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Infection, Disease & Health xxx (xxxx) xxx

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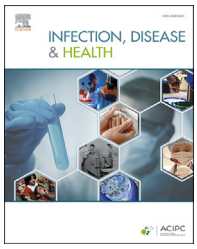

Research paper

Air purifiers for reducing the incidence of acute respiratory infections in australian residential aged care facilities: A study protocol for a randomised control trial

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Received 4 April 2023; received in revised form 29 May 2023; accepted 29 May 2023

KEYWORDS
Infection control;
Cross infection;
Nursing home;
Aged care;
Aerosols;
Patient safety

Abstract *Introduction:* Adults living in Residential Aged Care Facilities (RACFs) are highly susceptible to seasonal respiratory infections. Evidence indicates that the aerosols contaminated with virus particles in closed indoor spaces may play a significant role in the transmission of respiratory infections. In this protocol paper, we outline details of a planned RCT which aims to evaluate the effectiveness of portable in room air purifiers in reducing the risk of ARIs among residents in Australian RACFs.

This study uses a multi-centre double-blind randomised crossover design. Three RACFs in a regional area of New South Wales will be invited to participate in the study. Air purifiers with or without high-efficiency particulate absorbing (HEPA) filters will be placed in the rooms of residents who are enrolled in the trial. The primary outcome will be a reduction in the incidence of ARI and the secondary outcomes will be the time to first infection, number of emergency department admissions, hospital admissions, and medical consultations due to an ARI.
Conclusion: To our knowledge, this will be the first RCT using air purifiers in resident rooms to identify their effect in reducing ARIs in RACFs. If our findings indicate some potential benefit

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https://doi.org/10.1016/j.idh.2023.05.006

Please cite this article as: B. Thottiyil Sultanmuhammed Abdul Khadar, J. Sim, J. McDonagh et al., Air purifiers for reducing the incidence of acute respiratory infections in australian residential aged care facilities: A study protocol for a randomised control trial, Infection, Disease & Health, https://doi.org/10.1016/j.idh.2023.05.006

for in-room air purification, it will help provide support and justification for larger trials, which may include a facility wide approach to air purification.

Highlights

- The study aims to identify the effect of in room air purifiers on the incidence of acute respiratory infections.
- The study will use a cross-over RCT design to help control for individual confounders.
- The double blinding will enhance the reliability of the outcomes measured.

Introduction

Background and rationale

Age-related frailty and related immune senescence are known to be the leading factors responsible for older adults' susceptibility to various infections [1—3]. Residents of residential aged care facilities (RACFs) are highly vulnerable to developing acute respiratory infections [4]. Although older adults in RACFs are susceptible to a variety of viral agents [4], influenza and RSV are known to be clinically important in this cohort [5—8]. Despite the existence of various modes of transmission of respiratory viruses such as droplets, aerosols, direct and indirect contact [9,10], the spread of viral agents through aerosols has received more attention in recent times [11—13], The transmission of respiratory pathogens through aerosols has a strong evidence base[14—17].

Well-ventilated, clean air free of pathogens is an important component in reducing the risk of respiratory infection. Air purifiers (also called air cleaners or scrubbers) are used to provide additional protection where there is an increased risk of aerosol transmission. These should be used, in addition to other layers of protection, including but not limited to improving ventilation, vaccination, and the use of personal protective equipment (PPE).

Air purifiers have been shown to be effective in removing potentially harmful aerosols. A study that employed air purifiers in a COVID-19 ward demonstrated clearance of 99% of aerosols within 5 min [18]. Simulation studies using air purifiers in a classroom setting have also suggested benefits [19].

Air purifiers are also being used in people's homes, with the goal of reducing the risk of respiratory infection. To date, we are not aware of any multi-centre randomised control trials (RCT) examining the effect of using air purifiers in the rooms of RACF residents on the incidence of respiratory infection. We propose a pragmatic RCT to address this issue, acknowledging that there are challenges in undertaking such a trial in 'real world' conditions. In this protocol paper, we set out our planned approach to undertaking a RCT and present this consistent with the SPIRIT statement [20].

