Airway Hygiene in Children and Adults for Lowering Respiratory Droplet Exposure in Clean and Dirty Air

Carolin Elizabeth George\textsuperscript{1}, Jonathan Salzman\textsuperscript{2}, Leebker Raja Inbaraj\textsuperscript{1}, Sindhulina Chandrasingh\textsuperscript{1}, Chris Klein\textsuperscript{2}, Lidia Morawska\textsuperscript{3} and David Edwards\textsuperscript{2,4,*}

Respiratory illness threatens the learning potential of hundreds of millions of children around the world. We find in a human volunteer study involving three sites and 253 volunteers that respiratory droplets — of the size and nature to potentially contain COVID-19, influenza, allergens and other contaminants — diminish in number on exhalation by up to 99% via the “airway hygiene” administration of a nasal saline rich in calcium. Exhaled particles were significantly higher and efficacy of airway hygiene greatest at the site (Bangalore India) with highest fine particle ambient air burden. We argue for the use of airway hygiene for pandemic and post-pandemic global learning.

Keywords: Aerosols; Hygiene; Exhaled Breath; COVID-19; Pollution; Airborne Infection; Nasal Saline; Calcium.

INTRODUCTION

Foreign particles ranging from soot to airborne pathogens enter the human upper airways daily. Many of these land on airway lining mucus and are eventually cleared from the lungs to the mouth, where they are either eventually swallowed\textsuperscript{1} or re-aerosolized as respiratory droplets\textsuperscript{2}, risking to leave the respiratory tract on exhalation or travel deeper into the lungs on inhalation\textsuperscript{2}. This airborne movement can worsen infection (on inhalation) or spread infection (on exhalation)\textsuperscript{4,5}, and is recognized to play a particularly significant role in the promotion of severe symptoms and the spread of COVID-19\textsuperscript{5}.

Respiratory droplets are predominantly submicron in size\textsuperscript{6,7}, and largely escape gravity sedimentation\textsuperscript{8}, consequently they tend to travel long distances and can accumulate in poorly circulated indoor settings.

Global awareness of the potential danger of these small droplets has grown since the start of the COVID-19 pandemic, exposing the challenge that uncontrolled respiratory droplet movement poses to childhood health and learning\textsuperscript{8}. Nearly half of the 1.6 billion school age children around the world live in low- and middle-income countries, often without good access to traditional hygiene measures, unlikely to soon benefit from the availability of effective vaccines, and frequently

\textsuperscript{1}Bangalore Baptist Hospital, Hebbel, Bangalore, India. \textsuperscript{2}Sensory Cloud Inc, 50 Milk St, Boston MA, USA. \textsuperscript{3}Queensland University of Technology, 2 George Street, Brisbane, QLD 4001 Australia. \textsuperscript{4}Harvard John A. Paulson School of Engineering & Applied Sciences, Harvard University, Cambridge MA, USA. *Correspondence should be addressed to: D.E. (dedwards@seas.harvard.edu). Published online 29 December 2020; doi:10.1142/S2529732520400076

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breathing polluted air. The consequences to long-term respiratory health are dramatic, ranging from rising rates of asthma\textsuperscript{10} to alarming rates of deaths from influenza\textsuperscript{11}, and now to COVID-19\textsuperscript{12}. Helping lower respiratory droplet exposure for children and teachers should be a priority even after the COVID-19 pandemic.

We each breathe into our airways between around 100 million to 10 billion particles per day\textsuperscript{13}. A majority of these particles are smaller than a single micrometer\textsuperscript{6}. During natural breathing they enter our noses and mouths, and deposit along the respiratory tract and in the gas-exchange ("lower") region of the lungs where alveolar sacs exchange molecular matter rapidly and effectively with the bloodstream. Probability and location of deposition depends on particle size\textsuperscript{13}. Particles smaller than 5 \(\mu\)m easily enter the lungs, and if less than 1 \(\mu\)m may remain airborne in the lungs for multiple breaths before depositing or being exhaled\textsuperscript{14}.

