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Effect of Relative Humidity in Air on the Transmission of Respiratory Viruses

Adriaan Davidse[1] and Richard N. Zare[2]

Viral respiratory infections have plagued mankind over its known history. Unfortunately, there has been a lack of meaningful progress in preventing the spread of viral respiratory infections globally. The central dogma appears to be that viruses are the villains. This framing focuses on a viral load balance (VLB) in the air. It follows that physical dilution through various means have been the primary focus of attempts to reduce the spread of infections. The problem of obesity provides a good example of how paradigm blindness can slow down progress in a field. Obesity has been framed as an energy balance disorder that blames overeating and lack of exercise for weight gain. Reframing obesity as a disorder of fat metabolism and storage caused by the quantity and quality of carbohydrates in the diet, referred to as the carbohydrate-insulin model (CIM), opened an alternative line of questioning with a testable hypothesis. Similarly, we postulate an alternative way to frame the spread of viral respiratory infections that would lead to new insights and potentially new ways to prevent infections.

It has long been recognized that viral respiratory infections show a pronounced seasonal variation, referred to as seasonal forging, such that they increase in the winter but decrease or virtually disappear in the summer. In temperate regions, people spend over 90% of their time indoors. This is, therefore, where most respiratory infections are expected to occur. Evidence has been accumulating for decades on the strong correlation between variations in indoor relative humidity (RH) and variations in infection rates. Within a RH Goldilocks zone of 40%-60%, encapsulated viruses like influenza and SARS are optimally inactivated outside the infected host. Below 40% and above 80%, viruses can survive for extended periods in the air or on surfaces. This may explain in part the seasonality of infections as the indoor level of RH in winter is typically about 20% and above 40% in summer in temperate regions. However, the mechanism for the inactivation at midrange RH (in summer) is not well understood. This paper offers a hypothesis that could explain these observations.

We have demonstrated that H_2O_2 and other reactive oxygen species (ROS) are formed spontaneously at the water-air interface of pure water microdroplets. Using only water and a nebulizing gas in the presence of oxygen, we have demonstrated the significant disinfectant potential of pure water microdroplets caused by the activity of H_2O_2 and other ROS. We postulate that spontaneous H_2O_2 and ROS formation in viruses containing exhaled microdroplets have a similar virucidal effect at mid-range RH. The droplet evaporation rate is sufficient to concentrate the solutes and provide enough time for reactions to occur at significantly higher rates than in bulk solutions. The concentration of H_2O_2 has also been shown to be positively correlated to RH. In addition, several other ROS/RNS may be present or formed through interactions with H_2O_2 that may act as even more effective virucide disinfectants to inactivate the virus. Below RH 40% evaporation happens too rapidly for these reactions to make an impact before the droplet is desiccated, and above RH 80% the solutes remain too diluted. Rapid inactivation of viruses at midrange RH may therefore play a greater role in preventing infections than physical dilution of virus load in the air through excessive mechanical ventilation. Similar to obesity, we suggest that a new paradigm that considers virus infectivity outside the host rather than the virus load balance in the air alone could greatly contribute to our understanding of respiratory infections. The proposed new "Relative Humidity Infectivity" RHI paradigm could explain the causal mechanisms underlying seasonal respiratory infections.

[1]PO Box 93167 Headon PO, Burlington, Ontario, L7M 4A3, Canada. Email: adavidse@protonmail.com, [2]Department of Chemistry, Stanford University, Stanford, CA 94305 USA. Email: zare@stanford.edu. Corresponding author. Published online 17 December 2021; doi:10.1142/S252973252140006X

This can point to better prevention strategies that avoid further distortion of our indoor environment and create conditions within which humans can thrive and be optimally protected. We need more focus on testing the various hypotheses and more data to determine which of the two paradigms will lead us in the right direction or how to use the best of both in an optimal combination. The stakes cannot be higher, and the potential for eradicating future viral respiratory pandemics with nature-based solutions may be right under our noses, literally.

Keywords: Relative Humidity; Seasonality; Microdroplets; Influenza; SARS-CoV-2; Viral Transmission; Indoor Air Quality; Reactive Oxygen Species.

BACKGROUND

Viral respiratory infections have plagued mankind over its known history. Unfortunately, there has been a lack of meaningful progress in preventing the spread of viral respiratory infections globally. The central dogma appears to be that viruses are the villains and that pandemics are inevitable and unpreventable. Once these viruses become endemic, we must accept that we must live indefinitely with reoccurring seasonal infections. This virus-as-a-villain framing focuses on a viral load balance (VLB) in the air. With the VLB paradigm, we have concentrated our efforts mainly on attacking the virus by external means that include physical dilution of the virus in the air through excessive mechanical or natural ventilation, filtration, UV irradiation, chemical fumigation, and chemical sanitation of hands and surfaces, even when it is evident that transmission of the virus is not occurring through touching of contaminated surfaces.

These methods of intervention are nonselective, and many sanitize the air and surfaces through mass sterilization. There is always a concern that the destruction of the external biome will promote the survival of more virulent pathogenic viruses that could further mutate via horizontal gene transfer into even more virulent species. The framing of the virus-as-a-villain paradigm justifies such extreme measures that indiscriminately annihilate all viruses (and all other living organisms in the air and on surfaces). The vast majority of viruses are nonpathogenic to humans and play a vital role in maintaining healthy ecosystems. Phages are critical to managing bacterial populations, and the benefits of viruses far outweigh their negative impact. Virologists tend to study almost exclusively pathogenic viruses, which further contributes to our distorted view of viruses. Without viruses, we probably would not survive for longer than a day[1]. By attempting to eradicate all viruses from our environment, we lose the opportunity to train our adaptive immune systems with weakly pathogenic viruses that could infer immunity to more virulent viruses later. Evidence suggests that immune cells for the common cold may recognize SARS-CoV-2[2]. Both belong to the larger family of coronaviruses. The VLB paradigm commonly pays little attention to the seasonality of viral infections. We argue that a deeper consideration of the reasons why seasonal variations occur leads to a different paradigm for addressing this critical need for reducing the spread of viral respiratory diseases.

