Clinical Infection in Practice 20 (2023) 100236

Contents lists available at ScienceDirect

Clinical Infection in Practice

journal homepage: www.sciencedirect.com/journal/clinical-infection-in-practice

Practical clinical reviews

The reduced incidence of respiratory viral infections in transplant recipients during the COVID-19 pandemic – A retrospective observational cross-sectional analysis of admissions to a tertiary haematology unit

Hamzah Z. Farooq [a,b,c,d,1,*], Shahid Iqbal [e,1], Emma Davies [a,b], Eleni Tholouli [e], Nicholas Machin [a,b,2], Fiona L. Dignan [e,2]

[a] Department of Virology, Manchester University NHS Foundation Trust, Manchester, UK
[b] UK Health Security Agency (UKHSA) Manchester, Manchester, UK
[c] Department of Infectious Diseases and Tropical Medicine, North Manchester General Hospital, Manchester University NHS Foundation Trust, Manchester, UK
[d] Blizard Institute, Queen Mary University of London, London, UK
[e] Department of Clinical Haematology, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, UK

ARTICLE INFO

Keywords:
Respiratory infections
Viral infections
Transplant patients
Single organ transplant
SOT
Haematopoietic stem cell transplants
HSCT

ABSTRACT

This study examines the prevalence of respiratory viral infections (RVIs) in transplant recipients during the COVID-19 pandemic. Patients were admitted to a regional haematology unit (RHU) in England which provides a tertiary referral service for haematological malignancy, stem cell transplantation, CAR-T therapy, thrombosis, haemostasis and haemoglobinopathies. Weekly screening for RVIs was conducted on all inpatients in the RHU wards, and data were collected retrospectively for all admissions from August 2018 to February 2021. There was a significant drop in the circulation of non-SARS-CoV-2 RVIs in transplant recipients during the COVID-19 pandemic. The most common viral pathogen in the transplant cohort was rhinovirus, followed by para-influenza 3, adenovirus, and RSV. The study also highlights the importance of infection prevention and control measures to reduce the risk of nosocomial transmission of RVIs and SARS-CoV-2 in transplant recipients. Further studies are needed to observe whether this effect is pronounced in multiple transplant centres.

Introduction

Patients with an unknown cause of pneumonia were isolated in Wuhan, China in December 2019 with a novel coronavirus identified (2019-nCoV) and eventually classified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronaviridae Study Group of the International Committee on Taxonomy, 2019). The clinical disease was termed "COVID-19" with a ranging clinical syndrome (WHO, 2020). A pandemic was declared by the World Health Organization (WHO) and as of 10th March 2023, 679 million people have been infected with 6.8 million deaths globally (University JH, 2020).

Due to its rapid asymptomatic spread and lethality, the COVID-19 pandemic is associated with substantial morbidity and mortality (Oster et al.). It has caused an immense burden on health services globally with numerous overwhelmed health systems (Tangcharoensathien et al., 2021; Narain et al., 2020). In the first wave of the COVID pandemic, a secondary concern was of the increased burden to health systems on the potential surge due to seasonal respiratory viral infections (RVI), especially Influenza in the 2020 winter season. Besides general medical hospitals, this surge was of particular concern for tertiary haematology units which cater for severely immunosuppressed patients (Thng et al., 2021).

RVI incidence was reduced in the community in multiple countries in both the Northern (Olsen et al., 2020; ECDC ECfDPaC, 2020) and Southern Hemispheres (Olsen et al., 2020; Sullivan et al., 2020; Huang et al., 2021) likely due to the COVID-19 restrictions (Tang et al., 2021). Although non-pharmaceutical interventions (NPIs) and IPC measures exerted a strong impact on the circulation of influenza in both primary and secondary care settings (Sullivan et al., 2020); some RVIs such as rhinoviruses became more predominant, relatively unaffected by the

* Corresponding author.
E-mail address: Hamzah.farooq@qmul.ac.uk (H.Z. Farooq).
[1] **Joint first authors.**
[2] **Joint senior authors.**

https://doi.org/10.1016/j.clinpr.2023.100236
Received 23 May 2023; Received in revised form 14 August 2023; Accepted 16 August 2023
Available online 26 August 2023

