SARS-CoV-2 and most respiratory viruses replicate more efficiently below the normal body temperature of their hosts

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In April 2021 we published a review of the factors underlying the 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, allowing them to confine themselves to the upper airways. This tropism can give them at least two important advantages: (1) they are well-placed to be transmitted; and (2) they are less likely to immobilize their hosts, increasing transmission.

Several recent studies have shown SARS-CoV-2 is indeed thermally sensitive, which has important consequences for predicting epidemics and preventing progression to Covid-19 illness. Herder et al [2] found 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 SARS-CoV-2/ACE2 binding was less affinitive 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, and higher viral attachment, 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, agreeing with these viruses' preference 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 at 37-40°C.

The existence of this thermal sensitivity suggests that natural selection normally *moderates* the pathogenicity of endemic respiratory viruses [1]. This is indeed 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-α. 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 other meteorological parameters [9].

Our review considers that the thermal sensitivity of respiratory viruses has been noticed in some form since the early days of virology, but the effect on individuals is unfortunately mostly overlooked as a driving cause of respiratory viral illness outbreaks. We also note that many respiratory viruses are more common in the Tropics year-round and often move from tropical to temperate regions,

likely due to viral adaption to local environment. Lastly, we suggest wet-lab experiments and randomized controlled trials exploring temperature-based interventions for avoiding and treating respiratory illnesses, including Covid-19 [1, 10].

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-1 and MERS-CoV favored 37˚C, in accordance with these viruses' preference 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 housed at 12-15˚C were significantly higher than in groups at 21-33˚C seven days after infection.	The low-temperature group expressed higher levels of TNF-α, IFN-γ, IL-1β, and CCL3, and a lower level of the antiviral IFN-α 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.

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

[1] Shaw Stewart, P.D. and Bach, J.L. Temperature dependent viral tropism: understanding viral seasonality and pathogenicity as applied to the avoidance and treatment of endemic viral respiratory illnesses. *Reviews in medical virology* 32.1 (2021): e2241. https://doi.org/10.1002/rmv.2241

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[3] V'kovski, P. et al. Disparate temperature-dependent virus–host dynamics for SARS-CoV-2 and SARS-CoV in the human respiratory epithelium. *PLoS biology* 19.3 (2021): e3001158. https://doi.org/10.1371/journal.pbio.3001158

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[6] Laporte, M. et al. The SARS-CoV-2 and other human coronavirus spike proteins are fine-tuned towards temperature and proteases of the human airways. *PLoS pathogens* 17.4 (2021): e1009500. https://doi.org/10.1371/journal.ppat.1009500

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