Possible Effects of Air Temperature on COVID-19 Disease Severity and Transmission Rates

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Abstract

Currently available data are consistent with increased SARS-CoV-2 replication at temperatures encountered in the upper airways (25-33°C when breathing room temperature air, 25°C) compared to those in the lower airways (37°C). One factor that may contribute to more rapid viral growth in the upper airways is the exponential increase in SARS-CoV-2 stability that occurs with reductions in temperature, as measured *in vitro*. Because SARS-CoV-2 frequently initiates infection in the upper airways before spreading through the body, increased upper airway viral growth early in the disease course may result in more rapid progression of disease and potentially contribute to more severe outcomes. Similarly, higher SARS-CoV-2 viral titer in the upper airways likely supports more efficient transmission. Conversely, the possible significance of air temperature to upper airway viral growth suggests that prolonged delivery of heated air might represent a preventative measure and prophylactic treatment for COVID-19.

Highlights

- The stability of SARS-CoV-2 *in vitro* increases exponentially with decreases in temperature proximate to normal core body temperature (37°C).
- Even room temperature air (25°C) cools upper airway surfaces to several degrees below body temperature (25-33°C), which may promote rapid viral growth.
- Increased upper airway viral growth may contribute to higher transmission rates and more severe disease.
- Heated, humidified air may represent a post-exposure prophylactic treatment for COVID-19.

Keywords

virology, COVID-19, thermodynamics, air temperature

1. Introduction

The stability of viruses is affected by changes in temperature, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), is no exception.[1–10] Heat denatures the proteins that comprise each SARS-CoV-2 virion, inactivating it.[3,8] Laboratory data indicate that, as temperatures increase, the rate at which virions are inactivated increases exponentially.[3,9] These *in vitro* data suggest that lower temperatures within the body might result in lower rates of thermal inactivation and therefore higher rates of viral growth, potentially affecting viral shedding, viral load densities, transmission rates, and patient outcomes.

SARS-CoV-2 replicates abundantly in the upper airways,[11–13] and the temperature of the upper airways is directly affected by air temperature. Air below body temperature is warmed during inhalation through heat exchange with upper airway surfaces, reaching core body temperature (37°C) at the level of the lower airways.[14] This process cools the upper airways: Respiration of room temperature air (25°C) reduces the upper airways to an average ambient temperature of 33°C, which evolves from 25°C at the nasal vestibule to 34°C at the nasopharynx to ~37°C near the trachea.[15–17] Lower air temperatures as well as faster and deeper respiration cause further cooling.[16,18–20] The airstream ordinarily rises to within 0.5°C of body temperature by the trachea,[14] making lower airway temperatures unique to the upper respiratory tract.

Although complicating factors preclude the trivial extension of SARS-CoV-2 *in vitro* decay rates to the *in vivo* environment, currently available data support increased viral replication at the cooler temperatures of the upper airways relative to the warmer temperatures of the upper airways.[21–23]

Abundant SARS-CoV-2 replication in the upper airways is a driver of its high transmissibility and is pivotal to the pathogenesis of COVID-19.[11,12,21,22,24–27] If air temperature affects SARS-CoV- replication rates in the upper airways, then air temperature may also contribute to transmission rates and progression of disease.

This article outlines the possible relevance of air temperature to COVID-19, with an emphasis on how the temperatures encountered in the airways may influence the decay rate and replication dynamics of SARS-CoV-2. While presently available data do not permit quantification of the impact of air temperature on COVID-19 transmission and disease progression, this article suggests that the potential for such an effect warrants further study.