Most inhaled particles deposit in the upper (non-gas-exchanging) regions of the lungs, where a mucus layer captures the particles, and cilia beneath the mucus sweep the mucus and trapped particles toward the mouth where they can be swallowed\textsuperscript{15}. Depositing on mucus surfaces, particles can remain there by "wetting" phenomena\textsuperscript{15}. Bound to air/liquid surfaces, small particles alter surface tension\textsuperscript{16} and surface viscoelasticity\textsuperscript{17}. These changes alter the stability of surfaces and can render them more prone to droplet breakup following air flow\textsuperscript{18,19}. For these reasons prolonged human exposure to large numbers of micron and submicron foreign particles might be expected to promote generation of respiratory droplets in the airways, increase exhaled aerosol and threaten to worsen the tendency for lung infection and the spread of infectious disease — possibly underlying the observed increased rates of death from COVID-19 for those who live in polluted air\textsuperscript{20}.

We recently observed that the delivery of a nasal saline comprised of a mist of 10 \(\mu\)m droplets containing a mixture of calcium and sodium chloride salts can reduce the exhalation of respiratory droplets by up to 99% for up to 6 hours post administration\textsuperscript{21,22}. The salts (a hypertonic mixture called FEND) associate with mucin macromolecules near the mucus surface, binding mucus molecules together, thereby increasing mucus surface tension and surface viscoelasticity\textsuperscript{23}. These effects help mucus surfaces withstand the stresses that occur on air passing over mucus during normal breathing\textsuperscript{24}, resulting in fewer respiratory droplets in the airways, and fewer exhaled aerosol particles — a form of "airway hygiene."

Airway hygiene follows a millennia-long tradition of nasal saline administration for cleaning mucous surfaces of foreign particulate matter\textsuperscript{24}. Salts ranging from pure sodium chloride (table salt) at physiological tonicity (0.9% by weight) to more complex mixtures of salts including calcium chloride, magnesium chloride and others, have long been commonly administered as gavages and nasal sprays\textsuperscript{25}. Hypertonic salt compositions can particularly increase cilia beat, facilitating the clearance of mucus and associated particulate matter toward the mouth\textsuperscript{25}.

We sought to explore the effects of airway hygiene in educational settings in the USA (Grand Rapids Michigan and Cape Cod Massachusetts) and in comparison with a setting (Bangalore India) of relatively high airborne particulate burden. We wished to determine whether the needs of airway hygiene might differ in polluted versus less polluted settings with particular attention to elementary, secondary and college learning environments. We examined two kinds of nasal saline administration — FEND and Simply Saline Nasal Spray. We report on our findings here.

**METHODS**

We conducted human volunteer studies at Bangalore Baptist Hospital (BBH), Grand Rapids Community College (GRCC), and Cape Cod Academy (CCA). We received IRB approval for these (non-drug cosmetic) studies from the BBH Ethics Committee, the GRCC Ethics Committee, and for the CCA study a waiver of the need for IRB approval from E & I Review, an independent accredited ethics review board. We recruited 40 human volunteers in Bangalore, ages 26 to 63; 120 human volunteers in Grand Rapids, ages 11 to 68; and 93 human volunteers on Cape Cod, ages 10 to 70. Overall we recruited 253 females, 104 males, and 23 undeclared. Of the 253 human subjects, 164 were Caucasian, 10 were African American, 13 were Asian, 12 were Hispanic, and 54 were undeclared. Participants were not screened for SARS CoV-2 infection by serology or polymerase chain reaction (PCR) before enrollment. All participants in all studies provided written informed consent prior to enrollment. Figure 1a illustrates the general design of the protocol for the three study sites (specifically the GRCC study site).

