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Efficacy of 3 COVID-19 vaccine doses in lung transplant recipients: a multicentre cohort study

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Take-home message

Three mRNA COVID-19 vaccine doses rarely induced a serological response in lung transplant patients. COVID-19 was rare, suggesting cellular immunity and/or strong adherence to shielding measures. Other protective methods should be sought.

ABSTRACT

Question addressed by the study: Do three COVID-19 vaccine doses induce a serological response in lung transplant recipients?

Patients and Methods: We retrospectively included 1071 adults (551 [52%] males) at nine transplant centres in France. Each had received three COVID-19 vaccine doses in 2021, after lung transplantation. An anti-spike protein IgG response, defined as a titre >264 BAU/mL after (median, 3.0 [1.7–4.1] months) the third dose was the primary outcome, and adverse events were the secondary outcomes. Median age at the first vaccine dose was 54 [40–63] years and median time from transplantation to the first dose was 64 [30–110] months.

Results: Median follow-up after the first dose was 8.3 [6.7–9.3] months. A vaccine response developed in 173 (16%) patients. Factors independently associated with a response were younger age at vaccination, longer time from transplantation to vaccination, and absence of corticosteroid or mycophenolate therapy. After vaccination, 51 (5%) patients (47 non-responders [47/898, 5%] and 4 [4/173, 2%] responders) experienced COVID-19, at a median of 6.6 [5.1–7.3] months after the third dose. No responders had severe COVID-19, compared to 15 non-responders, including six who died of the disease.

Answer to the question: Few lung transplant recipients achieved a serological response to three COVID-19 vaccine doses, indicating a need for other protective measures. Older age and use of mycophenolate or corticosteroids were associated with absence of a response. The low incidence of COVID-19 might reflect vaccine protection via cellular immunity and/or good adherence to shielding measures.

INTRODUCTION

The repeated worldwide waves of coronavirus disease 2019 (COVID-19) due to severe-acute-respiratory-syndrome coronavirus-2 (SARS-CoV-2) require urgent efforts to optimise vaccine responses in immunocompromised patients, including lung transplant recipients. In France, this population was among the first to be vaccinated, starting in January 2021, with the two mRNA COVID-19 vaccines approved by the European Medicines Agency: mRNA BNT162b2 (Comirnaty®, Pfizer-BioNTech), and mRNA-1273 (Spikevax®, Moderna). The two non-mRNA COVID-19 vaccines ChAdOx1 nCoV-19 (Vaxzevria®, AstraZeneca-Oxford University) and Ad26.COV2.S (Janssen®, Janssen) were approved and used later.

Recent reports showed higher mortality rates in hospitalised transplant recipients than in non-transplant patients after adjustment for co-morbidities. In a French matched case-control study comparing outcomes of kidney transplant recipients and non-transplanted patients, all of whom were admitted for COVID-19, the 30-day cumulative incidence of severe COVID did not differ between the two groups, whereas 30-day mortality was significantly higher in the transplant group (17.9% vs. 11.4% respectively, p=0.038); however, by multivariable analysis, kidney transplantation was not independently associated with mortality.[1] In an international cohort of 482 transplanted patients, COVID-19 mortality was 20.5% overall but was 33% in the 30 lung transplant recipients.[2] In a French cohort of 35 lung transplant recipients who experienced COVID-19 during the first few months of the pandemic, hospital admission was usually required and mortality was 14.3%.[3] These data support the strong recommendation from the International Society for Heart and Lung Transplantation to vaccinate all transplant candidates and recipients, despite the exclusion of these from all phases of COVID-19-vaccine trials.[4,5]

Data on COVID-19 vaccine responses in solid-organ transplant recipients are emerging,[6,10] with most studies using the production of anti-spike or anti-receptor-binding-domain antibodies as a marker for vaccine efficacy. These patients proved capable of generating a robust humoral response to natural SARS-CoV-2 infection, with 78% testing positive for antibodies more than three months after the diagnosis.[6] However, in several studies, only 40% to 69% had positive serological tests after three doses of COVID-19 vaccine.[7–13] The response to COVID-19 vaccines may vary according to the type of organ transplant, and data in the sub-group with lung transplantation remain sparse.[11,12] In a previous study, the proportion of serological responders to two vaccine doses was 62% among heart transplant recipients but only 36% among lung transplant recipients, reflecting the greater intensity of immunosuppression required after lung transplantation.[11] Although, the evaluation of vaccination efficacy usually relies on serology, further information on the humoral and cellular responses to, and clinical effectiveness of, COVID-19 vaccines in lung transplant recipients is needed to develop optimal vaccination guidelines. France was among the first countries to recommend a booster dose in immunocompromised patients including transplant recipients, in early April 2021, based on preliminary evidence of a poor response to the first two doses.[17]

The objective of this retrospective observational cohort study was to assess the spike-protein IgG antibody response and clinical protection offered by three mRNA COVID-19 vaccine doses in lung transplant recipients.

METHODS

Study design and population

We conducted a multicentre, retrospective, observational cohort study. Patients with three doses of COVID-19 vaccines approved in France were included between 1 January 2021 and 31 August 2021. Participants were recruited at nine lung transplant centres belonging to the *Groupe de Travail de Transplantation de la Société Française de Pneumologie*, a network composed of all lung transplantation centres involved in biomedical research projects in France. Exclusion criteria were age younger than 12 years, vaccination before transplantation, fewer or more than three vaccine doses, absence of data on postvaccination SARS-CoV-2 antibody levels, COVID-19 infection before vaccination or before serological testing, and treatment with monoclonal antibodies to SARS-CoV-2 before serological testing. Patients who received monoclonal antibodies to SARS-CoV-2 as prophylaxis due to vaccination failure were kept in the study if this treatment was delivered after serological testing.

The study was conducted in accordance with French legislation on biomedical research and the Declaration of Helsinki. The study protocol was approved by the ethics committee of the *Société Française de Chirurgie Thoracique et Cardio-Vasculaire* (#IRB00012919). Written informed consent was obtained from each patient before study inclusion. Details on the lung transplantation procedures and management of COVID-19 are available in the online-only supplement.

