OPEN

Reduced Community-acquired Respiratory Virus Infection, but Not Non–virus Infection, in Lung Transplant Recipients During Government-mandated Public Health Measures to Reduce COVID-19 Transmission

Brian C. Keller, MD, PhD,[1] Jianing Ma, MS,[2] Jing Peng, PhD,[2] and Verai Ramsammy, MD[3]

Background. Community-acquired respiratory viruses (CARVs) are an important cause of morbidity and mortality in lung transplant (LTx) recipients. Despite routine mask-wearing, LTx patients remain at a higher risk of CARV infection than the general population. In 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19 and a novel CARV, emerged leading federal and state officials to implement public health nonpharmaceutical interventions (NPIs) to curb its spread. We hypothesized that NPI would be associated with the reduced spread of traditional CARVs.
Methods. A single-center, retrospective cohort analysis comparing CARV infection before a statewide stay-at-home order, during the stay-at-home order and subsequent statewide mask mandate, and during 5 mo following the elimination of NPI was performed. All LTx recipients followed by and tested at our center were included. Data (multiplex respiratory viral panels; SARS-CoV-2 reverse transcription polymerase chain reaction; blood cytomegalovirus and Epstein Barr virus polymerase chain reaction; blood and bronchoalveolar lavage bacterial and fungal cultures) were collected from the medical record. Chi-square or Fisher exact tests were utilized for categorical variables. A mixed-effect model was used for continuous variables. **Results.** Incidence of non-COVID CARV infection was significantly lower during the MASK period than during the PRE period. No difference was noted in airway or bloodstream bacterial or fungal infections, but cytomegalovirus bloodborne viral infections increased. **Conclusions.** Reductions in respiratory viral infections, but not bloodborne viral infections nor nonviral respiratory, bloodborne, or urinary infections, were observed in the setting of public health COVID-19 mitigation strategies, suggesting the effectiveness of NPI in preventing general respiratory virus transmission.

(Transplantation Direct 2023;9: e1445; doi: 10.1097/TXD.0000000000001445.)

Lung transplantation is a recognized treatment for end-stage lung disease, but outcomes are limited by the development of chronic lung allograft dysfunction, of which bronchiolitis obliterans syndrome is the most common form of chronic rejection. Community-acquired viral (CARV) infections have been linked to bronchiolitis obliterans syndrome development and worse outcomes following lung transplantation.[1] Lung transplant recipients remain at higher risk of CARV infection than the general population despite routine masking in public and hand hygiene, practices

Received 8 December 2022.

Accepted 26 December 2022.

[1] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Massachusetts General Hospital, Boston, MA.

[2] Center for Biostatistics, The Ohio State University College of Medicine, Columbus, OH.

[3] Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, OH.

B.C.K. is a consultant for CareDx and Zambon and has received research funding from CareDx and Natera. The other authors declare no conflicts of interest.

ORCID

B.C.K.: 0000-0003-2997-6712

J.M.: 0000-0001-7777-9014

J.P.: 0000-0002-8835-4545

The dataset generated and analyzed for this study is not publicly available because of patient confidentiality and privacy protections but may be available in de-identified form from the corresponding author on reasonable request.

B.C.K. conceived and supervised the study, collected and analyzed data, and wrote and revised the article. J.M. analyzed the data and wrote and revised the article. J.P. analyzed the data and revised the article. V.R. collected and analyzed data and wrote the manuscript. All authors approved the final article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Brian C. Keller, MD, PhD, Lung Transplant Program, Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, 55 Fruit St, Bulfinch 148, Boston, MA 02114. (bckeller@mgh.harvard.edu).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001445

encouraged by our and other programs. Current guidelines recommend avoiding others with respiratory illnesses; avoiding crowded areas, especially during viral epidemics; and using masks when avoidance is not feasible.[2] Before COVID-19 and in the setting of these precautions, the yearly incidence of symptomatic CARV infections in lung transplant recipients was reported as 5% to 8%.[1,3] There is a paucity of data on the incidence of non–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) CARVs in the lung transplant population during the COVID-19 pandemic.

In 2019, SARS-CoV-2, a novel CARV and the causative agent of COVID-19, emerged, leading to one of the largest viral pandemics in the last 100 y with >596 000 000 cases as of August 23, 2022.[4] Because of the morbidity and mortality of SARS-CoV-2, public health mandates were instituted to reduce virus transmission. In the United States in the state of Ohio, Governor Mike DeWine instituted a stay-at-home policy from March 23, 2020, to May 1, 2020, followed by a gradual reopening of businesses and schools. On July 23, 2020, a state of Ohio mask mandate was implemented that lasted until June 2, 2021.[5,6]

Lung transplant recipients at our institution are routinely tested for viral, bacterial, and fungal pathogens at the time of transplant and serially during the first posttransplant year with additional testing employed when clinically indicated. This protocol provides a unique opportunity to evaluate the community spread of CARVs and other infections in this closely monitored population. We hypothesized that public health nonpharmaceutical interventions (NPIs) instituted to limit the spread of COVID-19 would be associated with the reduced spread of traditional CARVs, as well as respiratory bacterial infections. In contrast, we hypothesized that NPI measures would not be associated with changes in nonrespiratory bacterial, fungal, or viral infections.