Exhaled particles were measured, before and after nasal saline administration, by a particle detector (Climet 450-t) designed to count airborne particles in the size range of 0.3 to 5 micrometers. The particle detector air port was attached over a period of about one minute of breathing with subjects lips tightly sealed around the mouthpiece and pinching their noses. The rate of flow of the particle counter (50 L/min) was near...
The typical peak inspiratory/expiratory rate of flow of human subject breathing such that the direction of air flow remained into the particle counter. Each standard nebulizer tubing and mouthpiece were removed from sealed packaging before each subject prior to the subject’s first exhaled particle detection. On subsequent counting maneuvers the same mouthpiece, tubing and HEPA filter were reattached by the participant to insure the absence of contamination from one subject to the next. Before each test the mouthpiece was replaced by a stopper and the particle detector was turned on to verify the absence of leakage of particles from the environment. Background of less than 10 particles per liter of air was deemed “well sealed.” With the mouthpiece placed back onto the tubing, subjects performed normal tidal breathing through the mouthpiece while plugging their noses with their fingers over 1 to 2 minutes — beginning with two deep breaths to empty their lungs of environmental particles. Over this time frame particle counts per liter of air pulled from the exhaled breath into the particle counter diminished and subsequently fluctuated around a baseline number. Given the assurance of no leakage from the outside environment, the tight lip seal and the pinched nose, we assumed this baseline number to equate to the particles generated within the

Figure 1. Protocol for measuring exhaled aerosol, dosing, and reassessing exhaled aerosol. (a) Particular protocol used at Grand Rapids Community College — protocols in Bangalore and Cape Cod Academy were of similar nature and scope. (b) The particle counting system with air exchange between the human subject and the outside air via the HEPA filter and sampling of the exhaled air via the particle counter.
subject's airways. Once the lower plateau of particle counts was reached subjects continued to breathe normally for the determination of exhaled aerosol particle number. Participants sat opposite to the study administrator with a plexiglass barrier in between.

We used two nasal salines in our studies. FEND is a drug-free nasal saline hygiene formulation comprised of calcium chloride and sodium chloride in distilled water. Overall salt composition (4 X isotonic composition) is in the range of sea water, specifically with 0.43M CaCl₂, 0.05M NaCl (4.72% CaCl₂, 0.31% NaCl). FEND compositions were manufactured at Pharmasol (MA) in a GMP mixing and filling facility and contained in sealed plastic bottles (0.5 ounces). FEND bottles were opened and emptied into glass vials of the FEND Mister device. The hand-held, vibrating-mesh nebulizer is produced at Perfect Electronics in Shenzhen, China, with a 6 µm pore size to produce, on tipping of the device, an aerosol cloud with a particle size distribution optimal for delivery to the nose through natural nasal inspiration. Generating a median volume particle diameter of 9–10 µm, optimal for nasal and upper airway deposition of aerosol following a deep natural tidal inspiration through the nose and with relatively uniform distribution of deposition from the anterior to the posterior of the nose, Nimbus produces on tipping 57 mg +/- 2 mg within a 10 second actuation, after which power ceases until tipped back upright and again overturned. The device delivers a dose of approximately 33 mg (1.56 mg CaCl₂) by filling an empty 6 oz glass with the cloud for the internally programmed 10 s actuation of the device and then inspiring the cloud directly from the glass into the nose. Dosing can also be achieved by creating the cloud before the nose with deep nasal inspiration.

Simply Saline by Arm & Hammer, a nasal spray of isotonic sodium chloride available on the market, was bought and used (one spray per nostril) as a control.

Data analysis
The Climit 450-t particle counter reports particle counts as a function of aerodynamic particle size ranges for particles larger than 0.3 µm, particles larger than 0.5 µm, particles larger than 1 µm, and all particles larger than 5 µm. The numbers reported represent average values of particle counts automatically measured by the light-scattering detector over six seconds. For our determination of exhaled aerosol particle number we averaged three to eight average particle counts (each integrating a six second interval) as reported by the particle detector to determine the mean exhaled particle count and the standard deviation. All error bars shown in our figures represent standard deviation values. Significance of differences in individual and collective aerosol numbers were determined by twin-tailed T Test.

