Control of airborne infectious disease in buildings: evidence and research priorities

Running title: Controlling airborne infection indoors

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Abstract

The evolution of SARS-CoV-2 virus has resulted in variants likely to be more readily transmitted through respiratory aerosols, underscoring the increased potential for indoor environmental controls to mitigate risk. Use of tight-fitting face masks to trap infectious aerosol in exhaled breath and reduce inhalation exposure to contaminated air is of critical importance for disease control. Administrative controls including the regulation of occupancy and interpersonal spacing are also important, while presenting social and economic challenges. Indoor engineering controls including ventilation, exhaust, air flow control, filtration, and disinfection by germicidal ultraviolet irradiation can reduce reliance on stringent occupancy restrictions. However, the effects of controls—individually and in combination—on reducing infectious aerosol transfer indoors remain to be clearly characterized to the extent needed to support widespread implementation by building operators. We review aerobiologic and epidemiologic evidence of indoor environmental controls against transmission and present a quantitative aerosol transfer scenario illustrating relative differences in exposure at close-interactive, room, and building scales. We identify an overarching need for investment to implement building controls and evaluate their effectiveness on infection in well-characterized and real-world settings, supported by specific, methodological advances. Improved understanding of engineering control effectiveness guides implementation at scale while considering occupant comfort, operational challenges, and energy costs.

Practical Implications

Emerging variants of SARS-CoV-2 have led to increased infectivity by the aerosol inhalation mode and increasing infection incidence. Even in the absence of symptoms, people infected with respiratory viruses can exhale infectious aerosols that can be inhaled, deposit in the respiratory tract, and initiate infection. Indoor environments are the predominant settings for respiratory infection transmission because people spend most of their time indoors, and because concentrations of infectious aerosols can accumulate, resulting in hazardous inhalation exposure

at close-interactive, room (even at distances much greater than two meters), and building scales. We illustrate the relative respiratory aerosol transfer and exposure at these scales, provide an overview of the scientific basis of engineering controls that can be deployed in buildings to reduce transfer between people, and outline priority research directions to guide widespread implementation of controls in buildings.

Keywords

Infectious aerosols, COVID-19, ventilation, filtration, germicidal ultraviolet irradiation, engineering controls

Main Text

Introduction

When a pathogen has an important or predominant aerosol inhalation transmission mode, as is the case for SARS-CoV-2, shared indoor spaces pose elevated infection risk, and controls in buildings can mitigate spread [1–5]. Emerging variants of the COVID-19-causing SARS-CoV-2 virus pose increased risk of aerosol inhalation transmission and reduced vaccine effectiveness [6–10], elevating the importance of non-pharmaceutical approaches in combination with vaccines to control the pandemic. Widespread use of face coverings and interpersonal distancing including quarantine, isolation, and occupancy restrictions in public and commercial places contributed to the control of COVID-19 [11–14], and were relied upon to control the 1918–1920 pandemic [15–17]. But, restricting interactions can cause harm to economic and educational development, and social wellness [18–20]. Engineering controls—including ventilation (i.e., outdoor air supply), air filtration, and air disinfection with germicidal ultraviolet irradiation (GUV)—can reduce risk while enabling some in-person, communal activities.

COVID-19 transmission has occurred almost entirely in indoor settings of close congregation [21–27]. Transmission from superspreaders, who may transmit to several or more others throughout their infection may drive community spread in public settings [28,29], while settings of small gatherings have also facilitated transmission [27]. Exhaled aerosols that can carry infectious viruses, remain in indoor air for minutes to hours, and can rise to high concentrations in spaces without an adequate combination of ventilation and filtration. Although transmission risk is greatest between those interacting at close range, there can be substantial infectious aerosol transfer between people co-occupying an interior space even for a few minutes at nominally acceptable spacing (e.g., >2 m) [30]. Despite their potential for societal health and economic benefits, ventilation and filtration standards for non-healthcare settings are not usually designed to control airborne infection [31]. Instead they have focused on reducing occupant dissatisfaction with odor and thermal conditions [32,33]. Efforts to define a sufficient level of ventilation for infection mitigation are complicated by the range of effectiveness reported in the few available studies, and the inherent limitations in study methodology [34,35]. Despite these uncertainties,

engineering interventions were recommended [1,3,30,36–43] and have been implemented in varied combinations in many buildings during the COVID-19 pandemic.

Engineering controls provide several key benefits. First, they are not reliant on knowledge of occupant infectious status as required for quarantine, isolation, and contact tracing. This is helpful because asymptomatic and pre-symptomatic COVID-19 cases were shown to shed at least as much virus as symptomatic cases and were estimated to contribute to a majority of transmission events [44–49]. Second, engineering controls reduce infectious aerosol exposure that can prevent infection, reduce severity of disease [50], and possibly reduce subsequent propagation [51]. Third, engineering controls provide some protection without having to address opposition to requirements such as masking or vaccination. Meanwhile, opposition to engineering controls centers on cost and energy use, and any individual control measure cannot achieve the benefits of an integrated set of controls that include the wearing of well-fitted masks and vaccinations for any who are able to access them once they are available. Fourth, increasing ventilation and improving filtration each bring substantial additional benefits, with ventilation improving cognitive performance [52–54] and reducing building-related illness and sick leave [55,56], and filtration reducing a variety of health risks from exposure to fine particulate matter [57–59]. Fifth, infection resilience conferred through built environments helps address inequities in hazardous indoor exposures, and reduce inequalities in disease resulting from inequitable access to testing, personal protective equipment (PPE), or vaccination [60–64]. The reliance on school and business closures for infection control presents the greatest hardship to public-facing workers and communities who experience health, educational, and economic disadvantages [65]. Sixth, the societal benefits from infection control are expected to greatly outweigh the costs of implementing infrastructure upgrades [31].

Despite uncertainties along the aerosol infection pathway related to variations in the quantity of infectious pathogens shed into different aerosol sizes, sites of infection within the respiratory tract, variations of these factors by pathogen, stochastic effects, the physical dynamics of aerosols in buildings, and heterogeneity in population susceptibility, it is clear that viral aerosols play a driving role in respiratory infection, including for SARS-CoV-2 [1,66]. A recent study that detected infectious SARS-CoV-2 in fine aerosols ($\leq$5 μm) from the exhaled breath of COVID-19 cases, showed that, controlling for viral load in upper respiratory mucosa, viral genome shed into aerosols was over an order of magnitude larger among alpha variant versus original “wildtype” infections [67]. This suggests that the SARS-CoV-2 virus is evolving to become more transmissible by the airborne mode, underscoring the importance of tight-fitting masks and respirators and airborne contaminant removal strategies in buildings. Research supporting the implementation and evaluation of engineering control measures on human infection and health outcomes is urgently needed in response to emerging SARS-CoV-2 variants and supports a better empirical understanding of the potential to reduce risk indoors. In recognition of the simultaneous and urgent need to reduce carbon emissions to slow climate change, the energy required to provide increased ventilation and air cleaning [68,69] motivates research to identify efficient practices that confer substantial infection control benefits [70–72]. To support widespread implementation of engineering controls, this manuscript presents a non-exhaustive summary of literature reporting intervention effectiveness, considered within a framework of exposure scales and settings, and proposes critical research aims and methods.

Sources, sizes, and transport of infectious aerosols

Infectious pathogens can be transferred between people in respiratory fluid via small, inhalable aerosols (≤100–200 µm in diameter) and drops (>100–200 µm) that can deposit on facial mucosa but cannot be inhaled [73]. Drops follow ballistic trajectories with momentum, often move independently of bulk air currents, and rapidly fall out of the air by deposition on surfaces. Particles with diameters below a few micrometers generally move with bulk fluid streamlines and have low enough deposition velocities that they mix similarly to gases, and are often removed from a room by ventilation and other processes faster than deposition [74]. Aerosols up to 20–30 µm have low enough settling velocities that they remain airborne for several minutes or more and mix throughout an indoor space, driven by thermal plumes, HVAC air supply and other mechanisms of indoor airflow [73]. Particles as large as approximately 60 µm can be kept aloft with typical room air speeds of 1–10 cm/s, and particles up to ~300 µm experience balanced flow conditions with air currents reaching 100 cm/s [75].

Exhaled breath aerosols and drops containing water, salts, proteins, microbes and sometimes viruses are generated from several locations within the respiratory tract, resulting from the biophysics of breathing, vocalizing, or coughing [73,76–80]. Based on a review of published studies, during respiration, a distribution of aerosols with number concentration modes <1 µm in diameter are generated by the breaking of films that form in the lung airway reopening after closure [75,81,80]. Shear forces and vibrations during vocalization generate aerosols from the throat region (larynx), with a larger size distribution and mode size of approximately 1 µm (ibid). Particles are also generated from the mouth with modes of 10 and 96 µm for vocalization, and 11 and 128 µm for coughing (ibid). In some studies, vocalization and coughing increased the average generated particle size by up to ten-fold [78,82]. “Speech superemitters,” for reasons that are largely unknown, were shown to generate ten times more respiratory aerosol while talking than the study population mean (N=48) [83]. Heavy breathing (e.g., with physical exertion), speech loudness, speech articulation, coughing, and singing have been observed to generate more aerosol particles than tidal breathing, likely due to changes in physical processes and greater expiratory volume [83–86]. Presumably, laughing could present a different profile, though we are not aware of any studies quantifying emissions from this expiratory mode. Sneezing can release respiratory aerosols [87], and may be associated with some respiratory infections, however, was rarely observed in over 200 half-hour observational sessions from symptomatic influenza cases [88].

Virus-containing aerosols also can result from defecation and be spread via toilet use and from drain-waste vents. Wastewater sampling has been widely used as a research tool for population surveillance of SARS-CoV-2 infections [89,90]. SARS-CoV-2 aerosols have been recovered in relatively high quantities from toilet rooms in hospital settings [91,92]. Viral aerosolization from apartment building waste vents was epidemiologically implicated in the transmission of SARS [93,94] and SARS-CoV-2 [95]. Vomiting is another potential source of infectious aerosols [96].

Studies of exhaled breath from infected humans are necessary to understand the quantity of pathogens released into aerosols of various sizes. The published body of such research over the last decade includes samples from several hundred individuals. These studies have reported higher pathogen loads in the aerosol fraction ≤5 µm in diameter compared with larger aerosols

[97]. Influenza A and B viral genome copies (an indicator of the number of pathogens present) quantified from 218 exhaled breath samples from 142 symptomatic cases from a university campus community had a geometric mean three times higher in aerosols ≤5 μm versus >5 μm [88]. Genome copies were correlated with infectiousness measured by quantitative culture (Spearman correlation coefficient 0.34, p <0.0001). No association was found between viral quantity shed into exhaled breath aerosols (determined by Gesundheit-II bioaerosol sampling) and into upper respiratory mucosa (determined by nasopharyngeal swab samples), suggesting distinct compartments of infection in the upper and lower respiratory tract. A study of exhaled breath among a smaller population of symptomatic cases showed over eight times more viral genome in the fine versus coarse fractions (95% confidence interval 4.1–19) [98]. A similar pathogen load breakdown was observed in cough aerosols of influenza cases [99]: 65% of all influenza genome copies in the collected aerosol sample were recovered from particles ≤4 μm and almost twice as much was recovered from particles <1 μm compared with those 1–4 μm in diameter. A study of SARS-CoV-2 aerosols in exhaled breath during singing and talking from 22 asymptomatic to febrile COVID-19 cases detected viral genome in 59% of exhaled breath samples, with less shedding during breathing than talking or singing and a predominance in fine aerosol (≤5 μm) [100]. A study of 49 SARS-CoV-2 seronegative cases detected RNA in 45% of fine and 31% of coarse samples, and infectious virus in two fine aerosol samples despite the use of masks [67]. A paired analysis of masked and unmasked aerosol samples in this study showed that loose-fitting face masks reduced SARS-CoV-2 RNA in fine aerosol by 48% (95% CI 3%-72%) and in coarse aerosol by 77% (95% CI 51-89%). Given these findings, the authors emphasize the importance of tight-fitting masks, respirators, and air cleaning strategies, especially for protecting public-facing employees and those in crowded settings. The site of viral replication in the respiratory tract is expected to influence the particle sizes generated and lend to some variation in shedding sizes that could vary throughout the course of infection and between infection instances. However, there is substantial evidence that fine aerosols commonly carry infectious material that poses transmission risk via inhalation.

The size distributions relevant to airborne exposure assessment are those that result when infectious aerosols shrink by evaporation as they move from saturated conditions in the respiratory tract to indoor air with lower relative humidity [96,101–104]. Under common indoor conditions of <60% RH, expired droplets rapidly evaporate to a final diameter that is approximately 20–40% of the starting diameter in the environmentally equilibrated form, sometimes referred to as droplet residua or droplet nuclei [75,101,105,106]. Aerosol droplet transport and diffusion distance after exhalation depends on the momentum (increasing from breathing to sneezing) of the multiphase turbulent cloud of exhaled air in which the aerosols are suspended and scales with the time from exhalation. The cloud decelerates and the aerosol concentration decreases as its growth entrains slower-moving ambient air [107–109]. Inhalation doses, therefore, decrease with distance from the infected person [110] and are dominated by aerosols <50 μm compared with larger aerosols and ballistic drops >100 μm, unless the source was very close while talking (≤0.5 m away) or coughing [111]. Once the cloud's velocity is comparable to the velocity within the room (typically at <2 m), the ambient air currents dominate transport of the infectious aerosols [107–109].

