



Quantity, Size Distribution, and Characteristics of Cough-Generated Aerosol Produced by Patients with an Upper Respiratory Tract Infection

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ABSTRACT

It is generally recognized that most nosocomial infections are spread by exposure to expelled particles at close range (usually within 1 m) or through contact. Although the Korea Centers for Disease Control established a 2-m cut-off for transmittance from patients during the Middle East Respiratory Syndrome (MERS) outbreak in Korea in 2015, questions have been raised regarding possible infection due to aerosols transported beyond this distance. The aim of this study was to characterize cough-generated aerosol emissions from cold patients and to determine the transmission distance of cough particles in indoor air. The study was conducted using subjects with acute upper respiratory infections. The number and size distribution of the particles generated from each cough were measured after participants coughed into a stainless steel chamber in a clean room. The total particle concentration was measured for each subject in the near field (< 1 m) and far field (> 2 m). The number of particles emitted by the cough of an infected patient was $560 \pm 5513\%$ greater than that generated by patients after recovery ($P < 0.001$). The number of particles was also significantly higher ($P < 0.001$) than the background concentration when infected patients were coughing, even in the far field. These results suggest that the 2-m cut-off should be reconsidered to effectively prevent airborne infections.

Keywords: Cough aerosol; Airborne transmission; Respiratory infections; Disease transmission; Droplet nuclei.

INTRODUCTION

Infectious diseases have many pathways of transmission. Infectious disease transmission through respiratory secretions can be divided into droplet transmission and airborne transmission. The World Health Organization (2014) defined droplet transmission as the transmission of diseases by particles expelled at close range, usually within 1 m from the site of generation, and occasionally through contact. They also recommended a 5- μm aerosol diameter cut-off to classify droplet (> 5 μm) or airborne (< 5 μm) transmission. This size-based relationship between droplet and airborne transmission is underpinned by Wells (1934) and Hamburger and Robertson (1948).

It is generally recognized that most nosocomial infections are spread by contact (Beggs, 2003). However, several studies of the airborne transmission of infectious pathogens in indoor environments, using this framework of single cut-off delineation, have failed to acknowledge the size of particles. In addition many studies have not considered that pathogens are not exclusively dispersed by airborne or droplet transmission, but can use both pathways simultaneously (Gratton *et al.*, 2011). Although many nosocomial infections are associated with direct person-to-person contact in indoor environments, there is a strong association between the transmission of many pathogens, such as measles, smallpox, tuberculosis, and severe acute respiratory syndrome (SARS), and indoor air movement (Li *et al.*, 2007). Hence, determining aerosol diameter and indoor airflow is important to understand pathogen-containing aerosol movement. Nevertheless, some studies have suggested that infections are airborne-transmitted among humans in healthcare settings, because epidemic diseases, such as influenza, are

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believed to have a relationship with respiratory airborne transmission (Roy and Milton, 2004). Human coughing seems to promote the spread of cough-generated aerosols by producing more airborne aerosols than vocalizing or breathing (Morawska *et al.*, 2009). According to Blachere *et al.* (2009), viral RNA of seasonal influenza was detected in the emergency room of a hospital and aerosol transmission was implicated (Wong *et al.*, 2010). Inadequate categorization of close contact by the Korea Centers for Disease Control and Prevention (KCDC) was suggested as the key factor in the spread of Middle East respiratory syndrome (MERS) in South Korea in 2015. “Guidelines for the Management of Middle East Respiratory Syndrome (MERS),” published by the KCDC in December 2014, refers to the contact person as “a person who has had physical contact with (or been within 2 m of) a confirmed or suspected patient,” and does not consider the possibility of airborne transmission of aerosols. Consequently, the response guidelines of the Korea Ministry of Health and Welfare and the KCDC for MERS outbreaks pertaining to close contact are considered inadequate due to insufficient data (Choi *et al.*, 2015).

Due to the wide-ranging and potentially long-term transmission of cough-generated airborne particles, it is important to understand the dynamics of cough particles of different sizes. Coughing can release higher concentrations of particles than breathing or talking, because it discharges a large quantity of airborne particles at a high discharge velocity. It has been demonstrated experimentally that the influenza A virus remains infectious in small particle aerosols and can transit across rooms (Noti *et al.*, 2012). The influenza virus and viral RNA can be detected in droplets $> 5 \mu\text{m}$ and nuclei $< 5 \mu\text{m}$ (Lindsley *et al.*, 2010; Milton *et al.*, 2013). It is very likely that a cough jet from a respiratory disease patient contains pathogens and spreads airborne diseases that can be inhaled into the respiratory tracts of other individuals. Furthermore, cough particles have a wide range of sizes and different transport characteristics. Lindsley *et al.* (2012) reported that cough particles have a size range of 0.35–10 μm and Yang *et al.* (2007) reported a mean size distribution of cough droplets of 0.62–15.9 μm , with nuclei sizes of 0.58–5.42 μm . A review conducted by Gralton *et al.* (2011) summarized the size of coughed particles from a large number of studies and concluded that the size of cough-generated particles ranged 0.1–100 μm . However, no study has been performed on the transmission of cough-generated airborne nanosized particles ($< 0.1 \mu\text{m}$) at a distance greater than the direct contact distance. This study focused on the emission and persistence of airborne particles before sedimentation and their potential for long-range transmission. Hence, the objectives were to characterize cough-generated aerosol emissions and to determine their characteristics in indoor air under the relative humidity and temperature conditions of a healthcare facility.

MATERIALS AND METHODS

This study consisted of two experiments; one was conducted in a cylindrical exposure chamber and the other was conducted in a clean room. The exposure chamber was

used to estimate the quantity and size distribution of cough-generated aerosols. We observed cough-generated aerosol diffusion in the near field ($< 1 \text{ m}$) and far field ($> 2 \text{ m}$) in a clean room, as well as variations in number and surface area concentrations with size and distance. The two experiments were repeated after the subjects recovered, to assess any differences between pre- and post-recovery.

Recruitment

Patients with cold symptoms were recruited from August to November 2016 using posters in communities and social networks. Subjects were diagnosed with acute upper respiratory infections (hereafter, “colds”) at medical institutions, which was confirmed through production of a medical certificate. Subjects were excluded if their symptoms had receded between the time they obtained certification and the first experiment. For inclusion in the study, all subjects were required to be 18–39 years of age, male or a non-pregnant female, to have no other health problems, to be a lifetime non-smoker, and to have received no vaccination against influenza within the last six months (thus eliminating any bias from including influenza patients). Subjects were asked a few questions about their illness and current symptoms. Twelve subjects were recruited to the study. Of these, ten (five males and five females; mean age: 22–33 years) were confirmed as having a cold on their first visit to the experimental room. They returned for the second test session after their symptoms had resolved.

All recruitment and study processes were approved prior to the start of the study by the Seoul National University Institutional Review Board (IRB No. 1608/001-015).

