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Portable HEPA Purifiers to Eliminate Airborne SARS-CoV-2: A Systematic Review

David T. Liu, MD[1], Katie M. Philips, MD[2], Marlene M. Speth, MD, MA[3], Gerold Besser, MD, PhD[1], Christian A. Mueller, MD[1], and Ahmad R. Sedaghat, MD, PhD[2]

Abstract

Objective. Current epidemiologic predictions of COVID-19 suggest that SARS-CoV-2 mitigation strategies must be implemented long-term. In-office aerosol-generating procedures pose a risk to staff and patients while necessitating examination room shutdown to allow aerosol decontamination by indwelling ventilation. This review summarizes the current state of knowledge on portable high-efficiency particulate air (HEPA) purifiers' effectiveness in eliminating airborne SARS-CoV-2 from indoor environments.

Data Sources. Medline, Embase, Cochrane Databases, and the World Health Organization's COVID-19 Global Literature on Coronavirus Disease.

Review Methods. Data sources were systematically searched for original English-language published studies indexed up to January 14, 2021 per the following search strategy: ("HEPA" OR "High-efficiency" OR "High-efficiency particulate air" OR "Efficiency particulate" OR "Purifier" OR "Filter" OR "Cleaner" OR "Filtration") AND ("COVID" OR "COVID-19" OR "SARS-CoV-2" OR "Coronavirus"). Additional relevant studies were identified by searching the reference lists of included articles.

Results. Eleven published studies have evaluated the effectiveness of portable HEPA purifiers in eliminating airborne SARS-CoV-2 with relevantly sized surrogate particles. Ten studies evaluated aerosols and submicron particles similar in size to SARS-CoV-2 virions. In all studies, portable HEPA purifiers were able to significantly reduce airborne SARS-CoV-2-surrogate particles. The addition of portable HEPA purifiers augmented other decontamination strategies such as ventilation.

Conclusion. Experimental studies provide evidence for portable HEPA purifiers' potential to eliminate airborne SARS-CoV-2 and augment primary decontamination strategies such as ventilation. Based on filtration rates, additional air exchanges provided by portable HEPA purifiers may be calculated and room shutdown times potentially reduced after aerosol-generating procedures.

Keywords

COVID-19, coronavirus, HEPA, portable air purifier, air quality, SARS-CoV-2, aerosol-generating procedures, air purifier

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The airborne transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent for coronavirus disease 2019 (COVID-19), represents one of the most common—and therefore significant—disease transmission routes.[1-3] As indoor environments may increase the risk of transmission for SARS-CoV-2 by containment and concentration of airborne virus, different air decontamination strategies have been recommended for transmission control.[4] While indwelling ventilation systems that have been designed and built for infection control are the ideal means for clearance of airborne virus, many facilities are neither equipped with such ventilation systems nor able to be retrofitted in a practical or cost-effective way. In response to the urgent and continued need for infection control strategies for airborne SARS-CoV-2, portable air purifiers have been recommended as an adjunctive means for indoor decontamination.[4-6] Indeed, portable high-efficiency particulate air (HEPA) purifiers have been recommended to increase the aerosol decontamination efficiency of more traditional systems, such as indoor and outside air ventilation.[5,6] Hence, there is a need to better understand the efficacy of portable HEPA purifiers and how they should be implemented for indoor decontamination of airborne SARS-CoV-2 and control of COVID-19 spread.

Aerosol-generating procedures (AGPs) are frequently performed in clinics worldwide.[7-10] While it is recommended to

[1]Department of Otorhinolaryngology–Head and Neck Surgery, Medical University of Vienna, Vienna, Austria
[2]Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA
[3]Department of Otorhinolaryngology, Kantonsspital Aarau, Aarau, Switzerland

