



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Characterization of Experimental and Clinical Bioaerosol Generation During Potential Aerosol-Generating Procedures



Nathan Doggett, MSc; Chung-Wai Chow, MD, PhD; and Samira Mubareka, MD



BACKGROUND: During medical procedures with the potential to produce aerosols such as bronchoscopy, intubation, or CPR, health-care workers (HCWs) may be exposed to infectious bioaerosols. This scenario is of particular concern when high consequence pathogens such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are circulating. Thousands of HCWs have been infected with SARS-CoV-2. However, the determinants of aerosol generation during medical procedures and their relative risk to HCWs remain poorly characterized.

RESEARCH QUESTION: The goal of this study was to characterize aerosols produced during airway intubation by using an uninfected translational animal model and in human subjects undergoing elective aerosol-generating procedures. The study also determined the particle size distribution of generated particles.

STUDY DESIGN AND METHODS: Aerosol generation was measured during highly controlled experimental (pig) intubations (N = 16) and elective bronchoscopies in uninfected patients (N = 49) using an optical particle counter. Recovery of normal respiratory flora was used as a surrogate for pathogen dispersion.

RESULTS: There was a small but significant ($P = .03$) decrease in 0.3 μm size particles during highly controlled pig intubations compared with baseline. The concentration of 1.0 μm and 5.0 μm aerosol particles did not significantly change, although oral bacteria were collected from the air. For elective patient bronchoscopies, there was a significant decrease in the generation of larger particles (1.0 μm and 5.0 μm) compared with baseline ($P < .01$); however, 18 of 39 (46%) patients showed increased aerosol production in 0.3 μm size particles, four of whom exhibited measurable increases.

INTERPRETATION: Although the total amount of aerosols produced during intubation and bronchoscopy did not increase significantly relative to preprocedural levels, a small number of participants exhibited a measurable increase in submicron particle emission, meriting further research to delineate determinants of fine particle production during aerosol-generating procedures.

CHEST 2020; 158(6):2467-2473

KEY WORDS: aerosol-generating procedures; bioaerosols; bronchoscopy; particle counts

FOR EDITORIAL COMMENT, SEE PAGE 2251

ABBREVIATIONS: AGP = aerosol-generating procedures; COVID-19 = coronavirus disease-19; HCW = health-care worker; OPC = optical particle counter; PPE = personal protective equipment; SARS = severe acute respiratory syndrome

AFFILIATIONS: From Biological Sciences (Mr Doggett and Dr Mubareka), Sunnybrook Research Institute, Toronto, ON, Canada; and the Department of Laboratory Medicine and Pathobiology (Mr Doggett and Dr Mubareka), University Health Network (Dr Chow),

Take-home Point

We characterized aerosols produced during aerosol-generating procedures and found a small number of participants showed an increase in submicron particle emission, meriting further research to delineate determinants of fine particle production during aerosol-generating procedures.

Medical procedures with the potential to produce aerosol particles include endotracheal intubation,^{1,2} extubation, and bronchoscopy.^{3,4} Bioaerosols (aerosol particles of biological origin) generated during these aerosol-generating procedures (AGPs) may represent a risk to exposed health-care workers (HCWs) when patients are infected or colonized with a respiratory pathogen. The importance of understanding the risks associated with AGPs was emphasized during the severe acute respiratory syndrome coronavirus 1 epidemic of 2003, when HCWs experienced a substantial burden of the total severe acute respiratory syndrome (SARS) cases despite adherence to enhanced droplet and airborne precautions.^{1,2,5,6} Furthermore,

retrospective analyses revealed evidence of potential airborne transmission of SARS.⁷⁻⁹ However, empiric data regarding bioaerosol production and quantification during AGPs are lacking, and associated risks remain poorly characterized. The current situation with coronavirus disease-19 (COVID-19) underscores the importance of understanding these risks, given the implications for patient management, risk mitigation, and HCW health, given their essential roles and the risk of transmission to other HCWs and patients.

Airway manipulation during bronchoscopy triggers the cough reflex in many patients, potentially producing significant aerosols which may contain pathogenic microorganisms. Small-scale studies have found that a significant number of aerosols were produced during bronchoscopy and identified an increase in aerosol-borne respiratory bacteria during the procedure compared with an empty room.^{10,11} The objective of the current study was to measure the quantity and size of aerosols produced in highly controlled experimental and clinical settings, including a pig animal model and elective patient bronchoscopies, respectively.

