

Antibody responses and risk factors associated with impaired immunological outcomes following two doses of BNT162b2 COVID-19 vaccination in patients with chronic pulmonary diseases

Zitta Barrella Harboe ^{1,2} Sebastian Rask Hamm ³ Laura Pérez-Alós ⁴ Pradeesh Sivapalan ⁵ Helene Priemé,⁵ Torgny Wilcke ⁵ Peter Kjeldgaard,⁵ Saher Shaker,⁵ Alexander Svorre Jordan ⁵ Dina Leth Møller ³ Line Dam Heftdal ^{3,6} Johannes Roth Madsen,⁴ Rafael Bayarri-Olmos ⁴ Cecilie Bo Hansen ⁴ Mia Marie Pries-Heje ⁷ Rasmus Bo Hasselbalch ⁸ Kamille Fogh ⁸ Jose Juan Almagro Armenteros ⁹ Linda Hilsted ¹⁰ Erik Sørensen ¹¹ Birgitte Lindegaard ^{1,2} Andrea Browatzki,¹ Tor Biering-Sørensen ⁸ Ruth Frikke-Schmidt ^{2,10} Sisse Rye Ostrowski ^{2,11} Kasper Karmark Iversen ⁸ Henning Bundgaard ^{2,7} Susanne Dam Nielsen ^{2,3} Peter Garred ^{2,4} Jens-Ulrik Stæhr Jensen ^{2,5,13}

To cite: Harboe ZB, Hamm SR, Pérez-Alós L, *et al.* Antibody responses and risk factors associated with impaired immunological outcomes following two doses of BNT162b2 COVID-19 vaccination in patients with chronic pulmonary diseases. *BMJ Open Resp Res* 2022;**9**:e001268. doi:10.1136/bmjresp-2022-001268

Received 6 April 2022
Accepted 11 June 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Zitta Barrella Harboe;
zitta.barrella.harboe@regionh.dk

ABSTRACT

Introduction Responses to COVID-19 vaccination in patients with chronic pulmonary diseases are poorly characterised. We aimed to describe humoral responses following two doses of BNT162b2 mRNA COVID-19 vaccine and identify risk factors for impaired responses.

Methods Prospective cohort study including adults with chronic pulmonary diseases and healthcare personnel as controls (1:1). Blood was sampled at inclusion, 3 weeks, 2 and 6 months after first vaccination. We reported antibody concentrations as geometric means with 95% CI of receptor binding domain (RBD)-IgG and neutralising antibody index of inhibition of ACE-2/RBD interaction (%). A low responder was defined as neutralising index in the lowest quartile (primary outcome) or RBD-IgG <225 AU/mL plus neutralising index <25% (secondary outcome), measured at 2 months. We tested associations using Poisson regression.

Results We included 593 patients and 593 controls, 75% of all had neutralising index $\geq 97\%$ at 2 months. For the primary outcome, 34.7% of patients (n=157/453) and 12.9% of controls (n=46/359) were low responders (p<0.0001). For the secondary outcome, 8.6% of patients (n=39/453) and 1.4% of controls (n=5/359) were low responders (p<0.001). Risk factors associated with low responder included increasing age (per decade, adjusted risk ratio (aRR) 1.17, 95% CI 1.03 to 1.32), Charlson Comorbidity Index (per point) (aRR 1.15, 95% CI 1.05 to 1.26), use of prednisolone (aRR 2.08, 95% CI 1.55 to 2.77) and other immunosuppressives (aRR 2.21, 95% CI 1.65 to 2.97).

Discussion Patients with chronic pulmonary diseases established functional humoral responses to vaccination, however lower than controls. Age, comorbidities and immunosuppression were associated with poor immunological responses.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Today, close to 545 million people live with chronic pulmonary diseases, making such diseases some of the leading causes of morbidity and mortality worldwide. Patients with chronic pulmonary diseases are among the most susceptible individuals to developing severe and critical COVID-19. Until now, responses to COVID-19 vaccination in patients with chronic pulmonary diseases are poorly characterised.

WHAT THIS STUDY ADDS

⇒ This is the first study that explores humoral responses following two doses of mRNA BNT162b2 COVID-19 vaccination for up to 6 months.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Most patients with chronic pulmonary diseases responded adequately to vaccination, however, humoral responses were lower compared with controls. Furthermore, we found that age, comorbidities and use of systemic corticosteroids and other immunosuppressants, were all independently associated with having a lower response to vaccination.

INTRODUCTION

Patients with chronic pulmonary diseases, including chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), severe asthma and bronchiectasis, are at increased risk of severe and critical COVID-19.¹⁻⁴ In addition, several retrospective cohort studies and case

series have reported an increased risk of hospitalisation, intensive care unit admission and mortality related to severe COVID-19 in patients with chronic pulmonary diseases,⁵⁻⁷ with risk estimates differing between disease groups. Thus, protective means, including vaccination of individuals with chronic pulmonary diseases, are crucial in preventing morbidity and mortality related to SARS-CoV-2 infection.

High vaccine effects after two doses of mRNA COVID-19 vaccination have been reported from both phase III randomised placebo controlled studies and large population observational studies.⁸⁻¹¹ Over time, a gradual decline in vaccine efficacy has been described, raising concerns about the sustained long-term protection conferred by vaccination and the subsequent introduction of an additional third or fourth vaccine dose in several countries.¹²⁻¹⁵ Published studies indicate that vaccine efficacy estimates reported from non-immunocompromised patients with chronic diseases are similar between risk groups.^{12 16 17} However, the characteristics and dynamics of humoral responses after mRNA COVID-19 vaccination in patients with chronic pulmonary diseases remain to be described.