Objectives

The study aims to evaluate the effectiveness of air purifiers in reducing the risk of acute respiratory tract infection (ARIs) among residents in Australian RACFs**.** We hypothesise that the use of air purifiers in the rooms of RACF residents will reduce the incidence of ARIs.

Trial design

The proposed study will deploy a multi-centre double-blind randomised crossover design (Fig. 1). The trial is registered with the Australian New Zealand Clinical Trial Register (ACTRN12623000347662).

Methods: participants, interventions, and outcomes

Study setting

Three RACFs in a regional area of New South Wales will be invited to participate in the study A purposive sampling approach based on the research team's networks will be used to invite facilities. The choice of sampling approach for facilities is pragmatic. In the first instance, we seek to invite RACFs that are geographically positioned in close proximity to the researchers. The research team will contact the Chief Executive Officer or Director of Nursing/Care in RACFs to explain the study and gauge interest in participation. Where facilities are unwilling or unable to participate, invitations to RACFs will be extended to RACFs in other geographical locations in New South Wales. To be eligible for participation, the RACFs must be accredited by the Aged Care Quality and Safety Commission and be geographically based in New South Wales, Australia.

Participant eligibility criteria

The eligibility criteria have been identified for individual participants in the project. The study's participant inclusion criteria are: being a permanent resident of an Australian RACF enrolled in the study, residing in their private room (i.e. not a shared room); not being on Trajectory- C comfort care (palliative care); and ability to provide consent or guardian's approval if available. The exclusion criteria are being a respite resident, residing in a shared room, being on a palliative trajectory-C comfort care plan, inability to provide consent and requiring a public guardian's approval.

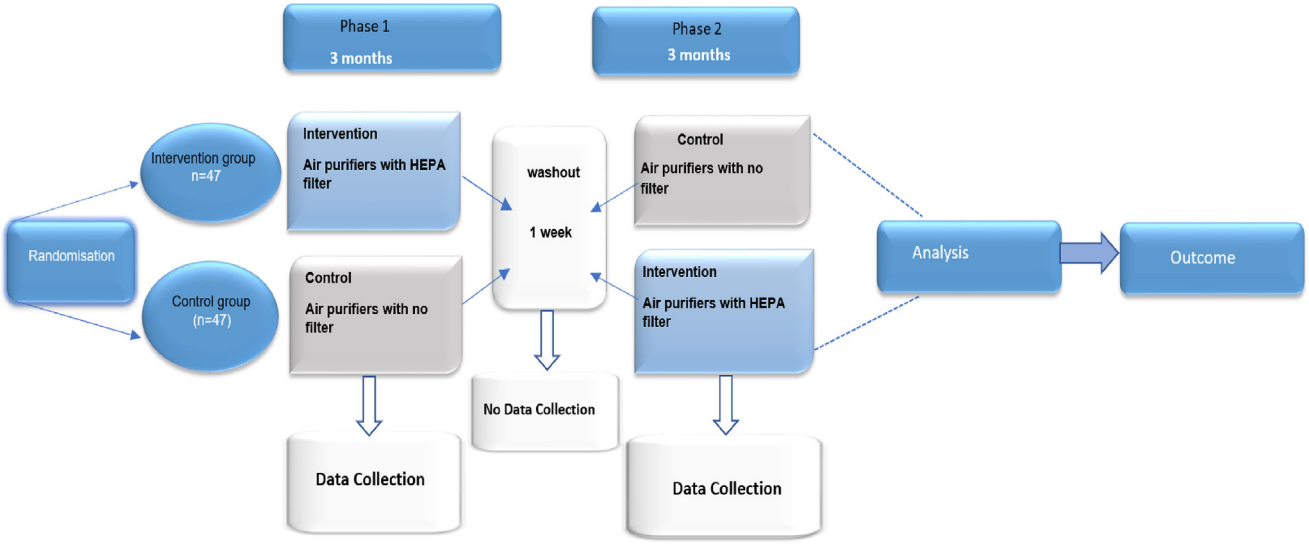

Figure: 1 **Study design**. Note: The sample size used in this figure excludes the attrition rate described in methods section.

Participant recruitment

A participant will be considered enrolled in the study if they meet the eligibility criteria and they or their nominated responsible person (enduring power of attorney or legal guardian) have provided informed written consent.

