Relative humidity in droplet and airborne transmission of disease

Anže Božič · Matej Kanduč

Abstract A large number of infectious diseases is transmitted by respiratory droplets. How long these droplets persist in the air, how far they can travel, and how long the pathogens they might carry survive are all decisive factors for the spread of droplet-borne diseases. The subject is extremely multifaceted and its aspects range across different disciplines, yet most of them have only seldom been considered in the physics community. In this review, we discuss the physical principles that govern the fate of respiratory droplets and any viruses trapped inside them, with a focus on the role of relative humidity. Importantly, low relative humidity—as encountered, for instance, indoors during winter and inside aircraft—facilitates evaporation and keeps even initially large droplets suspended in air as aerosol for extended periods of time. What is more, relative humidity affects the stability of viruses in aerosol through several physical mechanisms such as efflorescence and inactivation at the air-water interface, whose role in virus inactivation nonetheless remains poorly understood. Elucidating the role of relative humidity in the droplet spread of disease would permit us to design preventive measures that could aid in reducing the chance of transmission, particularly in indoor environment.

Keywords relative humidity · droplets · airborne transmission · viruses

1 Introduction

One of the prevalent ways in which numerous viruses, bacteria, and fungi spread among plants, animals, and humans is by droplets of various sizes [1–3]. Humans produce respiratory droplets during talking, coughing, sneezing, and other similar activ-
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ities [4,8]. These droplets, which can potentially contain pathogens, then spread outside the human body in various ways, enabling the pathogens to find a new host [1–3, 9, 10]. Most of the droplets deposit on various objects (e.g., buttons, door knobs, tabletops, and touchscreens), turning them into infectious “fomites”. The droplets can also be inhaled by another person in close proximity (≈ 1 to 2 m), which provides a direct path for infection. And not least, some droplets—particularly smaller ones—can remain airborne for longer periods of time and can travel considerable distances, providing yet another important path for disease transmission.

Droplet spread is the main mode of transmission for respiratory viruses such as influenza, common-cold viruses, and some SARS-associated coronaviruses, including the novel SARS-CoV-2 [3, 11–15]. A typical and very common feature of respiratory infections is seasonality, a periodic upsurge in infection incidence corresponding to seasons or other calendar periods. In fact, in temperate regions, most—but not all—human respiratory pathogens exhibit an annual increase in incidence each winter, with variations in the timing of onset and magnitude of the increase [16–19], as shown in Fig. 1 for several respiratory viruses. For instance, “flu season” in cold winter months is such a widespread and familiar phenomenon that we typically do not wonder why influenza viruses appear to have a greater reproduction rate when it is cold outside, even though they circulate year-round [20]. On the other hand, tropical countries have much weaker annual climate cycles, and outbreaks show less seasonality and are more difficult to explain by environmental correlations [14, 21–25]. Yet even though the recognition of seasonal patterns in infectious diseases dates back to the era of Hippocrates, the underlying mechanisms are still not well understood [20].

Numerous factors have been suggested to drive the distinct seasonality of various pathogens: human behavior (staying indoors more in colder months, school schedules) [24, 27], human immune function (diminished daylight and its impact on vi-

Fig. 1 Seasonality of four different respiratory viruses (influenza virus, adenovirus, respiratory syncytial virus (RSV), and coronavirus) in Paris during years 2012 to 2015. Shaded regions show the winter period (November to April). Image adapted from Ref. [19].
tamin D metabolism [28], ultraviolet radiation [29], and indoor relative humidity (RH)—the ratio of the partial pressure of water vapor to the equilibrium vapor pressure of water at a given temperature. RH is the environmental factor that we will discuss in this review in detail. One may of course wonder what the role of temperature is, as this is an environmental parameter that clearly correlates with seasons in temperate regions. However, there is little scientific evidence to suggest that lower winter temperatures are important direct drivers of wintertime seasonality of respiratory infections [20]. In particular, in indoor environments, where people spend 90% of their time and where most infections occur [6, 18], the temperature does not vary much, since buildings are heated as it gets cooler outdoors [26]. Nevertheless, what the outdoor temperature does affect indirectly is the RH inside buildings. Heating the buildings in winter dries the cold air coming in from outside, causing the RH to drop dramatically. As a result, indoor RH in temperate regions typically varies between 10% and 40% in the winter months, which is significantly lower compared with its range of 40% to 60% in the summer months [30–33]. By way of example, Fig. 2 shows the mean RH variation (blue bars) over the period of one year in a Swedish residential building: as winter turns to summer, RH increases from 30% to 50%. The indoor RH clearly correlates with the outdoor temperature (red line). In tropical regions, on the other hand, indoor RH is significantly higher throughout the year [18, 33, 34].

Research shows that RH plays a paramount role in the spread of infections through a number of different mechanisms. First, RH directly impacts how and to what extent the exhaled human droplets can spread through the air. Second, the stability of winter viruses trapped in those droplets shows a striking correlation with low RH (20% to 50%), while the stability of summer or year-round viruses is enhanced at higher RH (80%) [18]. And finally, there is also a physiological factor related to RH: Dry air dries out mucous membrane in the nose, which eases the invasion of infectious viruses into the respiratory tract [36–38]. A better understanding of the role of RH for virus viability in droplets thus not only helps us understand the droplet spread of infections and seasonality of some viruses, but can also guide our understanding of using humidity as a non-pharmaceutical intervention [39, 40].

![Fig. 2](image-url)

Fig. 2 Indoor RH (blue bars; left scale) and outdoor temperature (red line; right scale) over the period of one year in a residential building. Shaded region shows the winter period (November to April). Data for Gothenburg, Sweden [30, 35].
This review aims to summarize those physical mechanisms of droplet and airborne transmission of disease in which RH plays a role. In particular, we address the question of why and how the (seemingly small) difference in RH between 30% and 50% (Fig. 2) influences the spread of respiratory disease. By first estimating the droplet size and composition (Sec. 2), we use simple approximations to determine the general physics of a falling droplet (Sec. 3) and look at how it is influenced by RH and by both the presence of solutes as well as efflorescence effects. We then separately discuss how RH impacts the sedimentation of larger droplets (Sec. 4) and the deposition of aerosol (Sec. 5). Finally, we look into virus-laden droplets (Sec. 6), the survival of viruses in these droplets with respect to changes in RH, and the various factors that are responsible for this behavior.

2 Respiratory droplet size and composition

2.1 Droplet size

The size of droplets expelled during various human activities such as breathing, talking, singing, coughing, and sneezing is an important factor determining their fate: whether they evaporate, sediment, or persist in the air [4–8]. Often, a distinction is made between larger respiratory droplets, which do not spread far from their origin and quickly sediment onto neighboring surfaces, potentially contaminating them and thus facilitating transmission of droplet-borne disease, and smaller aerosol particles, which are small enough to persist in the air, are influenced by various kinds of airflow, and can potentially transmit disease over larger distances (Fig. 3). While most definitions of droplets and aerosol distinguish them by a certain size cutoff—current WHO guidelines put this at 5 µm [41]—these have varied over time, reflecting the fact that the transition between droplet and aerosol behavior is continuous rather than sharp [5]. Most often, the term droplet transmission is defined as the transmission of disease by respiratory droplets that tend to settle quickly to the ground (typically within 1 to 2 m from of the site of generation). Conversely, airborne transmission is defined as the transmission of infection by particles that are much smaller in size.