2. Cool air may support SARS-CoV-2 replication in the upper airways

The temperature gradient of the airways affects the replication kinetics of many respiratory viruses, including rhinoviruses, influenza viruses and coronaviruses.[21,22,28–32] Airway temperatures also influence the replication kinetics of SARS-CoV-2,[21,22] which replicates abundantly in the human airways.[11–13] A study that used an *in vitro* model for the human respiratory epithelium found that SARS-CoV-2 replicated 10- to 100-fold more efficiently over 96 hours at temperatures found in the upper airways than those in the lower airways, 33 and 37°C respectively.[21] Possible differences in upper and lower airway viral replication kinetics *in vivo* depend upon many factors, including

temperature-dependent innate immune response that is more robust at warmer air temperatures and higher humidities,[21,33–38] as well as cellular expression of the SARS-CoV-2 cell-entry factor angiotensin-converting enzyme 2 (ACE2) which has a gradient expression in the airways.[11] Another contributing factor may be the temperature-dependent decay rate of SARS-CoV-2, which is the focus of this article.

Like many viruses, SARS-CoV-2 decays exponentially across a variety of mediums—including surfaces, aerosols, and solutions such as virus transport medium, nasal mucus, and sputum.[1–10] The rate of exponential decay increases with temperature as heat denatures the proteins that comprise the SARS-CoV-2 virion.[1–3,5–10] The SARS-CoV-2 spike protein—which is necessary for cell entry—is temperature-dependent, in relation to the temperature required for optimal virus replication.[22] SARS-CoV-2 spike proteins exhibit temperature preference to match the upper (~33°C) airways over lower (37°C) airways, with further reductions in infectivity found as temperature increases to fever levels (41°C).[22,23] Analytical models based on laboratory data for SARS-CoV-2 in solution and on inert surfaces at various humidity conditions indicate that virus half-life decreases exponentially with increases in temperature (Figure 1).[3,9]

Complicating factors make the *in vivo* environment difficult to compare with the laboratory data currently available, and additional research is necessary to determine whether the rates of viral decay *in vivo* are similarly affected by temperature. Existing clinical data generally support the concept that viral pathogenicity decreases with elevations in temperature, although exact mechanisms for this effect remain under investigation. For example, more rapid recoveries are observed from chickenpox and rhinovirus infections with avoidance of antipyretic medication.[39–41] Whether these clinical findings, including the prolongation of viral shedding with the use of antipyretics, represent an influence of body temperature on viral decay is uncertain; however, the data are at least consistent with this factor.

3. Cool air may contribute to COVID-19 disease severity and transmission rates

While much remains to be understood about the pathogenesis of COVID-19, available data indicate that the rate of viral replication in the upper airways—especially during early stages of disease—may have a significant impact on disease severity. The upper airways play a pivotal role in the pathogenesis of COVID-19. Like SARS-CoV-1,[42] SARS-CoV-2 may primarily initiate infection on nasal surfaces.[11,13] Nasal epithelial cells have high ACE2 expression, and cell cultures of nasal epithelial cells indicate high infectivity.[11,21] Clinically, high SARS-CoV-2 viral titers are observed in the upper respiratory tract early in infection (0-5 days).[12,13,24] Moreover, the primary mode of COVID-19 transmission is via aerosols,[43–45] and aerosol deposition modeling suggests that inhalation of virus-laden aerosols deposits virus in the highest concentrations on nasal surfaces.[11,46–48]

After establishing infection in the nasal cavity, SARS-CoV-2 infection may spread from nasal surfaces through the respiratory tract, with high upper airway titers potentially enabling continual infection. Similar to other human coronaviruses, SARS-CoV-2 replicates productively on the nasal and

