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Particle sizes of infectious aerosols: implications for infection control

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See Online for appendix

The global pandemic of COVID-19 has been associated with infections and deaths among health-care workers. This Viewpoint of infectious aerosols is intended to inform appropriate infection control measures to protect health-care workers. Studies of cough aerosols and of exhaled breath from patients with various respiratory infections have shown striking similarities in aerosol size distributions, with a predominance of pathogens in small particles (<5 µm). These are immediately respirable, suggesting the need for personal respiratory protection (respirators) for individuals in close proximity to patients with potentially virulent pathogens. There is no evidence that some pathogens are carried only in large droplets. Surgical masks might offer some respiratory protection from inhalation of infectious aerosols, but not as much as respirators. However, surgical masks worn by patients reduce exposures to infectious aerosols to health-care workers and other individuals. The variability of infectious aerosol production, with some so-called super-emitters producing much higher amounts of infectious aerosol than most, might help to explain the epidemiology of super-spreading. Airborne infection control measures are indicated for potentially lethal respiratory pathogens such as severe acute respiratory syndrome coronavirus 2.

Introduction

The global pandemic of COVID-19, caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) has been associated with infections and deaths among health-care workers.¹ There have been conflicting recommendations from health authorities on the use of masks or respirators to protect health-care workers.^{2–4} When I first reviewed personal respiratory protection against tuberculosis for health-care workers more than 20 years ago,⁵ there was very little information on infectious aerosols. Since then, colleagues in various disciplines have provided a wealth of data. The purpose of this Viewpoint is to review the scientific literature on the aerosols generated by individuals with respiratory infections, and to discuss how these data inform the optimal use of masks, respirators, and other infection-control measures to protect health-care workers from those aerosols. This is not a review of the literature on the use of surgical masks or respirators, as several have been done already.^{6–11}

Traditional view of infectious aerosols

Current infection control policies are based on the premise that most respiratory infections are transmitted by large respiratory droplets—ie, larger than 5 µm—produced by coughing and sneezing, then deposited onto exposed fomite or mucosal surfaces.¹² Proximity has often been considered a proxy for respiratory droplets,^{13,14} reflected by statements such as “Proximity to the index case was associated with transmission which is consistent with droplet spread.”¹⁵ Airborne transmission has often been attributed to infectious droplet nuclei produced by the desiccation of suspended droplets, and defined as 5 µm or smaller in size. This has been thought to occur only for tuberculosis and a few other pathogens. Thus, surgical masks have been recommended for use against most respiratory infections.

Particles and plumes

Infectious aerosols are suspensions of pathogens in particles in the air, subject to both physical and biological laws. Particle size is the most important determinant of aerosol behaviour. Particles that are 5 µm or smaller in size can remain airborne indefinitely under most indoor conditions¹⁶ unless there is removal due to air currents or dilution ventilation. This same size range of particles (ie, <5 µm) deposits in the lower respiratory tract in humans^{12,17} as well as in guinea pigs, mice, and monkeys.¹⁸ Particles sized 6–12 µm deposit in the upper airways of the head and neck.¹⁸

Sophisticated imaging studies have shown that plumes of aerosols are generated by sneezing or coughing (appendix p 1).^{19,20} The aerosol plume contains the highest concentration of particles, which then dissipate in the air over time and distance. That distance is now much farther than previously appreciated, travelling up to 7–8 m.¹⁹ A re-analysis²¹ of the size of particles emitted by an average person that would fall to the ground within 2 m is 60–100 µm, and these can be carried more than 6 m away by sneezing. Obviously, health-care workers doing procedures close to a patient's mouth, such as intubations, bronchoscopies, or dental work can easily be exposed to such aerosol plumes. There is a wide range of particle sizes within the plumes.²² However, the most important questions are whether pathogens are in those plumes and whether their size is consistent with transmission. Studies of cough aerosols and exhaled breath offer answers to those questions.

Cough aerosol studies

Pathogens have been isolated in the aerosols generated by coughing from patients with various respiratory infections. Studies of those that included methods to measure particle sizes have consistently found pathogens in small particles (ie, <5 µm; table 1). Other studies