Intervention

All participants will receive an air purifier for use in their rooms. This is in addition to usual care, practice, and infrastructure. An air purifier will contain a HEPA-14 filter for air purification (intervention) or not contain a HEPA filter (control). The air purifier to be used in this trial has an ioniser function, but this is disabled for this trial. The positioning of air purifiers will be based on the published guidelines [21]. Air purifiers will only be placed in an individual resident's room, not in communal and shared areas. They will remain on at all times, on a setting that provides a clear air delivery rate of at least two-thirds of the room area.

The cleaning of air purifiers, in particular the pre-filter, will be undertaken by a person not involved in the study. Air purifiers will have a sticker placed over the join of the pre-filters, indicating not to be opened. This will enable the researchers to determine if blinding has been compromised. The placement and ongoing monitoring of air purifiers will be undertaken by one member study team, with the support of local staff. Instructions on how to use the air purifier will be provided to participants, including information on the minimum setting to be used.

The first phase of the study will continue for three months. After the first phase of the study, a washout period of one week will be applied. As the mean incubation and infectious period for common respiratory viral pathogens is less than 7 days [22—24] a one week washout period will be sufficient within this study. This wash-out period will be used to clean and swap/change air purifiers and eliminate carryover effects of air filtration (in the intervention group). Where a person acquires an infection during a phase, the infection will be attributed to that phase (noting that we are measuring infection as a dichotomous variable). Because our measurement of infection is a dichotomous variable, symptoms must resolve before a new infection can be counted. The second phase of the study will continue for another three months and commence immediately following the 1-week wash-out period.

Outcomes

Outcomes will constitute primary and secondary outcomes. Each participant will have a binary outcome, no infection, and infection, for their control and intervention study period. The primary outcome for this study is the incidence of ARI. Secondary outcomes include time to first infection, number of emergency department visits, number of hospitalisation due to ARI and the number of medical consultations due to ARI.

The case definition for Acute Respiratory Infection (ARI) is the sudden/acute onset of at least one of the following four respiratory symptoms: cough, sore throat, shortness of breath, coryza AND a clinician's judgement that the illness is due to an infection [25]. This definition is consistent with World Health Organization (WHO) Regional Office for Europe [26] Episodes of ARI may be further classified when there is a supporting pathology.

Sample size calculations

The assumptions for the proportions of participants with a respiratory infection are based on data from a systematic review [27]. The current incidence rate of ARIs in RACFs is estimated to be 40% (Childs et al., 2019). We estimate that air purification will result in a 50% reduction in ARIs. These are best estimates based on the limited available published data on this topic and informed by local data. Therefore, assuming the proportion of respiratory infections under control conditions is 40% and the expected proportion of

respiratory infections is 20% when using air purification, a cross-over trial with 94 participants (47 in each sequence) will have 80% power to detect this difference at the 5% significance level. This corresponds to an odds ratio of 0.375 for air purification (filtration) vs control (no filtration). Given the study population, we have included a 40% attrition rate. Therefore, our target sample is 132 participants.

Methods: assignment of interventions

Sequence generation and allocation concealment

One investigator (BM) will randomise participants using a protocol of randomisation stratified by site. This approach will ensure an even balance of participants in the intervention and control arms at each site. Randomisation will occur in a 1:1 ratio into one of the two sequences of intervention and control groups using a computer-generated randomisation schedule. Allocation concealment will be ensured as the same researcher will not disclose the outcome of randomisation to the remainder of the team and will hold the allocation in a password-protected database on a file not accessible to the remainder of the team. Upon the immediate commencement of the trial at a site BM will inform the remainder of the team of which air purifier should be provided to which participant.

Blinding

As air purifiers are pre-labelled, researchers allocating the air purifiers to participants will not be able to visually tell whether an air purifier is an intervention or control. The person responsible for cleaning the air purifiers and changing HEPA filters will be a member of the research team who is not responsible for collecting or determining outcome data. The changeover process will occur in a way in which the resident remains blinded to the intervention. For example, a HEPA filter will not be removed or installed in view of a resident. These practices will ensure the double-blinding of the trial.

