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Aerosol Generation During High Intensity Exercise—Implications for COVID-19 Transmission

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Background and Aim
COVID-19 can be transmitted through aerosolised respiratory particles. The degree to which exercise enhances aerosol production has not been previously assessed. We aimed to quantify the size and concentration of aerosol particles and evaluate the impact of physical distance and surgical mask wearing during high intensity exercise (HIE).

Methods
Using a prospective observational crossover study, three healthy volunteers performed high intensity cardiopulmonary exercise testing at 80% of peak capacity in repeated 5-minute bouts on a cycle ergometer. Aerosol size and concentration was measured at 35, 150 and 300 cm from the participants in an anterior and lateral direction, with and without a surgical face mask, using an Aerodynamic Particle Sizer (APS) and a Mini Wide Range Aerosol Spectrometer (MiniWRAS), with over 10,000 sample points.

Results
High intensity exercise generates aerosol in the 0.2–1 micrometre range. Increasing distance from the rider reduces aerosol concentrations measured by both MiniWRAS (p=0.003 for interaction) and APS (p=0.041). However, aerosol concentrations remained significantly increased above baseline measures at 300 cm from the rider. A surgical face mask reduced submicron aerosol concentrations measured anteriorly to the rider (p=0.031 for interaction) but not when measured laterally (p=0.64 for interaction).

Conclusions
High intensity exercise is an aerosol generating activity. Significant concentrations of aerosol particles are measurable well beyond the commonly recommended 150 cm of physical distancing. A surgical face mask reduces aerosol concentration anteriorly but not laterally to an exercising individual. Measures for safer exercise should emphasise distance and airflow and not rely solely on mask wearing.

Keywords
Coronavirus • COVID-19 • Aerosol • Exercise • Sport • Indoor air quality
Introduction

Aerosol production during high intensity exercise (HIE) has not been definitively demonstrated or quantified. This has significant implications in the current COVID-19 pandemic, in which the transmission of aerosolised particles is increasingly considered the dominant cause of viral transmission. Many nations have attempted to minimise the impact of the pandemic by entering various stages of lockdown, with closure of facilities deemed nonessential [1]. This has included major professional sporting organisations, postponement of the Olympic Games and closure of local amateur sport and gyms [2-4]. COVID-19 outbreaks have been reported in indoor fitness facilities, with over 20% of exposed participants of a fitness dance class becoming infected [5-7]. Additional outbreaks have occurred during basketball [8], indoor recreational squash and ice hockey [9]. These risks have to be balanced against the mental, physical and economic benefits of sport which are well documented [3,10].

SARS-CoV-2, the virus responsible for COVID-19, is spread by close contact, and almost certainly by airborne transmission [4,11-16]. SARS-CoV-2 has a diameter of around 0.1 micrometres and viable RNA virus has been cultured from air samples exhibiting aerosol sizes ranging from submicron to several microns [12]. In a health care setting, SARS-CoV-2 has been found in aerosol in two peaks of 0.25–1.0 micrometres and >2.5 micrometres [17].

Based on concerns of viral transmission, there has been considerable research into the generation and dispersion of droplet and aerosol during normal breathing, talking, coughing, and sneezing [13-15,18-20]. These droplets/aerosols range in size from 0.05 to 500 micrometres, depending on their origin [18-20].

Aerosols are arbitrarily defined by the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) as small respirable particles <5 micrometres that remain airborne for potentially prolonged periods (hours or days). These can penetrate into alveolar spaces [21]. Droplets are arbitrarily defined as particles >5 micrometres that tend to fall towards the ground, with 10 micrometre particles falling within 20 minutes and 100 micrometre particles falling to the floor in seconds [21].

Aerosol generation during HIE research, in the setting of a global pandemic is difficult to perform. It requires sophisticated, expensive, high fidelity aerosol measurement equipment with operator expertise; a low background particle count to detect small increases in aerosol concentration; comparison between interventions such as face masks and circumferential distance from the participant; and accurate measures of minute ventilation and work rate. To date, the available data for aerosol generation during HIE has limitations [22-24].

Public health recommendations on the topic have extrapolated findings from other aerosol generating activities. Many nations have introduced and enforced the concept of ‘social distancing’ or physical distancing of individuals 1.5–2 metres apart, including during indoor sport [23]. The evidence base supporting this recommendation is limited [25]. Given coughing and sneezing can propel droplets and aerosols further than 7–8 metres, there are concerns that 1.5 metres may not be adequate during HIE if significant aerosol is generated [2,26].

