Drivers of Infectious Disease Seasonality:
Potential Implications for COVID-19

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Abstract
Not 1 year has passed since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19). Since its emergence, great uncertainty has surrounded the potential for COVID-19 to establish as a seasonally recurrent disease. Many infectious diseases, including endemic human coronaviruses, vary across the year. They show a wide range of seasonal waveforms, timing (phase), and amplitudes, which differ depending on the geographical region. Drivers of such patterns are predominantly studied from an epidemiological perspective with a focus on weather and behavior, but complementary insights emerge from physiological studies of seasonality in animals, including humans. Thus, we take a multidisciplinary approach to integrate knowledge from usually distinct fields. First, we review epidemiological evidence of environmental and behavioral drivers of infectious disease seasonality. Subsequently, we take a chronobiological perspective and discuss within-host changes that may affect susceptibility, morbidity, and mortality from infectious diseases. Based on photoperiodic, circannual, and comparative human data, we not only identify promising future avenues but also highlight the need for further studies in animal models. Our preliminary assessment is that host immune seasonality warrants evaluation alongside weather and human behavior as factors that may contribute to COVID-19 seasonality, and that the relative importance of these drivers requires further investigation. A major challenge to predicting seasonality of infectious diseases are rapid, human-induced changes in the hitherto predictable seasonality of our planet, whose influence we review in a final outlook section. We conclude that a proactive multidisciplinary approach is warranted to predict, mitigate, and prevent seasonal infectious diseases in our complex, changing human-earth system.

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COVID-19

This review is written during the coronavirus disease 2019 (COVID-19) pandemic. Not a year (1 seasonal cycle) has passed since its emergence in Asia in late 2019, and great uncertainty still surrounds the potential for COVID-19 to establish seasonality. At the time of writing, the steep autumnal increase in the number of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Europe and North America may indeed point to seasonality.

Seasonality, characterized by systematic within-year changes that repeat across years, is a feature of many infectious diseases, including respiratory infections such as endemic human coronaviruses (CoV) (Nickbakhsh et al., 2020). The particular shape, timing (phase), and degree of seasonality differ between diseases, climatic regions, and geographic locations (Altizer et al., 2006; Fisman, 2007; Lal et al., 2012; Martinez, 2018) for reasons that are not fully understood. If SARS-CoV-2 (the virus that causes COVID-19) establishes seasonal outbreak patterns in the long term (Cohen, 2020), it will have important implications for public health planning and forecasting. At present, the potential impact of COVID-19 seasonality is being discussed widely within academia, medical organizations, and in politics. These discussions highlight the importance of predicting the cyclical pattern of emerging infectious diseases that are of major societal, public health, and economic concern.

Human civilizations have paid close attention to seasons regarding health, not least in terms of infectious disease. For example, the four humors (i.e., fractions of clotted blood) well characterized by ancient Greek medicine (Hart, 2001), and thought to be responsible for health, growth, and metabolism, were described as seasonal (Jouanna, 2012). Until recently, most humans lived in a highly seasonal environment. Modern westernized lifestyles, including use of artificial light to extend day length and climate control, resulted in eternal summer conditions (Wehr, 2001). For these and further changes in seasonality of humans, such as antibiosis, pathogen control, and a nonseasonal diet (Anderson and Nieman, 2016), the direct and indirect health consequences remain to be fully determined (Stevenson et al., 2015).

Disease-specific seasonal patterns can arise from both ultimate (evolutionary adaptations to the seasonal environment of host and pathogen, for example, internal clocks, photoperiodism, and climate tolerance) and proximate causes (e.g., direct influence of environmental conditions or human behavior).

Understanding the drivers of disease seasonality is crucial for the fundamental understanding and control of diseases (Grassly and Fraser, 2006; Fisman, 2007, 2012). If drivers influencing the timing and magnitude of outbreaks are identified, existing disease surveillance methods can be tailored to these seasonal processes to generate appropriate prevention and treatment strategies, develop validated prediction models, and enhance cross-border cooperation. Furthermore, mechanistic understanding of seasonal drivers for specific diseases can help identify medical targets, such as putative molecular pathways that underlie infection, to enable potential future modulation of host susceptibility and resistance.

In this article, we first review the putative environmental drivers of infectious disease seasonality. We then discuss seasonal within-host changes that may affect infectious disease susceptibility, morbidity, and mortality. Such underlying mechanisms may drive the timing of rises in infections at the population level. Based on this, we discuss the potential of COVID-19 to develop seasonality and highlight 2 priority areas to understand and predict such patterns. One area is the emergence of a promising model for drug development in seasonal hamsters. The second is the rapid, human-induced changes in the hitherto predictable seasonality of our planet, which is expected to affect infectious diseases in the future.

SEASONALITY

The Earth rotates around its axis with a 23.5° tilt relative to the plane of its annual orbit around the sun. This tilt generates predictable seasonal changes in environmental conditions, including day length, UV radiation, and ambient temperatures (Foster and Kreitzman, 2009). These changes are more pronounced at higher latitudes, whereas seasonality in tropical regions is usually more nuanced (e.g., local patterns of dry and rainy seasons). Most living organisms (including humans) have developed adaptations to cope with seasonal changes (Foster and Kreitzman, 2009). Such adaptations enable hosts and pathogens (and vectors and reservoirs) to function, survive, reproduce, or transmit within the seasonal environment (including the seasonal internal environment that occurs within hosts due to seasonal physiology). The seasonal environment may thus directly affect organisms, for example, through annual changes in UV radiation, humidity, and ambient temperature, or do so indirectly.
through interactions with corresponding internal physiological regulatory mechanisms. The fact that the amplitude and phase of disease seasonality often change with latitude suggests an important role of clines in the environment, particularly changes in day length (photoperiodism). Over evolutionary time, photoperiod has been a noise-free environmental condition with high predictive value to signal future environmental conditions and associated challenges and opportunities. For example, in temperate regions, autumn photoperiods signaled the approach of winter and challenging energetic conditions; similarly, the increasing photoperiod after winter solstice signaled the approach of spring and potentially favorable environmental conditions. Due to this predictive value of photoperiod, organisms have evolved mechanisms to time biological processes either by directly responding to photoperiod or by synchronizing a circannual internal biological clock using photoperiod (Gwinner, 1986; Bradshaw and Holzapfel, 2007; Lincoln, 2019).