Materials and Methods

An AeroTrak optical particle counter (OPC Model 9303; TSI Incorporated) was used to quantify aerosol production based on particle number and size. This instrument operates on the basis of light scattering generated by individual particles as they pass through a light cell. This OPC adheres to the International Organization for Standardization 21501-4 calibration requirements for light-scattering airborne particle counters, indicating a volumetric flow rate of $\pm 5\%$, a counting efficiency of $50 \pm 20\%$ at the minimum detectable particle size, $100 \pm 10\%$ for particles 1.5 to 2 times larger than the

minimum detectable size, and a size resolution (the maximum difference in size measured by the OPC compared with selected size) of $\leq 5\%$.

This instrument was selected based on portability, ease of use, and minimal disruption to patient care. Particles were captured and counted in three size categories (0.3 μm , 1.0 μm , and 5.0 μm), representing particle size ranges with preferential deposition throughout the upper and lower respiratory tracts. Bioaerosols within the respirable aerosol size fraction can include fungi (0.5-30 μm), bacteria (0.3-10 μm), viruses (0.02-0.3 μm [often found in clusters or attached to larger particles]), and smaller cellular debris and biotoxins.¹²

Division of Respiriology, Department of Medicine, Institute of Medical Science (Dr Chow), and the Dalla Lana School of Public Health (Dr Chow), University of Toronto, Toronto, ON, Canada.

Mr Doggett is currently at Dalhousie University (Halifax, NS, Canada). Part of the article has been presented at the Canadian Critical Care Conference on October 3, 2017 in Whistler, BC, Canada and the conference on Transmission of respiratory viruses: from basic science to evidence based options for control, on June 20, 2017 in Hong Kong, China.

FUNDING/SUPPORT: The research presented in this article was funded in part by the C. David Naylor fellowship, the Ontario Graduate Scholarship program, and through operating grants from the Ontario Ministry of Labour [13-R-052].

CORRESPONDENCE TO: Samira Mubareka, MD, Sunnybrook Health Sciences Centre and Sunnybrook Research Institute, 2075 Bayview Ave, Ste B103, Toronto, ON, Canada, M4N 3M5; e-mail: samira.mubareka@sunnybrook.ca

Copyright © 2020 Published by Elsevier Inc under license from the American College of Chest Physicians.

DOI: <https://doi.org/10.1016/j.chest.2020.07.026>

Aerosol Production in an Animal Model

To pilot a protocol using an OPC for the enumeration of particles from a mammalian host and the recovery of normal respiratory flora from these particles, aerosol production was measured in a highly controlled experimental setting during pig intubations; these were conducted for unrelated imaging studies. This model was used to pilot both our sampling protocol and to establish a baseline sampling method under experimental, controlled conditions. The suite in which the pigs were intubated was a negative pressure room operating at 12 air exchanges per hour. Animals were administered atropine and ketamine and a small amount of isoflurane via an anesthetic mask prior to intubation. However, the isoflurane was turned off and removed immediately prior to intubation; no mask ventilation was administered. Aerosol generation measured during and immediately following intubation (10 s postintubation) was compared with a baseline concentration of aerosols immediately prior to intubation (10 s preintubation). In addition, bioaerosol content was assessed by using a high-volume (300 L/min) Coriolis

