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Expiratory Aerosol pH is a Driver of the Persistence of Airborne Influenza A Virus

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Abstract: To mitigate the spread of a viral disease, it is crucial to understand the factors that influence airborne virus transmission. However, the micro-environment to which the virus is exposed in expiratory aerosol particles is highly complex. The relative humidity, the aerosol particle size and composition, and the air composition affect virus infectivity by modulating the salt and organic concentrations within the particle, as well as the phase state. A parameter that has been overlooked is the aerosol pH. Several viruses are sensitive to acidic pH; for example, the inactivation of influenza A virus becomes very fast at pH 5.5 and below, a threshold that is quickly reached in an expiratory aerosol particle exhaled in a typical indoor environment. Therefore, aerosol acidity plays a significant role in controlling the persistence of airborne, acid-sensitive viruses such as influenza virus, and aerosol pH control could be applied to limit the risk of airborne virus transmission.

Keywords: Acidity · Airborne virus persistence · Expiratory aerosol particles · Influenza A virus

Aline Schaub did her Bachelor degree at EPFL (Ecole Polytechnique Fédérale de Lausanne) in Chemistry and Chemical Engineering, where she received an excellence scholarship to pursue her Master studies in the same university, which she completed in 2017 in the Institute of Chemical Engineering and Biotechnology. After a two-year break from academy, she joined the Environmental Chemistry Laboratory, the group of Prof. Tamar Kohn, as a PhD student. Her research focuses on the airborne transmission of influenza virus, along with a group of 15 researchers from EPFL, ETH Zurich and the University of Zurich. In particular, she is interested in the environmental and physicochemical conditions favoring, or decreasing, the infectivity of the virus.

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1. Introduction

When breathing, talking, singing, coughing or sneezing, we emit small particles[1–3] composed of respiratory fluid (nasal mucus, saliva or airways lining fluid)[4,5] that may contain infectious viruses. The larger particles, commonly referred to as droplets, can be inhaled by a host close to the emitter (1–2 m),[3] and/or deposit quickly on surfaces (fomites). Smaller particles can travel much further and stay airborne for hours to days.[6] The cut-off size between droplets and aerosol particles has long been considered to be 5 µm, but has recently been increased to 100 µm, which separates the two categories based on their aerodynamic behavior.[3] Long underestimated,[3,7] these aerosol particles have recently been acknowledged as an important vector for virus transmission, including influenza viruses[1,8–11] and coronaviruses.[12–18] However, this pathway is still poorly understood and was long neglected in pandemic mitigation measures.[19]

To be transmitted to a new host, the virus needs to remain infectious during its airborne journey; but its infectivity depends on the conditions it is exposed to. The micro-environment surrounding the virus is modulated by various parameters including the relative humidity (RH), the temperature, the air composition, and the aerosol particle size and composition. These parameters determine the solute concentrations, pH, and phase state attained by the aerosol particle after exhalation, which in turn affect virus persistence. These factors are so intertwined that their individual role in virus inactivation is difficult to disentangle. For example, the effect of the relative humidity on virus infectivity has been studied,[20–30] but the results depend widely on the presence of organics in the fluid matrix.[31] Likewise, a high salt concentration has been shown to enhance viral inactivation,[29,32] but is attenuated when organics are present.[33] Liquid–liquid phase separation[4] or the efflorescence of salts also modulate the infectivity of the virus.[34,35] Similarly, the pH of aerosol particles is likely to influence the transmission of viruses, but its effect remains poorly documented.[29] Therefore, it is of interest to investigate the pH of expiratory particles, in order to determine its importance in airborne virus transmission.