MATERIALS AND METHODS

Cohort Information and Data Collection

We conducted a retrospective cohort analysis of CARV infection during the 2 y before implementation of the Ohio stay-at-home order ("PRE," March 23, 2018–March 22, 2020), during the stay-at-home order and subsequent statewide mask mandate ("MASK," March 23, 2020–June 2, 2021), and in the 5 mo after the expiration of the order ("POST," June 3, 2021–November 11, 2021). Participants included all adult lung transplant recipients followed by The Ohio State University Wexner Medical Center. Data collected from the medical record included 33 399 results, including all multiplex respiratory viral panels (RVPs); SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR); bronchoalveolar lavage (BAL) bacterial, acid-fast, and fungal cultures; BAL *Aspergillus* antigen tests; BAL cell differentials; and donor and recipient bronchial brush cultures (bacteria and fungi). Results from nonairway blood bacterial cultures, blood cytomegalovirus (CMV) and Epstein Barr virus (EBV) polymerase chain reaction (PCR), and urine cultures were included as controls. RVP tests utilized by our institution were updated over time with tests used at the beginning of the study including the following pathogens: coronavirus (CoV) 229E, CoV HKU1, CoV NL63, CoV OC43, influenza A, influenza B, metapneumovirus (MPV), parainfluenza (PIV) 1, PIV2, PIV3, PIV4, respiratory syncytial virus (includes serotypes A and B), and rhinovirus/enterovirus (RV). Updated RVP tests contained all viral pathogens in earlier RVP versions plus the following: adenovirus (AdV), *Bordetella pertussis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* (added August 2018), and SARS-CoV-2 (added August 2021). This study was deemed exempt by the institutional review board.

Indications for Testing

Bacterial and fungal donor and recipient bronchial brush cultures were collected at the time of transplantation from donor lungs before implantation and from recipient explanted lungs. All subjects underwent protocolized surveillance bronchoscopy with BAL in the first week after transplant and then at 1, 3, 6, 9, and 12 mo posttransplant, which accounted for the majority of the BAL samples analyzed. BAL was tested for multiplex RVP; bacterial, acid-fast, and fungal culture; *Aspergillus* antigen; and BAL cell differential testing. Multiplex RVP testing of nasopharyngeal swabs was only performed for cause and represented <20% of all multiplex RVPs tested. SARS-CoV-2 RT-PCR testing of nasopharyngeal samples was performed for clearance before procedures (lung transplant surgery, bronchoscopy) and for cause. Blood CMV and EBV PCR tests were performed as part of routine surveillance protocols and for cause in a small minority of cases. Blood bacterial and fungal cultures and urine cultures were performed for cause only.

Calculation of Incidence Rate and Statistical Analyses

Cumulative incidence was calculated by dividing the number of positive tests in a cohort by the total number of tests performed. The incidence rate was calculated by dividing cumulative incidence by the number of days in each cohort and multiplying by 100 000 to get the rate per 100 000 test-days. Microbiological and clinical tests for viral, bacterial, and fungal pathogens were compared (PRE versus MASK; MASK versus POST; PRE versus POST) using chi-square or Fisher exact tests, as appropriate, for categorical variables. A mixed-effect model was used for continuous variables. $P < 0.05$ was considered statistically significant. Statistical analysis was performed with RStudio (v. 2022).

RESULTS

Non-COVID Respiratory Virus Infection

A total of 1190 multiplex RVPs and 892 SARS-CoV-2 RT-PCR tests from 193 lung transplant recipients were included in the analysis (Table 1). We first evaluated the cumulative incidence of a positive non-COVID respiratory virus test during the 2-y period before the implementation of NPI strategies (PRE, 730 d in cohort) compared with the period of state-imposed stay-at-home and mask mandates (MASK, 436 d in cohort). We found higher non-COVID RVP positivity in the PRE cohort than in the MASK cohort (0.169 versus 0.062, $P = 1.28E-07$). This relationship held true when incidence was normalized to the number of days in each cohort (incidence rate, Figure 1A; PRE, 23.1 versus MASK, 14.3 positive tests per 100 000 test-days). For all individual viruses except RV, we observed lower incidence rates in the MASK cohort than in the PRE cohort, with respiratory syncytial virus and PIV3 reaching statistical significance (Figure 1B–L).

TABLE 1.