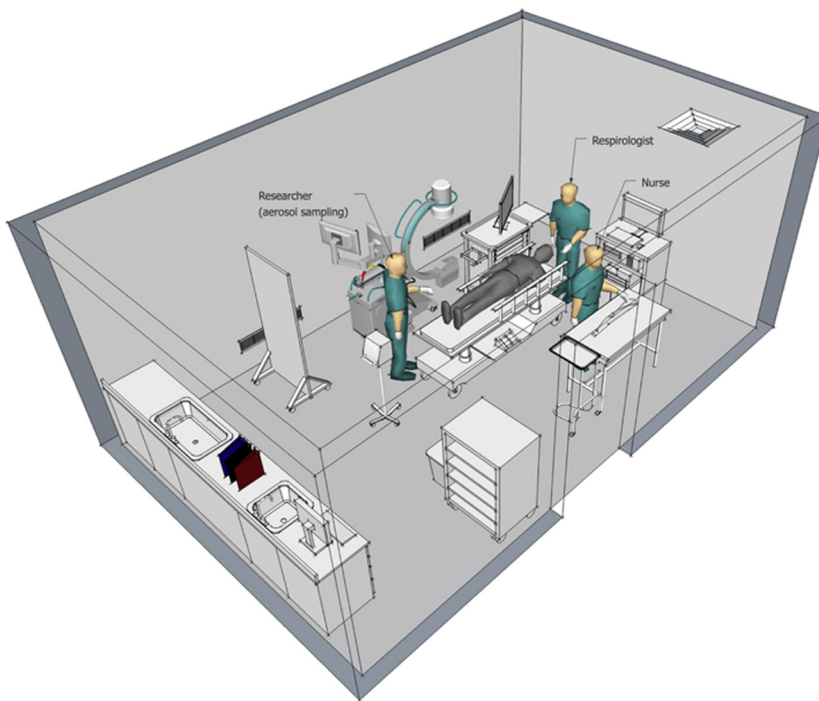


Figure 1 – Schematic representation of the layout and research and medical personnel in an endoscopy suite during elective bronchoscopy sampling.

air sampler that collects particles in a liquid medium (phosphate-buffered saline) and a low volume 1.0 μm polytetrafluoroethylene filter cassette sampler drawing air at 3.5 L/min. Both samplers were placed within the breathing zone of research personnel performing the intubation at the head of the bed and within 3 feet of personnel performing the intubation. Samples collected were plated on blood agar, and colony-forming units were identified by using matrix-assisted laser desorption ionization time-of-flight mass spectrometry.¹³

Aerosol Production During Elective Bronchoscopy

Aerosol generation was also measured during elective patient bronchoscopies. Inpatients and outpatients were identified through the scheduling roster and approached by the attending respirologist. Inclusion criteria were age > 18 years and capability of providing informed consent. In patients undergoing urgent bronchoscopy in the ED or critical care units were excluded.

Elective bronchoscopies were performed in endoscopy suites at two separate tertiary care centers (center 1, N = 25; center 2, N = 24). Both procedure rooms were negative pressure endoscopy suites with 12 air changes per hour. Neither of the rooms had an anteroom; however, all doors were closed prior to and during the procedure.

Particle generation during and immediately following bronchoscope removal (100 s postprocedure, or time to door opening if shorter than 100 s) was compared vs a preprocedure baseline immediately preceding the insertion of the bronchoscope (100 s preprocedure), with all medical personnel present and donned in personal protective equipment (PPE). This baseline was chosen over an empty room due to the observation that the presence of personnel alone generated aerosols despite wearing N95 masks. This may be

attributed to re-entrainment of settled particles and skin desquamation. Aerosols were sampled 0.75 m from the patient's head at the foot of the bed at a flow rate of 2.83 L/min (Fig 1). Timing of specific procedural events (including scope insertion, scope removal, coughing, suction, BAL, and biopsies) was recorded for later analysis of aerosol generation.

In addition, the presence of bacteria in the air was measured during a subset of bronchoscopies using a small portable personal air sampler (3.5 L/min) consisting of a 1.0 μm polytetrafluoroethylene filter cassette worn within the breathing zone (at the collar) of research personnel for potential exposure to oral flora from the patient as a surrogate for possibly infectious pathogens of airway origin; the collection of oral or respiratory flora was used as an indicator of potential HCW exposure during the procedure.

The study was approved by the University Health Network (17-5161) and Sunnybrook Research Institute Research Ethics Boards (257-2014); informed consent was obtained, and the study was conducted in accordance with the amended Declaration of Helsinki.

The primary outcome for this study was enumeration of aerosol generation during bronchoscopy compared with a baseline value immediately prior to the procedure. A Wilcoxon matched pairs signed-rank test was used to evaluate statistical difference for the primary outcome measure. The secondary outcome of this study was aerosol generation with respect to specific procedural activities, including bronchoscope insertion, scope removal, coughing, suctioning, BAL, and biopsy. A Friedman test was used to evaluate statistical significance for the secondary outcome. All statistical analyses were performed by using GraphPad Prism version 8.4.2.