Key messages

- Infectious aerosols are particles with potentially pathogenic viruses, bacteria, and fungi suspended in the air, which are subject to the same physical laws as other airborne particulate matter. The biology of the pathogens predicts their airborne survival, infectivity, virulence, and other characteristics.
- Particle size is the most important determinant of aerosol behaviour.
- Small aerosol particles smaller than 5 µm in aerodynamic size are most likely to remain airborne for indefinite periods (unless there is removal due to air currents or dilution ventilation), and to be deposited in the lower respiratory tract.
- Infection control guidelines have stated that most respiratory infections are transmitted by respiratory droplets—ie, particles larger than 5–10 µm in size. Airborne transmission has been attributed to only a few pathogens, notably *Mycobacterium tuberculosis*, via infectious droplet nuclei that are particles sized 5 µm or smaller. The use of airborne infection isolation rooms and respirator masks has been recommended only to protect against airborne transmission.
- These recommendations have been based on old data and inferences. Over the past two decades, investigators have collected and directly measured the particle sizes of infectious aerosols emitted from individuals with respiratory infections from aerosols generated by cough and from exhaled breath.
- The studies reviewed in this paper consistently show that humans produce infectious aerosols in a wide range of particle sizes, but pathogens predominate in small particles (<5 µm that are immediately respirable by exposed individuals.
- Data are accumulating that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, is transmitted by both small and large particle aerosols.
- These data suggest that health-care workers should be protected from these potentially infectious aerosols when working in close proximity to patients.
- Some surgical masks might offer respiratory protection compared with not wearing a mask. Filtering facepiece respirators offer more respiratory protection than surgical masks, and powered air purifying respirator (PAPRs) hoods offer the best protection for most health-care settings.
- Face shields can help decrease exposures to and contamination from large particle aerosols, but they do not offer inhalation protection against small particle aerosols.
- PAPRs have built-in eye protection. Surgical masks and other respirators require a face shield or goggles to protect the eyes to prevent infection.
- Masking of patients can help to partly reduce infectious aerosol exposures to health-care workers, but are not a substitute for physical distancing and other infection control measures.
- Aerosolisation of respiratory pathogens is highly variable, at least partly due to the log-normal distribution of infectious aerosols, consistent with so-called super-spreading.
- Airborne infection isolation rooms and other infection control measures against airborne infection are indicated for virulent respiratory pathogens such as SARS-CoV-2.

without particle size data focused on other outcomes,^{16,33,34} or used methods that could not provide sizing data.^{35–40}

Tuberculosis

When culturable cough aerosols produced by patients with tuberculosis were directly measured, most (96%) of the culturable *Mycobacterium tuberculosis* were in particles smaller than 4·7 µm (figure 1).²⁴ There were few *M tuberculosis* in large particles (ie, >7·0 µm) and on settle plates (11% with any colony-forming units [CFU]).²⁴ Culturable cough aerosols from index cases of tuberculosis were found to be the best predictor of new infections of tuberculosis in their household contacts.³⁴ A consistent finding in tuberculosis studies is the variability of infectious aerosol production from patients with pulmonary tuberculosis.³³ These data suggest that a few patients with tuberculosis are infectious via cough aerosols, and some are very infectious,⁴¹ coherent with the epidemiological observation of super-spreading.^{42,43}

M tuberculosis has also been detected in a 1·4 m³ chamber, using both molecular and culture-based methods.²⁵ Most (59%) of the particles were smaller than 3·3 µm. In the largest study²⁶ of cough aerosols in tuberculosis, almost half of the patients with drug-

resistant-tuberculosis generated cough aerosols, and the highest counts of viable bacilli were in the 2·1–4·7 µm size range, consistent with previous studies.^{24,25}

Cystic fibrosis

Pseudomonas aeruginosa has been collected from cough aerosols in patients with cystic fibrosis.²⁷ These patients generated a particle size distribution that was only slightly larger than that noted in patients with tuberculosis (figure 1). There were relatively few large particles containing bacteria on the settle plates (median 6 CFU) or in a wash of the connecting tubing (1120 CFU, 95% CI 200–6060).²⁷ In a follow-up study, the investigators found that viable *P aeruginosa* from cough aerosols could travel 4 m and remain culturable for up to 45 min.²⁸

Influenza and other viruses

To study the effect of distance, cough aerosols were collected at distances of 1 ft, 3 ft, and 6 ft from 61 patients with influenza (influenza A or influenza B).³¹ Particles smaller than 4·7 µm were collected at all three sampling sites. At 6 ft (1·83 m), hardly any large particles (ie, ≥4·7 µm) were detected. The magnitude of the influenza aerosol output was log-normally distributed, again coherent with

	Pathogen, n/N (%) patients	Containment method and sampling time	Aerosol sampling method	Small particle size range (μm ; % of total aerosol)	Median CFU (range)	Comment
Denver, CO, USA (Fennelly et al, 2004) ²³	<i>Mycobacterium tuberculosis</i> , 4/16 (25%)	Plexiglass box, 2 x 5 min	Two Andersen cascade impactors	Most <4.7	NR (3–633)	Development study: all MDR-TB; no HIV
Kampala, Uganda (Fennelly et al, 2012) ²⁴	<i>M tuberculosis</i> , 28/101 (28%)	Stainless steel cylinder: 30 L, 2 x 5 min	Two Andersen cascade impactors	<4.7 (96%)	16 (1–710)	Feasibility study: 8 (8%) MDR-TB; 49/84 (58%) HIV-positive
Cape Town, South Africa (Patterson et al, 2018) ²⁵	<i>M tuberculosis</i> , 15/35 (43%) by culture; 25/27 (93% by PCR)	Custom chamber 1400 L	Andersen cascade impactor and polycarbonate filter	<4.7 (59%)	2.5 (1–14)	..
Cape Town, South Africa (Theron et al, 2020) ²⁶	<i>M tuberculosis</i> , 142/452 (31%)	10 L polypropylene chamber; 5 min	One Andersen cascade impactor	<4.7 (60%)	2–4 (1–310)	..
Brisbane, QLD, Australia (Wainwright et al, 2009) ²⁷	<i>Pseudomonas aeruginosa</i> , 25/28 (89%)	Stainless steel cylinder: 30 L, 2 x 5 min	Andersen cascade impactor	<4.7 (72%)	NR (0–13 485)	..
Brisbane, QLD, Australia (Knibbs et al, 2014) ²⁸	<i>P aeruginosa</i> , 17/18 (94%) at 4 m	Stainless steel distance rig	One Andersen cascade impactor	<4.7 (58%) at 4 m	Mean 14.3 (95% CI 10.9–18.7) for small fraction	..
Morgantown, WV, USA (Lindsley et al, 2010) ²⁹	Influenza A, 32/38 (84%)	Mechanical spirometer (10 L)	NIOSH sampler	<4 (65%)
Morgantown, WV, USA (Lindsley et al, 2012) ³⁰	Influenza, N=9	Mechanical spirometer with HEPA filtered air	Laser particle spectrometer	Average count median diameter 0.63 (SD 0.05)	Average particles per cough 75 400 (SD 97 300)	No viable sampling
Winston-Salem, NC, USA (Bischoff et al, 2013) ³¹	Influenza A and B, 26/61 (43%)	Inpatient rooms and emergency department	Andersen cascade impactor	<4.7 (more than 75% at 1 ft); almost 100% at 6 ft	..	5 (19%) emitted 32 times more than others
Sydney, NSW, Australia (Galton et al, 2013) ³²	23/28 (80%) mixed viruses	Custom unit	Andersen cascade impactor	<4.7	Not measured	HRV, RSV, influenza A, and parainfluenza