**POSSIBLE DRIVERS OF INFECTIOUS DISEASE SEASONALITY**

Many factors likely contribute to seasonal patterns of infection, including pathogen survival in the environment and transmissibility, changes over time in pathogen reservoirs (human and non-human) and vectors, frequency of pathogen-host interactions (cultural, socioeconomic, linked to lifestyle), and a relatively understudied factor: host susceptibility to infection (rhythms in immunology) (Lal et al., 2012) (Figure 1).

In the context of human respiratory infections, and particularly COVID-19, it is noteworthy that endemic human CoV typically exert the greatest health care burden during winter months in temperate regions (Figure 2), reflecting high community incidence in these periods (Li et al., 2020b; Monto et al., 2020; Nickbakhsh et al., 2020). Meteorological factors are the most commonly studied drivers of such seasonality in host-host transmission of respiratory viruses (Price et al., 2019; Moriyama et al., 2020). Animal experiments have demonstrated, for example, that influenza transmits more readily in conditions of cold temperatures and low relative humidity, possibly as a result of reduced mucociliary clearance or viral stability in the upper respiratory tract (Lowen et al., 2007; Lowen and Steel, 2014). These experimental findings corroborate epidemiological modeling studies which suggest the effect of weather on influenza transmission is sufficient to explain the typical winter timing of outbreaks in temperate regions (Shaman and Kohn, 2009). A common hypothesis is that cold weather leads to crowding indoors and therefore enhanced person-to-person contact, although the role of indoor heating systems that generate conditions of low relative humidity also merits consideration as a mechanism of enhancing transmission (Moriyama et al., 2020).

Additional hypotheses regarding the autumn/winter occurrence of respiratory infections include the magnitude of temperature fluctuations impacting transmission. In particular, the correlation between indoor and outdoor temperatures is strong during warmer months, yet substantially weakens when the weather gets cooler (Nguyen et al., 2014). This suggests that people may experience greater temperature swings during a given day in the winter, compared to in the summer, especially in
important for the transmission dynamics of several patterns of school-aged children are recognized as Bakker and Helm, 2015). For example, the mixing frequency of host-pathogen interactions (Martinez-Bakker and Helm, 2015) can create seasonality in the frequency of infection (Nguyen et al., 2009).

In addition to environmental conditions, host behavioral changes can create seasonality in the frequency of host-pathogen interactions (Martinez-Bakker and Helm, 2015). For example, the mixing patterns of school-aged children are recognized as important for the transmission dynamics of several infectious diseases, including measles, varicella, influenza, and other common respiratory infections. However, the role of this school-term forcing of disease transmission in explaining the timing of outbreaks of seasonal infectious disease is not fully established (Cauchemez et al., 2008; Eames et al., 2011; Luca et al., 2018). Similarly, seasonal changes in outdoor activities including tourism, recreation, and management of crops and livestock may drive seasonal exposure to vectors and/or environmental reservoirs of pathogens, resulting in disease seasonality (Altizer et al., 2006).

Another, albeit largely understudied, factor likely contributing to infection seasonality is host seasonality, including seasonality of the immune system (discussed at length below), and other biological functions, such as birth seasonality. Birth seasonality affects disease incidence and timing by replenishing the pool of susceptible individuals. For wildlife hosts, birth seasonality also affects population density and hence disease transmission (He and Earn, 2007; Begon et al., 2009; Duke-Sylvester et al., 2011; Dorélien et al., 2013). Large amplitudes of seasonal birth pulses can induce corresponding increases in childhood disease, while changes in seasonal phase can influence the timing of the outbreaks. In both cases, the effect is larger at higher birth rates (He and Earn, 2007; Dorélien et al., 2013).

A well-described driver of infectious disease seasonality is vector biology. For example, dengue incidence in Bali is highly seasonal, with most cases reported during the rainy season between December and April. Evidently, the many water bodies and occurrence of lowland flooding provide excellent conditions for the vector, Aedes mosquitoes, to reproduce and undergo their larval aquatic life stage (Dhewantara et al., 2019). Similarly, Anopheles mosquitoes are required for the malaria parasite to complete its life cycle prior to human transmission, so seasonality of the disease in humans is primarily caused by seasonality in climatic conditions required for the vector to breed (Herekar et al., 2020). Malaria has been shown to exert significant selective pressure on the human genome, thereby potentially implicating seasonal mechanisms (Kwiatkowski, 2005).

It is important to note that the drivers of disease seasonality are not mutually exclusive, and that the proximate mechanisms driving seasonality for a specific pathogen may involve several organisms and be affected by the ecological context. For example, disease seasonality could result from epidemiological interactions with other pathogens sensitive to environmental conditions, as studied for influenza and non-influenza respiratory viruses (Nickbakhsh et al., 2019). Moreover, broad-acting host immune responses (e.g., shifting between Th1 and Th2 immune response)
caused by one seasonal pathogen may change the host susceptibility to other pathogens and could lead to seasonality in risk, duration, or severity of infections and co-infections (Cizauskas et al., 2014). Thus, diseases resulting from non-seasonal pathogens may exhibit seasonality as a result of immunomodulation by co-circulating seasonal pathogens. Seasonal immunomodulation and other within-host factors, such as circannual rhythms, are not well-integrated topics within epidemiological research but may hold important clues as to disease seasonality, as discussed below.

**SEASONAL WITHIN-HOST CHANGES: PHOTOPERIODISM AND CIRCANNUAL RHYTHMS**

Seasonal changes in the vertebrate immune system have long been widely documented (Nelson et al., 2002). Recently, such data are also becoming available for humans with unprecedented data depth and sample sizes (Sailani et al., 2020; Wyse et al., 2020). Whereas we will review some emerging patterns in this rapidly growing research field in a subsequent section, here we focus on underlying mechanisms that generate seasonal within-host changes. Principally, changes in the immune system can arise as direct responses to seasonal immune challenges and from seasonally changing modulating factors, for example, nutrition. Alternatively, such changes can arise from biological time-keeping programs that are triggered by changes in photoperiod or oscillate endogenously as circannual rhythms (Gwinner, 1986; Nelson et al., 2002). Distinguishing direct responses to the seasonal environment from photoperiodism and circannual cycles requires experimental approaches whereby animals are tested under controlled laboratory conditions. Under these conditions, pervasive changes in the immune system persist in many species. Strikingly, different immune parameters vary independently across the seasons (Nelson et al., 2002) so that, in effect, the immune system is reconfigured, rather than simply upregulated or downregulated. The discovery of programmed changes in the immune system, on an annual as well as on diel time-scales (Bormann et al., 2021), is of fundamental importance for understanding the etiologies of diseases. Once rhythmicity is established, its features can be adjusted through various modifications, for example, population-level changes in photo-responsiveness within a murine species (Heideman and Pittman, 2009) or switches between short-day (SD) and long-day (LD) breeding within closely related mammalian or avian taxa (e.g., Helm, 2009). Such modifications can adjust the timing (phase), waveform, amplitude, and robustness of particular aspects or of the entire annual cycle, as well as the degree of photoperiodism.