Numbers of subjects and individual test results analyzed by cohort period

	PRE	MASK	POST	Cumulative
Subjects	101	165	111	193
Respiratory viral panel				
Adenovirus	457	546	154	1157
Coronavirus 229E	490	546	154	1190
Coronavirus HKU1	490	546	154	1190
Coronavirus NL63	490	546	154	1190
Coronavirus OC43	490	546	154	1190
Human metapneumovirus	490	546	154	1190
Influenza A	1089	549	154	1792
Influenza B	498	549	154	1201
Parainfluenza virus 1	490	546	154	1190
Parainfluenza virus 2	490	546	154	1190
Parainfluenza virus 3	490	546	154	1190
Parainfluenza virus 4	490	546	154	1190
Respiratory syncytial virus	531	549	154	1234
Rhinovirus	490	546	154	1190
SARS-CoV-2	0	8	51	59
SARS-CoV-2 RT-PCR	4	751	137	892
Bronchoalveolar lavage				
Acid-fast culture	684	711	151	1546
Bacteria culture	933	1033	255	2221
CMV PCR	118	188	58	364
Fungi culture	634	678	146	1458
Aspergillus antigen	408	313	108	829
Bronchial brush				
Bacteria, donor culture	151	173	9	333
Bacteria, recipient culture	293	110	15	418
Fungi, donor culture	59	112	8	179
Fungi, recipient culture	245	100	14	359
Blood				
Bacteria culture	638	599	162	1399
CMV PCR	1404	2178	1033	4615
EBV PCR	174	613	281	1068
Urine culture	176	165	34	375

The total number of respiratory viral panels performed was 1190 with the breakdown of specific viruses in the panels listed above. In August 2018, adenovirus was added to the hospital's respiratory viral panel, and SARS-CoV-2 was added in August 2021, hence the lower cumulative adenovirus and SARS-CoV-2 test numbers. On the other hand, early forms of the respiratory virus panels included multiple tests for influenza A (eg, H1N1, H5N1), influenza B, and respiratory syncytial virus (eg, types A and B). For each of these viruses, results were condensed into a single positive or negative test for influenza A, influenza B, or respiratory syncytial virus, respectively, for analysis.

CMV, cytomegalovirus; EBV, Epstein Barr virus; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

We next investigated whether the expiration of the public health mitigation strategies was associated with changes in the cumulative incidence of non-COVID CARV infections. Compared with the MASK cohort, the POST cohort (161 d in cohort) demonstrated a rebound in CARV incidence rate (Figure 1A; MASK, 14.3 versus POST, 33.6 positive tests per 100 000 test-days), but the difference in CARV cumulative incidence did not reach statistical significance (0.062 versus 0.054, MASK versus POST, respectively, $P = 0.86$). On an individual virus level, POST cohort incidence rates were significantly increased for PIV3 (12.6 versus 0.0 positive tests per 100 000 test-days, $P = 0.01$) with increasing trends for CoV-OC43 and RV. Individual positive CARV tests are plotted as a function of time in Figure 2.

SARS-CoV-2 Infection

Because of the nature of the pandemic, SARS-CoV-2 prevalence in the Ohio general population increased throughout the MASK cohort, with daily average cases peaking for the study period on December 12, 2020 (Figure 2). A second, smaller peak in average daily cases occurred on September 16, 2021, during the SARS-CoV-2 Delta variant.[8] Despite this trend in the general population, we observed trends in the incidence rate of SARS-CoV-2 to be comparable to non-COVID viruses among the 3 cohorts (Figure 1M), although we note that the PRE cohort only included 2 SARS-CoV-2 tests, one of which was positive. SARS-CoV-2 RT-PCR tests were performed as part of a new version RVP test or as a standalone RT-PCR test on nasopharyngeal or BAL samples.

To consider the effect of testing frequency on the cumulative incidence of SARS-CoV-2 and non-COVID viruses, we conducted a mixed-effect logistic regression model using cohort as a fixed effect and subjects as random effects. MASK was used as the reference group. Because of the large amount of 0 positive cases in MASK and POST cohorts for most non-COVID viruses, the model can be only performed for rhinovirus and SARS-CoV-2 with nonzero positive tests in all 3 cohorts. Compared with patients in the MASK cohort,