In the setting of high intensity exercise, we aimed to:

1. Determine if droplets and aerosol are generated.
2. Characterise the size, concentration and distribution of droplet and aerosol particles.
3. Determine the impact of a surgical mask and increasing physical distance from the participant on droplet and aerosol concentration.

Materials and Methods

The project was approved by the Alfred Health Human Research Ethics Committee (Project 709/20). The project was registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR) (Registration number ACTRN12621000130864).

Study Cohort

The inclusion criteria were healthy, active adult volunteer participants, free of major medical co-morbidities, >18 years of age, who met the WHO recommendations of 150 minutes per week of moderate to vigorous exercise [10] and were available to exercise during the weekend of data collection. Three participants were recruited.

Study Design

This was a prospective observational crossover study.

Exercise and Measurements

The participants underwent a cardiopulmonary exercise test (CPET) 48 hours before the experiment according to published guidelines [27]. A continuous ramp protocol was conducted on an electronically braked cycle ergometer (Lode Excalibur Sport, Lode BV Medical Technology, Groningen, NL) to obtain measures of heart rate, respiratory rate, minute ventilation, peak flow, and oxygen uptake at given power outputs and maximum workload. The same CPET protocol was suitable for all participants to achieve an optimal exercise duration between 8 and 12 minutes. Two (2) minutes passive rest preceded a minute warm-up at an initial resistance of 50 Watts. Thereafter, workload increased progressively at a rate of 30 Watts per minute until volitional fatigue. Gas exchange data was collected continuously throughout the test using a calibrated metabolic cart (Vyntus CPX, Carefusion, San Diego, CA, USA). VO2 peak was calculated as the maximum value from a 30-second rolling average of six consecutive 5 second averaged data points with the peak workload recorded.
A second CPET at 80% of peak workload for a duration of 5 minutes, was performed on a different day, to replicate conditions during the experiment and to derive measurements of ventilation and respiratory rate. We opted for 80% of maximum workload for the 5-minute exercise bursts as the acceptable intensity that would be sustainable for the multiple repeat measures and allow sufficient exertional breathing consistent with working out in a gym setting.

Two (2) methods to detect droplet/aerosol were utilised. An Aerodynamic Particle Sizer (APS model 3320, TSI Incorporated, Shoreview, MN, USA) spectrometer measures particles in the size 0.5–20 micrometres at 1 second intervals using the acceleration of particles between two laser beams. To extend the measurement range to smaller sizes, a Mini Wide Range Aerosol Spectrometer (MiniWRAS model 1371, GRIMM Aerosol Technik, Airing, Germany) was employed which measures 0.01–35 micrometre particles using electrical mobility and optical light scattering at 1-minute intervals. The sampling inlet utilised during the study limited the measurable size range to an upper limit of 10 micrometres for both instruments. The sampling device was carefully positioned at the same level as the head, with subjects in the cycling position. Air was sampled at 6 litres per minute, through an inlet common to both instruments constructed of a stainless-steel funnel (100 mm opening, tapering to 12 mm over a 100 mm distance) inserted into a 2,500 mm long, 12 mm diameter conductive silicone tubing.

Setting

It has been well demonstrated that it is difficult to detect aerosol production in a standard indoor environment setting in which background particulate counts are high [24]. We found that measures of ambient particulate matter (‘noise’) within our exercise laboratory to be prohibitively high for detection of aerosol generation. Thus, we used a 7 x 6 x 3 m operating room (OR) at 3.3 Pascals positive pressure, at 21.5°C with a relative humidity of 40%, with 25 volume air exchanges per hour and high efficiency particulate air (HEPA) filtration to provide a ‘clean’ environment with negligible background particulate count [28,29]. This HEPA filtered air entered the OR from a large central outlet in the roof and exited via four smaller air-return vents at each corner (floor level), with the cyclist and sampling devices positioned adjacent to this flow path. Baseline particle measurements were obtained overnight within this operating room to accurately quantify background particulate counts, and this was used as the zero steady-state condition.