![Fig. 3](image_url)  
Fig. 3 Droplet and airborne spread of respiratory droplets. The size of the droplets influences whether they sediment quickly (droplet/fomite spread) or persist in the air for a longer period of time (airborne spread).
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![Graph showing droplet size distribution while talking.](image)

**Fig. 4** Droplet size distribution while talking. Blue circles show measurements by Xie et al. [46], performed at RH = 70%, and the full red line shows the fit of Eq. (1).

and can remain suspended in air for prolonged periods of time and can consequently travel much greater distances [5, 42, 43]. Furthermore, the size of respiratory droplets also influences where in the respiratory tract they can deposit [7, 8], and by that the severity and spread of a disease. For the purposes of this review, we will refer to all particles produced by respiratory activity as **droplets**, regardless of their size, but we will examine both the regime when they are large enough to quickly sediment as well as the regime when they are small and transmitted as aerosol particles.

Different human respiratory activities in general produce different amounts of droplets with varying size distributions [8, 44, 45]. Figure 4 shows an example of a size distribution of deposited droplets produced by talking, obtained in experiments of Xie et al. [46]. The distribution can be fitted well by a Gaussian curve in the lin-log scale:

$$P(R) \sim \exp \left[ -c \left( \ln R / R^* \right)^2 \right].$$  \hspace{1cm} (1)

The radii of the vast majority of droplets in Fig. 4 are in the range of $R \sim 10$ to 100 $\mu$m, and only a minority of droplets has size below 10 $\mu$m. Nonetheless, the latter importantly contribute to the airborne route of transmission, as we shall see in later sections. Size distribution of droplets does not depend greatly on the activity that produces them [45–47], although droplet particles originating in the lower respiratory tract in general tend to be smaller than the particles produced in the upper respiratory tract [48]. Some studies have also reported multimodal size distributions, which has been explained in terms of different physiological production mechanisms [48, 49].

While the size distributions of exhaled droplets produced by various activities are mostly similar, the activities differ greatly in the number of droplet particles produced, spanning several orders of magnitude [1, 50]. In general, more sensitive methods developed recently thus show that all human respiratory activities produce more droplets than previously thought [51, 52]. Talking, for instance, produces over $\sim 10^2$ particles per second [44, 46, 51], while a single sneeze can produce upwards of $10^4$ particles [1]. Thus, several minutes of talking can still produce as many droplets as a single cough or a sneeze [44]. The number of exhaled droplets also varies between individuals, with some emitting an order of magnitude more than the others—so-called superspreaders [44, 53, 54].
### Table 1 Composition of droplets of various origins (RF: respiratory fluid).

| Component | Concentration | Origin Description | Reference |
|-----------|---------------|---------------------|-----------|
| Proteins | 80 mg/ml | Exhaled condensate of RF | Effros et al. [56] |
| | ≲ 0.01 mg/ml | Exhaled condensate of RF | Scheideler et al. [62] |
| | 12 mg/ml | Sputum (non-purulent) | Spicer & Martinez [58] |
| | 20 mg/ml | Sputum (purulent) | Spicer & Martinez [58] |
| | 40 mg/ml | Sputum (cystic fibrosis) | Spicer & Martinez [58] |
| | 30 mg/ml | Sputum (clinical diagnosis) | Gould & Weiser [63] |
| | 3 mg/ml | Nasal airway surface fluid | Gould & Weiser [63] |
| | 8 mg/ml | Nasal mucus | Ruocco et al. [64] |
| | ≲ 0.03 mg/ml | Nasal wash | Reynolds & Chrétien [65] |
| | 4.0 mg/ml | Stimulated saliva (healthy) | Sanchez et al. [60] |
| | 4.7 mg/ml | Stimulated saliva (periodontitis) | Sanchez et al. [60] |
| | 3 mg/ml | Model RF | Vejerano & Marr [66] |
| Salt ions | 91 mM [Na\(^+\)] | Exhaled condensate of RF | Effros et al. [56] |
| | 60 mM [K\(^+\)] | Exhaled condensate of RF | Effros et al. [56] |
| | 100 mM [Cl\(^-\)] | Exhaled condensate of RF | Effros et al. [56] |
| | 9 mg/ml [NaCl] | Model RF | Vejerano & Marr [66] |
| Lipids | 11 mg/ml | Sputum (non-purulent) | Spicer & Martinez [58] |
| | 18 mg/ml | Sputum (purulent) | Spicer & Martinez [58] |
| | 33 mg/ml | Sputum (cystic fibrosis) | Spicer & Martinez [58] |
| | 0.01 mg/ml | Stimulated saliva | Larsson et al. [67] |
| | 0.5 mg/ml | Model RF | Vejerano & Marr [66] |

#### 2.2 Droplet composition

Human respiratory droplets are composed mainly of water (≈ 90% to 99%), with the remainder being mostly inorganic ions, sugars, proteins, lipids, and DNA. The exact composition, however, strongly depends on the type and the location of secretion [48, 55–58]. Table 1 shows an overview of the basic components measured in droplets of different origins, such as respiratory fluid and saliva. Variation in droplet composition depends not only on their origin but also on the health of the person [58–60]. Notably, the levels of the mucin protein can be elevated by a factor of four in an infected individual [58]. There is also a great amount of variability both among different subjects as well as within single-subject samples collected at different times [56]. The knowledge of droplet composition is important as it influences both their transmission as well as the viability of pathogens they might be carrying (Sec. 6), so much so that Poon et al. [61] have recently termed such droplets biopolymer-lipid-salt-virus (BLSV) droplets, reflecting the basic nature of their composition.

#### 3 Physics of a falling droplet

After droplets are expelled from the mouth or nose into the air, they undergo various physical and chemical processes—evaporation being the most notable among them—that change their structural properties in an important way. In the air, these droplets (or droplet particles) are subject to gravity, Brownian motion, electrical forces, ther-
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This enormous repertoire of phenomena that accompany droplets in the air leads to a variety of possible outcomes, and our ambition is not to summarize all of them in a single article. In this section, we will instead focus only on the essential physics that is necessary to explain the basics of a falling droplet, its sedimentation, and airborne spread, as well as the ways in which RH impacts this behavior.

3.1 Evaporation of a falling water droplet

We first consider a pure water droplet of radius $R_0$ in air (Fig. 5A). Because of the gravitational force $F_g = (4\pi/3)\rho_w g R_0^3$ acting on the droplet (where $\rho_w$ is the water density and $g$ the gravitational acceleration), the droplet starts to accelerate downwards. This motion is opposed by air drag, given by the Stokes law (applicable in the regime of low Reynolds numbers) $F_d = 6\pi \eta R_0 v$, where $v$ is the droplet velocity and $\eta$ the air viscosity. Soon, the drag balances the gravity ($F_d = F_g$) and the droplet reaches sedimentation (terminal) velocity of

$$v_{sed} = \frac{\xi}{2} R_0^2$$

where $\xi = 2g \rho_w / 9 \eta \approx 1.2 \times 10^8 \text{ m}^{-1} \text{s}^{-1}$. Sedimentation velocities for different droplet sizes are given in Table 2, where we can see that they span six orders of magnitude as droplet size decreases from 100 to 0.1 $\mu$m. Acceleration time needed for a droplet to reach terminal velocity is $t_{acc} = v_{sed} / g$. For a 100-$\mu$m-large droplet with $v_{sed} = 1 \text{ m/s}$, this amounts to around $t_{acc} \approx 0.1 \text{ s}$. Since respiratory droplets are mostly smaller than 100 $\mu$m, this means that they quickly reach their terminal velocities and we can thus neglect any acceleration effects.