Data collection

Data were entered ~~prospectively~~ into a secure and anonymised database. We recorded demographic features, characteristics of the transplantation procedure, medications, the nature and timing of the vaccine doses, the occurrence of COVID-19 infection after vaccination, and the administration of monoclonal antibodies to treat or prevent COVID-19. The maintenance immunosuppressive regimen at the time of vaccination was collected, as well as whether intensified immunosuppression was given within 6 months before vaccination. Follow-up for the study was ended on December 31, 2021.

Vaccination protocol and vaccine response assessment

Starting in January 2021, all French lung-transplant centres implemented a proactive strategy to provide COVID-19 vaccination to eligible lung transplant recipients. Due to the high level of immunosuppression required initially, the first vaccine dose was given no sooner than 3 months after lung transplantation. Three doses were given following French recommendations, with intervals of at least four weeks between doses.[18] A cut-off of 256 BAU/mL was chosen by French health authorities to separate responders from non-responders,[19] based on serological and clinical data from a UK trial of the AstraZeneca vaccine done before the emergence of variants.[20] In line with French recommendations,[18] patients with titres between 51 and 264 BAU/mL received a fourth vaccine dose, consisting in the BNT162b2 mRNA vaccine (Pfizer, New York, NY); the response to this dose was not investigated in the current study. Patients with titres of 50 BAU/mL or less were offered monoclonal antibody treatment against COVID-19.

SARS-CoV-2 spike-protein IgG antibody assays

Blood samples were collected locally three weeks to six months after the third vaccine dose. Samples were analysed using locally available CE-marked enzyme immunoassays among the following: Architect® SARS CoV-2 (Abbott, Chicago, IL), Liaison® (DiaSorin, Saluggia, Italy), Elecsys® Anti-SARS-CoV-2 (Roche Diagnostics, Basel, Switzerland), Novalisa® (Novatec, Leinfelden-Echterdingen, Germany), Access SARS-CoV-2 IgG® (Beckman Coulter, Brea, CA), and Atellica® IM SARS-CoV-2 (Siemens, Munich, Germany).

All assays were used, and results converted to BAU/mL if needed, according to manufacturer instructions.

Outcome measures

The primary outcome was the proportion of patients with a spike-protein IgG antibody titre of 264 BAU/mL or more.

The secondary outcome was the proportion of patients with COVID-19, defined as a positive nasopharyngeal SARS-CoV-2 polymerase-chain-reaction (PCR) test after the third vaccine dose. Testing was done when there was a known contact with a patient who had COVID-19 or when symptoms consistent with COVID-19 developed. Moderate COVID-19 was defined as clinical signs of pneumonia (fever, cough, dyspnoea, high breathing rate) without signs of severe pneumonia, notably with $SpO_2 \geq 90\%$ on room air. Severe COVID-19 was defined as clinical signs of pneumonia plus at least one of the following: respiratory rate >30/min; severe respiratory distress; and/or $SpO_2 < 90\%$ on room air. Critical COVID-19 was defined as presence of acute respiratory distress syndrome.[21]

Statistical analysis

Continuous variables were shown by the Shapiro-Wilk test to have a skewed distribution and were therefore described as median [interquartile range] and compared between the groups with vs. without a vaccine response using the Mann-Whitney U test. Categorical variables were described as number (percentage) and compared by applying the chi-square test, with Monte-Carlo simulations when counts were below five.

The robust Bianco-Yohai procedure was chosen to build a multivariable logistic regression model designed to identify factors associated with a vaccine response. Backward and forward stepwise selection was applied to variables associated with *p* values below 0.10

by univariate analysis of variance. The odds ratios and 95% confidence intervals were computed. All tests were two-sided, and values of *p* smaller than 0.05 were taken to indicate significant differences. The statistical analyses were conducted using the R programme, version 3.6.1.

RESULTS

Patients

Figure 1 is the flow chart. Between January and August 2021, 2458 patients were screened at the nine participating centres, and 1071 patients were included in the study (**Table 1**). The distribution of inclusions across centres was as follows: Le Plessis Robinson, n=218 (20%); Suresnes, n=208 (19%); Strasbourg, n=170 (16%); Marseille, n=112 (10%); Nantes, n=109 (10%); Paris-Bichat, n=97 (9%); Bordeaux, n=65 (6%); Paris-Cochin, n=63 (6%); and Grenoble, n=29 (3%). Supplemental **Table S1** reports the main differences between included and excluded patients.

Spike-protein IgG response (primary outcome)

Of the 1071 patients, 173 (16%) had an antibody response, defined as a titre greater than 264 BAU/mL. Table 1 compares the main features in the responders and non-responders. In the sub-group of responders, age at vaccination was younger, more patients had cystic fibrosis as the reason for lung transplantation, fewer patients took corticosteroids and mycophenolate for maintenance immunosuppression, and fewer patients received intensified immunosuppression within 6 months before the first vaccine dose.

Figure S1 details the times of anti-spike IgG assays in the overall population (Panel A) and in subgroups defined by time from LTx to vaccination (Panel B). Antibody titres did not decrease over time. In the subgroup vaccinated sooner after LTx, antibody titres increased over time, perhaps due to a decrease in immunosuppressant therapy intensity.

Table 2 gives details on the vaccination protocols and serological testing methods. The time from lung transplantation was significantly longer in the responders than in the non-responders. Most patients received an mRNA vaccine.

Factors associated with a vaccine response

Table 3 reports the results of the univariate and multivariate analyses done to identify factors associated with an antibody response. By multivariate analysis, younger age at vaccination, longer time from lung transplantation to vaccination, and not taking corticosteroid or antimetabolite therapy were significantly and independently associated with an antibody response.