We aimed to describe humoral responses following two doses of BNT162b2 mRNA COVID-19 vaccination and identify risk factors for impaired immunological responses in patients with chronic pulmonary diseases since this is a large group of patients with increased risk for severe COVID-19.

PATIENTS AND METHODS

Setting and study design

We conducted a prospective cohort study. Patients attending an outpatient clinic at the Department of Pulmonary Medicine at Herlev, Gentofte or North Zealand University Hospitals in Copenhagen, Capital Region, Denmark, from 15 January 2021 to 31 May 2021, were invited to participate in the study. The BNT162b2 mRNA COVID-19 vaccine (Comirnaty, Pfizer-BioNTech) was administered free of charge and used as one of the COVID-19 vaccines recommended by the Danish Health Authority in the vaccination programme.¹⁸ Participation in the study did not alter the vaccination timing or schedule.

The design and report of the study were done following the Strengthening the Reporting of Observational Studies in Epidemiology statement.¹⁹

Participants

Inclusion criteria

Patients aged 18 years and older, attending one of the outpatient's clinics at one of the study sites due to any of the following diagnoses of chronic pulmonary diseases (all requiring respiratory medicine specialist treatment): COPD, α -1 antitrypsin deficiency, ILD (including idiopathic pulmonary fibrosis), sarcoidosis, severe asthma, bronchiectasis or sleep apnoea. Healthcare personnel aged 18 years and older, who have received the BNT162b2 mRNA COVID-19 vaccine were included as the control

population, as previously described.²⁰ Approximately 89.7% of the population has Danish origin.²¹

Exclusion criteria

SARS-CoV-2 laboratory-confirmed infection determined by the presence of antibodies against the nucleocapsid protein (N-protein) before vaccination or during follow-up. To compare antibody responses between patients and controls, we matched by sex and the nearest age at the time of first vaccination (1:1).

Exposures, variables and outcomes

Exposure

BNT162b2 mRNA COVID-19 vaccine.

Variables

Age, sex, diagnosis of underlying chronic pulmonary disease, comorbidities (estimated by Charlson Comorbidity Index (CCI)), lung function expressed as the forced expired volume in the first second (FEV1), body mass index (BMI), immunosuppression (eg, use of oral steroids, another immunosuppressive drug (Anatomical Therapeutic Chemical codes L04), inhaled corticosteroids (ICS) and antifibrotic drugs. In addition, we categorised patients with the following diagnoses: (1) COPD, α -1 antitrypsin deficiency, asthma, bronchiectasis and sleep apnoea as obstructive lung diseases (OLD); (2) patients with diffuse parenchymal pulmonary disease and sarcoidosis as ILD.

Follow-up

Baseline (from inclusion and to up to 13 days after the first dose), at 3 weeks (from 14 days and up to 33 days after the first dose and before administration of a second dose), at 2 months (between 34 days and up to 90 days after the first dose and only after administration of a second dose); and at 6 months (from 91 days and up to 273 days after the first dose). These time points correspond to the median time of the obtained samples.

Outcomes

Defined as a responder or low responder after two BNT162b2 mRNA COVID-19 vaccine doses. In the absence of an internationally validated cut-off value for a serological correlate of protection, we defined arbitrary outcomes based on current data suggesting that postimmunisation antibody levels and neutralising activity can be used as a valid measure to estimate short-term protection.²²⁻²⁴ Therefore, we defined the primary outcome as the antibody neutralising activity alone, expressed as the percentage (%) of inhibition of ACE-2 host receptor and the spike-glycoprotein receptor-binding domain (RBD) of SARS-CoV-2 interaction. For the primary outcome, a low responder was defined as an individual having a neutralising antibody index in the lowest quartile of the study population measured at least 2 weeks after the second dose of BNT162b2 mRNA COVID-19 vaccine

(categorised as ‘2 months sample’). As a secondary outcome, we defined low responder as a combined outcome based on (1) the detection of RBD IgG antibodies expressed as arbitrary unit per mL (AU/mL) <225 AU/mL, concomitantly with (2) the detection of neutralising antibodies index <25% measured at least 2 weeks after the second dose of BNT162b2 mRNA COVID-19 vaccine (categorised as ‘2 months sample’). Laboratory analyses were performed as previously described.^{20 25 26}

Data sources and statistical methods

Baseline clinical information was retrieved from patients’ medical files and for healthcare personnel from questionnaires fulfilled by study subjects at study entry. We matched patients and controls by the nearest age at the time of first vaccination in a 1:1 ratio using nearest neighbour matching with the *Optmatch* package in R.^{27 28} Continuous data were reported as medians with IQR, and differences were assessed by Mann-Whitney U test or t-test, as most appropriate. Categorical data were reported as frequency counts and percentages, and differences were evaluated using the χ^2 test or Fisher’s exact test, as most appropriate. Missing data were handled by using complete-case analysis.

Sample size

We estimated that we needed to include 500 patients with chronic pulmonary diseases to detect a clinically significant risk increase for being a low responder (primary outcome) of at least an OR of 1.4 or more, using a two-tailed z-test of proportions between two groups with power $(1-\beta)$ of 0.8 and an α of 0.05.

For the immunological assays, we reported RBD IgG antibody levels as geometric mean concentrations (GMC) with 95% CI, and neutralising antibodies were reported as the neutralising index (%) of inhibition of ACE-2 and RBD interaction. We calculated the proportion of responders for the primary and secondary outcomes and compared it between patients and controls. To visualise the observed antibody concentration and neutralising index, the GMC of anti-RBD IgG or mean neutralising index with 95% CI at each visit was plotted for each sample.