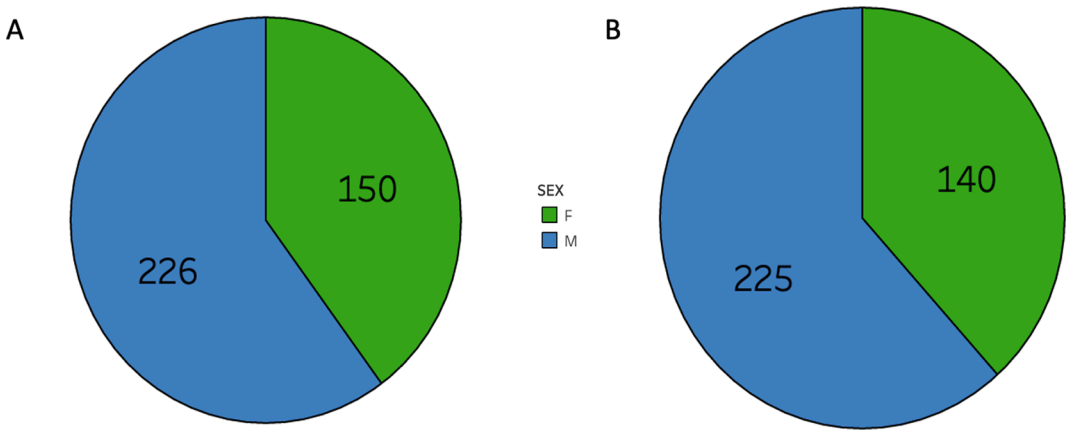

Fig. 1. Sex of patients: A = Transplant cohort; B = Non-Transplant cohort.

Table 1
Demographics of patients and testing.

Variable	Transplant	Non-transplant	Total
Age (in Years)			
Number	376	365	741
Mean +/- SD	58.62 +/- 13.60	60.19 +/- 18.44	
Range	22.4–85.5	18.49–93.35	
Sex			
Male	226	150	376
Female	225	140	365
Samples Received	2309	974	3283

COVID-19 restrictions. Rhinoviruses and other RVIs are particularly concerning in transplant recipients and are associated with high morbidity and mortality. Single organ transplant (SOT) and haematopoietic stem cell transplants (HSCT) patients experience a prolonged viral shedding, duration of illness, with increased likelihood of progression to pneumonia (Abbas et al., 2017).

The regional haematology unit (RHU) at Manchester Royal Infirmary provides a tertiary referral service for haematological malignancy, stem cell transplantation, CAR-T therapy, thrombosis, haemostasis and haemoglobinopathies. Consequently, it has a large cohort of patients with immunosuppression who are at high risk of developing RVIs. The transplant service has been consistently expanding over the recent years and approximately 150 transplants are undertaken per year. As community and nosocomial spread occurs in all RVIs and strict adherence to infection control measures is key to preventing outbreaks, the RHU initialised a protocol for RVI surveillance in all patients admitted to the unit. This process has been in place since 2008 and thus captures patients before and during the COVID-19 pandemic era. In this study we describe the distribution of RVIs in transplant recipients at the RHU in Manchester, UK during the COVID-19 pandemic. Correspondingly, we compare the distribution of RVIs in transplant recipients at the RHU from the preceding years. Consequently, we aim to present a retrospective analysis on the prevalence of RVIs in this transplant cohort before and during the COVID-19 pandemic.

Methods

The RHU commenced weekly screening for all inpatients from 2008. All patients were tested for respiratory viruses by real time reverse transcription PCR (rRT-PCR) for Influenza A (Flu A -H1 and H3), Influenza B (Flu B), Respiratory syncytial virus (RSV), Rhinovirus, Adenovirus (Adeno), Human Metapneumovirus (MPV) and Parainfluenza Virus (PF Types 1–3). Testing is performed using a mixture of triplex (FluA/FluB/RSV, PF1-3), duplex (Adeno/Rhino) and singleplex (MPV) PCR assays with targeted rapid testing for Flu A, Flu B and RSV via Cepheid if clinically deemed necessary. With the advent of the COVID-19 pandemic, all patients subsequently were tested from SARS-CoV-2 via by a semi-quantitative rRT-PCR on admission. Retrospective data were collected for all admissions to the RHU wards from 1st August 2018 to 28th February 2021.