tracheobronchial epithelium and sheds over time onto the luminal surface of the epithelium.[21,49,50] The abundance of ACE2 on luminal surfaces of conducting airway epithelium may enable considerable and progressive viral growth and spread throughout the airways.[11,51–54] For many lower respiratory tract infectious diseases, oral-lung aspiration contributes to disease progression and severity.[11,55–59] Nasal secretions containing relatively high viral titers can accumulate in the oropharynx and are predicted to subsequently spread to lower airways via aspiration.[11,60–64] Chest CT and autopsy studies from COVID-19 patients indicate patchy pulmonary infection, consistent with aspiration of virus into the lung from the upper respiratory tract.[11,65] Clinical data from COVID-19 patients indicate early viral replication in the upper airways followed by pulmonary infection, consistent with viral spread from upper to lower airways.[11,13] Taken together, these data suggest that SARS-CoV-2 may establish infection in the nasal cavity and progressively replicate and spread through the airway epithelia, especially via aspiration. The data are also consistent with the concept that the upper respiratory tract serves as a viral reservoir that enables continual reinfection of proximate airway surfaces, supporting repeated cycles of viral replication and spread through the airways, which would suggest that viral growth in the upper respiratory tract might remain pathogenically significant even after infection has spread beyond the upper airways.

Rapid SARS-CoV-2 replication in the nasal cavity and upper airways may therefore contribute to greater and more rapid infection of the lower airways. Data on viral load are consistent with this hypothesis: SARS-CoV-2 upper respiratory tract viral load is strongly correlated with adverse outcomes and has been hypothesized to be a predictor of disease severity.[27] The nasopharyngeal viral load of severe COVID-19 cases has been found to be about 60 times higher than that of mild cases.[27]

As such, factors that promote more rapid viral growth in the upper airways may contribute to greater disease severity. Because cool air potentially promotes more rapid SARS-CoV-2 growth by reducing viral decay rate in the upper airways and suppressing innate immune response, cool air may contribute to greater disease severity. The contribution of reduced viral decay rate may be considerable, as the virion half-life of SARS-CoV-2 *in vitro* increases exponentially with decreases in temperature. For SARS-CoV-2 in virus transport medium, a 3-log (99.9%) reduction in viral titer is predicted to occur in 7.1 hours at the temperature of the lower airways (37°C), 12.5 hours at the average temperature of upper airways (33°C), and 52.2 hours at the temperature of the nasal vestibule (25°C), where airway temperatures assume room temperature air (25°C) (95% confidence interval of 2.8-17.7, 5.1-31.0, and 19.8-138.9 hours, respectively) (Figure 2).[3] Lower temperatures correspond to exponentially longer SARS-CoV-2 half-life. Significantly enhanced viral growth at the lower temperatures encountered in the upper airways also likely supports the efficient transmissibility of SARS-CoV-2, as higher viral titer in the upper airways produces higher viral titer in expelled respiratory droplets.[12,21,22,24–26]

The seasonality of respiratory viruses is a widespread and well-established phenomenon, affecting both transmission rates and mortality.[66–68] A variety of factors have been identified as drivers of seasonality, among which outdoor air temperature features prominently. The transmission and severity of many acute respiratory viruses—including rhinoviruses, influenza viruses, and coronaviruses—are negatively correlated with outdoor air temperature.[33,35,67–69] Seasonality has

been widely hypothesized to occur for SARS-CoV-2, and many studies have sought to determine the relationship between the rate of COVID-19 transmission and meteorological factors—including outdoor air temperature. The majority of currently available studies suggest that outdoor temperature is negatively correlated with COVID-19 transmission rates, although findings are not unanimous.[70–76] Despite an abundance of studies on this topic, the implications are still unclear as the data are rife with confounding variables. Some confounding variables are behavioral: For instance, during cold weather, people spend more time indoors, which supports more efficient transmission. Other confounding variables are associated with geography, such as: population density,[72,77] social distancing practices,[78] quality of available health care, frequency of international travelers,[72,79] and prevalence of viral variants associated with transmissibility and virulence.[80–84] Furthermore, other meteorological factors may affect transmission rates: Humidity results in more rapid SARS-CoV-2 decay *in vitro*,[6,7,9,10] improves airway immune response to infection by respiratory viruses,[33] and is negatively correlated with the transmission of many respiratory viruses[66,67]; while ultraviolet radiation from sunlight rapidly inactivates SARS-CoV-2 viral particles, both on surfaces and in the air.[85–88] An additional factor to consider when attempting to use meteorological data to evaluate the effect of respired air temperature on transmissibility is that outdoor air temperature is not always equivalent to the temperature of air respired: In developed nations, people spend the majority of their time in temperature-controlled environments,[89,90] which is where the majority of respiratory virus transmission occurs.[33] Studies on areas where people do not utilize temperature-controlled environments may be more useful in this capacity, although such studies of course face many of the same issues that other historical meteorological studies do. In sum, despite widespread interest in the topic and an abundance of studies, it is still difficult to assess the degree to which the temperature of respired air contributes to transmission rates for SARS-CoV-2, although the data generally indicate decreases in transmission with increases in temperature.