2. Expiratory Aerosol Particle Composition

The aerosol particles we emit are composed of a respiratory fluid whose composition varies from person to person and depends on where it originated within the host (*e.g.* lungs, bronchi or the nose).[30,36] However, independent of the site of production, the main fluid components are water, salts (especially NaCl), proteins, lipids, sugars, and surfactants.[4,30,36–38] These constituents also form the ingredients of synthetic lung fluid (SLF), a solution of well-defined composition suggested in the literature to represent respiratory tract lining fluids.[37,38] After exhalation, the water contained in the respiratory fluid rapidly evaporates, leading to a concentration of the solutes. The evaporation will take place until the water activity of the particle corresponds to the ambient relative humidity. If the RH is lower than the efflorescence RH of the salts contained in the particle, crystallization will occur

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and a solid core will be formed. Moreover, gas partitioning between the particle and its environment (*e.g.* NH_3, HNO_3, CO_2 and HCl) will change the composition of the particle, and therefore, modulate the micro-environment to which the virus is exposed. A deep understanding of this micro-environment is crucial to study its effect on virus infectivity, and fluid and air compositions are sensitive parameters to consider when investigating virus fate in expiratory particles.

3. pH of Expiratory Aerosol Particles

It has been suggested that the pH of aerosol particles decreases after exhalation, due to the loss of water and the resulting increase in the concentration of H^+ ions.[39] Conversely, a recent study observed the opposite behavior, suggesting an increase of the pH value within the particle due to loss of CO_2 after exhalation.[40] The reason for this discrepancy is that neither study fully represents a realistic particle–air system; the particle pH at any time is modulated by the aerosol composition and initial size, but also by the composition of the air into which it is emitted, and these parameters must thus be included in assessing aerosol pH.[41]

Unfortunately, direct measurement of the pH in small aerosol particles is not possible to date. To nevertheless gain an accurate understanding of the evolution of the pH of an expiratory aerosol particle after exhalation into indoor air, a computational model was developed that calculates the water content of an expiratory particle over time, as well as the concentrations of the particle components, considering its initial size and composition and the relative humidity and composition of the indoor air.[42] The calculations furthermore consider experimentally determined thermodynamic and kinetic properties of SLF. The model then allows to determine the pH of the aerosol particle (Fig. 1). We observed that when emitted into indoor air, which typically contains traces of ammonia (emitted from occupants) and nitric acid (from outdoor combustion processes and brought indoors through ventilation),[43] expiratory particles acidify and can reach a pH as low as 3.7. Such pH levels are also commonly reached in atmospheric aerosols.[44] In small expiratory aerosols, this acidification occurs rapidly (less than two minutes; Fig. 1). The final pH is mainly determined by partitioning of trace gases that are commonly present in air,[41] specifically NH_3 and HNO_3. This underlines the importance of including such trace gases when evaluating the pH of expiratory particles.

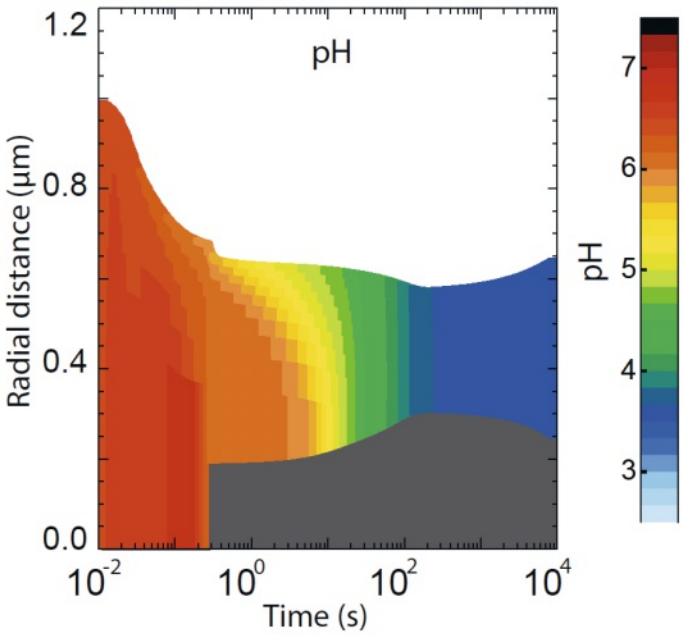

Fig. 1. Evolution of pH (modelled) of an expiratory aerosol particle composed of SLF after exhalation in an indoor environment at 50% RH and 20 °C. The initial radius of the particle is 1 μm, an aerosol size typically emitted when breathing. The decreasing radius is due to water evaporation. The decrease in pH results from the concentration of ammonium ions and the uptake of nitric acid from the room air. The grey area represents the crystal core formed by effloresced salts. Figure from Luo *et al.* 2022.[42]