Direct effects of photoperiod on the immune system were demonstrated by evidence that acclimation to SD or LD induces enhancement and suppression of several components within the immune system in vertebrates (Nelson et al., 1995; Baillie and Prendergast, 2008; Stevenson and Prendergast, 2015; Weil et al., 2015; Onishi et al., 2020). Circannual rhythms, on the contrary, oscillate endogenously under constant photoperiodic, thermal, and dietary conditions, with period lengths that may differ slightly from 1 year (from Latin: circa—about, annus—year). Strong evidence for circannual rhythms requires observing animals for two or more annual cycles, but even cyclic changes over 1 year indicate a high level of endogenous control (Gwinner, 1986). Circannual rhythms are evident for many processes, including hibernation, reproduction, metabolism, molt, and migration (Gwinner, 1986; Visser et al., 2010; Stevenson et al., 2015). In most species, these rhythms entrain readily to photoperiod, but the extent of their persistence in the absence of photoperiodic change differs between species and even within taxonomic groups such as ungulates and rodents (Lincoln, 2019).

Circannual studies of the immune system have been scarce but have confirmed that changes in the host can be hard-wired, independent of photoperiodic change. Major circannual changes in the immune system are reported for hibernators, where lymphoid tissue can entirely regress during hibernation, but recrudesce spontaneously in anticipation of arousal (Shivatcheva and Hadjioloff, 1987). Similar, but weaker cycles have been reported for nonhibernating rodents. Even in laboratory mice, which in some strains have retained some seasonality despite rigid breeding against it, immune cycles have been repeatedly reported. For example, cultured spleen lymphocytes harvested at different times of year from BALB/c mice showed marked annual cycles in proliferation response to several mitogens, across sex and age groups (Planelles et al., 1994). Similarly, the blastoegenic response in C57BL/6 mice, in different age groups, also showed circannual cycles under strictly controlled conditions, which the authors found relevant for mortality patterns and seasonal virus infections (Brock, 1983, 1987). An alternative interpretation of such immune cycles, as arising from cyclic pathogen exposure, is unlikely because circannual period lengths deviate from 1 year (Brock, 1983, 1987) and because animals with different genetic backgrounds may show different immune cycles under identical conditions (Versteegh et al., 2014).
An example of population-specific immune cycles is shown in Figure 3. Several populations of a songbird taxon, stonechats (genus *Saxicola*), were kept under identical conditions in mixed groups. At defined phases of the annual cycle, such as migration, molt, or reproductive activation, several measures were taken to assess immunity (Versteegh et al., 2014). The study focused on constitutive immunity as a general, first line of defense, including against viral and bacterial pathogens (Paludan et al., 2020). Most measures differed across the birds’ annual cycle, as well as between populations. Figure 3 shows annual patterns of bacteria-killing ability of whole blood, an activity that combines various mechanisms of the innate immune system, for example, phagocytic activities of leukocytes and microbicidal activities of humoral proteins (Millet et al., 2007; Versteegh et al., 2014). In addition to published data from birds kept under simulated European photoperiod, we include unpublished data of a circannual control group that was kept under constant photoperiod (LD 12.25:11.75 h). These birds showed highly similar cycles in bacterial killing, although individual differences between free-running individuals slightly damped the amplitude.

Pervasive evidence of host immune cycles brings up the question why immune defense is not simply consistently upregulated. A possible answer may lie in trade-offs between different seasonal functions, including reproduction, migration, hibernation and molt, with different immune parameters (Nelson et al., 2002). Changes in vertebrate immunity often, but not necessarily, associate with such major physiological changes. For example, some arms of the immune system are depressed specifically during times of reproduction (Nelson et al., 1995; Weil et al., 2015). Lymphoid tissues in mammals express androgen and estrogen receptors, and may regress during photoperiodic reproductive activation, resulting in T-lymphocyte reduction (Nelson et al., 2002). However, castrated individuals also show some photoperiodic change, indicating steroid-independent components of immune cycles (Prendergast et al., 2008).

**WITHIN-HOST CHANGES THAT MAY AFFECT SUSCEPTIBILITY, MORBIDITY, AND MORTALITY**

In the human immune system, seasonal molecular immunological phenotypes have been widely described (Dopico et al., 2015; Aguirre-Gamboa et al., 2016; Lockett et al., 2016; Ter Horst et al., 2016; Thysen et al., 2016; Ucar et al., 2017; Calov et al., 2020; Sailani et al., 2020; Wyse et al., 2020). Several of these studies highlight seasonal effects on the transcriptome, cytokine signaling, and cell numbers and ratios (Figure 4; Dopico et al., 2015). The results show that despite the
widespread modification of putative seasonal cues in modern environments, seasonal genetic networks continue to impinge upon immune function. Different vaccine responses, for example, have been found to show seasonal variation in humans (World Health Organization, 1995; Deming et al., 1997; Moore et al., 2006; Lalor et al., 2009).

An understanding of seasonally responsive genetic systems could broadly inform clinical medicine, as many common diseases of modernity are typified by both immunological and metabolic dysregulation (Herder et al., 2007; Pedersen, 2007; Insull, 2009; Mathis, 2013; Bauer and Teixeira, 2019). This is especially important as an increasing number of health conditions are known to have a seasonal component to diagnosis and disease activity, including different cancers (Moan et al., 2010), cardiovascular diseases (Nguyen et al., 2016), multiple sclerosis (Harding et al., 2017), type 1 diabetes (Moltchanova et al., 2009), and psychological disorders (Quera Salva et al., 2011).