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Corresponding Author:
Ahmad R. Sedaghat, MD, PhD, Department of Otolaryngology–Head and Neck Surgery, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0528, USA.
Email: ahmad.sedaghat@uc.edu

perform these procedures in airborne infection isolation (negative pressure) rooms—including those procedures that pose the risk of coughing and uncontrolled respiratory secretions, such as bronchoscopy or peritonsillar abscess drainage—the numbers of these specialized rooms available in clinics and hospitals around the world are not sufficient to accommodate the volume of patients who need AGPs.[11-15] In the absence of rooms with appropriate negative air pressure control, many indoor spaces (especially older buildings) rely on heating, ventilation, and air conditioning (HVAC) systems alone.[16,17] The US Centers for Disease Control and Prevention (CDC) has provided guidance for the length of time that a room should be closed (''shutdown time'') to adequately decontaminate airborne SARS-CoV-2 with an HVAC system, which is based on the system's air exchange rates (air changes per hour [ACHs]).[5] Indeed, many otolaryngology clinics have been depending on their indwelling HVAC for air decontamination after AGPs and hence shutting down clinic examination rooms in between patients for time periods based on CDC guidelines. Because the time required for efficient airborne-contaminant removal is strongly associated with the indwelling HVAC's ACH, room shutdown time has been a major challenge for medical practices that perform frequent AGPs. If the ACH is low, it can take 45 minutes to >1 hour (for realistic ACHs currently faced by providers) until airborne contaminants are efficiently removed from indoor environments.[5] Although warmer weather leading to more outdoor activities and the proliferation of SARS-CoV-2 vaccines are anticipated to provide better control of COVID-19, the development and spread of SARS-CoV-2 mutants suggest that COVID-19 will be a lasting challenge to society and the practice of medicine. As a result, practical long-term options are needed for air decontamination after the performance of AGPs in the office, without the need to close down clinic examination rooms and reduce clinical volume for unsustainable lengths of time.

Portable air cleaners (PACs) represent an affordable option to enhance air filtration. Indeed, portable HEPA purifiers—specifically, PACs that are equipped with a filter that removes at least 99.97% of airborne particles approximately 0.15 μm in diameter—have been proposed by the CDC for infection prevention and control during and immediately following an AGP.[6,18-20] However, as the research literature on the effectiveness of HEPA filters and PACs during COVID-19 and relevant airborne particle sizes has been scant and scattered in different fields of research, there is a lack of a summary of the data supporting HEPA purifiers as an adjunctive decontamination strategy. Hence, this review aimed to accumulate and synthesize the evidence for portable HEPA purifiers' efficiency to decontaminate airborne SARS-CoV-2.

Methods

Search Strategy

We performed a systematic review according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses).[21] Two independent reviewers (D.T.L. and A.R.S.) searched Medline, Embase, the Cochrane Library, and the World Health Organization's COVID-19 Global Literature on Coronavirus Disease database. The search strategy included a combination of keywords for the following 2 concepts: HEPA purifier and COVID-19. We searched databases from inception to January 14, 2021, for the following search terms: (HEPA OR High-efficiency OR High-efficiency particulate air OR Efficiency particulate OR Purifier OR Filter OR Cleaner OR Filtration) AND (COVID OR COVID-19 OR SARS-CoV-2 OR Coronavirus). Additional articles were identified by screening reference lists of all articles meeting the inclusion criteria.

Selection Criteria

We followed the PICO approach to formulate the following research question[22]: What is the efficiency (O: outcome) of portable HEPA filter–based PACs (I: intervention) in an indoor/closed-chamber setting to eliminate airborne SARS-CoV-2 with relevantly sized surrogate particles (P: problem)? This review is limited to experimental studies comparing PACs with HEPA and non-HEPA filters, no ventilation, and natural ventilation settings (C: comparison) to evaluate filter efficiency. Experimental studies required the following criteria to be eligible for this systematic review: reported particle sizes <1 mm (<1000 μm), published in the English language, used HEPA filter–based PACs, and conducted in an indoor environment.

Data Extraction

Following inclusion and full-text review, 2 reviewers (D.T.L. and A.R.S.) independently extracted the following information when available: author, year of publication, room setting in which the experiment was conducted, ventilation setting, air purifiers evaluated, aerosol particle generator, particle sizes evaluated, particle detector used, experimental setting, main results, and interpretation of results.