COVID-19 infection and other events

Median follow-up was 8.3 [6.7–9.3] months after the first vaccine dose. No patient was lost to follow-up. Among 777 patients with titres of 50 BAU/mL or less after the third vaccine dose, 221 (28%) were given monoclonal antibody treatment against COVID-19. COVID-19 occurred after the third vaccine dose in 51 (5%) patients, 47 non-responders and four responders, a non-significant difference (p=0.12). Among the 47 non-responders who experienced COVID-19 infection, 26 had no detectable anti-spike IgG antibodies, and the median titre in the remaining 21 patients was 31 [10–65] BAU/mL. The disease was severe and critical in 8 and 7 non-responders, respectively; no responders had severe or critical disease. Six non-responders, all of whom had critical disease, died of COVID-19, yielding a mortality rate of 6/47 (13%), compared to none of the responders; however, the difference was not statistically significant (Table 2). This 13% mortality rate was lower than the 29%

rate in the 17 patients who experienced COVID-19 before vaccination, although the difference was not statistically significant (p=0.14). No patients experienced COVID-19 during the vaccination protocol.

The proportion of patients with COVID-19 was significantly higher in the patients who were excluded because they received 0, 1, or 2 vaccine doses than in the study patients (14% vs. 5%, p<0.001), whereas mortality was similar in these two groups (14%, p=0.25).

Of the 1071 patients, 12 died. In addition to the six patients who died of COVID-19, two patients died of chronic lung allograft dysfunction and one each of pulmonary embolism, lung cancer, kidney failure, and septic shock.

Safety

Information on vaccine safety was collected retrospectively at each transplant centre. Symptoms occurring mainly within three days after the second injection were considered vaccine-related. Most vaccine-related symptoms occurred after the second injection (%) and were mild, with the most common being tiredness (25%), headache (16%), fever (11%), and chills (7%). No serious vaccine-related adverse events were reported.

DISCUSSION

We report data on the spike-protein IgG antibody response to three doses of COVID-19 vaccine in the largest cohort to date of lung transplant recipients with no history of COVID-19. The humoral response to vaccination was poor, with only 16% of patients producing protective levels of anti-spike IgG antibody. Clinically, severe COVID-19 did not occur in any of the responders. Of the non-responders, 1.7% had severe COVID-19 and 0.7% died of COVID-19 during study follow-up.

The recruitment at multiple transplant centres involved in research and the sample size of over a thousand patients are major strengths of our study. No patients with a history of COVID-19 or anti-SARS-CoV-2 antibody treatment before vaccination, or of antibody treatment before serological testing, were included. All study centres used the same vaccination protocol. Our study had no control group of healthy vaccinated adults. There was also no control group of unvaccinated lung-transplant recipients for comparison of clinical events, as vaccination is recommended to all immunocompromised individuals in France. Anti-spike IgG antibodies, but not neutralising antibodies or the memory T-cell response, were investigated. However, anti-spike IgG titres correlate closely with geometric mean titres of neutralising antibodies.[22] Since patients were tested for COVID-19 only in the event of a documented contact or compatible symptoms, we may have missed cases of asymptomatic COVID-19. It is the development of symptoms, however, that is of greatest concern and, given the very close monitoring offered to all lung transplant recipients in France, symptomatic cases are very unlikely to have been missed. Although titres of anti-spike IgG antibodies correlate with those of neutralising antibodies, no threshold or correlate of protection has been established for variants of concern. Lower levels of neutralising antibodies have been reported with variants compared to the ancestral strain [23]. Data on correlations between antibody titres and disease severity are lacking.[24] No change in the 264 BAU/mL anti-spike IgG antibody threshold has been recommended since the emergence of variants of concern. The use of monoclonal antibodies in a quarter of the non-responders may have decreased the number of COVID-19 cases. Several different immunoassay brands were used to determine the antibody titres. Nonetheless, manufacturers have established standardised results.[25] Due to the start of the omicron wave, follow-up was ended on 31 December, limiting our ability to diagnose subsequent COVID-19 episodes. Finally, safety of the vaccination protocol was not specifically assessed, although no serious adverse effects of the vaccine were recorded and neither was the frequency of transplant rejection unusually high.

Our findings are consistent with published data on the humoral response to three COVID-19 vaccine doses in solid-organ transplant recipients[7–13] and add to the scant information available on lung transplant recipients,[6,14–16] for whom the effect of three vaccine doses had not yet been reported in substantial cohorts. The marker for vaccine efficacy was usually anti-spike antibody production,[6–8,11–13,15,16,26] with only a few studies assaying anti-receptor-binding-domain[10,26] and neutralising antibodies.[10] With two doses of mRNA vaccine, the proportion of lung transplant recipients who achieved a serological response was only 10% to 39% in earlier work.[11,15,26] In populations of solid-organ transplant recipients, most of whom had received kidney transplants, the proportion of responders to three doses ranged from 40% to 69%.[7–13] In our cohort, this proportion was only 16%, in marked contrast to the high proportions of responders in the original clinical trials in immunocompetent individuals.[27,28] Two factors associated with less immunosuppression, namely, a longer time since lung transplantation and absence of current exposure to corticosteroid or mycophenolate therapy, were significantly associated with a better response in our study, although our study design did not allow an assessment of potential causality. Treatment with antimetabolites such as mycophenolate was also associated with a poorer vaccine response in lung transplant recipients in two earlier studies,[15,16] suggesting that decreasing the dosages of these drugs during vaccination might improve the immune response. Consistent with this possibility, the subgroup of patients vaccinated sooner after LTx experienced increasing anti-spike IgG titres over time (Figure S1, Panel B). Younger patients more often achieved a vaccine response, in keeping with other studies of the effects of mRNA COVID-19 vaccines.[6,15,16]

Despite the low proportion of vaccine responders, COVID-19 was uncommon, occurring in 5% of patients overall, 5% of non-responders, and 2% of responders. This low incidence may reflect good patient education about, and adherence to, protective measures such as mask wearing and hand hygiene, in addition to the limited overall incidence of COVID-19 during the study period in France[29]. Moreover, monoclonal antibodies to SARS-CoV-2 were given to 25% of non-responders and may have contributed to decrease the risk of COVID-19. The routine use of monoclonal antibodies early in the course of COVID-19, starting in June 2021, may have diminished the proportion of severe and fatal cases. Finally, vaccination confers immunity via mechanisms other than the production of anti-spike IgG antibodies. A robust CD8+ T-cell response was documented one week after the first dose of BNT162b2 mRNA vaccine in immunocompetent healthcare workers.[30] Importantly, T-cell responses in immunocompetent individuals after two vaccine doses were of similar magnitude to those seen after natural infection, although they seemed somewhat more differentiated.[31] Although not observed in our population (Figure S1), antibody waning after vaccination remains a concern.[32] T memory stem cells develop after vaccination and may be more long lasting. However, severe or fatal COVID-19 was seen only among non-responders in our study, suggesting a possible protective role for cellular immunity. Last, during the study period, the alpha and delta SARS-CoV-2 variants predominated. Although recent data suggest that boosters may increase effectiveness against severe omicron-variant disease in immunocompetent patients,[32] whether our results apply to current and emerging variants in immunocompromised populations remains to be investigated.