CFU=colony-forming units. NR=not recorded. MDR-TB=multidrug-resistant tuberculosis. HEPA=high-efficiency particulate air. NIOSH=US National Institute of Occupational Safety and Health. HEPA=high efficiency particulate air. HRV=human rhinovirus. RSV=respiratory syncytial virus.

Table 1: Summary of studies of infectious aerosols collected from coughs with particle size data

super-spreading (figure 2). In a separate study using a different bioaerosol sampler,²⁹ viral RNA was detected in cough aerosols in 38 (81%) of 47 patients with influenza. 35% of the viral RNA was in particles larger than 4 μm , and 65% was in particles sized 4 μm or smaller (figure 2).

In children and adults with upper respiratory infections, PCR assays have detected various viruses.³² During coughing, 82% of participants produced small particles (<4.7 μm) containing virus, versus 57% who produced larger particles.

Exhaled breath aerosol studies

In studies of exhaled breath aerosols with particle size measurements, pathogens were consistently found in small particles (<5 μm ; table 2). Other studies assayed exhaled breath condensates or filters,^{38,48} or used other methods that cannot provide particle size distributions such as direct impaction onto a Petri dish⁴⁰ or into liquid media.³⁶ However, most particles in exhaled breath are smaller than 4 μm , with a median between 0.7 and 1.0 μm .⁴⁹

Several virus types have been detected in exhaled breath condensates using PCR, such as influenza,^{50–52} human rhinovirus,^{50,52} respiratory syncytial virus,^{50,52} cytomegalovirus,^{53,54} Epstein-Barr virus,⁵³ human papillomavirus,⁵⁵ and *Torque teno* virus.⁵⁶ Bacteria have also been detected by PCR in exhaled breath condensates, especially

Haemophilus influenzae, and also *P aeruginosa*, *Escherichia coli*, *Stenotrophomonas maltophilia*, methicillin-sensitive *Staphylococcus aureus*, and methicillin-resistant *S aureus*.⁵⁷ Viral and bacterial pathogens were isolated from exhaled breath condensates in the same patients, including influenza A, respiratory syncytial virus, *S aureus*, *H influenzae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*.⁵⁸ *Cladosporium*, *Alternaria*, and *Penicillium* species have been detected in the exhaled breath condensates of patients with asthma.⁵⁹ In a study of exposures to patients with *Pneumocystis jirovecii* colonies, the exhaled breath was positive by PCR in two (50%) of four critically ill patients and in two (22%) of nine exposed health-care workers with colonies.⁶⁰

Once direct measurement of particles containing viruses in exhaled breath was technically feasible, most particles (87%) with influenza viral RNA were found to be smaller than 1 μm .⁴⁴ Exhaled influenza viral generation rates were estimated to be from fewer than 3.2 to 20 virus particles per min. Further developments enabled detection of so-called fine versus coarse particles (ie, $\leq 5 \mu\text{m}$ vs $> 5 \mu\text{m}$).⁴⁵ Influenza viral RNA was detected in the exhaled breath of 34 (92%) of 37 adults.⁴⁵ The fine particles contained 8.8-times (95% CI 4.1–19.0) more viral copies than did the coarse ones. Respiratory viruses have been found in both coughs (82% of participants) and exhaled breath (81% of participants).³² Similarly, influenza virus was

found in similar amounts in coughs (53% of participants) and breath (42% of participants).³⁶ Human rhinovirus was collected more frequently in exhaled breath than in cough aerosols using a filter method.³⁸ Findings from two studies with comparable particle size data showed that influenza virus in exhaled breath is contained in smaller particles than influenza virus in cough (figure 3).^{29,44}

Three studies did not detect *M tuberculosis* in exhaled breath condensates.^{61–63} In a study of 16 patients with tuberculosis requiring mechanical ventilation, PCR assays of filters in the expired air were positive in 12 (75%).⁶⁴ However, two studies^{65,66} using face-mask sampling from patients with tuberculosis have detected *M tuberculosis* in exhaled breath. In the first,⁶⁵ a N95 respirator with a sampling membrane was worn for 5 min. Patients with tuberculosis were instructed to cough, talk, and breathe normally. *M tuberculosis*-specific RNA, suggesting viability, was detected in all 15 participants. In a more detailed 24-h study of 78 patients with tuberculosis, *M tuberculosis* was detected more frequently in face-mask samples (86%) than in sputum (21%).⁶⁶

The most probable mechanism to explain the presence of pathogens in exhaled breath is that the opening of collapsed bronchioles generates aerosols, but there are other theories such as vocal cord closure and vibration.^{49,67} These mechanisms might explain transmission from asymptomatic individuals.⁶⁸ However, there are no data supporting transmission from infectious aerosols in exhaled breath, as most of these studies were focused on diagnostics.