Results

Search and Study Characteristics

The initial screening process returned 2653 citations, from which we removed 522 due to duplicate results. We screened the titles and abstracts of 2131 articles, from which we performed full-text review for 40 articles (**Figure 1**). Finally, 11 articles met our inclusion criteria and were included in the review (Supplementary Tables S1 and S2, available online). All studies performed experiments in an indoor environment and evaluated the aerosol removal efficiency of HEPA filter–based PACs. Studies were published between 1985 and 2021.[23-33]

Room Setting and Room Ventilation

Experimental room sizes varied considerably among studies,[23-33] ranging between 14.75 and 108 m^3. Two studies evaluated filter efficiency in a setting with no additional ventilation.[24,25] Five studies performed experiments in a minimal ventilation setting,[28,31-34] while the remaining 4 studies compared ventilation and no-ventilation settings.[26,27,29,35] Room ventilation was reported as ACH (h^{-1}), which is defined as the air volume that is added to or removed from the testing room in 1 hour, divided by the room's volume. In those 4 studies that compared ventilation with no-ventilation settings, all air

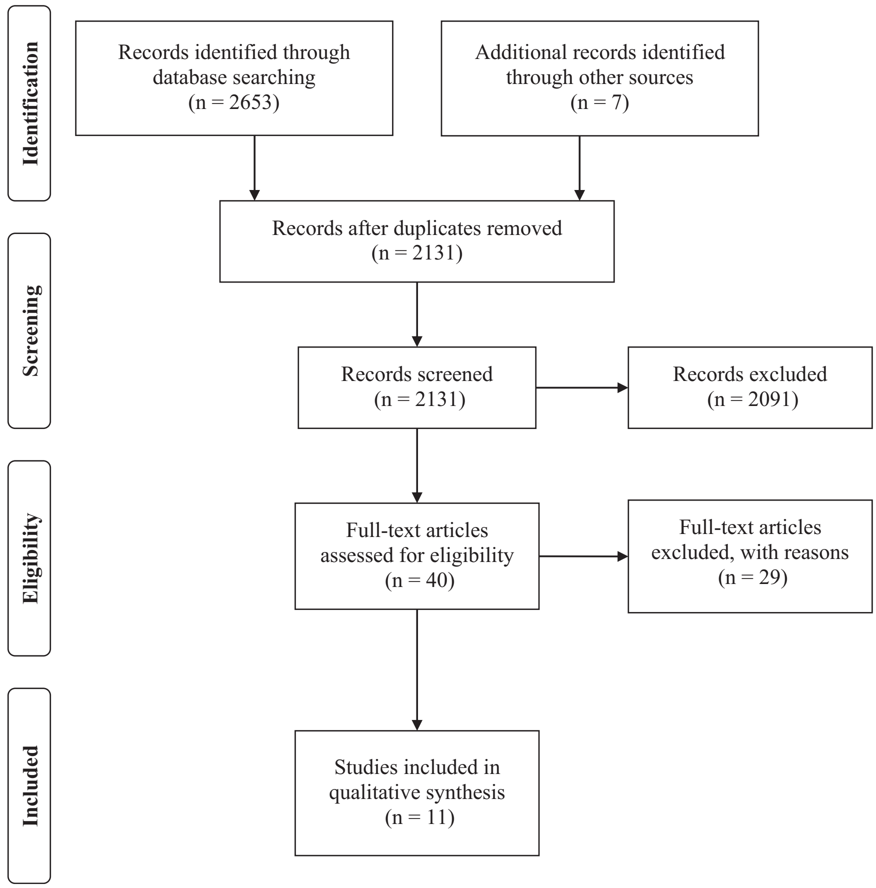

Figure 1. PRISMA flowchart.

Table 1. Filter Types and Specifications.

Portable air cleaner	Specifications
Mechanical air filter	Removes by capturing particles in filter material
Panel/flat filter	Most simple filter type
Extended surface/pleated filter	Advanced panel filters with higher efficiency
HEPA filter	Most efficient mechanical filter type
Hybrid air filter	Combines mechanisms of mechanical and electronic air filter
Electret filter	Electrically charged filter media augments mechanical filtering
Electronic air cleaner	Uses electrostatic attraction to trap particles
Electrostatic precipitator	Charges particles that are then collected within the device
Negative ion generator	Releases ions into the air
UV light pollutant eliminator	Uses UV light technology to destroy pollutants
UV germicidal irradiation	Uses short-wavelength UV light to inactivate and kill pathogens
Photocatalytic oxidation	UV light activates a catalyst, which then releases electrons that interact with water molecules
Ozone (O_3) generator	Generates ozone

Abbreviations: HEPA, high-efficiency particulate air; UV, ultraviolet.

change rates ranged from 2 to 32 h^{-1} (one study did not specify ventilation rates).

