-vaccination samples, levels in the lung and nose were not, suggesting the absence of transduction. Comirnaty induces nasal anti-spike IgA [9] within 15 days of second vaccination, with levels depleted within 3 months [9]. Our samples were collected over a longer period, perhaps explaining the lack of nasal IgA response observed. Early nasal IgA responses are also vaccine-dependent, with CoronaVac not inducing a response [9]. Vaccine-induced mucosal IgG persists for longer than IgA [10], which reflects our nasal and sputum IgG results.

Comirnaty is known to induce higher systemic anti-spike immunoglobulins than Vaxzevria [11], which we also observed for plasma and airway samples. Similar proportions of COPD and healthy controls received the two vaccines.

Airway anti-spike IgA levels post-SARS-CoV-2 infection are locally produced, with anti-SARS-CoV-2 IgA detected in bronchial aspirates from COVID-19 patients [12]. We observed higher levels of NELF anti-spike IgA in healthy controls with a history of SARS-CoV-2 infection plus vaccination compared to vaccination only. Unlike systemic influenza vaccinations, nasally administered vaccines induce a sustained mucosal IgA response [13]. Nasally administered SARS-CoV-2 vaccines in development might induce similar IgA responses [14]. As secretory IgA levels are reduced in the airways of severe COPD patients, IgA responses to nasal vaccines should be assessed in these COPD patients. Smoking may impair airway IgA production [15], but this would not affect our vaccination results as 91% of the COPD patients were ex-smokers.

Systemic immune responses to COVID-19 vaccinations decrease with age [9]. We observed no relationship between age and immune responses, although we lacked subjects <40 years old to fully assess this.

Our results demonstrate that COPD patients develop immune responses to COVID-19 vaccines that are similar to those in healthy controls. Future vaccines which induce sustained anti-SARS-COV-2 IgA responses in the upper airways may offer additional protection for both COPD patients and healthy subjects.

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Conflict of interest: T. Southworth and N. Jackson declare no competing interests for this work. D. Singh reports personal consulting fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Epiendo, Genentech, GlaxoSmithKline, Glenmark, Gossamerbio, Kinaset, Menarini, Novarti, Pulmatrix, Sanofi, Synairgen, Teva, Theravance and Verona.

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