Data were extracted from the laboratory information management system into MS Excel. After initial screening with removal of patient duplicates and stratifying by transplant and non-transplant patients, data were extracted and analysed in SPSS. Utilising SPSS and Tableau Desktop, results and figures were produced.

Results

During the study period (01/08/2018 to 28/02/2021), 3,283

Table 2
Results of PCR testing.

Respiratory Virus	Transplant Positive	Transplant Negative	Positivity	Transplant Not Tested (X)	Transplant Inhibitory (I)	Transplant Null	Transplant Z	Total	Non-Transplant Positive	Non-Transplant Negative	Non-Transplant Not Tested (X)	Non-Transplant Inhibitory (I)	Non-Transplant Null	Non-Transplant Z	Total
Adenovirus	13	2241	0.58%	48	1	4	2	2309	1	954	17	0	2	0	974
Cepheid Flu A	0	25	0.00%	0	1	2283	0	2309	6	18	0	1	949	0	974
Flu A	4	2298	0.17%	4	1	0	2	2309	6	961	7	0	0	0	974
Cepheid Flu B	0	25	0.00%	0	1	2283	0	2309	0	24	0	1	949	0	974
Flu B	0	2302	0.00%	4	1	0	2	2309	1	967	6	0	0	0	974
HMPV	11	2230	0.49%	48	1	17	2	2309	3	947	17	0	7	0	974
Parainfluenza 1	7	2247	0.31%	48	1	4	2	2309	4	951	17	0	2	0	974
Parainfluenza 2	10	2244	0.44%	48	1	4	2	2309	1	954	17	0	2	0	974
Parainfluenza 3	31	2223	1.38%	48	1	4	2	2309	14	941	17	0	2	0	974
PJP	2	53	3.64%	0	0	2254	0	2309	1	22	0	0	951	0	974
Rhinovirus	108	2146	4.79%	48	1	4	2	2309	51	904	17	0	2	0	974
Cepheid RSV	0	0	0.00%	25	1	2283	0	2309	2	22	0	1	949	0	974
RSV	12	2290	0.52%	4	1	0	2	2309	5	963	6	0	0	0	974
Total	198	20,324		325	12	9140	18	30,017	95	8628	121	3	3815	0	12,662

samples were received for respiratory virus testing for all haematology patients. Of these, 2309 samples were from transplant patients with 974 from general haematology patients (non-transplant cohort; patients with haematological malignancies).

From a patient perspective, there were 376 transplant patients (226 Males/150 Females) and 365 general haematology patients (225 Male/140 Female) with a mean age of 58.62 (+/- 13.60) and 60.19 (+/-18.44) respectively (Fig. 1 and Table 1). As screening was performed for these patients during the observation period, multiple samples were received.

Of these 3,283 samples, a total 42,679 PCR tests were requested for multiple respiratory viruses (RVs) (Table 1) with 30,112 performed due to multiple reasons (Table 2). Of the 30,112 PCR tests performed, there were 198 tests positive for RVs in the Transplant cohort compared to the 95 in the non-transplant cohort – odds ratio 0.9738 (CI: 0.7616 to 1.2452; p-value 0.8324 – Table 2).

There was seasonal variation in the number of samples received and requests for RVIs with corresponding RVs demonstrated (Figs. 2 and 3). During the COVID-19 pandemic, the number of viral infections dropped from 161 RVs over 14-months to 84 RVs over 14-months (1st November 2018 to 31st December 2019 compared to 1st January 2020 to 31st March 2021 – Table 3 and Fig. 4 - relative risk of 0.42 of non-COVID RVI during COVID pandemic.

In the Transplant cohort, the most common viral pathogen seen was Rhinovirus (108), followed Parainfluenza 3 (31), Adenovirus (13) and RSV (12). Similarly, the most common viral pathogen in the non-transplant cohort was Rhinovirus (51), followed by Parainfluenza 3 (14), Flu A (12) and RSV (5).

Due to the infection prevention and control needs, 50 rapid (Cepheid) tests were performed on the Transplant cohort with 72 on the non-transplant cohort of which more were positive in the non-transplant cohort compared to the transplant patients (11 vs 0). Of the 11 positives, the main RV was RSV (5), followed by Influenza A (6) and Influenza B (1) (Table 3).