Applied to an emerging disease pandemic, seasonal changes in immune function can be important, for example, by altering the permeability of within-host barriers, contributing to zoonotic spillover (Plowright et al., 2017). Both SARS-CoV and SARS-CoV-2 recently emerged during winter (February 2003 and December 2019), when human CoV exhibit increased incidence and health care burden in temperate regions (Plowright et al., 2017; Nickbakhsh et al., 2020). Notably, interleukin 6 (IL-6) signaling is increased in humans during winter and is associated with mortality in COVID-19 (Grifoni et al., 2020). Coronavirus are not alone in their predilection for winter, whereas some other pathogens display preferences for other seasons and environmental conditions, putatively exploiting differences in host biology.

Due to ethical, logistical, and technical difficulties of performing appropriately powered studies in humans, quantification of seasonal phenotypes in controlled experiments is lacking. Systems analyses of the interactions between diet (including timing of meal intake), photoperiod, ambient temperature, and immune challenge in animal models will provide greater understanding of the evolutionary mechanisms at work. In mice, for example, herpes and influenza viruses replicate more efficiently in the absence of the key circadian protein, ARNTL (BMAL1) (Bunger et al., 2000; Nguyen et al., 2013; Edgar et al., 2016), whose expression is reduced in the human immune system during winter (Dopico et al., 2015), perhaps contributing to increased virus dissemination at this time.

Furthermore, recent developments highlight a central role for molecular metabolism in immune function. Elegant studies have demonstrated how various small molecules (such as itaconate) and different metabolic pathways are critical to separate anti-pathogen responses (Buck et al., 2015; West et al., 2015; Mills et al., 2018; Peruzzotti-Jametti et al., 2018; Weisel et al., 2020). In humans, seasonal metabolic phenotypes that could impinge upon the immune system, or vice versa, include adiposity (Bartness et al., 2002), osmoregulation (Yoshimura, 1958; Dopico et al., 2015), body mass index (Visscher and Seidell, 2004), cognition (Meyer et al., 2016; Lim et al., 2017), hair growth rate (Randall and Ebling,
As demonstrated by investigations of humans and seasonal animal species, dietary metabolism is critical for immune competence (Luca et al., 2010; Singh et al., 2013; Carrillo et al., 2016; Singh et al., 2017; Zandkarimi et al., 2018). Worryingly, humans globally suffer from an increasing and considerable metabolic disease burden, where chronic inflammation is a major morbidity factor and immune competence is impaired (Brouwer et al., 2015). This includes various cancers, cardiovascular diseases, and diabetes and is largely attributed to obesity, diet-associated metabolic impairment, circadian disruption (Zimmet et al., 2019), and a lack of physical exercise. Preliminary findings suggest that comorbidities such as obesity are associated with an 86%-142% higher risk of developing severe pneumonia, another major risk factor for COVID-19-associated mortality (Stefan et al., 2020). Therefore, further research into the interactions between human immune and metabolic networks, biological rhythms, and numerous environmental factors that impinge upon them will contribute to a more complete understanding of human molecular physiology (Renz et al., 2017; West and Wood, 2018), with implications for improved societal health and well-being (Naumova, 2006).

**POTENTIAL EFFECTS OF HOST IMMUNE SEASONALITY ON SARS-COV-2 INFECTION**

It is possible that changes in the immune system are directly relevant for susceptibility, morbidity, replication, and transmission dynamics of SARS-CoV-2. For example, early infection steps involving the spike glycoprotein (S) may be affected by host seasonality. In vitro analyses have identified that SARS-CoV-2 infects cells by the coordinated action of 2 domains of its surface spike glycoprotein: S1 and S2. Enzymes such as transmembrane protease serine 2 (TMPRSS2) and Furin cause conformational changes separating the S1 and S2 domains to allow cell entry. The catalyzed separation facilitates S1 binding to angiotensin-converting enzyme 2 (ACE2) and S2 to the cell membrane, leading to endocytosis into the cytoplasm (Tay et al., 2020).

Recent genome-wide transcriptomics of human leukocytes identified that Furin transcripts exhibit seasonal rhythmicity in children, with high expression in summer and low levels in winter (Dopico et al., 2015). These findings raise an exciting hypothesis that there may be endogenous seasonal variation in immune defense against SARS-CoV-2. Here, the availability of leukocyte Furin expression may underlie increased endocytosis of viral mRNA in a season-dependent manner. As SARS-CoV-2 RNA is detectable in the blood of patients (Young et al., 2020), longitudinal analyses of samples could be a significant avenue to understand seasonal disease dynamics. A second lead to possible effects of seasonal within-host changes comes from genome-wide analyses of UK Biobank patients who developed severe COVID-19. Through analyses of multi-SNP (single nucleotide polymorphism) genotype signatures compared to controls, these patients were found to possess 68 risk-associated protein-coding genes (Taylor et al., 2020). Of these, 9 were linked to host responses to viral infections including SARS-CoV-2. One potentially exciting gene of these 9 robust markers was Anthrax toxin receptor 1 (ANTXR1). In hamsters, Antxr1 shows robust photoperiodic regulation with high leukocyte expression in long summer-like days (Figure 4). Other transcriptome analyses of leukocytes in humans have also identified ANTXR2 expression as seasonally dependent (Dopico et al., 2015).

Anthrax receptors are potentially important for seasonal disease dynamics as Furin has the capacity to regulate viral propagation (e.g., SARS-CoV-2) and bacterial toxin (e.g., Anthrax) activation. The site of action for TMPRSS2- and Furin-mediated SARS-CoV-2 endocytosis is homologous to the processing site of anthrax toxin PA protein (Barile et al., 2020). One conjecture is that seasonal variation in immune responses to SARS-CoV-2 may entail the inadvertent activation of other pathogenic pathways (e.g., anthrax receptor) and increase the incidence of severe cases. If confirmed, these findings would indicate that at least one component of the molecular driver of seasonal cycles in disease includes the co-activation of multiple antigen pathways and not necessarily a “singular” immune response pathway.

