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Impact of COVID-19 social distancing measures on lung transplant recipients: decline in overall respiratory virus infections is associated with stabilisation of lung function

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Impact of COVID-19 social distancing measures on lung transplant recipients: decline in overall respiratory virus infections is associated with stabilisation of lung function.

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Take home message

Strong reduction in respiratory viruses during social distancing was associated with stabilisation of lung function in lung transplant recipients, suggesting a possibly more important role for these infections in lung function decline than previously appreciated.

Abstract

Background

COVID-19 social distancing measures led to a dramatic decline in non-COVID respiratory virus (RV) infections, providing a unique opportunity to study their impact on annual FEV_1 decline, episodes of temporary drop in lung function (TDLF) suggestive of infection and chronic lung allograft dysfunction (CLAD) in lung transplant recipients (LTR).

Methods

All FEV_1 values of LTR transplanted between 2009-April 2020 were included. Annual FEV_1 change was estimated with separate estimates for pre- social distancing (2009/2020) and the year with social distancing measures (2020/2021). Patients were grouped by individual TDLF frequency (frequent/infrequent). RV circulation was derived from weekly hospital-wide RV infection rates. Effect modification by TDLF frequency and RV circulation was assessed. CLAD and TDLF rates were analyzed over time.

Results

479 LTR (12,775 FEV_1 values) were included. Pre- social distancing annual change in FEV_1 was -114ml [95%CI; -133; -94], while during social distancing FEV_1 did not decline: +5ml [-38; 48] (difference pre- vs. during social distancing: $p<0.001$). The frequent TDLF subgroup showed faster annual FEV_1 decline compared to infrequent TDLF (-150ml [-181; -120] vs. -90ml [-115; -65] p=0.003). During social distancing, we found significantly lower odds for any TDLF (OR 0.53 [0.33; 0.85], p=0.008) and severe TDLF (OR 0.34 [0.16; 0.71] p=0.005) as well as lower CLAD incidence (OR 0.53 [0.27; 1.02] p=0.060). Effect modification by RV circulation indicated a significant association between TDLF/CLAD and RVs.

Conclusion

During social distancing the strong reduction in RV circulation coincided with markedly less FEV_1 decline, fewer TDLFs and possibly less CLAD. Effect modification by RV circulation suggests an important role for RVs in lung function decline in LTR.

Introduction

In December 2019 a novel human Coronavirus called SARS-CoV-2 causing COVID-19 emerged and spread in the subsequent months from the Wuhan region in China across the world.[1,2]
Like many other countries the Dutch government launched unprecedented social distancing measures to limit the spread of COVID-19. Initial measures (March 2020) in the Netherlands included closing of schools, social distancing and closing of the catering and entertainment industry, which were later followed by mandatory wearing of face masks and a curfew. These social distancing measures also led to a striking reduction in other respiratory virus (RV) infections, both worldwide and in The Netherlands.[3–6] Of note, sharp reductions in circulation of viruses with well-established seasonal patterns like influenza virus, respiratory syncytial virus, human metapneumo virus, parainfluenza virus, rhinovirus and non-SARS-CoV-2 coronaviruses were seen across both hemispheres.[3–6] These RVs are increasingly recognised as an important cause of exacerbations, morbidity and mortality in patients suffering from asthma, chronic obstructive pulmonary disease and in the elderly.[7] One group especially at risk from adverse outcomes post-RV infection are lung transplant recipients (LTR), in who presentation with an RV is often accompanied by a range of airway symptoms combined with an acute, temporary drop in lung function (TDLF). Furthermore, RV infections have been linked to the development of chronic lung allograft dysfunction (CLAD). CLAD is the most important expression of pulmonary decline in LTR, and is characterised by a sustained and often progressive reduction in airflow which is notoriously difficult to treat, affects quality of life and is the main factor limiting survival after transplantation.[8,9]

All LTRs have lifelong follow-up which results in a wealth of longitudinal pulmonary function tests over time. We hypothesised that given the proposed impact of RVs in LTR, the broad reduction in RV circulation during social distancing will lead to less FEV_1 decline and less pulmonary function defined events including CLAD. In this study we aimed to investigate 1) change in FEV_1 decline during social distancing compared to pre- social distancing and 2) incidence of events possibly associated with RV infections such as CLAD, TDLF, acute rejection and death. In addition, we studied the role of RV circulation in explaining the occurrence of these events and annual FEV_1 decline.

Patients and Methods

All adult patients transplanted from January 2009 until March 2020 at the University Medical Center Groningen were included. All patients in our lung transplant program have consented to lifelong routine follow-up visits including a pulmonary function test in our center every three months in stable patients, with a higher frequency shorter after transplantation or in unstable patients. Furthermore, patients are strongly encouraged to contact the hospital in case of symptoms suggestive of airway infection or a decline in lung function which is monitored at home on the their personal spirometry device, and is an effective measure to detect early lung function decline in lung transplant recipients.[10]

Standard immunosuppression during the studied period consisted of induction with basiliximab followed by a triple immunosuppressive regimen of tacrolimus (target trough level 7-9 microgram/L), mycophenolate mofetil and prednisolone.

All in hospital measured FEV_1 values were extracted from the clinical records and were included from

the moment patients reached their post-transplant baseline (according to International Society of Heart and Lung Transplantation (ISHLT) criteria)[9] onwards, as from that moment patients are either stable or in the declining phase of FEV_1 after transplantation. Patients for whom baseline could not be determined because lung function was still improving early after lung transplantation were excluded. All FEV_1 values from patients infected with SARS-CoV-2 were excluded beyond two weeks prior to the positive test and onward. These patients were excluded since the goal of this study was not primarily to investigate the total impact of the pandemic in and of itself (including social distancing measures and impact of COVID-19 as a disease), but to investigate whether the absence of respiratory viruses that normally circulate in the general population would be associated with changes in lung function. To make a more accurate estimation we therefore compared the annual lung function decline during the social distancing year with the years prior only in COVID-19 negative patients.