Notably, although COVID-19 patients often develop fever, fever does not heat upper airway surfaces as effectively as it does other areas of the body.[91,92] Even in a feverish patient, inhaled air begins at ambient temperature at the nostrils and converges to the patient's body temperature as it moves through the airway, cooling upper respiratory tract surfaces along the way.[15] This cooling implies diminished thermal inactivation of SARS-CoV-2 in the upper respiratory tract relative to other locations in the body. As such, the temperature of the upper airways would be relatively conducive to viral growth compared to other areas of the body, even during fever.

4. Heated, humidified air may represent a post-exposure prophylactic treatment for COVID-19

The pathogenetic significance of the upper airways to the severity of COVID-19 suggests that reduction of SARS-CoV-2 viral titer in the upper airways early in the disease may result in less severe disease and reduced transmission. Suppression of upper respiratory tract viral replication would likely have a greater impact in preventing escalation of severity if suppression occurs when SARS-CoV-2 is mostly contained in the upper respiratory tract, immediately post-exposure or early in SARS-CoV-2 infection. This suggests that administration of warm air may potentially represent a therapeutic measure as a post-exposure prophylaxis and an early-stage treatment to prevent

disease progression. For SARS-CoV-2 in solution *in vitro*, a 3-log (99.9%) reduction in viral titer is predicted to occur in 12.5 hours at the average temperature of upper airways (33°C), in 7.1 hours at normal core body temperature (37°C), and in just 1.7 hours at 45°C, an air temperature tolerable by healthy individuals for prolonged periods (95% confidence interval of 5.1-31.0, 2.8-17.7, and 0.6-4.6 hours, respectively) (Figure 3).[3,93] Longer exposure to heat results in greater total reductions in viral decay. In addition to the possible effect on viral decay rates, warm air temperature and high relative humidity also facilitate a strong airway immune response, which could further contribute to the benefit of warm humidified air.[21,33–38]

It is important to note that air above core body temperature is cooled during inhalation, limiting the effectiveness of very warm air in reducing viral stability in lower areas of the respiratory tract. It should also be noted that warm air does not warm the entire upper respiratory tract evenly but rather elevates the temperature range in the upper airways.[14] Temperature changes caused by respiration begin immediately, with the temperature of upper airway mucosal surfaces equilibrating within 7 minutes at resting respiratory rate.[19]

The necessary air temperature and duration of treatment depend on the exposure dose. A larger exposure dose would require greater reduction in order to be reduced to less than infectious levels and for that reason it would require a longer treatment duration with warm air and/or a higher air temperature (Figure 3b).

Importantly, prophylactic treatment with warm air need not reduce viral titer below infectious levels to be of potential benefit. The severity of many viral diseases is believed to be proportional to the initial viral inoculum.[94] Clinical studies conducted with influenza and coronaviruses indicate a dose-dependent increase in disease severity.[95,96] Masks might reduce the inoculum exhaled by an infected host, and outbreaks of COVID-19 within populations where mask-wearing is enforced have resulted in lower rates of severe disease and fatality.[94,97] This concept is consistent with clinical data on COVID-19 patients that indicate a strong correlation between upper respiratory tract viral load and disease severity.[27] Studies in the Syrian hamster model found that lower doses of administered SARS-CoV-2 virus led to less severe disease than higher doses.[98] Taken together, these data suggest that reduction of SARS-CoV-2 viral titer early after introduction to the upper airways may result in less severe disease. Similarly, reduced viral titer in the respiratory droplets expressed by that individual may result in less severe disease in naive hosts who contract COVID-19 from that infected individual.