**IS COVID-19 EXPECTED TO BE SEASONAL AND WHY?**

The knowledge on drivers of seasonal respiratory viral infections, summarized above, can inform cautious considerations of the potential future seasonality of COVID-19. For SARS-CoV-2, studies have highlighted moderate temperature and dry
environmental conditions under which the virus appears to thrive most optimally (Brasley et al., 2020), with studies describing the influence of every 1 °C increase in temperature and 1% increase in relative humidity as lowering the effective R₀ by 0.0383 and 0.0224, respectively (where the base reproduction number R₀ of SARS-CoV-2 is estimated to fall between 1.5 and 3.5 (Brasley et al., 2020; Li et al., 2020a)). A recent cohort study of 50 cities identified a corridor roughly between 30 °N to 50 °N latitude and with consistent mean temperatures of 5-11 °C, combined with low humidity, as the most conducive to large COVID-19 community outbreaks, further implicating seasonality of the virus (Sajadi et al., 2020). A systematic review of global surveillance data found seasonal patterns of endemic human CoV in many temperate regions, as anticipated (Kissler et al., 2020; Li et al., 2020b). Indeed, the incidence of SARS-CoV-2 infections has risen in autumn 2020 (European Centre for Disease Prevention and Control [ECDC], European Union [EU]) as predicted for temperate regions (Li et al., 2020b; Scafetta, 2020).

The preference for cool and dry conditions (e.g., typical air-conditioned environments) of SARS viruses has previously been described during the 2002-2003 SARS-CoV outbreak (Chan et al., 2011). However, other factors that correlate with such environmental conditions have been largely neglected thus far, including behavioral changes described above. Moderately cool temperatures below 10 °C or 11 °C are conducive to persons spending time indoors, and differences between indoor and outdoor temperatures can impact transmission through physiological and behavioral factors. Thus, for COVID-19, which is transmitted via droplets with a lingering debate regarding its potential for aerosol-based transmission (Klompas et al., 2020), spending time indoors and closer to each other has likely contributed to a second wave of the COVID-19 pandemic in the fall in the absence of stringent social distancing and lockdown interventions. Current evidence for SARS-CoV-2 does not provide support for low vitamin D—beyond its known impact on human immune response (Bordon, 2017)—as a causal factor for heightened receptivity of the infection (Lanham-New et al., 2020), but rather as a potential surrogate marker surrounding the optimal conditions to leverage spread and impact of the virus (i.e., cooler temperatures, more time spent indoors, comorbidities, older age).

Overall, there is good reason to believe SARS-CoV-2 may display seasonality in the long run, although the relative contribution of the weather, behavior, and seasonal immunity to SARS-CoV-2 replication and transmission warrants further investigation.

**OUTLOOK: PRIORITY AREAS FOR UNDERSTANDING THE SEASONALITY OF INFECTIOUS DISEASES**

Our assessment of the current knowledge base for predicting seasonality of COVID-19 indicates promising avenues but also major deficiencies. Below, we highlight 2 areas that we consider particularly important for understanding and mitigating seasonal infectious diseases more broadly. First, from a physiological perspective, we endorse the need for animal models that can inform human disease seasonality. Second, from an environmental perspective, we emphasize the importance of understanding the causes of disease spillovers and outbreaks to be able to predict, prepare for, and even prevent new emerging pandemics. Importantly, we note that predicting the net impact of climate change on global infectious disease burden, whether in the form of increased or decreased infection risks, is particularly challenging when considering likely interactions with other geographically varying anthropogenic factors.

**Animal Models and the Potential Mechanisms of Seasonal COVID-19**

A major challenge limiting our knowledge of SARS-CoV-2 infection and pathology is developing a broad range of suitable animal models. Small animal models are vital to identify potential mechanisms of transmission and immune responses. Due to the ability of respiratory transmission and similar SARS-CoV-2 infection, animals such as hamsters, ferrets, and cats have emerged as valuable investigative models (Imai et al., 2020; Richard et al., 2020; Shi et al., 2020; Sia et al., 2020). Other domesticated animals such as dogs, pigs, chickens, and ducks show low or absent susceptibility to infection (Shi et al., 2020). Common biomedical models (e.g., rats and mice), while being well positioned to address some aspects of nonrespiratory-based SARS-CoV-2, typically exhibit low seasonal immune dynamics and critically lack the ACE2 homology required for SARS-CoV-2 infection (Lutz et al., 2020). One advantage of mouse models is the ability to create transgenic animals to explore SARS-CoV-2 viral replication and pathology. Transgenic mice that produce human ACE2 are susceptible to SARS-CoV-2 infection and show some viral-induced pathologies observed in humans (Lutz et al., 2020). Unfortunately, the low homology in human-mouse respiratory inflammatory responses (Seok et al., 2013) limits our ability to develop from these models solid interpretations for seasonal immune dynamics associated with COVID-19.
The rodent subfamily of hamsters (Cricetinae) contains 19 species, of which the Syrian hamster (*Mesocricetus auratus*) and Siberian hamster (*Phodopus sungorus*) are 2 models that exhibit seasonality, respond to changes in photoperiod, and express circannual rhythms, including robust seasonal variation in immunity. These animal models provide a rewarding approach to examine the potential seasonal basis of SARS-CoV-2 due to reliable immune responses to changes in day lengths (Stevenson and Prendergast, 2015). Recently, Syrian hamsters were identified as an excellent model due to the capability of SARS-CoV-2 to infect respiratory epithelium and macrophages in a manner similar to human pathologies (Imai et al., 2020; Sia et al., 2020). Moreover, there is a high level of transmission between hamsters providing a valuable opportunity to examine between-subject transmission (Imai et al., 2020; Sia et al., 2020). A recent study reported high vaccination success even against severe clinical forms of the disease in this species (Tostanoski et al., 2020). These findings indicate that hamster models provide a powerful approach to examine seasonal variation in SARS-CoV-2 transmission, mechanisms of disease progression, and potentially vaccination success (Tostanoski et al., 2020).

For both Syrian and Siberian hamsters, a simple switch in laboratory day length (e.g., 1600:0800h light:dark schedule to 0800:1600h light:dark schedule) induces a wide range of changes in innate and adaptive immunity. Exposure to winter-like short days (SD) increases spleen mass and numbers of macrophages and lymphocytes in Syrian (Brainard et al., 1987) and Siberian hamsters (Bilbo et al., 2002) (Figure 5a). These physiological changes in immune markers are thought to enhance fitness, as SD hamsters show enhanced innate (Stevenson et al., 2014) and adaptive (Bilbo et al., 2002) immune responses when challenged. The Siberian hamster is a key model species due to the broad range of documented photoperiodic changes in immune function (reviewed in Stevenson and Prendergast, 2015). In contrast, Syrian hamsters do not exhibit photoperiodic differences in some adaptive immune responses including delayed-type hypersensitivity reactions or antibody production, which limits the viability of this species for some immune measures (Zhou et al., 2002). To date, there is no evidence that either TMPRSS2 or ACE2, key molecules involved in SARS-CoV-2-induced immune reactions, changes across seasonal phenotypes in any mammal studied. However, in hamsters housed in SD conditions, the leukocyte expression of anthrax receptor 1 is significantly downregulated (unpublished data, Figure 5b and 5c), in a manner potentially consistent with findings of human leukocyte ANTXR2 (Dopico et al., 2015). These data indicate that seasonal rhythms in immune responses might be associated with lower anthrax receptor signaling and subsequent reduction in infection incidence.