Discussion

RVIs are ubiquitous, primarily spread via droplet transmission and associated with high morbidity and mortality in transplant recipients. Studies have shown there has been a reduction in the circulation of seasonal respiratory viruses in the general population due to the impact of pandemic restrictions and particularly the case for Influenza viruses (Huang et al., 2021). Our observational study confirms this finding in our transplant population, however of note, we had ongoing Rhinovirus cases during this period despite NPI measures (Fig. 3). This does correlate with ongoing Rhinovirus transmission even with lockdown restrictions in the general UK population particularly in children aged 0–14 years old (Phe, 2021). However, the incidence of Rhinovirus remained constant from April 2020 in our haematology cohort compared to the overall general UK population (Phe, 2021) likely due to their immunocompromised state. Similarly, we had occasional cases of adenovirus, HMPV and RSV in our cohort, contrasting to little or no detectable activity in other settings (Tang et al., 2021).

The paramount challenge for transplant centres is to optimise IPC practices to reduce the incidence of RVIs in transplant recipients. Furthermore, transplant recipients are increasingly exposed to outpatient and community settings thus increasing their risk of RVIs. Droplet precautions, routine masking, hand-washing and active cohorting of symptomatic patients is known to reduce RVI transmission in transplant recipients (Pergam, 2016). With the advent of the COVID-19 pandemic, additional measures were required such as admission and surveillance viral testing to rapidly identify, isolate and reduce the risk of nosocomial transmission of RVIs and SARS-CoV-2.

Our findings demonstrate there was a greater number of RVI positive samples in the transplant cohort compared to the non-transplant cohort (198 vs 95). However, the proportion was less (0.96% vs 1.09%) with an odds ratio of 0.9738 (CI: 0.7616 to 1.2452; p-value 0.8324) indicating

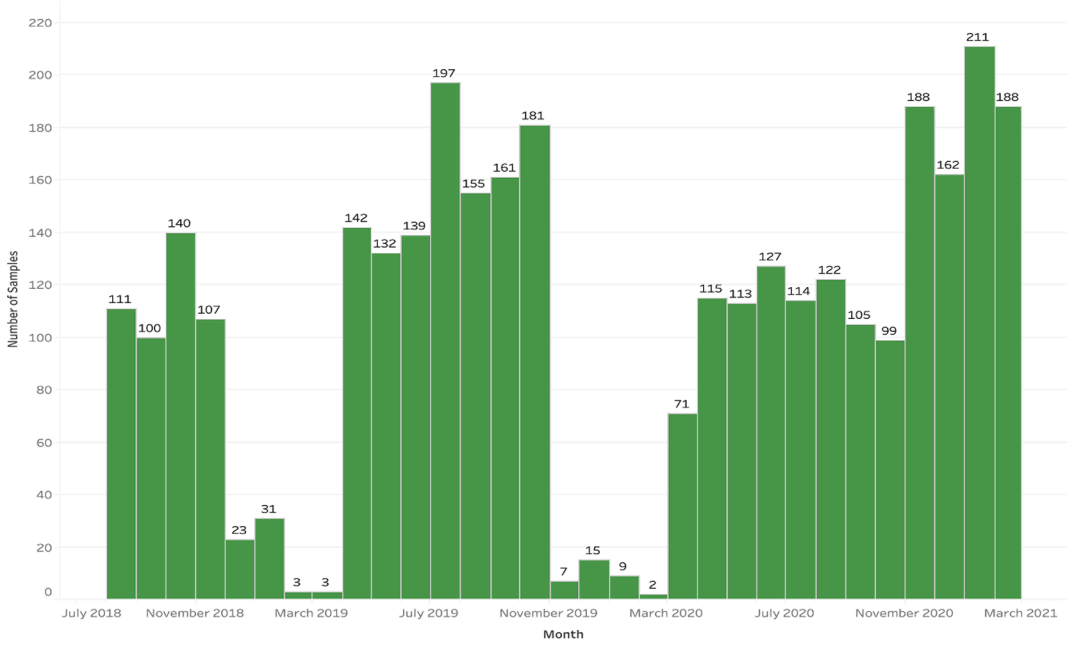

Fig. 2. Number of samples received per month.