The sites of infectious aerosol deposition along the respiratory tract can influence the risk of infection and severity of illness. Larger aerosols deposit in the upper respiratory "head region"

and cannot reach the lower respiratory tract. Thoracic aerosols (≤10–15 μm) can deposit above and below the larynx. Respirable aerosols (≤2.5–5 μm) can deposit throughout the respiratory tract and more readily than larger aerosols in the lung [73,75,80,112,113]. *Mycobacterium tuberculosis* must reach lung alveoli to initiate infection [114]. Influenza poses increased risk of infection and severe disease at lower doses when depositing in the lungs compared with the upper respiratory mucosa [73,115], and such anisotropic transmission may describe other infections. Although it appears that SARS-CoV-2 infection is possible throughout the respiratory tract based on the presence of relevant receptors [116], the relative sensitivity to infection at different sites is unclear. An experimental challenge study of SARS-CoV-2 showed that cynomolgus macaques exposed to viral aerosols were more likely to develop fever and severe respiratory disease compared with those exposed to drops in the upper respiratory mucosa [117]. The effect was not observed in rhesus macaques, but nonetheless, suggests the possibility of aerosol inhalation as a sensitive mode of infection and important for control.

There are few field studies that have measured size-resolved pathogenic aerosols in buildings. An indoor air sampling campaign at an apartment showed a predominance of infectious influenza A in sampled aerosols with diameters ≤1 μm at 2 and 4 m from a bedridden case, with some infectious virus detected in particles larger than 1 μm at 1.2 m away [118]. Infectious SARS-CoV-2 aerosols with diameters <1.0 to 10 μm were recovered at 2 and 4.8 m away from hospitalized COVID-19 cases [119]. Other field studies have recovered viral genomic material in aerosols from a variety of settings. SARS-CoV-2 aerosols were detected in patient, staff, and public areas in hospitals [92]; SARS-CoV-2 [120] and influenza A [121] in patient rooms; influenza A in a health center waiting area, a day-care center, and in airplanes [122]; adenovirus and influenza A in a pediatric ward [123]; influenza A in an emergency room [124]; adenovirus, respiratory syncytial virus, and influenza A in metro rail cars [125]; and influenza A in an elementary school [126].

In their seminal book on infection control, Riley and O'Grady hypothesized that pathogens with an important aerosol transmission mode, such as tuberculosis, evolved a level of resistance to infectious decay during residence time in the air between hosts [127]. Laboratory quantification of infectious decay in rotating drums injected with aerosols containing influenza viruses, coronaviruses, and other viruses demonstrated infectious half-lives over an hour [128–130]. Psychrometric features could play a role in determining not only the fate of aerosol deposition and size change due to evaporation, but also aerosol infectious decay. A population-based study in Buenos Aires showed a correlation between reductions in relative humidity to approximately 60% and increased risk with a nine-day lag [131]. This relationship was only detected during the winter and did not rule out behaviors related to time spent indoors and indoor air ventilation. Despite this and other suggestions of increased viral aerosol decay in intermediate humidities [101,132–134], a study that aerosolized influenza virus from human respiratory tract cell lining fluid showed no effect of humidity on infectiousness during the course of an hour [135]. A potentially protective effect of this lining fluid (the main component of exhaled breath aerosols) on infectious decay may be related to its chemical composition, compared with lab media used in other studies [136]. Simulated saliva aerosols suspended in a rotating drum were shown to decay faster at 70% versus 20% RH at temperatures of 10–30°C; however, this effect was not clear under increased ultraviolet-B irradiance simulating sunlight [137]. A commonly cited infectious decay rate of 0.63 h^{-1} comes from a study that aerosolized SARS-CoV-2 using non-human-based media in an aerosolization procedure likely to be more stressful than natural processes, leading to

potential overestimates when generalizing to human generated exhaled aerosol [130]. Yet even if infectious decay were to occur at such a rate, it would represent a relatively small portion of total removal unless removal by ventilation is very low. Low relative humidity may be more likely to affect transmission by decreasing mucociliary clearance and innate immune function, as has been observed at 10% compared with 50% RH in mice [138]. Yet, intentionally increasing humidity without careful oversight increases risks of dampness, mold, and other allergen exposures that are well established contributors to respiratory disease [139].

Critical scales and settings

The application and assessment of infectious aerosol controls indoors can be considered at three transfer scales: a) close-interactive, b) room, and c) building (between-room). Table 1 describes each scale and corresponding engineering controls. Administrative controls for all scales of transfer include pre-entry screening, face mask or respirator use as source control and PPE, activity limits (e.g., restricted loud speech, singing, or exercising), and frequent cleaning of common touch surfaces. Distancing tailored to setting-specific activities helps reduce close-interactive transfer. Limits to co-occupancy time, and cohort separation reduce room scale transfer. Distances 1–2 m have been commonly used to differentiate close- and long-range transmission along a continuum [140], related to likelihood of exposure to drops and aerosols. Features of close-interactive contact related to elevated airborne transmission have been described elsewhere [141,142]. To differentiate between close-interactive—"garlic breath" scale of exposure [143]—and room scale exposure we define close-interactive aerosol transfer within 1–2 m during a duration consistent with the US CDC's definition of contact, which is 15 min or more within a 24 h period [144]. A similar distinction in aerosol transfer exposure by proximity has been suggested by Nazaroff [75]. Aerosol transfer from infectious to susceptible individuals within rooms is relevant when transport occurs much faster than deposition, removal, or viral inactivation. A modelling study predicted that the predominant scale of respiratory infection transmission can switch between close-interactive and longer-range, within-room exposures as a function of variation in infectious aerosol size, interpersonal distance, and exposure time [145]. Increasing interpersonal distance within a room reduces the proportion of close-interactive transfer and increases the proportion of room scale transfer which is often more easily mitigated by ventilation, filtration, and GUV.

Table 2 lists features of settings that pose elevated risks owing to higher emission activities, limits on the applicability or ability to enforce administrative controls, or the likelihood that existing facilities have the equipment needed for engineering controls. Dining and sporting activities are less amenable to face mask wearing. Settings with higher occupant density, greater magnitude of interaction, and activity level present greater challenges relative to those with lower density and stationary occupants. Studies have implicated specific settings for SARS-CoV-2 and other respiratory infection transmission. These include school lunchrooms, restaurants, and small, private gatherings [25,146]; classroom learning [147]; a variety of occupational settings and worker dormitories [24]; meat processing [148]; religious services [149,150]; public entertainment [151]; buses [152,153]; nursing homes [154]; and fitness centers [155–159]. Residential settings, which typically foster extended exposure at close proximity, lend to transmission risk. A study of over 33,000 laboratory-confirmed influenza hospitalizations over two influenza seasons across the USA showed that having ≥5% of people living in crowded households—defined as more than one

person per room—was associated with a 17% (95% CI 11-23%) increase in influenza hospitalizations, suggesting a possible role of within-household transmission in crowded environments [160]. A meta-analysis of household contacts estimated that spouses had a SARS-CoV-2 transmission rate of 38% (95% CI 26–51%) compared with 18% (12–25%) for other household contacts [161]. Overall, the meta-analysis estimated within-household SARS-CoV-2 transmission risk of 16.6% (95% CI 14.0–19.3%) [161]. Settings with immunologically susceptible populations and extended contact times include senior housing and assisted living communities, detention centers, homeless shelters, and healthcare settings. These settings may commonly have limited ventilation and air cleaning. Healthcare settings represent specialized environments with higher risks of exposure among and between patients and staff owing to increased sources of infectious aerosol [162–164]. Protection of immunologically susceptible patients is a priority and risk among staff is elevated with inadequate PPE and engineering controls [43,165–169]. Because of their unique exposures and elevated ventilation and infection control standards, healthcare settings are not a focus of this paper; however, many of the same controls applied in healthcare could be applied to other environments.

Community-level settings are likely to contribute to population transmission risk in unequal ways and this should be considered when assessing differential population exposure burdens in various settings. A study of US county level data showed that the effect of distancing policies on reducing COVID-19 cases and mortality was lower among communities of color, those with lower incomes, and those with higher levels of household crowding [170], potentially related to cumulative exposure burdens related to built environment factors in occupational and residential settings. This is despite data that shows increased adherence to masking and physical distancing among Black and Hispanic communities in a national US survey, after controlling for socioeconomic status [62]. Comprehensive, community-level prioritization of venues by risk level can be supported by risk estimation tools. For the purpose of minimizing overall spread and health impacts, priority intervention settings are those that serve as hubs for community transmission and those with populations that have higher risk of severe disease and adverse outcomes when infected.

Modeling risk and protective effects

Numerous tools have been developed to estimate SARS-CoV-2 aerosol exposure, infection risk, and the effect of controls in various indoor settings (Appendix 1). The Wells-Riley equation is often used to estimate risk of transmission at the room scale, where inhalation exposure and risk increase with the strength of infectious dose generation and decrease with removal via dilution ventilation and other mechanisms. The Wells-Riley equation is,

$$P = \frac{D}{S} = 1 - exp\left(-\frac{Ipqt}{Q}\right), \quad (1)$$

with P probability of infection, I number of infectors shedding pathogens into aerosols, q quantum generation rate, p pulmonary ventilation rate, t time sharing the air of an indoor space (assuming an evenly mixed environment), and Q uncontaminated air supply rate [171]. The quantum generation rate, q, is the generation rate of inhalation doses, with one quantum defined as the dose that will cause infection in 63% of those exposed. It is estimated using data from outbreaks, based on the duration of shared air exposure between defined numbers of infectious and exposed individuals, the rate of removal by dilution or other means, and infection rates

among the total number of exposed susceptibles. Risk responds stochastically with a Poisson distribution proportional to the cumulative exposure to infectious aerosols. An infectious dose may be greater than a single, inhaled pathogen over the exposure period, but the likelihood of infection responds stochastically as though it were a single dose [172].

Rudnick and Milton built on the Wells-Riley equation by proposing the use of CO_2 concentration as a marker of how much air being inhaled in a room is composed of exhaled breath [173]. This works given that exhaled breath is the predominant source of CO_2 in indoor environments with vented combustion sources (e.g., cooking). Their rebreathed-air equation is,

$$P = \frac{D}{S} = 1 - exp\left(-\frac{fIqt}{n}\right), \quad (2)$$

with n people sharing the air, and rebreathed-fraction f equal to the CO_2 concentration in the room minus the CO_2 concentration outdoors divided by the CO_2 concentration of exhaled breath—approximately 38,000 ppm at low levels of exertion [173]—integrated over the exposure time. Aside from providing direct estimates of exposure to exhaled breath (not accounting for removal via filtration, inactivation, and deposition) in a well-mixed room, and providing a solution for non-steady state conditions, the rebreathed-air equation can be used with data collected from CO_2 sensors, thus avoiding the challenges involved with estimation of room ventilation over time. Given a certain number of people occupying an indoor environment of a specified volume, the CO_2 concentration is a function of the rate of ventilation as outdoor air with lower CO_2 replaces indoor air containing exhaled breath. The transport of particles ≤3.5 μm has been shown to be well approximated by tracer gas [110]. Although larger aerosols were not tested in that study, their dispersion would not typically be well-mixed and are likely to correlate less strongly with CO_2 concentration. The magnitude of this limitation is unlikely to negate the use of the rebreathed-fraction for practical, public health risk assessment in well-mixed settings, especially given the known importance of infectious aerosols ≤5 μm for transmission. Application of well-mixed, Wells-Riley based approaches to differentiate between close-interactive and room scale exposures has yet to be well explored [75]. Existing estimates of quanta generation rates are often given as population averages, yet they can vary widely between infector-susceptible pairs [174,175]. Precautionary approaches should consider superspreader scenarios as a function of supershedding, immunologic susceptibility, and elevated exposure to pathogen-laden air.

The Effective ReBreathed Volume (ERBV) builds on the rebreathed-fraction concept in a well-mixed space and provides a metric for characterizing infectious aerosol exposure as a result of transfer and removal processes occurring for aerosols of different sizes at various distances from a source [176]. ERBV characterizes exposure related to the physical transport of aerosols. This enables estimation of the influence of distance and filtration for aerosols across the range of relevant aerosol sizes. Improved knowledge of immunologically vulnerable sites along the respiratory tract (i.e., head, thoracic, and lung regions) by pathogen informs the risk implications of inhalation exposure of different sizes. Estimation of a person's cumulative inhalation exposure to infectious aerosols of various sizes would support improved assessment of aerosol infectious dose in well-characterized transmission scenarios. This would help with translating quantum generation rates into infectious aerosol copies per infectious dose, thus enabling aerosol sampling campaigns from human sources and/or indoor air to directly estimate risk in an indoor environment with known removal properties.