In conclusion, lung transplant recipients had an impaired anti-spike IgG response to three COVID-19 vaccine doses. Older age and stronger immunosuppressive regimens including mycophenolate or corticosteroids were significantly associated with failure to achieve a vaccine response. During the study period, when the alpha and delta SARS-CoV-2 variants predominated, COVID-19 was very uncommon despite the low frequency of vaccine responses, and the few fatal or non-fatal severe cases occurred only in non-responders. However, a protective role for monoclonal-antibody prophylaxis is possible, and whether our results apply to current and emerging variants is unclear. Additional research is needed to clarify these findings, characterise the T-cell response to COVID-19 vaccines, and determine the extent to which cellular immunity contributes to protect immunocompromised patients against COVID-19.

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Data-sharing statement

Anonymised participant-level data, the study protocol and informed consent form, and the statistical analysis plan will be available from the corresponding author upon reasonable request, after study publication and after signature of a data-sharing agreement.

Guarantor statement

J Le Pavec takes responsibility for the content of the manuscript, including the data and analysis, and affirms that the manuscript is an honest, accurate, and transparent account of the reported study and omits no important aspects of the study. No discrepancies from the original study protocol occurred.

Author contributions

1: Conception and design; 2: Acquisition of data; 3: Analysis and interpretation of data; 4: Article drafting and revising

GD: 1, 2, 3, 4; LB: 2, 3, 4; LBLN: 1, 3, 4; BRP: 2, 3, 4; MP: 2, 3, 4; BC: 2, 3, 4; MS: 2, 3, 4; XD: 2, 3, 4; CSR: 2, 3; NC: 2, 3, 4; JM: 2, 3, 4; MRG: 2, 3, 4; ID: 2, 3; FG: 2, 3; AR: 2, 3, 4; JLP: 1, 2, 3, 4

The corresponding author, Jérôme Le Pavec, as the guarantor of the study, accepts full responsibility for the work and the conduct of the study. He had access to the data, and controlled the decision to publish. The corresponding author also attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflict of interest

None for any authors

Table 1: Main features of the study patients

	Overall n = 1071	Responders n = 173	Non-responders n = 898	p value
Male, n (%)	551 (52)	82 (47)	469 (52)	0.27
Age at transplantation (y), med [IQR]	47 [31 – 58]	32 [24 – 52]	50 [34 – 58]	0.001
Age at vaccination (y), med [IQR]	54 [40 – 63]	45 [33 – 58]	56 [43 – 64]	0.002
Transplantation indications, n (%),				0.0035
Cystic fibrosis	327 (31)	87 (50)	240 (27)	
Chronic obstructive pulmonary disease	323 (30)	36 (21)	287 (32)	
Fibrosis	160 (15)	13 (7)	147 (16)	
Pulmonary arterial hypertension	121 (11)	18 (10)	103 (11)	
Other	140 (13)	20 (11)	120 (13)	
Transplantation procedure, n (%)				0.37
Double-lung	918 (86)	156 (90)	762 (85)	
Single-lung	75 (7)	9 (5)	66 (7)	
Heart-lung	62 (6)	7 (4)	55 (6)	
Multiorgan	16 (1)	2 (1)	14 (2)	
Maintenance immunosuppression, n (%)				
Cyclosporine	197 (20)	24 (15)	173 (21)	0.30
Tacrolimus	786 (79)	132 (83)	654 (78)	0.49
Corticosteroids	903 (85)	123 (71)	780 (87)	0.004
Mycophenolate	675 (63)	89 (51)	586 (66)	0.03
Azathioprine	157 (15)	36 (21)	121 (14)	0.15
Everolimus	195 (18)	39 (23)	156 (17)	0.18
Sirolimus	11 (1)	3 (2)	8 (1)	0.19
Intensified immunosuppression within 6 months before vaccination, n (%), n =1064	90 (8)	7 (4)	83 (9)	0,03
Methylprednisolone, n(%)	52 (5)	5 (3)	47 (5)	0.24
Rituximab, n (%)	12 (1)	0 (0)	12 (1)	0.24
Anti-thymocyte globulins, n (%)	2 (0)	0	2 (0)	0.99
Intravenous immunoglobulins, n (%)	25 (2)	2 (1)	23 (3)	0.23
Plasmapheresis, n (%)	1 (0)	0	1 (0)	0.99
Follow-up (months,) med [IQR]	8.3 [6.7 – 9.3]	8.6 [7.2 – 9.3]	8.3 [6.7 – 9.3]	0.08
Death, n (%)	13 (1)	0	13 (1)	0.14