Potential TDLFs were identified by inspecting individual patient graphs of FEV_1 over time for abrupt and reversible periods of drop in FEV_1 , similar to the concept described by Reddel and colleagues[11] and previously used by Bai and colleagues.[12] Any TDLF was defined as a drop in ≥10% and ≥200ml compared to the average of the four previous values, of which the drops of ≥20% and ≥500ml were sub-classified as severe TDLF.

CLAD staging was characterised by a persistent (>3 months) FEV_1 decline to ≤80% of post-transplant baseline, according to the most recent ISHLT criteria.[9] New-onset CLAD was classified as a new diagnosis of CLAD in a CLAD-naïve patient (i.e. CLAD stage 0 to CLAD stage 1 or higher); progressed CLAD was defined as progression to a higher CLAD stage in a patient with pre-existing CLAD.

As a marker for viral circulation the incidences for the following respiratory virus infections were extracted from the weekly reports on all positive viral PCR tests from the microbiology department of our hospital: influenza virus A/B , respiratory syncytial virus A/B, parainfluenza virus types 1-4, human metapneumo virus, non-SARS-CoV-2 coronaviruses (OC43, 229E, NL63 and HKU1), and rhinovirus. The total weekly counts (hospital wide) of these virus infections were used to define RV circulation. Routine screening of asymptomatic lung transplant recipients for RV infection is not performed but instead a low threshold is used for testing of mildly symptomatic patients. Since we were interested in impact of viruses circulating in the general population on pulmonary function we used the hospital-wide viral incidence rates as a reflection of this circulation, rather than study specific viral samples of symptomatic lung transplant patients.

Since social distancing measures in the Netherlands started in week 12 of 2020 we included a two week washout period (week 14, beginning of April) and subsequently defined all years from April to April (April 2009 up to and including March 2010 classified as year 09-10, etc.).

Statistical analysis

Linear mixed effects models were used to estimate the annual decline in FEV_1, with time being defined relative to April 1st 2020. Separate estimates of annual decline (slopes) were calculated for the pre- social distancing period (2009-2020) and the social distancing year (2020-2021), including random effects to account for individual variation in the slopes. A single intercept with random effect was used. To assess the effect of TDLF rate on annual FEV_1 decline pre- social distancing and during

the social distancing year, patients were divided into two groups using an indicator variable based on the median TDLF rate of 0.17/patient/year. Patients with above median TDLF rate were classified as having frequent TDLFs while patients with lower than median TDLF rate were classified as having infrequent TDLFs. This variable and its interactions with the separate time periods (pre- social distancing and social distancing year) were added to the model. The event rates of new or progressive CLAD, any TDLF and severe TDLF, rejection and death over the years and months were analyzed using binomial generalised linear models both with and without adjustment for RV circulation by incorporating this as covariate. Event rates were calculated by determining the total number of events per month and normalising this number with the number at risk for that period.

To test robustness of results, sensitivity analyses were performed on three additional subsets of data. We separately analyzed a subset of the full cohort (2009-2021) consisting of patients who had additional inclusion criteria of at least two FEV_1 values both before 2020/21 and during 2020/21 as well as at least 180 days follow-up in both time periods. Furthermore, two additional samples consisting of only inclusions since 2014 were tested, one in full and one with the same additional inclusion criteria mentioned above. 2014 was chosen because the introduction of a new and faster antiviral assay in our hospital in that year.

This study was approved by the local ethics committee (METc 2021/390). All patients had provided written informed consent for the anonymised use of their data at the start of the transplantation course.

Results

Patient cohort

In total 479 patients were included, contributing a total of 12,775 FEV_1 values (11,961 values pre-social distancing [median 1027/year] and 814 values during the social distancing year. Main cause of the lower number of FEV1 values during the social distancing year was a lower in-office attendance in April when regular care was limited (median each April 2009-2020: 111 function tests, April 2020: 24 function tests). Characteristics of the included cohort are reported in table 1. Thirty patients were excluded because their baseline could not yet be determined and 25 FEV_1 values of 21 patients were excluded from two weeks prior to SARS-CoV-2 infection until the end of follow-up.
In total 259 patients had data available both pre- social distancing period and during the social distancing period. This sensitivity cohort had similar baseline characteristics as the full cohort (supplementary table S1).

Respiratory virus circulation

Figure 1A depicts a heatmap of the general RV circulation within the total patient population of the hospital over the evaluated years and figure 1B depicts the full breakdown of virus types. Intensity of social distancing measures fluctuated throughout the year and is displayed in the figure 1A. There was a clear reduction in general RV circulation in the year 2020-2021, which was most pronounced in the winter months. Percentage change in total incidence in 2020-2021 compared to the average of the previous four years for the different viruses were: Influenza -99%, non-SARS-CoV-2 coronavirus -80%, respiratory syncytial virus -95%, parainfluenza virus -85%, and human metapneumovirus -94%.

Rhinovirus showed a less pronounced change with -23% and was the most prevalent RV in 2020-2021.