Results

Aerosol Production During Pig Intubations

A total of 16 pig intubations were sampled in this study. There was no significant increase in aerosol production in any size category (Fig 2). There was a small but significant decrease in 0.3 μm size particles of -37.6 particles/cycle (CI, -164.7 to -10.67) during intubation compared with baseline ($P = .03$). The air sample collection for bacteria using the Coriolis was performed during eight pig intubations. One sample yielded bacterial growth that included oral flora (*Streptococcus mitis*, nonpathogenic *Neisseria* species, and *Streptococcus salivarius*) and *Leclercia adecarboxylata*, which is part of the normal flora in swine. Polytetrafluoroethylene filter cassette samples were collected during the remaining eight intubations. Three of eight samples resulted in growth of commensal or environmental bacteria such as *Micrococcus* species.

Aerosol Production During Patient Bronchoscopy

A total of 49 elective bronchoscopies, performed under procedural sedation, were sampled. Ten were excluded from analysis for technical reasons due to different OPC flow rate settings or battery failure ($n = 4$) and interruptions such as staff unmasking or the door opening for extended periods of time during sampling ($n = 6$). Forty-six percent (18 of 39) of procedures showed increased aerosol production in 0.3 μm size particles, whereas 2.6% (1 of 39) and 5.1% (2 of 39) showed increased generation compared with baseline for 1.0 and 5.0 μm size particles, respectively (Fig 3). When analyzed as a group, no significant difference in aerosol production was observed in 0.3 μm size particles when compared to baseline at either study site (Table 1). Four patients exhibited a measurable increase in 0.3 μm size particles. A significant decrease in aerosol production was observed for 1.0 μm size particles at both study sites, as

well as overall ($P < .01$). Bronchoscopies at both sites had a significant decrease in aerosol production for 5.0 μm size particles individually ($P < .01$ and $P < .01$, respectively) and overall ($P < .0001$). Importantly, a considerable amount of interprocedure variation was also observed in all size categories.

The data were further analyzed to determine aerosol generation during specific procedural events, including scope insertion, scope removal, coughing, suction, BAL, and biopsies. Both suction ($P = .10$) and BAL ($P = .11$) were associated with increased aerosol production in the smaller 0.3 μm size particles, although neither reached statistical significance (Fig 4). Bacteria were recovered from the portable personal air sampler in three of 18 bronchoscopy samples.

Discussion

AGPs have been implicated in the transmission of respiratory pathogens.^{3,14,15} A systematic review evaluating the risk of acquiring SARS for HCWs performing AGPs compared with those providing care, but not involved in AGPs, found that endotracheal intubation was associated with a significant increased risk of acquiring SARS.¹⁵ Although endotracheal intubation and bronchoscopy are listed as suspected AGPs and are considered high-risk medical procedures for HCWs, this classification has been made primarily based on epidemiologic data and expert opinion.¹⁵ There is now sufficiently robust prospective data outlining the dangers to HCWs involved in high-risk procedures; the adjusted relative risk for these HCWs is 2.9 for developing a respiratory tract infection.¹⁴ Fine aerosol particles can travel extended distances and may be inhaled deep into the lungs, representing a potential risk of infection if laden with pathogenic microorganisms.¹² A substantial number of HCWs have

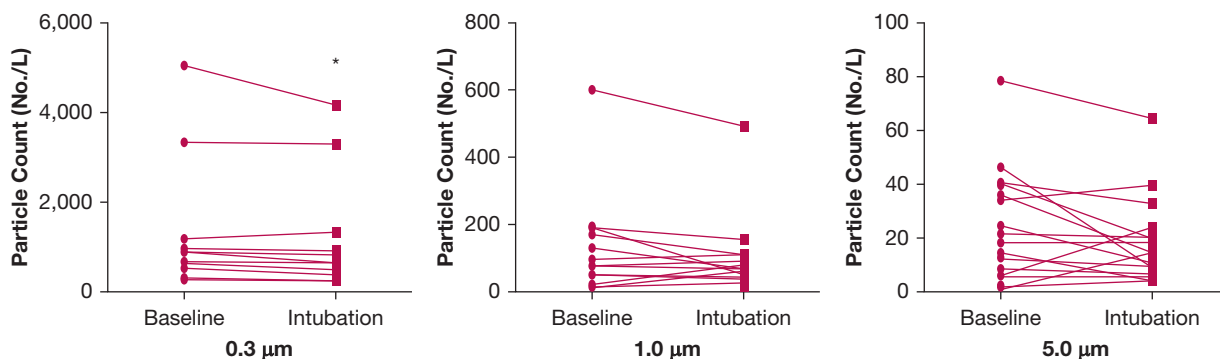


Figure 2 – Particle counts for 0.3, 1.0, and 5.0 μm size aerosol particles sampled during pig intubations ($N = 16$). A Wilcoxon matched pairs signed-rank test was used to evaluate statistical difference. * $P < .05$.