Table 2: Details on vaccination protocols and post-vaccination COVID-19

	Overall n = 1071	Responders n = 173	Non-responders n = 898	p value
Vaccine manufacturer, n (%)				0.14
BNT16b2 (Pfizer-BioNtech)	777 (73)	118(68)	659 (73)	
mRNA-1273 (Moderna)	145 (13)	28 (16)	117 (13)	
ChAd0x1 nCoV-19 (Astra-Zeneca)	16 (1)	0	16 (2)	
Combined mRNA	6 (1)	2 (1)	4 (0)	
Combined mRNA and Astra-Zeneca	127 (12)	25 (15)	102 (12)	
Times to serology, months [IQR]				
Time from lung transplantation to first vaccine dose	64 [30 – 110]	96 [56 – 156]	57 [26 – 104]	0.002
Time from third vaccination dose to serology	3.0 [1.7 – 4.1]	3.3 [2.1 – 4.1]	2.8 [1.6 – 4.1]	0.034
Intervals between vaccine doses, days [IQR]				
First to second	27 [27 – 30]	27 [24 – 30]	30. [27 – 31]	0.18
Second to third	43 [30 – 64]	46 [30 – 70]	43 [30 – 61]	0.10
Type of immunoassay, n (%)				0.005
Abbott	635 (59)	69 (40)	566 (63)	
DiaSorin	207 (19)	52 (33)	155 (17)	
Elecsys	96 (9)	6 (5)	90 (10)	
Cerba	75 (7)	23 (12)	52 (6)	
Roche	43 (4)	11 (7)	32 (4)	
NovaTec	15 (2)	12 (3)	3 (0)	
COVID-19 after vaccination, n (%)	51 (5)	4 (2)	47 (5)	0.12
Moderate, n(%)	36 (3)	4 (2)	32 (4)	0.40
Severe, n (%)	8 (1)	0	8 (1)	0.71
Critical, n (%)	7 (1)	0	7 (1)	0.83
Deaths due to COVID, n (%)	6 (1)	0	6 (1)	0.99
Curative monoclonal antibodies, n (%)	13 (1)	1 (1)	12 (1)	0.99
Time from third vaccine dose to COVID-19, months [IQR]	6.6 [5.1 – 7.3]	7.1 [6.6 – 7.4]	6.4 [4.9 – 7.3]	0.33

Table 3: Univariate and multivariate analyses to identify factors associated with a vaccine response (titre ≥264 BAU/mL)

	Univariate					Multivariate				
	Reference	Modality	HR	95%CI	p value	Reference	Modality	HR	95%CI	p value
Sex	Female	Male	0.82	0.59 – 1.14	0.24					
Age at vaccination	Continuous		0.97	0.96 – 0.98	0.0045	Continuous		0.97	0.96 – 0.98	0.0056
Time from lung transplantation to the first vaccine dose	Continuous		1.01	1.00 – 1.01	0.009	Continuous		1.01	1.00 – 1.01	0.0094
Lung transplantation indication	Fibrosis	COPD	1.42	0.49 –1.22	0.30					
		CF	4.10	2.21 – 2.60	0.005					
		PAH	1.98	0.93 – 4.21	0.08					
		Other	1.79	0.85 –3.77	0.13					
Lung transplant procedure	Single	Double	1.50	0.73 – 3.07	0.27					
		Heart-lung	0.93	0.33 – 2.67	0.90					
		Multiorgan	1.05	0.20 – 5.39	0.95					
Increased immunosuppression within 6 months before vaccination	No	Yes	0.41	0.19 – 0.90	0.03					
Methylprednisolone	No	Yes	0.53	0.21 – 1. 36	0.19					
Rituximab	No	Yes	0.01	0.00 – >100	0.97					
Anti-thymocyte globulins	No	Yes	0.01	0.00 – >100	0.97					
Intravenous immunoglobulins	No	Yes	0.44	0.10 – 1.89	0.27					
Plasmapheresis	No	Yes	0.01	0.00 – >100	0.98					
Calcineurin inhibitors	No	Cyclosporine	0.76	0.16 – 3.65	0.73					
	No	Tacrolimus	1.11	0.24 – 5.07	0.89					
Corticosteroids	No	Yes	0.36	0.25 – 0.53	0.005	No	Yes	0.43	0.28 – 0.66	0.005
Mycophenolate	No	Yes	0.57	0.39 – 0.84	0.0037	No	Yes	0.66	0.42 – 1.02	0.06
Azathioprine	No	Yes	1.12	0.69 – 1.83	0.96	No	Yes	0.73	0.41 – 1.32	0.30
mTOR inhibitors	No	Everolimus	1.40	0.94 – 2.08	0.10					
	No	Sirolimus	2.09	0.55 – 7.99	0.28					
Vaccine manufacturer	BNT16b2 (Pfizer-BioNtech)	mRNA-1273 (Moderna)	1.34	0.85 – 2.11	0.21					
		ChAd0x1 nCoV-19 (Astra)	0.00	0.15 > 100	0.98					
		Combined mRNA	2.79	0.51 – 15.42	0.24					
		Combined mRNA & Astra	1.99	0.71 – 5.64	0.11					
Serology assay	Abbott	DiaSorin	3.13	2.08 – 4.72	<0.01					
		Elecsys	0.81	0.39 – 1.68	0.57					
		Cerba	3.60	1.81 – 7.15	<0.01					
		Roche	2.22	0.97 – 5.07	0.06					
		Novatec	5.40	1.19 – 24.60	0.03					
Time from third vaccine dose to serological testing	Continuous		1.15	1.04 – 1.29	0.0025					