Insights from an aerosol transfer model in an office

To elucidate the importance of scale, we provide a quantitative example of aerosol transfer between an infected worker and susceptible workers at the three scales of exposure in an office setting (Figure 1; schematic in Figure A1). The simulation used CONTAM models of a single-zone (SZ) HVAC system serving a 92.9 m^2 room with an infected person, and a multi-zone (MZ) system serving 929 m^2 total floor area with at least two zones, one of which being the 92.9 m^2 infector room. Models were non-steady-state and the exposure lasted for one hour. All the spaces had 3 m tall ceilings and the HVAC systems supplied 0.47 L/s/m^2 (1 cfm/ft^2) with 10% outdoor air, corresponding to 7.5 L/s/person of ventilation and 15 m^2/occupant. Based on published data of exhaled breath aerosol size distributions, knowledge of the lung as a sensitive site for respiratory infection, and some uncertainty about sites of infection initiation along the respiratory tract for different infections, respirable aerosols ≤5 μm were included as relevant for infectious aerosol transmission along with thoracic aerosols ≤10-15 μm [73,102,82,177]. These sizes were environmentally equilibrated, achieved by taking 40% of emitted diameters [75] (listed in Appendix 2). Exploring this range of aerosol sizes allowed the model to show a quantitative estimation of relative exposure risk across scales of aerosol transfer. Despite the majority of exhaled breath and speech aerosol particles being ~1μm [82,83], and others showing a majority of influenza and SARS-CoV-2 virus in exhaled breath aerosols ≤5 μm [67,88,98,100], a single particle at 10μm or larger could potentially contain a greater viral load. It is unclear whether smaller aerosol particles might deliver fewer defective virions or facilitate binding to host receptors more readily than larger ones, but these possible explanations have been suggested for the detection of culturable SARS-CoV-2 in fine aerosol samples despite low viral load [67].

Close-interactive exposure is estimated as the aerosol number concentration at inhalation by a susceptible person whose head is within the same 1 m^3 well-mixed subzone with the infected occupant. That subzone mixes with the surrounding room at a rate of 360 h^{-1}, corresponding to a mean air speed of 0.1 m/s. Mean exposures are considered at room scale, for susceptibles outside of the close-interactive zone within the infector room (Inf. room), with SZ or MZ systems, and at building scale outside the infector room served by the MZ system. If occupants are moving around the space, then local concentration extremes that can occur within a room are of less relevance as air becomes more well-mixed and occupants are exposed to air throughout the space. The effects of cloth face masks worn by both the infector and the susceptibles, are estimated in the simulation from size-resolved intake and out-flow removal efficiencies corresponding to a MERV 8 filter, consistent with published data on cloth masks [178,179]. Out-flow efficiency considered aerosol sizes at emission, while intake efficiencies assumed aerosol sizes at equilibrium, which made breath aerosol filtration efficiency higher for exhalation than for inhalation. Additional sources of aerosol removal are dilution by outdoor air ventilation, deposition in HVAC ducts and on surfaces in the simulated rooms, and filtration by MERV 13 HVAC return filters (this example uses MERV 13, although >MERV 13 would be a reasonable approach also). The values of all model parameters and the differential equation that represents the material balance in the SZ infector room (as an example) are provided in Appendix 2. Results, shown in Figure 1, are presented as the ratios of hourly aerosol concentrations in the infector room and other rooms (building scale) relative to exposure concentrations within the close-contact sub-zone. The hourly, integrated number and volume distributions are shown in Figure A2 (Appendix 2).

The model represents an approximation of respiratory aerosol transfer. Aerosol number concentrations were highest at close-interactive scale (i.e., within the infector subzone), lower at room scale, and lowest at building scale (Figure 1; Figures A1, A2). It is possible that exposure could be even higher within the infector subzone compared with the other scales, depending on proximity of interaction of the individuals within the 1 m^3 subzone and the dynamics of the exhalation plume from the infector which was not modelled in this scenario. Mask use among the infector and susceptibles reduced close-interactive exposure by 53, 97 and 98% for equilibrated particles with diameters of 0.3, 4.8, and 14.4 µm, respectively. Exposure reductions attributable to masking were similar for room and building scale transfer. Compared with the infector subzone, exposure concentrations in the infector room with an SZ HVAC system, without masking, were reduced by 79, 88, and 94% of those that occurred for 0.3, 4.8, and 14.4 µm, respectively. With masking, exposure was reduced further, to 90, 99.7, 99.9% of unmasked subzone levels. Compared with SZ, exposures in the infector room served by MZ HVAC were lower at the smallest particle sizes due to a greater supply of uncontaminated recirculated air, assuming no infectors in the connected spaces. Building scale exposure with the MZ system was dramatically lower than the other scenarios and declined faster as aerosol size increased. Other engineering controls could be applied to reduce exposure at the three scales (Table 1).

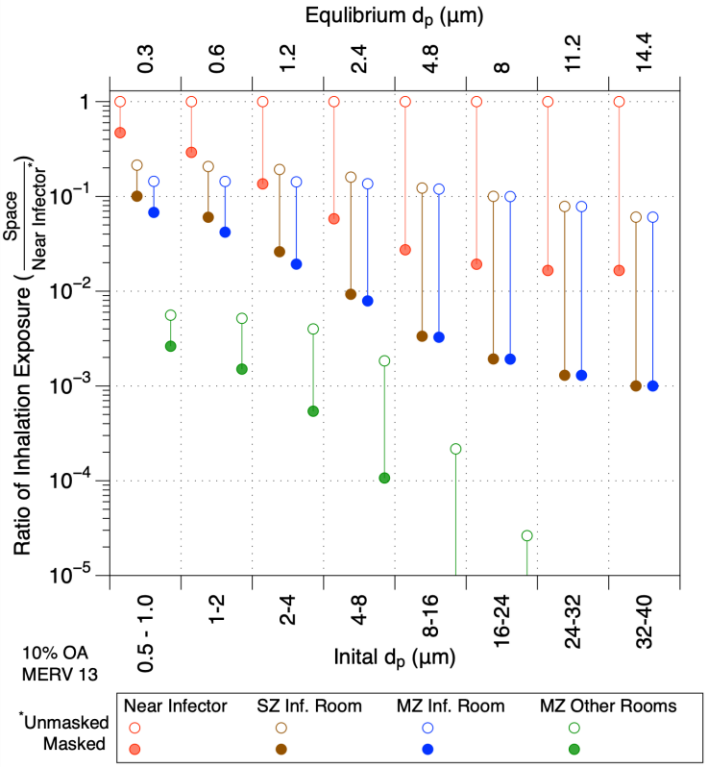

Figure 1. Relative inhalation exposure attributed to aerosols at different exposure scales compared with close-interactive exposure in the SZ Inf. Room. SZ Inf. Room = Single-zone HVAC system serving 93 m^2 with an infector in the room; MZ = mixed-zone HVAC system serving a total 929 m^2 with infector in the room; d_p = aerosol diameter; OA = outdoor air.

Intervention points to reduce infectious aerosol transfers

To support the prioritization of research needs, this section summarizes what is known about the efficacy of interventions to interrupt transfers of infectious aerosol. Source control measures and use of PPE are important measures in combination with the engineering controls and a brief description is included in Appendix 3.

I. Close-interactive scale

As illustrated in Figure 1, exposure at the close-interactive scale contributes the highest risk of aerosol transfer due to the contributions of concentrated aerosols close to the source and the possibility of large drop sprays. After more than a year of public information campaigns about transmission risk during close contact, there is broad awareness of the risk posed at this scale. Masking and distancing remain important controls at this scale, while airflow management and air cleaning at close range face implementation challenges at the population level.

Barriers

Although empirical effectiveness data are limited, a review of existing literature suggests that physical barriers such as plexiglass shields confer protection from ballistic drops and larger aerosols at close-interactive scale [180], and may also help encourage physical separation between people. Physical barriers have been suggested in hospital settings to reduce between-patient and patient-visitor transfers and studied using computational fluid dynamics and tracer gas analysis [181,182]. Plexiglass-type shields deployed widely throughout an indoor space, such as between student desks in a classroom, may reduce exposure between adjacent individuals by increasing the distance for an aerosol to travel between people resulting in greater dilution potential. But they can also interrupt mixing and dilution ventilation, potentially leading to increased concentrations and exposures at some locations within room [180]. Rapid exhaust of air—at 114 L/s—above a fog-generating manikin reduced exposure between pupils seated next to each other at partitioned desks, however, the effectiveness of partitions under realistic classroom ventilation and air flow conditions may be low and could increase exposure due to interruption of dilution via air flow and mixing [183]. A thermo-fluid simulation using CO_2 tracer data to mimic the conditions of an office environment with plastic sheeting as shielding between groups of desks found that shielding likely reduced delivery of clean supply air to some spaces, leading to elevated risk [184]. A large-scale survey of pre-kindergarten through high school environments showed that classroom desk shields between pupils were associated with a 12% increase in odds of a positive COVID-19 test, and 29% increase in odds of COVID-19-like illness, after controlling for county infection incidence, and individual and household covariables [185]. Additional information about airflow, in this study or other classroom exposure scenarios, including where air enters and leaves the spaces and their interaction with barrier size and shape could help elucidate potential barrier-mediated airflow dynamics associated with risk and inform specific barrier use strategies to reduce risk. Settings where clean airflow delivery is not hindered by barriers such as at checkout registers in large market environments, could take advantage of protective effects of barriers without negative consequences.

Airflow management

Airflow management strategies to reduce direct transfer of infectious aerosol at the close-interactive scale include delivery of clean air directly to the breathing zone and establishment of beneficial airflow patterns. Directing expiratory air volumes toward upper-room GUV, into unoccupied volumes such as upper air spaces in high-ceilinged warehouses, or toward exhaust registers for in-duct cleaning and/or exhaust to outdoors can reduce between-person transfer. In general, mixing air improves performance of GUV [186]. Directing air across a room would risk increasing the delivery of contaminated air from an infected person towards others in the space. The introduction of an uncontaminated airstream "curtain" between people was shown to reduce microbial contamination during surgical procedures [187], and could be applied to other contexts. An example of directed airflow around an infectious person is a ventilated headboard (such as that developed by NIOSH) that exhausts patient generated aerosols to reduce exposure to others nearby [188]. Compared with a well-mixed space and the objective of cleaning the entire space, when room air is not well-mixed, provision of air cleaning and delivery close to the source can be more effective. This basic principle of air cleaning is well known and examples of the effectiveness of local air cleaning have been shown in recent studies [189,190]. Although airflow and air cleaning measures can reduce close-interactive transfer when applied continuously, effective risk reduction strategies at this scale would benefit from addressing knowledge gaps about the distance and time required for source aerosols to dissipate to well-mixed levels within rooms.

II. Room scale

Exposure at room scale is important because of the potential for high concentrations of infectious aerosols, large numbers of exposed individuals, and prolonged exposure durations. Superspreading has been well-documented at this scale [25,153,191,192], and controls effective at this scale have the greatest potential to mitigate exposures and outbreaks at the community level [28,29,174]. Room scale airflow controls offer greater protection at longer versus shorter range, and could offer better protection against respirable aerosols (≤2.5–5 μm) that are more easily entrained in air flow than larger aerosols and sprays with greater deposition removal [140]. Transfer can be mitigated by ventilation, filtration, GUV, and air distribution to maximize control effectiveness (Figure 2). These approaches aim to reduce direct airflow connections between occupants, reduce well-mixed aerosol concentrations, and increase pathogen inactivation rates. There remain important research gaps in demonstrating the efficacy of individual room scale engineering controls and their effectiveness to reduce risk in population-based studies. Environmental quality and engineering controls in buildings are often not reported or their effects are not assessed in investigations of infection transmission. For example, two, high-profile population-based studies of SARS-CoV-2 transmission interventions in grad schools did not address the effects of controls like increased ventilation or air cleaner use because data on such controls was not collected [185,193], perhaps because there were no improvements in ventilation or infectious aerosol removal. There is a greater availability of evidence on controls that are commonly recorded such as distancing, masking, and symptom checks.

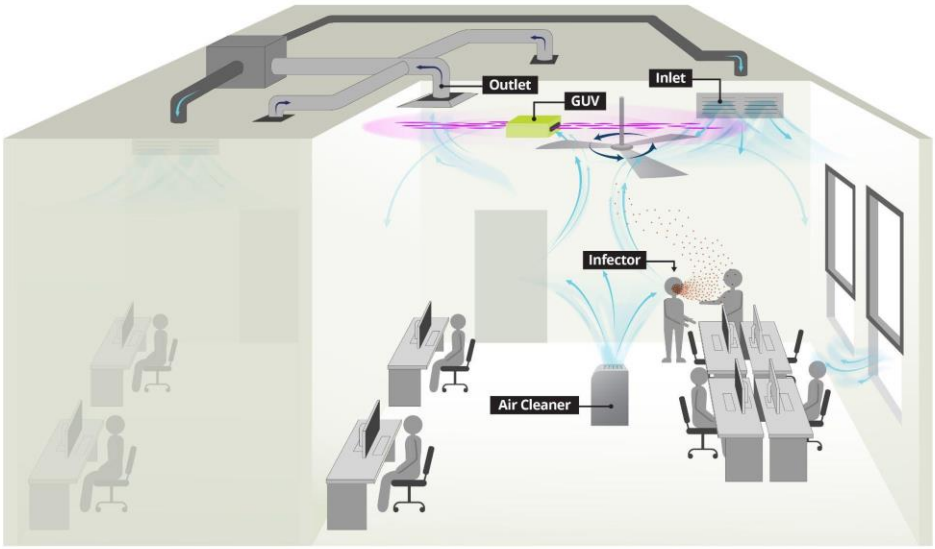

Figure 2. Scales of infectious aerosol transfer and control measures in buildings. Arrows depict airflow. Red dots depict infectious aerosols emitted from a single infectious person. These aerosols are likely to spread throughout spaces, beyond what is illustrated here, with relative exposures at different scales illustrated in Figure 1, however, control measures can reduce their transfer. Air flows in blue; GUV in light purple (although bluer in actuality when reflected off a surface).

