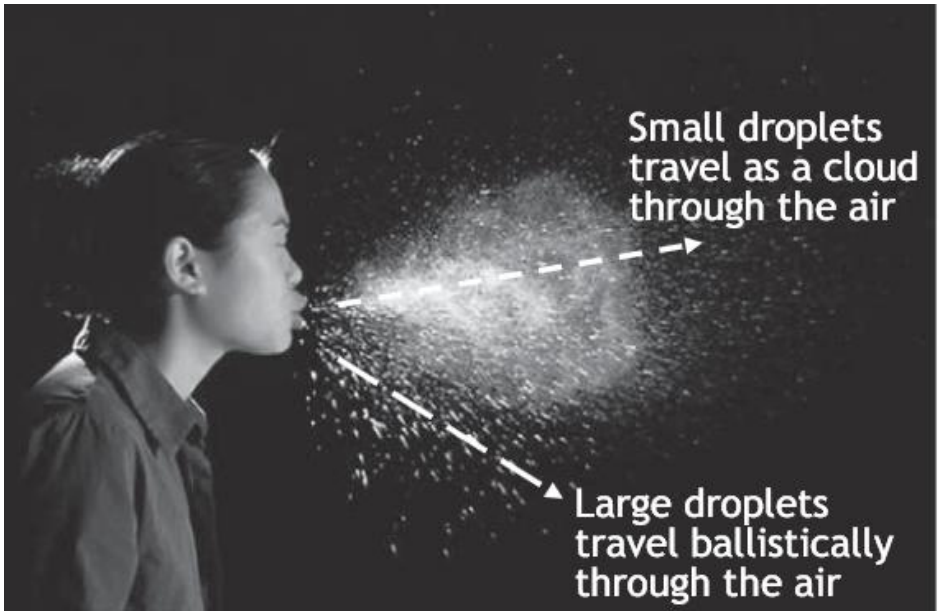
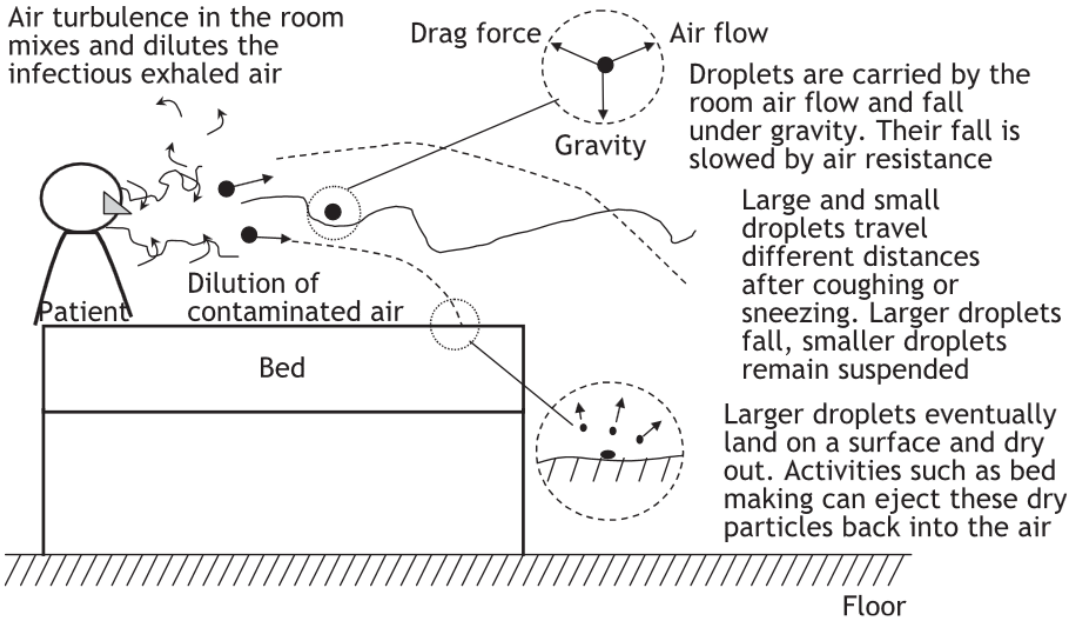
Is there aerosol spread SARS-CoV-2?