4. Virus Susceptibility to pH

It is known that influenza A virus (IAV) is sensitive to acidic pH,[45,46] which can be attributed to its pH-dependent entry mechanism.[47] Specifically, IAV binds to the sialic acids on the cell membrane and enters the cell through an endosome.[48] When inside, the endosome is acidified to pH 5–5.5, which induces a conformational change in one of the surface glycoproteins of the virus, the haemagglutinin (HA).[49] This conformational change is required to allow membrane fusion between the virus and the endosome, and let the virus penetrate the cell (Fig. 2A). However, the pre-fusion form of HA is required to bind to the cell receptors; therefore, if the virus is exposed to an acidic environment prior to binding the cell, the conformational change will occur outside of the cell (Fig. 2B) and the virus will lose its ability to attach to the cell. Typically, pH-mediated IAV inactivation is only measured at physiologically relevant pH (down to *ca.* pH 5). In the aerosol system, however, lower pH values can be encountered. We therefore exposed influenza A virus (strain A/WSN/33) in an aqueous buffer at pH values ranging from 2.5 to 7.4 (Fig. 3A) and measured the inactivation over time.[42] The experiments were performed in bulk to avoid confounding effects resulting from water loss and changing solute concentrations. At near-neutral pH, the observed first-order inactivation rate constant (k_{obs}) is low and several days are needed to inactivate 99% of the virus population. However, when the pH shifts below 5.5, inactivation increases rapidly, and the resulting k_{obs} reach values >100 min^{-1}. This corresponds to a 99%-inactivation time of only a few seconds at pH below 4. We repeated the experiments in SLF and in nasal mucus harvested from epithelial nasal cells in order to confirm results in a more realistic fluid. Two SLF concentrations were tested: one corresponding to the composition of lung lining fluid (1×), and one with an 18-fold enrichment of all solutes (18×) to represent their final concentration in an aerosol particle exhaled into an environment at 80% RH. We observed that the inactivation kinetics in nasal mucus are very similar to those in SLF 1×, indicating that SLF is a good surrogate for respiratory fluid. Furthermore, both mucus and SLF

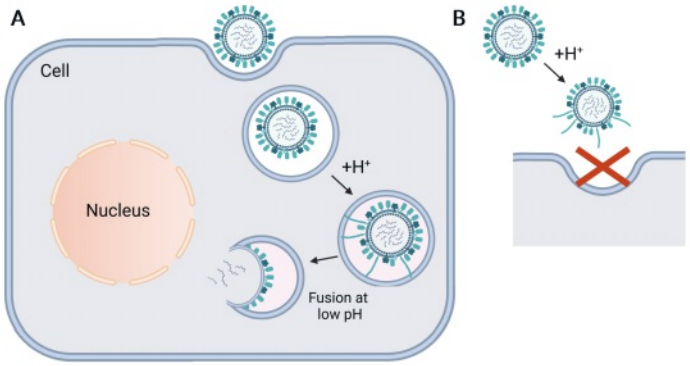

Fig. 2. Entry of IAV into a host cell (schematic). A) IAV binds to the cell and penetrates it through an endosome. The acidic conditions (pH 5–5.5) in the endosome trigger the HA conformational change, schematically represented by the blue lines representing unfolded proteins. This conformational change allows the fusion between the virus and the endosome membranes and the virus can release its genetic material into the cytoplasm. B) When IAV is exposed to acidic conditions, the conformational change of HA is triggered outside of the host cell and the virus cannot attach to the cell anymore (represented by the red cross). Adapted from Cohen 2016.[53] Created with Biorender.com.