Portable Air Purifier Tested

We summarize all PAC models in this review in **Table 1**. The exact PAC model type was reported in 6 studies. Four studies evaluated 1 portable HEPA model. Six studies compared PACs with HEPA and non-HEPA filters, while the remaining study compared 6 portable HEPA filter–based PACs. Zuraimi et al compared filter efficacy among PACs based on an electret filter, HEPA filter, electrostatic precipitator (ESP), negative ion generator (ION), photocatalytic oxidation (PCO), ozone generator (O_3), and ultraviolet germicidal irradiation (UVG).[32] Offermann et al evaluated the efficiency of PACs based on a foam filter, electret filter, HEPA filter, ESP, and ION.[28] Similarly, Zuraimi et al compared the filter efficacy of PACs based on a electret filter, HEPA filter, ESP, and ION.[33] Likewise, Mølgaard et al compared PACs based on a particle filter, HEPA filter, ION, and ESP.[31] Waring et al compared the filter efficacy of PACs based on a HEPA filter, ION, and ESP, while Miller-Leiden et al compared a HEPA filter–based PAC against a standard PAC with a filter of 95% efficiency at 0.3 μm.[27]

Aerosol Particles and Sizes Evaluated

The aerosol particle–generating procedure was reported in all studies except for 1. Two studies used NaCl aerosols (sodium chloride),[32,33] while 1 study used NaCl and oily aerosols (di-ethyl-hexyl-sebacat) for its experiments.[31] Miller-Leiden et al assessed filter efficiency based on chemical aerosols (oleic acid) and bacterial particles (suspension of *Bacillus subtilis*).[27] Ren et al[35] and Waring et al[34] created particles by burning incense sticks, while Bluyssen et al[26] used air-filled soap bubbles. Peck et al evaluated diesel particles and KCl (potassium chloride) particles during their experiments.[25] Offermann et al used tobacco smoke generated by a cigarette smoking machine to assess PAC efficiency. The exact sizes and range of aerosol particles investigated were reported in all studies.[28] Bluyssen et al evaluated air-filled soap bubbles ''with diameters in the submillimeter range'' (<1000 μm). All other studies evaluated aerosol particle sizes ranging between 0.012 and 19.81 μm.[26]

Experimental Settings

The test protocol to measure PAC efficiency varied significantly among studies. The clean air delivery rate (CADR)—usually cubic feet per minute (ft^3/m) or square meter per hour (m^3/h)—is defined as the volume of purified air that has had all the particles of a given size distribution removed. Thus, the higher the CADR, the more efficient the PAC for particles of a given size range. The CADR was reported in 5 studies. Among these, 4 used a similar protocol in which the authors measured (1) the aerosol concentration with the PAC turned off (''natural decay'') and (2) the aerosol concentration with the PAC turned on after an aerosol injection phase. The CADR was also reported in the study by Mølgaard et al, in which the authors measured particle concentration in no-PAC and PAC settings while the aerosol generator was constantly turned on.[31]