Methods: data collection, management, and analysis

Data collection

Reliability is being assessed through a random observation and review of data. The primary data collector is a registered nurse with infection control training. The local IPC lead and their data acts as a cross-reference (validation) to data collected from the research team. The duration of the study is two 3-month periods with one week washout period. The intended starting date for the study is April 2023. This will allow the change between phases to coincide with the peak period of the influenza season in the southern hemisphere, thus allowing a relatively equal distribution of potential influenza risk in both phases, based on historical epidemiological data. After enrolment in the study, a researcher not involved in the randomisation process will be responsible for collecting baseline and demographic data from all participants.

The baseline and demographic data to be collected includes age, sex, past medical history, history of an ARI (if any), current medication, vaccination status, advanced care directives, facility residency status, mobility status, residents room size, bathroom (shared/private), external windows and details on the room heating, cooling, and ventilation system. During the course of the study, a researcher will visit participating facilities fortnightly to collect routine data. During this visit, the researcher will screen the medical, nursing, and laboratory records of all participants for any evidence of an ARI. Where an ARI is determined, the data such as signs and symptoms of ARI with the date of onset of the first symptom, laboratory tests (if any), rapid antigen test (RAT) results (if any), real-time-Polymerase Chain Reaction (RT-PCR)/culture/serum examination (SE) result (if any), the number of medical consultations including general and nurse practitioners reviews due to an ARI, the number of visits to an emergency department (ED) due to an ARI, the number of hospital admissions due to an ARI will be collected. Potential confounders will also be captured during routine data collection each fortnight. Participants in the study will not be subject to additional diagnostic tests to confirm ARI as part of the study. The use of diagnostic tests will be determined as part of their medical care, facility procedure, or usual practice, and results from diagnostic tests will be collected as part of routine data collection. Outbreaks will be identified through working in partnership with the IPC lead in the participating sites. Details regarding outbreaks and measures taken will be captured. These will be presented descriptively to help explain and interpret results. Data on the number of visitors to each facility is kept routinely. These data will be reviewed for identifying any major trends during the study period and will be described in any future publication if necessary.

We will use the De Morton Mobility Index (DEMMI)-Modified to conduct mobility assessments on each participant [28,29]. We will also collect data on the time spent in the dining room, activities room, or in other social activities and aims to capture a baseline of time spent out of their room as part of regular or routine activities. Data on the pattern of mobility will be collected in Phase 1 and Phase 2 of the trial to ensure that changes over time are captured.

Ongoing data collection in participating facilities will be carried out by one member of the research team who will be blinded to the intervention. These data will be collected and recorded electronically via an iPad using an online data collection form.

Statistical methods

Primary outcome

The effectiveness of the intervention will be assessed by comparing the proportion of infections over the two cross-over study periods. Each participant will have a binary outcome, no infection, and infection, for their control and intervention study period and analysis will include a fixed effect for each site. The treatment effect will be measured

using logistic regression mixed effects models, where the main effects in the model will be intervention, study collection time, and cross-over design characteristics. A random intercept effect for an individual will correct for non-independent observations made between the cross-over study periods. The model will estimate an odds ratio that will compare the odds of infection when having air filtration active against not having air filtration active. Where a person acquires an infection during a phase, the infection will be attributed to that phase (noting that we are measuring infection as a dichotomous variable). Because our measurement of infection is a dichotomous variable, symptoms must resolve before a new infection can be counted.

Secondary outcomes

Time to respiratory infection will be modelled using survival analysis with lost-to-follow-up and death to be considered as censoring events. Kaplan-Meir curves will be used to estimate the survival function. A mixed-effect cox regression model will be used to assess the change in hazards between the treatment and control arms of the study, where a random effect will account for within-patient correlation. The effect of the treatment will be assessed by the hazard ratio, which will compare the change in hazards between the two-treatment cross-over arms.

Due to a high possibility of participants being lost-to-follow-up in this sample, demographics and clinical characteristics will be used to conduct the analysis using multiple imputations if death or discharge from the RACF occurs. An alpha threshold of 0.05 will be used to assess statistical significance and the reported results will include 95% confidence intervals.