### Changing Seasonality in the Anthropocene

Infectious diseases have plagued humanity since the earliest days, and human activities are accelerating their emergence. Hence, in this section we will broadly explore potential drivers of such changes, widening our perspective to include a wide range of pathogens. The majority of recently emerging human infectious diseases are zoonotic, and most of these originate in wildlife (Johnson et al., 2015), indicating that as wildlife populations are increasingly affected by anthropogenic impacts, the incidence of emerging diseases is expected to rise (Figure 6; for example, Jones et al., 2008; Guo et al., 2019; Rizzoli et al., 2019). These rapidly increasing threats develop against the backdrop of equally rapid change in the formerly highly predictable seasonality of our planet, under human-induced drivers of global change. Changes in patterns of Earth’s seasonality may thereby play a significant role in changing emerging disease burden, through increases or decreases in risk of emergence and spread, depending on geographical location.

Anthropogenic impacts on seasonality are particularly evident for climate change, land-use change, and exposure of wild organisms to artificial light at night (ALAN). These factors may render the cues for diel and seasonal rhythms unintelligible or misleading (e.g., ALAN interfering with photoperiodism). Through their impact, the biotic and abiotic environment may differ substantially from that expected at a given time under the prevalent cues. Climate change may thus impact the seasonality of certain infectious diseases, making it more difficult to predict when surges of cases may appear (Figure 7; for example, Smith, 2019). The above factors may act in concert with changes in species distributions, including the global increase in invasive species, which are often disease vectors (Figure 7; for example, Stuart et al., 2020). The results of anthropogenic changes are therefore expected to be complex, interdependent, and differ between species. Thereby, they may, for example, result in mismatches between an individual’s physiology and the environment, between individuals within a species, and between species (Visser and Gienapp, 2019; Sanders et al., 2020).

Combinations of the main parameters that characterize environmental rhythmicity (i.e., level, variation, amplitude, phase, and waveform) have all been reported to change. The global level of ambient temperature is steadily increasing, affecting infectious disease (e.g., Marcogliese, 2008; Altizer et al., 2013),
for example, through changes in species distributions, where range shifts and dispersal of disease vectors are well documented (e.g., Iwamura et al., 2020).

In addition, increases in variability occur depending on time of year (Dillon and Woods, 2016), and episodic climate events such as heat waves, common
under climate change, may also have a complex impact on disease dynamics (Claar and Wood, 2020). The phenology of many biological processes advances with climate change (Thackeray et al., 2010), affecting given species and those that ecologically interact with them, including the phenology of parasites (Rizzoli et al., 2019). Altered timing of vector emergence can increase the impact of viruses on hosts, for example, if infections coincide with sensitive developmental periods, as shown for Zika (Martinez, 2016). Moreover, through the changes in level, temperature-sensitive phases of phenology, such as the growing season, are extended in many global habitats (McCabe et al., 2015) but shortened in others, for example, depending on aridity (Sarr, 2012), with consequences for activity phases of vectors, synchrony of birth pulses, and many other aspects of seasonality. These changes are not limited to ambient temperature: seasonal rhythms of precipitation are also changing (Dunning et al., 2018). Such changes may impact pest populations and disease vectors but possibly also fomite transmission pathways. A recent study of respiratory syncytial virus in current and future climates found consistent patterns of climate drivers at

Figure 7. Effects of anthropogenic global changes on drivers of infectious disease seasonality. Global change of the environment (orange box and arrows), and cultural and socioeconomic changes (gray), can affect the seasonality of infectious diseases directly, but also indirectly through their effects on environmental conditions (green). Color version is available online.
Rödiger et al., 2020), and dams cause river fragmentation and dewatering (e.g., Farah-Pérez et al., 2020); these, in turn, may affect species patterns of distribution, abundance, and seasonality.

Another important form of land-use change that raises disease risk is urbanization, where multiple aspects of seasonality are buffered, for example, by year-around availability of open water and food (Govoetchan et al., 2014; Becker et al., 2015). Also given high human population density and disproportionately high zoonotic capacity of species that tolerate human land use (Gibb et al., 2020), it is little wonder that cities are hot spots for emerging infectious diseases (Santiago-Alarcon and MacGregor-Fors, 2020).

Disconcertingly, even the putatively most stable and reliable environmental rhythm, the alternation between light and darkness, is changing through increasing ALAN (Kyba et al., 2017). ALAN disrupts circadian biology in humans and many other organisms, with cascading effects on seasonal processes (Knop et al., 2017). For humans, additional to circadian disruption, indoor ALAN exposure masks the annual change in photoperiod through continuously available LD. Outdoors, wild species may show altered seasonality when exposed to ALAN, which physiologically elicits LD responses (Robert et al., 2015). Consequences of ALAN for immunity have been well established in laboratory species, notably in Siberian hamsters (Bedrosian et al., 2011), and are now suggested to also increase risk from viral diseases. Recent research on West Nile virus, a disease that can be transmitted from birds to humans, has shown that ALAN increased exposure risk and vector competence of avian hosts (Kernbach et al., 2019, 2020a, 2020b, 2020c). Furthermore, ALAN also increased avian host morbidity, indicating that risks of rhythm disruption are not limited to effects on vectors. Bats have been described as natural host reservoirs for several recently emerged viruses (Marburg, Ebola, SARS (Moratelli and Calisher, 2015; Olival et al., 2017)) and they, too, are adversely impacted by artificial light on multiple scales, potentially contributing to enhanced viral spread (Stone et al., 2015).