Participants performed HIE at 80% of their peak work rate for 5 minutes. The aim was to perform sampling at 35, 150 and 300 cm directly anterior and lateral to the head position of the cyclist, with participants wearing no mask, a standard three-ply surgical face mask (Purist Australian, Sydney, NSW, Australia) and a fit checked N95 surgical face mask (BYD Care, Los Angeles, CA, USA). A single 150 cm posterior measurement was also performed. Subjects reached 80% of their peak work rate and then maintained this level for a 5-minute period, with the MiniWRAS and APS sampling continuously. The 5-minute exercise bout was used as a standardised representation of a typical HIE session that could be sustained for a reasonable period of time. It approximates settings such as in indoor cycling ‘spin class’ sessions or high intensity interval classes.

Each participant commenced exercise only after background aerosol levels had returned to near zero baseline. All investigators and participants wore an N95 face mask when entering and leaving the OR between exercise bursts to minimise background contamination. The experimental set up is demonstrated in Figure 1.

Analysis

Aerosol size distributions are predominantly lognormal and are presented using normalised concentration in aerosol literature as dN/dlogDp, where dN is the particle concentration and dlogDp is the log of the midpoint particle diameter [30]. Total concentrations from instruments are reported as particles per cm³ of air. For each subject in each setting (varied distance with and without a mask) sampling was acquired continuously, and data was selected after an equilibrium was reached, resulting in an average of 245 and 5 sample points per subject per setting, for the APS and MiniWRAS, respectively. The average size distribution and total concentration of the background period was subtracted from each measurement resulting in just the perturbation above background. The average of the resulting samples was used to provide a single value for each rider in each experimental setting.

Repeated measured factorial analysis of variance (ANOVA) was used with distance and mask wearing considered as within subject variables. Thus, the significance of an interaction for distance (i.e. was there a significant impact of distance from the subject on aerosol concentration?) and mask wearing (i.e. did the wearing of a mask significantly impact on aerosol concentration?). Measures were obtained anterior and lateral to the subject. Thus, in addition, an interaction between direction of sampling and mask wearing was considered (i.e. was the effect of mask wearing on aerosol concentration different in an anterior vs lateral position?).

Results

Demographics and CPET Results

Demographics and the summary of the baseline and 5-minute high intensity burst CPET results of the three participants are displayed in Table 1.

A baseline was established in the OR during two overnight sampling periods, during which the OR was closed with the particle count very close to zero (<0.02 cm³ identified using the APS).
All three participants were able to perform the 5-minute burst of high intensity exercise with and without a surgical face mask at the planned work rate. None of the three riders could achieve the target workload using an N95 mask. Given that none of the three fit and healthy cyclists could exercise beyond mild to moderate intensity exercise wearing an N95 mask, this line of inquiry in the experiments was considered futile and subsequent planned bouts of exercise using an N95 mask were abandoned. In total, each participant performed 14 separate HIE bursts over 2 days, seven without a face mask, six with standard surgical mask and one with an N95 mask.

As depicted in Figure 2a, the three participants produced a statistically similar quantity and distribution of aerosols. During 5 minutes of high intensity with sampling at 35 cm anterior to the face, the highest concentration of aerosol generation occurred within the 0.2–1.0 micrometre range. There were almost no particles 5 micrometres (Figure 2a and Table 2). The pattern of aerosol generation between the three riders was consistent in all conditions and positions and are subsequently presented as a single mean value. Exercise resulted in the generation of aerosol particles that were measured almost exclusively in the range 0.25–1 micrometres (Figure 2).

**Impact of Distance on Aerosol Concentration**

The impact of increasing distance on droplet/aerosol count from the exercise participant was evaluated at 35, 150 and 300 cm from the rider, with results shown in Table 2 and Figure 1b.
Figure 2a Aerosol generation by each rider. Distribution of aerosol measured by the MiniWRAS with sampling anterior to the rider exercising without a face mask. The shaded area indicates the standard deviation of the average of the three riders. Abbreviations: MiniWRAS, Mini Wide Range Aerosol Spectrometer.

Figure 2b Impact of distance on aerosol concentration. Average of three riders measured in front of the rider with no mask at increasing distances of 35 cm, 150 cm and 300 cm. The mean aerosol size distribution during exercise is shown on the left, with the mean and standard deviation of the total concentration of each case shown in panels on the right. Statistically significant reductions are present with increasing distance. Abbreviations: APS, aerodynamic particle sizer.