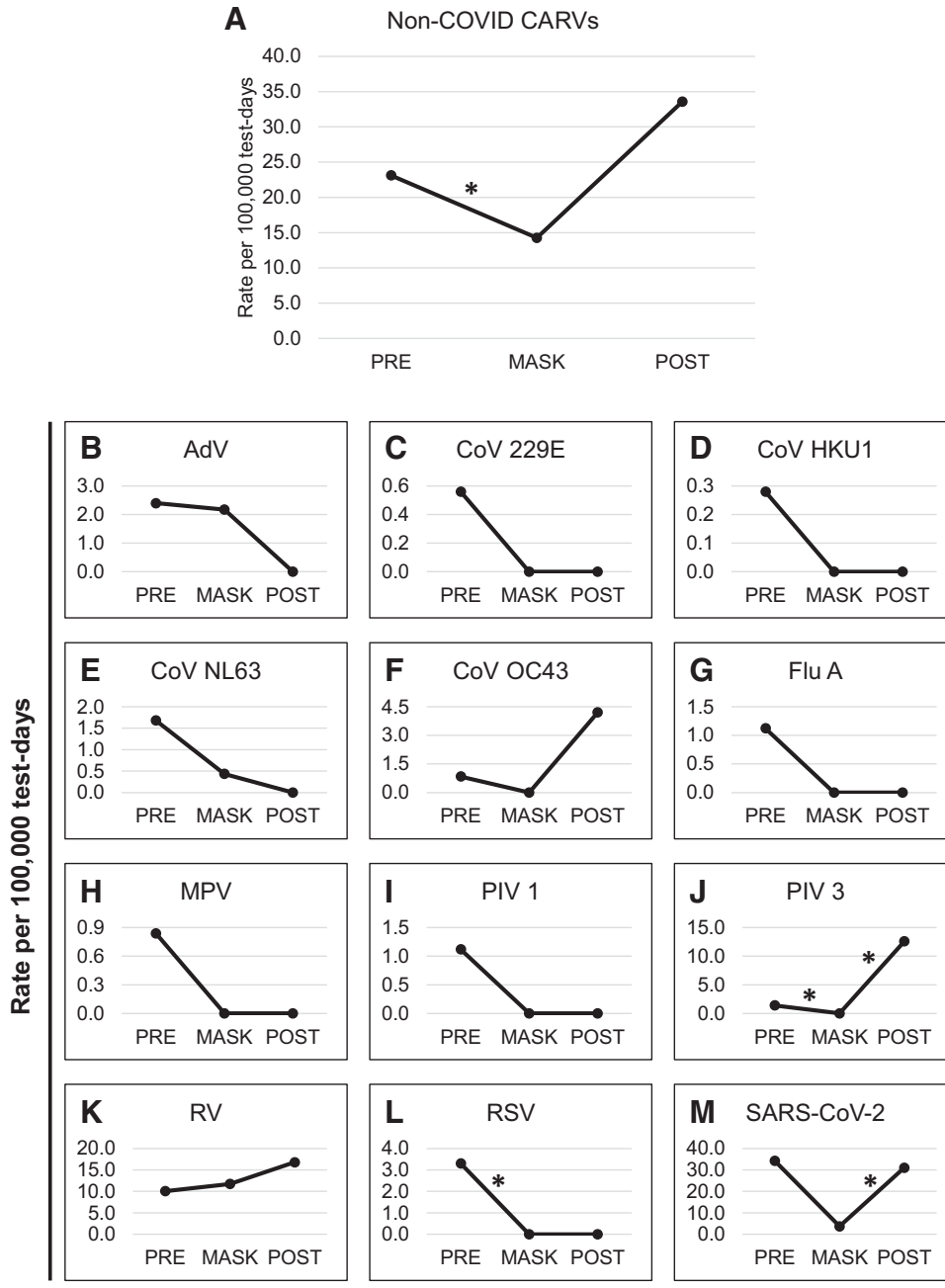

FIGURE 1. CARV incidence rates across time periods. Incidence rates for (A) all non-COVID CARV and (B–M) individual CARV positive tests in the period prior to nonpharmaceutical intervention (PRE), during nonpharmaceutical intervention measures (MASK), and following expiration of government-mandated nonpharmaceutical intervention measures (POST). Rates are plotted per 100 000 test-days. *$P < 0.05$. AdV, adenovirus; CARV, community-acquired respiratory virus; CoV, coronavirus; COVID, coronavirus disease; MPV, metapneumovirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus; RV, rhinovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

subjects in the PRE cohort were 2.171 (1.044–4.515) times more likely to have a positive test ($P = 0.038$) for rhinovirus. For SARS-COV-2, compared with patients in the MASK cohort, subjects in the POST cohort were 19.41 (3.59–105.02) times more likely to have a positive test ($P = 0.001$) (**Table S1, SDC**, http://links.lww.com/TXD/A501). These results suggest that testing frequency was not responsible for the differences in positive tests between cohorts.

Non-CARV Airway Infection

We next analyzed the cumulative incidence of positive cultures or PCR tests for a variety of pathogens for which our lung transplant population is routinely tested. In contrast to CARV infections, we found no difference in the incidence of respiratory bacterial, fungal, or acid-fast bacteria infections as determined by BAL culture or of BAL CMV PCR across cohorts (Figure 3A–D). Bronchial brush cultures are collected at the time of transplant from the donor lung's large airways and the explanted recipient lung's large airways. No difference in the incidence of positive fungal bronchial brush cultures was identified from patients undergoing lung transplantation during the study period (Figure 3G and H), whereas there was an increase in positive donor bronchial brush bacterial cultures in the MASK cohort (Figure 3E).