Currently available data are consistent with the hypothesis that warm air delivered early in the disease may reduce viral titer and prevent escalation of severity. An interventional study provided 7 asymptomatic or pauci-symptomatic COVID-19 patients with 20 minutes of steam inhalation for 4+ consecutive days.[99] Symptomatic patients reported clinical improvement at the end of the protocol, and all patients tested negative after the first day of steam inhalation. This observation is preliminary—the study being limited in part by small sample size and the lack of a control group—and needs confirmation in a controlled trial, but the promising results suggest that further investigation of warm air as an early-stage treatment is warranted.

Warm air delivery can be tolerated for long periods of time. Air that is humidified and heated to 37°C or 41°C and delivered via nasal high flow therapy (35 L/minute) for multiple hour-long sessions daily is well tolerated by healthy individuals.[100] Temperatures as high as 45°C are also well tolerated for prolonged periods.[93] Risks of aerosolizing SARS-CoV-2 must be considered when determining method of warm air delivery for COVID-19 patients.

5. Discussion

SARS-CoV-2 viral stability increases exponentially with decreases in temperature, as measured for virus in solution.[3,9] The temperature-dependent decay rate suggests that cool air temperatures might enable increased rates of SARS-CoV-2 growth in the upper airways.[15–17] This is a proposed effect based on the review and survey of existing laboratory data, and conclusive demonstration of an effect *in vivo* remains to be performed. The concept is supported by currently available data: In epithelial cell cultures, SARS-CoV-2 replicates more efficiently at temperatures encountered in the lower airways than those in the upper airways (33 and 37°C, respectively).[21–23] Further proof of this concept will require more complex clinical studies.

More rapid SARS-CoV-2 replication in the upper airways has potential implications for disease severity. Clinical and laboratory data suggest that SARS-CoV-2 frequently initiates infection in the nasal cavity and progressively spreads through the airways, especially via aspiration.[11,13,21] Rapid SARS-CoV-2 replication in the upper airways may support greater and more rapid infection of the lower airways, possibly contributing to more severe outcomes. Clinical data support this concept: SARS-CoV-2 upper respiratory tract viral load is strongly correlated with adverse outcomes and has been hypothesized to be a predictor of disease severity.[27] As such, respiration of cool air might be a contributing factor to COVID-19 severity. Enhanced SARS-CoV-2 viral growth potentially enabled by the lower temperatures of the upper airways might also contribute to more efficient transmission, as higher viral titer in the upper airways produces higher viral titer in expelled respiratory droplets.[12,24–26] Studies based on meteorological data generally indicate negative correlation between COVID-19 transmission and outdoor air temperature, although the strength of this correlation is obscured by a multitude of confounding variables.[70–76] Further research is necessary to quantify the potential impact of respired air temperature on disease severity and transmission rates. It may be productive to examine the impact of air temperature on upper respiratory tract viral load in an animal model after exposure to air at various temperatures and for various durations.

Conversely, warmer air may reduce upper airway viral titer of SARS-CoV-2, which may contribute to less severe disease if upper airway viral titer is suppressed when infection is local to the nasal cavity and upper airways, immediately post-exposure or very early in SARS-CoV-2 infection.[94,97,98] This suggests that administration of warm air may potentially represent a therapeutic measure as a post-exposure prophylaxis and an early-stage treatment to prevent disease progression. This concept is supported by preliminary clinical data: A study that provided 7 asymptomatic or pauci-symptomatic COVID-19 patients with 20 minutes of steam inhalation for 4+ consecutive days found that symptomatic patients reported clinical improvement at the end of the protocol and all patients tested negative after the first day of steam inhalation.[99] While these observations are

preliminary, they suggest that further investigation of warm air as an early-stage treatment is warranted.