Ventilation

In rooms that are well mixed, ventilation provides first order contaminant removal at the air exchange rate. Exposure reductions can be even higher with effective directional airflow patterns. Increased air exchange typically reduces exposure, unless a susceptible person is directly downwind of air flowing from the infectious source. Directional ventilation can reduce risk by controlling flows of potentially contaminated air [194]. The importance of clean air supply for controlling infectious aerosols was described by both Nightingale and Billings in the 19th century [195,196], and by Wells in his foundational work in the mid-20th century [172]. Evidence from observational, experimental, and modelling studies supports the relationship between ventilation, occupancy, exposure time, and airborne infection rate [171,173,174,197–203]. Systematic reviews have concluded that indoor ventilation levels are an important factor in airborne infection control [34,35,204]. Without a more precise characterization of the effects of ventilation and other controls on infection risk, public health precaution supports an abundance of clean air delivery, which could potentially waste energy beyond what might be needed for infection control or other health benefits [30]. A summary of how authoritative bodies have considered ventilation for infection control is included in Appendix 4.

There have been numerous case reports of respiratory infection transmission events in poorly ventilated environments. A report of nine secondary SARS-CoV-2 infections from a single primary case in a restaurant with recirculating air-conditioning units and an estimated ventilation rate of 0.9 L/s/p suggested a ventilation rate requirement of 38.6 L/s/p to inhibit transmission [25]. Extensive transmission in poorly ventilated indoor environments contrasts with comprehensive contact tracing efforts that have detected very few instances of transmission during outdoor

exposures where dilution ventilation is abundant, as detected by comprehensive contact tracing efforts [21,23,24,26,27,151,205–207]. When ventilation systems are limited in their capacity to increase the supply of outdoor air, some have suggested vacating indoor environments periodically to allow for air clearance [208–210].

Table 3 provides a summary of the main findings from a selection of epidemiologic studies that linked ventilation with respiratory infection risk. The studies included measured or estimated ventilation during exposure between primary and secondary cases, and calculated infection risk given an assessment of the total number of people exposed. Some were included in previous reviews [34,35]. These studies consistently showed statistically significant increases in risk ranging from approximately 25–300% or more when comparing lower versus higher ventilation conditions. The generalizability of these existing studies is limited due to small sample sizes and designs that often fell short of achieving scrupulous exposure assessment and confirmed transmission under varying levels of well-characterized ventilation conditions. Human-challenge transmission studies in controlled environments with engineering interventions could provide stronger internal validity. External generalizability of such studies may be limited unless realistic exposure scenarios can be achieved. Human-challenge trials require substantial financial investment, careful design, execution, and attention to ethical concerns. A relatively large human-challenge influenza transmission trial failed to detect more than one transmission event, likely due to high ventilation rates in the quarantine facility in which it was conducted, and low infectious potential of the experimentally infected primary cases [211]. Other designs that test lower ventilation levels and/or draw from symptomatic, naturally infected populations could improve on this approach.

High ventilation rates of 6–12 air changes per hour (ACH) or more are often required in health care settings (Appendix 4) and can be achieved through natural and mechanical means [212]. Depending on the anticipated occupant density, minimum outdoor air exchange may be <1 ACH. When using natural ventilation, WHO suggested an hourly average flow rate of 160 L/s/p in airborne precaution rooms and 80 L/s/p (equivalent to 12 ACH in a 4x2x3 m space) in other health care spaces [213]. This is consistent with total clean air flow delivery of 160 L/s/p in aerosol precaution spaces recommended by WHO interim guidance on COVID-19 infection prevention in healthcare settings [214]. Natural ventilation is capable of achieving abundant air exchange but can also be much lower and is highly variable, dependent on wind speed, direction, and temperature. Window opening and natural cross ventilation in Peruvian hospitals resulted in air exchange up to 17 ACH in a consulting room and 66 ACH in a waiting room [215]. Cross ventilation in a UK hospital achieved 27 ACH and uniform aerosol concentration across an open plan ward, given strong wind outside [181]. Natural ventilation can be influenced by the positioning of the room with respect to other building structures and thermal sources. Mechanically supplied ventilation can supplement low, natural, air flow delivery to assure an abundance of air exchange and mixing for infection control. Field studies of California schools found ventilation rates commonly below the ASHRAE standard of 7 L/s/p, suggesting the potential for widespread improvements in ventilation to meet standard rates [216,217].

Filtration

Filtration in recirculating HVAC units and in portable air cleaners removes respiratory aerosols, reducing exposure and infection risk [218,219]. A 2020 ASHRAE position document states that filter efficiency of MERV 13 or better can effectively remove infectious aerosols [220]. MERV 13 filters

are rated to capture at least half of 0.3–1 µm, 85% of 1–3 µm, and 90% of 3–10 µm particles. If most of the infectious pathogens are contained in super-micron particles, then MERV 11 filters could provide comparable filtration efficiency. Compared with MERV 13 filters, they are less costly and tend to have lower air flow resistance, enabling higher airflows (and more air cleaning) or lower energy demand [221]. Filters with MERV ratings below 13 are not certified to capture submicron particles, but published filter performance evaluation indicates that MERV 8–12 filters can capture submicron aerosols [221–223]. Single pass filter efficiency typically increases with loading [224]. Modeling studies of non-healthcare settings with various levels of assumed inhaled infectious aerosols have shown that air filtration in recirculating HVAC systems could decrease aerosol inhalation transmission [218,225]. A study of aerosol removal by four portable HEPA cleaners with a total 1026 m^3/h CADR (5.5 equivalent ACH) in an active classroom (128 m^3) with well-mixed air showed a 95% reduction in particles 0.01–10 µm after 37 minutes [226]. Teachers and students indicated little disturbance by the noise of the air cleaners in the classroom, however, portable air cleaners can generate noticeable or uncomfortable noise levels in roughly the 50-60 dB range at maximum fan speed and ASHRAE has suggested selecting air cleaners based on reduced fan speed if noise is a concern [227]. Do-it-yourself box fan cleaners with panel filters are generally noisier than commercial portable cleaners [228]. It is clear that air filtration can reduce the indoor concentration of potentially infectious airborne particles when applied alone or in combination with other sources of contaminant removal via air exchange. Additional research could assess removal performance in a variety of real-world versus laboratory settings, effects on human health outcomes, and barriers to widespread use.

Germicidal ultraviolet irradiation (GUV)

Within-room infectious aerosol transfer can be controlled through the inactivation of pathogen infectivity using upper-room or far GUV. It is helpful to coordinate GUV use with airflow management to increase air movement to, and residence time in, zones of irradiance. GUV (sometimes abbreviated UVGI) has been used successfully for nearly a century to control airborne infections including E. coli, tuberculosis, measles, and influenza [175,229–235]. Upper-room GUV uses high energy, short wavelength radiation, within the UVC band of 200-280 nm, to damage the genetic material in viruses, bacteria, mold, and other organisms, rendering them noninfectious. Common GUV sources are mercury vapor or amalgam lamps that primarily produce ~254 nm UVC, which is close to the peak wavelengths for microbial inactivation (260–270 nm) with lower potential for skin or eye damage relative to longer wavelengths [236]. More recently, LED lamps have been developed to produce similar wavelength with sufficient irradiance for disinfection [237]. UVC is almost entirely absorbed in the outermost layer of the skin and is unlikely to pose cancer risk like longer wavelength UVA or UVB [238]. A minor, yet painful irritation—erythema (skin) or photokeratitis (eye)—which normally resolves in 1–2 days, can occur from direct exposure prompting caution. The potential risk associated with eye exposure prompted the American Conference of Governmental Industrial Hygienists Committee on Physical Agents to assign a threshold limit value (TLV) of 6 mJ/ cm^2 at 254 nm, however measured human exposures in a variety of healthcare and other workplace settings showed that exposure is generally far below the TLV, rarely reaching a third of the TLV at maximum [236]. A trial of upper-room GUV (254 nm) at U.S. homeless shelters with thousands of staff and homeless participants found no difference in skin or eye symptoms between placebo and control periods [239]. Exposure limits for a range of wavelengths provided by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) reflects reduced penetration potential, and tests of 222 nm wavelength at a level seven times the ICNIRP resulted in no harmful effects in a

human skin model [240,241]. Environmental conditions and contact networks can influence the effectiveness of GUV controls at the population scale. GUV may have the greatest effect when applied in crowded, high-risk spaces. Interruption of aerosol transmission has been estimated to contribute to meaningful community-level infection control at hubs of human network connection, including when the inhalation mode accounts for as few as 20% of infections [199,200,242]. Lab-based studies of pathogen inactivation that assign "Z" or "k" rate constant values to indicate susceptibility to GUV facilitate estimation of inactivation rates across levels of exposure to GUV irradiance and under scenarios of varying humidity, air flow, and temperature [230,233,243–246].

Upper-room GUV is typically installed on walls or ceilings to irradiate the upper zone of an indoor space. It has the advantage of rapidly treating large volumes of indoor air, making it highly efficient for infection control. Some studies have shown that, paired with a ceiling fan to increase air movement between the sanitization and breathing zones, upper-room GUV was capable of achieving an order of 10 or even 100 equivalent ACH [235,243,247,248]. The addition of a ceiling fan to stimulate air movement up into zones of upper-room irradiation was estimated to increase GUV-generated air change per hour equivalents by a factor of 2 or more [186,249]. Thermal plumes from occupants and objects in the room that are warmer than room air temperature (including e.g., any operating electronic equipment) create within room flow patterns of air moving into the sterilization zone in the upper part of the room then circulating back to the breathing zone along cold walls or cooler places without warm bodies. Wells and colleagues demonstrated that upper-room GUV substantially reduced transmission of measles, mumps, and chickenpox in suburban grade schools [234,250]. Subsequent epidemiologic investigations in other schools showed no significant effect, likely due to increased sources of transmission outside of schools in more urban settings [127,231]. Rates of infection in a Veterans Administration hospital deploying upper-room GUV during an influenza season were nearly 90% lower than those in nearby hospitals without GUV [251]. With regards to safety, upper-room GUV can achieve effective air disinfection while keeping exposure to irradiance, including that from reflections off ceilings, below workplace exposure limits [236,252]. Overall, the body of evidence supports upper-room GUV as an efficient and highly effective control against infectious aerosol transmission.

In-duct GUV can reduce within-room exposure during air recirculation to an extent similar to filtering recirculated air. A typical HVAC system in a non-healthcare application will supply approximately six ACH at most, and much less on average for a variable air volume system. Consequently, this is the maximum disinfected air delivery rate of such a system. On the other hand, upper-room systems can provide equivalent air changes much greater than six ACH. Nevertheless, both modeling and field measurements suggest that in-duct GUV can have cost-effective, beneficial health effects. Simulation of an in-duct system in three climates found that room air concentrations of pathogens were reduced by approximately 50-70%, with a median reduction of approximately 65% [253]. A double-blind evaluation of GUV installed in office air handling units reported reduced levels of microbial contamination on air-handling unit surfaces and in the air, and lower levels of respiratory and other symptoms during GUV operation among 771 participating workers [254]. An additional benefit of in-duct GUV, when done in an air-handling unit, is control of microbial growth on cooling coils and in condensate pans [255]. Biofouling on cooling coils reduces air-side heat transfer coefficient and can reduce air flow or increase fan energy use. Recent field investigations report net energy use benefits of coil

irradiation as well as reductions in maintenance cost relative to mechanical and chemical cleaning [256–259].

Whole-room GUV floods the occupancy zone and can be useful for surface decontamination [260]; however, dust and crevices can provide shielding, thus reducing effectiveness. Thorough surface cleaning to access small crevices and remove particles may be warranted; and if an effective cleaning solution is used for that purpose, then additional disinfection may not be necessary. Depending on the wavelength used, it may be necessary to avoid exposure of skin and eyes to the whole-room GUV. Far GUV (UVC 200–230 nm) is designed to bathe occupied spaces with irradiance, leading to direct inactivation of infectious pathogens in the air or on surfaces within the occupied zone. Far GUV may have a similar capacity to inactivate microorganisms as the well-characterized higher UVC wavelengths (250–270nm), while reducing safety concerns with human exposure [241,261]. Available studies using mammalian cell culture, animals, and humans have shown that 222nm far UVC can inactivate respiratory pathogens does not cause skin irritation associated with exposure to the 254nm wavelength [241,261,262] GUV "barriers," or beams of germicidal light to sterilize air between office workers, have been used in the past with 254 nm sources, but safety concerns and declining TB rates in the US led to their disuse [127]. Should further safety and efficacy evaluation of far GUV yield favorable results, far GUV could provide an update to GUV barriers of the past and contribute to infection control at room scale, and between infectious and susceptible individuals in close-interaction. Far GUV lamps can generate low levels of ozone, however, filtered lamps and lower power modes can ensure generation well below limits to protect health [241,263,264]. Upper-room GUV applications that deploy wavelengths above 240 nm and block wavelengths below that do not produce ozone. Overall, with some care toward proper deployment to ensure effective and safe application, GUV can offer a helpful layer of airborne infection control, and perhaps a critical one in settings where other controls are not readily available.