Annual FEV_1 decline

Mean annual change in FEV_1 over all years (2009-2021) for the total cohort was -111 ml (95%CI -130; -94) (a negative estimate indicates FEV_1 decline). Annual change for the total cohort pre- social distancing (2009-2020) was -114 ml (95%CI -133; -94, p<0.001) and was significantly more rapid compared to the social distancing period (2020-2021), p<0.001), during which annual FEV_1 did not change significantly: +5ml (95%CI -38; 48, p=0.82) [Figure 2]. When analyzing the frequent and infrequent TDLF subgroups, both groups showed significantly less FEV_1 decline during social distancing than before social distancing (Figure 2). For a patient with frequent TDLF, mean FEV_1 decline pre- social distancing was -150ml (95%CI -181; -120), which was significantly faster than the decline of a patient with infrequent TDLF of -90ml (95%CI -115; -65) with the difference between groups being statistically significant (p=0.003) (Figure 2). During the social distancing year this difference between the groups was not significant (p=0.568), and both groups showed no significant change in FEV_1 during this period (frequent TDLF: -6ml [95%CI -59; 47] vs. infrequent TDLF: +21ml [95%CI -54; 95]). To assess potential improvements in post-transplant management throughout the years we plotted the year-to-year variation in FEV_1 decline, but found no clear indication of reduction in decline in later years compared to earlier years (supplementary figure S2)

Results were robust across sensitivity cohorts, as described in supplementary figures S3-S4.

Incidence of events

Figure 3A and 3B depict the incidence of any TDLF and severe TDLF per patient as well as RV circulation per month for the time periods 2009-2020 and 2020-2021, respectively. Both any TDLF and severe TDLF followed the same seasonal trend as infections, with a higher incidence in the winter months (Figure 3A). January, February, March, April, November and December showed significantly higher incidence of any TDLF and severe TDLF compared to July. When RV circulation was added as covariate to the model, all these differences in TDLF were less pronounced and most disappeared. After adjustment, only December showed a significantly higher odds for any TDLF (unadjusted OR: 2.62 [1.59; 4.49], p<0.000; adjusted OR: 1.97 [1.14; 3.52], p=0.017) whereas the other months showed no significant difference. For severe TDLF, less pronounced but significant differences remained for January (unadjusted OR: 3.31 [1.72; 6.88], p<0.000; adjusted OR: 2.30 [1.05; 5.31], p=0.043), December (unadjusted OR: 2.86 [1.48; 5.95], p=0.003; adjusted OR: 2.28 [1.12;4.94], p=0.029) and March (unadjusted OR: 3.19 [1.65; 6.63], p<0.001; adjusted OR: 2.35 [1.11; 5.28], p=0.03). Figure 3B depicts the incidence of TDLF for 2020-2021, showing a relative absence of both TDLF and RV circulation compared to 2009-2020.

Figure 4 depicts incidences of any TDLF, severe TDLF and new or progressive CLAD over the years. The social distancing year showed significantly lower incidences of any TDLF (OR 0.53 [0.33; 0.85], p=0.008) and severe TDLF (OR 0.34 [0.16; 0.71, p=0.005). Adjustment for RV circulation again reduced these differences for TDLF frequency, with no significant change remaining for any TDLF (adjusted OR 0.77 [95%CI 0.47; 1.24], p=0.278) and a less pronounced difference for severe TDLF (adjusted OR 0.38 [95%CI 0.17; 0.79], p=0.010). The social distancing year also showed a suggestive, though not significantly lower incidence of new or progressive CLAD (OR 0.53, 95%CI [0.27; 1.02],

p=0.060), with a more pronounced difference for new CLAD (OR 0.36 [0.11; 1.03], p=0.067) compared to progressive CLAD (OR 0.67 [0.27; 1.55], p=0.353, figure S3 A and B). There were no significantly different incidences of rejection episodes (OR 1.11 [0.55;2.29], p=774) or death (OR 1.20 [0.63;2.34], p=0.583) between the social distancing year compared to any other year pre- social distancing (S5 C and D). Absolute numbers of all events per year are available in supplementary table S6.

Discussion

The sharp reduction of respiratory virus (RV) infections after initiation of the social distancing measures in The Netherlands in 2020 provided a unique opportunity to study the impact of these infections on annual decline and temporary drops in lung function, as well as the incidence of Chronic Lung Allograft Dysfunction (CLAD) in lung transplant recipients. Our findings suggest a considerable impact, as the annual FEV_1 stabilised, the frequency of temporary drops in lung function reduced significantly, and a trend towards less CLAD in the lockdown year compared to previous years was seen.

To evaluate if the decrease in decline in lung function was related to the rate of RV circulation we studied the relation between RV circulation and Temporary Drops in Lung Function (TDLF). Our results show that the frequency of TDLFs correlates with the seasonal viral prevalence and therefore that a large portion of variance in TDLF frequency likely is explained by RV circulation. This is in line with the idea that many episodes of sudden pulmonary function decrease are caused by RV infections.[13–15] In pursuance of this, LTR with frequent TDLFs had a faster annual FEV_1 decline, thereby also suggesting a notable attribution for RVs in explaining the annual decline in FEV_1 in LTR.

CLAD is the most important marker of airway damage in LTR and is characterised by sustained and often progressive decline in FEV_1 below 80% of post-transplant baseline.[9] The relation between RV infection and CLAD has been suggested before, and seems especially clear in case of RV infections with more severe presentation.[16–18] By analyzing the temporal relation of circulating RVs with CLAD we hope to have deepened an aspect about the understanding and thinking about CLAD development in lung transplantation.[19] Although we found a trend of lower CLAD incidence in 2020-2021, this was not statistically significant (p=0.06). This may be due to lower statistical power due to the relatively low total number of CLAD events overall, or because CLAD can have multifactorial causes, some of which might not have been altered due to the lockdown period such as gastro-esophageal reflux disease, acute rejection episodes and allo-immunity.[9]