Instrumentation and Monitoring Procedure

A scanning mobility particle sizer (SMPS; NanoScan Model 3910; TSI Inc., Shoreview, MN, USA) and an optical particle spectrometer (OPS; Model 3330; TSI Inc.) were used to measure the particle concentration and size distribution in real time (1-min measurement intervals). The detectable size ranges of the instruments were 10–420 nm for the SMPS and 300–10,000 nm for the OPS. An ultrasonic spirometer (EasyOne; Medical Technologies, Andover, MA, USA) was used to measure the mean coughed aerosol volume and peak air flow during coughing, and a 40-L stainless steel cylinder chamber was used to collect coughed aerosols. The collection chamber was fitted with an inlet port for the spirometer and an outlet linked to the SMPS and OPS.

The subjects participated in two experiments. As shown in Fig. 1(a), the 40-L stainless steel chamber was used to evaluate aerosol emissions. To evaluate the emissions of cough-generated aerosols, the participant was seated in front of the steel chamber and asked to breathe high efficiency particulate air (HEPA)-filtered air normally for 5 min to remove background aerosols from their respiratory tract. At the same time, an air pump was used to remove background particles from the chamber. After breathing for 5 min, the air pump was turned off, and the subject was asked to inhale as deeply as possible and then cough with maximum force through the spirometer mouthpiece, which

was connected to the chamber. After coughing, the participant breathed normally and exhaled the aerosol that remained in their respiratory tract, but the aerosol emitted during this stage was not included in the concentration per cough shown in Table 2. After analysis, the chamber was evacuated for 10 min using the air pump, and the subject was asked to repeat the coughing procedure two more times for a total of three coughs. After each participant finished the procedure, the spirometer mouthpieces and equipment, including the chamber, were cleaned with disinfectant and UV light.

The second experiment to evaluate the characteristics of the cough-generated aerosol in an indoor environment was conducted in a clean room, which controlled background particulates to < 10 particles cm^{-3} using a HEPA filter-equipped ventilation system. The volume of the clean room was 40.32 m^3 ($7.0 \text{ m [W]} \times 2.4 \text{ m [L]} \times 2.4 \text{ m [H]}$). The participant was asked to put on dustproof clothing and to take an air shower to exclude the possibility of any particulate matter from other sources, such as dust dispersion. The temperature and relative humidity were constantly monitored using a real-time thermo-hygrometer (Model

TR-72U; T&D Inc., Redmond, WA, USA) to ensure that the room conditions were maintained.

Fig. 1(b) shows the sampling system. Direct reading instruments for measuring the particle concentration and size distribution were placed in each sampling location. Based on the reported respiratory disease air transmission from previous studies, the clean room area was divided into a near field ($< 1 \text{ m}$) and far field ($> 2 \text{ m}$). SMPS-1 was located 0.5 m from the participant to evaluate the aerosol emissions in the direct contact transmission range. SMPS-2 and the OPS were located 3 m from the participant to measure particle dispersion and airborne exposure. The OPS was placed in the far field to observe the transmission of larger particles and their overall size distribution and concentration. Due to a lack of monitoring devices, we did not use the OPS in the near field.

Relative humidity and temperature were maintained at $30\text{--}50\%$ and $21\text{--}25^\circ\text{C}$, respectively, to represent the indoor air conditions in a hospital or emergency room (Ninomura and Hermans, 2008; Geshwiler, 2003). When the subjects had a cold, the mean temperature in the clean room was 24.0°C (standard deviation [SD] = 0.59) and mean relative

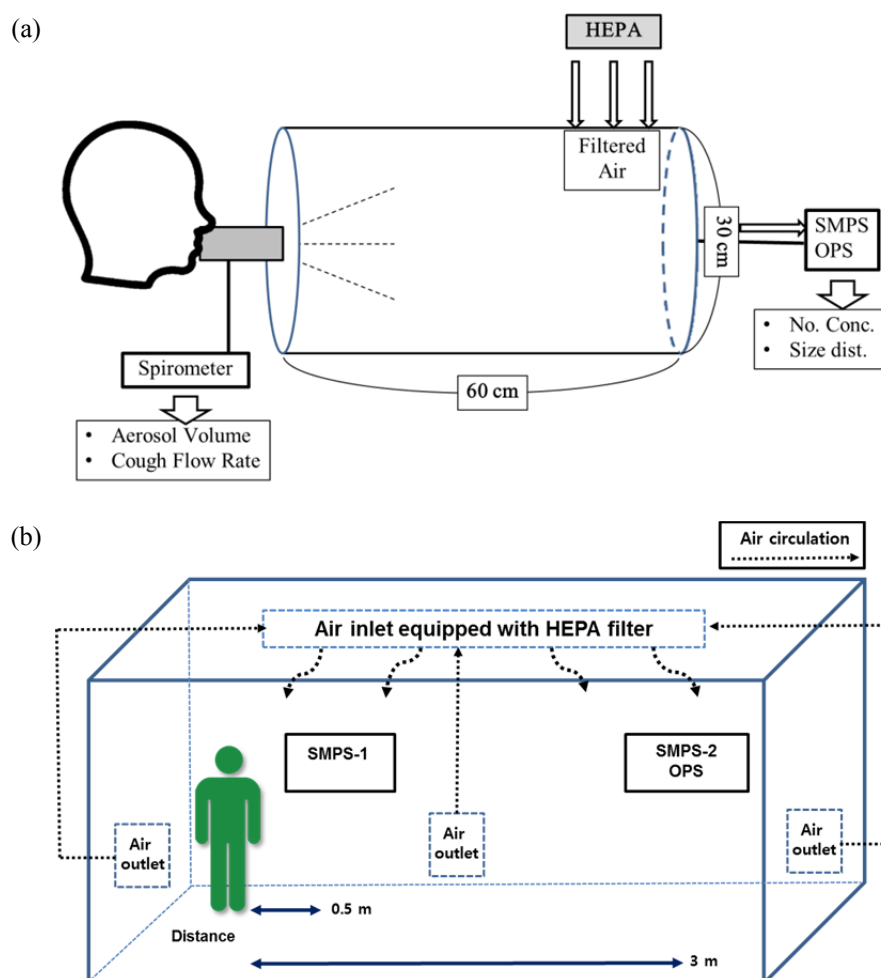


Fig. 1. Schematic of the exposure (a) chamber for the experiment conducted in the (b) clean room. In the experiment (b), filtered air was circulated for approximately 60 min before the experiment to lower the background aerosol concentration. Circulation was suspended during the experiment.

humidity was 38.3% (SD = 3.42). After the subjects had recovered, the mean temperature in the clean room was 23.8°C (SD = 0.36) and the mean relative humidity was 37.2% (SD = 1.28).