Talking, laughing, sneezing, and even just breathing put respiratory particles into the air. Most of these are large particles. Fortunately most of these, especially the large particles fall out of the fairly quickly. Also tiny water aerosols evaporate quickly; those smaller than 5 μm evaporate in less than a second even under fairly high humidity.



It may be easiest to understand respiratory transmission of infections as being a dichotomy of either large droplets that have a short range of direct person to person spread, generally under a meter, and small droplet transmission that allows long-range spread, which can spread a disease considerably further and which can remain if the air for a much longer period of time.



In the graphics above,[1] it can be seed that the large droplets are subject to gravity and fall quickly fall out of the air, while the small droplets can be carried in the air for hours. These tiny droplets have a half life of just over an hour in indoor air, so it takes about 8 hours to decrease the number of droplets to less than one percent, and about 10 hours to get the number down to 0.1 percent. One definition of an aerosol is a liquid or particle less than 1 μm that stays suspended in the air, however larger particle are also considered aerosols by some definitions. Smoke and fog are examples of solid and liquid aerosols. Grass pollen which is a common airborne allergen commonly is around 20 – 25 μm.

Medium sized droplets that are small enough to stay aloft for even a short period may evaporate sufficiently to become small enough to stay aloft as aerosols. Respiratory particles contain salts and proteins that may prevent evaporation, and thus do not dry completely, and help maintain viral viability, and these particles can stay in the air a considerable length of time.

As of today, the CDC has not made a conclusion to whether the SARS-CoV-2 virus can be spread by aerosols. This is an important issue, as it should be taken into consideration when considering interventions for disease prevention. For example the recommendation the people should stand 6 feet apart is based on avoiding large droplet contamination from people who spray it when they say it or shower you when the cough. The large respiratory droplets fall out of the air onto surfaces, and the virus on those surfaces remains infectious for days – even weeks if the temperature is cool enough. At room temperature the virus can survive on surfaces for several days. We now know that fine respiratory aerosols with SARS-COV-2 are infectious. Thus it is important to wash hands as the virus can be picked up by touching items that have had respiratory droplets from an infected individual precipitate on them, or have been touched by someone with the disease that had contaminated their own hands.

That leaves the question of contamination by way of aerosols. They are tiny and can stay aloft a much longer period of time. They can travel greater distances. Opening or closing a door walking through a room can stir them up and get them re-dispersed in the air.

Different activity causes particle sizes of different distributions. Breathing creates particles less than 2 μm, but expels them at low force, and likely in low numbers. Speaking creates mostly much larger particles. Shouting and playing the vuvuzela creates particles with mean diameter of 1.0 μm and 1.3 μm, respectively. Sneezing causes mostly large particles over 7 μm and coughing creates mostly large but also small particles. Thus, coughing and sneezing creates larger particles that stay in the air a shorter period of time, and that are more likely to contaminate surfaces. COVID-19 is not associated with a lot of sneezing, but rather with a dry cough. These large particles are those most clearly associated with transmission of common respiratory viruses. Some diseases such as measles and TB however, can be spread by aerosols.

The airway has evolved to protect itself from inhaling dust and pathogens. The nose and nasal cavity with the moist mucous lined turbinates capture large airborne particles. Those particles that get trapped are often swallowed, and mostly sterilized by stomach acid or enzymatic degradation.

