Seasonality of influenza and other respiratory viruses

Gabriele Neumann1 & Yoshihiro Kawaoka1,2,3,*

In virology, the term seasonality describes variations in virus prevalence at more or less regular intervals throughout the year. Specifically, it has long been recognized that outbreaks of human influenza viruses, respiratory syncytial virus (RSV), and human coronaviruses occur in temperate climates during the winter season, whereas low activity is detected during the summer months. Other human respiratory viruses, such as parainfluenza viruses, human metapneumoviruses, and rhinoviruses, show highest activity during the spring or fall season in temperate regions, depending on the virus and subtype. In tropical climates, influenza viruses circulate throughout the year and no distinct seasonal patterns are observed, although virus outbreaks tend to spike during the rainy season. Overall, seasonality is more pronounced with greater distance from the equator, and tends to be less pronounced in regions closer to the equator (Li et al, 2019).

EMBO Mol Med (2022) 14: e15352

The fairly regular seasonal patterns of epidemics, caused by respiratory viruses circulating in humans, are in contrast to sporadically occurring pandemics, which are caused by viruses to which most humans lack immunity. The 1918 H1N1 influenza pandemic killed an estimated 50 million people worldwide during three major waves in the spring and fall of 1918, and in the winter/spring of 1919. The H2N2 influenza pandemic of 1957 emerged in East Asia in the spring of 1957, first detected in the US in the summer of 1957, and caused peaks of excess death in October 1957 and February 1958. In 1968, a novel H3N2 pandemic influenza virus was first reported in the US in September 1968 and caused excess mortality in the winter of 1968/1969. In the spring of 2009, a novel H1N1 influenza virus emerged and spread widely during the summer and fall of 2009. Similarly, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in late 2019/early 2020, caused its first pandemic wave in Europe in the spring of 2020, and has since caused several waves with high case numbers around the globe. Thus, epidemic human respiratory viruses and novel pandemic respiratory viruses follow different patterns of dissemination that may be driven by different factors.

In recent years, at least three mechanisms have been discussed to explain the seasonality of epidemic respiratory viruses in humans (reviewed in Moriyama et al, 2020): (i) virus stability and transmissibility under changing environmental conditions (most prominently, humidity and temperature); (ii) human behavior (including indoor/outdoor activities, indoor crowding, number of close contacts, holiday, and vacation travel, etc.); and (iii) the impact of changing environmental conditions on host defense mechanisms. Currently, the relative contribution of these factors to the seasonality of respiratory viruses is not fully understood.

Virus stability and transmissibility under changing environmental conditions have long been discussed as an important factor in the seasonality of epidemic human respiratory viruses. Human-to-human transmission of respiratory viruses occurs through aerosols or contact with virus-contaminated objects. The water content of (virus-laden) aerosols shrinks through evaporation after the aerosols have been exhaled into the ambient air; this evaporation process is affected by the ambient temperature and relative humidity (reviewed in GAeF 2020). The final size of the virus-laden particles will determine how long they stay in the air: While larger aerosols sink to the ground rapidly (i.e., within seconds-to-minutes), smaller aerosols remain in the air for several hours and can disperse over greater distances than larger aerosols (reviewed in GAeF 2020); the infectivity of virus-laden small aerosols may differ among the respiratory viruses.

Several experimental studies have assessed the stability and transmissibility of respiratory viruses at different temperatures and relative humidity. In general, viruses that cause seasonal spikes during the winter months in temperate climates are more stable and transmissible in animal models at low temperature (about 5°C) and humidity (approx. 10–40% relative humidity) (i.e., conditions that are typical for the winter season in temperate regions) than at the higher temperature (about 25°C) and relative humidity (≥60%) found during the summer season in temperate climates.

For influenza viruses, in vitro studies and studies in guinea pigs and ferrets have revealed a biphasic pattern with high virus stability at low relative humidity of 10–40% (typical for the winter season in temperate climates), low virus stability and viability at intermediate relative humidity of 40–60% (typical for the spring and fall seasons in temperate climates), and high virus stability and viability at high relative humidity of