THE SEASONALITY OF VIRAL RESPIRATORY SICKNESS

It has long been recognized that viral respiratory infections show a pronounced seasonal variation, referred to as seasonal forging, such that they increase in the winter but decrease or virtually disappear in the summer[3]. Figure 1 presents one of many similar examples. Encapsulated viruses cause many of the most severe viral respiratory infections, most notably influenza and SARS. These infections all follow reoccurring and highly periodic seasonal patterns that sometimes escalate into full-blown pandemics. The H1N1 influenza A virus responsible for the 1918 Spanish flu and the 2009 swine flu pandemic are still with us today. The seasonal nature of these infections is ingrained in our language and culture. We refer to the "flu season" without considering where the virus "retreats" to during the virus "off-season," and why it seems to disappear.

Viral respiratory infections occur mostly *indoors* in temperate regions. Often, it is said that seasonal transmissions are a behavioral issue that suggest infection rates increase in winter because we spent more time indoors and in closer proximity to other people who may be infected. This blames people for what they cannot control if social proximity is not the primary causal driver for the rise of infections during winter. We know that people, on average, spend more than 90% of their time indoors in temperate regions[5]. Thus, seasonal behavioral variations are not sufficiently significant to explain variation in seasonal infection rates. If anything, people are more likely to travel in summer, stay in hotels, frequent restaurants, and attend other crowded indoor events. Indoor temperatures also do not vary significantly between the seasons because of the nearly ubiquitous presence of HVAC systems in wealthy countries in temperate regions.

Similarly, mechanical ventilation and filtering do not vary significantly between the seasons. Because ventilation and filtering are required to maintain acceptable levels of air quality, there is no reason to assume that this requirement would be affected by variations of the seasons. During mild summer days, people may choose to reduce mechanical ventilation and augment it with natural ventilation by opening windows.

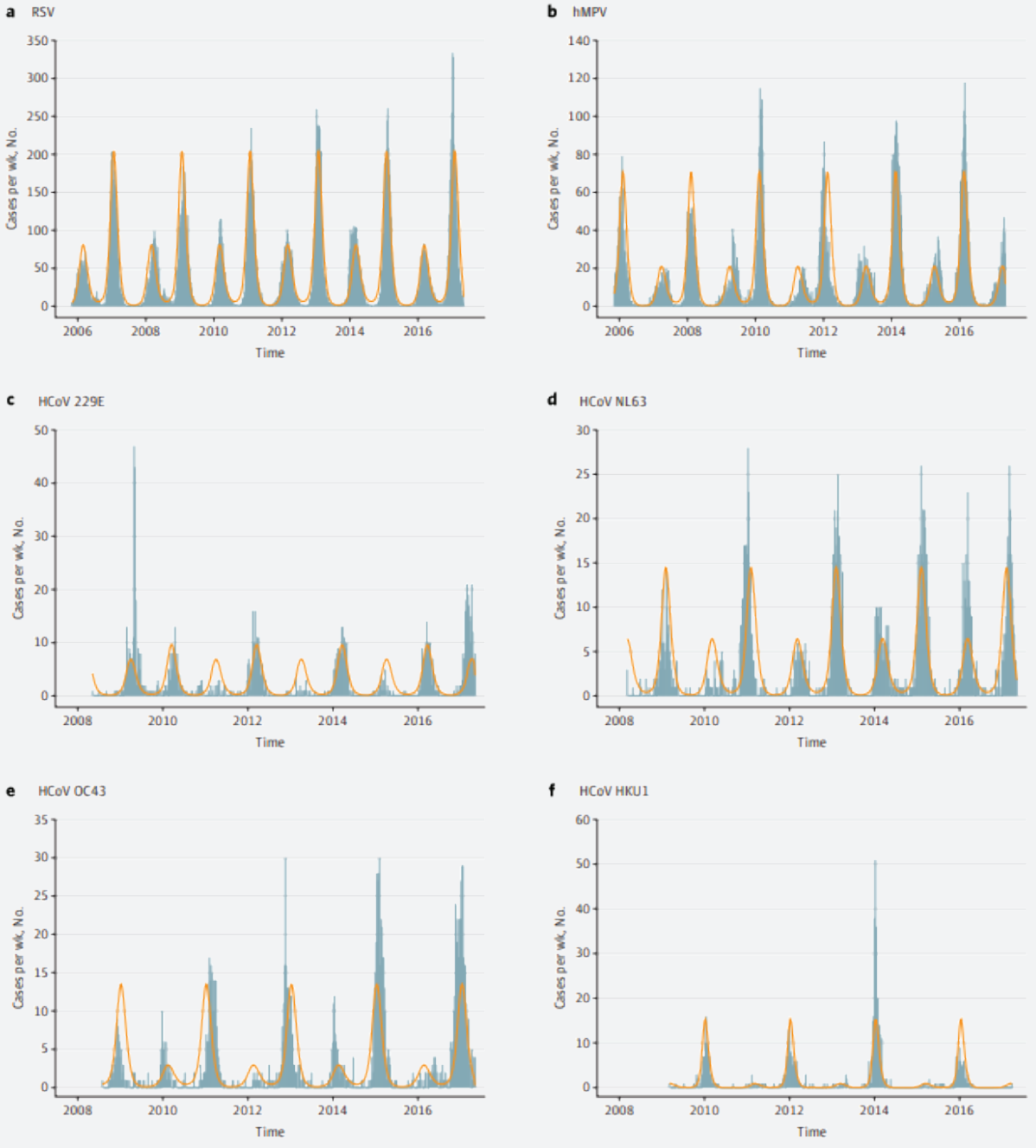

Figure 1. Seasonal epidemics of selected respiratory viruses in Alberta, Canada, 2005–2017[4].