CAPTIONS

Figure 1

Patient flow chart

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Figure 1

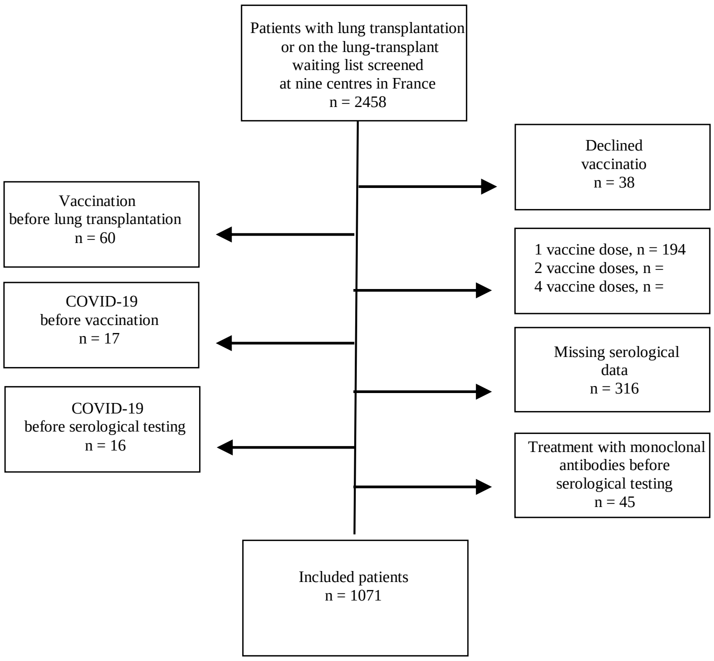

Patients with lung transplantation or on the lung-transplant waiting list screened at nine centres in France n = 2458
Declined vaccinatio n = 38
Vaccination before lung transplantation n = 60
1 vaccine dose, n = 194
2 vaccine doses, n =
4 vaccine doses, n =
COVID-19 before vaccination n = 17
Missing serological data n = 316
COVID-19 before serological testing n = 16
Treatment with monoclonal antibodies before serological testing n = 45
Included patients n = 1071

Table 1: Main features of the study patients

	Overall n = 1071	Responders n = 173	Non-responders n = 898	p value
Male, n (%)	551 (52)	82 (47)	469 (52)	0.27
Age at transplantation (y), med [IQR]	47 [31 – 58]	32 [24 – 52]	50 [34 – 58]	0.001
Age at vaccination (y), med [IQR]	54 [40 – 63]	45 [33 – 58]	56 [43 – 64]	0.002
Transplantation indications, n (%),				0.0035
Cystic fibrosis	327 (31)	87 (50)	240 (27)	
Chronic obstructive pulmonary disease	323 (30)	36 (21)	287 (32)	
Fibrosis	160 (15)	13 (7)	147 (16)	
Pulmonary arterial hypertension	121 (11)	18 (10)	103 (11)	
Other	140 (13)	20 (11)	120 (13)	
Transplantation procedure, n (%)				0.37
Double-lung	918 (86)	156 (90)	762 (85)	
Single-lung	75 (7)	9 (5)	66 (7)	
Heart-lung	62 (6)	7 (4)	55 (6)	
Multiorgan	16 (1)	2 (1)	14 (2)	
Maintenance immunosuppression, n (%)				
Cyclosporine	197 (20)	24 (15)	173 (21)	0.30
Tacrolimus	786 (79)	132 (83)	654 (78)	0.49
Corticosteroids	903 (85)	123 (71)	780 (87)	0.004
Mycophenolate	675 (63)	89 (51)	586 (66)	0.03
Azathioprine	157 (15)	36 (21)	121 (14)	0.15
Everolimus	195 (18)	39 (23)	156 (17)	0.18
Sirolimus	11 (1)	3 (2)	8 (1)	0.19
Intensified immunosuppression within 6 months before vaccination, n (%), n =1064	90 (8)	7 (4)	83 (9)	0,03
Methylprednisolone, n(%)	52 (5)	5 (3)	47 (5)	0.24
Rituximab, n (%)	12 (1)	0 (0)	12 (1)	0.24
Anti-thymocyte globulins, n (%)	2 (0)	0	2 (0)	0.99
Intravenous immunoglobulins, n (%)	25 (2)	2 (1)	23 (3)	0.23
Plasmapheresis, n (%)	1 (0)	0	1 (0)	0.99
Follow-up (months,) med [IQR]	8.3 [6.7 – 9.3]	8.6 [7.2 – 9.3]	8.3 [6.7 – 9.3]	0.08
Death, n (%)	13 (1)	0	13 (1)	0.14

Table 2: Details on vaccination protocols and post-vaccination COVID-19

	Overall n = 1071	Responders n = 173	Non-responders n = 898	p value
Vaccine manufacturer, n (%)				0.14
BNT16b2 (Pfizer-BioNtech)	777 (73)	118(68)	659 (73)	
mRNA-1273 (Moderna)	145 (13)	28 (16)	117 (13)	
ChAd0x1 nCoV-19 (Astra-Zeneca)	16 (1)	0	16 (2)	
Combined mRNA	6 (1)	2 (1)	4 (0)	
Combined mRNA and Astra-Zeneca	127 (12)	25 (15)	102 (12)	
Times to serology, months [IQR]				
Time from lung transplantation to first vaccine dose	64 [30 – 110]	96 [56 – 156]	57 [26 – 104]	0.002
Time from third vaccination dose to serology	3.0 [1.7 – 4.1]	3.3 [2.1 – 4.1]	2.8 [1.6 – 4.1]	0.034
Intervals between vaccine doses, days [IQR]				
First to second	27 [27 – 30]	27 [24 – 30]	30. [27 – 31]	0.18
Second to third	43 [30 – 64]	46 [30 – 70]	43 [30 – 61]	0.10
Type of immunoassay, n (%)				0.005
Abbott	635 (59)	69 (40)	566 (63)	
DiaSorin	207 (19)	52 (33)	155 (17)	
Elecsys	96 (9)	6 (5)	90 (10)	
Cerba	75 (7)	23 (12)	52 (6)	
Roche	43 (4)	11 (7)	32 (4)	
NovaTec	15 (2)	12 (3)	3 (0)	
COVID-19 after vaccination, n (%)	51 (5)	4 (2)	47 (5)	0.12
Moderate, n(%)	36 (3)	4 (2)	32 (4)	0.40
Severe, n (%)	8 (1)	0	8 (1)	0.71
Critical, n (%)	7 (1)	0	7 (1)	0.83
Deaths due to COVID, n (%)	6 (1)	0	6 (1)	0.99
Curative monoclonal antibodies, n (%)	13 (1)	1 (1)	12 (1)	0.99
Time from third vaccine dose to COVID-19, months [IQR]	6.6 [5.1 – 7.3]	7.1 [6.6 – 7.4]	6.4 [4.9 – 7.3]	0.33

Table 3: Univariate and multivariate analyses to identify factors associated with a vaccine response (titre ≥264 BAU/mL)