Each experiment was divided into three phases. Before the cough, the HEPA-filtered air circulation system was operated for at least 60 min to remove contaminants from the clean room. After the particulate concentration level was stabilized, the ventilation system was stopped and 30 min of sampling was conducted to obtain a background aerosol concentration. Cao *et al.* (2015) reported that the existence of a downward air flow from a ventilation system attached to the ceiling can greatly affect aerosol transmission. For this reason, the ventilation system was shut down prior to the experiment, and we assumed that there was no air movement apart from the air flows due to coughing and the sampling instrument intake. The air changes per hour (ACH) of the system during the sampling process were 0.0037 and there were 0.0056 air exchanges per sampling interval. We therefore considered the air flow low enough to be ignored, and assumed that the inlet flow of the monitoring devices did not affect the transport efficiency in the clean room.

The coughing phase comprised both coughing and rest periods. The participant was asked to cough continuously for 1 min and then rest for 5 min to exhale the aerosol remaining in the respiratory tract. This cough cycle was repeated five times for 30 min of cough-generated aerosol emissions.

After the cough, real-time monitoring was conducted for 30 min to monitor the residence and diffusion of cough-generated aerosols.

Calculations and Data Analysis

The concentration and size distribution data measured by the SMPS and OPS were used to estimate particle number concentrations and the size distribution. The SMPS provided aerosol particle counts in 13 size bins and the OPS provided 5 bins. The particle concentrations of 18 optical bins in the 10 nm–10 μm diameter range were monitored. Data from the SMPS and OPS channels were merged using the Multi Instrument Manager software (MIM-2 ver. 2.0; TSI Inc.) provided by the manufacturer. For effective observation of the characteristics of nanosized aerosol, data were converted from a number concentration into a surface concentration, assuming that the particles were ideal spheres.

All data acquired from real-time monitoring were analyzed statistically. Descriptive statistics were recorded to compare the aerosol concentrations during and after coughing. The number and surface area of aerosol particles per cough were presented as arithmetic means (AM) ± SD because the results were acquired from experiments that were repeated three times. The particle concentrations in the clean room experiment are shown as AMs ± SD because data for each phase and location were normally distributed and the size distribution was proven to be unimodal.

Because the individual data of subjects were not normally distributed when we tested them with a Shapiro-

Wilks Test, the results of each subject's coughing while ill were compared to coughs done after recovery using the Mann–Whitney *U* test. However, because the normalized aerosol concentration data in the clean room were normally distributed, the amount of data per experimental phases was the same. A one-way analysis of variance was conducted to compare the particle concentration according to elapsed time (before, during, and after the cough) and Tukey's HSD test was applied because it is the most reasonable way to control type 1 error and has a lot of statistical power. Tukey's test was applied to determine the differences in particle concentration by elapsed time. A result was considered significant at $P \leq 0.05$. All analyses were conducted using SAS software (v. 9.4; SAS Institute, Cary, NC, USA). SigmaPlot software (ver. 10; Systat Software, San Jose, CA, USA) was used to visualize the results.

The particulate concentrations in the chamber were assumed to be the same everywhere and it was also assumed that the aerosol dispersed equally when the concentration was highest 5 min after the cough. Eq. (1) was used to estimate the aerosol emissions for each subject:

$$\text{Number of aerosol per cough} = \left(C_{\text{particle,max}} - \bar{C}_{\text{particle,bg}} \right) \times V_{\text{chamber}} \quad (1)$$

where $C_{\text{particle,max}}$ is the particle concentration inside the chamber 5 min after the cough, V_{chamber} is chamber volume (m^3), and $\bar{C}_{\text{particle,bg}}$ is the mean background concentration inside the chamber 5 min before the test. There are several assumptions in Eq. (1) that may lead to inaccuracies when estimating aerosol emissions. Size-resolved particle dynamics, coagulation, and constant particle loss rates were ignored. Because we did not use ventilation systems while sampling, the ventilation rate of each experiment was determined only by the inlet flow of the sampling devices. In the chamber experiment, the total inlet flow of the sampling devices was 1.75 L min^{-1} . The ACH of the system was 2.5 and there were 0.20 air exchanges per sampling period. Because of dilution and deposition, we considered the use of average aerosol number concentration during sampling inappropriate, and therefore $C_{\text{particle,max}}$ was used as the representative value of a well-mixed state.

RESULTS

Characteristics of Individual Subjects

The mean time from the first to the second visit was 32.1 ± 12.1 days. Cough volume and cough peak flow rate were measured during illness and after recovery, whereas the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and peak expiratory flowrate (PEF) of subjects were measured when they were ill.

As summarized in Table 1, the air volume of each cough, and the peak cough flow rate, increased slightly after recovery compared to during the cold (cough volume, $P = 0.57$; peak cough flow rate, $P = 0.27$). Mean air volume and peak cough flow rate during the cold were

Table 1. Characteristics of the individual test subjects.

ID	Gender	Age	Height (cm)	Weight (kg)	FVC (L)	FEV1 (L)	PEF (LPS)	Cough volume (L)		Cough peak flowrate (LPS)	
								While ill	After recovery	While ill	After recovery
1	F	25	158	49	2.75	2.61	4.00	0.81	1.33	4.56	2.83
2	F	24	160	49	2.52	2.30	4.59	0.45	0.44	3.58	3.90
3	F	24	158	46	3.03	2.45	4.22	0.73	0.95	5.84	6.37
4	F	29	162	52	3.10	2.28	3.59	1.12	1.60	5.35	6.02
5	F	22	158	63	3.18	2.97	6.53	1.53	2.37	5.92	6.45
Subtotal	F	24.8 ± 2.3	159.2 ± 1.6	51.8 ± 5.9	2.92 ± 0.24	2.52 ± 0.25	4.59 ± 1.02	0.93 ± 0.36	1.34 ± 0.64	5.05 ± 0.88	5.11 ± 1.47
6	M	26	177	77	4.75	4.26	9.29	1.23	3.39	6.28	8.25
7	M	25	173	75	4.77	4.09	10.37	3.87	3.30	8.11	9.19
8	M	30	174	77	3.24	3.12	7.10	1.61	1.50	6.12	8.43
9	M	26	182	90	4.97	3.85	9.18	1.44	1.37	5.52	5.88
10	M	33	174	77	4.95	4.07	9.40	4.02	3.39	8.79	8.58
Subtotal	M	28 ± 3.0	176 ± 3.2	79.2 ± 5.4	4.54 ± 0.65	3.88 ± 0.40	9.07 ± 1.07	2.43 ± 1.24	2.59 ± 0.94	6.96 ± 1.25	8.07 ± 1.13
Total	-	26.4 ± 3.1	167.6 ± 8.8	65.6 ± 14.8	3.73 ± 0.94	3.20 ± 0.75	6.83 ± 2.47	1.69 ± 1.18	1.96 ± 1.02	6.01 ± 1.44	6.59 ± 1.98
P-value		0.07	0.01	0.01	0.01	0.01	0.01	0.04	0.09	0.04	0.06

LPS, liters per second; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flowrate.