Therefore, ventilation alone cannot explain why we observe such a significant decline of infections in summer and such increased infection rates during winter. Reducing the viral respiratory load in the air through physical dilution with excessive ventilation is therefore unlikely to be effective. Something else that has largely remained invisible or ignored must be causing the significant variation in seasonal infection rates. The fact that seasonal infections are so consistently periodic and predictable suggests that there exists one or more powerful systemic causal drivers involved. What are they, and can they be controlled to provide the same benefits of low infection rates during summertime if applied all year to indoor environments?

WHAT IS THE MAIN DRIVER BEHIND SEASONAL INFECTION RATE VARIATIONS?

Evidence has been accumulating for decades on the strong correlation between variations in humidity and the variation in the seasonal viral respiratory infections in temperate regions[6]. Figure 2 presents two such examples. A key shortcoming of these typically large-scale statistical studies is that they often rely on meteorological climate data and epidemiological infection data to explore these correlations. Researchers are forced to use outside meteorological data because of the lack of sufficient direct empirical data on indoor humidity. Despite the fact that both data sets are not ideal representations of the microenvironments within which the majority of infections occur, the correlation between changes in indoor relative humidity levels and changes in seasonal infections stand out statistically as the strongest single relationship in the system.

Previous research shows that low relative humidity (RH) significantly impacts the susceptible host defenses negatively in multiple ways[8]. The components and processes of the structural/intrinsic immune system involved in trapping the inhaled virus in mucus and the mucociliary clearance that eliminate the inhaled viruses from the respiratory epithelial surface are unable to perform their function in low RH environments. This fact leaves people much more susceptible to infection if the virus has been transmitted to them. In addition, a recent report[9] showed that low RH could increase the number of exhaled droplets generated by the infected host by up to as much as double compared to properly humidified environments. The same researchers argued that face masks are effective at preventing the spread of respiratory diseases in part because of a localized humidity effect[10].

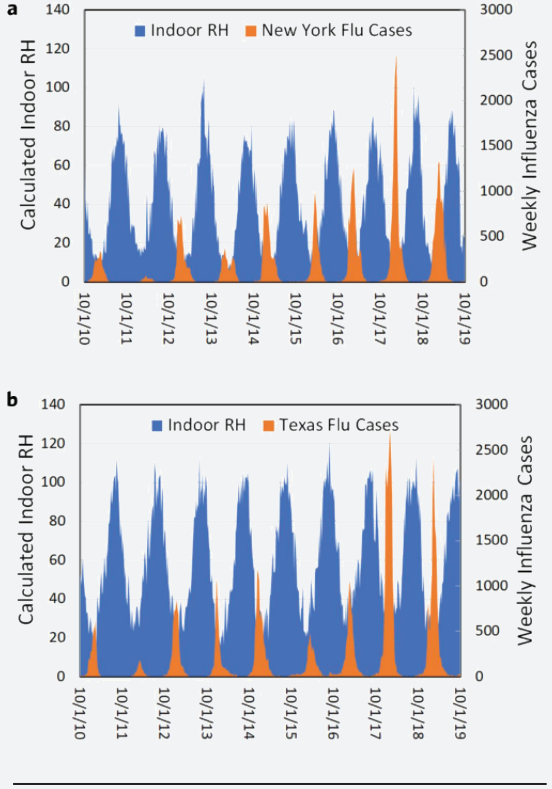

Figure 2. The strong correlation between seasonal infections and indoor relative humidity[7].

Evidence of the relationship between virus decay in the environment outside a host and the level of RH has also been presented before[11]. This confirms that RH acts independently on the virus in the exhaled droplet outside of the body and simultaneously on the infected and susceptible host as well. However, unlike bacteria and fungi, which show a linear relationship between decreasing RH and decreasing pathogen survival, respiratory viruses show a U-shaped relationship between indoor RH and viability, surviving best in high or low RH, but surviving much more poorly in the relative humidity range of 40%–60%[11]. Figure 3 illustrates this behavior.

At RH below 40%, viruses proportionally survive for longer the lower the indoor RH is. For reference, natural outdoor RH rarely drops below 40% at any point of the year for any significant period in virtually any location where people live. Nature always works to maintain a water balance in the air well above 40%. However, in temperate regions, during winter, the indoor RH is on average 20% or lower in some cases[13,14]. We are responsible for this unnatural distortion of the humidity component in our indoor air quality (IAQ) during the winter months, which may be at the heart of the seasonal rise in infection rates during that period. When RH drops below 20% inside our buildings, respiratory viruses can survive for hours suspended in the air and travel long distances where they can infect people through inhalation. This may be the most critical insight to understanding the reason behind the seasonality of viral respiratory infections and the peaking of infections during the winter months. Because the primary driver is the indoor RH of the air, and not the outdoor temperature per se, we may experience the same low indoor RH during summer. Excessive use of air-conditioner (AC) systems or dehumidifiers can remove too much moisture from the air. The degree to which these effects will show up in the epidemiology data will depend on how pervasive these AC systems are, what the external conditions are, and how these systems are operated. The same influence of low indoor RH on infections will still be present, but the effect on the spread of airborne respiratory diseases will be more localized, and not as pervasive as in winter months where heating is regulated and therefore ubiquitous, and humidification is unregulated and typically rare. Because we sense small changes in temperature directly but cannot sense even large changes in RH