Together, both the seasonal association in the years prior to social distancing and the sharp concurrent reduction of TDLF and CLAD and RV circulation during the social distancing year suggest an important association of RV circulation with lung function decline in LTR. However, they do not prove causality. Ours is the first study to investigate lockdown effects in lung transplant patients. Similar results have been found in studies in asthma and COPD patients, showing reduced incidences of exacerbations during social distancing in the United Kingdom[20,21] and the Netherlands.[22] Accelerated decline in lung function, the hallmark of COPD, which was in the past considered to be a continuous process, has now been shown to be episodic and linked to the occurrence of

exacerbations[23] many of which are induced by RV infection.[13] Two other studies evaluating patients with cystic fibrosis subjected to regular pulmonary function testing also found positive associations of social distancing periods with FEV_1 as well as a lower exacerbation risk during periods with social distancing measures.[24,25]

The incidence of viral infections in our hospital (which has a large regional function) correlated well with the incidence rates from the Dutch nationwide sentinel network of primary care physicians for surveillance of respiratory viruses, thereby suggesting that the incidence in the hospital population correlated with the incidence of symptomatic infections in primary care. Furthermore, the incidence rates in our hospital also correlate with published data from other surveillance systems in both primary care and secondary care across Europe.[3,4,6]

The major strengths in this study reside in the life-long, regular follow-up of all our LTR which enabled us to compile a robust dataset of pulmonary data over a long time period allowing for assessment of dichotomous events, as well as an accurate estimation of TDLF and annual FEV_1 decline. Furthermore, in contrast to other studies evaluating social distancing outcomes, we not only assessed the event rate and FEV_1 decline during social distancing, but also associations of RV circulation over multiple years with these outcomes to be able to more precisely investigate the role of RVs on pulmonary function. Our study also has limitations. While our methods are suitable to quantify change over time of FEV_1, TDLFs and CLAD and investigate associations with RV circulation, they are not sufficient to demonstrate a causal relationship and therefore results should be interpreted with care. Furthermore, while the association of our findings with RV circulation seems clear, there are other factors that might have contributed. Factors that we were not able to incorporate in this study, but that may explain residual variation are air pollution[26] (which shows both a seasonal trend and a sharp drop during social distancing measures),[27] change in self-care routines of patients (including changes in exercise and better disease management due to COVID-19 concerns)[28] and incidence of bacterial airway infections[29]. Also, because in stable patients some outpatient visits were switched to telephone controls, some events may have been missed, especially during April 2020 when the social distancing measures were first implemented and regular care was most reduced. However, since our patients check their lung function with a home spirometer and all patients with abnormal home spirometry or symptoms were seen, the risk of missing a decline in lung function in the lockdown year was minimal. In addition, rates for more severe events such as acute rejection (often first presenting with airway symptoms) and deaths were not altered during 2020-2021 suggesting adequate monitoring of our patients. We therefore believe the number of missed events not to be substantial.

The COVID-19 pandemic has raised great awareness for the effectiveness of social and hygienic measures against most RVs. The positive impact on pulmonary function that this reduction in RV circulation has had, especially in LTR, is increasingly clear and underlines the importance of social hygiene and patient education in patient groups at high-risk for morbidity of RV infection. Simultaneously, the impact of social measures on quality of life must also not be underestimated and considerations must be made which individual strategies can be implemented without disproportionally impacting quality of life.[30,31]

In conclusion, during the social distancing year 2020-2021 the marked reduction in RV circulation coincided with substantially less FEV_1 decline, TDLFs and possibly CLAD. Effect modification by RV

circulation, also outside the social distancing period, demonstrates a greater than previously appreciated role of RV infections in lung transplant recipients.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. No authors were precluded from accessing data in the study and all accept responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Table 1 Characteristics of included patients

	All patients n=479	Infrequent TDLF n=310	Frequent TDLF n=169	*p*
Tx indication, n (%)				
COPD	218 (46)	135 (44)	83 (49)	0.25
Cystic Fibrosis	67 (14)	41 (13)	26 (15)	0.58
Pulmonary fibrosis	108 (23)	75 (24)	33 (20)	0.25
Pulmonary hypertension	47 (10)	33 (11)	14 (8)	0.52
Other	39 (8)	26 (8)	13 (8)	0.86
Sex, female, n (%)	247 (52)	161 (52)	82 (49)	0.50
Bilateral Tx, n (%)	406 (85)	261 (84)	145 (86)	0.69
Age at inclusion, years	54.3 (17)	54.2 (18)	54.3 (15)	0.82
CMV match, n (%)				
D+R+	147 (31)	96 (31)	51 (30)	0.92
D+R-	99 (21)	61 (20)	38 (22)	0.48
D-R+	118 (25)	73 (24)	45 (27)	0.51
D-R-	115 (24)	80 (26)	35 (21)	0.22
Follow-up, years	6.8 (6.3)	6.5 (7.6)	7.2 (5.5)	0.17
n of FEV1 values/patient/year pre-SD year	4.0 (1.5)	4.0 (.50)	4.0 (2.0)	0.56
n of FEV1 values/patient/year SD year	3.0 (2.0)	3.0 (2.0)	3.5 (1.5)	0.22
Donor age, years	48.5 (20)	48.5 (20)	50.0 (20)	0.67
Donor type DBD, n (%)	361 (75)	234 (76)	127 (75)	0.82

TDLF: temporary drop in lung function, CMV: cytomegalovirus, D: donor, R: recipient, SD: social distancing, Tx: transplantation, IQR: interquartile range, DBD: donation after brain, COPD: chronic obstructive pulmonary disease. Continuous variables are presented as median (interquartile range). p-value is from the comparison of infrequent (< 0.17 /yr) TDLF group with frequent TDLF group (≥0.17/yr).