Airflow management

Given that infectious respiratory aerosols are transported by air currents, air flow dynamics strongly influence transfer and intervention efficacy. Highly controlled laminar and unidirectional air flows can be used to reduce patient exposure to contaminants in operating theatres, and could be selectively adapted to high-risk, non-healthcare settings [265]. Experiments have been done to characterize air flow dynamics related to a variety of ventilation systems [204]. Although downward ventilation, displacement ventilation, mixing ventilation, and personalized ventilation influenced air flow in a room with a single patient, the investigators found that regardless of the type of ventilation, exhausting air at the top of the room represented a relatively effective means of removing aerosols, attributed to upward flow. Inlets positioned in the lower portion of the room to generate displacement ventilation can increase delivery of HVAC supply air to the breathing zone, although repositioning existing inlets may not be easy. A tracer gas study of aerosol exposure between stationary manikins ≤1.5 m apart showed that displacement ventilation was associated with lower time-averaged exposure compared with mixing or stratum air distribution [266], consistent with what has been observed in previous modelling studies with intake fractions several orders of magnitude higher for ≤5 μm particles [110]. The effectiveness of displacement ventilation for removing exhaled breath aerosols can be diminished with increasing temperature gradients between the breathing zone and the upper zones of the room. Thermal stratification where air is warmer in the upper portion of the room compared with the air meant

to rise from the breathing zone can promote a locking effect of air within horizontal layers, thus reducing the rate of dilution [267–269]. The addition of human movement throughout an indoor space promotes well-mixed conditions and, while helping to distribute infectious aerosol and reduce intense concentrations around a source, can also attenuate the speed of upward aerosol removal by a displacement ventilation scheme [268,270]. Thermal stratification can also reduce effectiveness of systems intended to supply mixing ventilation, and is particularly problematic when the supply air is heated and provided at or along the ceiling [271,272]. These potential problems with achieving maximum dilution ventilation spur future research directions. The addition of air currents and dispersion from human movement, portable air cleaners, and ceiling fans offer approaches to reduce thermal locking and increase mixing. This can help to deliver contaminated air more readily toward exhaust or GUV zones, and to deliver more clean air to breathing zones.

Deposition and control against resuspension

For respirable aerosols, deposition onto surfaces reduces airborne particle concentrations to a lesser extent than other mechanisms, and the extent to which deposition can be manipulated as an aerosol transfer control mechanism is limited. For aerosols larger than respirable size (>5 μm) deposition is a major, if not dominant, source of removal. Deposition loss-rate coefficients in the range of approximately 0.1–7 h^{-1} for particle sizes 0.55–8.66 μm have been reported for a bare space with neither furnishings, occupants, nor mechanical air mixing [273,274]. Surface deposition was shown to be increased by a factor of 1.3–2.4 by increasing airspeed from <5 to 19 cm/s with fans, with a stronger effect on smaller particles [274]. However, compared with still air, some air movement from open windows or doors to the outside, mechanical systems, and occupants moving around can lengthen the airborne residence time. By adding 12 m^2 surface area via furnishings to a room with total volume 14.2 m^3, deposition increased by a factor of up to 2.6 with a stronger effect on larger particles (ibid). Studies of aerosols 1 to >10 μm introduced to HVAC ducts with typical velocities (~2–9 m/s) showed in-duct deposition increasing with aerosol size and velocity [275,276]. Tests of aerosols 1–10 μm in an HVAC coil apparatus showed up to 30% deposition, with increased deposition with aerosol size, and very mild increases in deposition with air speed change from 1-5 m/s [277]. The extent to which strategies to promote deposition can reduce infectious aerosol transfer in practice has not been extensively studied.

Once deposited on surfaces, potentially infectious material can be resuspended through disturbances, posing a potential source of transmission [278–285]. Eight-hour room exposures to aerosols <1 to >10 μm were shown to increase by up to three orders of magnitude as a result of resuspended particles in an experimental HVAC duct [286]. Running HVAC systems for a "washout" period before occupancy can reduce exposure to particles that are re-aerosolized within supply ducts, and surface cleaning offers to reduce other sources of re-aerosolization. The infectivity of pathogenic aerosols that have settled and reaerosolized over various scales of residence time outside of hosts is not well characterized.

III. Building scale

Although building scale transfer is typically low, due to concentration dilution with distance from the source – including dilution within HVAC systems – (Figure 1), there exist scenarios where it could present non-negligible risk, with implications for populations larger than those at room scale. Air can be transferred between rooms by forced air HVAC, exhaust or pressure-

driven internal flows; vertically driven by stack effects and solar load; and horizontally driven by wind and temperature gradients. Beginning 20 years ago in response to the threat of weaponized anthrax, several modeling studies have presented strong evidence for building scale pathogenic aerosol transfer. A SARS superspreading event within a hospital ward was consistent with CFD showing the dispersion of airflow and aerosol viral concentrations from an infected person's cubical throughout an open ward [287,288]. Similarly, a large MERS outbreak in a hospital was linked with airflow between patient rooms [289]. Detection of infectious MERS in the air outside of a makeshift MERS isolation unit suggested a failure of interzonal airflow control [290]. Beyond the healthcare setting, air flow patterns – constructed from tracer gas experiments, CFD, and statistical models – predicted the spatiotemporal distribution of SARS cases in a high-rise apartment complex, from a plausible source of viral aerosol from a plumbing vent, rising throughout buildings, and spreading across a courtyard to other buildings [93,94,291]. Viral aerosolization from wastewater vents or natural ventilation air ducts has also been implicated in the vertical spread of SARS-CoV-2 in high-rise apartment buildings [95,292,293]. In a university dormitory wing, multi-zone airflow modelling showed that the room of a resident with acute respiratory infection in the wing had an airflow connection with the only secondary case in the wing, suggesting a plausible aerosol transmission mode [203]. Although between-room connections within a house are generally different than between-room connections in a commercial or multi-unit building, available studies suggest that there could be more building scale transfer of submicron-sized aerosols within-unit than may be reported, missed by lack of investigation of between-zone connections.

Forced air thermal conditioning (HVAC) systems in commercial buildings typically mix air that is returned from the occupied zone with outdoor ventilation air. A common risk reduction recommendation early in the COVID-19 pandemic was to increase the amount of outdoor air and minimize recirculation [220]. ASHRAE Core Recommendations from several months later suggest that outdoor air supply meet code and the adoption of an effective clean air delivery approach [294], consistent with parallel goals of energy savings and appropriate thermal conditioning. Filtration and inactivation by GUV within the HVAC system (along with deposition in the duct) can reduce infectious aerosol concentrations within and between rooms at much lower energy cost than outdoor air ventilation, which often requires thermal conditioning. An exception to this is the use of economizers, which, when outdoor conditions are suitable, increase the outdoor air fraction to achieve "free" cooling. Demand-controlled ventilation, on the other hand, reduces outdoor airflow in proportion to occupancy in order to save energy during periods when economizer operation is not possible, potentially increasing aerosol transfer. The risk associated with between-room transfer, although largely uncharacterized, would be greatly mitigated by the dilution that necessarily happens when air is mixed in an HVAC system serving a larger area (Figure 1). Nonetheless, air cleaning in-duct presents an opportunity for efficient pathogen mitigation contributing non-infectious air supply equal to the HVAC recirculation rates, which can often be as high as 4–6 ACH.

Building scale airflow interventions aim to reduce the magnitude of aerosol transfer from spaces with higher probabilities of infected people to spaces with susceptibles. Beyond healthcare settings, airflow management is especially relevant in residential environments where people spend extended periods of time and infected individuals are less likely to practice controls related to activities or masking. Yet knowledge on the efficacy of building-scale airflow interventions is

limited. A tracer gas study showing 2–35% transfer between-units in multiunit residential buildings showed sealing interventions resulted in a slight increase in median between-unit airflow [295]. Negative pressure, as deployed in hospital isolation areas, residential care, or household settings, can effectively move contaminated room air through an exhaust and reduce or eliminate exposure to individuals in the adjacent rooms or corridors [194,296–298]. Yet such design strategies remain to be thoroughly explored for feasible translation, related to market and technician acceptance, in occupational, school, multiunit residential, and other settings.

Other benefits from infectious aerosol controls

Infection control has secondary health benefits beyond reducing acute disease. COVID-19 has resulted in numerous adverse sequelae including cardiovascular, brain, and long-term effects ("long COVID") [299]. Reducing inhalation exposure to rhinovirus can lower the prevalence of severe asthma in children [300]. Elevated ventilation and filtration can lower exposure to dampness (related to climate), mold, and other indoor air contaminants of concern [55,56,301,302]. Several studies reiterate the efficacy of filtration-based portable air cleaners for removing particulate matter as small as ultrafine (≤0.1 μm), associated with respiratory and cardiovascular disease [303–307]. Cognitive function scores, work productivity, and performance on attention, speed, accuracy, and decision-making tests could also be improved with increases in ventilation [52,54,308,309]. Several studies have documented reduced absenteeism in schools and workplaces with increased ventilation, related to reduced prevalence of respiratory illness [54,217,310,311]. The costs of increasing ventilation are small compared with the health and wellness benefits in schools and workplaces [31,312], including in tropical climates where dehumidification costs are much greater [313]. A 2002 multidisciplinary review estimated billions of dollars in economic savings in the US associated with health benefits from ventilation [314], an underestimate in today's population and economic terms.

Research priorities

Knowledge gaps

Based on the reviewed literature, several key knowledge gaps have emerged that impede efforts to implement engineering controls for infection control, other health benefits. These gaps, posed below as questions, can be addressed through proposed research priorities in controlled and well-characterized environments, in real-world, practice-based settings, and through methodological advancements. A condensed version of knowledge gaps and research priorities is given by Figure 3.

1. For SARS-CoV-2, influenza viruses, and other respiratory pathogens, how much infectious virus is released through exhaled breath in aerosols of various sizes and what are the immunological, physiological, and activity-related predictors of infectious aerosol shedding? How many infectious virions are contained in individual aerosol droplets of different sizes, where are the most immunologically susceptible sites and population subgroups, and how do these factors influence infectious dose?

2. Given common configurations of airflow and patterns of human activity, how quantitatively heterogeneous is room scale aerosol concentration? How can controls reduce the distance between intense, close-interactive exposure, thus shifting exposure to the room scale that can be much more effectively controlled?
3. Which settings across societies represent the highest risk for aerosol inhalation transmission? To what extent do cumulative exposures, including environmental pollutants and psychosocial stress that are often unequally distributed across sociodemographic groups, mediate infection risk?
4. What advancements in modelling are needed to account for cumulative exposure to a range of relevant infectious aerosol sizes to provide substantially more specific estimates of infection risk? Which models can provide accurate estimation of engineering control effectiveness in a variety of real-world settings?
5. How can engineering controls be deployed in real-world environments (e.g., best configurations and combinations) to confer the greatest levels of protection? How can airflow management reduce close-interactive exposure and improve the effectiveness of ventilation, filtration, and GUV strategies? Which strategies can provide efficient evaluation and validation of emerging control technologies?
6. What arrangement of engineering controls can provide the greatest cumulative health benefits for the amount of energy required?
7. What strategies are most effective in facilitating implementation of engineering controls at scale given investment, operational, behavior change, and energy challenges related to adoption?

Research in controlled and well-characterized environments

Controlled experiments in well-characterized environments enable quantitative evaluation of intervention effectiveness in specific settings. Key elements include occupant positioning, spacing, movement, and interaction; airflows induced by human movement, natural or direct outdoor air mechanical ventilation, and forced air thermal conditioning systems; and common layouts, including open versus enclosed offices, large superstores versus smaller markets, configurations for congregant care facilities, table and seating arrangements in restaurants, etc. Better characterization of the physical properties and removal mechanisms of aerosols that carry infectious material would support the targeting of controls to specific pathogens, heterogeneous host populations, and the various indoor settings. The following activities would be particularly valuable.

1. Measure size-resolved infectious aerosol transfer (including respirable, thoracic, and larger aerosols) from human or simulated sources in relevant settings where masks cannot be worn (e.g., dining halls, restaurants) or where masks may not work effectively owing to activity or improper fit. Quantify the benefits of administrative and engineering controls in these settings.
2. Characterize the aerosol exposure dynamics differentiating close-interactive and room scale transfers, especially in environments that are not well-mixed and where connections between occupants vary widely with positioning, human movement, and use of barriers, intentional stratification, and other airflow management strategies. Identify effective controls for common configurations.