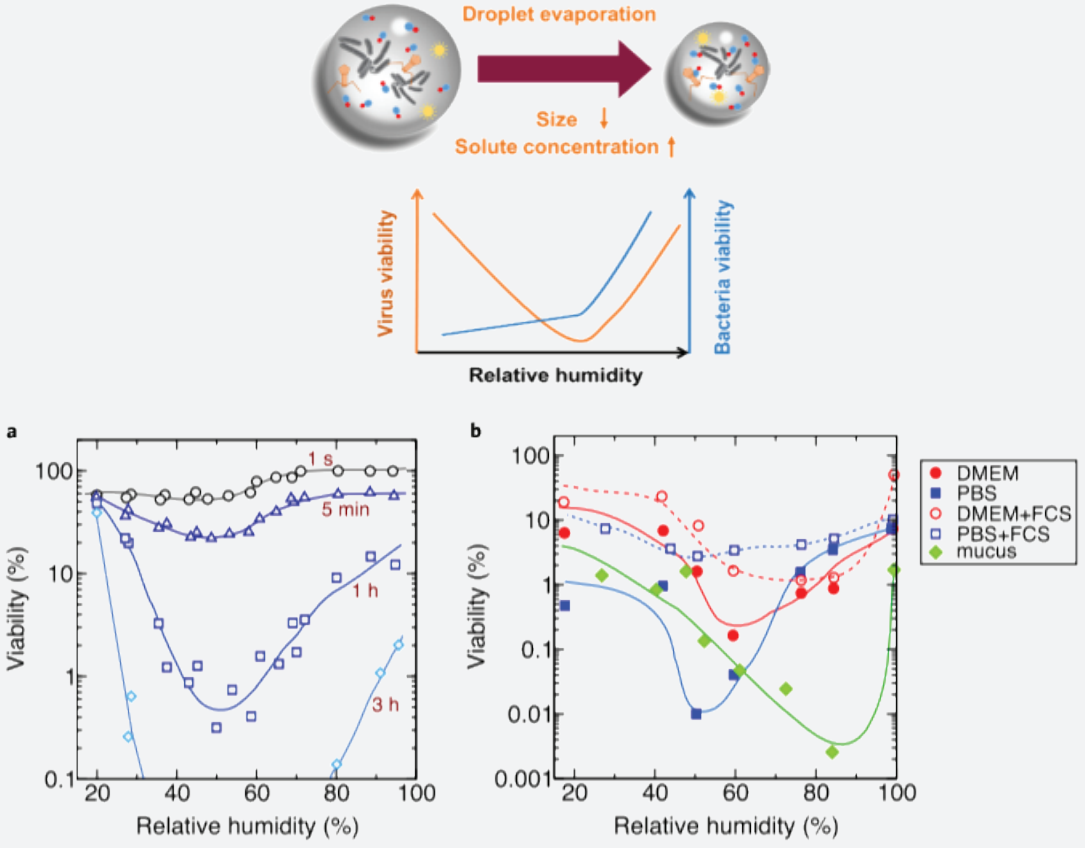

Figure 3. The difference in the relationship of viruses and bacteria with percentage relative humidity of the air[11,12]*. a = Langat virus, b = influenza A virus.*

directly, we are more conscious and therefore more focused on thermal comfort than relative humidity†.

The negative effects of low RH that leads to the release of more viruses into the air, that accumulates and can remain active for longer and therefore increase the likelihood of transmission, and the decrease in the ability of the susceptible host to avoid infection and limit the severity of disease development lead to significant compounding negative outcomes for people individually and collectively. Maintaining indoor RH in the Goldilocks zone of 40%–60% is critical for limiting or even eliminating the spread of viral respiratory diseases and for providing a natural environment within which humans can thrive, but we need to maintain a whole systems perspective to fully appreciate it.

THE VALUE OF EXPLORING CAUSALITY

Even if we can accept that indoor RH is strongly correlated with infection rates in the U-shaped relationship shown in Figure 3, as we explained above, we still need to elucidate the causal mechanism by which RH changes impact rates of infections. By proposing a mechanistic view on the relationship between RH and infection rates with supporting evidence, we hope to enhance the scientific discourse toward developing a better theory of RH-mediated infection prevention. Such a theory will allow us to better understand and interpret infection patterns in other regions of the world. It will also allow us to design better proactive healthcare interventions to prevent the spread of viral respiratory infections, by better understanding the potential impact of differences in local

†In addition to the direct impacts of indoor RH on infection rates described above, low indoor RH affects our bodies in other ways that may also negatively impact our ability to respond to infections optimally. A lack of proper sleep arising from an excess of the stress hormone cortisol in the blood may compromise the effectiveness of our adaptive immune system. It was recently discovered that when the skin is stressed, it can independently produce cortisol[15]. Prolonged exposure to a low RH environment leads to chronic dehydration that stresses the skin sufficiently to trigger this feedback loop.

circumstances. It will help us to recognize and limit potential unintended negative consequences of any interventions proactively.

The problem of obesity provides a good analogy for the problems we are facing in considering viral respiratory disease and the lack of progress we have made in preventing uncontrolled spread. Even though obesity has been the focus of significant research for over a century, we have seen a rapid worldwide increase in Body Mass Index (BMI) of populations and a considerable increase in type-2 diabetes. How can this be? For almost this entire time, research was based on the flawed paradigm that obesity is an energy balance disorder. When you take in more calories than you expend, the excess energy is stored, resulting in weight gain. Energy balance considered the principles of physics without considering the biological mechanisms that promote fat storage and weight gain[16]. Weight gain is the positive energy balance, but it does not explain why it happens. Because obesity was defined as a behavioral problem of overeating and lack of exercise, treatment and prevention were focused on why people are overeating and ways to promote more movement and exercise. None of these insights and efforts made an impact on limiting the growth of obesity and type-2 diabetes, which is a global pandemic today.