The effects of global change in ambient temperature, rainfall, daylight hours, diet, social activity, and land use on respiratory virus infection risks and spread, including SARS-CoV-2, and their manifestation as increases or decreases in disease burden, are likely to vary geographically and require further research attention. For instance, climate change is thought to lead to both warmer and dryer conditions in some tropical regions, with expected opposing effects on SARS-CoV-2 transmissibility. Thus, rather than postulating net effects, our intention has been to provide the base material for researchers to use when addressing these important problems in particular context.

CONCLUSIONS

We have presented a brief overview of environmental and physiological seasonality, which may contribute to potential future seasonality of COVID-19, as well as of other infectious diseases. On the side of host physiology, we encourage further studies on seasonal restructuring of the immune system in relevant animal models and through the generation of seasonal omics data in humans. We propose that such research should complement current efforts to understand climatic and behavioral drivers of infectious disease seasonality. Even in the absence of host adaptations, seasonal predictability of diseases has major advantages for medical applications (Kissler et al., 2020), as evidenced by the success of seasonal influenza vaccination campaigns (Chung et al., 2020). To the extent that host physiology, too, is seasonal, such consistent patterns can be further exploited, analogous to the growing importance of circadian research for medical intervention. Based on the broad impact of Earth’s seasonality, it is reasonable to assume that global change can affect host immunity and susceptibility; enhance or reduce pathogen survival and proliferation depending on region; modify pathogen load in animal reservoirs; and alter transmission season and human-pathogen interactions. A proactive, multidisciplinary approach to disease control and prevention aiming to better understand these complex interactions, with a greater emphasis on all aspects of health—human, environmental, animal—as exemplified by the notion of One Health, could mitigate some of the expected impacts of global change.

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CONFLICT OF INTEREST STATEMENT

The author(s) have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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REFERENCES

Aguirre-Gamboa R, Joosten I, Urbano PC, van der Molen RG, van Rijssen E, van Cranenbroek B, Oosting M, Smeekens S, Jaeger M, and Zorro M (2016) Differential effects of environmental and genetic factors on T and B cell immune traits. Cell Rep 17:2474-2487.

Altizer S, Dobson A, Hosseini P, Hudson P, Pascual M, and Rohani P (2006) Seasonality and the dynamics of infectious diseases. Ecol Lett 9:467-484.

Altizer S, Ostfeld RS, Johnson PT, Kutz S, and Harvell CD (2013) Climate change and infectious diseases: from evidence to a predictive framework. Science 341:514-519.

Anderson JJ and Nieman DC (2016) Diet quality—the Greeks had it right! Nutrients 8:636.

Becker DJ, Streicker DG, and Altizer S (2015) Linking anthropogenic resources to wildlife-pathogen dynamics: a review and meta-analysis. Ecol Lett 18:483-495.

Bedrosian TA, Fonken LK, Walton JC, and Nelson RJ (2011) Chronic exposure to dim light at night suppresses immune responses in Siberian hamsters. Biol Lett 7:468-471.

Begon M, Telfer S, Smith MJ, Burton S, Paterson S, and Lambin X (2009) Seasonal host dynamics drive the timing of recurrent epidemics in a wildlife population. Proc Biol Sci 276:1603-1610.

Bilbo SD, Dhabhar FS, Viswanathan K, Saul A, Yellon SM, and Nelson RJ (2002) Short day lengths augment stress-induced leukocyte trafficking and stress-induced enhancement of skin immune function. Proc Natl Acad Sci U S A 99:4067-4072.

Bloom-Feshbach K, Alonso WJ, Charu V, Tamerius J, Simonsen L, Miller MA, and Viboud C (2013) Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PLoS ONE 8:e5444.

Bordon Y (2017) Vitamin D primes neonatal immune system. Nat Rev Immunol 17:467-467.

Borrmann H, McKeating JA, and Zhuang X (2021) The circadian clock and viral infections. J Biol Rhythms 36:9-22.

Brassard K, Alonso WJ, Charu V, Tamerius J, Simonsen L, Miller MA, and Viboud C (2013) Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PLoS ONE 8:e5444.

Brock MA (1983) Seasonal rhythmicity in lymphocyte blastic responses of mice persists in a constant environment. J Immunology 130:1051-1052.

Brouwer A, van Raalte DH, Diamant M, Rutters F, and Bremmer MA (2015) Light therapy for better mood and insulin sensitivity in patients with major depression and type 2 diabetes: a randomised, double-blind, parallel-arm trial. BMC Psychiatry 15:169.

Buck MD, O’Sullivan D, and Pearce EL (2015) T cell metabolism drives immunity. J Exp Med 212:1345-1360.

Bunger ME and Teixeira AL (2019) Inflammation in psychiatric disorders: what comes first? Ann N Y Acad Sci 1437:57-67.

Brainard GC, Knobler RL, Podolin PL, Lavasa M, and Lublin FD (1987) Neuroimmunology: modulation of the hamster immune system by photoperiod. Life Sci 40:1319-1326.

Braun C, Heneghan C, Mahtani K, and Aronson J (2020) Do weather conditions influence the transmission of the coronavirus (SARS-CoV-2). Oxford (UK): The Centre for Evidence-Based Medicine.

Brock MA (1983) Age-related changes in circannual rhythms of lymphocyte blastic responses in mice. Am J Physiol 252:R299-R305.

Brooks R, van Raalte DH, Diamant M, Rutters F, van Someren EJW, Snoek FJ, Beekman AT, and Bremmer MA (2015) Light therapy for better mood and insulin sensitivity in patients with major depression and type 2 diabetes: a randomised, double-blind, parallel-arm trial. BMC Psychiatry 15:169.

Roure A, van Raalte DH, Diamant M, Rutters F, and van Someren EJW, Snoek FJ, Beekman AT, and Bremmer MA (2015) Light therapy for better mood and insulin sensitivity in patients with major depression and type 2 diabetes: a randomised, double-blind, parallel-arm trial. BMC Psychiatry 15:169.

Roure A, van Raalte DH, Diamant M, Rutters F, and van Someren EJW, Snoek FJ, Beekman AT, and Bremmer MA (2015) Light therapy for better mood and insulin sensitivity in patients with major depression and type 2 diabetes: a randomised, double-blind, parallel-arm trial. BMC Psychiatry 15:169.