Poisson regression with robust SEs was used to test associations between humoral response and independent

variables. In the multivariable models, we adjusted for age (per decade increase), sex, CCI (per point increase), immunosuppression (none, oral steroids, other drugs), FEV1 (increase per litre), use of ICS versus none, and use of antifibrotic drugs versus none. P values <0.05 were considered significant. Statistical analyses were performed using R V.3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

Patients were not involved in developing the research question and outcome measures, design, recruitment and conduction of the study. The laboratory analysis results have been made available to study participants through electronic patient records.

RESULTS

Baseline characteristics

We included 626 patients diagnosed with chronic pulmonary disease who received a BNT162b2 mRNA COVID-19 vaccine, 33 patients were excluded since they only received one dose of vaccine, 593 were included in the further analysis. Baseline characteristics of patients and controls are shown in [table 1](#). Compared with controls, patients with chronic pulmonary diseases were older, were more often males and had higher BMIs. The interval between the first and second vaccine dose was shorter for patients than for controls. Among patients, 67% (n=398/593) had OLD, 30% (n=183/593) had ILD, 8% (n=50/593) had both, 27% (n=160/593) had moderate to high levels of comorbidities (CCI ≥ 2). At the time of vaccination, 13% (n=76/593) were on systemic oral steroids (excluding those given during acute exacerbation), 11% (n=64/593) were on other immunosuppressive drugs, 7.4% (n=44/593) on anti-fibrotic agents, 29% (n=170/593) on ICS, 5% (n=30/593) were active smokers, 51% (n=305/593) were previous smokers.

Primary and secondary humoral outcomes in patients and controls

Humoral responses for the primary and secondary outcomes at different sampling time points during follow-up are shown in [table 2](#). After two doses of the BNT162b2 mRNA COVID-19 vaccine, the three upper

Table 1 Baseline characteristics of patients with chronic pulmonary diseases and controls included in the study

	Patients	Controls	P value
N	593	593	
Median age, years (IQR)	68 (58–74)	62 (57–64)	<0.001
Male gender, n (%)	283 (47.7)	193 (32.5)	<0.001
Median time between first and second vaccine dose, days, (IQR)	23 (22–25)	30 (29–32)	<0.001
BMI, mean (SD)	27.2 (6.4)	25.4 (6.4)	<0.001
BMI, body mass index.			

**Table 2** Humoral responses to the BNT162b2 mRNA COVID-19 vaccine in patients with chronic pulmonary disease and controls according to the primary and secondary immunological outcomes at different times during follow-up

Primary outcome						
Time of sampling	Patients (N, %)		Controls (N, %)		Difference (%)	P value
	Responder	Low responder	Responder	Low responder		
Baseline	0 (0)	566 (100)	0 (0)	581 (100)	0	–
3 weeks	4 (0.88)	447 (99.1)	2 (0.43)	455 (99.6)	0.45	0.67
2 months	296 (65.3)	157 (34.7)	313 (87.1)	46 (12.9)	21.8	<0.0001
6 months	44 (38.9)	69 (61.1)	243 (63.9)	137 (37.1)	25	<0.0001
Secondary outcome						
Time of sampling	Patients (N, %)		Controls (N, %)		Difference (%)	P value
	Responder	Low responder	Responder	Low responder		
Baseline	3 (0.01)	563 (99.9)	2 (0.6)	579 (99.4)	0.59	0.98
3 weeks	217 (48.1)	234 (51.9)	272 (59.5)	185 (40.5)	11.4	0.0007
2 months	414 (91.4)	39 (8.6)	354 (98.6)	5 (1.4)	7.2	<0.0001
6 months	87 (76.9)	26 (23.1)	366 (96.5)	14 (3.7)	19.6	<0.0001

Humoral responses are expressed as the proportion of responders and low responders in each group. For the primary outcome, a low responder was defined as an individual having a neutralising antibody index measured in the lower quartile of the study population measured at least 2 weeks after the second dose of the vaccine (2 months sample). In the secondary outcome, a low responder was defined as a combined outcome based on the detection of RBD IgG antibodies <225 AU/mL concomitantly with the detection of neutralising antibodies index <25% measured at least 2 weeks after the second dose of the vaccine (2 months sample). P values for the difference between the proportion of responders in patients versus controls. 'Baseline samples' were taken from inclusion and to up to 13 days after the first dose, '3 weeks' samples from 14 days and up to 33 days after the first dose and before administration of a second dose, '2 months samples' were collected between 34 days and up to 90 days after the first dose and only after administration of a second dose; and '6 months samples' from 91 days and up to 273 days after the first dose.

quartiles of the total study population had a detectable neutralising index of 97%. For the primary outcome, 34.7% patients (n=157/453) and 12.9% of controls (n=46/359) were low responders (p<0.0001). For the secondary outcome, 8.6% patients (n=39/453) and 1.4% of controls (n=5/359) were low responders (p<0.001). At 2 and 6 months of follow-up, a significantly higher proportion of patients with chronic pulmonary diseases were low responders following two doses of the BNT162b2 mRNA COVID-19 vaccine than controls for both the primary and secondary outcomes (table 2). For the secondary outcome, the differences in humoral responses were also significant after the first dose of the vaccine (table 2).