Warm air delivery would need to occur for extended durations in order to suppress viral replication to a degree that would be beneficial, as decreases in virus infectivity are dependent on duration of exposure to elevated temperatures (Figure 3b).[3,9] Warm, humidified air is well-tolerated over long durations.[93,100] It is important to note that air above body temperature will be cooled during inhalation, limiting the effectiveness of very warm air in reducing viral stability in lower areas of the respiratory tract. Care must be taken when administering air to COVID-19 patients to avoid aerosolizing viral particles. Post-exposure prophylaxis applications may be of particular relevance for healthcare professionals who have insufficient personal protective equipment, as well as for populations who are at risk of more severe disease.

There could also be opportunities for innovation in mask design to not only capture respiratory droplets and aerosolized viral particles, but also to warm inhaled air. Heating masks already exist and could be modified or directly applied to the aim of increasing thermal inactivation of virus in the upper respiratory tract.[101–105] Even simple face masks have been shown to conserve heat loss from breathing and diminish upper airway cooling,[101] suggesting that simply increasing the duration of mask usage may be beneficial. Mask design and usage could be a promising area for innovation and further study.

The impact of temperatures in the body on viral growth may help explain COVID-19 transmission rates and disease severity. Advances made in understanding the various impacts of temperature on COVID-19 could inform both disease prevention and treatment, with potentially significant impacts on patient outcomes and global disease burden.

Conflict of Interests

EK has equity interest in Attune Medical, a company involved in patient temperature management.