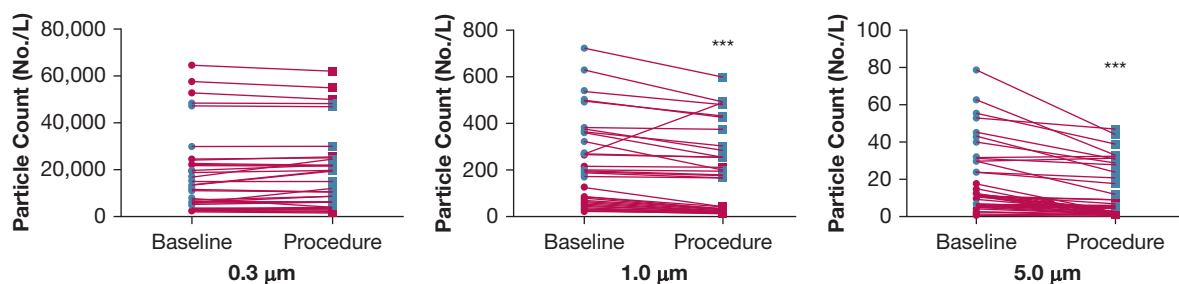


Figure 3 – Combined particle counts for 0.3, 1.0, and 5.0 μm size particles sampled during elective bronchoscopies ($N = 39$) compared with baseline. Blue data points indicate procedures done at Site 1. Results are expressed as particle count per cycle (1 cycle = 10 s sampling). Significance was assessed by using a Wilcoxon matched pairs signed-rank test. *** $P < .001$.

been infected with SARS-coronavirus 2, although it is unclear which activities during the course of clinical care were associated with exposure and transmission.¹⁶ It is imperative that this important knowledge gap be filled to mitigate further morbidity and mortality among HCWs.

In one study, Lavoie et al¹¹ evaluated aerosol and bioaerosol generation during 15 bronchoscopies using a UV-APS and found a significant increase in particles across a range of size categories. However, the baseline in this study was an empty room. The use of an empty room as baseline may overestimate the quantity of particles attributed to the procedure, when in fact a proportion is due to the presence of personnel and preprocedure activities. We used the period immediately preceding the insertion of the bronchoscope as the representative baseline, with personnel in the room. Incorporation of particles generated by the presence of personnel allowed us to attribute changes in particle concentration to the bronchoscopy alone.

We observed no significant change in aerosol generation in the experimental setting during pig intubations. This outcome was not entirely unexpected given the degree of sedation and paralysis prior to intubations. Bacteria known to be normal oral flora in human and pigs

(*S mitis*, nonpathogenic *Neisseria* species, and *S salivarius*), and *L adedecarboxylata* were detected. This suggests that the sampler collected oral secretions via droplets and/or aerosols from the pig during the intubation, as the research personnel were masked and are unlikely to be the source of the oral flora.

We detected a small increase in fine particle production in 46% of bronchoscopies, and a sizable increase in four participants. Unfortunately, this study is insufficiently powered to identify determinants of increased fine particle production and to definitively exclude the possibility that this observation is due to random variation; this topic could be addressed through a larger study and comprehensive metadata collection. This underscores the potential risk for HCW exposure in the absence of adequate ventilation and personal protection. In the setting of COVID-19, this is particularly important, highlighting the need to avoid bronchoscopy where possible.

We noted a reduction of larger particle generation. This finding may be attributed to obstructions such as the inserted bronchoscope and gauze used around the scope and bite block, which may have obstructed the release of larger particles during some procedures, although this practice varied. Alternatively, the fact that 1.0 and 5.0 μm

TABLE 1] Median Aerosol Particle Generation During Elective Bronchoscopy Compared With Ambient Preprocedural Levels in Individual Endoscopy Suites at Two Tertiary Care Centers