Antibody profiles in patients and controls

Changes in the antibody concentrations and neutralising antibody index with 95% CI of the mean at different sampling time points during follow-up are shown in figures 1 and 2. Antibody concentrations in patients and controls increased significantly from baseline to 3 weeks after the first dose and at 2 months sample (figure 1). There was a decline in measured antibody concentrations from 2 to 6 months after the first vaccine dose in both patients and controls (figure 2).

Risk factors associated with a lower response to vaccination in patients with chronic pulmonary diseases

Risk ratio (RR) from the univariate and multivariate analysis, including factors of clinical importance associated with being a low responder in patients with chronic pulmonary disease at 2 months of follow-up are shown in table 3. Increasing age per 10 years (crude RR (cRR) 1.19, 95% CI 1.05 to 1.35; adjusted RR (aRR) 1.17, 95% CI 1.03 to 1.32), an increase in CCI (cRR 1.20, 95% CI 1.10 to 1.31; aRR 1.15, 95% CI 1.05 to 1.26), use of prednisolone (cRR 2.12, 95% CI 1.59 to 2.81; aRR 2.08, 95% CI 1.55 to 2.77) and use of other immunosuppressive drugs (cRR 2.04, 95% CI 1.52 to 2.72; aRR 2.21, 95% CI 1.65 to 2.97) were significantly associated with an increased risk for being a low responder.

DISCUSSION

In this prospective cohort study, including patients with chronic pulmonary diseases who were vaccinated with two doses of the BNT162b2 mRNA COVID-19 vaccine, we found that most patients could establish functional humoral responses to vaccination characterised by high antibody titres and high levels of neutralising antibodies. However, humoral responses were lower at 2 and 6 months in patients with chronic pulmonary diseases than those observed in controls, and varied at different

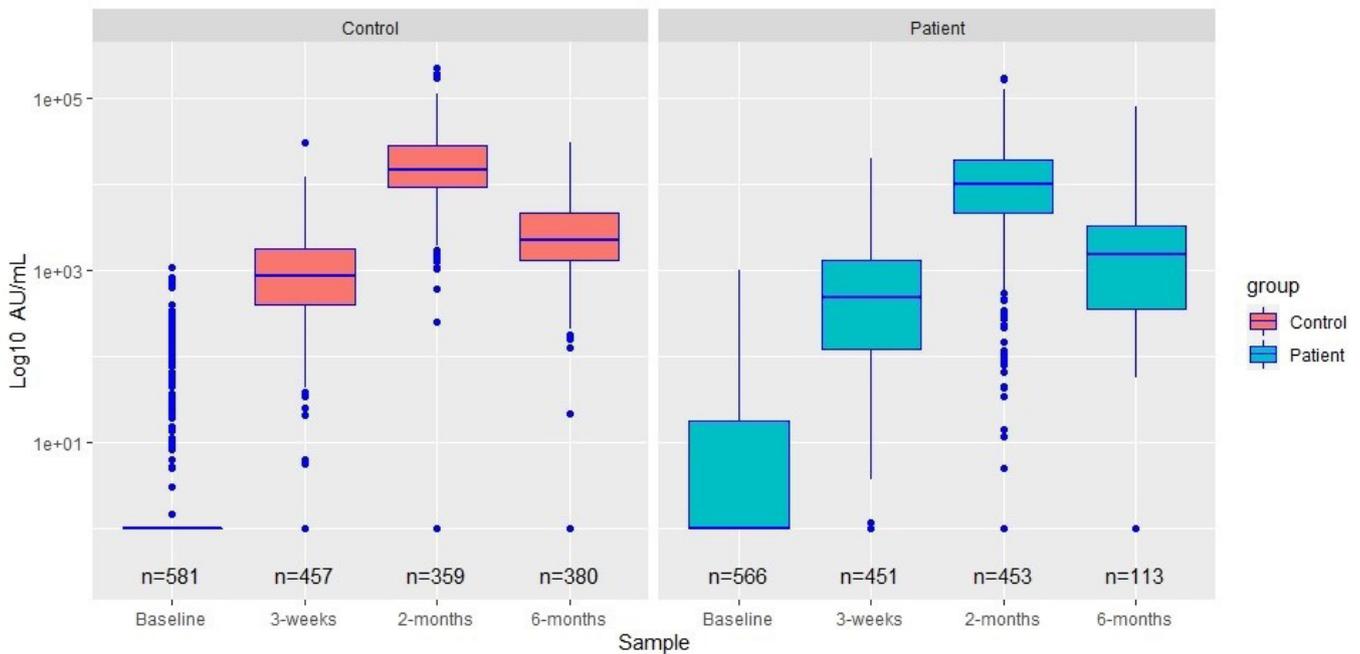


Figure 1 Anti-RBD IgG Geometric Mean Concentrations (GMC) in patients with chronic pulmonary diseases and controls during follow-up. GMCs and 95% confidence intervals (95% CI) are expressed in arbitrary units/mL (AU/mL) and plotted in a logarithmic scale. The N indicate the number of individuals contributing with samples at each time point. GMC of anti-RBD IgG in patients and controls increased from baseline (3.42 AU/mL; 95% CI 2.88–4.05 and 2.12 AU/mL; 95% CI 1.84–2.46 respectively), to three weeks after the first dose (223.43 AU/mL; 95% CI 175.91–284.29 and 752.28 AU/mL; 95% CI 658.52–862.64, respectively), ($p < 0.0001$), and at two months sample (6525.51 AU/mL; 95% CI 5431.66–7863.60 and 14943.50 AU/mL; 95% CI 13359.73–16647.24, respectively), ($p < 0.0001$). From two to six months after the first vaccine dose, there was a decline in measured GMCs anti-RBD IgG (737.78 AU/mL; 95% CI 459.43–1187.98 and 2239.57 AU/mL; 95% CI 2018.27–2489.90, respectively), ($p < 0.0001$).

sampling points. We also identified risk factors of clinical importance for an impaired response to vaccination in patients with chronic pulmonary diseases, including increasing age, having more underlying comorbidities and using oral steroids or other immunosuppressive drugs. However, these results must be interpreted with caution in the absence of correlates of protection against severe outcomes when we are report our results.