An alternative paradigm[16] proposes that the quality of the food we eat, rather than the quantity alone, leads to a hormonal response that is the main driver behind fat storage and developing a positive energy balance. By reframing obesity as a disorder of fat metabolism and storage caused by the quantity and quality of carbohydrates in the diet, referred to as the carbohydrate–insulin model (CIM), opened an alternative line of questioning with a testable hypothesis. The evidence supporting the CIM paradigm can be used to objectively challenge the existing and likely fatally flawed energy balance paradigm. The healthcare implications would be that the focus of prevention and treatment should shift toward changing the quality of the diet rather than focusing on the behavioral aspects that are driving the quantity of calorie intake and calories spent exercising.

A MECHANISTIC VIEW OF THE FATE OF A VIRUS IN AN EXHALED DROPLET

When the exhaled droplet exits the lung from an environment of RH nearly 100%, it encounters the external environment that is at a lower RH[††]. The difference in the water vapor pressure between the droplet and the air leads to the rapid evaporation of water from the droplets. The rate of evaporation was characterized before[17]. Upon entering the air, droplets rapidly lose almost half their volume within seconds or faster, and then evaporation slows down. Smaller droplets tend to evaporate much faster than bigger ones. Smaller droplets also tend to contain more of the virus, and there is more of them by count, even though they make up a small portion of the overall volume of water exhaled[18].

An often-suggested hypothesis focuses on the impact of gravity on the path of exhaled droplets[12]. With higher levels of indoor RH, evaporation would occur more slowly, and more droplets would fall to the ground faster and within a shorter distance. In contrast, with low indoor RH, evaporation will happen faster and convert more droplets to aerosols that can remain suspended for longer times and travel farther distances. This work was done under the assumption that 5 μm defined the boundary between what was considered an aerosol or a droplet. Recent research substantially redefined this boundary to 100 μm[19]. Also, with this reasoning, we should see the greatest reduction of infections at the highest indoor RH approaching 100% where evaporation of droplets virtually stops, and the maximum droplet weight is conserved. While gravity may indeed be more impactful at higher RH than lower RH, it does not satisfactorily explain the U-shaped relationship between indoor RH and infection rates.

The changes in chemistry within the smaller droplet sizes have been proposed as a cause of influenza virus degradation. The stability of viruses may depend on chemical events such as osmotic bursting or changes in pH that may alter a protein's geometry, but such claims have not been proven experimentally yet[20]. An important but less noticed phenomenon that accompanies the evaporation of respiratory droplets is efflorescence[21]. Solutes are concentrated above the relative humidity efflorescence point by evaporation. When RH drops below this point and evaporation continues, solutes effloresce, forming crystals. This takes the virus out of solution and protects it from the hyper ionic environment that could be chemically harmful. The RH at which the aerosol efflorescence is around 40% after which the remaining water is expelled, and the virus is preserved in a near fully dried state, but still intact. No chemical reactions can take place at this point. Rehydration can occur at RH of about 75%. This can happen when a susceptible host inhales a fully desiccated

[††]We can express humidity in absolute terms (AH) or RH. AH refers to the absolute amount of water in air, typically expressed as grams of water per kilogram of air. RH, described in percentage terms, refers to the amount of water in the air as a proportion of the total amount of water that the air can hold at saturation level at a particular temperature and air pressure. Because AH and RH in the same location are correlated to each other through temperature, outdoor AH and indoor RH change are highly correlated when the indoor temperature is held constant, and no water is added or removed from the indoor air. Therefore, outdoor meteorological AH data is a very close proxy for indoor RH at a given temperature and air pressure. The correlation between outdoor AH and indoor RH with infections over the same period is therefore equivalent.

virus particle in low RH conditions. The virus is then reactivated in the high RH environment in the lung that leads to infection. These mechanisms explain why viruses can survive and accumulate in the air for extended periods as desiccated, dormant, but still infectious particles when indoor RH is below 40%.

In summary, the impact of RH of the water vapor pressure gradient between the droplet and the air, which drives evaporation rates, and droplet deposition physics are well studied and understood. The effect of efflorescence at low RH that protects the virus from harmful chemical reactions has been demonstrated below RH of 40%. However, the mechanism responsible for the rapid inactivation of encapsulated viruses prior to efflorescence has been claimed in the past to not be understood. To put it more simply, we know why viruses survive for long periods in the air at RH below 40%, but we do not know how they are inactivated in the RH Goldilocks zone between 40% and 60%, only that they are optimally inactivated in this range of RH. A better understanding of the underlying mechanism of virus inactivation may lead to the development of a general theory of respiratory virus inactivation that we could use to test on other nonencapsulated viruses.

Virus inactivation at the air–water interface of an aerosolized droplet has been proposed, although the mechanism is poorly understood[12]. Our own studies of water microdroplets offer insight into the chemistry that could play a key role in the inactivation of pathogenic species. The chemical microenvironment of a water microdroplet involves the spontaneous formation of reactive oxygen species (ROS), which includes the hydroxyl radical (•OH) and hydrogen peroxide (H_2O_2) because of the high electric field present at the air–water interface of a microdroplet[22–24]. Aqueous microdroplets of nominal 10-μm size have been shown to act as a bactericide in the inactivation of *Escherichia coli* and *Salmonella typhimurium*, where the presence of ROS in microdroplets and the surface charge of microdroplets play roles in the destruction of these bacterial cells[25]. We also showed that the concentration of H_2O_2 in a water microdroplet has a linear relationship within a given range of RH that aligns with the seasonality of infectious diseases[26]. This spontaneous formation of H_2O_2 in water microdroplets in the presence of O_2 has been demonstrated to occur in microdroplets up to 20 μm in diameters with forced air generation of microdroplets similar to what happens on exhaling droplets from the lungs. As previously stated, the bulk of the droplets that are exhaled by normal breathing are small, with a normal distribution around 7 μm in diameter[27]. While the bulk of the water volume is contained in few, but much larger droplets that tend to form in the mouth, the larger number of smaller droplets that originate in the lungs typically carries the bulk of the virus, especially in cases of severe COVID-19 that leads to greater virus shedding. Human respiratory droplets are composed mainly of water (~90%–99%), so there is no reason to believe that the spontaneous formation of H_2O_2 will not occur in infectious respiratory microdroplets similar to pure water droplets. Further research is planned to confirm this.