If a droplet is released from height $h$, the time it takes for it to reach the ground (sedimentation time) in an undisturbed atmosphere and without evaporation (i.e., the droplet falls as a rigid body) is simply $t_{sed} = h / v_{sed}$. Using Eq. (2), this reads

$$t_{sed} = \frac{h}{\xi R_0^2} \text{ (no evaporation).}$$

The sedimentation time is inversely proportional to the square of the droplet size and again spans orders of magnitude for the most typical respiratory droplet sizes.

| $R_0$ ($\mu$m) | $v_{sed}$ (m/s) | $t_{sed}$ (no evaporation) | $t_{ev}$ (RH = 50%) |
|----------------|-----------------|---------------------------|---------------------|
| 100            | 1               | 2 s                       | 20 s                |
| 10             | 1 cm/s          | 3 min                     | 0.2 s               |
| 1              | 1 mm/s          | 5 h                       | 2 ms                |
| 0.1            | 1 $\mu$m/s      | 23 days                   | 20 $\mu$s           |

Table 2: Initial droplet radius $R_0$, sedimentation (terminal) velocity $v_{sed}$ [Eq. (2)], sedimentation time $t_{sed}$ [Eq. (3)] from the height of $h = 2 \text{ m}$ in the absence of evaporation and in an undisturbed atmosphere, and evaporation time $t_{ev}$ [Eq. (6)] at 50% RH.
Fig. 5 (A) Droplet falling through air with a constant, sedimentation (terminal) velocity $v_{\text{sed}}$. The gravitational force is balanced by the Stokes drag. (B) Evaporating droplet stagnant in air. The vapor density profile (inset) is given by Eq. (4). (C) Wells falling-evaporation diagram, showing evaporation [blue lines; Eq. (5)] and sedimentation [orange line; Eq. (6)] times of droplets as a function of the initial radius of the droplet.

(Table 2). Note that for droplets smaller than several microns, airflow considerably disturbs the actual deposition to the ground, as we will discuss in Sec. 5.

As soon as a droplet enters unsaturated air, it starts to evaporate and its radius shrinks with time. We will demonstrate by a simple calculation that evaporation plays an essential role in falling droplets. To that end, we assume a motionless droplet with respect to the surrounding air, which defines the stagnant-flow approximation [68]. Water molecules that evaporate from the surface of the droplet undergo diffusion in the surrounding air. Thus, the vapor number density $c$ around the droplet can be described by the diffusion equation $\frac{\partial c}{\partial t} = D \nabla^2 c$. The steady-state solution ($\frac{\partial c}{\partial t} = 0$) in spherical geometry yields

$$c(r) = c_0 + (c_{\text{sat}} - c_0) \frac{R}{r},$$

which fulfils two relevant boundary conditions: the concentration approaches the ambient vapor concentration $c(r \to \infty) = c_0$ far away from the droplet on the one hand and the saturation value at the droplet surface $c(R) = c_{\text{sat}}$ on the other. The latter condition is valid in the so-called diffusion-limited regime in which evaporation is limited by the speed at which water molecules diffuse away from the droplet, creating “free space” for new water molecules to evaporate. Only for droplet radii below 70 nm does the evaporation process cross over into the reaction-limited regime in which the limiting factor is the rate at which water evaporates from the droplet surface [68]. Typical respiratory droplets thus fall well into the diffusion-limited regime, described by Eq. (4).

Evaporation flux density can be obtained from Fick’s first law of diffusion as $j = -D \frac{dc}{dr}|_{r=R}$. The total flux is then $J = 4\pi R^2 j = 4\pi RDc_{\text{sat}}(1 - \text{RH})$, where we have used the definition of relative humidity $\text{RH} = c_0/c_{\text{sat}}$. This now allows us to use the relation $J = -c_w dV/dt$ to connect the droplet volume $V = \frac{4}{3}\pi R^3$ with evaporation time, where $c_w = 33$ nm$^{-3}$ is the number density of liquid water. From here, we can derive the time-dependent radius of an evaporating droplet

$$R(t) = R_0 \sqrt{1 - \frac{t}{t_{\text{ev}}}} \quad \text{(pure water droplet)},$$

where $t_{\text{ev}}$ is the evaporation time, which is given by

$$t_{\text{ev}} = \frac{4\pi R_0^3}{3c_w} \frac{1 - \text{RH}}{Dc_{\text{sat}}},$$

$D$ is the diffusion coefficient of water vapor in air, and $c_{\text{sat}}$ is the saturation vapor density at the local temperature. This expression shows that the evaporation time scales inversely with the droplet radius, and hence, even a small increase in droplet radius can significantly reduce the evaporation rate. This is important for understanding the behavior of droplets in the atmosphere and for modeling the deposition of liquid droplets in respiratory systems.
where $R_0$ is the initial radius. The droplet vanishes completely at the evaporation time

$$t_{ev} = \frac{R_0^2}{\theta (1 - RH)},$$

(6)

where $\theta = 2DC_{cal}/c_w = 1.1 \times 10^{-9} \text{ m}^2\text{s}^{-1}$. The estimates for evaporation times of different initial droplet sizes $R_0$ are given in Table 2 as we can see, a 100-µm-large droplet takes several seconds to evaporate, whereas a 10-µm-large droplet evaporates in just a fraction of a second.

Equation (6) is, of course, only an approximation. Evaporation is a process accompanied and influenced by various phenomena [69–73], and detailed overviews of them are given by, for instance, Xie et al. [43] and Netz [68, 74]. Some of the most notable effects are (i) evaporation cooling effects, where owing to the large evaporation enthalpy of water, droplet surface cools down by about 10 K at RH = 50% [68], which decreases the evaporation rate and the diffusion coefficient [43]; (ii) Stefan flow, an induced flow of air away from the droplet caused by the evaporated vapor, which increases the evaporation rate [75]; (iii) ventilation effects, where the airflow around the falling droplet speeds up evaporation, and is relevant for radii larger than a few tens of microns [68, 75]; and (iv) the presence of solutes, which lowers the chemical potential of water and the rate of evaporation [68, 74]. Also, once droplet radius is less than 70 nm, evaporation switches over to the reaction-limited regime and the radius decreases linearly with time [68, 74]. Any lipids present in the droplets (Table 1) complicate things further, since a lipid layer can form on its surface and significantly slow down the evaporation [75, 77]. Nevertheless, for our purposes, Eq. (6) is sufficient to estimate the droplet evaporation time and to demonstrate the effect of RH.

We thus arrive at the question of what happens with a falling water droplet—does it fall to the ground or does it evaporate before reaching it? The answer to this question was first provided by William F. Wells in his seminal work in 1934 [78], where he established what we call today Wells evaporation-falling curves, shown in Fig. 5C. These curves are diagrams of time (traditionally in the inverse sense) versus the initial droplet size. Orange line in Fig. 5C shows the time needed for a droplet to reach the ground (i.e., the sedimentation time of Eq. (3) in absence of evaporation), and blue lines show the evaporation times at different RH [Eq. (6)]. The diagram demonstrates a clear dichotomy of two distinct fates that depend on the initial size of the droplet: small droplets will evaporate before reaching the ground, whereas larger ones will reach the ground before they disappear. With this diagram, Wells suggested that large respiratory droplets ($R > 60 \mu m$) settle on the ground quickly whereas smaller ones ($R < 60 \mu m$) dry out and any nonvolatile materials (including bacteria and viruses) stay suspended in the air for significant periods of time.

This notion provided the first clue about the difference between the transmission of infections by deposition of large droplets and by airborne routes. Wells evaporation-falling curves depend on ambient RH and suggest that higher RH slows down evaporation and increases the amount of droplets that deposit on the ground. But while Wells curves are historically important, they oversimplify the actual fate of respiratory droplets: One of the main reasons is that respiratory droplets never evaporate entirely but instead only to around half their initial size, as we will see next.
Fig. 6 Drying out of a respiratory droplet. The droplet progressively evaporates and shrinks in size. Its final size depends on the amount of non-water solutes in the droplet and on the ambient RH—the larger the RH, the larger the final size of the droplet residue.