3. Conduct experimental studies to validate CFD modelling with the goal of supporting the development of simple, computationally tractable engineering models that can characterize within-room spatiotemporal evolution of infectious aerosol concentration. Identify modelling techniques that provide robust and practically informative results with acceptable computational burdens.
4. Quantify the effectiveness of controls such as portable filters and GUV (upper-room and far GUV) on aerosol and infectious agent surrogates in actual or simulated occupied buildings through controlled experiments, with particular focus on environments in which masks have limited applicability, people move around, or strict density limits have high costs (e.g., school hallways, grocery and retail, public transit, institutional dining, etc.). Studies are needed to characterize the performance of controls in generalizable ways (e.g., single pass efficiency of a filter) and then to quantify how the application of control measures under different conditions modulates performance (e.g., CADR in practice compared with nominal rating by AHAM test procedure).
5. Lower priority: Quantify potential transfers of infectious aerosols via resuspension from filters, floors, and other surfaces in rooms, and aerosol transfers between rooms, to address concerns that they could present significant risks under some circumstances.

Practice-based research

Practice-based research includes field studies and other investigations that support implementation of infection control measures targeted to specific settings.

1. Conduct retrospective, infectious disease outbreak investigations at sites where transmissions are suspected or confirmed to determine the transfer mechanisms (i.e., aerosols, direct transfer via drops, fomites), and build a knowledge base of the relationships between infection risk, exposure, and existing controls. Documentation of ventilation system configuration and operation and any extant filtration should be a standard part of outbreak investigations that cannot be entirely attributable to close contacts.
2. Invest in resource-intensive, population-based epidemiologic studies to improve understanding of the effectiveness of engineering and administrative controls to reduce exposure and transmission in specific settings. Study designs valuable to substantially advancing public health infection control include prospective infection monitoring with a) large populations (hundreds to thousands of participants) and crude evaluation of indoor environmental conditions including ventilation, filtration, or other features related to infectious aerosol transfer, and b) smaller populations and comprehensive characterization of indoor environmental quality and controls related to infectious aerosol transfer. The latter includes blinded interventions and sampling for infectious aerosols from environmental air and the exhaled breath of naturally infected occupants.
3. As is done for chemical hazards, conduct infectious aerosol transmission risk assessment using modelling that accounts for uncertainties in control effectiveness and variability in infectious dose generation rates associated with aerosol shedding, pathogen infectivity, and immunologically vulnerable exposed groups. To support risk assessment related to controls, develop algorithms to estimate the adequacy of outdoor and filtered air delivery when employing economizers, demand-controlled ventilation, or other dynamic systems, and evaluate associated energy savings.

4. Identify high priority settings for controls, including evaluation of exposure based on building features, use activities, socioeconomic features of building occupants and their cumulative exposures. Attention should be directed toward reducing exposures for socioeconomically disadvantaged communities and settings where building infrastructure facilitates elevated risk of transmission. Investigate the effects of winter minimum relative humidity—especially in cold climates—on health and vulnerability to respiratory infection.
5. Use research methods from social science and industrial engineering to systematically study the common challenges and barriers faced by building owners and operators who aim to implement recommended infection control guidance from ASHRAE, AIVC, CDC, WHO, etc. Challenges, listed below, may limit implementation or reduce control effectiveness.
    a. Operational and energy-related challenges. Indoor air quality for thermal comfort and health and energy use are coupled; and increasing ventilation can increase energy use including peak demand. Achieving improved indoor air quality within the context of decarbonizing the built environment is an important need. Alternatives to ventilation or more effective ventilation are needed. The opening of windows to improve ventilation may complicate efforts to manage thermal comfort. There also exist challenges with achieving effective and reliable design and deployment of GUV given irradiance strength, room volume, and air flows.
    b. Behavioral challenges. For example, controls that rely on human behavior, such as opening windows or manually-controlled mechanical ventilation or filtration systems, may not be implemented reliably or as intended. In some settings, open windows could increase exposure to ambient noise and air pollution, and could raise security concerns.
    c. Institutional and financial challenges. Retrofits to upgrade HVAC equipment to improve ventilation or filtration may take years to implement. Those tasked with purchasing air cleaners may be influenced by sales pitches to buy higher cost units with unhelpful features and as a result not provide adequate coverage with conventional options. An example is high-priced portable air cleaners that utilize ionization but provide lower clean air delivery rates where devices with media filters could provide much more delivered clean air at lower cost.

Methods

The development and assessment of methods and metrics, listed here, supports priority studies in controlled and applied settings, including large-scale, prospective, transmission monitoring in buildings and control measure evaluation.

1. Develop metrics and supporting test methods for infectious aerosol inactivation. Methods should include surrogate viruses or organisms reflecting a range of pathogen susceptibility. The predicted effectiveness of exposure mitigation via GUV within a room currently requires complex modelling given knowledge of pathogen susceptibility. Metrics that enable estimation of the airborne infection control potential of GUV in combination with other controls would be particularly useful, including a CADR-like measure for infectious particle inactivation at different sizes. Metrics and methods (e.g., a chamber test procedure) can be used to evaluate efficacy of developing technologies

including those that release disinfectants into the air (e.g., ionization, hydrogen peroxide vapor, triethylene glycol) along with safety tests related to potential byproduct formation and health effects.

2. Develop methods to improve the sensitivity of infectious aerosol detection and quantification from exhaled breath and ambient air sampling. Improvements could be targeted for a) increased resolution of size-resolved aerosol collection, b) increased usability and accessibility of samplers to enable widespread use in research contexts and potentially also operationally in sensitive buildings, and c) recommended strategies to quantify aerosol pathogen loads in occupied buildings, considering sampling location, duration, and frequency.
3. Prepare computational models for use by building operators to estimate infectious aerosol inhalation exposure (e.g., via CONTAM) and energy demand (e.g., via EnergyPlus) as a result of individual or combined controls that consider the empirical assessment of a) expected transfer of aerosols of different sizes following release, and b) the in-situ effectiveness of control measures. The goal is to reduce the difficulty of working with multiple modeling tools and of generating appropriate validation data (e.g., well-mixed conditions to match CONTAM).

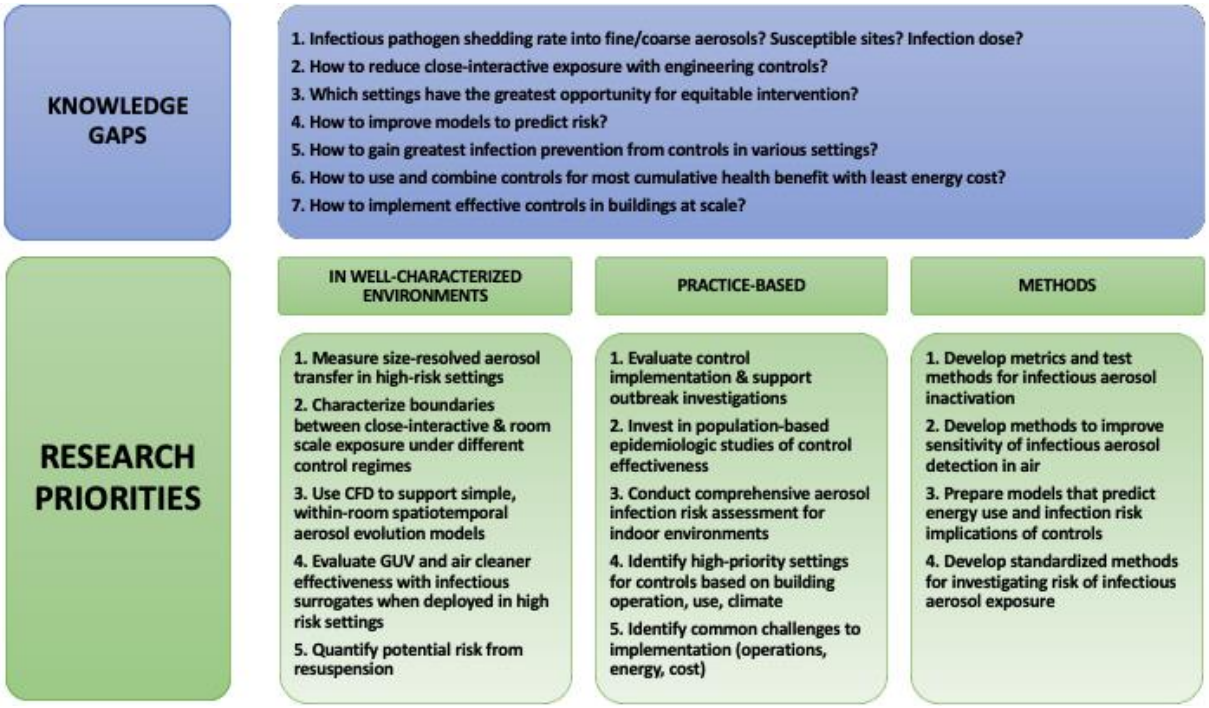

Figure 3. Knowledge gaps and research priorities to support implementation of indoor control measures against airborne infection.

Conclusions

Emerging variants of SARS-CoV-2 with increased transmissibility underscore the importance of controls for aerosol inhalation transmission. Ventilation, filtration, GUV, and airflow management can effectively reduce exposure to pathogenic aerosols in buildings, with

substantial public health benefit; but real-world demonstration and evaluation is needed to advance systematic and widespread implementation. Quantitation of viral shedding from study populations into saliva or upper respiratory mucosa have reported lognormal distributions [48,315], and few individuals shedding the most virus have been implicated in driving population transmission [28,29]. If SARS-CoV-2 aerosol shedding across the population follows a lognormal distribution, as has been considered elsewhere [316], then controls that lower total viral aerosol exposure by a factor of 10 can approach a meaningful reduction in infectivity of the highest shedders by an order of magnitude, thus reducing the impact of supershedders and the chances of encountering someone shedding enough to pose transmission risk. Building-level, engineering controls provide opportunities to reduce reliance on the challenging physical distancing measures experienced during COVID-19 and other plagues. Engineering controls can add to risk reduction achieved by administrative approaches and thus support in-person gatherings that provide for social wellness, learning, and commerce. They also present an important opportunity to advance social justice in the wake of a pandemic with highly inequitable health and economic burdens.

This review identified gaps in existing knowledge that point to the need for studies and methods to measure, quantify, and model the relationships between control-mediated aerosol transfer and actual infection risk. We have built on previous reviews of engineering control effectiveness [3,5,175,204] and contextualized priority research directions for evaluating controls at specific scales and settings. The goal is to support efforts to tailor and modify control measures akin to personalized medicine, based on the infectiousness of various pathogens of concern and based on the exposures hosted by the setting. Evaluation of implemented control measures must consider aerosol transfer mechanisms specific to the close-interactive, room, and building scales. The overarching research goal spurred by the COVID-19 pandemic is to inform infection controls that reduce risk to acceptably small levels, thus minimizing disruption of indoor activities, while also minimizing energy and economic impacts. We provide a framework for considering the physical processes governing pathogenic aerosol transfer, independent of pathogen infectivity and host susceptibility, which may be highly variable. This supports efforts to select setting-specific control strategies with well-predicted effects on aerosol transfer and energy requirements.

Data availability statement

The data that support the findings of this study are openly available in GitLab at https://gitlab.com/jacobbueno/building_controls_for_infectious_aerosols.

Author contribution statement

P. Jacob Bueno de Mesquita: Conceptualization (lead), Methodology (lead), Data curation (supporting), Supervision (equal), Formal analysis (equal), Visualization (lead), Writing-original draft (lead), Writing-review & editing (lead).

William W. Delp: Conceptualization (supporting), Methodology (equal), Data curation (lead), Formal analysis (equal), Visualization (lead).

Wanyu R. Chan: Funding Acquisition (lead), Conceptualization (supporting), Visualization (supporting), Methodology (supporting), Writing-review & editing (supporting), supervision (supporting).

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Conflict of interest statement

PJBdeM received fees from PandemicProof Productions for advising on strategies to reduce SARS-CoV-2 transmission during film production.
WB conducted air cleaner research at Penn State funded by ActivePure Technologies.