Particles greater than about 10μm generally get trapped in the nose or throat. This occurs as these particles have sufficient mass that they can't negotiate the sharp turns in the airway, and

impact the mucous layer where they get stuck. This is why pollens generally cause allergic rhinitis – the pollen gets caught in the mucous layer in the nose and triggers an immune reaction. If large particles are inhaled they are likely to be captured in the mucous layer in the nose or airway rather than get deep in the lung. In contrast, shouting creates mostly small particles that can make their way deep into the lungs.[2]

As the air moves past the larynx the airway expands in diameter and the air slows. This less particles 0.003 μm to 5 μm get deposited, mostly in the tracheobronchial surfaces. Here too, most of the particles impact the mucous layer on mucous membranes and are washed away by the mucociliary escalator. In asthma, particles that land in the small airways can cause broncho-constriction.

By the time air has reached the alveoli, there is little "wind". Generally only particles less than 0.5 μm make it this far.

Inhaled medication for asthma and lung disease is formulated so that the medication can get deep into the lung and be absorbed there. To get deep in the long below the carina, the point at which the bronchi bifurcate, the particles need to be less than 5 μm. The most efficient size for deposition of medication into the alveoli are medications with particles less than 2 μm. It is generally considered that particles much less than 1 μm have so little mass that they are not deposited and just exit in the exhaled breath. The ideal particle size for alveolar deposition appears to be around 1.1 μm. [3]

This is the size of particle created by shouting or playing the vuvuzela. Shouting was found to, on average, create 3,700 particles in the 0.5 to 5 μm range per liter at a peak flow rate of 1.8 liters per second. Blowing the vuvuzela was found to produce 658,000 similarly sized particles at a peak flow of 6.1 liters per second.[4] Vuvuzela may be an efficient means of creating dangerous infectious respiratory particles. However, the vuvuzela is making particles by vibration of the lips, and likely contains almost entirely saliva. There is very little ACE2 in salivary glands, so there are few SARS-CoV-2 virus particles in the saliva, so while avoiding vuvuzela during the COVID pandemic is a good idea, it may not be the ideal method for creating SARS-CoV-2 aerosols.

After a two choir practice in Washington State in early March 2020, in which none of the participants were known to be ill, and no one was sneezing or coughing, there was an extremely high disease transmission rate. Of 56 persons at the practice, 45 were diagnosed with COVID-19. Allowing for a single likely asymptomatic carrier, this means that 45 of 55 persons developed symptomatic disease.[5] This is much higher than the typical 15% to 50% symptomatic disease rate thought to generally occur with this disease. Two members of the choir died; a 4.4% case fatality rate and a *3.6% percent exposure mortality rate*. This seems a mortality rate in comparison to what the general public has had in the U.S. Here is an example of an asymptomatic "super spreader" in the United States. The original COVID-19 super-spreader was a 61 year-old woman in South Korea who infected at least 37 people[6] at church in which loud singing of hymns was encouraged as an important part of the religious service.[7]

A bulwark never failing: I speculate that singing is an efficient means of creating 0.8 to 2 μm respiratory particles. There is high air pressure against the vocal cords. The vocal cords are then

vibrating at a high rate; stretched tight like a guitar string and vibrating at 60 to 1000 cycles per second, with higher frequency for high pitch singing. Choirs sing loudly, so there is more pressure than singing lullabies to get one's child to sleep. Singing may create large amounts of very fine particulates in the same range as does shouting. These are the perfect size to be inhaled and deposited deep in the lung, settling on alveolar endothelial cells bearing ACE2 proteins that the virus uses to enter the cell. Unlike vuvuzela spray of saliva particles, the larynx would be likely to atomize mucous, that in an infected person, would contain a high density of virus particles.

Choir singing also typically involves deep respirations though mouth breathing. Thus choir singing may not only be an idea mechanism for both creating perfectly sized respiratory particles for deposition in the alveoli, it is also great and for capturing them. Christmas carols may help increase the spread of seasonal flu, which most frequently peak in February.

There is emerging data that suggest that many cases, likely at least half, but perhaps as many as 85% of COVID-19 are asymptomatic. Nevertheless, these church-super-spread cases appear to have a high exposure-case rate and may have a high exposures fatality rate.