### 3.2 Droplets containing solutes

Droplets exhaled by humans contain saliva or mucus and other matter derived from the respiratory tract. Typical mass or volume proportion of non-water content in a droplet is around $\phi_0 = 1\%$ to $10\%$, consisting predominantly of salt, proteins, lipids, and potentially pathogens (Table 1). A hypothetically completely dried-out droplet devoid of water would thus have a radius of

$$R_{\text{dry}} = R_0 \phi_0^{1/3} \quad \text{(completely dried-out droplet, RH = 0).}$$

Consequently, we can estimate that a completely dry droplet residue would have a radius between 22\% and 46\% of the initial droplet radius. However, a droplet never dries out completely but some water remains sorbed inside, its amount governed by RH [79]. Currently, it is unclear how droplet composition influences the final droplet size and the response to RH [80]. Clearly, respiratory droplets contain very complex organic macromolecular structures, made out of mostly hydrophilic molecules with considerable hydration effects, which are consequently strongly hygroscopic [80]. In the following, we will examine two extreme cases of the response of droplet size to RH (Fig. 6). In the first case, we will assume ideal mixing of solutes with water, which allows for a simple mathematical derivation. The second case involves crystallization of salt in the droplet, triggering an abrupt change in the droplet size.

#### 3.2.1 Droplet size: ideal mixing

From a thermodynamics perspective, evaporation occurs because the liquid water in the droplet has a higher chemical potential than the unsaturated vapor phase surrounding the droplet. The chemical potential of the vapor phase at a given RH relative to bulk water (or saturated vapor at RH = 100\%) is given as $\Delta \mu_v \approx k_B T \ln \text{RH}$, where $k_B$ is the Boltzmann constant and $T$ the temperature. When a nonvolatile solute is introduced into the droplet, the water chemical potential subsides. In the approximation of ideal mixing, the chemical potential of water with solute is smaller than the one of pure water by $\Delta \mu_w \approx k_B T \ln x_w$, with $x_w$ being the mole fraction of water. If the initial
amount of solute in the droplet is small \( x_w \ll 1 \) and the surrounding relative humidity is \( \text{RH} < 100\% \), water starts to evaporate from the droplet. With that, \( x_w \) decreases over time, and so does the chemical potential. Evaporation continues until the chemical potential of water in the droplet reaches the one of vapor, \( \Delta \mu_w = \Delta \mu_v \). From here, we obtain an estimate that the evaporation stops once the water fraction in the droplet reaches \( x_w \approx \text{RH} \) and, likewise, when the solid content is \( x_s = 1 - x_w \approx 1 - \text{RH} \).

The final, equilibrium volume of the dried out droplet, termed the \textit{droplet residue} or \textit{droplet nucleus}, is the sum of the water and solute content. For simplicity, we assume that solute molecules are of similar size as the water molecules, which makes the total volume of the droplet residue larger than the volume of a completely dried out droplet \[ \text{Eq. (7)} \] by a factor of \( 1 + x_w/x_s = 1/(1 - \text{RH}) \), namely \[ \text{Eq. (8)} \]

\[
R = R_0 \left( \frac{\phi_0}{1 - \text{RH}} \right)^{1/3} \text{ (droplet residue).}
\]

If we assume the solute content of respiratory droplets to be between \( \phi_0 = 1\% \) and 10\% (Sec. 2.2), the radius of a dried out droplet shrinks down to 27\% to 58\% of the initial radius at \( \text{RH} = 50\% \). In other words, a droplet residue is between 1/4 and 1/2 of the initial size of the exhaled respiratory droplet, as has already been suggested by numerous studies \[ 26, 79, 80 \]. \( \text{RH} \) thus controls not only the evaporation rate \[ \text{Eq. (6)} \] but, as implied by \text{Eq. (8)}, also the final size of the residue (already noted by, e.g., Effros \textit{et al.} \[ 56 \] and Nicas \textit{et al.} \[ 79 \]). An important consequence is that at higher \( \text{RH} \), droplet residues are larger, which in turn makes them sediment to the ground faster. According to \text{Eq. (8)}, increasing \( \text{RH} \) from 30\% to 50\% increases the residue size by \((0.7/0.5)^{1/3} \approx 10\% \). This result is, of course, very approximate and merely provides qualitative insights. More complex mathematical models take into account the non-ideality of mixing and even distinguish between aqueous salt phase and the insoluble solid material (e.g., mucous organics and potential pathogens) \[ 80 \].

The qualitative conclusions are, however, always the same: droplet nuclei maintain a larger size in humid air than in dry air. However, the precise relationship between the size of a respiratory droplet residue and \( \text{RH} \) is still largely unknown, and research on how \( \text{RH} \) influences the final size of droplet residues is surprisingly very limited and consequently the relation not well understood \[ 80 \].

\[ \text{3.2.2 Droplet size: efflorescence} \]

Non-ideal mixing of solutes with water can lead to dramatic, non-continuous processes in a shrinking droplet during evaporation. For instance, when a water droplet containing inorganic salts such as \( \text{NaCl} \) evaporates, the salt concentration can at a certain point overcome the solubility limit in bulk and push the system deep into a supersaturated, metastable state \[ 81 \]. If the evaporation continues and salt concentration increases further (e.g., if \( \text{RH} \) is low enough), salt eventually crystallizes and all the water evaporates in an \textit{efflorescence} transition (Fig. 7A). The inverse process, termed \textit{deliquescence}, occurs at significantly higher \( \text{RH} \). Whether or not efflorescence and deliquescence transitions occur depends both on the type of salt \[ 82, 83 \] as well as on the size and composition of the droplet \[ 82, 84, 85 \]. For instance, \( \text{NaCl} \)
Fig. 7 (A) Illustration of a hygroscopic shrinkage and growth of a NaCl-water droplet. Upon dehydration, a liquid droplet undergoes efflorescence at around RH = 40% and crystallizes, whereas upon hydration, a NaCl particle undergoes deliquescence at RH = 75% and turns into a liquid droplet. (B) Radius of NaCl-water droplets containing bovine serum albumin protein with an initial dry mass fraction of 10%, measured upon dehydration (Mikhailov et al. [83]). Red dashed line is a fit of Eq. (8) to the data points at RH > 50%. The green-shaded region denotes the most typical ambient conditions of RH = 30% to 50%. (C) Size distribution of droplet residues at different RH, recalculated from Fig. 4 using Eq. (8).

has efflorescence RH of around 40% [81, 83, 86, 87], while on the other hand, no transitions are observed for ammonium nitrate [83].

Are these crystallization phenomena important also for respiratory droplets? The majority of our knowledge on hygroscopic properties of small particles comes from atmospheric sciences [88–92], which is unfortunately difficult to generalize to respiratory droplets, as the latter contain a different and typically much more complex organization of organic compounds such as proteins and lipids [83, 93, 94]. Furthermore, as noted in Sec. 2.2, droplet composition varies widely between individuals and within individuals over time, especially in the case of disease, and so does the response of the droplets to RH.

A good starting point for understanding the hydration nature of respiratory droplets are thus salt-water droplets containing proteins. As an example, Fig. 7B shows how a droplet containing NaCl and 10% of bovine serum albumin protein—a popular model for proteins and macromolecular compounds—shrinks upon dehydration when lowering the ambient RH, obtained from experiments by Mikhailov et al. [83]. At high RH, droplet size follows very well the approximate expression given by Eq. (8). At around RH = 40%, however, the radius suddenly drops, indicating an efflorescence transition. Consequently, the difference in the sizes of droplet residues at 30% and 50% RH is almost 40%—much larger than predicted by the ideal-mixing model [without an efflorescence transition, Eq. (8)]. Interestingly, efflorescence of aqueous particles, whether with NaCl and/or protein content, occurs at RH of around 40%—this is in fact right in the middle of the typical span of ambient RH of 30% to 50%!

Notably, this shows that the efflorescence transition can be an essential player at typical indoor conditions that govern the dynamics of respiratory droplets. Mikhailov et al. [83] further observed that upon dehydration, proteins seemingly limit the nucleation of salt crystals, leading to higher stability of supersaturated salt solution and inhibition of NaCl efflorescence.