RESULTS
Total exhaled aerosol versus ambient inhaled particle mass exposure
We assessed exhaled aerosol particle numbers and sizes at the three sites of our study, including 40 human subject volunteers in Bangalore (Fig. 2a), 120 human volunteers in Grand Rapids (Fig. 2b), and 93 human volunteers on Cape Cod (Fig. 2c). At each site a small group of subjects exhaled around 80% of the sum of all average exhaled aerosol counts of the group, adhering to the classical 20:80 rule of “super spreading” of infectious disease.

In our study we refer to as “Super Emitters” (of aerosol particles) those individuals who exhale 80% of baseline aerosol particles summed up from the exhaled breath of all of the members of the group (while being less than 20% of all subjects). We find classic super spreader distributions at our US sites: in Grand Rapids 24 (20%) of the 120 subjects produce 79.5% of the exhaled aerosol of the group, while at the Cape Cod site 19 (20%) of the 93 subjects produce 79.7% of the exhaled aerosol of the group. However, only 10% (4 of the 40) subjects in India produce 82.6% of the exhaled aerosol of the group, while 20% of all subjects (8 subjects) produce 95.1% of all exhaled aerosol.

We hypothesize skewing of the importance of high emitters in India reflects the fact that exhaled aerosol numbers are dramatically higher at the Indian relative to the US sites. The top 20% aerosol emitting individuals in Bangalore had mean exhaled aerosol particle numbers of 3.06 x 10⁴ +/- 1.14 x 10⁴ particles per liter of air. Mean exhaled aerosol number concentration (particles per liter) were statistically lower (p < 0.0002) at the US sites, notably 532 +/- 668 in Grand Rapids and 818 +/- 722 on Cape Cod. These differences mirror the differences in burden of airborne particulate matter between the Indian and US sites. Reported particulate mass (PM₁₀) smaller than 10 µm over this same time frame in India (Bangalore) was 150 µg/m³ while for the USA sites it was an order of magnitude lower (17 µg/m³ in Grand Rapids and 7 µg/m³ on Cape Cod).

We compared baseline exhaled aerosols for Caucasian (n = 164), Black (n = 10), Hispanic (n = 16) and Asian (n = 13) among our two US sites. Mean exhaled aerosol particle numbers per liter for all subjects were statistically the same for Caucasian (177 +/- 422), African American (95 +/- 133), Asian (60 +/- 95), and Hispanic (76 +/- 182) subjects. We did observe significant differences between exhaled aerosol as a function of BMI years (BMI multiplied by age), as described in a companion article, while differences in mean BMI years between the three study sites of this study were insignificant.
Figure 2. Effect of FEND on exhaled breath particles at: (a) Bangalore Baptist Hospital, (b) Grand Rapids Community College, and (c) Cape Cod Academy.
**Exhaled aerosol versus time post airway hygiene administration**

We evaluated the effect of airway hygiene on exhaled aerosol in Bangalore as a function of time post administration and in comparison to the saline nasal spray control.

In the case of those subjects who received FEND \((n = 20)\), post administration, exhaled aerosol numbers fell within 15 minutes and remained suppressed for at least three to four hours (Fig. 3a). In the case of those subjects who received the saline nasal spray control \((n = 20)\), post administration...

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**Figure 3.** Total exhaled breath particles at Bangalore Baptist Hospital: (a) versus time prior to and post administration of FEND; (b) versus time prior to and post administration of saline nasal spray control; (c) before and 2 hours post administration of FEND; and (d) before and 2 hours post administration of saline nasal spray control.
Exhaled aerosol numbers fell to a lesser degree, and were mixed over the several hours post administration (Fig. 3b).