PACs: HEPA Filter vs Non–HEPA Filter

While SARS-CoV-2 virions are approximately 0.1 μm in diameter,[36] larger respiratory droplets and aerosols (>1 μm) have been found to harbor the virions as well.[37,38] As mentioned, studies that assessed filter efficiency of HEPA and non-HEPA PACs covered not only the size of SARS-CoV-2 virions themselves but also that of larger respiratory droplets and aerosols that may harbor the virions. Starting with the study that evaluated the smallest particle size (ascending order), Mølgaard et al compared the filter efficiency of PACs based on a particle filter, HEPA filter, ION, and ESP for particles between 0.012 and 10 μm. The authors found that the HEPA filter–based PACs removed particles most effectively (highest CADR) and with an efficiency that was essentially independent of particle size, followed by the particle filter. In comparison, the ION- and ESP-based PACs were least efficient, and CADR was particle size dependent: while the ION-based PAC was more efficient at smaller particle sizes, the ESP was more efficient at larger sizes.[31] Waring et al assessed and compared the filter efficiency of PACs based on a HEPA filter, ION, and ESP for particles ranging from 0.0126 to 0.514 μm. The authors found the highest CADR (m^3/h) for 1 of the HEPA filter–based PACs, followed by the ESP-based and the other HEPA filter–based PACs. Both ION-based PACs were least efficient during their study.[34] Zuraimi et al compared the filter efficiency of PACs based on an electret filter, HEPA filter, ESP, and ION for particle sizes ranging from 0.0141 to 19.81 μm. The authors indicated that the PACs based on ESP, a HEPA filter, and electret filter were similarly effective, with the ESP-based PACs showing the highest size-resolved CADR across nearly all particle sizes evaluated. The least efficient was the ION-based PAC during their study.[33] Zuraimi et al conducted a second study in which they compared the filter efficiency of PACs based on a electret filter, HEPA filter, ESP, ION, PCO, O_3, and UVG for particle sizes ranging from 0.014 to 0.532 μm. They classified evaluated PACs into 3 groups according to their efficiency: high-performing PACs (HEPA filter, electret filter, and ESP), low-performing PACs (ION based), and very poorly performing PACs (PCO, O_3, and UVG).[32] Miller-Leiden et al compared PACs with HEPA and non-HEPA filters with 95% efficiency at 0.3 μm for chemical and bacterial particles >0.8 μm and >0.4 μm, respectively. They concluded that PACs with efficient but non-HEPA filters were as efficient as those with true HEPA filters.[27]

Efficiency of HEPA Filter–Based PACs: Particle Size

Peck et al evaluated the efficiency of 6 HEPA filter–based PACs for particles sized between 0.03 and 10 μm. The authors found that the CADR varied significantly by particle size, with the lowest CADRs for particles <0.1 μm.[25] Ren et al assessed 1 HEPA filter–based PAC's efficiency for particles of 3 distinct sizes: 0.3, 0.5, and 1.0 μm. The authors noted that the HEPA filter–based PAC removed particles of all sizes evaluated after a 5-minute injection phase, followed by a 30-minute observation-and-filter period.[35] Similarly, Mousavi et al evaluated the filter efficiency of 2 identical HEPA filter–based PACs for particles of 3 distinct sizes: 0.3, 1.0, and 3.0 μm. The authors showed that the HEPA filter–based PAC reduced aerosol concentration noticeably, even when operating only for a short period (ie, 3 minutes).[24] Qian et al evaluated the filter efficiency of a single HEPA filter–based PAC for particles of 4 size ranges: <1, 1 to 5, 5 to 10, and >10 μm. They showed that a HEPA filter–based PAC effectively decreased the particle concentration of all sizes evaluated.[29] Bluyssen et al evaluated the filter efficiency of a single HEPA filter–based PAC for particles <1000 μm. The authors stated that the particle count was significantly lower when the HEPA filter–based PAC was turned on as compared with a no-filter setting after 10 minutes of particle generation.[26]

Impact of Room Ventilation on Filter Efficiency

Three studies evaluated the impact of different room ventilation settings on PAC filter efficiency. Miller-Leiden et al performed experiments with 3 ventilation rates (ie, HVAC ACH): 0 (no ventilation), 2 h^{-1}, and 6 h^{-1}. The authors found contrary results regarding the association between ventilation rates and filter efficiency. While the effectiveness increased with higher ventilation rates in some settings, they observed the opposite in other cases.[27] Ren et al also evaluated the impact of mechanical ventilation and PAC on particle removal efficiency. The authors assessed various ventilation settings, with ACH rates ranging from 2 to 32 h^{-1}. They indicated that particle concentrations decreased faster in rooms with higher ventilation rates and that a HEPA filter–based PAC additionally augmented the decrease of particle concentration.[23] Qian et al evaluated the impact of an operating HVAC system and a HEPA filter–based PAC on particle decay rates and noted that the particle decay curve was steepest when both systems were turned on.[29] In other words, HEPA purifiers were found to augment other means of room ventilation for airborne particle decontamination.