Synthetic droplets with a respiratory-fluid-like composition were also shown to undergo a phase separation upon dehydration where mucin proteins separate and lo-
calize at the droplet surface and form an envelope \[66\]. This can inhibit access of water vapor to the particle core and lead to kinetic limitations of water exchange, phase transitions, and microstructural rearrangement processes \[83, 90\]. Besides surface and kinetic effects, proteins and comparable organic macromolecules can also influence the thermodynamic properties of the aqueous bulk solution, and there is even indirect evidence for changes in pH and gelation processes \[66\]. It is also important to stress that phase transitions of sub-micron particles can behave very differently than predictions made using phase diagrams of bulk materials \[95\].

From the above discussion, we can conclude that when RH is lowered from 50% to 30%, a respiratory droplet residue can shrink in diameter anywhere from 10% [in the case of ideal mixing, given by Eq. (8)] to \(\sim 40\%\) (when efflorescence occurs, based on Mikhailov et al. \[83\]) of its initial size. RH and efflorescence transition thus have important implications for the general distribution of respiratory droplet sizes: Using the droplet residue size distribution of Xie et al. \[46\] at RH = 70% (Fig. 4), we can recalculate the size distributions at RH = 50% and RH = 30% using Eq. (8), yielding the solid curves in Fig. 7C, while dashed line shows the case of efflorescence at RH = 30% (assuming a 40% shrinkage compared to the sizes at RH = 50%).

Despite these effects, the possibility that (at least some) droplets can effloresce has typically been neglected in most—but not all—theoretical models \[43, 96–100\]. In the following, we will discuss the implications of the droplet shrinking range (in the presence and absence of efflorescence) on the sedimentation dynamics and aerosol deposition of respiratory droplets.

### 4 Droplet sedimentation

When assessing the risk of droplet and airborne transmission of disease, a crucial parameter is the time that the respiratory droplets spend in the air before they deposit to the ground or other surfaces. In Sec. 3 we have seen that the evaporation of a typical respiratory droplet stops once it shrinks down to around half of its initial size [Eq. (8)]. In the following, we estimate the sedimentation time of such a droplet, already anticipating that RH will have a significant effect—unlike in our estimate for the sedimentation time of a droplet in the absence of evaporation [Eq. (3)]. We will follow the approximation recently proposed by Netz \[68\], according to which droplet radius shrinks from the initial value of \(R_0\) down to the equilibrium value \(R = \kappa R_0\), where \(\kappa\) is a shrinking factor, given by Eq. (8) for the case of ideal mixing. The shrinking occurs in time \(t_{ev}^\kappa = (1 - \kappa^2)t_{ev}\), where \(t_{ev}\) is the evaporation time of a pure water droplet shrinking to zero [Eq. (6)]. After \(t_{ev}^\kappa\), the radius remains constant at \(\kappa R_0\).

With this assumption in mind and using Eqs. (2) and (5), we can write the expression for time-dependent sedimentation velocity as

\[
v_{sed}(t) = \xi R_0^2 \begin{cases} 1 - t/t_{ev} & ; t \leq t_{ev}^\kappa \\ \kappa^2 & ; t > t_{ev}^\kappa \end{cases}.
\]

Since we can neglect acceleration effects (Sec. 3), we integrate the velocity in Eq. (9) up to the time when the droplet sediments. This gives us the height \(h\) from which the
droplet was released,

\[ h = \frac{\xi}{\kappa R_0^2} \left\{ \begin{array}{ll}
  t - t_e^2 / 2t_e; & t \leq t_e^* \\
  \kappa^2 t + (1 - \kappa)^2 t_e^2 / 2; & t > t_e^*
\end{array} \right. \]

Equation (10) provides the relationship between the initial droplet radius and its sedimentation time, and allows us to make a simple estimate of how quickly respiratory droplets settle to the ground at various RH. When we know the total number of pathogen particles contained within the droplets in the air—referred to as the *pathogen load*—we can estimate the concentration of the pathogen remaining in the air at a given time—for instance, after a single exhalation event, such as a cough or a sneeze. Assuming that the concentration of the pathogen is the same in all exhaled droplets (see Sec. 5), the initial pathogen load (*i.e.*, the total number of pathogen particles) is simply proportional to the total initial volume of the droplets exhaled into the air. Evaporation alone does not change the number of pathogens in the droplets, and we can thus evaluate the *relative pathogen load* \( f_{\text{load}} \) (the load at a given time relative to the initial load) as the cumulative volume of the (dried-out) droplet residues that have not yet sedimented to the ground divided by the volume of all initially exhaled droplet residues. To do this, we integrate the (dried-out) droplet volume weighted by a suitable size distribution \( P(R) \) from 0 up to the cutoff radius \( R_{\text{sed}}(t) \) that represents the upper droplet radius of those droplets that have not yet sedimented during time \( t \).

Thus, \( R_{\text{sed}}(t) \) is obtained directly as \( \kappa R_0 \) from Eq. (10). The relative load is then

\[ f_{\text{load}}(t) = C \int_0^{R_{\text{sed}}(t)} \frac{4\pi R^3}{3} \times P(R) dR. \]

The coefficient \( C \) ensures the normalization to the initial condition \( f_{\text{load}}(0) = 1 \), *i.e.*, that at \( t = 0 \) all the exhaled droplets are in the air.

As an example, we now calculate the relative pathogen load dynamics for the three droplet size distributions \( P(R) \) shown in Fig. 7C. We use Eq. (8) to calculate the initial distribution of droplet radii \( R_0 \) and assume that the initial volume fraction of dry material is \( \phi_0 = 10\% \). The resulting relative loads as a function of time [Eq. (11)] are shown in Fig. 8. We can see that the vast majority (around 90\%) of the initial load released in the exhaled droplets from the height of 2 m settles to the ground within 3 to 4 s, independently of RH. During this initial period, only the largest droplets, which did not significantly evaporate during the descent, have sedimented—they fall almost as rigid bodies [100]. Afterwards, the effects of evaporation and RH become noticeable. At RH = 50\% (blue curve), droplets settle more rapidly than at RH = 30\% (orange-shaded band), owing to the fact that (i) evaporation is slower and (ii) the final droplet residues are larger at higher RH. At RH = 30\% and in the absence of efflorescence (where the droplet residues are 10\% smaller than at RH = 50\% RH; shown by solid orange line), sedimentation is only marginally slower. However, sedimentation slows down significantly when efflorescence occurs (and the droplet residues are 40\% smaller than at RH = 50\%: indicated by the dashed orange line).

To express the result in another way, we can also calculate the ratio between the relative loads at RH = 50\% and RH = 30\%, as shown in Fig. 8B. The difference gradually increases over time: After 10 s, the relative load at 50\% RH is between
60% to 75% of that at 30% RH. After one minute, this difference already amounts to 2- to 6-fold. This simple calculation demonstrates that despite more or less tiny differences in the residue sizes in the RH range of 30% to 50%, the change in RH and the presence or absence of efflorescence still have a significant impact on the settling of droplets from the air.

The calculation presented in this Section demonstrates in a simple way how a decrease in RH from 50% to 30% affects the deposition of respiratory droplets. More complex models take many other hydrodynamic factors into account, such as the buoyancy effect and the speed of exhaled air jet, ventilation, breathing mode, and so on [43, 96–100]. The conclusions are always qualitatively consistent with the prediction of Wells [78] that droplets settle more slowly at lower RH. The studies, however, do not typically quantify the differences between 30% and 50% RH, relevant for ambient conditions. Moreover, most of them, as already noted, unfortunately do not take the possibility of salt efflorescence into account.