Location	Median Difference, 0.3 μm (Particles/Cycle)	Median Difference, 1.0 μm (Particles/Cycle)	Median Difference, 5.0 μm (Particles/Cycle)
Site 1 (n = 15)	-173.8 (-829.5 to 2380.0) $P = .49$	-62.7 (-123.4 to -5.1) $P = .01^a$	-8.6 (-19.6 to -0.95) $P < .001^b$
Site 2 (n = 24)	-84.1 (-498.5 to 85.3) $P = .14$	-27.7 (-39.7 to -11.9) $P < .001^b$	-3.0 (-5.1 to -1.6) $P < .001^b$
Combined (N = 39)	-85.5 (-389.2 to 85.3) $P = .44$	-29.4 (-46.8 to -16.0) $P < .001^b$	-4.1 (-7.2 to -2.2) $P < .001^b$

Statistical significance indicated by ^a $P < .05$, ^b $P < .001$.

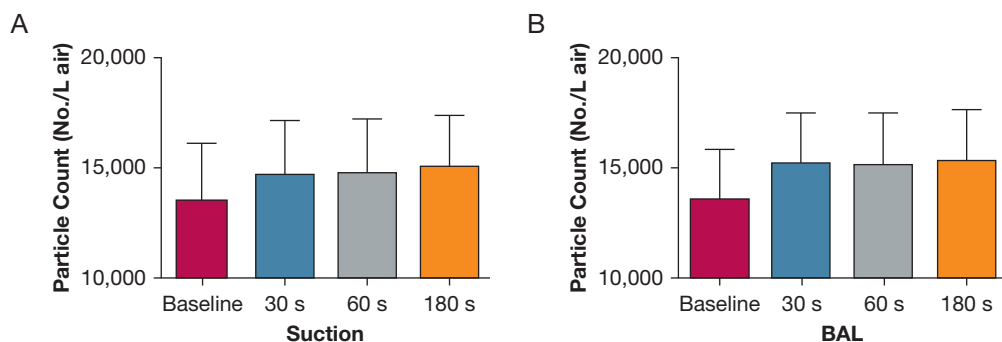


Figure 4 – Mean particle counts for 0.3 μm size particles sampled during elective bronchoscopy 30, 60, and 180 s following each event. A, Suction mean increases of 9.5% compared with baseline ($P = .86$). B, BAL mean increase of 7.7% compared with baseline ($P = .56$). Significance was calculated by using a Friedman test.

size range particles were higher during the preprocedural period may highlight a period of potentially unseen exposure risk, during which HCWs may be unknowingly exposed to an increased concentration of aerosols prior to donning PPE for the procedure, possibly as a result of particle re-entrainment. If procedures are performed serially, this particle re-entrainment may expose HCWs to potentially infectious bioaerosols from the previous procedure. It is also possible that the preprocedure aerosol concentrations are a result of unsettled aerosols generated by the clinical staff themselves, prior to donning PPE.

There were several limitations to the current study. Interpatient variation was observed, indicating that specific host and procedural factors may be determinants of aerosol generation during bronchoscopy. However, the precise quantity of increased aerosols that constitutes a significant increased risk of infection to HCWs remains unclear. Although this work represents one of the larger studies to quantify aerosols from patients undergoing bronchoscopy, it was not designed to identify determinants of significantly greater fine aerosol production, although it does provide the baseline data to design a sufficiently powered study. More research needs to be conducted to identify specific demographic, clinical, or procedural determinants for increased fine aerosol production and to correlate the dispersion of oral flora with potential pathogens. Ideally, we would establish a threshold of bioaerosol production that correlated clearly with risk to HCWs; however, this would depend on pathogen (eg, infectious dose, survivability in air, virulence, infectivity) and host (eg, PPE use, susceptibility, comorbidities) factors. In short, it is very difficult to determine a safe limit for bioaerosol exposure. This reinforces the need for risk reduction through engineering controls and PPE. Future studies

endeavoring to do so would be required to determine which situations may pose a risk to HCWs.

The choice of an OPC was for ease of use and portability. This instrument does not determine the presence of biological material in the air. Also, without knowing particle density, it is not possible to determine particle mass. Light scattering is affected by particle size, shape, and refractive index, which is another limitation of OPCs; a scanning mobility particle sizer would be more precise. Unfortunately, this instrument would not be portable, precluding nimble, nondisruptive sampling at multiple study sites.