1.68 ± 1.19 L and 6.01 ± 1.45 L sec⁻¹, respectively, which increased to 1.96 ± 1.02 L and 6.59 ± 1.98 L sec⁻¹ after recovery. Although patient cough peak flowrates (CPF) increased overall after recovery, the CPFs of IDs No. 1 and 10 decreased. Compared with the CPF of ID No. 10, in which the “after recovery” CPF did not decrease much from the “while ill” CPF, the “after recovery” CPF of ID No. 1 was much lower than the “while ill” CPF, and was outside the normal range. In previous studies, the normal CPF in healthy adults is typically in the range of 360–1,000 L min⁻¹, with CPFs under 160 L min⁻¹ considered ineffective for airway clearance (Bach, 1993). According to these criteria, the CPF of ID No. 1 (170 L min⁻¹) was effective but below the normal range. Although the CPF criteria may vary slightly depending on race and gender, there was a large difference between the CPF of ID No. 1 and the normal value. The results of measurements other than the CPF for ID No. 1 tended to match those of other subjects. The low CPF may therefore have been a measurement error.

The FVC, FEV1, and PEF were significantly higher in males than in females (all *P*-values = 0.01). The mean FVC, FEV1, and PEF values of female subjects were 2.92 ± 0.24 L, 2.52 ± 0.25 L, and 4.59 ± 1.02 L, respectively, whereas they were 4.54 ± 0.65 L, 3.88 ± 0.40 L, and 9.07 ± 1.07 L in males, respectively. The peak cough flow rate and cough volume of each cough during a cold were also significantly higher in males than in females (all *P*-values = 0.04), but the difference disappeared after recovery, although peak cough flow rate and cough volume were still higher in males than in females (*P* = 0.09 and *P* = 0.06, respectively).

Size and Quantity of Cough-Generated Aerosol

As shown in Table 2, the number of particles expelled per cough while the subjects had a cold ranged from 731,000 to 18,756,000 (mean: 4,914,600 particles/cough). The number of particles expelled per cough after the subjects recovered ranged from 200,900 to 450,000. The mean number of particles per cough was higher when the subjects had a cold than after they recovered (*P* < 0.001). However, the mean value was not significantly different between the sexes, either when subjects were ill or had recovered (*P* = 0.68 and *P* = 0.21, respectively).

The surface area of particles expelled per cough when the subjects had a cold varied from 156,000 to 66,824,000 μm² (mean: 7,210,000 μm² cough⁻¹). The surface area of particles expelled per cough after the subjects recovered ranged from 39,000 to 2,681,000 μm² (mean: 521,000 μm²). When the subjects had a cold, the mean surface area of particles per cough was higher than after they recovered (*P* = 0.002). However, patient ID No. 10 displayed the opposite trend. This result was induced by an increase in the proportion of particles with larger diameters in the cough of ID No. 10. The mean did not differ between the sexes, either when the subjects were ill or had recovered (*P* = 0.40 and *P* = 0.30, respectively).

Fig. 2(a) shows a plot of the number of aerosol particles expelled per cough, as detected in each size bin, and

Table 2. Number and surface area of particles expelled per cough—chamber ($n = 3$).

ID.	Gender	Number of particles/cough		P-value	Surface area of particles/cough (μm^2)		P-value
		While ill	After recovery		While ill	After recovery	
1	F	4,443,000 \pm 2,300,000	661,000 \pm 421,000	0.081	438,000 \pm 210,000	66,000 \pm 53,000	0.081
2	F	774,000 \pm 477,000	600,000 \pm 180,000	0.190	748,000 \pm 786,000	55,000 \pm 14,000	0.190
3	F	2,542,000 \pm 959,000	546,000 \pm 291,000	0.383	160,000 \pm 87,000	106,000 \pm 109,000	0.383
4	F	4,674,000 \pm 1,857,000	566,000 \pm 292,000	0.383	818,000 \pm 306,000	444,000 \pm 531,000	0.383
5	F	18,806,000 \pm 6,984,000	1,039,000 \pm 604,000	0.081	66,825,000 \pm 33,647,000	121,000 \pm 114,000	0.081
Subtotal		6,248,000 \pm 7,291,000	683,000 \pm 182,000	< 0.001	13,805,000 \pm 30,498,000	159,000 \pm 145,000	< 0.001
6	M	3,226,000 \pm 1,525,000	1,178,000 \pm 440,000	1.00	127,000 \pm 136,000	714,000 \pm 863,000	1.00
7	M	1,596,000 \pm 1,145,000	4,229,000 \pm 2,728,000	0.383	1,212,000 \pm 481,000	842,000 \pm 629,000	0.383
8	M	3,522,000 \pm 2,057,000	363,000 \pm 108,000	0.081	492,000 \pm 343,000	39,000 \pm 17,000	0.081
9	M	1,043,000 \pm 490,000	983,000 \pm 651,000	0.663	156,000 \pm 44,000	113,000 \pm 87,000	0.663
10	M	9,326,000 \pm 6,181,000	2,940,000 \pm 1,910,000	1.00	550,000 \pm 330,000	2,681,000 \pm 3,132,000	1.00
Subtotal		3,742,000 \pm 4,235,000	1,939,000 \pm 1,430,000	0.147	512,000 \pm 498,000	882,000 \pm 958,000	0.481
Total		4,995,000 \pm 6,090,000	1,376,000 \pm 1,459,000	< 0.001	7,210,000 \pm 19,901,000	521,000 \pm 774,000	0.002

Fig. 2(b) shows a plot of the surface area of aerosol particles per cough in each size bin. Around $99.9 \pm 90.3\%$ of all expelled particles had diameters $< 5 \mu\text{m}$ (airborne transmission) when the subjects had a cold, which accounted for $90.2 \pm 912.2\%$ of the total surface area. The particle number concentration decreased in each respective size channel of instruments.

The mean number of particles per cough and mean surface area of particles per cough were higher within certain diameter ranges ($< 100 \text{ nm}$, $100\text{--}300 \text{ nm}$, $420\text{--}1,000 \text{ nm}$, and $1.0\text{--}2.5 \mu\text{m}$) when the subjects had a cold versus after they had recovered ($P < 0.001$). The diameter distribution of the measured particles varied among patients, especially for larger particles. In particles with diameters $< 100 \text{ nm}$ and of $100\text{--}320 \text{ nm}$, the geometric means and standard deviations, GM (GSD,) of the particle number concentration were 1,467,000 (2.97) and 1,285,000 (2.73), respectively, for patients with positive symptoms, and 421,000 (3.02) and 413,000 (1.6), respectively, for patients with negative symptoms. However, for larger particles, the GSD was larger, ranging from 5.40 to 47.08.

Aerosol Characteristics

Table 3 shows a summary of the background particle concentrations during and after coughing in the near field (0.5 m) and far field (3 m) from the source (participant). In the far field, particle concentrations during coughing by subjects with a cold were considerably higher than the background level. After coughing the concentration increased considerably, but not significantly, in the near field. After subjects had recovered, particle concentrations during and after coughing were slightly higher than the background level, but the difference was less than that observed during the period when subjects had a cold (Fig. 3(a)).