Room air and personal sampling studies

Infectious aerosols have also been collected from room air, suggesting the potential for exposures to health-care workers. Varicella-zoster virus, known to be one of the most contagious viruses, was detected by PCR in the room air of 64 (82%) of 78 patients with varicella and in the room air of nine (70%) of 13 patients with herpes zoster, suggesting airborne transmission.⁶⁹ Measles is another very infectious virus. Aerosol sampling was done in the room of a young woman with measles at the head of her bed, and at 0.61 m and 0.91 m away from her head (0.91 m=foot of the bed). PCR assays were positive for measles RNA in the particles smaller than 4.7 µm collected at all locations; however, particles larger than 4.7 µm were only positive for virus at the head of the bed. None of the samples were positive by tissue culture.⁷⁰

M tuberculosis has been detected in hospital air by PCR from settle plates⁷¹ and filters.^{64,72,73} In an outpatient clinic in South Africa, *M tuberculosis* was detected by PCR more frequently from personal air samplers worn by health-care workers (in nine [36%] of 25) than by stationary samplers (in two [8.3%] of 24).⁷⁴ Influenza virus has been detected using PCR in personal samplers worn by health-care workers and in ambient air samples from an emergency department: 50% of the airborne virus particles were 4 µm or smaller.⁷⁵ Influenza A was

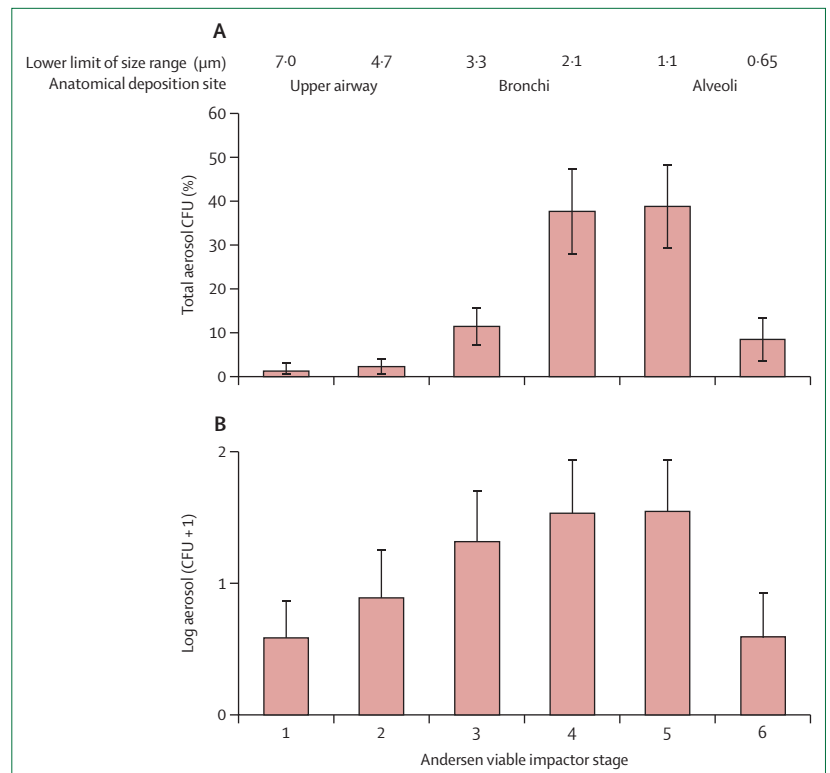


Figure 1: Particle size distributions of cough aerosols from (A) patients with tuberculosis²⁴ and (B) patients with cystic fibrosis infected with *Pseudomonas aeruginosa*²⁷ (A) Reproduced from Fennelly et al.,²⁴ by permission of the American Thoracic Society. (B) Reproduced from Wainwright et al.²⁷ Error bars represent 95% CIs. CFU=colony forming units.

also detected by PCR in 19% of personal samplers and 17% of stationary samplers in an urgent care clinic.⁷⁶ In the same clinic, respiratory syncytial virus RNA was detected in 38% of the personal samplers and 32% of the stationary samplers; 42% of the particles containing influenza and 9% of the particles containing respiratory syncytial virus were smaller than 4.1 µm. In a smaller study,⁷⁷ influenza A viral RNA was detected in five (50%) of ten sample collections. Most (four of five) were from particles larger than 4 µm, and one was from particles sized 1–4 µm. In another study,⁷⁸ six (37.5%) of 16 air samples near patients with influenza were positive by PCR in all particle size ranges tested—ie, smaller than 1 µm, 1–4 µm, and larger than 4 µm.