As a result of this limited evidence, I consider the probability of aerosol spread of SARS-CoV-2 to be considerable.

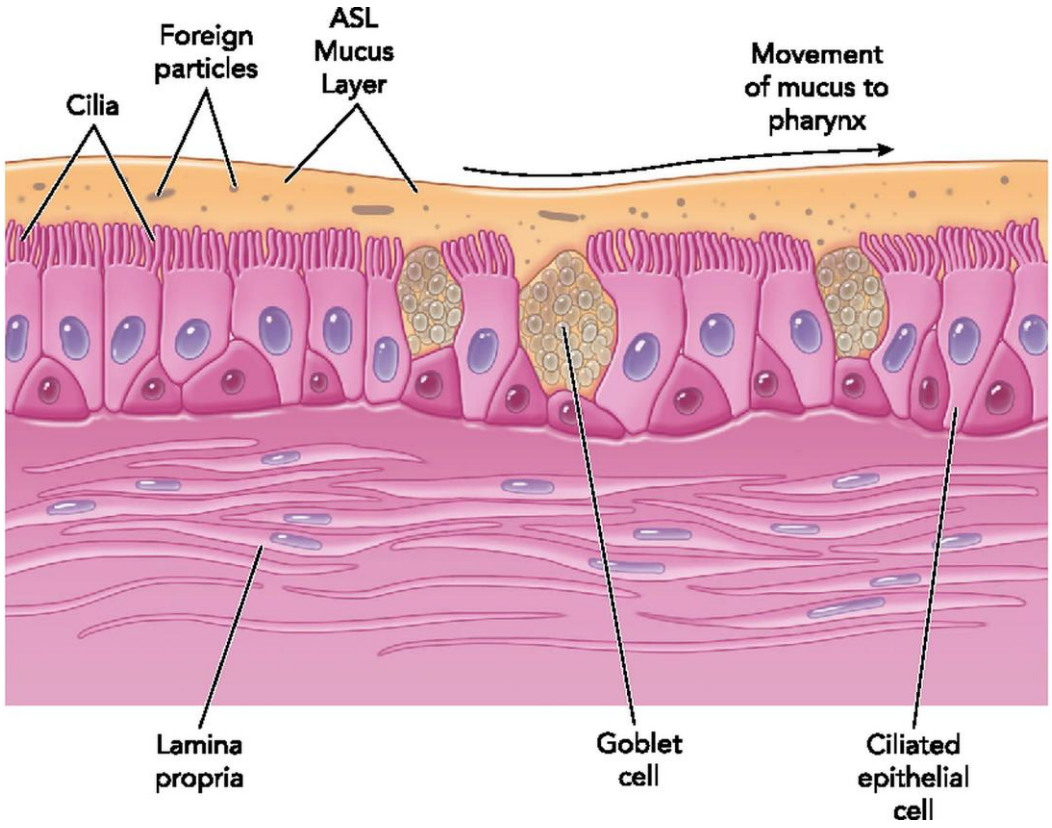
A study performed in a hospital demonstrated that opening windows can help quickly reduce small aerosols from a room. Outdoor air is many times less likely to have a high density of infectious SARS-CoV-2 aerosols as compared to a room with an infected person. If you have cross ventilation in your home, this may reduce person to person contamination.

Non-invasive ventilators (using masks puts large amounts of potentially infectious particles from the patients airway into the room air, putting small particles (< 5μm) from the patients airway into the hospital air, and thus pose risk of spreading infection from patients with respiratory infections. [8] This type of therapy puts health care workers at higher risk of becoming infected with respiratory diseases.

Assuming that aerosol spread occurs, does would it alter the disease presentation or pathology?

Perhaps droplets create different exposure pathways dependent on their size; one where a person is exposed to larger particles are captured in the nasal mucous and transported to the pharynx by the mucous escalator and swallowed, and the second where very small aerosols are directly deposited in the alveoli.