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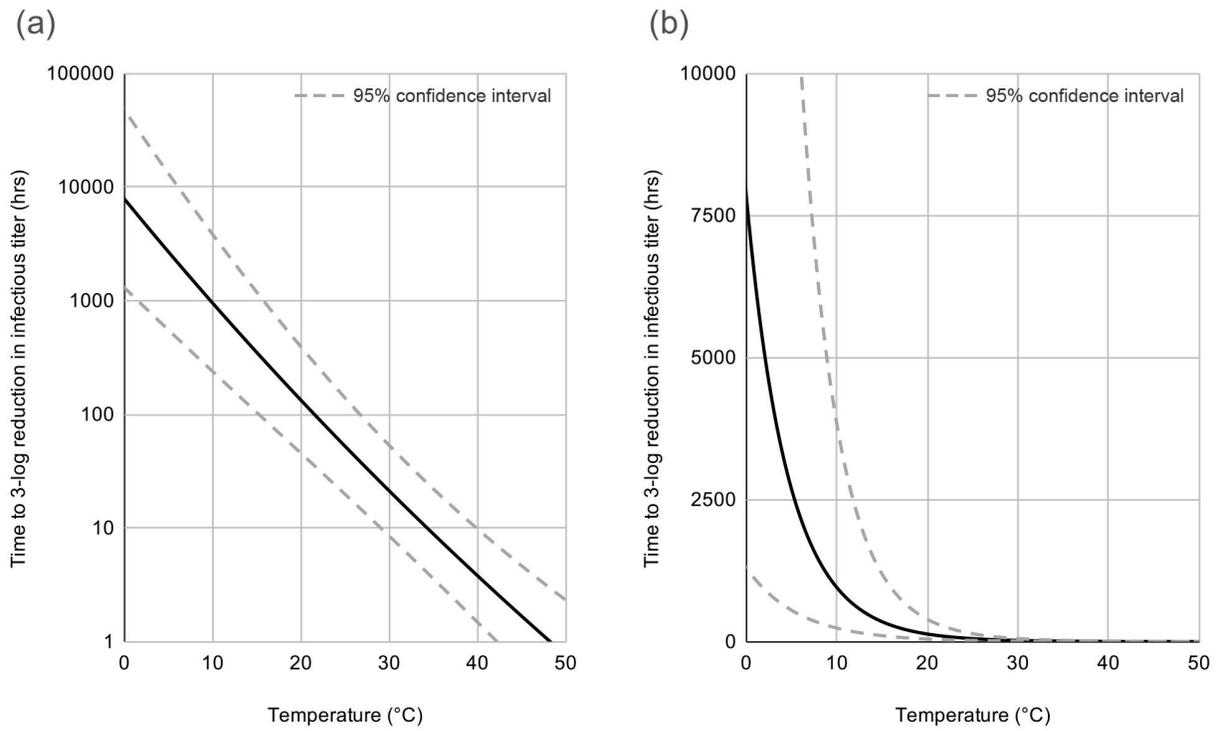
Figure 1. Virus lifetime as a function of temperature. Predictions are shown for the duration of time required to produce a 3-log (99.9%) reduction in infectious titer.[3] The analytical model was built on data for SARS-CoV-2 in viral transport medium.[1] (b) The lifetime axis is scaled linearly to emphasize the exponential relationship of virus lifetime and temperature.
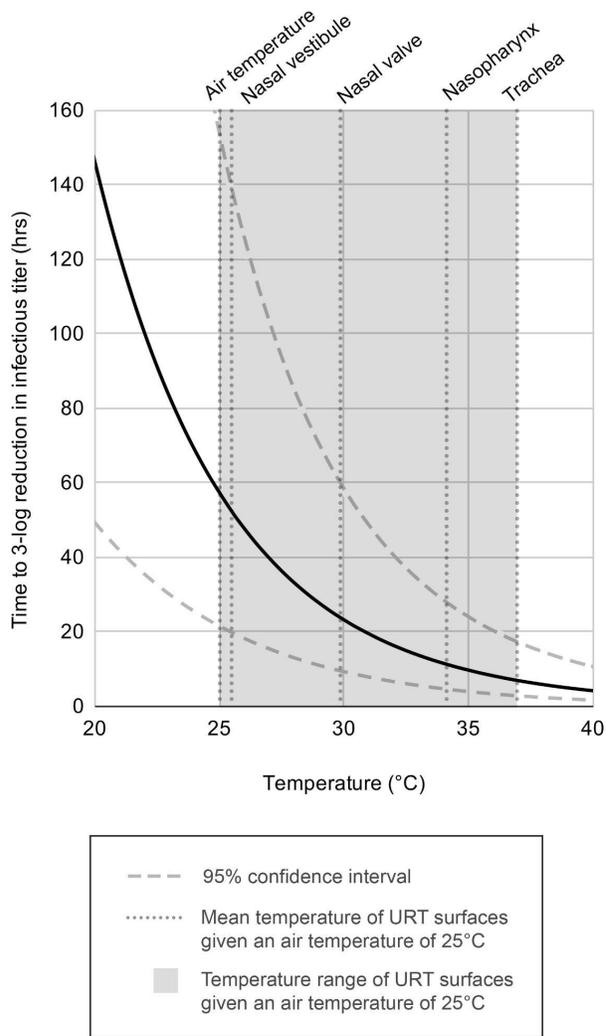
Figure 2. Virus lifetime at common indoor air temperatures. The mean temperatures of the upper respiratory tract when