Figures 3c and 3d present the suppression effect following FEND versus the nasal saline control on overall exhaled aerosol (the summation of the baseline exhaled aerosols) of all 40 subjects at two hours post dosing. The large difference in overall exhaled aerosol relative to baseline (86%) was highly significant (p < 0.011) for the FEND airway hygiene (n = 20), while the diminution in overall exhaled aerosol (34%) was insignificant (p < 0.62) for the Simply Saline control (n = 20).

Exhaled aerosol suppression by airway hygiene administration

We evaluated the effectiveness of nasal saline airway hygiene in Bangalore, Grand Rapids and Cape Cod by evaluating exhaled aerosol from all subjects before and 15 to 30 minutes post administration of FEND or Simply Saline. The results for the 20% highest emitting aerosol subjects are shown in Figs. 4a to 4c.

FEND administration reduces exhaled aerosol most significantly in the airways of those exhaling the greatest...
numbers of aerosol particles at each site, with the most significant % reductions appearing in the dirtiest air environment, notably Bangalore, where exhaled aerosol is most significantly elevated. The less significant individual subject FEND suppression relative to baseline seen in Fig. 4a relative to Fig. 3c relates to the continued decline in exhaled aerosol with time post FEND administration (Fig. 3a).

Figures 5a to 5c present the overall degree of suppression of exhaled aerosol at each site for both FEND and Simply Saline at 15 to 20 minutes post administration. Overall airway cleansing by the Simply Saline control is insignificant in every case (BBH p < 0.94, GRCC p < 0.83, CCA p < 0.65), while the overall FEND airway cleansing effect is marginally significant at each site of the study (BBH p < 0.169, GRCC p < 0.124, CCA p < 0.098), the marginality of the overall effect reflecting the large dispersion in exhaled aerosol numbers between Low Emitters and Super Emitters (Figs. 4a to 4c).

DISCUSSION

Airway hygiene is a simple hygienic intervention that reduces respiratory droplet formation as assessed by the numbers of particles exhaled from the airways. Previous in vitro studies 23

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**Figure 4.** Total exhaled breath particles prior to and 15 to 20 minutes after administration of FEND at: (a) Bangalore Baptist Hospital, (b) Grand Rapids Community College, and (c) Cape Cod Academy.
with mucus and mucus-mimetic layers have shown that administration of calcium and sodium salts increases surface viscoelasticity, most significantly via calcium-mucin interactions.\(^\text{19}\), suppresses droplet breakup, cleaning the upper airways of respiratory droplets. Our study indicates that the effectiveness of the intervention for removing respiratory droplets depends on

Figure 4. (Continued)

Figure 5. Total exhaled breath particles prior to and 15 to 20 minutes after administration of saline nasal spray control at: (a) Bangalore Baptist Hospital; (b) Grand Rapids Community College, and (c) Cape Cod Academy.
the success of application, and is generally significant within 15 minutes of administration (Fig. 5) and is remarkably consistent across all the sites of our study and all subjects. It is especially effective for those breathing dirty air (Figs. 3a and 3c) — up to 99% (Fig. 2c) for several hours (Fig. 2a).

By comparison the nasal saline spray control has little to modest effect — we observed no overall effect in the short-term (15–30 minutes) time frame of Figs. 5a to 5c while an indication of effect with certain subjects (1140, 1149, 1166) in Fig. 3b over time. Such an effect may reflect the modest effectiveness of isotonic saline as reported in our earlier work along with a post-nasal drip drainage of the saline solution from the nose to the trachea in those subjects where the effect is observed.