5 Deposition of aerosol

Our estimate of droplet sedimentation, presented in Fig. 8, implies that at RH = 50% around 99% of the initially exhaled droplet volume from a typical cough settles within ~ 30 s. The remaining droplet residues that are still in air at that point are smaller than 25 µm in radius [see Eq. (3)]. Even though these small particles present less than 1% of the initially exhaled pathogen load, they can travel substantially longer distances and are also more likely to be captured in the respiratory tract [101]. Moreover, infectious droplets smaller than 10 µm can penetrate deeper into the respiratory tract (i.e., pulmonary region, which is the most sensitive part of the lungs) and have more serious health implications [5, 79]. Unlike larger droplet residues, the settling of these small residues is not governed by gravitational sedimentation alone but is in fact influenced by other environmental factors [2, 6, 42, 102]. Specifically, the air in a typical indoor setting is never undisturbed but is overwhelmed with air currents and flows, which impact the sedimentation of these smaller droplets.
Fig. 9 (A) Airflow that influences small aerosol droplets in a typical indoor setting (from left to right): air exchange, walking, door vortices, thermal plume, heating convection. (B) Different deposition mechanisms of aerosol particles: interception, inertial impaction, and diffusion.

Typical airflow speeds inside buildings are around 0.1 m/s (convection currents, breathing, human thermal plume), but certain human activities (walking, closing or opening a door) produce short-lived flows of around 1 m/s (Fig. 9A) [103]. These currents perturb the sedimentation of those droplets whose sedimentation velocity is comparable to or smaller than the airflow speed, relevant for particles smaller than around 20 µm (see Table 2). The smaller the particle, the more it is influenced by the airflow rather than the gravity and the longer it remains in the air [42]. These small respiratory droplet residues form a suspension in air and are therefore often referred to as aerosol or even bioaerosol [6, 42]. As described in Sec. 2, the exact boundary for what should be considered aerosol is challenging to define, and the transition between the two regimes is not at all sharp, but continuous instead [5].

Small aerosol particles eventually collide and stick to the ground as a result of impact, which happens when the air stream changes its direction and the particle comes in contact with a surface (interception) or when it does not follow the changing air stream because of inertia (inertial impaction; relevant for larger particles). For sub-micron particles, on the other hand, Brownian diffusion becomes an important transport mechanism, enabling them to deviate from air streams, thus increasing the probability of deposition (Fig. 9B) [104]. The crossover between interception, impaction, and diffusion deposition mechanisms lies in the range of 0.1 to 1 µm, where the contribution of the three mechanisms is the smallest. Therefore, aerosol particles of this size stay in the air the longest [6, 105].

Deposition mechanisms of aerosol are, contrary to the sedimentation of larger droplets, not a deterministic, but a stochastic process. In a closed indoor environment, without active filtering and in a well-mixed condition, the concentration $c_R(t)$ of particles of radius $R$ decays exponentially with time [106]:

$$c_R(t) = c_R(0) e^{-(\lambda + \beta_R)t}. \quad (12)$$

Here, $\lambda$ is the air-exchange rate in the room and $\beta_R$ is the first-order deposition loss rate coefficient. Air-exchange rate vanishes in a perfectly sealed room, but typically varies between $\lambda = 5$ h$^{-1}$ in residential buildings and 20 h$^{-1}$ in public spaces [107] and does not depend on aerosol type. On the other hand, the deposition rate $\beta_R$ varies widely across different conditions [106]: It depends both on the aerosol properties
such as size and shape as well as on the environmental parameters such as surface area, surface roughness, setup (e.g., furnishing), airflow conditions, electrical charge, temperature gradients, and so on [105, 106, 108–112].

Figure 10A shows the loss rate coefficients for particles with radii in the range of 1 to 10 $\mu$m in a furnished room with several ventilation intensities (no fan, mild fan, and strong fan). We can see that the deposition rate scales roughly linearly with the particle size, $\beta \propto R$ (in this regime, interception and inertial impaction dominate over the diffusion deposition). Enhanced air movement increases the rate of particle deposition because air movement delivers particles more rapidly to the surfaces to which they deposit [6]. The mean deposition time, according to Eq. (12), scales as $(\lambda + \beta R)^{-1}$. For an aerosol residue with $R = 5 \mu$m at RH = 50% (with $\lambda = 5$ h$^{-1}$ and $\beta R = 1.5$ h$^{-1}$), this makes the mean deposition time approximately 9.2 min. When RH is lowered to 30%, this particular residue shrinks down to $R = 3$ to 4.5 $\mu$m, depending on whether efflorescence transition occurs or not (Fig. 7C). Consequently, the deposition rate is reduced, $\beta R = 0.66$ to 1.3 h$^{-1}$, and the mean deposition time extends to 9.5 to 11 min. Even though this might not seem much, owing to the exponential nature of deposition, the difference builds up with time, as shown in Fig. 10B. The difference is negligible in the first minutes, but after an hour, the ratio between the concentrations at 50% and 30% RH ranges from 0.44 to 0.82 (the span again reflecting the presence and absence of efflorescence).

Clearly, the effect of RH on the deposition of smaller aerosol particles is much weaker than its effect on the sedimentation of larger droplets (Sec. 4). Even though it is not entirely clear how RH influences the size of droplet residues, the physics of deposition in the two regimes is completely different. Namely, the sedimentation time of larger droplets ($R \gtrsim 20 \mu$m) scales inversely with the square of their size, $t_{sed} \propto 1/R^2$ [Eq. (3)], while the deposition time of smaller aerosol particles (between $\sim 1$ to 10 $\mu$m) scales roughly as $t_{dep} \propto 1/(\lambda + \alpha R)$ [Eq. (12)]. The size dependence of the deposition time of smaller aerosol particles is thus much weaker than for larger droplets. Finally, for aerosol sizes in the range of 0.1 to 1 $\mu$m, the deposition mecha-
and measurements consequently exhibit substantial variability. Therefore, it is much more difficult to predict the fate of sub-micron particles [6, 106].

6 Viruses in respiratory droplets

One of the important reasons to try to understand the behavior of respiratory droplets, their aerosolization, and sedimentation lies in the fact that they often carry viruses and other pathogens (bacteria, fungi) and are thus an important source of transmission of respiratory diseases [1–3, 9]. The amount of viable infectious particles in an individual droplet is characterized by a viral load—the amount of virus in a given volume of the droplet medium (sputum, saliva) [5]. A recent review by Poon et al. [61] pointed out that even at high viral loads of $10^6$ to $10^9$ copies/ml (as is characteristic of SARS-CoV-2 [113–117] and some other respiratory viruses [118, 119]), this will result in only approximately 1% of small, 5-µm-large droplets carrying a single copy of a virus. This is in accord with recent studies of respiratory viruses, which have shown that even large loads of viral RNA translate into only a small count of viruses in droplet and aerosol particles [52, 120] (note also that a viral load given by RNA counts can overestimate the number of infectious viral particles [113]). However, the large amount of droplets produced during various activities such as speaking or coughing (Sec. 2) can transmit a significant number of viruses even when a single droplet contains only a few copies [121]. Estimates for instance show that 1 minute of loud speaking can still generate more than $10^3$ virus-containing droplets that can remain airborne for more than 8 minutes [52] (see also Sec. 5).

As droplets are exhaled, viruses start a voyage that is all but “hospitable”—dehydrated droplet particles can be in fact a very hostile environment. Viruses are now directly exposed to various harmful factors such as temperature [3, 14, 122, 123], UV radiation [124–126], atmospheric gasses such as ozone [127, 128], some types of surfaces on which droplets deposit [12, 129–132], and others [133–136]. It is thus not surprising that in general viruses cannot survive in these conditions indefinitely. Nonetheless, many viruses can remain infectious for long periods in both airborne and deposited droplet particles [5, 133]. The most significant factors influencing virus survival in droplets appear to be temperature, humidity, and the nature and composition of the droplets themselves [3, 14, 18, 122, 123]. Of these, an increase in environmental temperature (e.g., from 10 to 30 °C) quite universally speeds up the decay of viruses in droplets [29, 137–140]. On the other hand, the impact that air humidity has on viruses is not universal and also not trivial to understand [3, 123, 141], as we will see in this section.