The turbinates in the nasal cavity are designed to warm, and humidify the inhaled air, and to act as impact filters – the nasal turbinates create turbulence in the airflow that causes heavier particles, (such as dust or the infectious aerosol droplets that spread respiratory disease) to collide with and get trapped in the moist mucous layer of the nasal mucosa. Thus the nasal mucosa and its mucous are part of our defense against disease. Some pathogens can subvert this defense.



The mucociliary escalator moves mucus down from the upper airway to the pharynx and up from the bronchial tube and trachea as well, into the pharynx. In persons with injury to these tissues from chronic diseases or smoking, the mucous may not be efficiently produced by the goblet cells, allowing exposure of the ciliated epithelium, and allowing those cells to become infected. Chronic injury of the respiratory epithelium also may disrupt the function of the ciliated cells. The ciliated cells may be replaced by non-ciliated cells. If the mucus is dry of sticky, it may not have an efficient flow. Stasis of the mucous layer can allow bacteria to proliferate and cause infection.

One reason that winter is a time of increased susceptibility to URI is that the humidity is often low, as cold air holds less water vapor. If the air is heated without adding humidity, it stays dry. Low humidity dries and thickens the mucus layer making it move less efficiently and more slowly. This is a likely contributor to the wintertime spikes in respiratory infections.

When we have nasal congestion, we are much more likely to mouth breath. People with severe lung disease may also mouth breath as they are short of breathe. Mouth breathing not only circumvents humidification of the air and dries the mucus of the lower respiratory tract, but also circumvents the important air filtration effect of the upper airway allowing deposition of fine dust and infectious aerosols. Additionally, aspiration of infected viral particles from the nasal cavity may increase the risk of lung infection.

Usually the common cold only affects the upper respiratory tract. Thus, these cold viruses have an affinity to infect the mucous membranes of nasal cavity, sinuses, pharynx, perhaps the tonsils. Some may affect the epiglottis and larynx. We now know that SARS-CoV-2 infects many tissues included the nasal mucosa, epiglottis, tonsils, trachea, lymph nodes and lungs, but also the heart and skeletal muscles, and small and large intestines, bladder, and to a lesser degree CNS and spinal cord.[9] SARS, MERS, and COVID-19 are devastating diseases, but there are also other human coronaviruses cause upper respiratory infections (URIs) (the common cold).

It is not rare for people, especially those with underlying lung disease to develop pneumonia in association with a viral URI, while most people just get URIs.

Bacterial pneumonias can develop after a viral URI, as the result of a secondary bacterial infection that occurs when the injured upper respiratory tract becomes colonized and infected with pathogenic bacteria. Those bacteria may get aspirated into the lower respiratory tract. Many cold viruses however can cause lung infection, including bronchitis or pneumonia. The airway is designed to prevent this, and it generally does not occur. Persons with chronic lung disease are at increased risk. Part of this risk may be a failure of the mucociliary escalator; a relatively thick layer of mucous that captures small particles including pathogens and sweeps them into the throat, where the mucous, dust and pathogens get swallowed. Most swallowed pathogens are killed by stomach acid. Certainly however, it is possible to aspirate viral particles from the nasal cavity. Snorting could do this. Inhale against closed vocal cords so that it causes vocalization – a strange thing to do, would likely produce tiny aerosols from the larynx into the lungs perfect for alveolar deposition.

The alveolar exposure may be a more dangerous route as it may be more likely to result in symptomatic disease, and perhaps more severe disease. When particles land in the nasal mucosa, there may be more chance to develop immunity. There are immune cells in the nasal mucosa. While nasal mucosal disease can injure the tissues sufficiently to cause a temporary loss of the sense of smell, this does not great harm to the infected individual. When virus particles are swept by the mucociliary escalator to the pharynx and are swallowed, they may be inactivated by stomach acid or digestive enzymes. If the particles survive and infect the GI mucosa, it may also help develop immunity, while apparently not causing severe disease.