	Univariate					Multivariate				
	Reference	Modality	HR	95%CI	p value	Reference	Modality	HR	95%CI	p value
Sex	Female	Male	0.82	0.59 – 1.14	0.24					
Age at vaccination	Continuous		0.97	0.96 – 0.98	0.0045	Continuous		0.97	0.96 – 0.98	0.0056
Time from lung transplantation to the first vaccine dose	Continuous		1.01	1.00 – 1.01	0.009	Continuous		1.01	1.00 – 1.01	0.0094
Lung transplantation indication	Fibrosis	COPD	1.42	0.49 –1.22	0.30					
		CF	4.10	2.21 – 2.60	0.005					
		PAH	1.98	0.93 – 4.21	0.08					
		Other	1.79	0.85 –3.77	0.13					
Lung transplant procedure	Single	Double	1.50	0.73 – 3.07	0.27					
		Heart-lung	0.93	0.33 – 2.67	0.90					
		Multiorgan	1.05	0.20 – 5.39	0.95					
Increased immunosuppression within 6 months before vaccination	No	Yes	0.41	0.19 – 0.90	0.03					
Methylprednisolone	No	Yes	0.53	0.21 – 1. 36	0.19					
Rituximab	No	Yes	0.01	0.00 – >100	0.97					
Anti-thymocyte globulins	No	Yes	0.01	0.00 – >100	0.97					
Intravenous immunoglobulins	No	Yes	0.44	0.10 – 1.89	0.27					
Plasmapheresis	No	Yes	0.01	0.00 – >100	0.98					
Calcineurin inhibitors	No	Cyclosporine	0.76	0.16 – 3.65	0.73					
	No	Tacrolimus	1.11	0.24 – 5.07	0.89					
Corticosteroids	No	Yes	0.36	0.25 – 0.53	0.005	No	Yes	0.43	0.28 – 0.66	0.005
Mycophenolate	No	Yes	0.57	0.39 – 0.84	0.0037	No	Yes	0.66	0.42 – 1.02	0.06
Azathioprine	No	Yes	1.12	0.69 – 1.83	0.96	No	Yes	0.73	0.41 – 1.32	0.30
mTOR inhibitors	No	Everolimus	1.40	0.94 – 2.08	0.10					
	No	Sirolimus	2.09	0.55 – 7.99	0.28					
Vaccine manufacturer	BNT16b2 (Pfizer-BioNtech)	mRNA-1273 (Moderna)	1.34	0.85 – 2.11	0.21					
		ChAd0x1 nCoV-19 (Astra)	0.00	0.15 > 100	0.98					
		Combined mRNA	2.79	0.51 – 15.42	0.24					
		Combined mRNA & Astra	1.99	0.71 – 5.64	0.11					
Serology assay	Abbott	DiaSorin	3.13	2.08 – 4.72	<0.01					
		Elecsys	0.81	0.39 – 1.68	0.57					
		Cerba	3.60	1.81 – 7.15	<0.01					
		Roche	2.22	0.97 – 5.07	0.06					
		Novatec	5.40	1.19 – 24.60	0.03					
Time from third vaccine dose to serological testing	Continuous		1.15	1.04 – 1.29	0.0025					

SUPPLEMENTARY APPENDIX

Overview of lung transplant management

Post-transplantation immunosuppression and induction therapy followed standard protocols at each of the nine participating centres. All patients received life-long *Pneumocystis jirovecii* pneumonia prophylaxis with cotrimoxazole. Valganciclovir for cytomegalovirus prophylaxis was given according to local guidelines. Monitoring transbronchial biopsies were obtained routinely or as clinically indicated depending on the standard protocol at each centre.

Patients with allograft dysfunction were investigated for acute cellular rejection, lymphocytic bronchiolitis/neutrophilic reversible allograft dysfunction, and airway injury caused by infection/colonisation. Chronic lung allograft dysfunction was diagnosed based on international criteria when the forced expiratory volume in the first second and/or the forced vital capacity declined to 80% or less of the best postoperative value during routine outpatient assessments at least three months after transplantation.[1] Comprehensive lung function testing including spirometry and lung volume measurements, high-resolution computed tomography of the chest, and bronchoscopy with bronchoalveolar lavage and transbronchial biopsy were performed to look for causes of lung allograft dysfunction, including persistent acute rejection, azithromycin-responsive allograft dysfunction, infection, anastomotic stricture, and recurrent sarcoidosis.

COVID-19 screening and management

COVID-19 infection was documented by positive real-time polymerase-chain-reaction testing of nasopharyngeal swabs obtained to evaluate symptoms consistent with COVID-19 or after contact with a patient known to have COVID-19. All patients with mild-to-moderate

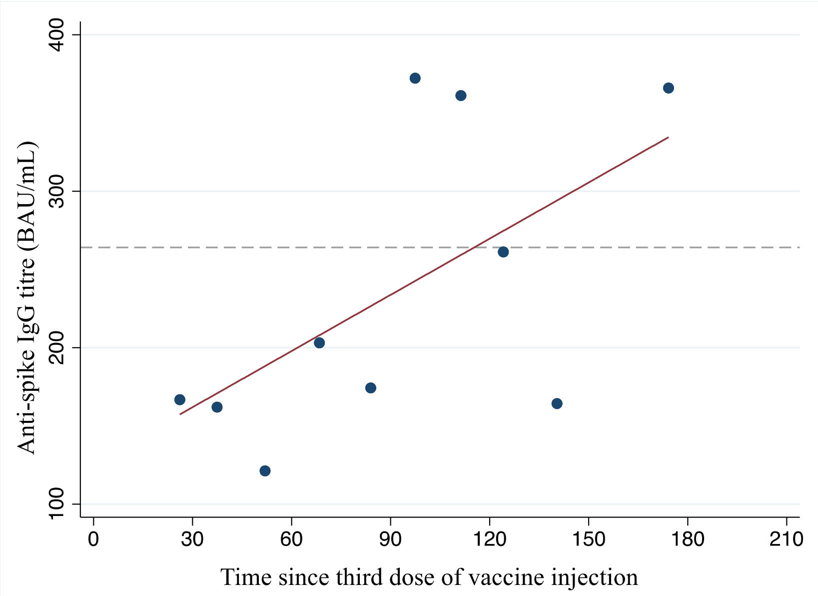
COVID-19 infection were treated within 5 days of symptom onset with casirivimab-imdevimab monoclonal antibodies, starting in June 2021. Patients with severe COVID-19 also received dexamethasone, antibiotics, oxygen as needed, and supportive care. Tocilizumab and remdesivir were given if deemed appropriate by the physician in charge.