In a large study⁷⁹ in a busy inner-city emergency department, influenza was detected in 53 (42%) of 125 personal samplers worn by 30 health-care workers, in 28 (43%) of 96 room air samples, in 23 (76%) of 30 surface samples, and on three (25%) of 12 respirators worn while exposed to a patient with confirmed influenza. In a separate study at a large hospital in China,⁸⁰ influenza was detected in 15 (79%) of 19 air samples in all particle size ranges (<1 µm, 1–4 µm, and >4 µm). Total influenza virus ranged from 3715 to 119 371 copies per m³. Similar to the study in which influenza virus and respiratory syncytial virus were both detected by PCR,⁷⁶ viable respiratory syncytial virus

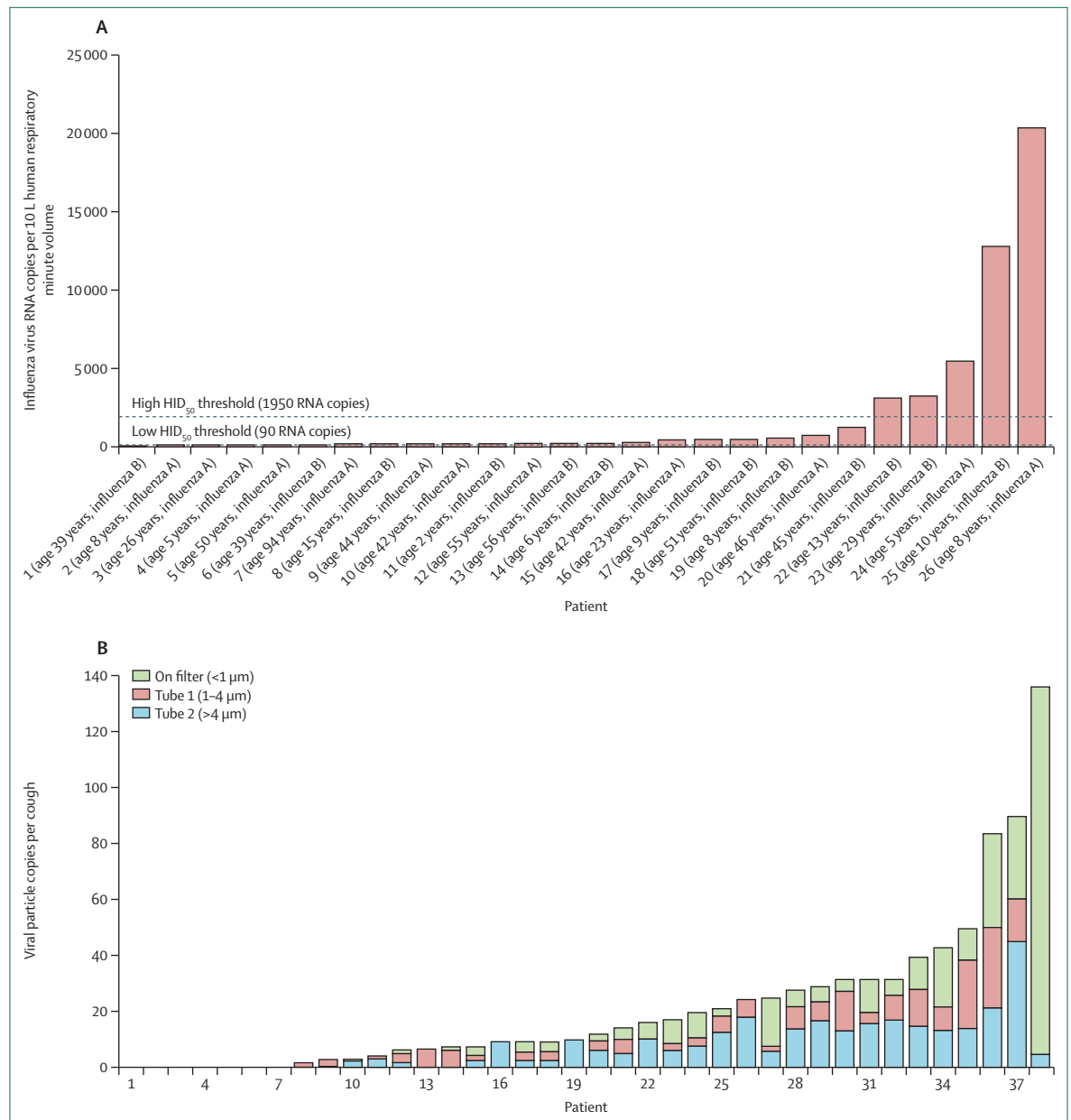


Figure 2: Log-normal distributions of the magnitudes of cough aerosols from patients with influenza using (A) an Andersen cascade impactor³¹ and (B) a NIOSH two-stage aerosol sampler,²⁹ coherent with super-spreading

(A) Reproduced from Bischoff et al.³¹ by permission of Oxford University Press. (B) Reproduced from Lindsley et al.²⁹ NIOSH=US National Institute of Occupational Safety and Health. HID_{50} =50% human infectious dose.

