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## The natural thermal sensitivity of SARS-CoV-2

We recently published a review of the factors underlying the winter seasonality and pathogenicity of respiratory viruses [1]. We showed that many respiratory viruses possess natural thermal sensitivity, meaning they replicate faster at temperatures below their hosts' normal body temperature, confining them to the upper airways. Our hypothesis suggests that this tropism gives the virus two important advantages: (1) it is well-placed to be transmitted; and (2) it is less likely to immobilize its host, increasing transmission.

Several recent studies have shown SARS-CoV-2 is thermally sensitive in the wet-lab. Herder et al. [2] found that elevated temperature inhibits SARS-CoV-2 replication in respiratory epithelial cells independently of interferon-mediated defenses. At 40 °C cells remained permissive to SARS-CoV-2 entry but refractory to viral transcription. Another study showed that SARS-CoV-2 replicated more efficiently at temperatures encountered in the upper airways (33 °C), with a temperature-dependent induction of interferon-mediated antiviral responses [3]. Zhou et al. [4] used molecular dynamic simulations and surface plasmon resonance to prove that SARS-CoV-2/ACE2 binding had lower affinity at 40 °C than 37 °C, while SARS-CoV-1/ACE2 binding was similar at both temperatures. Prévost et al. [5] found a stepwise increase in the affinity of the SARS-CoV-2 spike receptor binding domain towards ACE2 at low temperatures. Laporte et al. [6] showed that pseudoviruses bearing the spikes of SARS-CoV-2 and HCoV-229E, a common cold coronavirus, were more infectious when produced at 33 °C instead of 37 °C, while the spikes of SARS-CoV-1 and MERS-CoV favored 37 °C, explaining the prefer-

**Table 1**
Studies showing that SARS-CoV-2 is thermally sensitive.

| First author | Year | Ref. | Host or experimental system | Result | Comments |
|---|---|---|---|---|---|
| Herder | 2021 | 2 | Respiratory epithelial cells | High temperature inhibited SARS-CoV-2 replication independently of canonical interferon (IFN)-mediated innate immune defenses | Respiratory tissue incubated at 40 °C remained permissive to SARS-CoV-2 entry but refractory to viral transcription. |
| V'kovski | 2021 | 3 | Human airway epithelial cell culture | SARS-CoV-2 replicated to higher titers at 33 °C compared to 37 °C. | Time-resolved transcriptome analysis revealed temperature-dependent interferon and pro-inflammatory responses induced by SARS-CoV-2. |
| Zhou | 2021 | 4 | Surface plasmon resonance; Vero and Caco-2 cells | SARS-CoV-2 binding to ACE2 was less affinitive at 40 °C (18 nM) than at 37 °C (6 nM). | Cell-entry of pseudoviruses bearing SARS-CoV-2 spike was decreased at higher temperature. |
| Prévost | 2021 | 5 | Flow cytometry and other biochemical, biophysical, and functional assays | A stepwise increase in the affinity of SARS-CoV-2 receptor-binding domain to ACE2 was observed as temperature decreased. | Higher viral attachment was observed at low temperatures. |
| Laporte | 2021 | 6 | Entry of pseudoviruses into HEK 293 cells. | Pseudoviruses bearing SARS-CoV-2 spike were more infectious at 33 °C compared to 37 °C. | The spike proteins of SARS-CoV-2 and MERS-CoV favored 37 °C, in accordance with the preference of these viruses for the lower airways. |
| Iserman | 2020 | 7 | Liquid-liquid phase separation | Condensation of nucleocapsid protein with specific genomic RNA elements was greater at 33 °C than 37 °C, with condensation at 40°C being lower still. | Liquid-like N-protein condensates form in mammalian cells in a concentration-dependent manner and can be altered by small molecules. |
| Chan | 2021 | 8 | Golden Syrian hamsters | Live virus titers in animals seven days after infection were significantly higher for groups housed at 12–15 °C than in groups at 21–33 °C. | The low-temperature group expressed higher levels of TNF-$\alpha$, IFN-$\gamma$, IL-1$\beta$, and CCL3, and a lower level of the antiviral IFN-$\alpha$ in lung tissues. |
| Kaplin | 2021 | 9 | Confirmed human Covid-19 cases | A function derived from the doubling time of cases showed a stronger correlation with temperature than with other meteorological parameters. | The authors estimated that a 1°C decrease could be associated with a 6.7% increase in the log of daily cases. |

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ence of these viruses for the lower airways. Iserman et al. [7] showed that SARS-CoV-2 nucleocapsid protein undergoes liquid-liquid phase separation in the presence of viral RNA that is sequence-specific and temperature-sensitive, with greater condensation at 33 ˚C than 37–40 ˚C.

Thermal sensitivity is also borne out in observations of COVID-19 in animals and humans. In a study of golden Syrian hamsters [8], live virus titers seven days after challenge with SARS-CoV-2 in a group housed at 12–15 ˚C were significantly higher than in the groups housed at 21–33 ˚C. The low-temperature group demonstrated higher levels of proinflammatory cytokines/chemokines, and a lower level of the antiviral IFN-$\alpha$. Also, a study of COVID-19 cases in 50 countries found that a function derived from the doubling time of cases showed a stronger correlation with temperature than with any other meteorological parameter [9].

Our analysis and hypothesis have important practical implications for clinical practice. For example, standing still outside and wearing insufficiently warm winter clothing are correlated with increased risk of death from respiratory illness [1]. This suggests that steps taken by individuals to avoid chilling may be protective. Moreover, personal chilling after contracting a respiratory illness may increase disease severity. We suggest randomized controlled trials of advice to healthy individuals to avoid chilling in order to reduce the frequency of respiratory illnesses, and trials of interventions in clinical settings to prevent chilling of sick patients with respiratory illnesses in order to reduce disease severity [1,10] (Table 1).

## Declaration of competing Interest

We have no conflicts of interest associated with any aspect of the material covered by this manuscript.

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