In SARS-COV-2 infection, usually the virus first gets deposited on the upper airway mucosa. This virus reproduces well in the nasal mucosa tonsils and cervical lymph nodes. Immune cells, such as the immune dendritic cells that are professional foragers of antigen may also collect these particles from the nasal mucosa and present them to the immune cells in the lymph nodes. There is rapid proliferation of the virus in the nasal mucosa in the first days after inoculation, with viral load in these tissues likely peaking about the same time as the onset of fever. [10]

We know that mucociliary escalator is carrying high numbers of SARS-COV-2 virus particles to the throat and they are being swallowed in mild COVID-19. Testing has shown that the viral RNA is present in the stool in high amounts, but at least typically, these virus particles have been inactivated. The amount of COVID RNA in the stool is high enough, that sewer system

sampling is being done to track the virus outbreak as it spreads in various areas, and in hope in determining when the outbreak begins and begins to abate.[11]

The swallowing of the virus particles may be important for developing immunity. Over half of the body's immune system is in the intestines. Thus, this may be an important site for dendritic cell presentation of viral RNA or viral proteins to the immune system. There are M cells and dendritic cells in the intestinal mucosa that sample the contents of the intestine and process antigenic materials for the development of immunity. We know that the cells lining the small and large intestine bear ACE2 receptors and that these cells can become host of the SARS-CoV-2 virus. While some patients develop short-term diarrhea or have vomiting with COVID-19, gastrointestinal injury is not an important feature of this disease.

The oral polio vaccine, first developed by Albert Sabin is an attenuated polio virus that is alive but has low pathogenicity. This is in contrast to the "Salk Vaccine" which is an inactivated virus that is injected. Poliovirus is a single stranded RNA enterovirus, that although spreading mainly through fecal-oral transmission, may cause mild respiratory symptoms, and the virus can be isolated from the saliva and nasal secretions. Polio's major risk comes from is damaging effect on the spinal cord, causing flaccid paralysis in about one percent of cases. Poliovirus is adapted to survive the acidic environment of the stomach and it reproduces in the intestine.[12] The attenuated virus promotes both humoral and cell-mediate immunity[13] as a result of the infection it causes in the intestinal mucosa.

Perhaps stomach acid inactivates the virus, or attenuates its infectivity. Low levels of the virus were found in the lining of the stomach in an experimentally infected animal. Older patients often have achlorhydria, a condition in which the stomach does not produce much any gastric acid. This is often the result of chronic H. pylori infection. Many people, but especially older people may be using H2 blockers (i.e; ranitidine) or proton pump inhibitors (i.e.; omeprazole, pantoprazole) that prevent gastric acid production. It is possible that achlorhydria or these medications alters prevents viral inactivation. Digestive enzymes, including proteases and lipases may also degrade viral proteins and lipids rendering them inactive.

Although community-acquired-pneumonia generally results from upper airway inoculation, there is another common routes for developing pneumonia, especially for hospital patients. Hospital-acquired-pneumonia is often blood borne infection caused by bacteria that have escaped the GI tract or bladder. This is an especially common route for developing pneumonias caused by *Klebsiella pneumonia* and *E. coli,* bacteria that are frequent resident of the colon.[14]

Thus, it is possible that COVID-19 pneumonia occurs as a result of transient viremia, (virus particles in the blood) with virus particles having high affinity to ACE2 receptors in the lung, and certain others tissues, so that it is rapidly cleared from the blood. SARS-COV-2 virus is also found in high numbers in cardiac and skeletal muscle, and these are obviously not direct spread from inhalation or aspiration.

The SARS-CoV-2 virus is not isolated from the blood on testing. Nevertheless, for it to appear in skeletal muscles and CNS tissues, I assume it must transit through the blood, but rapidly be cleared form the blood.