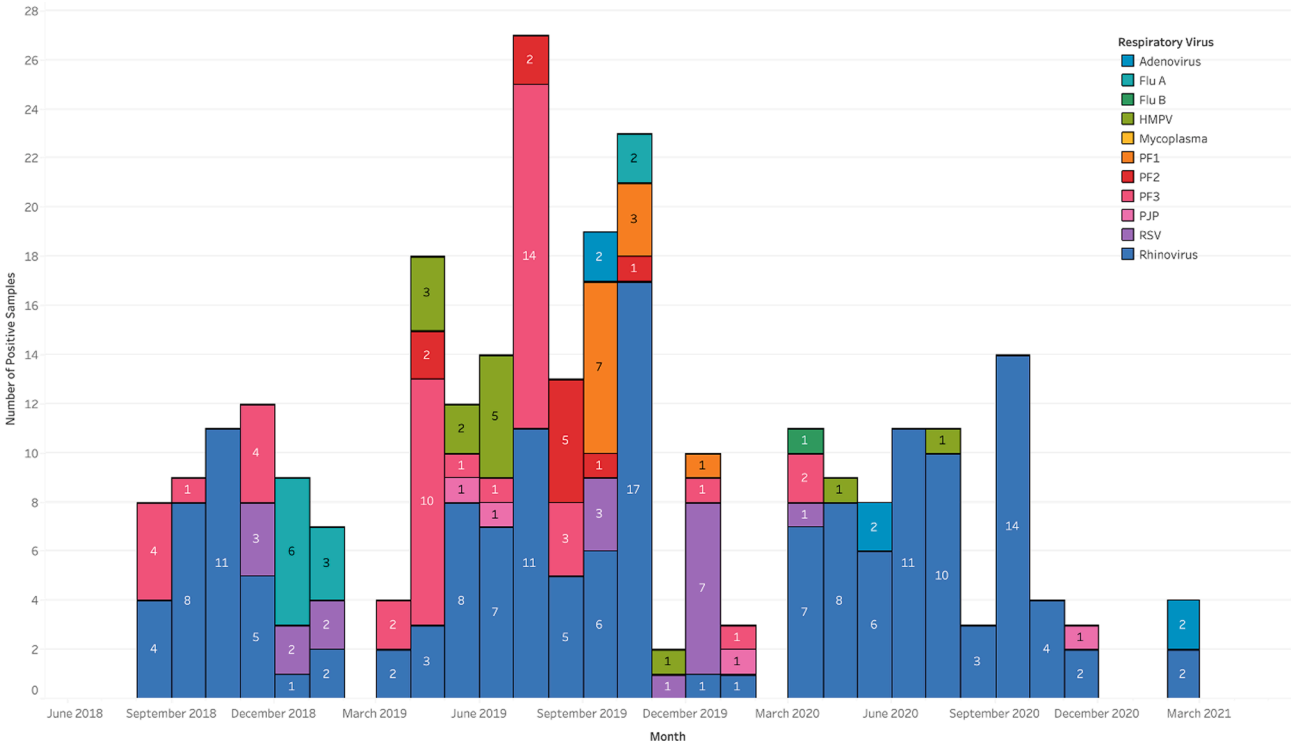

Fig. 3. All positive respiratory viruses.

further studies are required in multiple transplant centres to show an accurate effect.

The RHU had instituted RVI surveillance in the pre-COVID-pandemic era and subsequently ensured improved IPC measures and rapid screening of transplant recipients to reduce the risk of nosocomial transmission. Our findings demonstrate the incidental reduction of RVIs in our transplant cohort due to the emergence of SARS-CoV-2, indicating the beneficial use of targeted-weekly RVI screening with robust IPC measures and bed management. This corresponds to a reduction of RVIs in the community (Phe, 2021) however, comparison with the pre-pandemic data shows a drastic reduction in the prevalence on RVIs in the RHU. Previous studies (Oster et al.; Huh et al., 2021; Parry et al., 2020; Kistler et al., 2020; Ong et al., 2020) had hypothesised that with the advent of COVID-19 IPC measures would result in the reduced prevalence of RVIs in hospital and community settings. Our study confirms and establishes these findings in the transplant cohort whilst demonstrating the RVI prevalence in transplant recipients before the COVID-19 pandemic era.

The findings of this study does have some limitations - we have only observed a single haematological transplant centre and thus more

Table 3
Transplant vs non-transplant testing.