In patients with chronic pulmonary diseases and controls, we observed high antibody titres and neutralising antibody index when the peak of immunity after the mRNA BNT162b2 vaccine would be expected.^{29,30} An explanation for the use of two different immunological outcomes for assessing the results of humoral responses in our study is that at the time we designed the study, conducted and reported the analysis, there was no

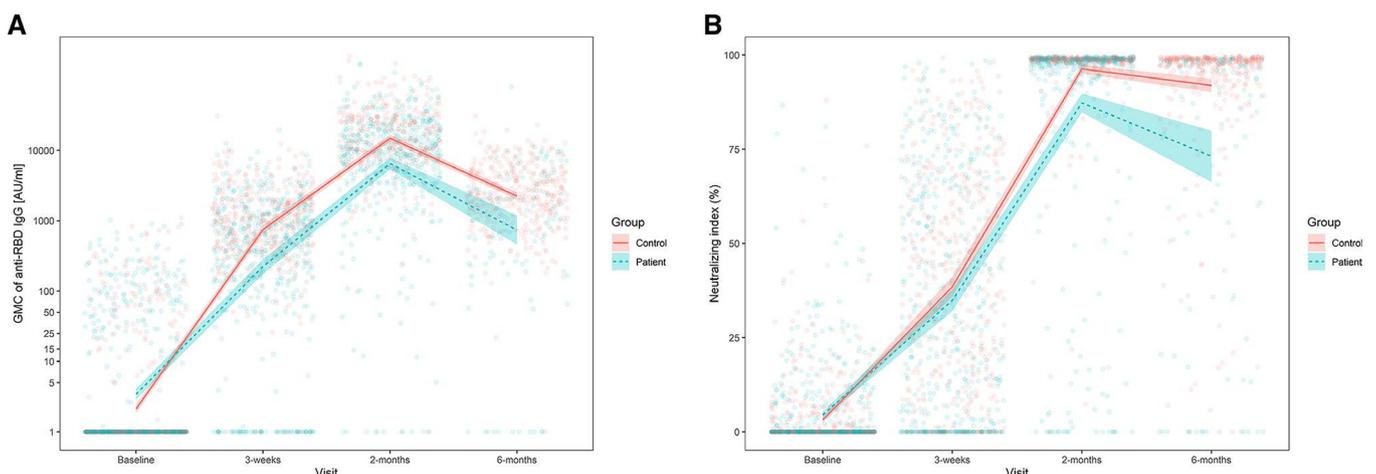


Figure 2 Changes in the Anti-RBD IgG antibody concentrations (GMC) (A) and neutralizing antibody index (%) (B) with 95% confidence intervals (CI) of the mean at different sampling time points during follow-up. GMC, geometric mean concentration; RBD, Receptor Binding Domain.

**Table 3** Univariate and multivariate analysis of risk factors of clinical importance associated with vaccine low response in patients with chronic pulmonary disease

	Crude risk rate (95% CI)	P value	Adjusted risk rate (95% CI)	P value
Age (per 10 years increase)	1.19 (1.05 to 1.35)	0.007	1.17 (1.03 to 1.32)	<0.001
Sex (male)	1.30 (1.01 to 1.68)	0.040	1.21 (0.94 to 1.54)	0.140
Charlson Comorbidity Index (per point increase)	1.20 (1.10 to 1.31)	<0.001	1.15 (1.05 to 1.26)	0.001
No Immunosuppression	Reference	<0.001	Reference	<0.001
Prednisolone	2.12 (1.59 to 2.81)	<0.001	2.08 (1.55 to 2.77)	<0.001
Other drugs	2.04 (1.52 to 2.72)		2.21 (1.65 to 2.97)	
Inhaled corticosteroids (ICS)	Reference	0.013	Reference	0.049
No ICS	0.67 (0.48 to 0.92)		0.74 (0.54 to 1.00)	
ICS				
FEV1 (per 1 litre increase)	0.99 (0.85 to 1.15)	0.905	1.00 (0.86 to 1.17)	0.951
Anti-fibrotic drugs	1.54 (1.07 to 2.23)	0.02	1.38 (0.90 to 2.10)	0.149

A multivariate poisson regression model was used adjusting for age, sex, comorbidity by Charlson Comorbidity Index, ICS, immunosuppression, antifibrotic drugs. P values <0.05 were considered significant. FEV1, forced expired volume in the first second; ICS, inhalation corticosteroids.

international consensus on the definition of correlates of protection after COVID-19 vaccination, either on the seropositivity threshold or the level of neutralising antibodies. Therefore, we considered it reasonable to define our primary outcome based on the measurement of neutralising index alone as an indicator of functional mediation of protection. We determined this threshold as the neutralising antibody level measured in the lower quartile of the study population. This showed to be a conservative assumption since several groups have reported a neutralising index >50% or median neutralising antibody titres (NT50) as thresholds.^{29 31 32} Thus, other thresholds for protection will lead to different estimates of humoral responses.