For nine of the ten subjects, the particle concentrations in the far field were higher than the background concentration when they were ill. The arithmetic mean (AM) of the particle concentration in the far field increased during coughing for infected subjects compared to the AM of the background concentration. The difference in particle number concentration in the clean room between the background and during coughing varied from 65 to 710 particles cm^{-3} , as shown in Fig. 3(b), and the difference was significant ($P < 0.001$).

The AM of the particle concentration in the near field was higher than the AM of the background concentration. The difference in the particle number concentration in the clean room between the background and during coughing varied from 8 to 448 particles cm^{-3} and the difference was not significant ($P = 0.22$). The distribution of particle concentrations during coughing were not different among the 13 different-sized bins, which ranged from 10 to 420 nm ($P = 1.000$).

In exposure chamber experiments, when subjects had cold symptoms, the number of aerosol particles generated from a single cough had no statistically significant correlation with FVC (0.93), FEV1 (0.90), PEF (0.65), volume of cough (0.28), CPF (0.43), body mass index (0.57), or sex (0.63). However, after subjects had recovered, the number

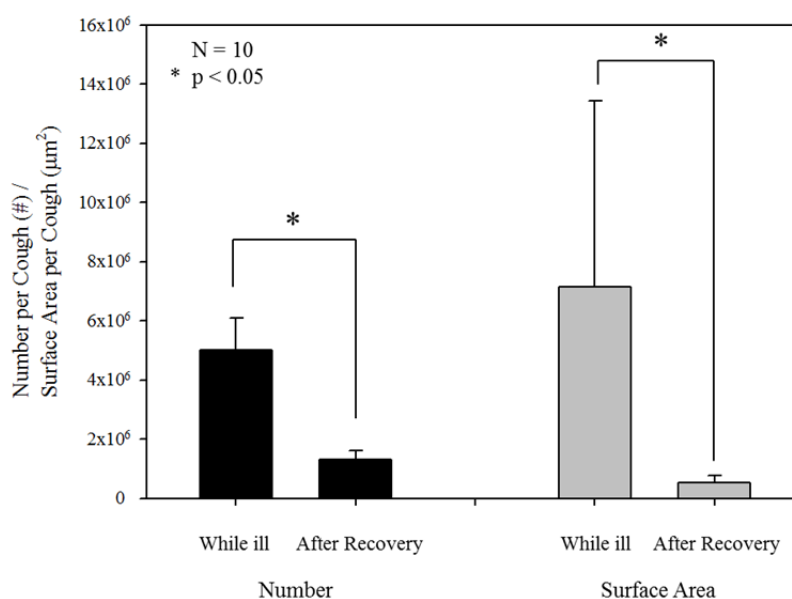


Fig. 2. Number and surface area of particles per cough while ill and after recovery. Results were derived from the chamber experiment. Each bar shows the average of three coughs, and the error bars show the standard error.

of aerosol particles generated from a single cough had a statistically significant correlation with FVC (0.04, $r = 0.65$), FEV1 (0.03, $r = 0.68$), PEF (0.01, $r = 0.78$), and volume of cough (0.02, $r = 0.72$), but did not have a statistically significant correlation with CPF (0.19), body mass index (0.33), or sex (0.19).

In clean room experiments, when subjects had cold symptoms, the ratio of aerosol number concentration during coughing to the background was significantly correlated with the number of coughs (0.04, $r = 0.65$). However, it had no statistically significant correlation with FVC (0.73), FEV1 (0.96), PEF (0.47), volume of cough (0.49), CPF (0.58), body mass index (0.56), or sex (0.27). After subjects had recovered, the ratio of the aerosol number concentration during coughing to the background had no statistically significant correlation with the number of coughs (0.65), FVC (0.75), FEV1 (0.85), PEF (0.65), volume of cough (0.38), CPF (0.38), body mass index (0.99), or sex (0.38).

DISCUSSION

In this study, we found that patients with a cold can release cough-generated airborne transmission-available particles. Transmission was detected at a distance of 3 m, which is considered to be beyond the contact transmission distance. Furthermore, we found that the number of particles expelled by coughing decreased after patients recovered, and most of the particles generated from coughing were $< 5 \mu\text{m}$ in size. Particles of this size can remain suspended in the air for at least 1 h. These results suggest that the airborne spread of pathogens based on aerosol diffusion or the forceful airflow produced by coughing may be possible even at distances > 3 m from a patient with a respiratory disease.

The possibility of airborne transmission of pathogen-containing aerosols is a critical issue for the public health

community. However, many questions remain unanswered regarding potentially infectious aerosols produced by ill people. Many recent studies have focused on the generation of aerosols expelled from the respiratory system, and their transmission possibility has usually been studied using models, such as those suggested by Xie *et al.* (2007), Redrow *et al.* (2011), and Wei and Li (2015), rather than experimental methods. The results of this study indicate that people produce more fine aerosols $< 5 \mu\text{m}$, as well as aerosols containing a larger number of particles, when they have a cold compared to after they have recovered. As in several similar studies, the number of cough-generated aerosol particles expelled by the test subjects in this study varied considerably from person to person (Fabian *et al.*, 2008; Stelzer-Braid *et al.*, 2009; Lindsley *et al.*, 2010).

As shown in Table 2, the number concentration and surface area concentration varied greatly. The reason the variation was large even though the participants were of similar ages, i.e., in their 20s and early 30s, was due to differences in gender, spirometric differences (FVC, FEV1, PEF), and differences in the amount of coughing and CPF. For this reason, we found that the number of particles released when suffering from a cold was higher than that after recovery for the same individual. The range of generated particles was 731,000–18,756,000 particles/cough when subjects had an infection. This suggests a “superspreader” effect, i.e., if a person expels large quantities of infectious particles, they may spread a virus or other infectious agents to others at a much higher rate. When calculating the number of particles per cough, the maximum concentration within 5 min after coughing was assumed to represent the conditions under which the aerosol was completely diffused in the air. We considered that the aerosol would be dispersed from a subject’s mouth over time and diffusion of the aerosol would cease when the aerosol reached the end of the chamber.

Table 3. Particle number concentration by experimental phase—clean room (#/cc, SMPS only).