The solutes that make up the remainder of the volume in respiratory microdroplets are mostly inorganic ions, sugars, proteins, lipids, DNA, and, potentially, pathogens. However, people who are infected with a respiratory virus, will have an immune response against the infection. Chemicals involved in the immune response that are not consumed by the immune reactions can be found in exhaled droplets. The use of these compounds has been explored as potential biomarkers to indicate when a person is under oxidative stress, that is, has inflammation or is launching an immune response against an invading pathogen. ROS like H_2O_2 and HOCl has been measured in the exhalant of people infected with a respiratory virus[28,29]. Given our recent findings of the auto-generation of H_2O_2 in microdroplets, more work is needed to understand the origin of the detected H_2O_2 in the droplets of infected people. Other compounds like myeloperoxidase (MPO) that occurs in the saliva or mucus of people with inflammation or undergoing oxidative stress in response to infection are also present in exhaled droplets of infected people and have been proposed as an active disease biomarker[30]. Reactions of proteins with HOCl produce chloramines that are more stable but still able to oxidize other proteins found in exhaled droplets as well. Reactive nitrogen species (RNS) have also been proposed as biomarkers for infection and can also be present in infected people's exhale droplets. In addition, RNS like nitric oxide (NO) is produced both inside neutrophils and also inside the nasal cavity. When active viruses are inhaled through the nose, NO can act as another intrinsic protection layer as it has strong virucidal properties. NO is also present in droplets exhaled through the mouth or the nose. In experimental models with simulated droplets, these compounds are typically not included. Emphases are placed on the role of NaCl, but not the "immune response" chemicals that are expected to be present in substantially higher quantities in the droplets of infected people compared to healthy people. Because these chemicals are produced in the proximity of the virus infection, they are more likely to occur with the viruses in the exhaled microdroplets as well.

At very high RH (~100%), the microdroplet microenvironment closely resembles physiological conditions. No, or very slow, evaporation occurs, and solutes remain diluted inside droplets with reactions limited by slower diffusion rates. In addition, it is important to point out that the spontaneous production of H_2O_2 (and presumably other ROS) depends on the size of the droplet, increasing markedly as the droplet diameter is varied from 10 to 1 μm[22–24]. Below RH of 40%, droplets are rapidly desiccated within a fraction of a second,

and no diffusion of chemicals can occur anymore, so no more chemical reactions are possible. The virus survival rates are very high in both high and low RH cases. At low RH, the impact on infection rates is speculated to be more significant because a greater number of desiccated virus particles will accumulate in the air. At high RH, more droplets are expected to fall to the ground. Between RH 40% and 60%, droplets below 10 μm can lose more than half their volume in under a second. This shrinkage increases the concentration of all solutes in the microdroplet, which brings the various ROS/RNS/N-Cl agents in much closer proximity to the sub-micron-sized virus particle. In addition, we hypothesize that the H_2O_2 that is formed spontaneously at the droplet–air interface can react with the increased hyperconcentration of Cl^- ions in the presence of the catalyst MPO to produce HOCl[31]. HOCl is over a 1,000 times more powerful than H_2O_2 as a virucide. In addition, reaction rates are often radically faster (greater than millions of time faster) in microdroplets compared to bulk solutions[32,33]. Therefore, it is plausible that as evaporation continues and the solutes get even more concentrated, significant amounts of compounds with powerful viricidal activity are produced and chemically inactivate the virus trapped inside the shrinking, by the highly oxidative environment. These reactions are expected to continue to increase the amount of the virucidal chemicals until the droplet is desiccated.

The microdroplet may achieve an equilibrium state without being fully desiccated in this range of RH. In that case, the continuous auto-production of H_2O_2 could continue to react with NaCl and MPO to continue the production of HOCl, which in turn can continue to react with anything in its environment, including the virus. Under these conditions, the shrinking microdroplet acts in an analogous way to a phagosome inside a neutrophil immune cell that undergoes a burst of HOCl production to inactivate the pathogen. Maintaining RH between 40% and 60% may increase the concentration of solutes at just the right rate to provide enough time for the radically enhanced reaction rates in microdroplets to create the virucidal chemicals to inactivate any virus particles trapped inside. Under these conditions, it is as if the body's immune response to invading viruses is extended to outside the body in the exhaled droplets and amplified by the hyperconcentration of the immune chemicals by evaporation. Such powerful oxidation reactions would be highly damaging for the epithelial cells in the lung if it occurred there. Therefore, we do not expect droplets at high RH that resemble physiological conditions to accelerate these types of reactions. The phagosome within which these oxidative bursts occur that kill invading virus shields the immune cells from these reactions.