Figure 2b. With sampling anterior to the rider, in direct line with expiration, there was a 35% and 65% reduction, respectively, in MiniWRAS determined aerosol counts at 150 cm and 300 cm relative to 35 cm (p=0.003 for distance interaction). Using APS aerosol quantification, there was an 18% and 20% reduction, respectively (p=0.041 for the distance interaction). With lateral sampling, there was a 24% and 74% reduction in aerosols at 150 and 300 cm, respectively (p=0.037). The 4% and 15% reduction in APS values was not significant (p=0.15, Table 2 and Figure 2b) reflecting the lower concentrations of larger particle aerosols at all distances.
Impact of Mask Wearing on Aerosol Concentration

With a standard surgical mask there was a 38%, 56% and 58% reduction in submicron aerosol counts measured with the MiniWRAS at 35 cm, 150 cm and 300 cm, respectively, when measured in front of the rider (p=0.031 see Table 2 and Figure 3). There were no significant reductions associated with mask wearing in the larger aerosols measured with the APS (28% at 35 cm, 21% at 150 cm and 29% at 300 cm, p=0.32).

The potential for further improvements in aerosol counts was assessed comparing a standard surgical mask as compared with a tightly fitting N95 grade mask at 35 cm from the riders with an anterior sampling position. The N95 did reduce MiniWRAS aerosol counts more than a standard surgical mask as compared with no mask (58% vs 38%, p=0.031, Figure 3 and Supplementary Table 1).

Impact of Angle on Aerosol Concentration

The influence of angle on aerosol concentration was evaluated by comparing sampling in the anterior position, and in a 90° lateral position (Figure 5). There was a significant reduction in aerosol concentration when measured in the lateral position relative to anterior using MiniWRAS (p=0.029). (Supplementary Figure 2a). The effect of position on aerosols of larger particle size measured with APS was similar but did not reach statistical significance (p=0.10, Supplementary Figure 2b).

Impact of Angle and Mask on Aerosol Concentration

In contrast to anterior position, mask wearing did not alter small or larger aerosol counts as compared to no mask when sampling was lateral to the rider (p=0.64 and p=0.58 for miniWRAS and APS respectively, Table 2 and Figure 6).

Discussion

Using state-of-the-art measures of aerosol concentration in a unique experimental setting with trivial background particle confounding, we demonstrated that HIE generates a significant number of expired aerosols, predominantly in the 0.2–1.0 micrometre range. Aerosol concentration was attenuated with the use of a surgical mask when sampled in front of the rider. However, the use of a surgical mask did not reduce aerosol concentration when measured lateral to the rider. Aerosol concentrations were reduced further with the use of an N95 surgical mask but high intensity exercise was not able to be sustained by any of the riders and was deemed incompatible with exercise beyond mild exertion.
Our methodology was enhanced by measuring particle concentration by two techniques enabling an assessment over a large range of particle size. Although there was some overlap in the range of detection, the greatest number concentrations of particulate at all distances were measured in the 0.25–0.75 micrometre range that was exclusively measured with the MiniWRAS. Thus, the MiniWRAS results provided greater sensitivity than APS for detecting changes due to distance, mask wearing and position of sampling relative to the rider. Despite this, the two techniques were generally complementary with the direction and nature of effect proving similar in most settings. These findings should inform the design of future experiments aiming to quantify aerosol generation during increased respiratory ventilation.

It is noted that both these devices measure number, rather than mass, concentration. Aerosol microphysics dictates that number concentrations are dominated by smaller aerosols, whereas most of the mass is present in the larger aerosols. This has important implications for pathogen spread via aerosols where the ability of an aerosol to transmit a disease depends on where in the respiratory tract aerosols can penetrate (smaller aerosols making it ‘deeper’), and the total viral load reaching the patient (the larger aerosols with more mass are likely to carry more virus).

High background particle concentrations in our daily environment make detection of relatively small concentrations of aerosol challenging [24]. We achieved a clean background signal through the use of an ultralow baseline particle operating room. A standard gym has in the order of 800 particles per litre background with a size spectrum from 0.3–10 micrometres [24] and typically 6–10 air changes per hour [2]. The high baseline particle count of such facilities explains the difficulty detecting aerosol in this environment [24].