Discussion

To our knowledge, this will be the first RCT using air purifiers in resident rooms to identify their effect in reducing ARIs in RACFs. If our findings indicate some benefit for in-room air purification, it will help provide support and justification for larger trials, which may include a facility wide approach to air purification. Our research study is focused solely on evaluating the effect of additional in-room air purification in a setting with a potentially high risk of ARI, compared to current practice. Our approach and research question were guided by the trend of using air purifiers for this purpose and by our available resources. The proposed study has limitations, many of which are a reflection of being a pragmatic trial.

The proposed project has confounders. The use of a cross-over trial design will help address many of these, including individual risk factors, medications, residents residing in single rooms with related infrastructure such as windows and bathrooms that remain consistent throughout the trial, personal care requirements (and thus contact time with staff), frequency of visitors and time spent outside their room. The settings for the study, at the time of publication, require all staff and all visitors to wear a mask. Similarly, all staff and visitors must have a negative COVID-19 rapid antigen test prior to entering the facility. We will monitor for changes in these throughout the study period.

One example of our approach to monitoring one potential confounder relates to exposure to other residents, such as communal games, meals, and socialising. Each resident's mobility status will be captured as part of baseline demographic data and in routine data collection every 2 weeks to document changes in mobility patterns over the course of the study. In addition, a cross-sectional audit of each resident's movement on a 'typical' day will be captured during each phase of the study. These data will be quantified to estimate the average amount of time a resident spends outside their room each day in hours. As this is a cross-over design with participants acting as their control for the purpose of data analysis, such confounders will hopefully have limited impact. However, we are undertaking these measures to identify changes in potential confounders that may influence results, should they change.

Strengths and limitations

The study is enhanced by double blinding and the cross-over design. Every participant in the trial will be exposed to the effect of portable in-room air purification. An important caveat of our study is that we are only evaluating the effect of adding portable air purifiers inside participants' rooms. No assumptions over and above this could be made. Our study is limited by the confounders described earlier, reduced by using a cross-over design. Our study is pragmatic in nature. Since participants are residents in RACFs, the likelihood of loss to follow-up in this study is comparably high. We have enhanced our sample size in response to this. Due to available resources, it is not possible to undertake genomic sequencing of positive cases, a limitation of our study. The purposive sampling approach used to recruit sites may present a source of bias. We acknowledge there are varying case definitions for ARI, particularly when attempting to encompass a range of infections in one broad category and in the context of aged care. Our case definition is broadly consistent with other published papers that used influenza like illness as an outcome [30], [-32] and our desire to determine whether in-room air purification disrupts transmission of respiratory infections. None the less, it comes with limitations.

Ethics and dissemination

Dissemination

The dissemination plan will be implemented by the investigators which include key communication strategies for all stakeholders, an open access publication plan, authorship requirements, and publication standards that align with the NHMRC Australian Code for the responsible conduct of research and the international committee of medical journal editors' recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Any third-party access to the data collected in this study will only be granted if appropriate ethical approvals have been sought. Full de-identified data sets and statistical codes will only be available by contacting the principal investigator and providing the appropriate ethical approval.

Data access

Data sharing is not applicable as no datasets were generated and/or analysed for this Protocol paper.

Trial status

The facility recruitment has been finalised and the study team is finalising the consent process and participant recruitment. The trial is due to commence in April 2023.

Ethics

Approval has been obtained from Hunter New England Human Research Ethics Committee (2022/ETH02470). The study has been registered with UON HREA (Ref. No: H-2023-0068). Informed written consent will be sought.

Author contributions

BM and AK conceived the idea. AK, JS, BM, JM and VM provided critical input into the design of the study. AK drafted the manuscript, and all authors provided critical input into the paper and approved the final version.

Conflict of interest

One of the authors has an editorial affiliation with the journal. This author played no role, whatsoever, in the peer review process, handling or decision making in relation to this paper.

Funding

The study is investigator-initiated. BK is supported by an Australian Government RTP scholarship. BM is a recipient of a NHMRC Investigator Grant (GNT 2008392).

Provenance and peer review

Not commissioned, externally peer reviewed.

Acknowledgments

Air purifiers for this study are being kindly supplied by GAMA Healthcare. They have and will play no role in the study design, conduct, data collection, analysis, and interpretation of study findings.

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