The combination of the above processes would explain the U-shaped virus survival rate, with RH 50% being ideal for minimizing the virus survival. More work is needed to validate these hypotheses experimentally, but the existing

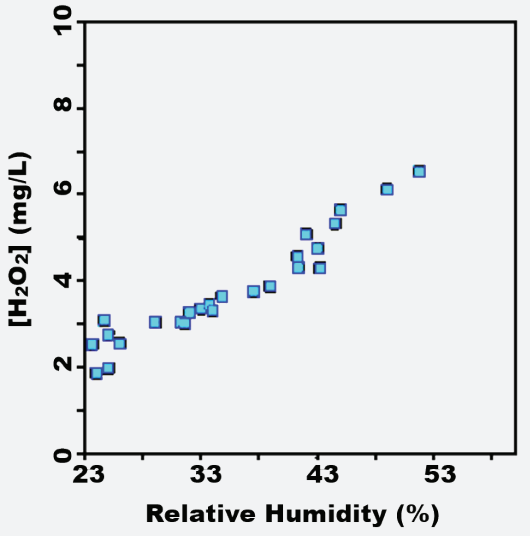

Figure 4. The relationship between change in relative terms (RH) and change in H_2O_2 production[26].

experimental evidence of the formation of H_2O_2 and the positive relationship between H_2O_2 formation and increasing RH levels from 23% to 55% provide significant support for the plausibility of these mechanisms and the validity of this direction of exploration (Figure 4)[26].

H_2O_2 by itself has been demonstrated to have a powerful bactericidal effect and may be sufficient on its own within the shrinking virus-containing microdroplet to inactive the virus in the Goldilocks RH zone. Under the RH 40% threshold, these chemical reactions are arrested, and at high RH, H_2O_2 will still form in microdroplets, but the lower H_2O_2 concentration and the low virus physiological concentration will slow inactivation considerably.

PROPOSING A NEW PARADIGM

By proposing a new "relative humidity-infectivity" (RHI) paradigm for explaining the causal mechanisms underlying seasonal respiratory infections and presenting new supporting evidence, we can explore alternative lines of questioning to develop more optimal strategies for *preventing* the spread of respiratory virus infections. This is in contrast to relying only on reactive strategies to mitigate the severity of pandemics that we inevitably expect to occur under the virus-as-a-villain VLB paradigm. Prevention strategies are never 100% effective, and therefore, we need to continue to develop better reactive strategies in parallel. However, with better prevention, we will likely require significantly less reliance on reactive strategies. The acceptance of the RHI paradigm might allow us to direct resources to the most vulnerable sections of the

population. The example of paradigm blindness in obesity research highlights the need for a more objective and balanced approach in exploring our relationship with respiratory pathogenetic viruses.

The COVID-19 pandemic has also illustrated how devastating new respiratory viruses can be. It is expected to become endemic and "settle" into a seasonal pattern of infections[34]. We are being warned that we will have to learn to live with the SARS-CoV-2 virus in a "new-normal," but we may have far more control than we believe.

THE ISSUE OF IAQ AND THE SLOW AND SYSTEMATIC DECLINE OF INDOOR RH

Over decades, our IAQ has deteriorated. Our focus has been primarily on physically removing unwanted elements from the air to make it "cleaner." The optimal strategy to address pollutant-based IAQ issues will depend on individual circumstances. Electrification can eliminate the combustion of fossil fuels indoors where possible, filters can prevent outdoor pollutants from coming indoors, and ventilation can move indoor contaminants outdoors. Ventilation and filtering remove pathogens from the air, and UV irradiation kills over 99% of pathogens. Adding moisture to the air to restore RH does not fit within the VLB paradigm, and therefore may not be recognized as a critical component of IAQ, especially in the absence of causal evidence for the impact of indoor RH on the spread of infections[†††].

Buildings and other engineered spaces have become more tightly sealed from the external environment to better control indoor environments in wealthier economies. The primary focus is on creating more energy-efficient buildings to reduce energy consumption and building-related greenhouse gas emissions. Energy makes up 30% of the "Leadership in Energy and Environmental Design" (LEED) Gold certification score and is twice as impactful as the next largest scoring category[35]. Indoor Environmental Quality makes up about 15% of the scoring. The primary focus of air quality is on ventilation and filtering. This is critical to managing the multitude of undesirable contaminants from the various sources that we have already discussed above. Thermal comfort makes up <1% of the scoring, and there is no mention of humidification standards whatsoever. WELL is another certification system that focuses primarily on the health and well-being of the occupants inside building environments[36]. Humidity control makes up part of the "thermal comfort" scoring and contributes 1 point to a total score of 80 points to receive platinum status. We frame humidity overwhelmingly as an issue more closely related to thermal comfort than air quality, whereas we frame ventilation and filtering overwhelmingly as the most critical factor in controlling IAQ. When we describe that low indoor relative humidity may lead to dryness and irritation of the airways, skin, eyes, throat, and mucous membranes, and may also be associated with longer survival (slower inactivation) of viruses, the cognitive bias known as the dilution effect significantly diminishes the weight of the last portion of the statement.

In temperate regions and wealthy countries, indoor temperatures are typically maintained within a narrow range of around 20°C throughout the year with HVAC systems. Minimum ventilation requirements are also in place to control air quality. Over the past decades, the tobacco industry has lobbied relentlessly to present mechanical ventilation as an alternative to smoke-free environments in North America[37]. Those ventilation standards remained even after buildings were declared smoke-free areas. In temperate regions, as previously stated, we spend on average more than 90% of our time inside engineered spaces throughout the year[5]. Given the amount of time we spend indoors, it is most likely that the human-to-human transmission of respiratory viruses occurs inside our engineered spaces like buildings. This also includes other engineered spaces shared by more than one person, like airplanes and other forms of shared transport systems. Researchers and public health officials have debated the dominant path of transmissions, as it would determine what the most important intervention strategy should be. When COVID-19 first appeared, public health authorities worried about the new coronavirus being spread by contact with large fluid droplets or residues upon droplet evaporation. The guidance for individual behavior included washing hands, cleaning groceries, wearing face coverings, avoiding people who sneeze or cough, and keeping some social distance apart from other individuals. But a detailed understanding of flu transmission, which took decades to develop, led scientists to understand only relatively recently that SARS-CoV-2 follows the same path of airborne transmission. Researchers found that the virus is breathed out in small particles by infected individuals while talking, singing, sneezing, coughing, and even normal breathing. And these viruses have been found in many indoor environments. Those infected can even spread the virus when showing no symptoms of being sick, which shows that transmission does not depend on coughing or sneezing. The transmission also does not require large wet droplets.