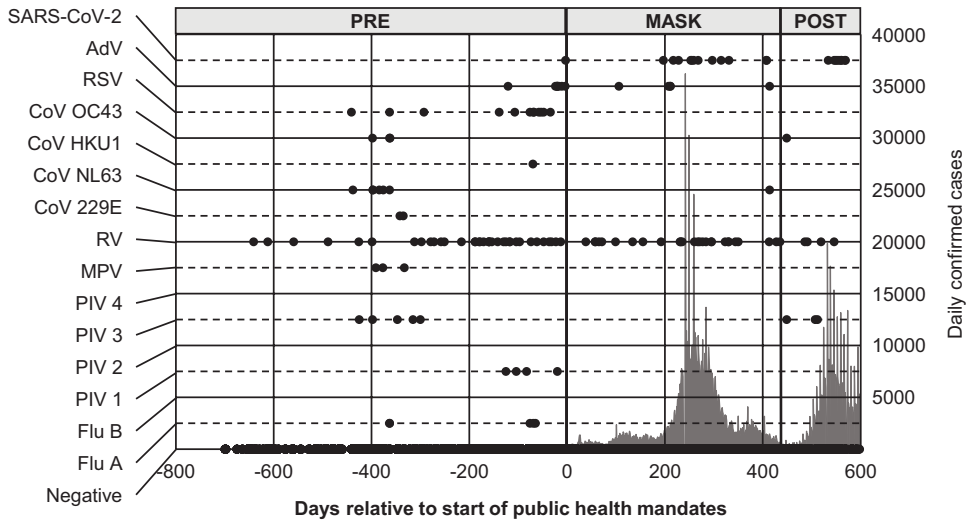

FIGURE 2. Timeline of virus positivity. Results of all respiratory virus panel or virus-specific polymerase chain reaction tests are plotted with time relative to the start of the MASK period on the x-axis. Individual viruses are labeled on the y-axis, and each dot represents an individual test. Underlaid behind the virus plot is a line plot of daily confirmed coronavirus disease 2019 cases (reported on right y-axis) as reported by the Ohio Department of Health and aggregated by USAFacts.[7] AdV, adenovirus; CoV, coronavirus; MPV, metapneumovirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus; RV, rhinovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Nonairway Infection

We hypothesized that NPI would impact CARV infections significantly compared with other types of infections, such as bloodborne or urinary tract infections. Accordingly, we found no difference in the positivity of blood bacterial cultures (Figure 3I) and EBV PCR tests (Figure 3K), but blood CMV PCR cumulative incidence increased between PRE and MASK cohorts and again between MASK and POST cohorts (Figure 3J). Urine cultures positivity was unchanged across cohorts (Figure 3L). Of the non-CARV tests, only the *Aspergillus* antigen test results demonstrated lower cumulative incidence in the MASK cohort than in the PRE cohort (0.030 versus 0.106, P = 1.18E-04, Figure 4A) with a trend toward a rebound in the POST cohort, particularly as evidenced by the trending incidence rate (Figure 4B). Overall, there were steady but not uniformly significant trends toward increased incidence across the study period for all non-CARV cultures and PCR tests except *Aspergillus* antigen, which mirrored the pattern observed with CARVs. Lastly, we evaluated the cellular composition of BAL in each of the cohorts and found no difference in the numbers of BAL neutrophils, macrophages, lymphocytes, or eosinophils across the study period (linear mixed model; P = 0.900, PRE versus MASK; P = 0.211, MASK versus POST, data not shown).

DISCUSSION

In this study, we evaluated the impact of government-mandated COVID-19 NPI mitigation measures on the incidence of CARV, bacterial, fungal, and other viral infections in a closely monitored, immunocompromised population of lung transplant recipients. We found that CARV infections were significantly reduced in the setting of NPI and that, following the cessation of these public health measures, CARV infection rates once again increased. We observed this pattern for nearly all CARVs, including SARS-CoV-2. The singular exception was RV, a finding consistent with previous studies.[9-11] Although it is difficult to definitively know why RV exhibited a pattern different than other CARVs, we hypothesize this may be due to factors such as the smaller virion size (~30 nm) of RV, the extremely large number of RV serotypes, and differences in seasonal and epidemiologic transmission of RV compared with other CARVs.[12]

It is possible that the introduction of a dominant CARV, in this case SARS-CoV-2, into a vulnerable population could lead to a reduction in the prevalence of other CARVs, but not all CARVs in our study showed the same effect. In fact, RV demonstrated a trend for increased incidence in the MASK and POST cohorts compared with the PRE cohort (Figure 1K). Based on our findings, we interpret the data to indicate that NPI, including mask mandates and stay-at-home orders, were indeed effective at reducing common CARV and SARS-CoV-2 transmission in our immunocompromised cohort.