was collected from room air near 22 (92%) of 24 infected infants and young children on a general ward and near all ten patients in the intensive care unit; most of the virus was contained in particles smaller than 4.7 μm .⁸¹ Human rhinovirus RNA has been isolated from the air of office buildings, but no specific size range was specified.⁸²

Adenovirus was detected by PCR from eight (29%) of 28 air samples in a paediatric ward in Singapore,⁸³ and in 18%⁸⁴ and 36%⁸⁵ of air samples from two paediatric emergency departments in Taiwan. Adenovirus DNA

was also detected in 21 (77%) of air samples and in 78 (72%) of surface samples in five toilets in the nephrology ward of an Italian hospital.⁸⁶ *M pneumoniae* DNA was also detected in 46% of air samples from a paediatric outpatient department in Taiwan.⁸⁴

P jirovecii DNA has been detected in the room air in multiple studies. The DNA was first isolated from 17 (57%) of 30 rooms of patients with *Pneumocystis pneumonia*, but was also detected in six (29%) of 21 other hospital rooms.⁸⁷ A subsequent study found DNA from

	Pathogen, n/N (%) patients	Containment method and sampling time	Aerosol sampling method	Particle size range (μm ; % of total aerosol)	Median CFU or viral copies (range)	Comment
Sydney, NSW, Australia (Gralton et al, 2013) ³²	Mixed viruses 31/52 (60%)	Custom unit 10 min	Andersen cascade impactor	<4.7; 25/31 (81%)	Not measured	HRV, RSV, influenza A, and parainfluenza
Hong Kong, China (Fabian et al, 2008) ⁴⁴	Influenza A, 3/5 (60%); Influenza B, 1/7 (14%)	Oronasal face mask 20 min	Teflon filters and optical particle counter	<1; >87%	(<3.2 to 20 viral particles)	
Lowell, MA, USA (Milton et al, 2013) ⁴⁵	34/37 (92%); 20 influenza A; 17 influenza B	Head inside cone-shaped collector 30 min	Gesundheit-II: slit impactor for coarse fraction; water condenser plus slit impactor for fine fraction	≤ 5 (fine fraction): 34/37 (92%) >5 (coarse fraction): 16/37 (43%)	Maximum viral copies: Fine: 1.3×10^5 Coarse: 2.9×10^4	Fine particles contained 8.8 times more virus than coarse particles
College Park, MD, USA (Yan et al, 2018) ⁴⁶	52/134 (39%) culture positive in fine aerosols; coarse aerosols not cultured	Head inside cone-shaped collector 30 min	Gesundheit-II: slit impactor for coarse fraction; water condenser plus slit impactor for fine fraction	≤ 5 (fine fraction): 166/218 (76%) PCR-positive >5 (coarse fraction): 88/218 (40%) PCR-positive	≤ 5 (fine fraction): 3.8×10^4 geometric mean RNA copies >5 (coarse fraction): 1.2×10^4 geometric mean RNA copies	
Hong Kong (Leung et al, 2020) ⁴⁷	Mixed viruses 49/132 (37%)	Head inside cone-shaped collector 30 min	Gesundheit-II: slit impactor for coarse fraction; water condenser plus slit impactor for fine fraction	≤ 5 (fine fraction): 4/10 (40%) coronavirus, 19/34 (56%) rhinovirus >5 (coarse fraction): 3/10 (30%) coronavirus, 6/23 (26%) influenza, 9/32 (28%) rhinovirus	Median \log_{10} copies; ≤ 5 (fine fraction): coronavirus 0.3, influenza 0.3, rhinovirus 1.8 >5 (coarse fraction): coronavirus 0.3, influenza 0.3, rhinovirus 0.3	

CFU=colony-forming units. HRV=human rhinovirus. RSV=respiratory syncytial virus.

Table 2: Summary of studies of infectious aerosols collected from exhaled breath with particle size data

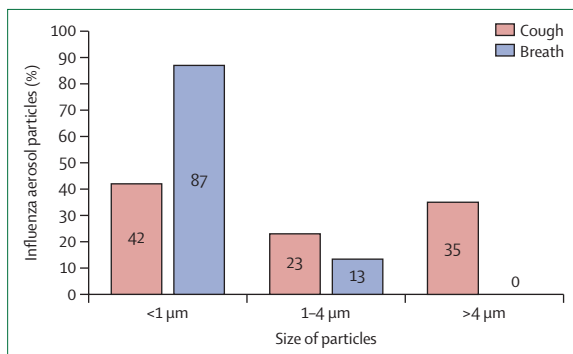


Figure 3: Proportions of influenza aerosol particles sizes in cough⁴⁹ and exhaled breath⁴⁴ sample collections

Data extracted from primary references^{29,44} for comparison. Influenza virus in exhaled breath is emitted in smaller particles than influenza virus in cough aerosols.

air samples taken at 1 m from the head of 15 (79.8%) of 19 patients, and in four (33.3%) of 12 of samples taken 8 m away.⁸⁸ Nosocomial transmission of *Pneumocystis* has been supported by the finding of air samples positive for the DNA in four (29%) of 14 air samples and in two (22%) of nine health-care workers exposed during bronchoscopy.⁸⁹ Similarly, air samples were positive for *P. jirovecii* DNA in seven (47%) of 15 critical-care unit rooms, and nine (8.8%) of 102 health-care workers had colonies.⁶⁰ This study was then extended to the detection of DNA from rooms of patients with *Pneumocystis* colonies (but without pneumonia).⁹⁰⁻⁹²