	Transplant	Non-Transplant	Total
Positive Samples	188	87	275
Negative Samples	2121	887	3008
Total Samples	2309	974	3283
	Transplant	**Non-Transplant**	Total
Positive PCR Tests	198	95	293
Negative PCR Tests	20,324	9495	29,819
Total PCR Tests	20,522	9590	30,112
	Pre-COVID*	**During COVID***	Total
Positive Sample	161	84	245
Negative Sample	1135	1542	2677
Total Samples	1296	1626	2922

* 14 months Pre- 1st January 2020 and 14 months post -January 2020.

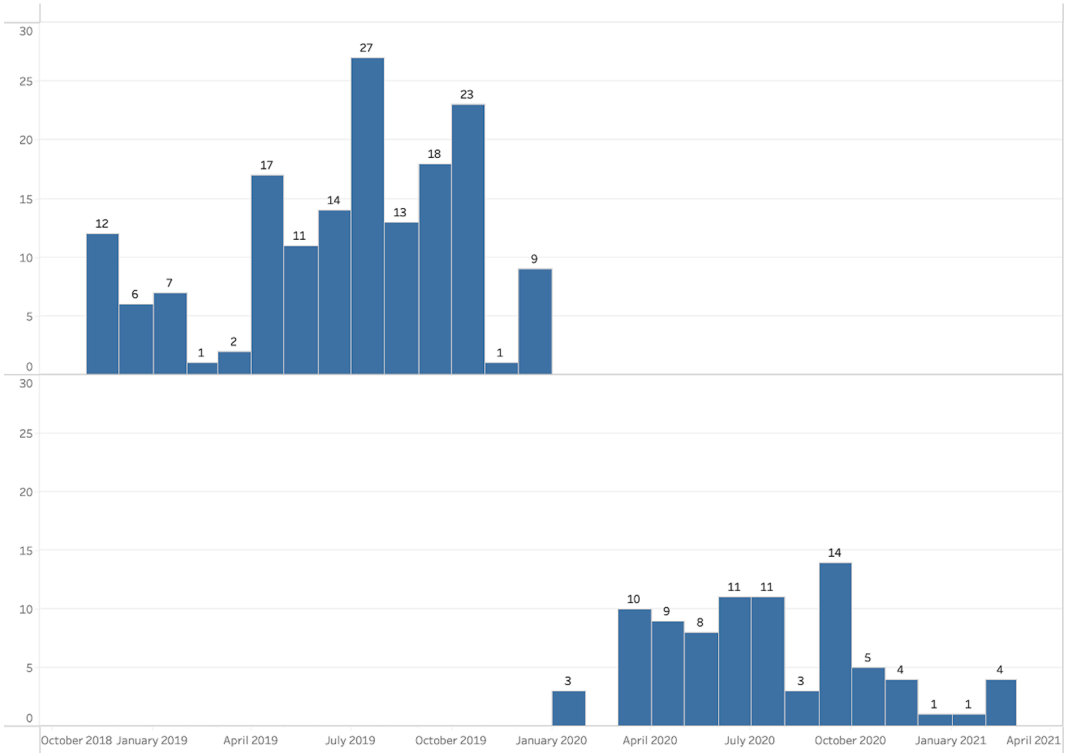

Fig. 4. Pre and post COVID positives.

centres need to be recruited for a general picture for RVI prevalence. Additionally, there were more tests performed for the transplant group due to more targeted surveillance as there were more concerns about patient's COVID status.

Conclusion

There was a significant drop in the circulation of non-SARS CoV-2 RVIs in transplant recipients during 2020 COVID-19 pandemic. Further studies are warranted to observe whether this effect is pronounced in multiple transplant centres.

CRediT authorship contribution statement

Hamzah Z Farooq: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Shahid Iqbal:** Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Emma Davies:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **Eleni Tholouli:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Nicholas Machin:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Fiona L. Dignan:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing.

Funding

HZF is supported by a clinical research fellowship grant from the Wellcome Trust, United Kingdom (227516/Z/23/Z).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We wish to acknowledge the contributions of the staff of the Department of Clinical Haematology and UKHSA Manchester laboratory.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinpr.2023.100236.

References

Abbas, S., Raybould, J.E., Sastry, S., de la Cruz, O., 2017. Respiratory viruses in transplant recipients: more than just a cold. Clinical syndromes and infection prevention principles. Int. J. Infect. Dis. 62, 86–93.

Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nature microbiology. 2020;5(4):536-44.