Although other studies have similarly found reductions in non-COVID CARVs in the setting of NPI to mitigate SARS-CoV-2 spread,[9-11] to our knowledge, this study is the first to evaluate the impact of NPI on non-CARV respiratory, bloodborne, and urinary tract infections. Lung transplant recipients are closely monitored for a variety of infections given their immunocompromised state, thus providing a unique population with which to study the effect of COVID-19 NPI on these other infection types. In contrast to CARV infections, we observed no decrease in the incidence of bacterial, fungal, and bloodborne viral infections during the period of NPI. In fact, there were trends in each of these categories toward an increase in the incidence of infection from PRE to MASK to POST, reaching statistical significance for CMV DNAemia and donor bronchial brush bacterial cultures. The reasons for trends in increased rates of non-CARV infections are not clear. Regarding the non-CARV airway infections, one hypothesis is that these infections may be the result of increased translocation of bacteria and fungi from the upper airways to the lungs. Whether this translocation might occur at higher frequencies in the setting of NPI measures is unknown because the literature to date has evaluated the effects of NPI and masking on the transmission of microbial pathogens between people. The effects of masking and NPI measures on a person's oropharyngeal microbiome and the

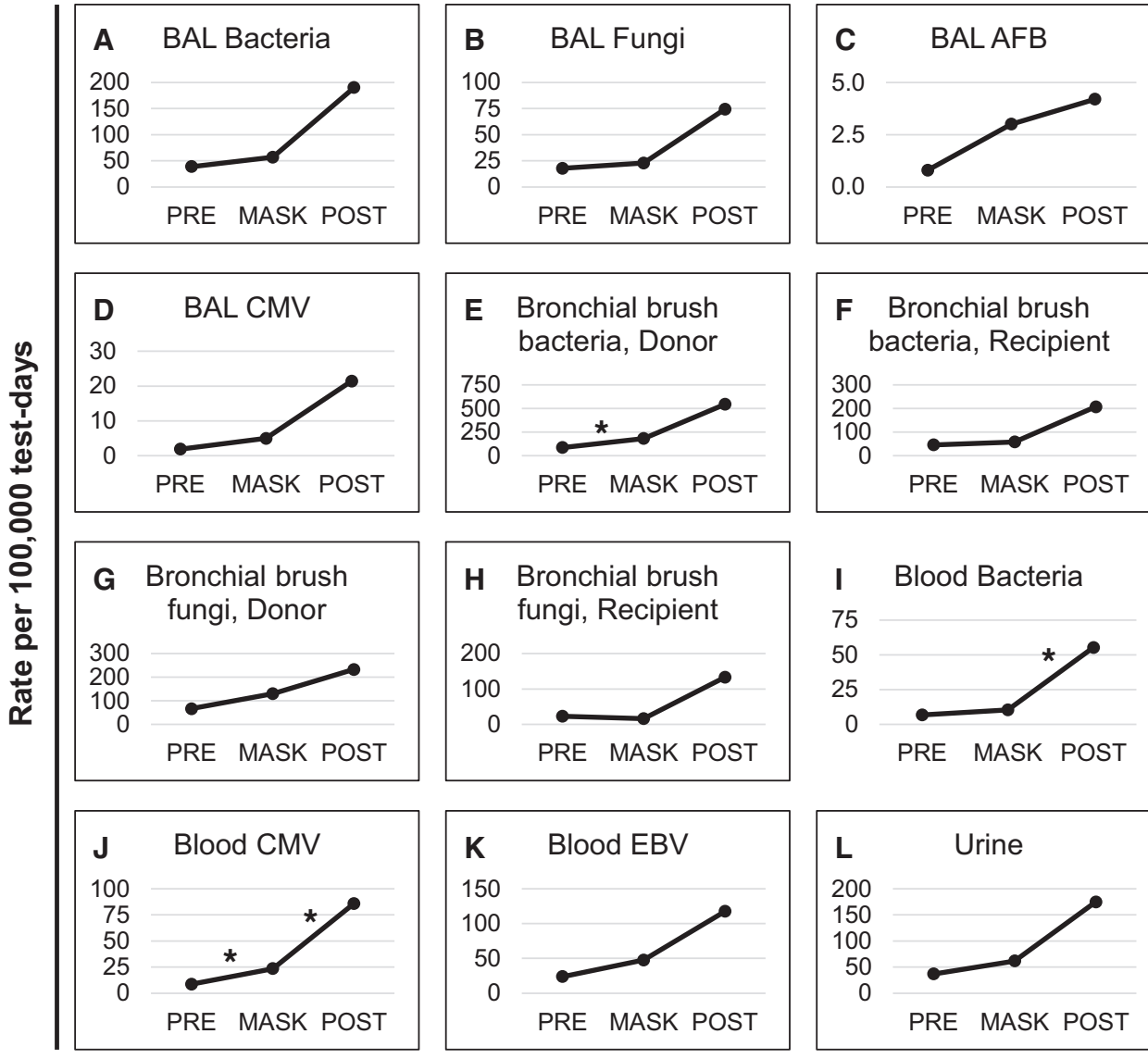

FIGURE 3. Incidence rates for non-CARV airway, blood, and urine bacterial, fungal, acid-fast, CMV and EBV positive tests. Plotted rates include all bacterial (A), fungal (B), acid-fast bacilli (C), and CMV PCR (D) test results from recipient BAL specimens collected during the respective time periods (PRE, MASK, and POST). Donor bacteria (E), recipient bacteria (F), donor fungi (G), and recipient fungi (H) bronchial brush specimens were collected at the time of transplant in the specified time periods. I–L, Incidence rates of positive blood bacterial cultures, blood CMV PCR, blood EBV PCR, and urine cultures, respectively. Rates are plotted per 100 000 test-days. *$P < 0.05$. AFB, acid-fast bacteria; BAL, bronchoalveolar lavage; CARV, community-acquired respiratory virus; CMV, cytomegalovirus; EBV, Epstein Barr virus; PCR, polymerase chain reaction.

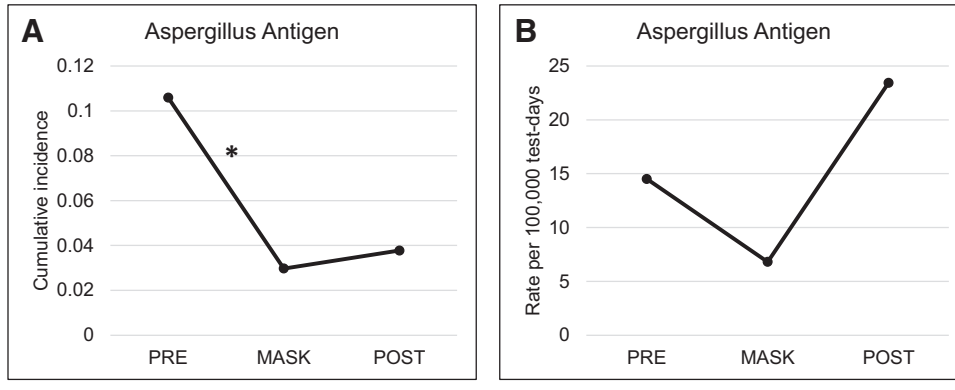

FIGURE 4. Airway *Aspergillus* antigen incidence across time periods. (A) Cumulative incidence and (B) rate of positive *Aspergillus* antigen tests from bronchoalveolar lavage samples in each study period. Rates are plotted per 100 000 test-days. *$P < 0.05$.