Few aerosol data were available from the SARS-CoV pandemic in 2003. In Toronto, air sampling with a slit

sampler yielded two of ten samples that were positive for SARS-CoV by PCR but negative on viral culture. Both PCR and cultures were negative on 28 filter samples.⁹³ Retrospective analyses strongly suggested that airborne transmission probably occurred in Hong Kong.⁹⁴⁻⁹⁶ The Middle East Respiratory Syndrome (MERS) coronavirus was isolated from seven room air samples from dedicated MERS units in two South Korean hospitals. All seven were positive by PCR and four of seven were positive on viral culture.⁹⁷

Infectious aerosols of SARS CoV-2

Since the outbreak of COVID-19, there has been a question over airborne transmission of SARS-CoV-2. Similar to that seen with SARS-CoV, there was only a mild reduction in viability over a 3-h period in an experimental aerosol generated in a laboratory, consistent with a potential for airborne spread.⁹⁸ To date, there are no published reports of cough aerosol or exhaled breath sampling from patients with COVID-19, but SARS-CoV-2 has been detected in the air of hospitals in China⁹⁹ and the USA.¹⁰⁰ The virus was detected in both surface and air samples in another hospital in Wuhan, China, with positive PCR tests on 14 (35%) of 40 air samples from the intensive care unit and two (12.5%) of 16 air samples from the general ward.¹⁰¹ It appears that SARS-CoV-2 has the potential to be spread by all modes of transmission: direct contact (ie, person-to-person) and indirect contact (eg, via contaminated objects and aerosol).¹⁰⁰ It is not yet clear which mode occurs most frequently. Air sampling for SARS-CoV-2 was negative in three studies,¹⁰²⁻¹⁰⁴ but two included small numbers of patients in rooms with high rates of dilution ventilation,^{102,103} and one study included a small number of air samples

using inefficient impinger devices.¹⁰⁴ The outbreaks of COVID-19 in nursing homes,¹⁰⁵ choirs,¹⁰⁶ and correctional facilities¹⁰⁷ are reminiscent of tuberculosis outbreaks and suggestive of both traditional airborne transmission and so-called super-spreading epidemiology.^{42,43,108} Experiments using the golden hamster model have shown 100% efficient aerosol transmission among animals caged separately as well as by direct contact.¹⁰⁹

A new paradigm of infectious aerosols

These data show that infectious aerosols from humans exist in a wide range of particle sizes that are strikingly consistent across studies, methods, and pathogens. There is no evidence to support the concept that most respiratory infections are associated with primarily large droplet transmission. In fact, small particle aerosols are the rule, rather than the exception, contrary to current guidelines.¹² These small particles occur without a need for a prolonged time to allow for desiccation, and they are of a size that is immediately respirable. These data also add evidence that could update the current dichotomous infection control guidelines, as was proposed 9 years ago.¹¹⁰

The logic that transmission within close proximity defines respiratory droplet spread is fallacious, as small particle aerosols are in the highest concentration close to patients and dissipate with distance. There is epidemiological evidence of an increased risk of tuberculosis transmission within close proximity.^{111–113} Individuals sharing a bed with a source patient with tuberculosis are more likely to be infected than people sharing the same room; in turn, people sharing the same room as the source case have a higher risk than individuals in a different room.^{114–116} An outbreak associated with an aerosol-generating device used to clean a tuberculous abscess revealed a gradient of tuberculin reactivity, with higher rates among patients in rooms closest to the source case's room.¹¹⁷ Physical distancing decreases transmission potential from pathogens in small particles as well as in large particles, although small particles have a greater capacity to travel further.

The variability of transmission among respiratory pathogens appears to be less dependent on the physical particle size emitted by the diseased person, as current guidelines suggest, but more by biological factors such as the size of the emitted inoculum, the ability of the pathogen to survive desiccation and other stresses of aerosolisation and airborne transport, and environmental factors such as air movement, temperature and humidity, and host defences.

Implications of infectious aerosol data for infection control practice

Because of the large number of patients in health-care settings, health-care workers are likely to have frequent exposures to highly infectious cases. They might also have more cumulative inhaled doses and infections, although it is unknown if this is involved in the pathogenesis

of COVID-19. Infection control measures might not only reduce the probability of infection, but might also reduce the size of the inhaled inoculum, which has been associated with disease severity in influenza^{118,119} and other diseases.¹²⁰ This might be especially important for small particle aerosols, as 1 µm aerosols of *Bacillus anthracis* caused higher mortality in animals than 12 µm aerosols in a seminal study.¹²¹

Masks versus respirators

Modelling studies^{122–124} and simulated workplace protection studies^{125–127} in the USA have shown benefits of various types of respirators and little to no protection from surgical masks. A study in the UK found that surgical masks could reduce inert aerosol exposure by two times, but filtering facepiece respirators reduced the exposure by a factor of 100 or higher.¹²⁸ In a study of influenza aerosols, surgical masks reduced exposure by an average of six times, but there was a wide range of reduction from 1.1 to 55 times, depending on the design of the mask.¹²⁹ Two randomised trials^{130,131} did not show any benefit of N95 respirators over surgical masks in reducing respiratory illnesses, and two showed that the respirators were protective.^{132,133} However, none of the trials used quantitative fit testing, and two had surprisingly low failure rates (1.1–2.6%)^{132,133} compared with 60% found in a panel study for the same N95 respirators.¹³⁴ The low failure rates suggest a problem with fit testing.