1 Influenza Research Institute, University of Wisconsin-Madison, Madison, WI, USA
2 Institute of Medical Science, University of Tokyo, Tokyo, Japan
3 Research Center for Global Viral Diseases, National Center for Global Health and Medicine, Japan
*Corresponding author: E-mail: yoshihiro.kawaoka@wisc.edu
DOI 10.15252/emmm.202115352 | EMBO Mol Med (2022) 14: e15352 | Published online 14 February 2022
humidity (Kong in the spring of 2013. This virus was
°
enza activity (Shaman
humidity in the weeks prior to increased influ-
climates, absolute humidity may be an impor-
tropical regions.
mission to na
ıve animals housed in the same cage (Lowen et al, 2007; Lowen & Palese, 2009). On the basis of these findings, Lowen and Palese (2009) hypothesized that influenza virus transmission occurs through aerosol transmission during the winter season in temperate climates, but may be
driven by direct contact transmission in tropical regions.
Overall, in temperate (but not in tropical)
climates, absolute humidity may be an impor-
tant factor in the seasonality of epidemic influ-
enza viruses, because spikes of influenza
activity are often associated with low absolute
humidity in the weeks prior to increased influ-
enza activity (Shaman et al, 2011), and a
model based on absolute humidity recapitu-
lated the seasonality of epidemic influenza
activity in temperate regions (Shaman et al, 2011). In contrast, pandemic influenza viruses
have spread widely during the spring and
summer in temperate regions, when the
climate conditions (i.e., intermediate ranges
of humidity and temperature) may not be ideal
for virus transmission. Therefore, climate
conditions do not seem to be a major factor in
the dissemination of pandemic influenza
viruses that encounter a naïve population.
SARS-CoV caused an outbreak in Hong
Kong in the spring of 2013. This virus was
relatively stable at room temperature (22–
25°C) and intermediate humidity (40–50%),
but high temperature (38°C) and high
humidity (> 95%) led to a rapid decline in
viability. Moreover, two studies found that
the optimal conditions for human-to-human
transmission of SARS-CoV were 16–28°C
and intermediate humidity of about 50%. Collec-
tively, these findings suggest that
certain subtropical climates (such as the
spring season in Hong Kong) and the condi-
tions in air-conditioned rooms may favor the
spread of SARS-CoV. Numerous studies have
now assessed the impact of climate on
the transmission and mortality of the current
pandemic SARS-CoV-2 virus (a meta-
analysis is described in Ref. (Romero Starke et al, 2021)). Although the data are
inconsistent, the authors of the meta-
analysis concluded that low temperature
and relative humidity are associated with
increased SARS-CoV-2 transmission (Romero Starke et al, 2021). However, as
stated earlier, climate may not be a major
factor in the spread of pandemic viruses that
encounter a naïve population.
The effect of human behavior on the
seasonality of epidemic human respiratory
infections is a topic of ongoing studies and
discussions, in part because of its complexity
with multiple confounding factors. The lower
temperatures during the winter season in
temperate climates may confine people to
indoor activities with indoor crowding, which
could facilitate virus transmission. In fact,
during cold or rainy weather, people tend to
spend more time indoors compared with
warmer, drier weather. However, in industrial-
cized countries in the temperate climate zone,
people annually spend more than 85% of
their time indoors (Klepeis et al, 2001; Schweizer
et al, 2007), suggesting that most person-to-
person contacts occur indoors. The number of
person-to-person contacts indoors may vary
among the seasons, due to holidays and holi-
day travel (several major holidays including
Thanksgiving [in the US], Christmas,
Hanukkah, New Year, and Chinese New Year
fall in the winter season in the northern hemi-
sphere) and the start of the academic school
year. In general, the number of person-to-
person contacts is greater on workdays than
on weekends, and greater during regular
weeks compared to holidays, suggesting that
most human-to-human transmission events
may occur during regular work weeks. While
the number of person-to-person contacts may
be lower on holidays compared to workdays,
travel and social gatherings during holidays
and vacation lead to person-to-person contacts
outside the regular circle of contacts, thereby
introducing the virus into new communities.
Thus, for epidemic human respiratory viruses,
human behavior may exacerbate climate-
driven seasonality in temperate regions, at
least in the northern hemisphere where low
humidity, low temperature, and major holi-
days coincide.
The pandemic SARS-CoV-2 virus is
encountering a naïve population and virus
‘seeding’ into communities during gather-
ings outside regular circles of contact may
be a major contributor to virus dissemination.
This may explain spikes in SARS-CoV-2
cases after the Thanksgiving and Christmas
Holidays in the US. For pandemic viruses,
human behavior is likely a more important
factor for virus dissemination than climate.
Once SARS-CoV-2 becomes an epidemic
human respiratory virus like the other four
human coronaviruses, seasonal outbreaks
may depend more on the climate and less on
human behavior.
In addition to the time spent indoors and
the number of indoor contacts, the indoor
environment may contribute to the seasonality
of respiratory viruses. The relative indoor
humidity in buildings during the winter
season is typically low. As stated earlier,
low humidity at room temperature facilitates
influenza virus transmission in animal
models, whereas no transmission occurs at
room temperature and high relative humid-
ity (Lowen et al, 2007). Thus, the low air
humidity in enclosed rooms in winter likely
facilitates human-to-human influenza virus
transmission, and therefore the seasonality
of influenza virus outbreaks.
In recent years, the effect of environmen-
tal conditions on host antiviral defense
mechanisms has gained more attention (re-
viewed in Moriyama et al, (2020)). The
mucus lining the epithelial cells in the upper
airways provides a first barrier by trapping
viruses before they infect cells. Dry air slows
the flow of mucus along the cilia of the
epithelial cell layer, resulting in delayed
virus clearance. Moreover, dry air causes
the loss of cilia on airway epithelial cells
and the detachment of epithelial cells. Thus,
lower humidity weakens the first line of
defense against infecting viruses.
Innate immune responses are an impor-
tant host defense mechanism after a virus
infected a cell. Several studies have demon-
strated seasonal molecular changes in human
immune responses with differences in cyto-
kine levels and the transcriptome between
the seasons. Higher levels of interleukin 6
(IL-6) are associated with the increased
mortality of highly pathogenic influenza and
SARS-CoV-2 infections; of note, IL-6 signaling
in humans is higher in winter than in
summer. Moreover, studies with rhino-
viruses have shown that innate immune
responses are lower at 33°C (i.e., the tempera-
ture of the upper respiratory tract) compared
to 37°C (i.e., the temperature of the
lower respiratory tract), allowing efficient
rhinovirus replication in the upper respira-
tory tract. Importantly, low relative humidity
dampens innate immune responses, particu-
larly the induction of IFN-stimulated genes
upon virus infection (Kudo et al, 2019).
However, one study reported similar innate immune responses in guinea pigs housed at either 5°C or 20°C (Lowen et al., 2007). Additional studies are needed to fully assess the impact of different environmental conditions on host innate immune responses.