Figure 11A shows how viability of aerosolized Langat virus diminishes with time, from seconds to hours after aerosolization: Remarkably, virus viability is non-monotonic with respect to RH, an observation which becomes more pronounced with time [133]. Furthermore, Yang et al. [142] systematically measured the viability of influenza A virus at RH ranging from 17% to 100% in droplets consisting of various model media (Fig. 11B), with the purpose to isolate the effects of salts and proteins that are found in respiratory fluid and human mucus (Table I). In all media, virus viability was highest when RH was either close to 100% or well below 50%. When RH
decreased from 84% to 50%, the relationship between viability and RH depended on droplet composition: Viability decreased in saline solutions, did not change significantly in solutions supplemented with proteins, and increased dramatically in mucus. Additionally, viral decay increased linearly with salt concentration in saline solutions, but not when they were supplemented with proteins.

Summarizing these observations, it may not be surprising that virus viability decreases as RH falls below 100%, since the droplet gets more and more dehydrated and the environment progressively deviates from physiological conditions. It is, however, surprising that virus viability very often recovers as RH is decreased even further, below 50%. This gives rise to a quite common U-shaped viability curve in response to RH, as seen in Fig. 11. In the relevant range of ambient conditions, RH = 30% to 50%, decreasing the air humidity increases the amount of viruses that survive in the droplets. Importantly, from the infection point of view, this effect acts together with the effect of weaker droplet deposition at decreased RH in making drier air more effective for the spread of infections.

In the following, we will discuss various reasons that lead to the peculiar, U-shaped RH dependence of virus viability inside respiratory droplets. Research shows that survival of viruses is affected in different ways and degrees by the structure of the virus, the presence, composition, and concentration of solutes, pH gradients, and the available air-water interface, making it difficult to draw general conclusions. These observations are sometimes further complicated by the interplay between temperature and humidity [123, 138, 143, 144] and the varying conditions under which the experiments are performed (droplet composition, aerosol ageing) [23, 122, 123, 141, 142].

6.1 RH and virus structure

Respiratory viruses include both RNA viruses (e.g., influenza virus, respiratory syncytial virus (RSV), rhinoviruses, and coronaviruses) as well as DNA viruses (e.g., adenoviruses and herpesviruses) [9, 119], which further differ in various aspects of their structure, most often by the presence or absence of a lipid envelope [145, 147].
Genome type clearly affects the survival of aerosolized viruses with respect to some factors: For instance, viruses with a single-stranded genome (either RNA or DNA) are more susceptible to UV and temperature inactivation than those with double-stranded genome \([123, 125]\). However, there is no clear indication that genome type plays a role in the response to changes in RH. On the other hand, the response of virus survival to RH has often been linked to the presence or absence of a lipid envelope \([3, 123, 141]\). Broadly speaking, enveloped viruses (such as influenza viruses, coronaviruses, and RSV) tend to survive longer at low RH \((\lesssim 30\%)\), while non-enveloped viruses (such as adenoviruses, rhinoviruses, and polioviruses) tend to survive longer at high RHs \((70\% \text{ to } 90\%)\), with RH \(\sim 100\%\) being in general favorable for virus survival regardless of the lipid envelope. Enveloped viruses furthermore often show the distinct, U-shaped non-monotonic pattern (Fig. 11) in the response of their survival to changes in RH, with a significant decrease in survival at intermediate RH \([3, 123, 141]\). These findings are, however, not always consistent, and exceptions to these general observations abound among both enveloped and non-enveloped viruses \([139, 140, 148, 151]\). The effects of RH on survival differ from virus to virus \([8, 152, 153]\) or even between different strains of the same virus \([14, 154]\), making it difficult to draw any conclusions based on the structure of the virus alone. For instance, Lin and Marr \([155]\) recently studied inactivation kinetics of two bacteriophages, the enveloped \(\Phi 6\) and the non-enveloped MS2. They observed that the magnitude of decay was similar between the two, and both viruses showed a non-monotonic pattern in viability with respect to changes in RH, suggesting a common inactivation mechanism.

6.2 RH and droplet composition

Not only does droplet composition influence the sedimentation behavior of respiratory droplets (as we exhaustively discussed in Sec. 3), but it also crucially affects the way an aerosolized virus survives or is inactivated \([66, 142, 156, 157]\). While the micro-environment in the droplet is close to physiological conditions at very high RH \((\sim 100\%)\) and becomes dry when RH is low \((\lesssim 30\%; \text{ Fig. 5})\), it is likely that virus viability at intermediate RH is governed mostly by the droplet composition, giving rise to the non-monotonic U-shaped pattern of the virus survival response to RH. Evaporation of water from the droplet induces various physico-chemical transformations in the droplet such as changes in the concentration of solutes \((\text{e.g., ions and proteins})\) as well as changes in the pH \([66, 142, 155, 158]\). These changes, obviously, also impact aerosolized viruses and their survival. Since RH outside the droplet governs the hydration of the droplet, it indirectly influences the survival and inactivation of viruses. To understand the role that droplet composition plays in the response of virus viability in droplets at different RH, we must see how the main components of respiratory droplets (salt, lipids, and proteins—see Sec. 2.2) react to RH, and how this affects virus viability. We have already seen that the majority of droplet particles remaining in the air for longer periods are in general rather small \((\text{Fig. 5})\). This implies that most of them carry at most a few copies of a virus, and when considering the role of RH on the stability of viruses in droplet particles, it appears to be sufficient to consider
the various effects on isolated viruses (i.e., viruses do generally not interact with each other inside a droplet).

6.2.1 Salt ions

Salt ions are a ubiquitous component in physiological fluids. When salt concentration changes, the viability of enveloped and non-enveloped viruses exhibits different responses. For instance, adding salt to a droplet medium has been shown to improve rather than reduce the viability of some non-enveloped viruses [156, 159]. Since viruses are highly charged macromolecules [160, 161], changes in ionic concentration can act to screen the electrostatic interactions in the system and thus influence both self-assembly and stability of non-enveloped viruses [162–168]. In contrast to non-enveloped viruses, salt ions usually have a toxic effect on enveloped viruses, yet the precise mechanisms remain unclear [141]. The way enveloped viruses acquire their lipid membrane varies from virus to virus [169–171], where in some cases the complexation of capsid protein and lipid membrane can be driven by electrostatic interactions [170, 172], which are modified by changes in the ionic concentration. Salt ions also interact with lipid membranes and can cause structural and mechanical changes [173, 176], potentially leading to inactivation of enveloped viruses [14, 141, 142, 177, 178]. Nonetheless, some enveloped viruses remain stable at medium and high RH despite their lipid bilayers being similar to those of other enveloped viruses [141, 151]. Furthermore, different salt ions also have different affinities for adsorption to lipid membranes [173, 175, 179].