Impact of PAC Placement on Filter Efficiency

One study evaluated the impact of PAC placement on filter efficiency. Bluyssen et al performed experiments where they placed 1 HEPA filter–based PAC in front and 1 behind a particle generator. The particles were counted in front of the particle generator.[26] While both PACs removed particles efficiently, the authors found that the PAC placed in front of the subject removed most particles when it was turned on the highest airflow rate setting. Interestingly, the PAC placed behind the subject removed most particles when it was turned on the second-highest airflow rate setting. The authors hypothesized that different PAC positions created different turbulence patterns within the room, leading to reported results.

Discussion

The COVID-19 pandemic has kept the world in suspense since its outbreak in December 2019, and its persistence—despite the proliferation of vaccines—is ensured by the development of mutant SARS-CoV-2 variants. Airborne transmission represents the dominant route of infection,[1-3] and several protective measures have been recommended for indoor environments, such as ensuring proper ventilation with outside air or activation of HVAC systems to decontaminate the air.[6] However, rooms without windows and older HVAC systems with a lower ACH limit those simple decontamination strategies. Hence, other strategies are urgently needed. The CDC has recommended using portable HEPA filter–based PACs to augment primary decontamination strategies based on HVAC systems for airborne infectious agents, including during the COVID-19 pandemic.[5] However, literature is limited on HEPA filter–based PACs' effectiveness in various settings and for different particle sizes. In this systematic review, we have synthesized experimental studies from various research fields and prevailing evidence for the efficacy of HEPA filter–based PACs to decontaminate airborne particles of sizes relevant for SARS-CoV-2. We found that HEPA filter–based PACs were among the most efficient PACs for removing particles in the size range of SARS-CoV-2 virions and larger aerosols or respiratory droplets that are believed to harbor the virions.

Regarding HEPA filter–based PACs' efficiency as compared with other PAC models, our review revealed that tested HEPA filter–based PACs were always the most efficient ones evaluated except for 1 study, in which an ESP–based PAC performed slightly better.[33] This is not surprising, as HEPA filters must adhere to very stringent standards, filtering at least 99.97% of aerosols tested with a size of approximately 0.15 μm in diameter and with even greater efficiency for other particle sizes (larger and smaller).[6,18,19] Furthermore, the US Environmental Protection Agency (EPA) recommends consideration of HEPA filter usage when choosing a PAC.[6]

With respect to decontamination of airborne particles and aerosols after AGPs in clinic or hospital treatment rooms, most facilities are equipped with HVAC systems.[39,40] However, many of these are limited in their ACH, which consequently limits turnover times significantly after AGPs (ie, from 46 to >120 minutes).[5] As common otolaryngology procedures are classified as AGPs or possible AGPs (based on the patient's response and therefore approached as an AGP),[7-10] the ACHs of older facilities or those not designed with infection control in mind could greatly limit the number of patient encounters due to the need for adequate room shutdown times. Portable air purifiers—especially those that are HEPA filter based—may provide an easy solution to augment primary decontamination strategies based only on HVAC systems and significantly improve turnover times after patient contacts.

The role of PAC placement on filter efficiency has been investigated, and the EPA has provided guidance on PAC placement in an indoor setting. In summary, the EPA recommends placing the PACs (1) near the source of pollutants if present, (2) near the breathing zone of residents, and (3) not behind furniture (ie, open space).[41] Similarly, Bluyssen et al tested 2 PAC positions and found that the HEPA filter–based PAC removed particles effectively, irrespective of positioning.[26]