Filtering facepiece respirators are only as effective as their fit, as the weak point of these respirators is the face-mask leak.^{135,136} Unfortunately, there has been little operational research on the process of fit-testing respirators for health-care workers. There is wide variability among filtering facepiece respirators, and “it may be of more benefit...to wear a respirator model with good-fitting characteristics without fit testing than to wear a respirator model with poor-fitting characteristics after passing a fit-test.”¹³⁴ Similarly, there are some surgical masks that offer good protection, but as they are not certified or regulated as devices for respiratory protection, it is difficult to know which is the best to use. There is a pressing need for research in this area. Face shields can decrease inhalation exposures to wearers and surface contamination of filtering facepiece respirators by aerosol particles of a median diameter of 8.5 µm by 96% and 97%, respectively, but they only reduce inhalation exposures to smaller particle aerosols of 3.4 µm by 23%.¹³⁷

Masks to prevent transmission from the wearer

Although surgical masks offer little protection from inhaled agents, they have a role in protecting health-care workers when worn by patients. Placing surgical masks on patients with multidrug-resistant tuberculosis decreased transmission to guinea pigs by 56%,¹³⁸ and masking of patients with cystic fibrosis reduced *P aeruginosa* air contamination by 8%.¹³⁹ Surgical masks reduced the quantity of influenza viral RNA by 2.8 times

in small particles and by 25 times in large ones.⁴⁵ More recently, surgical masks effectively reduced large droplets (>5 µm) of seasonal coronaviruses from three of ten patients to 0 of 11 ($p=0.09$) and small aerosols (<5 µm) from four of ten patients to 0 of 11 ($p=0.04$).⁴⁷ Similarly, surgical masks reduced droplets of influenza from six of 23 to one of 27 ($p=0.04$). However, the reduction in influenza small aerosols (<5 µm) was not significant. There is mounting evidence suggesting that the wearing of masks can reduce transmission of SARS-CoV-2 in community and health-care settings.¹⁴⁰

A major limitation to much of the data on infectious aerosols of viruses is the reliance on PCR findings; few studies have evaluated viability using cell cultures or other methods. Viability itself can be difficult to assess. Aerosolisation from the respiratory tract produces multiple stresses on microbes that can decrease their viability, usually defined by the ability to be cultured. Indoors, desiccation predominates, but temperature, radiation, oxygen, ozone and its reaction products, and other exposures can also damage viral lipids, proteins, and nucleic acids.¹⁴¹ Aerosol sampling itself can produce additional stresses, including mechanical trauma, additional desiccation, and injury in post-sampling processes and extraction.¹⁴² PCR assays are usually easier to do logistically than using cell cultures for viral sampling. For example, our group was able to directly sample influenza virus onto monolayers of cell cultures in the laboratory, but this proved impractical for transport to and from clinical sites because of the sensitivity of the cells to spillage and pH stresses.¹⁴³ These multiple factors, as well as inherent physical inefficiencies of air samplers, suggest that most infectious aerosol data are probably underestimates of the exposures to health-care workers.

Obviously, infectious individuals breathe continuously 24 h per day, but there are no data on possible circadian rhythms or variability in output. By contrast, coughing can be very paroxysmal and sporadic. Although 24-h cough frequency can be measured, it has not been linked to aerosol production. There is only one study of the association between cough aerosol production by tuberculosis index cases and new infections in exposed contacts;³⁴ however, no studies have documented transmission of any respiratory infections exclusively via large respiratory droplets or fomites. Although the data reviewed here indicate that there are small proportions of patients who are highly infectious and probably super-spreaders,^{42,43} until a diagnostic test or other method is available to identify them, we must consider all patients with respiratory pathogens as potentially infectious.

Discussion

This Viewpoint suggests that infection control guidelines should be re-evaluated to account for the predominance of small particles within infectious aerosols. Protective devices available to health-care workers have a range of protection, increasing from surgical masks to filtering facepiece

Search strategy and selection criteria

References in the English language for this Viewpoint were identified through searches of PubMed for articles published from 1966 to June, 2020, with the terms “particles”, “health care workers”, “coronavirus”, “COVID-19”, “SARS Co-V-2”, “cough aerosols”, “exhaled breath”, “TB”, “air”, “influenza”, “respirators”, “personal respiratory protection. Some papers known to the author were located using Google Scholar if not found in PubMed.

respirators to powered air-purifying respirators. Although these are indicated for close encounters, their limitations highlight the need for improved administrative controls, such as more rapid diagnosis and isolation, and the development of vaccines and treatments. These data support calls for the recognition of aerosol (ie, traditional airborne) transmission of SARS-CoV-2.¹⁴⁴ This could facilitate the use of enhanced dilution and directional ventilation and other environmental control options—eg, air disinfection with ultraviolet germicidal irradiation,¹⁴⁵ which might be especially helpful in congregate settings such as nursing homes. Implementation of improved infection control measures could prevent future morbidity and mortality among health-care workers.

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Declaration of interests

I declare no competing interests.

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