Previous data has demonstrated that glottic closure manoeuvres such as coughing and sneezing generate somewhere between 1,000–2,000 particles per episode [19]. Talking generates between 60–3,000 particles per litre [2]. At first glance, it would appear that high intensity exercise produces fewer particles. However, based on the typical 45-minute duration of an indoor cycling class, a single participant would be expected to generate a total aerosol count comparable to that of a glottic-closure manoeuvre. Furthermore, with participants in such an indoor cycling
class having a minute volume in the order of 100–150 litres per minute, it is likely that an individual will inhale large numbers of small particles generated by neighbouring participants in their immediate vicinity. Because the aerosol generated during HIE is in the submicron range, it is likely to remain suspended in the air for extended periods and thus be at an even higher risk of being inhaled. Lastly, exercise often stimulates upper airway irritation resulting in an increased rate of coughing and upper airway clearance that would compound aerosol concentration.

Respiratory droplets and aerosol can be generated from distal respiratory bronchioles and alveoli, larger airways, periglottic/laryngeal structures, and the oropharynx [14,19]. In general, smaller submicron aerosol is generated in terminal airways via a mechanism that relates to closure then reopening of terminal respiratory bronchioles. Terminal bronchioles collapse at smaller lung volumes and then reopen with inspiration, forming a plug that breaks up and generates small particles. These particles contain phospholipids and proteins commonly found in surfactant. This is particularly prominent with deeper respiration [19,20]. Forced exhalation with high velocity flow leaving large central airways generates larger particles in the 0.5–5 micrometre range. These have a different size and contain little to no surfactant material, supporting the different origin of the particles [19]. They are not prominent during quiet respiration and are usually deposited in the larger airways and larynx at rest. They may be more likely to appear with the high velocity short expiratory time typical of HIE [19]. As might be expected, we demonstrated a reduction in aerosol concentrations with greater distance from the source. However, we observed significant concentrations of aerosols at the 150 cm of physical distancing that is currently recommended in many Western countries [2,3]. There were further reductions at 300 cm, but even at this distance there were measurable concentrations of aerosol. Our findings suggest that we should not consider 150 cm to be a safe distance from an exercising individual in terms of aerosol exposure and should maintain as great a distance as possible, especially when indoors. The benefits of wearing a surgical mask have been widely debated during the COVID-19 pandemic [31,32]. Our data suggests that aerosol concentration reduces both with distance and with the use of a surgical mask. However, aerosol concentration with mask wearing is complex in that it clearly reduces aerosol concentration in the direction of exhalation (anteriorly) but not the concentration of aerosol particles when measured lateral to the rider at both 150 and 300 cm using either

Figure 4 Average aerosol concentrations when wearing a surgical mask measured in front of the rider at increasing distances.
The mean aerosol size distribution during exercise is shown on the left, with the mean and standard deviation of the total concentration of each case shown in panels on the right.
Abbreviations: APS, aerodynamic particle sizer; MiniWRAS, Mini Wide Range Aerosol Spectrometer.
sampling technique. It is possible that wearing of a surgical mask may direct the plume of aerosol laterally from the face. The increased resistance of air flow imposed by the mask could lead to gas and aerosol favouring directions of least resistance, such as gaps between the face and the side of the mask. The greater the minute volume and flow rate of expired air, the more aerosol could be directed in this manner. This could be an issue in indoor fitness facilities where exercise apparatus is often organised in a line with participants less than three metres lateral to one another. These findings have the potential to inform public policy in that the use of masks appear to reduce overall aerosol concentration but the efficacy of this intervention is far from absolute. The effect on aerosol concentration of wearing a mask appears similar to that resulting from distancing by an additional 1.5 metres. Furthermore, the effect of wearing a mask has lesser impact on exposure to aerosols lateral to the athlete. Therefore, the effect of mask wearing must be considered as only part of the strategy to reduce aerosol exposure in exercise environments.

All participants were able to perform HIE with the surgical mask with subjective discomfort but with no objective deterioration in the work rate achieved. Other recent studies have also suggested that standard surgical face masks have minimal impact on performance during HIE [33–35]. In part, this is probably consistent with the idea that inhaled and exhaled air finds pathways around the mask. On the other hand, our participants were unable to perform HIE wearing an N95 mask. An N95 mask is associated with a significant increase in the work of breathing [36] and an 8 mmHg increase in end tidal carbon dioxide compared with no mask or a standard surgical mask, even in young adults [34]. This likely explains the inability to exercise at the same intensity wearing N95 masks in our cohort.