Collectively, the data indicate that low humidity and temperature are important drivers in the seasonality of epidemic human respiratory viruses because these climate conditions increase virus stability and transmissibility, create an indoor environment conducive to virus transmission, and dampen host cell immune responses. Increasing the air humidity in enclosed rooms has been suggested as an easily implementable measure to reduce the transmission of respiratory viruses in wintertime. In contrast, the fulminant spread of pandemic respiratory viruses may be primarily driven by human behavior; once these viruses become epidemic, their continuing circulation in humans may adopt a seasonal pattern that correlates with climate changes in temperate regions.

Disclosure statement and competing interests
The authors do not have any competing interests.

References
Gesellschaft fuer Aerosolforschung (2020) Position paper of the Gesellschaft fuer Aerosolforschung on understanding the role of aerosol particles in SARS-CoV-2 infection. https://www.infogaef.de/positionspapier
Klepeis NE, Nelson WC, Ott WR, Robinson JP, Tsang AM, Switzer P, Behar JV, Hern SC, Engelmann WH (2001) The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants. J Expo Anal Environ Epidemiol 11: 231 – 252
Kudo E, Song E, Yockey LJ, Rakib T, Wong PW, Homer RJ, Iwasaki A (2019) Low ambient humidity impairs barrier function and innate resistance against influenza infection. Proc Natl Acad Sci USA 116: 10905 – 10910
Li Y, Reeves RM, Wang X, Bassat Q, Brooks WA, Cohen C, Moore DP, Nunes M, Rath B, Campbell H et al (2019) Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. Lancet Glob Health 7: e1031 – e1045
Lowen AC, Mubareka S, Steel J, Palese P (2007) Influenza virus transmission is dependent on relative humidity and temperature. PloS Pathog 3: 1470 – 1476
Lowen A, Palese P (2009) Transmission of influenza virus in temperate zones is predominantly by aerosol, in the tropics by contact: a hypothesis. PloS Curr 1: RRN1002
Moriyama M, Hugentobler WJ, Iwasaki A (2020) Seasonality of respiratory viral infections. Annu Rev Virol 7: 83 – 101
Romero Starke K, Mauer R, Karskens E, Pretzsch A, Reissig D, Nienhaus A, Seidler AL, Seidler A (2021) The effect of ambient environmental conditions on COVID-19 mortality: a systematic review. Int J Environ Res Public Health 18: 6665
Schweizer C, Edwards RD, Bayer-Oglesby L, Cauderman WJ, Ilacqua V, Jantunen MJ, Lai HK, Nieuwenhuijsen M, Kunzli N (2007) Indoor time-microenvironment-activity patterns in seven regions of Europe. J Expo Sci Environ Epidemiol 17: 170 – 181
Shaman J, Goldstein E, Lipsitch M (2011) Absolute humidity and pandemic versus epidemic influenza. Am J Epidemiol 173: 127 – 135

License: This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.