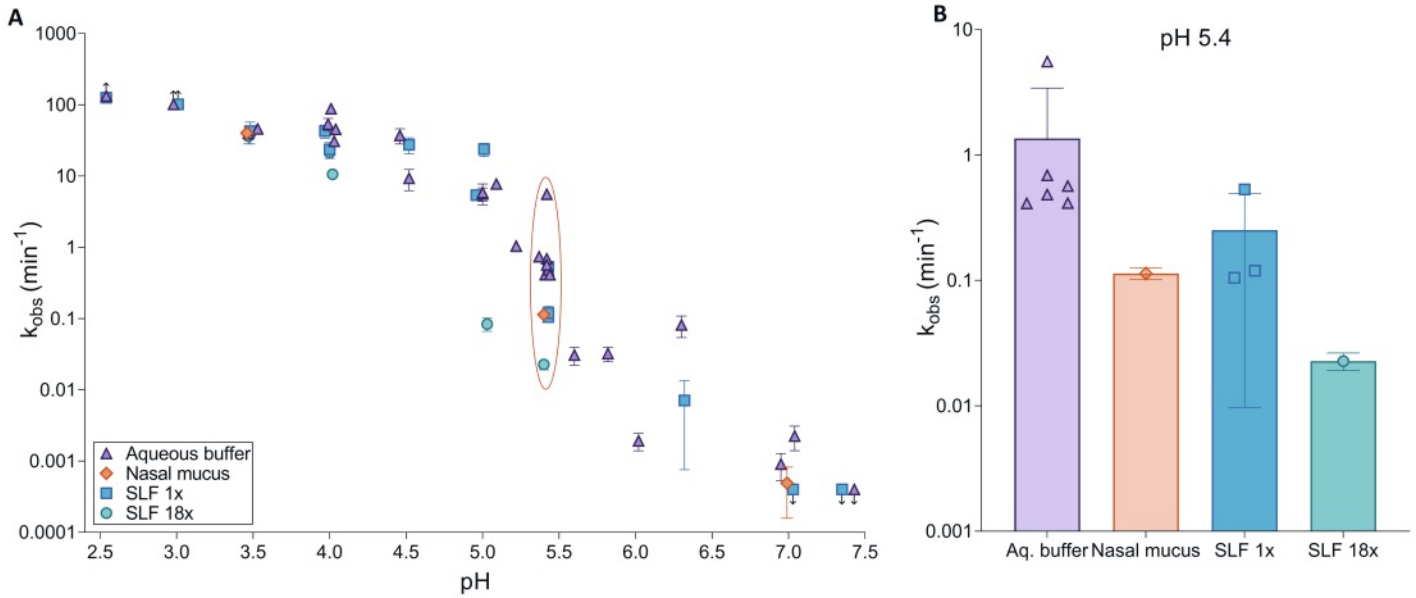

Fig. 3. Observed first-order inactivation rate constant of influenza A virus in various bulk media, A) as a function of pH and B) at pH 5.4. Each data point was measured in triplicate, with the error bars indicating 95% confidence intervals. The increasing concentration of SLF models the increasing concentration due to water evaporation after exhalation. pH measurements below 2.5 were not experimentally possible. Upward and downward arrows represent the highest and lowest experimentally observable rate, respectively. The data shown in panel B are indicated by a red ellipse in panel A. Figure adapted from Luo *et al*. 2022.[42]

offer some protection against inactivation compared to the aqueous buffer, and the more concentrated the SLF, the greater the protection (Fig. 3B). This effect is probably caused by organics present in these more realistic matrices, as observed by Kormuth *et al*.[31] However, the protection is only significant at pH values between 5 and 6, whereas at lower pH organics are not able to protect the virus against the damages due to acidity.

To characterize the physical effects resulting from the exposure to acidic conditions, we analyzed structural changes to the whole virus using hydrogen–deuterium exchange coupled to mass spectrometry.[47] After exposure at pH 4, fast conformational changes were observed in haemagglutinin and slower changes in the matrix protein 1. In contrast, only a limited effect was observed on the other proteins, the lipids and the genome of the virus. This confirms that unfolding of HA occurs outside the host cell and is the main driver of IAV inactivation at acidic pH.