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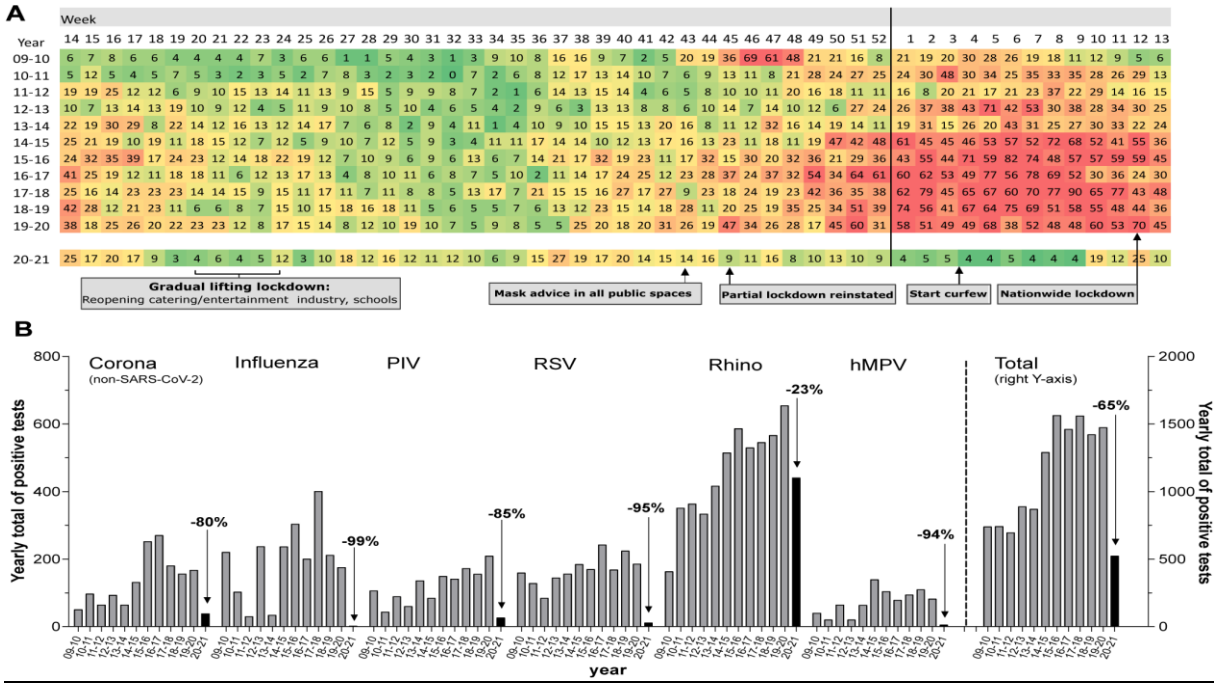
A
Week
Year
14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 1 2 3 4 5 6 7 8 9 10 11 12 13
09-10 6 7 8 6 6 4 4 4 4 7 3 6 6 1 1 5 4 3 1 3 9 10 8 16 16 9 7 2 5 20 19 36 69 61 48 21 21 16 8 21 19 20 30 28 26 19 18 11 12 9 5 6
10-11 5 12 5 4 5 7 5 3 2 3 5 2 7 8 3 2 3 2 0 7 2 6 8 12 17 13 14 10 7 6 9 13 11 8 21 28 24 27 25 24 30 48 30 34 25 35 33 35 28 26 29 13
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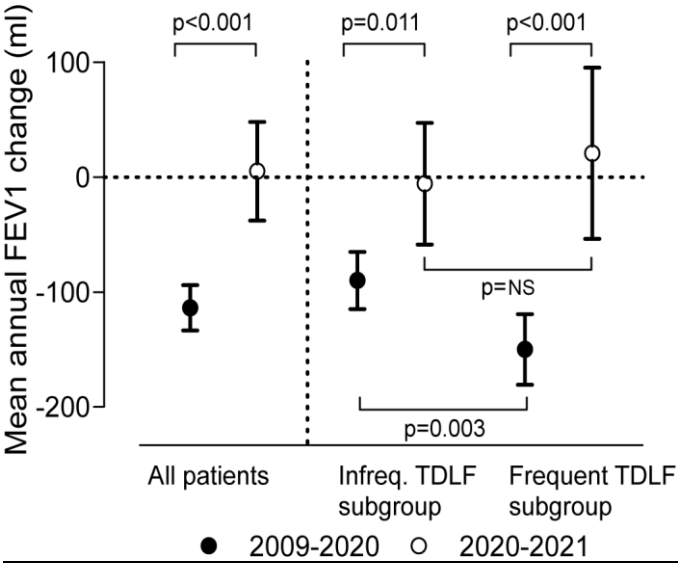
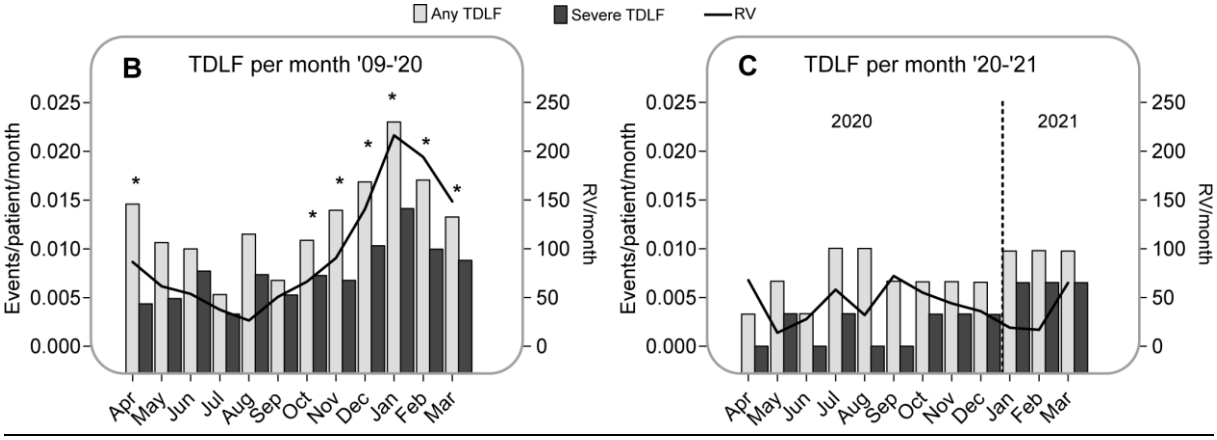
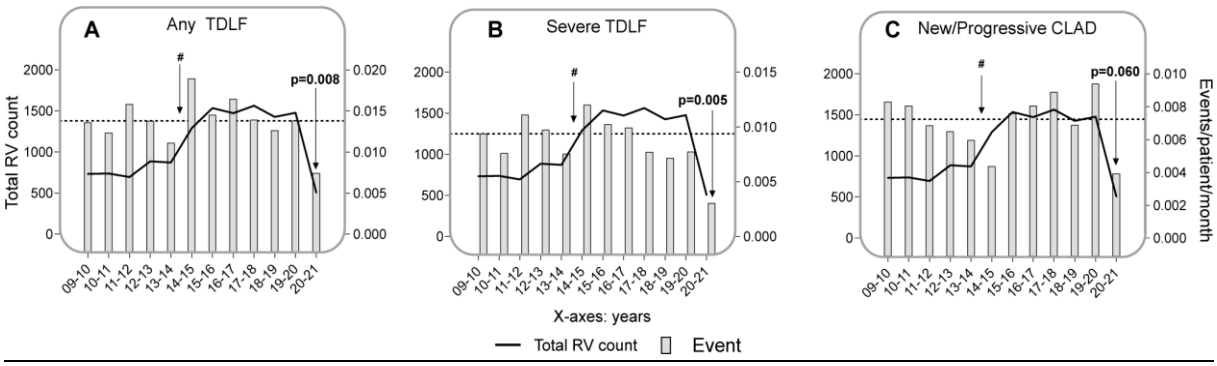
19-20 38 18 25 26 20 22 23 23 12 8 17 15 14 8 12 10 19 10 7 5 9 8 5 5 25 20 18 20 31 26 19 47 34 26 28 17 45 60 31 58 51 49 49 68 38 52 48 48 60 53 70 45
20-21 25 17 20 17 9 3 4 6 4 5 12 3 10 18 12 16 12 11 12 10 6 9 15 27 19 17 20 14 15 14 16 9 11 16 8 10 13 10 9 4 5 5 4 4 5 4 4 4 19 12 25 10
Gradual lifting lockdown:
Reopening catering/entertainment industry, schools
Mask advice in all public spaces
Partial lockdown reinstated
Start curfew
Nationwide lockdown
B
Corona
(non-SARS-CoV-2)
Influenza
PIV
RSV
Rhino
hMPV
Total
(right Y-axis)
-80%
-99%
-85%
-95%
-23%
-94%
-65%
Yearly total of positive tests
Yearly total of positive tests
year