HEPA filter–based PACs—combined with HVAC systems or as stand-alone air decontamination systems—remove SARS-CoV-2 surrogate particles effectively and may be considered in indoor rooms with limited air ventilation to reduce turnover times after AGPs and medical procedures in general. Although HEPA filter–based PACs can be easily purchased online, consumers are cautioned that a true HEPA filter–based PAC has to meet stringent criteria and has to be tested and certified by the International Organization for Standardization (ISO 29463) or the US Institute of Environmental Sciences and Technology (IEST-RP-CC001.6). The exact quantitative details of the degree to which HEPA purifiers may reduce room shutdown times in the clinic is still to be debated, and implementation policies must be determined on an institutional basis. However, several previously reported quantitative findings may be of help. Previous research by the EPA has shown that the concentration of an airborne particle as a function of time, $C(t)$, that is being decontaminated by an air purifier can be calculated as follows[42]:

$$C(t) = C_0 e^{-(\mathrm{CADR}/V)t},$$

where CADR reflects the clean air delivery rate for the particular particle size and V indicates the volume of the room where the air purifier is placed. Moreover, the ACH attributable to an air purifier could be calculated as follows:

$$\mathrm{ACH} = (\mathrm{CADR}/V) \times 60\mathrm{h}^{-1}.$$

The amount of time needed for an air purifier to decontaminate the concentration of an airborne particle by 99% (as used by the CDC to determine guideline room shutdown times)[5] can be calculated as follows:

$$\text{shutdown time(min)} = [-\ln(0.01) \times 60]/\mathrm{ACH}.$$

Finally, present-day commercially available air purifiers most commonly report CADR for 3 classes of particle size: smoke (0.1-1 μm), dust (1-30 μm), and pollens (2.5-80 μm). As the smoke CADR is typically the least efficient, one may reasonably consider it as conservatively reflective of a PAC's ability to decontaminate airborne particles of relevance to SARS-CoV-2, or one may even build in an additional safety buffer by arbitrarily lowering the smoke CADR in calculations related to room shutdown time. As an example, commercially available HEPA purifiers routinely have a smoke CADR of $\geq$200 ft^3/min. For a clinic treatment room that is 1000 ft^3 (10 × 10 × 10 ft), this could translate to 12 ACHs attributable to just the HEPA purifier, which by itself would allow a room shutdown time of 23 minutes. If added to a clinic room with an HVAC system that already provides 6 ACHs, such a HEPA purifier could shorten the room shutdown time after an AGP from 46 minutes (6 ACHs from the HVAC alone) to as low as 15 minutes (18 ACHs from the HVAC and HEPA purifier combined).

Although we performed a comprehensive and guideline-driven systematic review, the current study had limitations. First, there was substantial heterogeneity in the selected experimental studies. For example, the study protocol—including the particle-generating procedure and the experimental setup—was different in most studies. Furthermore, while some studies evaluated particle concentrations using optical particle counters, others used handheld particle counters or even integrated filter samples located throughout the test room. All of these factors limited the possibility to conduct a meta-analysis. Therefore, we performed a qualitative analysis of the studies to describe the effectiveness of HEPA purifiers to remove airborne particles of sizes that would have direct clinical relevance to SARS-CoV-2 and the COVID-19 pandemic. Moreover, while we have reported the quantitative means by which to calculate the ACH for a HEPA purifier and resultant room shutdown times, the exact implementation of these calculations is up to the practitioner, facility, and institution. For example, given the lack of direct studies of air purifiers for SARS-CoV-2, one could assume a lower CADR for airborne SARS-CoV-2 particles than the smoke CADR as a means of making a more conservative estimate for the efficacy of the PAC (although there is no evidence to suggest that SARS-CoV-2 virion, aerosol, or droplet would behave differently than a particle of the same size).

Conclusion

Experimental studies provide evidence for portable HEPA purifiers' potential to eliminate airborne SARS-CoV-2 and augment primary decontamination strategies such as ventilation by indwelling HVAC. Based on filtration rates, CADR, and additional air exchanges provided by portable HEPA purifiers, room shutdown times after AGPs may be calculated and potentially reduced.

Author Contributions

David T. Liu, concept of study, collection of data, review of studies, summary of results, write-up of manuscript, critical review of all contents; **Katie M. Phillips**, concept of study, critical review of all contents; **Marlene M. Speth**, concept of study, critical review of all contents; **Gerold Besser**, concept of study, critical review of all contents; **Christian A. Mueller**, concept of study, critical review of all contents; **Ahmad R. Sedaghat**, concept of study, collection of data, review of studies, summary of results, write-up of manuscript, critical review of all contents.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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