risk of infection with microbes already colonizing the airway are not known. A second hypothesis is that masking and NPI measures are, indeed, effective at reducing exposure of the lower airways to external bacterial and fungal pathogens but that this in turn also impairs innate immune surveillance of the environment. When the lower airways are then exposed to higher amounts of these potential pathogens following the relaxation of NPI measures, immune surveillance may no longer be as effective at preventing bacterial or fungal infection. Further work addressing the effects of NPI measures on bacterial and fungal lower airway infection is needed. Our results demonstrate that NPI measures implemented to reduce transmission of SARS-CoV-2 also were associated with reduced non-COVID CARV transmission but not bacterial, fungal, or nonrespiratory virus transmission.

All non-CARV infections showed trends toward increases across time periods, but bloodborne CMV infections were the only statistically significant non-CARV infection across all time periods. The reasons for elevated levels of CMV DNAemia are not immediately clear. No major changes were made to the immunosuppression or antiviral prophylaxis regimens patients received across the study period. Additionally, targeted tacrolimus levels were consistent throughout the study. For the few patients who tested positive for COVID-19, mycophenolate mofetil was temporarily dose-reduced by half if they remained out of the hospital or held if they required hospitalization. However, a reduction in immunosuppression would be expected to reduce the rates of CMV DNAemia, not increase them. Additional work is needed to determine if the change in CMV incidence was related to the COVID-19 pandemic in any way or a chance finding.

The *Aspergillus* antigen results were interesting. Rates of positive *Aspergillus* antigen tests from BAL were reduced during the MASK period compared with the PRE period but rebounded in the POST period. However, positive fungal cultures from these same BAL samples failed to follow a similar trend, suggesting that the positive *Aspergillus* antigen tests were not necessarily reflective of fungal infection and may have been artifactually elevated. In lung transplant patients, *Aspergillus* galactomannan has a sensitivity of 60% but is often positive in the absence of invasive aspergillosis, suggesting colonization.[13] None of the patients in our study were diagnosed with invasive aspergillosis. Further study is warranted to determine the full relevance of these findings.

The primary strength of our study is the closely monitored cohort of lung transplant recipients and the fact that most of these patients' care is through our transplant center. We also evaluated all tests performed in this population at our institution during the 3 cohort periods, minimizing data missingness. Another strength is the homogeneity of the population in terms of their normal, prepandemic infection prevention measures, including program-recommended masking and hand hygiene practices, that allowed us to evaluate the incidence of infection when only our patients were masking versus when they and the general public were masking and exercising infection prevention measures.