A recently published analysis of the immune correlate of mRNA-1273 COVID-19 vaccine from the efficacy trial indicated that vaccine efficacy increases with higher antibody titres and is highly mediated by neutralising antibodies.³³ Based on this consideration, we defined a secondary outcome as a composite outcome that combined antibody titres and neutralising antibodies.^{25 26} In both cases, by using any of the defined immunological outcomes, we found that humoral responses were consistently lower in patients with chronic pulmonary diseases compared with controls at 2 and 6 months after the first dose. Even though our results indicate that patients with chronic pulmonary diseases may have lower levels of protection, the specific link to clinical protection is unknown. These results should be validated by conducting epidemiological studies assessing vaccine efficacy against infection, hospitalisation and death in patients with chronic pulmonary diseases.

Several observational studies have described the decline in humoral responses elicited by COVID-19 vaccines over time, with the subsequent risk of breakthrough infections.^{29 34} Vaccine effectiveness might also be reduced

against current and forthcoming SARS-CoV-2 variants of concern.¹² Our results support that waning humoral immunity also occurs in individuals with chronic pulmonary diseases, similar to what we observed in the control population. While there have been conflicting reports on the risk of SARS-CoV-2 infection in patients with chronic pulmonary diseases, especially in asthma patients,^{34 35} their increased risk of severe outcomes after infection is well established.¹⁻⁴ Several industrialised countries have introduced additional third and fourth doses to their COVID-19 vaccination schedules in light of the waning immunity after vaccination, which is highly relevant for patients with chronic pulmonary diseases.³⁵

The identified risk factors for being a low responder have not been extensively characterised for other groups than severely immunocompromised patients. Iatrogenic immunosuppression, including corticosteroids, has markedly reduced humoral and cellular immunogenicity of mRNA COVID-19 vaccines compared with healthy controls.^{31 36 37} We did not find evidence to support that antifibrotic drugs of inhalation corticosteroids were associated with poorer immunological outcomes after vaccination. Interestingly, similar findings have been reported from patients with autoimmune diseases with lung involvement, which are more likely to receive immunosuppression.³⁶ Current guidelines for vaccination of immunocompromised patients recommend that vaccines should be administered before planned immunosuppression if feasible.³⁸ Such considerations should be based on the risk of severe COVID-19 infection with and without immunological responses and the risk of pausing immunosuppression.

Some potential limitations to our study deserve careful consideration. First, we do not have information on the cause of the lost to follow-up of some patients. Most severely ill patients have been prioritised for COVID-19



vaccination during the study period, leading to a selection bias of included patients and probably explaining at least in part the proportion of lost to follow-up in the cohort. Patients with incomplete data were similar to those with complete follow-up regarding baseline characteristics, besides a slightly higher proportion of males (data not shown) might affect the immunogenicity results. Second, although we matched patients and controls by sex and the nearest age, we could not match for age per-year increase, and healthcare personnel were younger and more often females. We conducted the analysis without matching, with similar results irrespective of whether matching or not was applied,³⁹ but we cannot rule residual confounding completely out. Third, medical information from the controls was incomplete. Fourth, the duration of follow-up was not sufficient to assess waning long-term immunogenicity. Furthermore, even if we did not find a statistically significant difference between the time interval between the first and second doses, the time between the two doses was numerically slightly shorter for patients than for controls. However, the optimal time interval has been identified as 8 weeks, and since we observed only a few days shorter interval in the patients than in the controls, we do not suspect this could alter significantly the signal of our results.^{40 41} Finally, we did not have immunological markers of cellular immunity, which are also related to immunological protection after vaccination.

CONCLUSIONS

Most patients with chronic lung diseases could establish functional humoral responses to vaccination, but humoral responses were lower at 2 and 6 months in patients with chronic pulmonary diseases than those observed in controls. Age, comorbidities and the use of different immunosuppressants were all associated with impaired immunological responses.

Author affiliations

¹Department of Respiratory Medicine and Infectious Diseases, Copenhagen University Hospital, North Zealand, Copenhagen, Denmark

²Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

³Viro-immunology Research Unit, Department of Infectious Diseases, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

⁴Laboratory of Molecular Medicine, Department of Clinical Immunology, Section 7631, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

⁵Department of Medicine, Section of Respiratory Medicine, Copenhagen University Hospital, Herlev and Gentofte, Copenhagen, Denmark

⁶Department of Haematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

⁷Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

⁸Department of Cardiology, Copenhagen University Hospital, Herlev and Gentofte, Copenhagen, Denmark

⁹Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

¹⁰Department of Clinical Biochemistry, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

¹¹Department of Clinical Immunology, Section 2034, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

¹²Department of Emergency Medicine, Herlev and Gentofte Hospital, Copenhagen University Hospital, Copenhagen, Denmark

¹³PERSIMUNE & CHIP: Department of Infectious Diseases, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark

Acknowledgements The authors wish to thank Mads Engelhardt Knudsen, Sif Kaas Nielsen, Emilie Caroline Skuladottir Bøgestad, Victoria Marie Linderod Larsen and Bettina Eide Holm from the Laboratory of Molecular Medicine at Rigshospitalet, Betina Poulsen from The Blood Bank, Department of Clinical Immunology, Rigshospitalet, Lisbeth Andreasen, Annie Mørk, Fie Andreasen, Ann Kristine Thorsteinsson, Tung Thanh Phan, and Ida Stenroos-Dam from the Department of Clinical Biochemistry at Rigshospitalet, for their excellent technical assistance in processing and analyzing the samples. We would also like to thank Alexandra Rosengård Røthlin Eriksen from the Department of Emergency medicine, Herlev and Gentofte Hospital, for her logistics and sample collection assistance.