In our research, we have found that children and young adults (under the age of 26) exhale very few particles. In the 120 children and young adults assessed in this and a recent publication, we have observed that only 6 of these young

Figure 5. (Continued)
people exhale more than 150 particles per liter, while 89% of the young subjects exhaled between 1 and 50 particles per liter of air. Of these six individuals all of these exceptions exhaled aerosols exceeding 1000 particles per liter. In three of these cases, all human volunteers from our Bangalore study, the young subjects breathed into their airways highly polluted air. In two of the cases, Grand Rapids siblings (16 and 19 years of age), the children were suspected to have been asymptomatic carriers of COVID-19 (a lung condition shown elsewhere to promote very high exhaled aerosol numbers), while in one case, a 17 year-old male on Cape Cod, there was no obvious airway particle burden causality. It appears that while young people as a rule are “low emitters” i.e. exhale very few respiratory droplets, they can become high emitters of respiratory aerosols, and especially should their airways be overriden by foreign particles, whether inbound particulate matter, or — as in the case of infection — proliferating virus.

Indeed, notwithstanding the tendency for young airways to generate few respiratory droplets, given the numbers of young people exposed to airborne contaminants, ranging from airborne pathogens to air pollution, among those most vulnerable to excessive respiratory droplet formation today may be children. Based on surveys of 70 countries around the world, UNICEF estimated prior to the COVID-19 pandemic 45% of school-age children were at severe risk of at least one of the dimensions of multidimensional poverty — without access to education, health care, housing, nutrition, sanitation or water. Presently, as a consequence of the pandemic, UNICEF estimates that an additional 150 million children are living in multidimensional poverty, and many with lack of basic hygiene and healthcare and in settings of poor air quality. Airway hygiene seems especially needful for these children and those who serve them in schools around the world. Cleaning airways, beyond its benefits with respect to the COVID challenge, might be of benefit for other respiratory illnesses, such as asthma or influenza. Asthma rates in children have risen over the last decades. Today asthma is the most prevalent chronic illness in children, and has particularly worsened in metropolitan and industrialized areas with poor air quality. Influenza also hits children particularly hard in lower and middle income countries lacking access to the seasonal flu vaccine.

The human subjects in Bangalore exhaled many more particles than the subjects at the US sites (Figs. 2a to 2c). While we observed no statistical differences between the exhaled aerosols of the different racial and ethnic groups evaluated here and in a previous study, we have not ruled out the possibility that there might be a uniqueness to the Indian population that promotes higher exhaled aerosol. Bearing this in mind, our preliminary assessment is that prolonged inhalation of high levels of particulate matter may promote the generation of large numbers of respiratory droplets, and skew these droplets to submicron size. Inhaled particles, by landing on mucus surfaces, may lower surface tension and surface viscoelasticity, rendering airway lining mucus more prone to breakup into droplets of smaller size. We have elsewhere observed these same trends in exhaled aerosol following viral (COVID-19) and bacterial (tuberculosis) infection in nonhuman primates. Exhaled aerosol increases, and exhaled aerosol particle size decreases, in tandem with proliferation of viral and bacterial burden in lung tissues.

Whether or not, in the development of respiratory diseases such as COVID-19 and tuberculosis, the accumulation of viral and bacterial particles at or near mucus surfaces has a similar surface property alteration effect as the accumulation of fine particles breathed in from the atmosphere — the findings of the present study at least point to the possibility that relatively high production of respiratory droplets caused by polluted air might be a factor in the spread of airborne infectious disease in dirty air settings, and be a contributor to trends that have been observed for heightened risk of COVID-19 death in polluted settings.

While a combination of environmental and biological factors clearly increase the risk that people will exhale large numbers of respiratory droplets, and therefore be of higher susceptibility to respiratory infections and the communication of airborne infectious disease, including COVID-19, the results of our study suggest that the administration of airway hygiene by nasal administration of calcium-rich saline aerosols that target the nose, trachea and main bronchi can be a simple approach to lower this risk and counterbalance these same environmental and biological factors. We believe such a new form of hygiene is especially needed today in learning environments around the world.

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CONFLICT OF INTEREST

DE is the founder, CSO and CEO of Sensory Cloud; CK and JS are employees of Sensory Cloud, the manufacturer of FEND. CEG, LM, LI and SC have no conflicts.
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