5. Effect of pH on Airborne Virus Persistence

To predict the infectivity of IAV in expiratory aerosol particles,[42] we combined the measured inactivation kinetics with the modelled data on aerosol pH evolution (Fig. 4). We find a rapid decrease of IAV infectivity (few minutes) in particles of the size range associated with breathing (~1 µm) in typical indoor air. However, our findings demonstrate that if air is purified to remove trace gases, as it is done in museums and libraries to protect art work or books, the persistence of IAV increases dramatically, resulting in a 99%-inactivation time of a day. In such situations, a good ventilation system is essential to decrease the risk of airborne virus transmission.[42] Conversely, if the pH of expiratory particles is lowered by modifying the air composition, such as scrubbing ammonia, IAV inactivation is accelerated to less than a minute. This process would be particularly beneficial in indoor environments were many people are present, such as classrooms and gyms; in these situations, the ammonia emissions are high and increase the indoor aerosol pH, thereby also increasing the inactivation time of viruses. By implementing ammonia scrubbing in such environments, the process could effectively reduce the concentration of ammonia, lower aerosol pH and lead to a significant reduction in IAV transmission.

6. Conclusions

The micro-environment surrounding a virus in an expiratory aerosol particle is complex, and this hampers our comprehension of the physicochemical parameters governing airborne virus persistence. Among these parameters, the effect of aerosol acidity has been mostly overlooked in the literature. Here we show that expiratory aerosol particles reach low pH values in indoor air, and that this low pH efficiently inactivates IAV. This study was focused on influenza A virus, but our findings could be applied to other pathogens that are airborne and acid-sensitive. For example, damages to structural integrity of measles virus[50] and human rhinovirus[51] have been observed at acidic pH, and an important

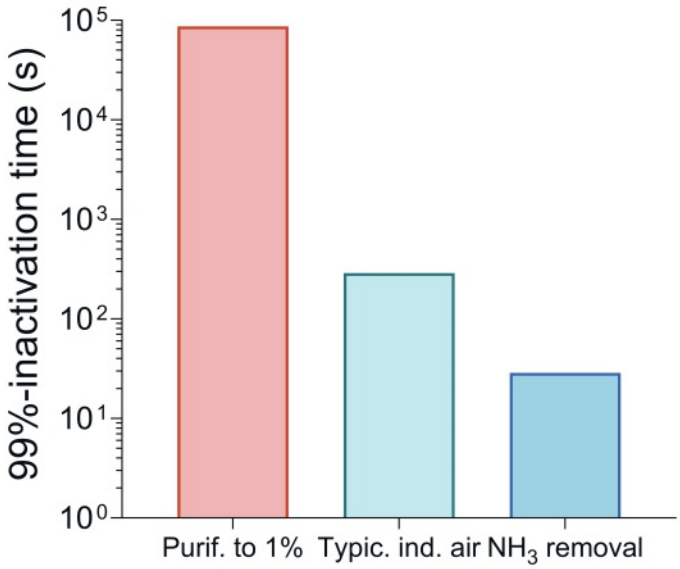

Fig. 4. 99%-inactivation time of influenza A virus in expiratory aerosol particles with an initial size of 1 µm (typical aerosol size emitted when breathing) in different air compositions. Three air compositions are shown: typical indoor air composition, in green; air purified with both NH_3 and HNO_3 reduced to 1% of their typical indoor concentrations, such as it can be found in museums and libraries, in red; and air depleted in ammonia to 10 ppt, in blue. Data from Luo *et al*. 2022.[42]

loss of infectivity of respiratory syncytial virus (RSV) has been reported.[52] In contrast, SARS-CoV-2 and HCoV-229, a common cold virus, are stable over a wide pH range and require very acidic pH (below 3 and below 2, respectively) to be inactivated.[42] The high stability of such viruses emphasizes the importance of a good ventilation system, which mechanically reduces the concentration of any pathogen. Nevertheless, the sensitivity of many airborne viruses to aerosol acidity opens possibilities for new mitigation strategies by controlling air composition, in order to efficiently reduce the spread of a disease in indoor environments.

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