ECDC ECfDPaC. COVID-19 situation update for the EU/EEA and the UK, as of 9 December 2020. 2020 [Available from: https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea.

Huang, Q.S., Wood, T., Jelley, L., Jennings, T., Jefferies, S., Daniells, K., et al., 2021. Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. Nat. Commun. 12 (1), 1001.

Huh, K., Kim, Y.-E., Ji, W., Kim, D.W., Lee, E.-J., Kim, J.-H., et al., 2021. Decrease in hospital admissions for respiratory diseases during the COVID-19 pandemic: a nationwide claims study. Thorax. 2021:thoraxjnl-2020-216526.

Kistler, C.E., Jump, R.L.P., Sloane, P.D., Zimmerman, S., 2020. The winter respiratory viral season during the COVID-19 pandemic. J. Am. Med. Dir. Assoc. 21 (12), 1741–1745.

Narain, J.P., Dawa, N., Bhatia, R., 2020. Health system response to COVID-19 and future pandemics. J. Health Manage. 22 (2), 138–145.

Olsen, S.J., Azziz-Baumgartner, E., Budd, A.P., Brammer, L., Sullivan, S., Pineda, R.F., et al., 2020. Decreased influenza activity during the COVID-19 pandemic - United States, Australia, Chile, and South Africa, 2020. MMWR Morb. Mortal. Wkly Rep. 69 (37), 1305–1309.

Ong, C.W.M., Migliori, G.B., Raviglione, M., MacGregor-Skinner, G., Sotgiu, G., Alffenaar, J.-W., et al., 2020. Epidemic and pandemic viral infections: impact on tuberculosis and the lung. Eur. Respir. J. 56 (4), 2001727.

Oster, Y., Michael-Gayego, A., Rivkin, M., Levinson, L., Wolf, D.G., Nir-Paz, R. Decreased prevalence rate of respiratory pathogens in hospitalized patients during the COVID-19 pandemic: possible role for public health containment measures? Clinical Microbiology and Infection.

Parry, M.F., Shah, A.K., Sestovic, M., Salter, S., 2020. Precipitous fall in common respiratory viral infections during COVID-19. Open Forum Infect. Dis.

Pergam, S.A., 2016. Infection prevention in transplantation. Curr. Infect. Dis. Rep.

PHE PHE. National flu and COVID-19 surveillance reports. In: Care DoHaS, editor. Online: PHE; 2021.

PHE PHE. Weekly national Influenza and COVID-19 surveillance report; Week 8 report (up to week 7 data) 25 February 2021 London: PHE; 2021 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/964754/Weekly_Flu_and_COVID-19_report_w8.pdf.

Sullivan, S.G., Carlson, S., Cheng, A.C., Chilver, M.B., Dwyer, D.E., Irwin, M., et al., 2020. Where has all the influenza gone? The impact of COVID-19 on the circulation of influenza and other respiratory viruses, Australia, March to September 2020. Eurosurveillance. 25 (47), 2001847.

Sullivan, S.G., Carlson, S., Cheng, A.C., Chilver, M.B., Dwyer, D.E., Irwin, M., et al., 2020. Where has all the influenza gone? The impact of COVID-19 on the circulation of influenza and other respiratory viruses, Australia, March to September 2020. Euro Surveill. 2020;25(47).

Tang, J.W., Bialasiewicz, S., Dwyer, D.E., Dilcher, M., Tellier, R., Taylor, J., et al., 2021. Where have all the viruses gone? Disappearance of seasonal respiratory viruses during the COVID-19 pandemic. J. Med. Virol. 93 (7), 4099–4101.

Tangcharoensathien, V., Bassett, M.T., Meng, Q., Mills, A., 2021. Are overwhelmed health systems an inevitable consequence of covid-19? Experiences from China, Thailand, and New York State. BMJ 372, n83.

Thng, Z.X., De Smet, M.D., Lee, C.S., Gupta, V., Smith, J.R., McCluskey, P.J., et al., 2021. COVID-19 and immunosuppression: a review of current clinical experiences and implications for ophthalmology patients taking immunosuppressive drugs. Br. J. Ophthalmol. 105 (3), 306–310.

University JH. John Hopkins University Coronavirus Resource Center 2020 [Available from: https://coronavirus.jhu.edu/map.html.

WHO. Naming the coronavirus disease (COVID-19) and the virus that causes it 2020 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.