p<0.001
p=0.011
p<0.001
Mean annual FEV1 change (ml)
100
0
-100
-200
p=NS
p=0.003
All patients
Infreq. TDLF subgroup
Frequent TDLF subgroup
2009-2020
2020-2021


Any TDLF
Severe TDLF
RV
B
TDLF per month '09-'20
C
TDLF per month '20-'21
2020
2021
Events/patient/month
RV/month
0.025
0.020
0.015
0.010
0.005
0.000
250
200
150
100
50
0
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Jan
Feb
Mar


A
Any TDLF
B
Severe TDLF
C
New/Progressive CLAD
#
p=0.008
p=0.005
p=0.060
Total RV count
Events/patient/month
0
500
1000
1500
2000
0.000
0.005
0.010
0.015
0.020
0.002
0.004
0.006
0.008
09-10
10-11
11-12
12-13
13-14
14-15
15-16
16-17
17-18
18-19
19-20
20-21
X-axes: years
Total RV count
Event

Supplementary material

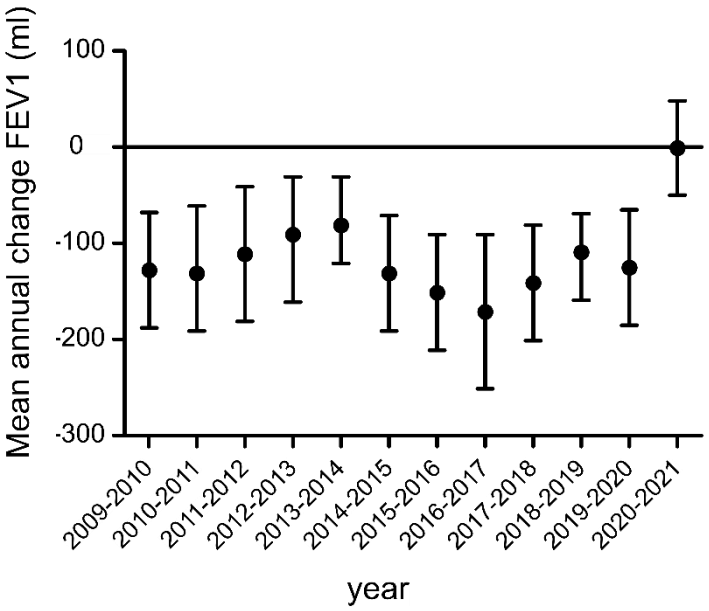
Supplementary table S1

Characteristics of patient with only FEV1 values both pre-and post-lockdown

	All patients	Infrequent TDLF	Frequent TDLF	*p*
	n=259	n=176	n=83	
Tx indication, n (%)				
COPD	118 (46)	79 (45)	39 (47)	0.79
Cystic Fibrosis	39 (15)	26 (15)	13 (16)	0.85
Pulmonary fibrosis	54 (21)	40 (22)	14 (17)	0.33
Pulmonary hypertension	25 (10)	17 (10)	8 (10)	1.00
Other	23 (9)	14 (8)	9 (11)	0.49
Sex, female, n (%)	133 (51)	92 (52)	41 (49)	0.69
Bilateral Tx, n (%)	231 (89)	157 (89)	74 (89)	1.00
Age at inclusion, years	54.4 (15)	54.3 (16)	54.5 (12)	0.97
CMV match, n (%)				
D+R+	74 (29)	52 (30)	22 (27)	0.66
D+R-	60 (23)	40 (23)	20 (24)	0.87
D-R+	65 (25)	40 (23)	25 (30)	0.22
D-R-	60 (23)	44 (25)	16 (19)	0.35
Follow-up, years	7.3 (7.2)	7.0 (7.6)	7.6 (6.5)	0.15
n of FEV1 values/patient/year pre-SD	4.0 (2.0)	4.0 (.50)	4.0 (2.5)	0.54
n of FEV1 values/patient/year during SD	3.0 (2.0)	3.0 (2.0)	3.0 (1.5)	0.74
Donor age, years	49.0 (20)	48.0 (19)	50.0 (18)	0.71
Donor type DBD, n (%)	179 (69)	123 (70)	56 (68)	0.82

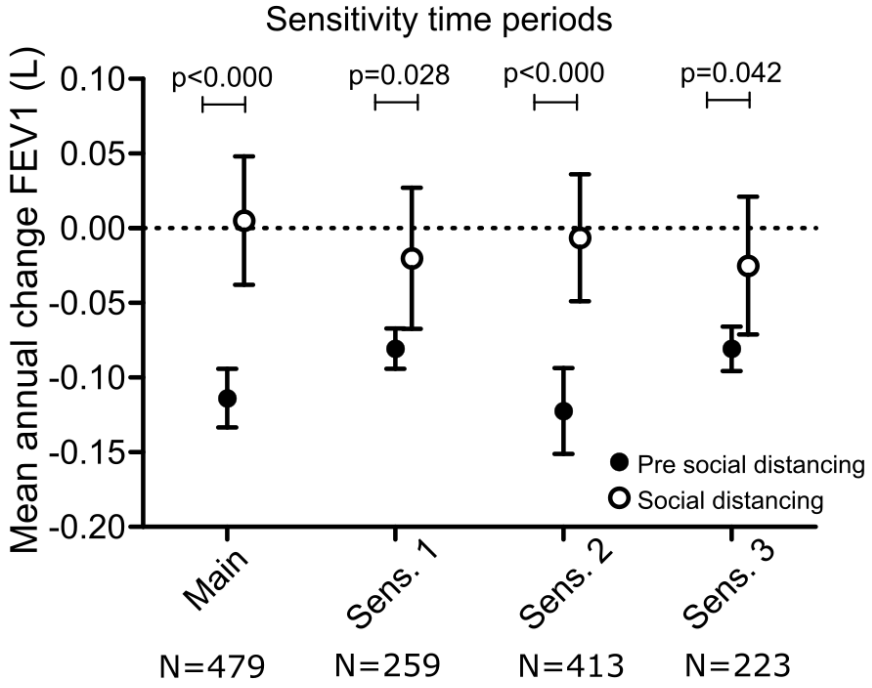
TDLF: temporary drop in lung function, CMV: cytomegalovirus, D: donor, R: recipient, SD: social distancing measures, Tx: transplantation, IQR: interquartile range, DBD: donation after brain, COPD: chronic obstructive pulmonary disease. Continuous variables are presented as median (interquartile range). p-value is from the comparison of infrequent (< 0.17 /yr) TDLF group with frequent TDLF group (≥0.17/yr).

Supplementary figure S2:
Mean annual FEV1 change reported per year
Symbols indicate point estimate with 95% confidence intervals.



S3. Sensitivity analyses of difference in mean annual FEV_1 decline between pre social distancing and during social distancing periods.

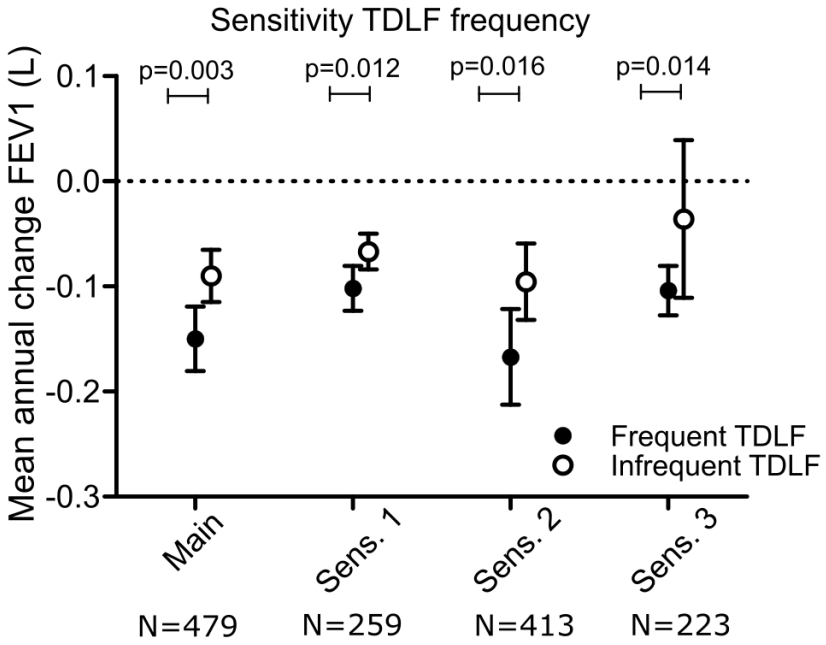
Same analysis performed on main cohort and three sensitivity cohorts. Symbols indicate point estimate with 95% confidence intervals.