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Tables

Table 1. Scales of infectious aerosol transfer in buildings and associated engineering controls

	Close-interactive scale	Room scale	Building scale
Scale description	Interactions within 1-2 m, occurring for at least 15 min per 24 h. Interactions include conversing, eating, laughing, working, and other. Risk increases with source emission and susceptible person inhalation rate, both related to activity. Risk increases with duration.	Exposure within-room, between individuals not having close-interactive transfer. Poses the greatest risk for superspreading given potential large numbers of exposed and high concentrations of infectious aerosol when uncontrolled.	Exposure between rooms or floors in a building with air transfer occurring through forced air heating, ventilating, and air conditioning (HVAC) systems or through pressure-induced airflow via connections including internal doorways and halls, plumbing, or common exhaust fan inlets.
Ventilation and airflow management	● Workstation airflow management. ● Room-scale directional airflow.	● Increase clean air delivery. ● Directional airflow and clean air supply to the breathing zone. ● Multi-zone HVAC systems (increase mixing volume and decrease high concentration transfer when an infected person is in the room).	● Increase clean air delivery. ● Directional airflow, e.g., exhausting from rooms expected to have greater presence of infectious aerosol.
Filtration by HVAC system	● Increase clean air delivery via in-duct filtration. Must mix with breathing zone air.	● Increase in-room clean air delivery via in-duct filtration.	● Increase clean air delivery with multi-zone sources via in-duct filtration.
Filtration by portable air cleaner	● Applied near the breathing zone (could be part of workstation airflow management). ● Personal air cleaning devices.	● Applied near the breathing zone and/or throughout the space.	● Approaches from other scales.
Infectious aerosol inactivation by GUV	● Far GUV (222nm wavelength) in the breathing zone.	● Far GUV in the breathing zone and/or throughout room space. ● Upper-room GUV (best with induced mixing of air to upper-room). ● GUV in recirculating HVAC ducts.	● Approaches from other scales.
Other strategies	● Physical barriers (more helpful for drop sprays and larger aerosols compared with smaller aerosols).	● Flushing between occupant cohorts	● Sealing openings between spaces

Table 2. Settings with elevated risk factors for infectious aerosol transmission

Priority settings (examples)	Potential risk factors related to activities done in the setting leading to exposure at room scale and sometimes close-interactive and/or building scale
Dining (school cafeteria, restaurant, institutional residential, event)	Impractical to wear masks; close-interactive; conversation, laughter; moderate duration (0.5–1 h) per encounter and possibly multiple encounters during infectious period; people moving makes directional airflow control challenging; many restaurants intended for high density occupancy; break rooms and dining areas may not be easily separable from mixing with other occupied areas, e.g., in schools, offices, and institutional residential buildings.
Risky occupational settings (slaughterhouse, meat packing, factory, call center, agricultural worker housing)	Long duration of co-occupancy over multiple days; conversation and loud speech may be required; PPE may not be available, may be uncomfortable to use, or poorly fitted; masking adherence may be problematic, especially in warm environments; special risks associated with some settings (e.g., talking at call centers, workstations that cannot be easily distanced, low temperature and relative humidity in meat processing plants); low ventilation; workers often limited to raise concerns; co-workers with elevated risk from living in high density homes with others also working in high risk occupational settings; limited/no paid leave discourages self-isolation/quarantine.
Schools, meetings (preschool, K-12, university, conference, classroom, dining hall, gym, auditorium)	Classrooms commonly have high occupant density, long periods of co-occupancy over consecutive days; loud speech often required for communication; conversations and small group interactions between classes and in halls are common; many facilities are older, with low ventilation or filtration in HVAC systems; students may have higher-risk living situations, e.g., sharing high-density housing with parents who work in high risk jobs; limited adherence to distancing and masking; limited or no access to respirators.
Local & regional public transit (train, bus, car sharing)	Economic viability of local and regional transit often depends on high rider densities during peak commutes; difficult to enforce mask rules and masks may not be correctly fitted or worn; screening is infeasible; co-occupancy with potentially large groups of strangers with unknown exposure for 0.5–1 h or more; limited or no access to respirators.
Institutional residential (dormitory, nursing home, long-term care, prison, shelter, military barrack)	Constant occupancy or for many hours per day; masking of residents is often infeasible; frequency and volume of conversation often cannot be controlled; close interactions between staff and residents needing care; many older facilities with inadequate ventilation and filtration; shared bedrooms; airflow connections between bedrooms and between dining areas and other common areas; natural ventilation often not practical; staff may work at multiple institutions and introduce infection between settings; residents may have comorbidities; worse conditions for underserved communities; limited or no access to respirators.
Grocery, retail	Employees exposed to large population (potentially infectious), close-interactive (e.g., cashier), long duration of workday exposure; infeasible to screen customers; some stores have small volume, narrow aisles, low ventilation; employees may not have paid sick leave; small businesses may not have enough staff to encourage staying home for infection control; limited or no access to respirators.
Oratory, singing, wind instrument, performance (rehearsal room, performance hall, religious gathering)	Many people present (potential for superspreading) and often high density; close-interactive; performers may be less likely to wear masks (e.g., film production), and are likely to use loud speech, shouting, or singing.
Offices	Conference rooms or similar space could host room-scale exposure for many people over a prolonged period of time (hours per day, over months); close interactions; limited or no access to respirators.
Athletics performance (fitness facility, playing field/court, spectator area)	Many people present; typically without face masks; close-interactive (among players, among spectators), loud speech, shouting, increased heavy breathing; building scale transfer from strong source generation.
Private residential (single- or multi-unit housing)	Constant occupancy or exposure for many hours each day; close-interactive; masks typically not worn; inadequate ventilation in many homes, especially when hot or cold outside; often higher density in underserved communities; toilet-generated aerosols; potential airflow connections between apartments, spanning multiple floors (e.g., shared HVAC, stack-driven flows in converted single-family residence, exhaust ventilation in multi-story building).

There are variations possible in each setting, and risk of transmission is related to multiple elements, including:

1. Number of potentially infectious people present
2. Number of people present with elevated immune susceptibility and risk of severe illness
3. Distancing and density of people in the indoor space
4. Use of face mask for emissions control
5. Use of PPE (including face masks, but especially N95 or equivalent filtering facepiece respirators)
6. Duration of exposure
7. Magnitude of respiration (speaking, speaking loudly or shouting, singing, breathing fast and/or heavy)
8. Presence of mechanical ventilation
9. Presence of filtration or GUV in forced air HVAC system
10. Differential burdens of exposures that increase risk for underserved socioeconomic and demographic groups

Table 3. Epidemiologic studies that evaluate the effect of ventilation on infection risk

Study	Exposure scenario	Infection assessment	Ventilation assessment	Ventilation comparison	Risk of infection[a]
[317] (Brundage et al., 1988)	Army trainees living in close quarters in barracks over 47 months.	Retrospective records assessment for febrile (≥38ºC) respiratory illness.	Estimated based on barrack design and occupancy [56].	0.9 vs 6.8 L/s/p; 'Modern', tighter sealed versus older, 'leaky' barracks.	Adjusted risk ratio 1.51 (95% CI 1.46-1.56).
[318] (Hoge et al., 1994)	Inmates living in different areas of a jail over 4 weeks during an *S. pneumoniae* outbreak.	Prospective culture of respiratory swabs & serology for *S. pneumoniae*.	Cross-sectional measurement of CO_2 and evaluation of air flow from the ventilation system.	>3.4 vs 2.0 L/s/p; Cell block style with more vs less outside air.	Adjusted odds ratio 2.02 (95% CI 1.07-3.82).
[202(p200)] (Menzies et al., 2000)	Health care workers exposed to TB cases over 3 years.	Cross-sectional analysis of tuberculin skin test (TST) conversion.	Cross-sectional CO_2 decay and smoke release experiments.	<2 vs ≥2 ACH; workers in lower versus higher ventilated spaces.	Adjusted hazard ratio 3.4 (95% CI 2.1-5.8) for TST conversion negative to positive.
[319] (Menzies, et al., 2003)	Laboratorians working in hospitals with TB cases over 3 years.	Cross-sectional analysis of tuberculin skin test conversion.	Cross-sectional CO_2 decay and smoke release experiments.	16.7 vs 32.5 ACH (averages); lower versus higher ventilated spaces.	Unadjusted infection risk greater ($p<0.001$; unpaired t test).
[320] (Sun et al., 2011)	University dormitory population in 17 buildings.	Questionnaire of common cold incidence over the previous year.	Cross-sectional measurement of CO_2 decay experiments (peak vs outdoor).	5 vs 1 L/s/p; Average dorm room ventilation rate of (CO_2 decay calculation).	Incident risk ratio 7 (35% versus 5% study population) for ≥6 common colds.
[197] (Du et al., 2020)	Retrospective cohort of household and university campus contacts (at least 30 hours of shared air) of infectious TB cases from an outbreak. Ventilation interventions applied.	Sputum tests and chest x-ray to detect active TB cases, with sequencing to confirm probable transmission clusters.	Measured CO_2 concentrations before and after intervention.	>1,000 vs <1,000 ppm CO_2 (pre- vs post-intervention classroom) with exposure to cases; CO_2 ppm (estimated clean air flow L/s/p) were 3,200 (1.7) & 600 (23.6-25.1).	Adjusted hazard ratio 32.8 (95% CI 2.0-540.3) for acquiring active TB infection.
[203] (Zhu et al., 2020)	University dormitory population in 'low' (LVB) and 'high ventilated (HVB) dormitory buildings.	Prospective symptom monitoring with qRT-PCR for acute respiratory infections.	Continuous measurement of CO_2 >5 mo. Measurement of building envelope pressure and local weather data.	2.0 vs 5.9L/s/p; LVB vs HVB participant room means. 1.9 vs 2.1L/s/p; leeward vs windward room means in LVB.	Unadjusted incident rate ratio 4.04 (95% CI 0.69-163.02) LVB vs HVB; 1.3 (0.7-2.61) leeward vs windward.
[321] (proof-of-concept [POC], Killingley et al., 2012); [211] (main study, Nguyen-Van-Tam et al., 2020)	Compared infection rate between 2 human challenge trials with different ventilation levels.	Daily, upper respiratory swab sample following inoculation, and pre- vs post-infection serology.	POC estimated given sealed suite with bathroom exhaust [174]. Main estimated by CO_2 decay & tracer gas experiments.	0.8 L/s/p vs 4 L/s/p; POC vs main study.	Unadjusted risk ratio of transmission 6.4 (8.3 vs 1.3%).

[a]Exposure is compared at lower vs higher ventilation level.

Appendices

Appendix 1

Table A1. Tools for estimating exposure or risk for SARS-CoV-2 in indoor environments

Tool/Source	Key parameters that can be manipulated
Safe Air Spaces Oregon Institute for Health in the Built Environment	Risk of SARS-CoV-2 transmission considers "high" or "low" viral emitter, number of occupants sharing air, ventilation, extra air cleaning from filtration.
Portable Air Cleaner Calculator for Schools v1 Harvard-CU Boulder	Considers the number of people and size of space, and risk of SARS-CoV-2 transmission; provides suggestion for how to increase effective air exchange rate through use of portable air cleaning devices.
COVID-19 Aerosol Transmission Estimator Jose Jiménez CU-Boulder	Aerosol transmission calculator. Considers infectious dose emission rate (quanta), inhalation rate, mask efficiencies for source. control and PPE, building ventilation rate, biological decay of virus and aerosol deposition onto surfaces, chance of encountering an infectious person, proportion of population immune. Visualization by El País using the Jiménez aerosol transmission estimator.
Estimation of COVID-19 infection risk from airborne transmission during classroom teaching Duke University	Adding probabilistic Monte Carlo approach to Jose Jiménez transmission risk estimator.
Airborne infection risk calculator International collaborators (USA, Italy, Australia), hosted by CUNY	Estimates risk as a function of time, viral inactivation/removal, room volume, number of infectious occupants, breathing level based on activity, and estimated quanta generation level based on comprehensive analysis of published findings.
COVID-19 Risk Calculator Harvard Healthy Buildings	Estimates risk based on model described in analysis of Diamond Princess cruise ship outbreak. Model adjusts risk based on room size, length of exposure, activity type, and controls including face mask use, distancing, ventilation, air cleaning, hand washing, and room cleaning.
FaTIMA (Fate and Transport of Indoor Microbiological Aerosols) NIST	Multizone modeling tool to help predict viral aerosol exposure given exposure within a building. Considers ventilation from building infiltration and mechanical sources, system filtration, portable air cleaner use. Describes exposure and does not make assumptions about the relationship between exposure and infection risk. (Documentation)
Equivalent outdoor air calculator ASHRAE	Estimates total equivalent air changes per hour in a space and the flush-out time to achieve 3 air changes per hour. The goal of the flush-out is to reduce exposure to contaminants that build up over time with occupants.
Ventilation calculator REHVA	Estimates the effect of ventilation on SARS-CoV-2 transmission risk.
COVID Exposure Assessment Tool (CEAT) Signature Science, LLC	Considers near-field and far-field exposure associated with numerous factors, including community infection prevalence and adherence to distancing measures. Benchmarks risk associated with inhalation exposure using OSHA "high risk" classification.

seco-Tool Michael Riediker and Christian Monn; SECO (Swiss State Secretariat for Economic Affairs)	Calculates concentration of aerosolized virus in a room and exposure within an arm's length (60cm) and at room-scale. Considers mask use, variable source emission, physical activity, speech, and room size, air exchange, and air flow velocity.
Facility Infection Risk Estimator v2.1 BranchPattern	Estimates number of infected adults and children per exposure scenario. Can build exposure scenarios based on age, activity level, room size, use of GUV, air exchange, filtration, exposure time, level of viral shedding into exhaled breath, mask use. Translates disease estimates into economic value, and associated, hypothetical reproductive ratio values.
Why Is the Risk of Coronavirus Transmission so High Indoors? Article with visualization and tool. Zeit Online Publication with advising from a Max Planck Institute for Chemistry research team (Jos Lelieveld et al. 2020)	Estimates transmission given available evidence and assumptions regarding generation of infectious aerosols including through speech, speech volume, singing, coughing, mask efficiency, room size, air exchange rate, and occupancy density, and length of exposure. The concentration of infectious virus contained in respiratory lining fluid is used to estimate infectious material concentration in aerosols. Measured concentrations of exhaled breath particles are used.
An analysis of three Covid-19 outbreaks: how they happened and how they can be avoided. El País in collaboration with numerous public health agencies advising.	Provides visual models of documented transmission of SARS-CoV-2 in an office, a restaurant, and a bus. Provides suggestion for mitigating transmission based on the hierarchy of controls.
City reduced probability of infection for indoor airborne transmission of COVID-19. Concordia	Draws on the Jiménez transmission estimator and building archetypes to infer infection transmission risk at the building level across Canada and the United States.