It is also important to clarify the link between salt concentration, RH, and virus viability. As water evaporates from a respiratory droplet (Sec. 3), salt ions become more concentrated, yet their concentration does not correlate with RH in a linear manner [67, 141, 155]. Concentration of salt in the droplet residue depends on the droplet composition and RH: an initial concentration of ~ 200 mM NaCl can thus increase all the way up to 10 M [155]. Even higher concentrations can lead to an efflorescence transition, where salt crystallizes (at least partially) out of the aqueous part of the droplet (Sec. 3.2.2). Yang et al. [141, 142] identified three regimes of RH for the viability of influenza A virus, connected to the oft-observed non-monotonic U-shaped viability curves (Fig. 11): (i) Close to RH = 100%, concentrations of salts in the droplet stay at levels close to physiological conditions, and virus viability is thus well-preserved. (ii) Intermediate values of RH (50% to ≲ 100%) involve concentrated and even supersaturated salt conditions, which act toxic to the virus, and viability consequently decreases with decreasing RH. (iii) In a very dry environment (RH ≲ 50%), salts can undergo the efflorescence transition and crystallize out of the solution. The concentration of remaining dissolved ions in the droplet residue is low, and consequently, virus viability improves. If that is the case, the phenomenon of efflorescence turns out once again to be one of the culprits for the higher likelihood of droplet transmission at low RH: it both reduces the size and sedimentation of droplets (Sec. 3.2.2) as well as improves the viability of aerosolized viruses.
6.2.2 Proteins and surfactants

Adding various proteins, biopolymers, and lipids into droplets can also drastically influence the effect of RH on the survival of aerosolized viruses. Respiratory droplets can differ to great extent both with respect to the type and the amount of molecules present in them (Sec. 2.2). This is important, since studies have observed different responses of viruses based on the origin and composition of droplets. Saliva has, for instance, been indicated to provide an important initial barrier to influenza A infection [180], and both cell culture medium and artificial saliva have been shown to be more protective still [157]. On the other hand, influenza virus has been observed to survive much longer on banknotes when in the presence of respiratory mucus [132], and extracellular material containing mucins has been shown to provide a (concentration-dependent) protective effect against RH-dependent decay of both influenza A and bacteriophage Φ6 infectivity [181]. At low RH, mucin has also been shown to protect viruses from damage by dehydration [66]. Peptones, lipids, and apolar amino acids also reduce virus losses, probably by protecting them against surface inactivation (Sec. 6.2.4) [66, 148, 182–185]. Protective effects have also been reported for polyhydroxy compounds [156, 186]. Importantly, the protecting concentrations of these components can be related to the salt concentration in the droplet medium [142, 156, 184]. The total composition of the droplet is the one determining how the droplet shrinks with time and whether or not it undergoes an efflorescence transition (Sec. 3.2.2).

6.2.3 Droplet pH

Droplets can also vary in the value of their pH [56, 187–189], which can change with RH and with that affect the viability of aerosolized viruses in the droplets. Already from a purely electrostatic perspective, a change in pH modifies the charge on the ionizable amino acids [190, 191], which can lead to conformational changes in viral proteins [141, 192], eventually destabilizing the virus [193–195]. Yang et al. [141] furthermore found that the response of enveloped viruses to changes in RH depends on whether the process of fusion requires low pH or not. Viruses that require acidification before fusion (such as influenza virus and SARS-associated coronavirus) were found to be less stable at intermediate RH (50% to 90%) compared to higher and lower RH. Evaporation at intermediate RH can significantly lower the pH while not drying the droplet out completely. Viruses that fuse at neutral pH (such as RSV) were found to be more stable at intermediate RH, and viruses that can fuse at both low and neutral pH (for example vaccinia virus and pigeon pox virus) were found to be insensitive to RH. pH also interacts with other variables: Stallknecht et al. [196] observed a strong interactive effect between pH and salinity on the viability of influenza virus. The viability was highest at zero salt and high pH, high at high salt and low pH, but lowest at both high salt and high pH as well as low salt and low pH.
6.2.4 Inactivation at the air-water interface

The fate of aerosolized viruses depends not only on the physico-chemical environment in the droplet but also on the precise location of the virus inside it, as droplets themselves can be internally heterogeneous [66]. It is known that viruses that adsorb at the air-water interface (AWI) of a droplet can be inactivated to a great extent. The reasons are dehydration and unfavourable interaction with the AWI, such as surface tension, shear stress, denaturation of proteins in contact with air, and conformational rearrangements driven by hydrophobicity [157,197–201]. The contribution of different mechanisms depends on RH, which affects droplet evaporation (Sec. 3) and in this way changes the AWI available for virus accumulation [141]. The extent to which a virus is attracted to the AWI is influenced both by the ionic strength and pH of the suspending medium as well as by the relative hydrophobicity, surface charge, and shape of the virus [202,205]. Both high ionic strength and large surface hydrophobicity create a high affinity for virus adsorption to the AWI [157,199]. Torres et al. [206] have measured the diffusion and adsorption of cowpea chlorotic mottle virus at different pH conditions, and found that the diffusion of the virus from the bulk solution to the AWI is an irreversible adsorption process that changes with pH (and therefore with the net surface charge of the virus [207,208]). Recent experimental and computational methods have shown that viruses differ among themselves with respect to their surface hydrophobicity [209,210], providing another possible clue into the different survival responses to RH in different viruses. Furthermore, enveloped viruses are more affected by surface inactivation at the AWI than non-enveloped ones [148], either because of differences in their affinity for the adsorption to the AWI or because they are not affected by interfacial forces in the same manner as non-enveloped viruses [199,211]. Surface-active compounds in the droplet, such as various proteins, amino acids, and surfactants, can accumulate at the AWI [212] and, in doing so, prevent the aerosolized viruses from reaching the AWI and being inactivated [199], showing once more the importance of droplet composition for the survivability of enclosed viruses.

6.3 Experimental factors

Often, droplet composition is simplified in both experimental and theoretical models and comprises salt ions, proteins, and surfactants to different extents [23,122,123]. For instance, salt ions are not always included in model respiratory droplets, and when they are, their typical concentrations range anywhere from 30 to 300 mM [66,142,158]. Thus, while various simplified models of respiratory droplets exist, the exact nature and concentration of salt ions or proteins could prove critical in determining the RH-dependent response of virus viability upon aerosolization. Different artificial means of producing virus aerosols may also not be comparable to the natural release of viruses in saliva or respiratory mucus [66,157], which can act as an organic barrier against environmental extremes [123]. The composition of both saliva and respiratory mucus is a complex mixture containing different electrolytes, proteins, and surfactants, with each of the components exceeding the mass of the virus by several
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orders of magnitude \[66,155,157\], and both have been shown to potentially influence virus survival \[213,215\].

7 Conclusions

Seasonal periodicity of respiratory infections in humans is driven by complex mechanisms, ranging from environmental to social. Mounting evidence suggests that a critical player in the observed seasonality is the RH of air inside buildings. Low indoor RH, as experienced during winter months or inside airplanes, directly or indirectly influences several mechanisms that increase the transmission of respiratory diseases.

In this review, we attempted to summarize and elucidate those known physical mechanisms of droplet and airborne transmission that are influenced by RH. RH starts to play a role the moment respiratory droplets are exhaled into the air. On the one hand, drier air accelerates the evaporation of the droplets, while on the other hand, it dehydrates them more, so that the size of droplet residues after evaporation has stopped is smaller than in more humid air. Both effects cause the droplets to settle to the ground more slowly and remain in the air longer at low RH, thereby leaving more potential pathogens suspended in the air. RH furthermore governs the extent to which viruses carried by the droplets survive. This relationship is complex and depends both on the droplet composition as well as on the structure of the virus, where enveloped viruses tend in general to be more vulnerable to environmental changes. Quite remarkably, the viability of several viruses improves when RH is lowered below 50%, which is also one of the explanations for the strong seasonality of the influenza virus. An important yet less noticed phenomenon that accompanies evaporation of respiratory droplets is efflorescence, which, as evidence suggests, occurs at least to some extent in respiratory droplets. It accentuates the effects of RH by rapidly changing droplet size, consequently affecting the detailed nature of droplet composition.

Indoor RH during winter in temperate climates is typically around 10% to 20% lower than during summer, and an important reason for this are heating and poor ventilation of indoor spaces, not necessarily healthy environment in itself \[40,216,217\]. This review shows that keeping the indoor RH at around 50% is not only the most comfortable level for humans but perhaps also a good target value to aid in preventing the spread of infectious diseases. A better understanding of where and how it affects the behavior of droplets and any pathogens contained in them would allow us to exploit this knowledge to control indoor RH in such a way as to minimize the spread of droplet- and aerosol-borne disease.

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