ID	Diagnosis	0.5 m						3.0 m					
		Background (N = 30)		During cough (N = 30)		After cough (N = 30)		Background (N = 30)		During cough (N = 30)		After cough (N = 30)	
		AM ± SD	AM ± SD	AM ± SD	AM ± SD	AM ± SD	AM ± SD	AM ± SD	AM ± SD	AM ± SD	AM ± SD	AM ± SD	AM ± SD
1	While ill	1,163 ± 173	1,443 ± 330	1,346 ± 90	1,098 ± 56	1,503 ± 192	1,200 ± 103	2,619 ± 202	2,605 ± 162	2,891 ± 171	2,437 ± 173	2,281 ± 130	2,596 ± 145
2	While ill	2,019 ± 110	2,159 ± 113	2,100 ± 98	1,730 ± 96	1,797 ± 96	1,754 ± 77	4,044 ± 163	3,920 ± 161	3,708 ± 173	3,275 ± 160	3,501 ± 139	3,251 ± 395
3	While ill	-	-	-	1,154 ± 100	1,460 ± 141	1,147 ± 74	884 ± 81	944 ± 86	1,037 ± 79	690 ± 63	755 ± 80	789 ± 65
4	While ill	-	-	-	3,732 ± 294	3,917 ± 180	1,282 ± 69	1,488 ± 117	1,202 ± 213	3,605 ± 187	3,494 ± 252	3,758 ± 266	3,605 ± 187
5	While ill	-	-	-	1,627 ± 85	1,752 ± 177	2,277 ± 198	2,260 ± 172	1,340 ± 76	2,260 ± 172	2,277 ± 198	2,987 ± 628	2,260 ± 172
6	While ill	-	-	-	2,137 ± 125	2,401 ± 155	2,645 ± 283	3,329 ± 131	3,162 ± 227	3,162 ± 227	1,270 ± 70	1,454 ± 92	1,340 ± 76
7	While ill	1,968 ± 134	2,141 ± 121	2,314 ± 159	1,611 ± 87	1,881 ± 141	2,061 ± 115	1,968 ± 134	2,141 ± 121	2,314 ± 159	2,032 ± 96	2,102 ± 148	2,314 ± 140
8	While ill	2,786 ± 169	2,815 ± 132	2,542 ± 147	2,547 ± 166	2,661 ± 141	2,350 ± 146	2,786 ± 169	2,815 ± 132	2,542 ± 147	2,547 ± 166	2,661 ± 141	2,350 ± 146
9	While ill	3,980 ± 316	4,006 ± 302	3,655 ± 221	3,548 ± 287	3,430 ± 284	3,150 ± 259	3,980 ± 316	4,006 ± 302	3,655 ± 221	3,548 ± 287	3,430 ± 284	3,150 ± 259
10	While ill	2,893 ± 238	3,341 ± 274	2,559 ± 129	3,421 ± 177	3,534 ± 152	3,382 ± 117	2,893 ± 238	3,341 ± 274	2,559 ± 129	3,421 ± 177	3,534 ± 152	3,382 ± 117
	After recovery	3,622 ± 482	3,747 ± 412	3,703 ± 447	3,293 ± 548	3,830 ± 357	3,124 ± 200	3,622 ± 482	3,747 ± 412	3,703 ± 447	3,293 ± 548	3,830 ± 357	3,124 ± 200
	After recovery	-	-	-	3,244 ± 206	3,873 ± 220	3,928 ± 335	-	-	-	3,244 ± 206	3,873 ± 220	3,928 ± 335

Table 3. (continued).

ID	Diagnosis	0.5 m			3.0 m		
		Background (N = 30) GM(GSD)	During cough (N = 30) GM(GSD)	After cough (N = 30) GM(GSD)	Background (N = 30) GM(GSD)	During cough (N = 30) GM(GSD)	After cough (N = 30) GM(GSD)
1	While ill	1,142(1.26)	1,362(1.54)	1,343(1.07)	1,096(1.05)	1,491(1.13)	1,196(1.09)
	After recovery	2,611(1.08)	2,600(1.07)	2,886(1.06)	2,431(1.07)	2,277(1.06)	2,592(1.06)
2	While ill	2,015(1.06)	2,156(1.05)	2,098(1.05)	1,728(1.06)	1,795(1.06)	1,751(1.04)
	After recovery	4,041(1.04)	3,917(1.04)	3,705(1.05)	3,271(1.05)	3,499(1.04)	3,291(1.09)
3	While ill	-	-	-	1,150(1.09)	1,454(1.10)	1,144(1.07)
	After recovery	881(1.10)	940(1.10)	1,034(1.08)	687(1.09)	751(1.11)	786(1.09)
4	While ill	-	-	-	1,280(1.06)	1,484(1.08)	1,185(1.18)
	After recovery	3,721(1.08)	3,994(1.06)	3,910(1.05)	3,485(1.07)	3,748(1.07)	3,600(1.05)
5	While ill	-	-	-	2,269(1.09)	2,928(1.22)	2,254(1.08)
	After recovery	1,625(1.06)	1,997(1.13)	1,744(1.10)	1,268(1.06)	1,451(1.07)	1,338(1.06)
6	While ill	-	-	-	3,326(1.04)	3,948(1.06)	3,154(1.07)
	After recovery	2,133(1.06)	2,396(1.07)	2,630(1.11)	2,030(1.05)	2,097(1.07)	2,310(1.06)
7	While ill	2,309(1.07)	2,138(1.06)	1,964(1.07)	1,608(1.06)	1,875(1.08)	2,058(1.06)
	After recovery	2,781(1.06)	2,812(1.05)	2,538(1.06)	2,542(1.07)	2,657(1.06)	2,346(1.06)
8	While ill	2,751(1.04)	2,757(1.06)	2,723(1.08)	2,513(1.04)	2,226(1.07)	2,423(1.07)
	After recovery	3,968(1.08)	3,995(1.08)	3,649(1.06)	3,536(1.08)	3,419(1.09)	3,139(1.09)
9	While ill	-	-	-	3,238(1.07)	3,867(1.06)	3,912(1.09)
	After recovery	3,875(1.05)	3,992(1.05)	3,975(1.04)	3,416(1.05)	3,531(1.05)	3,380(1.04)
10	While ill	2,883(1.08)	3,330(1.09)	2,556(1.05)	3,486(1.07)	3,783(1.10)	3,118(1.06)
	After recovery	3,589(1.15)	3,724(1.12)	3,675(1.14)	3,249(1.18)	3,817(1.09)	3,368(1.14)