Table S1: Main features of the screened patients and of the included and excluded patients

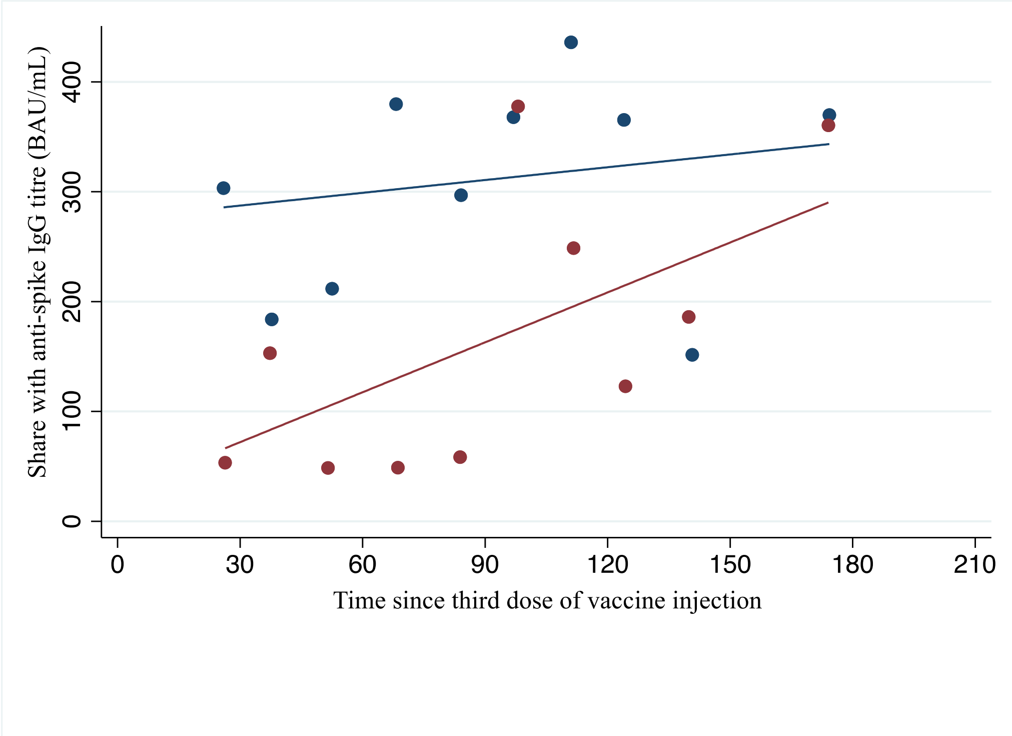
	Overall n = 2420	Included n = 1071	Excluded n = 1349	*p* value
Male, n (%)	1139 (48)	551 (51)	702 (53)	0.46
Age at lung transplantation (y), med [IQR]	47 [30 - 57]	47 [31 - 58]	46 [30 - 57]	0.04
Age at vaccination (y), med [IQR]	54 [40 - 63]	54 [40 - 63]	54 [39 - 62]	0.29
Transplantation indications, n (%),				0.09
Cystic fibrosis	769 (32)	327 (31)	442 (33)	
Chronic obstructive pulmonary disease	696 (29)	323 (30)	373 (28)	
Fibrosis	405 (17)	160 (15)	245 (18)	
Pulmonary arterial hypertension	257 (10)	121 (11)	136 (10)	
Other	293 (12)	140 (13)	153 (11)	
Transplantation procedure, n(%)				0.02
Double-lung	2074 (86)	918 (86)	1156 (86)	
Single-lung	196 (8)	75 (7)	121 (9)	
Heart-lung	115 (5)	62 (6)	53 (4)	
Multiorgan	35 (1)	16 (1)	19 (1)	
Maintenance immunosuppression at the time of vaccination, n (%)				
Cyclosporine	435 (18)	197 (20)	239 (18)	0,16
Tacrolimus	1946 (80)	786 (79)	1160 (86)	0.07
Corticosteroids	2057 (85)	903 (85)	1154 (86)	0,64
Mycophenolate	1562 (64)	675 (63)	887 (66)	0.53
Azathioprine	321 (13)	157 (15)	164 (12)	0.13
Everolimus	453 (18)	195 (18)	258 (19)	0,59
Sirolimus	21 (1)	11 (1)	10 (1)	0.19
Intensified immunosuppression within 6 months before vaccination, n (%), n = 2262	267 (12)	90 (8)	177 (15)	0,01
Methylprednisolone, n(%)	135 (6)	52 (5)	83(7)	0.05
Rituximab, n(%)	61 (3)	12 (1)	49 (4)	<0.01
Anti-thymocyte globulins, n(%)	21 (1)	2 (0)	19(2)	<0.01
Intravenous immunoglobulins, n(%)	77 (3)	25 (2)	52 (4)	0.01
Plasmapheresis, n(%)	16 (1)	1 (0)	15 (1)	<0.01

Figure S1: Times of anti-spike IgG assays

Panel A



Panel B



Each panel shows a binscatter plot with 10 bins of equal size (104 or 105 observations per bin). Panel A shows the relationship between anti-spike IgG titres and time from the third vaccine dose to the anti-spike IgG assay in the overall population. The solid line represents the best linear fit (beta=1.196, *p*=0.03) and the dashed line the 264 BAU/mL threshold used to categorise patients as responders. Panel B shows the same relationship in the two subgroups defined by time from lung transplantation to the first vaccine dose longer than the median of 5.3 years (blue dots, 50/% of the sample; beta=0.388, *p*=0.659) vs. shorter than 5.3 years (red dots, 50% of the sample; beta=1.514, *p*=0.025).