Limitations in our study include the retrospective and single-center nature of the study. We had no way of verifying the compliance of our patients or of the general public with NPI measures that could impact disease transmission. We also were unable to effectively incorporate COVID-19 vaccination in the analysis given evolving guidance regarding what constituted "full vaccination" in immunocompromised individuals. Initial COVID-19 vaccines became available to the general public in January 2021, approximately halfway through the MASK period. By the end of the MASK period, 46.1% of the Ohio population had received at least 1 vaccination dose.[14] COVID-19 positive tests in our cohort correlated with surges in community COVID-19 cases (Figure 2), suggesting that community spread and the emergence of new variants (eg, delta) were more impactful than increasing rates of vaccination in our cohort. We included all tests performed at our institution for this cohort during the study period, and therefore, we did not account for multiple positive tests in a single individual. Because our clinical practice, in terms of infection surveillance, did not change over the course of the study period, we felt that including all tests performed would be more appropriate to evaluate the overall positive test incidence. Finally, there are potentially other unaccounted-for measures that people utilized to reduce the risk of infection during the study period that may not have been included. Despite these limitations, our results confirm findings related to non-COVID CARVs observed in other studies, extend these findings to SARS-CoV-2, and provide a contrasting insight into the patterns of non-CARV respiratory and other infections in an immunocompromised patient population in the setting of government-mandated NPI.

In conclusion, NPI measures implemented to reduce the spread of COVID-19 were associated with reduced CARV infections in a cohort of immunocompromised lung transplant recipients but had no effect on the rates of bacterial, fungal, and nonrespiratory virus infections. These results support the use of NPI to reduce transmission of CARV infection, including COVID-19.

ACKNOWLEDGMENTS

The authors would like to acknowledge Desmond Wong and Jeff Sneddon in the Comprehensive Transplant Center at The Ohio State University (OSU) Wexner Medical Center for their assistance in data collection. The authors also acknowledge financial support from the OSU Department of Medicine for statistical analysis related to this project.

REFERENCES

1. Gottlieb J, Schulz TF, Welte T, et al. Community-acquired respiratory viral infections in lung transplant recipients: a single season cohort study. *Transplantation*. 2009;87:1530–1537.
2. Avery RK, Michaels MG; AST Infectious Diseases Community of Practice. Strategies for safe living following solid organ transplantation—guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33:e13519.
3. de Zwart AES, Riezebos-Brilman A, Alffenaar JWC, et al. Evaluation of 10 years of parainfluenza virus, human metapneumovirus, and respiratory syncytial virus infections in lung transplant recipients. *Am J Transplant*. 2020;20:3529–3537.
4. Johns Hopkins University of Medicine Coronavirus Resource Center. COVID-19 dashboard. Available at https://coronavirus.jhu.edu/map.html. Accessed August 23, 2022.
5. Governor of Ohio. Ohio issues "stay at home" order; new restrictions placed on day cares for children. 2020. Available at https://governor.ohio.gov/wps/portal/gov/governor/media/news-and-media/

ohio-issues-stay-at-home-order-and-new-restrictions-placed-on-day-cares-for-children. Accessed August 23, 2022.
6. Governor of Ohio. Governor DeWine issues statewide mask order, travel warning. 2020. Available at https://governor.ohio.gov/wps/portal/gov/governor/media/news-and-media/covid19-update-07222020. Accessed August 23, 2022.
7. USAFacts. Ohio coronavirus cases and deaths. Available at https://usafacts.org/visualizations/coronavirus-covid-19-spread-map/state/ohio. Accessed June 30, 2022.
8. Ohio Department of Health. COVID-19 dashboard. Available at https://coronavirus.ohio.gov/dashboards. Accessed June 30, 2022.
9. Shi HJ, Kim NY, Eom SA, et al. Effects of non-pharmacological interventions on respiratory viruses other than SARS-CoV-2: analysis of laboratory surveillance and literature review from 2018 to 2021. *J Korean Med Sci.* 2022;37:e172.
10. Olsen SJ. Changes in influenza and other respiratory virus activity during the COVID-19 pandemic—United States, 2020–2021. *MMWR Morb Mortal Wkly Rep.* 2021;70:1013–1019.
11. Oh DY, Buda S, Biere B, et al. Trends in respiratory virus circulation following COVID-19-targeted nonpharmaceutical interventions in Germany, January - September 2020: analysis of national surveillance data. *Lancet Reg Health Eur.* 2021;6:100112.
12. Dawre S, Maru S. Human respiratory viral infections: current status and future prospects of nanotechnology-based approaches for prophylaxis and treatment. *Life Sci.* 2021;278:119561.
13. Unterman A, Izhakian S, Geffen Y, et al. Routine comprehensive Aspergillus screening of bronchoalveolar lavage samples in lung transplant recipients. *Clin Transplant.* 2020;34:e13811.
14. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. *Nat Hum Behav.* 2021;5:947–953.