As with the nasal mucosa, the intestinal mucosa is protected by a mucous layer. Injury to the intestinal mucosa may facilitate infection of the enterocytes or viral transmigration from the lumen of the intestine into the bloodstream.

The digestive processes likely impacts whether the disease stays as a mild URI infection, or becomes a systemic disease. The GI tract is likely an area important for the development of immunity to this virus. We know that in mild to moderate disease, there is are high numbers of viral RNA copies in the stool, but they are not infectious. This is a different scenario from polio and other enteroviruses that have fecal-oral spread as the viruses in the stool for those disease are active and very infectious.

So, at least in mild disease, SARS-COVID-2 viruses in the stool are inactivated.[15] At which point and by what mechanism does the inactivation occur? Stomach acid and digestive enzymes are possible means for this inactivation. We also know that this virus has affinity to the enterocytes of the intestine and can infect those cells. In A Rhesus macaque with symptomatic COVID-19, the virus was isolated from the intestinal and colonic mucosa. Perhaps IgA antibodies inactivate the virus particles. Perhaps susceptibility to severe disease occurs when there is failure of a rapid GI immune response to the virus. The immune system does not like to fight two different battles at the same time. Cytokines promote immune function, directing activity against various adversaries: Th1 function against intracellular pathogens (viruses or intracellular bacteria), T2 function against extra cellular pathogens, or Th17 function against parasites and allergens. If a person's immunity is engaged in T2 or T17 function in the intestine, perhaps they will be slow to develop immunity to viruses that affect the mucosa of the intestine, and thereby allow the disease to gain the upper hand, and spread more vigorously. Are individuals with intestinal parasites, food sensitivities, or other intestinal diseases at higher risk of developing severe systemic COVID-19?

Does disease acquisition from small-aerosol, alveolar exposure or large-droplet nasal exposure differ? It may differ in the immune defense and ease in which one the adaptive immunity gets the disease under control. Severe disease appears to occur when the adaptive immunity is incompetent and the innate immune response goes into overdrive. Having the viral infection begin on the alveolar surface may also present differently than blood-borne infection to the lung.

A European study has found two distinct presentations of COVID-19 pneumonia; one characterized by low elastance (i.e., high compliance) low ventilation to perfusion ratio, and low lung weight (low edema), and another with high elastance, high shunting and high lung weight and more severe disease. These two different presentations require different management.[16] There is no evidence I am aware of to indicate that these two presentations reflect the route of infection, but it is a question worth asking.

Conclusions:

- Aerosol transmission of SARS-CoV-2 seems probable.
- Singing in a choir may be an efficient way to transmit COVID-19 and other respiratory viruses. This transmission is likely secondary to the creation of aerosols.
- Large infectious droplets captured in the nasal mucosa first infect this tissue and the virus is subsequently then swallowed. This process allows presentation of the virus to the immune system, perhaps without significant lung infection. Small aerosol exposure to SARS-CoV-2 can allow the virus to directly infect ACE2 bearing alveolar cells in the lung.
- Prevention measures should assume that there is aerosol spread of SARS-CoV-2. Surgical, N95, and even homemade cotton masks filter out most particles down to 0.65 μm. Thus, mask can prevent aerosol transmission of COVID-19.
- These two routes of infection (Nasal vs. Alveolar) may impart considerably different risk of disease severity.
- Low humidity that dries the nasal and respiratory mucosa may be a risk for COVID-19 infection, a higher R_0, and perhaps for more severe infection. Good hydration can help maintain proper fluidity of the mucous layer. Drinking warm beverages, such as tea, helps more than cool ones.
- Achlorhydria or medications that prevent stomach acid production such a proton-pump inhibitors may increase risk of systemic and COVID-19 and lung infection.
- Poor gastrointestinal mucosal function or concurrent immune reactivity in the intestine may weaken intestinal immune response to SARS-COV-2, which may increase risk of severe systemic COVID-19 and lung disease.

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