Contributors All authors contributed to drafting the paper and revised the manuscript for important intellectual content. J-USJ, PS, ZBH, KKI, PG, SRO, HB, PG and SDN designed the study. ZBH, SRH, PS, SH, PK, TW, HP, DLM, LPA, CBH, MMP-H, AS, DLM, LDH, RBH, KF, JRM, JJAA, RF-S, LDH, ES, AB, BLM, TB-S, RB-O and SDN contributed to data collection and analysis. ZBH, SRH, ASJ and PS verified data and had full access to raw data. ZBH is the guarantor. All authors had full access to summary data reported in this study. All authors gave final approval of the version to be published.

Funding The study is investigator-initiated, none of the authors declare conflicts of interest related to the current work. The study was funded by: Novo Nordisk Foundation grant no.: NNF200C0060657 (J-USJ) and NNF180C0030978 (SDN), NNF205A0063505 and NNF20SA0064201 (PG); Carlsberg Foundation grant no: CF20-476 0045 (PG), Svend Andersen Research Foundation Grant no.: SARF2021 (PG). Independent Research Foundation Denmark (ZBH), and the participating hospitals. Initial processing and biobank storage of samples was financed by Bio- and Genome Bank Denmark.

Disclaimer The funding sources did not influence study design, data collection, analysis, or reporting of data.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Regional Scientific Ethics Committee of the Capital Region of Denmark approved the study (H-20079890). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data collected for this study, including individual participant data and a data dictionary defining each field in the set, can be made available to others in form of deidentified participant data. The study protocol and statistical analysis plan for the original study is available at www.coptrn.dk. Informed consent forms will not be available according to Danish legislation. These data will become available from 1 August 2025, on reasonable request from investigators. Such requests, including study protocol with clear hypotheses, should be sent to the principal investigator, and the steering committee will review such a request. If the hypothesis does comply with the informed consent supplied by the participants, and the hypothesis is judged to be valid, a data transfer agreement will be prepared, after which the data will be transferred. If the hypothesis is not covered by the given informed consent, the steering committee will assist in preparing an application for dispensation to our ethics committee.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Zitta Barrella Harboe <http://orcid.org/0000-0001-5552-0095>

Sebastian Rask Hamm <http://orcid.org/0000-0002-2583-3442>

Laura Pérez-Alós <http://orcid.org/0000-0002-0368-4976>

Pradeesh Sivapalan <http://orcid.org/0000-0002-8620-3655>

Torgny Wilcke <http://orcid.org/0000-0003-4053-9927>

Alexander Svorre Jordan <http://orcid.org/0000-0002-5684-9375>

Dina Leth Møller <http://orcid.org/0000-0002-3909-0643>
 Line Dam Heftdal <http://orcid.org/0000-0002-6946-7341>
 Rafael Bayarri-Olmos <http://orcid.org/0000-0003-3202-9679>
 Cecilie Bo Hansen <http://orcid.org/0000-0002-7709-4522>
 Mia Marie Pries-Heje <http://orcid.org/0000-0002-9407-5112>
 Rasmus Bo Hasselbalch <http://orcid.org/0000-0003-4274-6268>
 Kamille Fogh <http://orcid.org/0000-0002-6669-6894>
 Jose Juan Almagro Armenteros <http://orcid.org/0000-0003-0111-1362>
 Linda Hilsted <http://orcid.org/0000-0003-3465-999X>
 Erik Sørensen <http://orcid.org/0000-0002-5002-9077>
 Birgitte Lindegaard <http://orcid.org/0000-0002-5236-8427>
 Tor Biering-Sørensen <http://orcid.org/0000-0003-4209-2778>
 Ruth Frikke-Schmidt <http://orcid.org/0000-0003-4084-5027>
 Sisse Rye Ostrowski <http://orcid.org/0000-0001-5288-3851>
 Kasper Karmark Iversen <http://orcid.org/0000-0003-0504-8487>
 Henning Bundgaard <http://orcid.org/0000-0002-0563-7049>
 Susanne Dam Nielsen <http://orcid.org/0000-0001-6391-7455>
 Peter Garred <http://orcid.org/0000-0002-2876-8586>
 Jens-Ulrik Stæhr Jensen <http://orcid.org/0000-0003-4036-0521>