Definition of main cohort and sensitivity cohorts:
Main: full cohort from 2009-2021
Sens. 1: cohort 2009-2021 and at least two FEV_1 values both before 2020/21 and during 2020/21 as well as at least 180 days follow-up in both time periods.
Sens. 2: full cohort from 2014-2021.
Sens. 3: cohort 2014-2021 and at least two FEV_1 values both before 2020/21 and during 2020/21 as well as at least 180 days follow-up in both time periods.

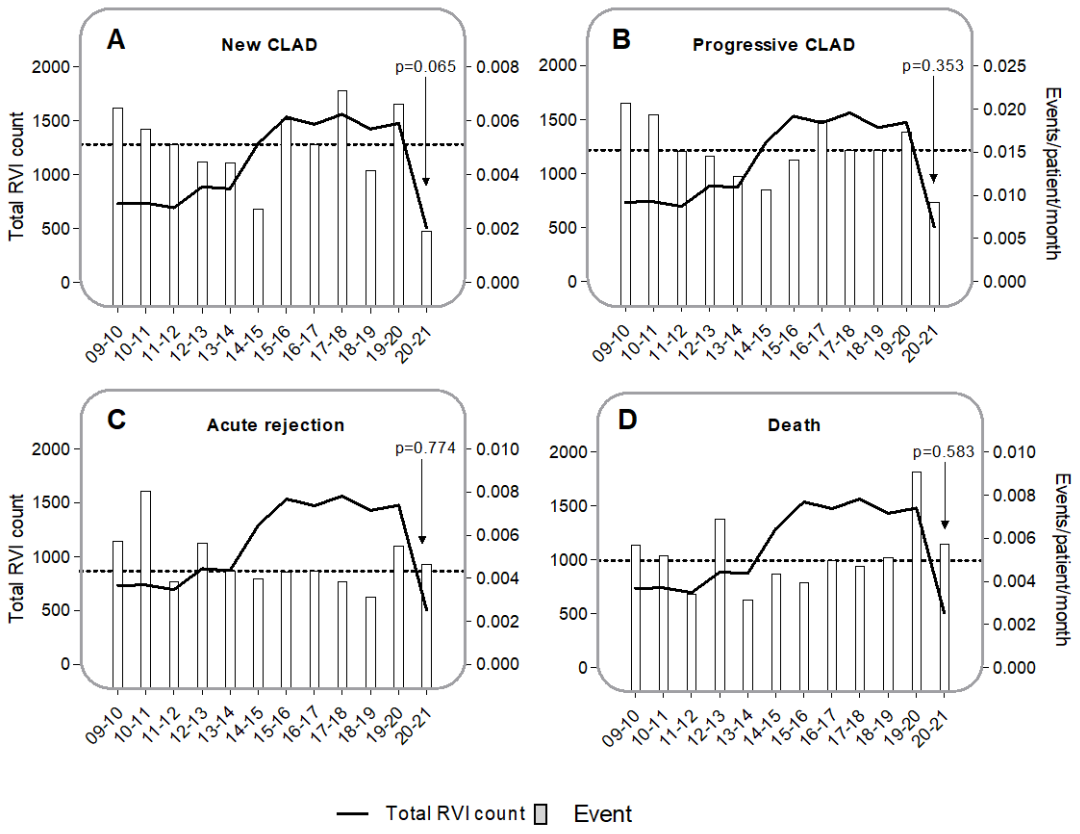
S4. Sensitivity analyses of effect of TDLF frequency (two groups: frequent TDLF and infrequent TDLF) on mean annual FEV_1 change.

Same analysis performed on main cohort and three sensitivity cohorts. Symbols indicate point estimate with 95% confidence intervals. TDLF: temporary decline in lung function



Definition of main cohort and sensitivity cohorts:
Main: full cohort from 2009-2021
Sens. 1: cohort 2009-2021 and at least two FEV_1 values both before 2020/21 and during 2020/21 as well as at least 180 days follow-up in both time periods.
Sens. 2: full cohort from 2014-2021.
Sens. 3: cohort 2014-2021 and at least two FEV_1 values both before 2020/21 and during 2020/21 as well as at least 180 days follow-up in both time periods.

S5. Event rates of new CLAD, progressive CLAD, acute rejection and death events over the years.



RVI: Respiratory Virus infection, CLAD: Chronic Allograft Dysfunction. X-axes represent the years, left Y-axes represent total RV infection count (solid line), right Y-axes represent event rates for the specific event (grey bars), dotted line represents the median of the event rates. P-values are from comparison of 2020-2021 with the median using binomial generalised linear models, unadjusted for RVI.

Supplementary table S6

Numbers at risk and absolute numbers of events per year for all events

		Event				New CLAD		Progressive CLAD		New or progressive CLAD	
year	n at risk	Any TDLF	Severe TDLF	Death	Rejection	n at risk	New CLAD	n at risk	Progressive CLAD	n at risk	New or progressive CLAD
2009-2010	160	26	18	11	11	141	11	20	5	161	16
2010-2011	176	26	16	11	17	146	10	30	7	176	17
2011-2012	195	37	26	8	9	162	10	33	6	195	16
2012-2013	206	34	24	17	14	166	9	40	7	206	16
2013-2014	210	28	19	8	11	169	9	41	6	210	15
2014-2015	229	52	33	12	11	182	6	47	6	229	12
2015-2016	253	44	31	12	13	206	15	47	8	253	23
2016-2017	269	53	32	16	14	211	13	58	13	269	26
2017-2018	282	47	26	16	13	222	19	60	11	282	30
2018-2019	291	44	25	18	11	220	11	71	13	291	24
2019-2020	302	50	28	33	20	225	18	77	16	302	34
2020-2021	303	27	11	21	17	217	5	81	9	298	14