breathing 25°C (room temperature) air are transposed over the predicted in vitro virus lifetime as a function of temperature.[3,15] The upper respiratory tract spans a temperature range from air temperature to body temperature.
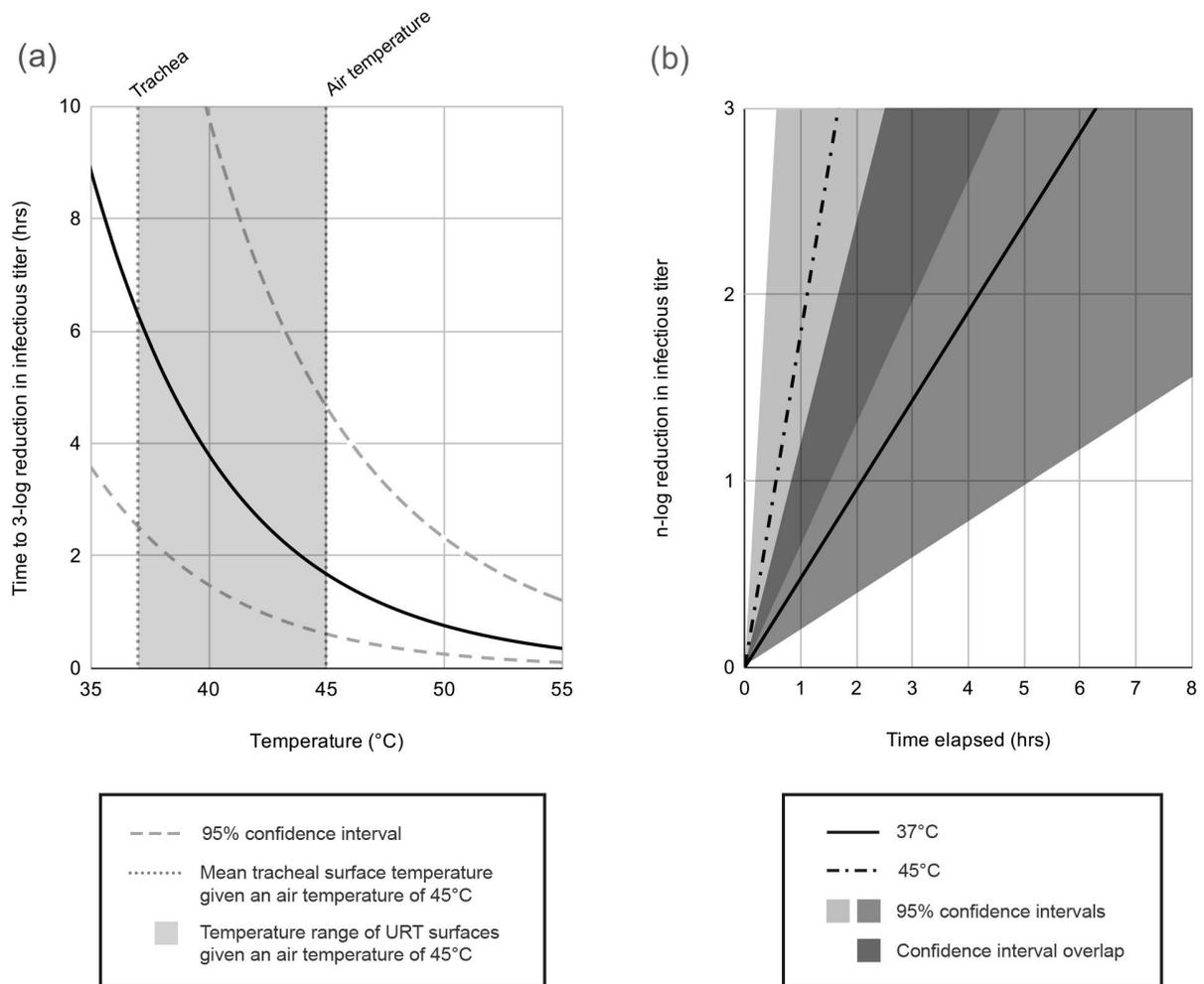
Figure 3. Virus lifetime at elevated air temperatures. (a) The temperature range of upper airway surfaces given an elevated temperature air (45°C) and assuming a body temperature of 37°C is transposed over the predicted in vitro virus lifetime as a function of temperature.[3] (b) The reduction in viral titer at 45°C is compared to that at body temperature (37°C).