REFERENCES

- Lacedonia D, Scioscia G, Santomasi C, et al. Impact of smoking, COPD and comorbidities on the mortality of COVID-19 patients. *Sci Rep* 2021;11:19251.
- Hadi YB, Lakhani DA, Naqvi SFZ, et al. Outcomes of SARS-CoV-2 infection in patients with pulmonary sarcoidosis: a multicenter retrospective research network study. *Respir Med* 2021;187:106538.
- Aveyard P, Gao M, Lindson N, et al. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. *Lancet Respir Med* 2021;9:909–23.
- Naqvi SF, Lakhani DA, Sohail AH, et al. Patients with idiopathic pulmonary fibrosis have poor clinical outcomes with COVID-19 disease: a propensity matched multicentre research network analysis. *BMJ Open Respir Res* 2021;8:e000969.
- Reyes FM, Hache-Marliere M, Karamanis D, et al. Assessment of the association of COPD and asthma with in-hospital mortality in patients with COVID-19: a systematic review, meta-analysis, and meta-regression analysis. *J Clin Med* 2021;10:2087.
- Beltramo G, Cottenet J, Mariet A-S, et al. Chronic respiratory diseases are predictors of severe outcome in COVID-19 hospitalised patients: a nationwide study. *Eur Respir J* 2021;58:2004474.
- Gerayeli FV, Milne S, Cheung C, et al. Copd and the risk of poor outcomes in COVID-19: a systematic review and meta-analysis. *EClinicalMedicine* 2021;33:100789.
- Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* 2021;398:2093–100.
- Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021;384:1412–23.
- Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384:403–16.
- Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383:2603–15.
- Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet* 2021;398:1407–16.
- Thomas SJ, Moreira ED, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. *N Engl J Med* 2021;385:1761–73.
- Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently Approved or authorized in the United States. Available: <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html> [Accessed 09 Dec 2021].
- European Medicines Agency. Comirnaty and Spikevax: EMA recommendations on extra doses and boosters. Available: <https://www.ema.europa.eu/en/news/comirnaty-spikevax-ema-recommendations-extra-doses-boosters> [Accessed 09 Dec 2021].
- Moline HL, Whitaker M, Deng L, et al. Effectiveness of COVID-19 vaccines in preventing hospitalization among adults aged ≥65 Years - COVID-NET, 13 states, February–April 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1088–93.
- Yelin I, Katz R, Herzel E. Associations of the BNT162b2 COVID-19 vaccine effectiveness with patient age and comorbidities. *medRxiv* 2021:21253686.
- Danish Health Authority. Vaccination against COVID-19. Available: <https://www.sst.dk/en/english/corona-eng/vaccination-against-covid-19> [Accessed 09 Dec 2021].
- Pulliam JRC, van Schalkwyk C, Govender N, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of omicron in South Africa. *Science* 2022;376:eabn4947.
- Hansen CB, Jarlhelt I, Hasselbalch RB, et al. Antibody-dependent neutralizing capacity of the SARS-CoV-2 vaccine BNT162b2 with and without previous COVID-19 priming. *J Intern Med* 2021;290:1272–4.
- Statistics Danmark. Population projections. Available: <https://www.dst.dk/en/Statistik/emner/borgere/befolkning/befolkningsfremskrivning>
- Goldblatt D, Fiore-Gartland A, Johnson M, et al. Towards a population-based threshold of protection for COVID-19 vaccines. *Vaccine* 2022;40:306–15.
- Bergwerk M, Gonen T, Lustig Y, et al. Covid-19 breakthrough infections in vaccinated health care workers. *N Engl J Med* 2021;385:1474–84.
- Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021;27:1205–11.
- Bayarri-Olmos R, Idorn M, Rosbjerg A, et al. SARS-CoV-2 neutralizing antibody responses towards full-length spike protein and the receptor-binding domain. *J Immunol* 2021;207:878–87.
- Hansen CB, Jarlhelt I, Pérez-Alós L, et al. SARS-CoV-2 antibody responses are correlated to disease severity in COVID-19 convalescent individuals. *J Immunol* 2021;206:109–17.
- Johannesen CK, Reza Hosseini O, Gybel-Brask M, et al. Risk factors for being seronegative following SARS-CoV-2 infection in a large cohort of health care workers in Denmark. *Microbiol Spectr* 2021;9:e0090421.
- Iversen K, Bundgaard H, Hasselbalch RB, et al. Risk of COVID-19 in health-care workers in Denmark: an observational cohort study. *Lancet Infect Dis* 2020;20:1401–8.
- Collier A-risY, Yu J, McMahan K, et al. Differential kinetics of immune responses elicited by Covid-19 vaccines. *N Engl J Med* 2021;385:2010–2.
- Falsey AR, Frenck RW, Walsh EE, et al. SARS-CoV-2 neutralization with BNT162b2 vaccine dose 3. *N Engl J Med* 2021;385:1627–9.
- Collier A-RY, Yu J, McMahan K. COVID-19 mRNA vaccine immunogenicity in immunosuppressed individuals. *J Infect Dis*.
- Payne RP, Longet S, Austin JA, et al. Immunogenicity of standard and extended dosing intervals of BNT162b2 mRNA vaccine. *Cell* 2021;184:5699–714.
- Gilbert PB, Montefiori DC, McDermott AB, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science* 2022;375:43–50.
- Goldberg Y, Mandel M, Bar-On YM. Waning immunity after the BNT162b2 vaccine in Israel. *N Engl J Med* 2021.
- Bloom CI, Drake TM, Docherty AB, et al. Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: a national, multicentre prospective cohort study using the ISARIC who clinical characterisation protocol UK. *Lancet Respir Med* 2021;9:699–711.
- Ferri C, Ursini F, Gragnani L, et al. Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. high prevalence of non-response in different patients' subgroups. *J Autoimmun* 2021;125:102744.
- Buttiron Webber T, Provinciali N, Musso M, et al. Predictors of poor seroconversion and adverse events to SARS-CoV-2 mRNA BNT162b2 vaccine in cancer patients on active treatment. *Eur J Cancer* 2021;159:105–12.
- Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014;58:309–18.
- Faresjö T, Faresjö A. To match or not to match in epidemiological studies—same outcome but less power. *Int J Environ Res Public Health* 2010;7:325–32.
- Grunau B, Goldfarb DM, Asamoah-Boaheng M, et al. Immunogenicity of extended mRNA SARS-CoV-2 vaccine dosing intervals. *JAMA* 2022;327:279–81.
- Skowronski DM, Febriani Y, Ouakki M, et al. Two-Dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada. *Clin Infect Dis*.