An additional, important limitation of this study was the exclusion of less controlled, urgent procedures such as intubations in the ED or in critical care, because these situations are perceived to bear higher risk for HCWs. This was attempted; however, high baseline levels of aerosols due to inconsistent mask use, HCW activities, and uncontrolled settings with highly variable ventilation precluded the ability to attribute changes in aerosol concentration to the AGP when these measurements were attempted at our institution. We appreciate that data from elective, controlled bronchoscopy will not necessarily reflect the abundance or infectivity of bioaerosols generated during activities that are more likely to be associated with virus transmission in the setting of COVID-19. However, they do support protocol development for empiric data collection for controlled intubations of patients infected with SARS-coronavirus 2.

Interpretation

We observed a measurable increase in fine-particle generation in a minority ($n = 4$) of patients. These data support the need for ongoing research, including clinical data collection to identify determinants of increased fine

aerosol production and underscore the importance of PPE while performing AGPs while avoiding bronchoscopy in COVID-19 confirmed cases. A more

complete understanding of bioaerosol generation during bronchoscopy will ultimately enhance risk assessment for HCW exposure to respiratory pathogens.

Acknowledgments

Author contributions: S. M. takes responsibility for the content of the manuscript, including the data collection and analysis. N. D. and S. M. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed substantially to the study design, data analysis and interpretation, writing of the manuscript, and approval of the submitted manuscript.

Financial/nonfinancial disclosures: None declared.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: We are grateful to Dr Karren Probst for manuscript review and input on statistical analysis.

References

1. Scales DC, Green K, Chan AK, et al. Illness in intensive care staff after brief exposure to severe acute respiratory syndrome. *Emerg Infect Dis.* 2003;9(10):1205-1210.
2. Fowler RA, Guest CB, Lapinsky SE, et al. Transmission of severe acute respiratory syndrome during intubation and mechanical ventilation. *Am J Respir Crit Care Med.* 2004;169(11):1198-1202.
3. Public Health Agency of Canada. Prevention and Control of Influenza during a Pandemic for All Healthcare Settings-Pandemic Influenza: Aerosol-Generating Medical Procedures. Ottawa, ON; 2011. <http://www.phac-aspc.gc.ca/cpip-pclcp/assets/pdf/ann-f-eng.pdf>. Accessed June 20, 2017.
4. Malasky C, Jordan T, Potulski F, Reichman LB. Occupational tuberculous infections among pulmonary physicians in training. *Am Rev Respir Dis.* 1990;142(3):505-507.
5. Fowler RA, Scales DC, Ilan R. Evidence of airborne transmission of SARS. *N Engl J Med.* 2004;351(6):609-611.
6. Varia M, Wilson S, Sarwal S, et al. Investigation of a nosocomial outbreak of severe acute respiratory syndrome (SARS) in Toronto, Canada. *CMAJ.* 2003;169(4):285-292.
7. Christian MD, Loutfy M, McDonald LC, et al. Possible SARS coronavirus transmission during cardiopulmonary resuscitation. *Emerg Infect Dis.* 2004;10(2):287-293.
8. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med.* 2003;348(20):1986-1994.
9. Yu IT, Li Y, Wong TW, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. *N Engl J Med.* 2004;350(17):1731-1739.
10. Marchand G, Duchaine C, Lavoie J, Veillette M, Cloutier Y. Bacteria emitted in ambient air during bronchoscopy—a risk to health care workers? *Am J Infect Control.* 2016;44(12):1634-1638.
11. Lavoie J, Marchand G, Cloutier Y, et al. Evaluation of bioaerosol exposures during hospital bronchoscopy examinations. *Environ Sci Process Impacts.* 2015;17(2):288-299.
12. Hinds WC. Properties, behavior, and measurement of airborne particles. In: *Aerosol Technology*. 2nd ed. Los Angeles, CA: Wiley & Sons; 1999:233-259.
13. Singhal N, Kumar M, Kanaujia PK, Viridi JS. MALDI-TOF mass spectrometry: an emerging technology for microbial identification and diagnosis. *Front Microbiol.* 2015;6:791.
14. Macintyre CR, Seale H, Yang P, et al. Quantifying the risk of respiratory infection in healthcare workers performing high-risk procedures. *Epidemiol Infect.* 2014;142(9):1802-1808.
15. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. *Aerosol-Generating Procedures and Risk of Transmission of Acute Respiratory Infections: A Systematic Review*. Ottawa, ON: Canada; 2011.
16. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA.* 2020;323(13):1239-1242.