The strengths of this study include the collaborative approach between clinicians, exercise physiologists and experts in atmospheric aerosols, using high fidelity aerosol detection equipment. The participants are typical of those found in an indoor fitness facility that exercise regularly. Formal cardiopulmonary testing adds additional value to quantify the volume of gas expiration occurring during high intensity exercise. Using an extremely low baseline aerosol concentration in an operating room enabled detection of a small signal. Our study examined aerosol generation in individual participants. It is likely that multiple participants performing simultaneous HIE would generate a higher total aerosol concentration. We used cycling as our model for exercise as cycling is widely used in gyms and in clinical exercise settings.
testing settings. It is possible that other forms of exercise and other equipment apparatus generate a different aerosol profile. The APS was unable to detect aerosol particles less than 0.78 micrometres in size. This likely explained the better sensitivity of the MiniWRAS to changes in aerosol concentrations with increasing distances and angle of the sampling devices relative to the rider. The techniques are complementary, detecting aerosol over a range of particle sizes.

Patient susceptibility to SARS-CoV-2 depends on a range of factors including viral load, duration of exposure and underlying comorbidities [25]. The minimum infectious ‘dose’ is currently unknown, and this study did not assess the

**Figure 6** Average aerosol concentrations in anterior and lateral positions at 300 cm away with riders wearing a surgical mask.
Mean aerosol size distribution during exercise is shown on the left, with the mean and standard deviation of the total concentration of each case shown in panels on the right.
Abbreviations: APS, aerodynamic particle sizer; MiniWRAS, Mini Wide Range Aerosol Spectrometer.

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**Table 3** Summary of findings and implications for public health policy and practice New findings.

- High intensity exercise generates aerosol predominantly in the 0.2–1 micrometre range.
- Increasing physical distance from the exercise participant reduces, but does not completely eliminate, exposure to aerosol.
- A surgical face mask worn during exercise reduces aerosol concentration measured anteriorly but not when measured laterally to an exercising subject. This may be due to high velocity jets between the face and mask during the higher minute volume and peak flow generated with exercise.

Impact on practice
- High intensity exercise in an indoor setting is likely to result in aerosol exposure to nearby participants.
- The commonly recommended 1.5 m distance rule reduces, but does not eliminate, aerosol exposure.
- Mask wearing has a relatively modest impact on aerosol spread that is only appreciable when measured in the direction of expiration. It should not be relied upon as the sole means of protection from airborne infections during exercise.
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infectivity of particles generated. The size distribution of aerosol generated during exercise make viral transmission plausible.

The safe reopening of indoor fitness facilities will likely require a combination of improvements in airflow, ventilation, in conjunction with physical distancing, screening of high-risk individuals and widespread vaccination.

Conclusion

High intensity exercise is an aerosol generating procedure with particles predominantly detected in the 0.2–1.0 micrometre range. Aerosol concentration is reduced with increasing distance in all directions but even at 300 cm from the source, aerosol concentrations are measurable. The commonly recommended ‘1.5 m rule’ would not safely protect other users from aerosol exposure in an indoor setting. The use of standard surgical masks results in modest reductions in aerosol concentration anteriorly but no reductions in concentration laterally. These findings have direct implications for public health advice as summarised in Table 3. If we were to extrapolate from aerosol concentration to risk of infection with a virus such as COVID-19, we may conclude that distances between exercising individuals need to be maximised and that masks provide an additional means of reducing aerosol exposure. However, the relatively modest protection from masks was only observed only in the direction of expiration of the exercising subject. Indoor exercise activities should not rely on masks alone for exposure minimisation but also emphasise distancing and ventilation.

Competing Interests

None of the authors have any competing interests or financial relationships that influenced this work.

Transparency Statement

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted.

Dissemination to Participants

Participants will receive a full copy of the peer reviewed manuscript.

Data Sharing

The authors commit to making the relevant anonymised patient data available on reasonable request.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2022.10.014

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Contributors

BC – study concept, design, data acquisition, data analysis and manuscript preparation
AY, IW, JW and RH — study design, data acquisition, data analysis and manuscript preparation.
KJ and SF — study design, data analysis and manuscript preparation.
FM and RD — study design and manuscript preparation.
ALG — study design, data analysis and manuscript preparation.

All authors take responsibility for the integrity and accuracy of the data analyses.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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