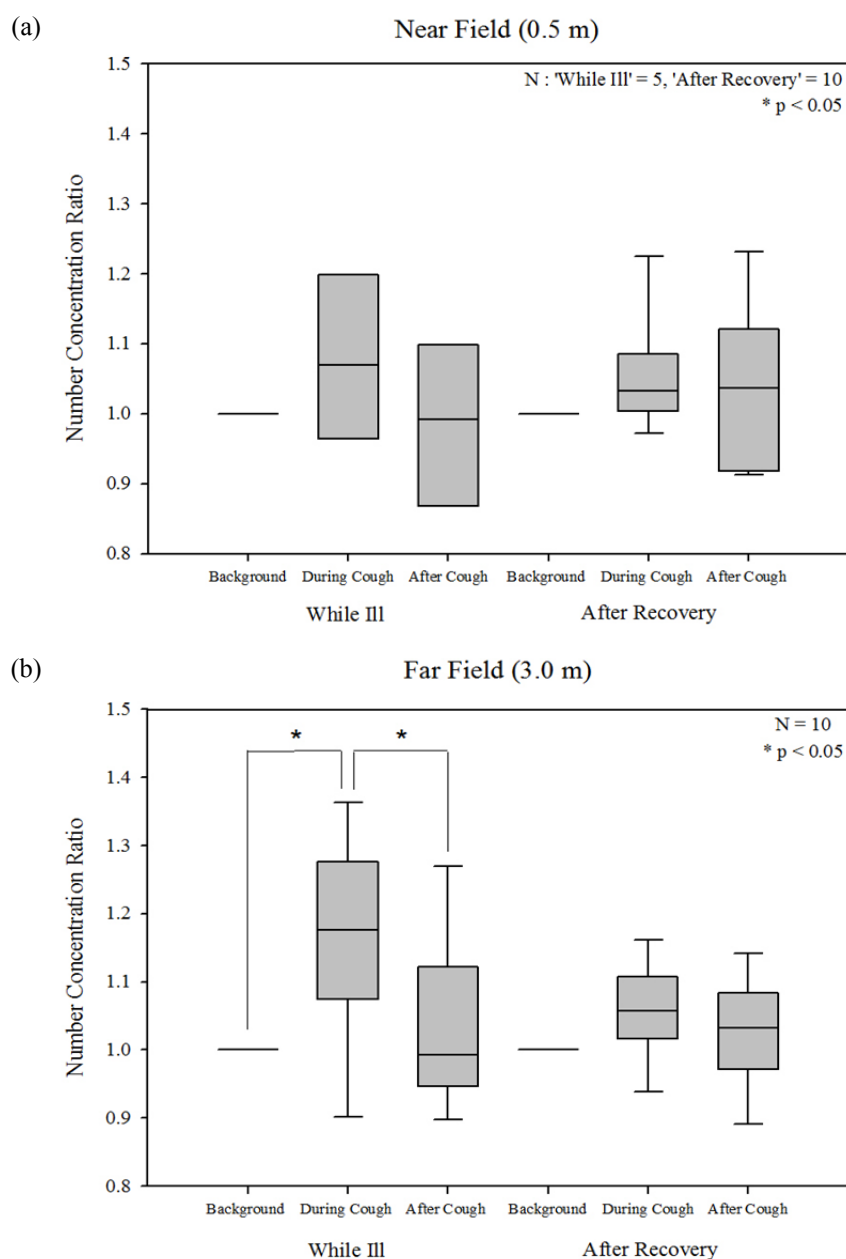


Fig. 3. Particle number concentration ratio in the (a) near field and (b) far field. The mean number concentration of each phase was normalized by dividing by the mean number concentration of the background. Values shown are medians (line within box), 25th and 75th percentiles (bottom and top of box, respectively), and 10th and 90th percentiles (lower and upper bars on whiskers, respectively).

Because of its ability to reach the alveoli, the respirable fraction of cough-generated aerosols is of great concern. Compared with particles deposited in the nasal region, a considerably lower dose of infectious particles deposited in the lungs can lead to infection (Tellier, 2006). Approximately 99.9% of the total number of particles expelled by the subjects in this study were < 5 μm in diameter (airborne-transmitted particles), accounting for 90.2% of the total surface area. As seen in Figs. 4(a)–4(b), most aerosols were < 5 μm , which meant they could enter and deposit in the alveolar region rather than the upper respiratory tract and bronchioles. Most cough-generated aerosols are in the

respirable particle size range and can enter the alveolar region. We also found that the mean number of particles per cough and mean surface area of particles per cough were higher within certain size ranges (< 100 nm, 100–300 nm, 420–1,000 nm, 1.0–2.5 μm), but the reason for a lack of statistical difference for particles in the other size ranges (300–420 nm and > 2.5 μm) was unclear. This may be due to the physical or chemical properties of particles with specific diameters or simply due to the lack of a sufficient sample size. We found no previous studies that reported the same result, and therefore this observation requires further study.

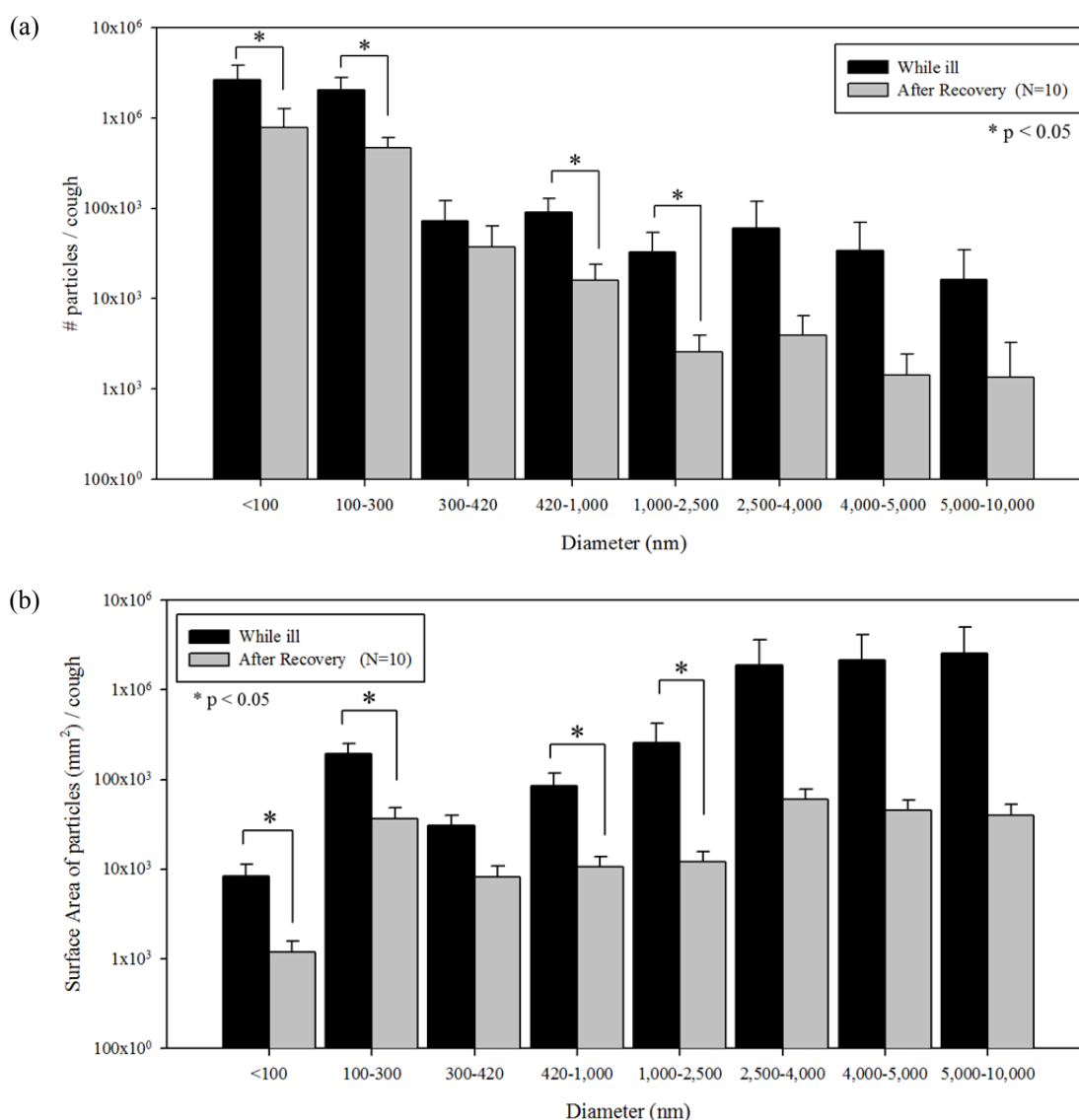


Fig. 4. (a) Number and (b) surface area of particles per cough in each size range. Results from the chamber experiment.