[†††]High RH above 80% makes it more difficult for people to thermoregulate as it becomes harder for sweat to evaporate. High humidity can influence the degradation of building materials. High humidity may promote the accumulation and growth of microbial pathogens, including bacteria, dust mites, and mold, which can lead to odors and cause respiratory irritation and allergies in sensitive individuals. If levels of RH are kept below 60%, most, if not all, of the issues above should not be of concern. Some building envelope insulation improvements may be required to avoid condensation caused by very low outside temperatures.

USING THE NEW RHI PARADIGM TO INFORM PUBLIC HEALTH POLICY

Public health interventions are still currently framed in the "virus-as-a-villain" VLB paradigm with a reactionary orientation, where a key objective is to intervene with the physical ability of the virus to enter the lungs of a susceptible host. When we cannot avoid the presence of "pollutants" indoors, physical dilution through mechanical ventilation and filtering are critical processes necessary to protect occupant health. However, promoting excessive ventilation as the preferred primary intervention to reduce the spread of infections without objectively considering alternative approaches frames respiratory viruses implicitly as biological "pollutants" that only exist in one stable state. This blinds us to exploring alternative pathways to prevent the spread of respiratory infections at scale and with potentially significantly fewer unintended consequences. The spread of respiratory infections requires that viruses can survive, that is, remain infectious, in the environment, outside the host. We must consider factors that influence the infectivity of viruses in the environment, and the potency of the susceptible host defenses again infection from transmitted viruses. It is not just about the viral load in the air. It also matters in what state of activation the virus is and if factors in the environment can materially impact the infectious state of the virus. A virus in the air can exist in an active state, dormant but still infectious, or inactive state. We can define a "virus infectious index" (VIX) of the air in an indoor space as the ratio of the number of active plus dormant (but still infectious) viruses in the air compared to the total number of the same viruses in all states present in the air. A VIX score of 1 means all viruses are active and can infect a host. A VIX score of 0 means that all viruses are inactive and are unable to infect a host. Therefore, the VIX score does not refer to the intrinsic level of infectivity or the virulence as an inherent property of a single type of virus, but rather the ratio of infectious versus noninfectious viruses of the same virus type in the air at any one time.

Because viruses need a host to survive, we expect the VIX score to decline to 0 over time. The rate of decline from the moment the virus is introduced into the air may be more important than the viral load that accumulate in the indoor air over time. Unfortunately, accurate direct measurement of the VIX score is tough for many reasons. Metagenomic sequencing to detect the presence of minute concentrations of the target virus in the environment destroys the virus structure to access the viral RNA. With sequencing, we can detect the presence of the target virus RNA, but not its infectious state. Methods that collect viral air samples to cultivate the virus to determine its infectious state are not trivial and suffer from many downsides. The low levels of virus concentration that may be detected with metagenomic analysis may not be sufficiently high to collect and successfully grow the virus in a cultivating medium, even if those viruses were infectious/active. Studies that have attempted to measure the decay of respiratory viruses under different environmental conditions required an artificial increase in the sample viral load before exposure to the environment to detect changes in viral activity[38]. We need to focus significantly more research on being able to differentiate between active and inactive viruses in samples with physiologically equivalent viral loads before we can reliably draw conclusions from these studies. The use of aptamers[39] to detect the presence of active viruses in the air may hold promise, but to our understanding, they have not been applied in this way to determine a VIX scoring.

If the rate of VIX decline is rapid under certain conditions, it would be even harder to measure accurately. However, it would be even more critical to avoid misinterpreting the specific results that may point to a new strategy of preventing infection spread. Ventilation and filtering make the most sense if the rate of VIX decline is slower than the period within which a susceptible host is expected to inhale the air containing the virus. The slower the rate of VIX decline and the longer the exposure time of the susceptible host, the greater the chance of transmission of the active virus.

A WAY FORWARD—VALIDATING THE RHI PARADIGM AT ALL SCALES AND LOCATIONS

Will maintaining the Goldilocks range of indoor RH all year lead to the expected low-to-no infections rates that we observe in summer for the whole year under normal levels of social interaction? Very few of our indoor engineered spaces are actively humidified currently. Restoring the naturally protective water balance in our indoor air through careful dynamically controlled humidification may be the most optimal investment in primary healthcare and would avoid further physical or chemical distortion of our indoor environment.

More empirical evidence is required to confirm that maintaining a certain level of indoor RH has a positive causal relationship with reducing viral respiratory infections all year round. One way to do this is to develop large-scale, multi-year, and highly controlled double-blind "clinical" trials. Another method is to invest in laboratory research to continue to elucidate the underlying causal mechanism(s). Given the importance of finding better ways to prevent viral respiratory pandemics, which can lead to devastating loss of lives and negative global consequences, like COVID-19, it is remarkable that so little research is focused on exploring the causal mechanism(s) by which RH could radically reduce infections indoors. We need more focus on testing the various

hypotheses and more data to determine which of the two paradigms will lead us in the right direction, or how to use the best of both in an optimal combination. The stakes cannot be higher, and the potential for eradicating future viral respiratory pandemics with nature-based solutions may be right under our noses, literally.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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