Appendix 2: Details of the aerosol transfer model in an office

A CONTAM simulation was performed to estimate respiratory aerosol concentrations a) in the infector subzone (close-interactive transfer), b) in a well-mixed room space occupied by the infector, that is supplied by, separately, SZ and MZ HVAC systems, and c) in a separate room connected by the MZ system (described in main text). The schematic for the MZ and SZ simulations showing airflows and aerosol deposition is given by Figure A1. The filtration efficiencies of the MERV13 filter and MERV8-like cloth masks for each aerosol size bin used in the model are given by Table A2. We used a mass balance approach to compute respiratory aerosol concentrations mediated by pressure and flow in the theoretical office space at the transfer scales of interest, described by

$$\frac{dC_i}{dt} = \frac{\dot{S}_i}{V} - \left(\lambda + \kappa_i + (1 - OA)\frac{Q_{HVAC}}{V}\,\eta_i\right) C_i, \quad (3)$$

where subscript i denotes respiratory droplet size bin, with C respiratory aerosol droplet concentration (number or volume) in air, $\dot{S}$respiratory aerosol number generation strength, V indoor space volume, λ ventilation rate, κ deposition rate, OA outdoor air fraction, Q_{HVAC} HVAC mechanical flow rate, and ηfilter efficiency. One minute injections of source aerosol were considered in the simulation for 60 consecutive minutes with constant HVAC air delivery. Details to guide reproduction of the CONTAM simulation are described at https://gitlab.com/jacobbueno/building_controls_for_infectious_aerosols.

Figure A2 depicts the volume (top panel) and aerosol particle number (bottom panel) concentrations at each scale of transfer. As expected, and based on Figure 1 (main text), the concentrations of respiratory aerosols are higher in the close-interactive scale (SZ infector subzone space), compared with the other aerosol transfer scales. Based on the available knowledge of respiratory aerosols generated during speech (Table A1) [82,177], the model predicts the highest volume concentrations for the close-interactive and room scale exposures at the upper end of the modeled particle diameters of approximately 14 µm. It predicts the highest number concentration for all scales at approximately 1 µm. A single $\log_{10}$ increase in diameter corresponds with a 3 $\log_{10}$ increase in volume for an aqueous sphere. The volume and number concentrations drop sharply at approximately 5 µm for the building scale transfer, due to an increasing role of deposition in removal, suggesting a meaningful role of deposition in the lower building scale transfer compared with the other scales.

Table A2. Input values for CONTAM model

Equilibrated size	Initial size	Number Distribution [a] (released / min)	Deposition [b] (% removed / h)	Mask filtration efficiency (% particles captured)		
				MERV 13	Out-Flow	In-Flow
0.3	0.5–1.0	74	1.20E-01	0.498	39.94	21.74
0.6	1–2	1129	6.00E-02	0.528	57.81	30.92
1.2	2–4	1176	2.80E-01	0.592	71.66	52.18
2.4	4–8	537	0.84996	0.754	81.97	67.79
4.8	8–16	133	2.30004	0.953	87.14	78.75
8	16–24	48	4.5	0.990	87.14	85.04
11.2	24–32	34	8.1	0.995	87.14	87.14
14.4	32–40	31	12.9996	0.998	87.14	87.14

[a] For continuous speaking. [b] Deposition on surfaces in the room and in the HVAC system.

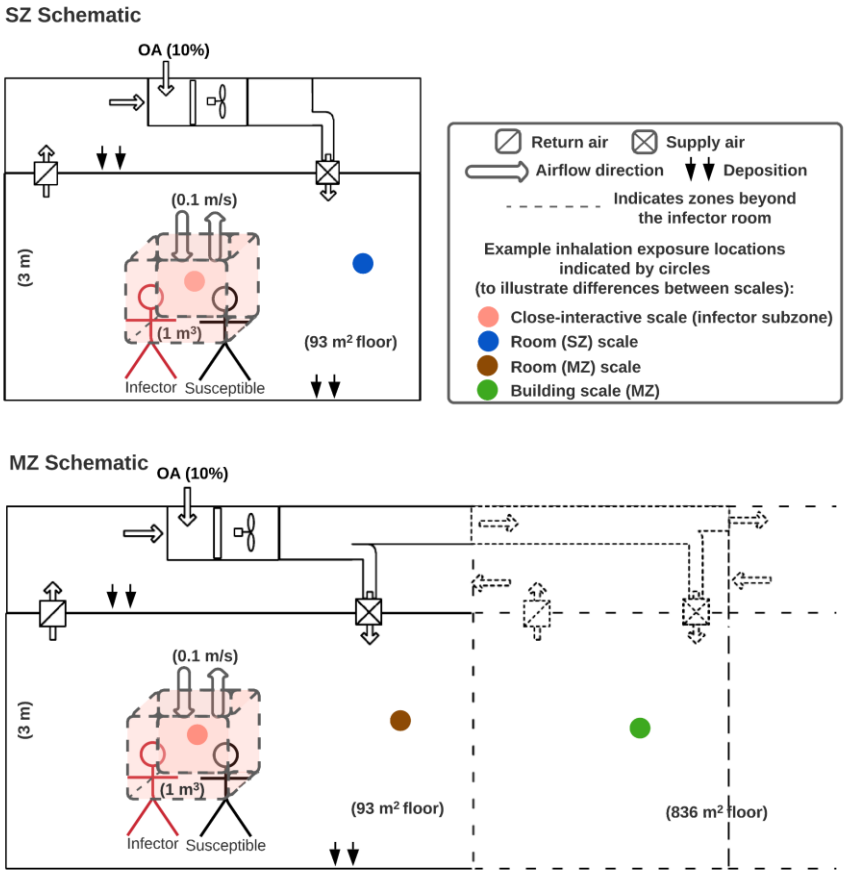

Figure A1. Model schematics. Single zone (SZ; top panel) and multizone (MZ; bottom panel) aerosol transfer model office spaces.

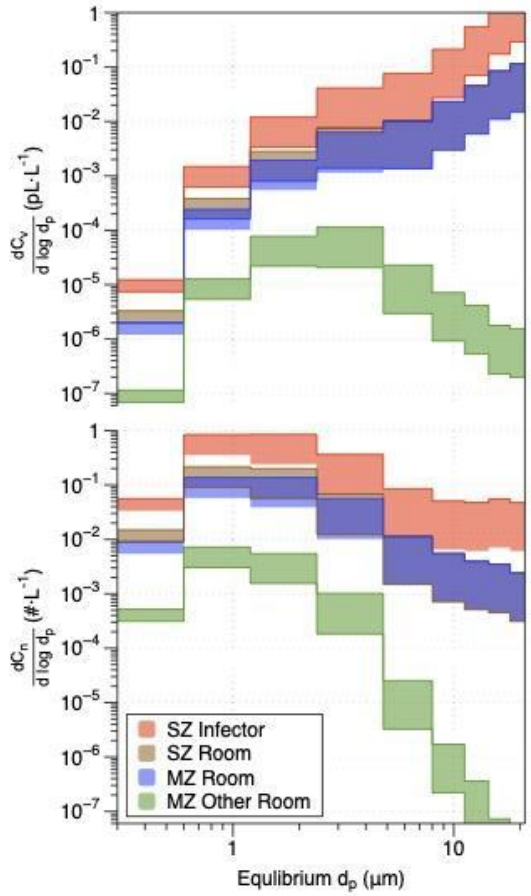

Figure A2. Volume and number concentrations at scales of transfer by equilibrated respiratory aerosol size**.** The volume concentration distribution by equilibrated particle size is given in pL respiratory volume per L air (top panel). The number concentration distribution by equilibrated particle size is the number of aerosol particles per L air (bottom panel). The eight equilibrated particle size bins correspond to those in Table A2. The top band of each shaded region corresponds to an unmasked scenario (no mask on both infector and susceptible) and the bottom band corresponds to a scenario where both infector and susceptible are wearing cloth masks.

Appendix 3: Source control and personal protective equipment (PPE)

Reduce the chances of an infectious person being present

Reducing or eliminating the source of a hazard is the most effective approach per the hierarchy of controls [322]. For airborne pathogens, the aim is to reduce the chance that an infectious person will enter a communal indoor space; and if they do enter, to minimize their emissions. This approach is particularly challenging when asymptomatic individuals can transmit infectious quanta, as occurs with SAR-CoV-2 [44,45,47]. Source controls include capacity and duration limits, symptom screening, contact and risk factor questionnaires to identify those with recent exposure in high risk settings, frequent testing, separation of cohorts (e.g., via scheduling in school) to limit contacts, and ventilation flushing or air cleaning via filtration or GUV between sequential occupancies of indoor spaces.

Reduce emissions from infectious occupants

Source control aims to reduce the release of infectious aerosols, sprays, or surface contamination to interrupt transmission modes when infectious status is known or unknown, works across all scales of control, and can enable lower risk even when other controls may be inadequate. Activity control, including reducing vocalization, shouting, singing, activities that elicit heavy breathing, can reduce the quantity of infectious aerosols generated, as described earlier. Face masks have demonstrated effectiveness at reducing the release of infectious aerosols of various sizes of concern for inhalation exposures [98,323–326]. In addition to their filtering capacity, face masks also reduce the velocity of expired air streams, thus reducing the likelihood of direct transfers of infectious aerosols at high concentrations. Aerosols that escape a face mask often become entrained in thermal plumes rising upward out of the breathing zone, although natural ventilation or mechanically driven air movement also influence aerosol dispersal and transport. It is unclear how respirators with exhalation valves affect respiratory jets, although they are likely to reduce outward velocities to some degree. Face mask use among the public has been characterized as an effective layer of protection against SARS-CoV-2 community transmission [327–330].

Reduce exposure with PPE

Individuals who spend time in settings with known or potential risk can use PPE to reduce or eliminate exposure to infectious aerosols, ballistic drops, and contaminated surfaces. Face masks can serve as PPE, reducing inhalation exposure to infectious aerosols [67]. The effect can be increased if multiple layers are used and the seal around the face is tightened [323]. Given that SARS-CoV-2 genomes have been detected in aerosols in PPE doffing areas [92], care should be taken to protect against doffing-associated exposure that could lead to infection. A meta-analysis of epidemiologic studies showed associations with surgical mask or respirator use with reduced infection risk of approximately half or more in healthcare and non-healthcare settings [331]. There still can be substantial risk of infection via aerosols despite surgical mask use, as has been noted in healthcare settings [166], which could be mitigated by well-fitted respirators that more effectively reduce aerosol inhalation [167]. Some epidemiological studies showed a protective effect of eye protection [165].

Appendix 4: Guidelines regarding building ventilation

Organizations have provided guidance for ventilation to control respiratory infections, and recently, SARS-CoV-2 (e.g., http://ashrae.org/covid19). There has been widespread acknowledgement of infectious aerosols contributing to the spread of infection epidemic, which has spurred efforts to advise building operators on infection control actions. Given the challenges of developing precise ventilation standards to effectively reduce airborne infection (specific beyond “more ventilation is better”), the collective wisdom of infectious disease experts and building engineers generally emphasizes some level of increased ventilation to mitigate SARS-CoV-2 spread, while maintaining thermal comfort, to reduce airborne transmission risk [40,332,333]. Upgrading HVAC filters to MERV13 or better, using portable air cleaners (with MERV13 filters or better), and using upper room germicidal UV (GUV) are also suggested to enhance infection control.

The Federation of European Heating, Ventilation, and Air Conditioning Associations (REHVA) recommends airborne infection isolation rooms (AIIR) to have at least 6–12 ACH, with new

builds having ≥12 [40]. REHVA suggests upgrading ventilation in any healthcare wards with infectious disease cases to match AIIR levels, and at least 4 ACH in other zones of healthcare facilities. The American Society of Heating, Refrigeration, and Air-Conditioning Engineers (ASHRAE) goes beyond this in Standard 170, advising at least 12 ACH in healthcare settings, regardless of aerosol generating procedure [212]. For school health clinics, ASHRAE provided guidance ranging from 6–10 ACH [334], and equivalent ventilation rates are still being researched by the Epidemic Task Force. This is generally higher than the non-pandemic standards.

REHVA shows how increasing ventilation above 1L/s/m^2 can reduce airborne infection risk and that 4L/s/m^2 may be advisable as a lower bound in office meeting rooms or classrooms (corresponding to 5ACH) [40]. They classify maintenance of indoor CO_2 levels below 800 and 1,000ppm (given outdoor CO_2 level of 400ppm) as "good" and "acceptable" ventilation, respectively. WHO suggested 5–6 ACH for public buildings in the context of SARS-CoV-2 pandemic control [42,43]. This is similar to what has been suggested in the US for holding K–12 school during the pandemic with 6 ACH as ideal, 5–6 as excellent, 4–5 as good, and 3–4 as bare minimum [38]. Guidelines are expected to evolve as understanding of ventilation infection control effectiveness increases. Ventilation is considered a helpful control within the context of other layers of protection including, in the context of the COVID-19 pandemic, use of face masks, physical distancing, de-densifying indoor spaces, upgrading filters in central HVAC systems, using portable air cleaners, deploying GUV, and considering air flow dynamics to reduce exposure to infectious aerosols.