There were some differences between the results of this study and those of previous studies. Yang *et al.* (2007) found that small droplet nuclei had a size distribution of 0.58–5.42 μm and 82% of droplet nuclei were centered in the range of 0.74–2.12 μm . This contrasted with the results of our study, in which a modal diameter of < 100 nm was obtained. Yang *et al.* (2007) used a novel process to transfer a respiratory-originating warm and water vapor-saturated cough aerosol to a dry bag at room temperature. This would have involved a disturbance to the original equilibrium size of the aerosol due to saturation on the walls of the bag. Therefore, the size distribution would have been larger than that of the aerosol in the respiratory tract. According to Johnson and Morawska (2009), particles of 8–10 μm are the most common size in a droplet distribution. The size of droplets in their study varied from 0.1 to 16 μm and the number concentration varied from 0.001 to 5.5#/cc. These differences were attributed to differences among monitoring devices. The lower diameter limit of the SMPS (10 nm) is

much smaller than the device (Aerodynamic Particle Sizer [APS]; TSI Inc.) used by Johnson and Morawska (2009), which has a lower diameter limit of 0.5 μm . We recorded the proportion of nanosized particles, which made a large difference to the aerosol number concentration. The size of pathogens may be informative regarding the size of particles that carry them. For example, larger pathogens, such as bacteria (1–2 μm), are found in larger particles (Wainwright *et al.*, 2009), whereas smaller pathogens, such as viruses (20–30 nm), are found in smaller particles (Fabian *et al.*, 2008; Hersen *et al.*, 2008). Hence, measuring aerosols with instruments capable of detecting a wide range of particle sizes is likely to be the most effective way to identify the particles that can induce viral infection.

From the results of the exposure chamber experiments, when subjects had a cold, the number of aerosol particles generated from a single cough had no statistically significant correlation with FVC (0.93), FEV1 (0.90), PEF (0.65), or volume of cough (0.28). However, after subjects recovered,

the number of aerosol particles generated from a single cough had a statistically significant correlation with FVC (0.04, $r = 0.65$), FEV1 (0.03, $r = 0.68$), PEF (0.01, $r = 0.78$), and volume of cough (0.02, $r = 0.72$). This raised the question of whether infection affects the emission characteristics of cough aerosols. From the results of the clean room experiments obtained with cold patients, we found that there was a correlation between the ratio of the aerosol number concentration during coughing and the background concentration, and the number of coughs (0.04, $r = 0.65$). However, other factors had no correlation with the aerosol emissions of cold patients. Our correlation analysis results were similar to those of Zayas *et al.* (2010). They reported that the concentration of droplets was not related to age, sex, weight, height, or body mass index in 45 subjects. However, Yang *et al.* (2007) found a significant difference in concentration depending on sex in 3 age groups. Their 30–50-year-old age group produced the highest aerosol concentration, and there was also a higher airborne droplet concentration in males than in females. Johnson *et al.* (2009) reported a significant correlation between the droplet concentration and age in 15 individuals, and the concentration differed markedly by particle size. In our study, the participants were all young and healthy adults; thus, our results may not be representative of the entire population. Furthermore, the total number of subjects was small, and aerosol production varied significantly from person to person. This study suggests that within the same age groups, the particle number concentration can vary significantly. According to several studies, relative humidity may also play a role in affecting particle trajectory. Yang and Marr (2011) showed that the total concentration of influenza A virus contained in aerosol particles decreased with increasing relative humidity across all particle sizes. Generally, evaporation can control droplet size, with fine droplets evaporating faster than large droplets. A high relative humidity slows the evaporation process. Yang and Marr (2011) showed that the total concentration of influenza A virus contained in aerosol particles decreased with increasing relative humidity across all particle sizes.

There were some limitations of this study. First, the number of participants was small and the study could therefore not reflect all age groups. Second, all subjects were infected with a cold at the time of the initial test, but their illnesses were in different stages. Some subjects were more ill than others, although all participants were diagnosed at a hospital. These factors may account for the wide variation in aerosols per cough within the same age group and gender.

Third, we attempted to determine the difference in aerosol concentration between the near and far field distances, but it was negligible. This was because the background concentration fluctuated, and the number of subjects was not large. We therefore normalized the concentration data, but further observations of changes in the cough aerosol size distribution with distance should be made with more patients under more stable background concentration conditions. Fourth, relatively large particles, i.e., $> 10 \mu\text{m}$, were likely deposited by impaction on the walls of the

exposure chamber and then sedimented in the clean room, resulting in an underestimation compared to smaller particles. In the exposure chamber experiment, the distance from a participant's mouth to the measuring instrument was less than 60 cm and the cough particles were propagated as a conical plume, which might have reduced the potential for impaction on the walls of the chamber, although some large particles would inevitably be deposited. In the clean room experiment, large droplets might have sedimented out over a short distance. However, the purpose of the study was to determine the potential for cough-generated aerosol transmission to the far field as well as the near field. The transmission of cough-generated aerosol over a long distance ($> 3 \text{ m}$) in this study suggests that the assumption that most cough-generated aerosol consists of large droplets that are deposited in the near field ($< 2 \text{ m}$) is wrong.

Although these limitations could lead to an underestimation of particle size in the study, we detected airborne particles that were small enough for transmission and a temporary increase in the particle number concentration in the far field by airborne transmission. We found no difference in size distribution between the direct contact range (0.5 m) and the airborne transmission range (3.0 m), which may have been due to a lack of monitoring according to distance. We only used the OPS for the far field measurement, whereas in the near field the upper limit of the SMPS (420 nm) was too small to detect changes in the size distribution of large particles, such as droplets or larger droplet nuclei. However, as shown in Fig. 4(a), most of the aerosol particles expelled from coughing were in the droplet nuclei size range. Thus, this result may not differ from the results obtained with the simultaneous use of monitoring devices with wide particle size detection ranges.

CONCLUSIONS

Individuals infected with a cold release potentially infectious aerosols when they cough, sneeze, and speak. Coughing is the most effective and frequent method of transmitting these agents. The results of this study show that most particles generated by coughing are small enough to be suspended in the air. Furthermore, patients with a cold can release airborne transmission-available particles, with transmission detected at a distance of 3 m. These results suggest that the airborne spread of pathogens may be possible even at a distance $> 3 \text{ m}$ from a patient with a respiratory disease. Hence, in order to prevent the spread of disease, more attention must be given to airborne infections.

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