Roure A, van Raalte DH, Diamant M, Rutters F, and van Someren EJW, Snoek FJ, Beekman AT, and Bremmer MA (2015) Light therapy for better mood and insulin sensitivity in patients with major depression and type 2 diabetes: a randomised, double-blind, parallel-arm trial. BMC Psychiatry 15:169.

Roure A, van Raalte DH, Diamant M, Rutters F, and van Someren EJW, Snoek FJ, Beekman AT, and Bremmer MA (2015) Light therapy for better mood and insulin sensitivity in patients with major depression and type 2 diabetes: a randomised, double-blind, parallel-arm trial. BMC Psychiatry 15:169.
Dorélien AM, Ballesteros S, and Grenfell BT (2013) Impact of birth seasonality on dynamics of acute immunizing infections in Sub-Saharan Africa. PLoS ONE 8:e75806.

Duke-Sylvester SM, Bolzoni L, and Real LA (2011) Strong seasonality produces spatial asynchrony in the outbreak of infectious diseases. J R Soc Interface 8:817-825.

Dunning CM, Black E, and Allan RP (2018) Later wet seasons with more intense rainfall over Africa under future climate change. J Clim 31:9719-9738.

Eames KT, Tilston NL, and Edmunds WJ (2011) The impact of school holidays on the social mixing patterns of school children. Epidemics 3:103-108.

Edgar RS, Stangherlin A, Nagy AD, Nicoll MP, Efstathiou S, O’Neill JS, and Reddy AB (2016) Cell autonomous regulation of herpes and influenza virus infection by the circadian clock. Proc Natl Acad Sci U S A 113:10085-10090.

Farah-Pérez A, Umaña-Villalobos G, Picado-Barboza J, and Anderson EP (2020) An analysis of river fragmentation by dams and river dewatering in Costa Rica. River Res Appl 36:1442-1448.

Fisman DN (2007) Seasonality of infectious diseases. Ann Rev Pub Health 28:127-143.

Fisman DN (2012) Seasonality of viral infections: mechanisms and unknowns. Clin Microbiol Infect 18:946-954.

Foster RG and Kreitzman L (2009) Seasons of life. New Haven (CT): Yale University Press.

Foxman EF, Storer JA, Fitzgerald ME, Wasik BR, Hou L, Zhao H, Turner PE, Pyle AM, and Iwasaki A (2015) Temperature-dependent innate defense against the common cold virus limits viral replication at warm temperature in mouse airway cells. Proc Natl Acad Sci U S A 112:827-832.

Gibb R, Redding DW, Chin KQ, Donnelly CA, Blackburn TM, Newbold T, and Jones KE (2020) Zoonotic host diversity increases in human-dominated ecosystems. Nature 584:398-402.

Goveoetran R, Gnanguenon V, Ogouwalé E, Oké-Agbo F, Azondekon R, Sovi A, Attolou R, Badirou K, Youssouf R, Osse R, et al. (2014) Dry season refugia for anopheline larvae and mapping of the seasonal distribution in mosquito larval habitats in Kandi, northeastern Benin. Parasit Vectors 7:137.

Grassly NC and Fraser C (2006) Seasonal infectious disease epidemiology. Proc Biol Sci 273:2541-2550.

Grifoni E, Valoriani A, Cei F, Lamanna R, Gelli AMG, Ciambotti B, Vannucchi V, Moroni F, Pelagatti L, and Tarquini R (2020) Interleukin-6 as prognosticator in patients with COVID-19: IL-6 and COVID-19. J Infect 81:452-482.

Guo F, Bonebrake TC, and Gibson L (2019) Land-use change alters host and vector communities and may elevate disease risk. Ecohealth 16:647-658.

Gwinner E (1986) Circannual rhythms. Heidelberg (Berlin): Springer, p. 154.
malaria and the climate in Karachi: an eight year review. Pak J Med Sci 36:533-537.

Imai M, Iwatsuki-Horimoto K, Hatta M, Loebel H, Halfmann P, Nakajima R, Watarabe T, Uije M, Takahashi K, and Ito M (2020) Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. Proc Natl Acad Sci U S A 117:16587-16595.

Insull W Jr (2009) The pathology of atherosclerosis: plaque development and plaque responses to medical treatment. Am J Med 122:S3-S14.

Iwamura T, Guzman-Holst A, and Murray KA (2020) Accelerating invasion potential of disease vector Aedes aegypti under climate change. Nat Commun 11:2130.

Jayaweer M, Perera H, Gunawardana B, and Manatunge J (2020) Transmission of COVID-19 virus by droplets and aerosols: a critical review on the unresolved dichotomy. Environ Res 188:109819-109819.

Johnson CK, Hitchens PL, Pandit PS, Rushmore J, Evans TS, Young CC, and Doyle MM (2020) Global shifts in mammalian population trends reveal key predictors of virus spillover risk. Proc Biol Sci 287:20192736.

Johnson PT, De Roode JC, and Fenton A (2015) Why infectious disease research needs community ecology. Science 349:1259504.

Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, and Daszak P (2008) Global trends in emerging infectious diseases. Nature 451:990-993.

Jouanna J (2012) The legacy of the Hippocratic treatise the nature of man: the theory of the four humours. In: Scarbrough J, van der Eijk PJ, Hanson AE, Ziegler J, editors. Greek medicine from Hippocrates to Galen. Leiden (the Netherlands): Brill, p. 335-359.

Kernbach ME, Cassone VM, Unnasch TR, and Martin LB (2020a) Broad-spectrum light pollution suppresses melatonin and increases West Nile virus-induced mortality in House Sparrows (Passer domesticus). Condor 122:1-13.

Kernbach ME, Martin LB, Unnasch TR, Hall RJ, Jiang RH, and Francis CD (2020b) Light pollution affects West Nile virus exposure risk across Florida. bioRxiv. doi:10.1101/2020.05.08.082974.

Kernbach ME, Newhouse DJ, Miller JM, Hall RJ, Gibbons J, Oberstaller J, Seelenkitt D, Jiang RH, Unnasch TR, and Balakrishnan CN (2019) Light pollution increases West Nile virus competence of a ubiquitous passerine reservoir species. Proc Biol Sci 286:20191051.

Kernbach ME, Unnasch TR, and Martin LB (2020c) Differential effects of spectral composition of nighttime lighting on west nile virus resistance and mortality in house sparrows. Integr Comp Biol 60:E122-E122.

Kissler SM, Tedijanto C, Goldstein E, Grad YH, and Lipsitch M (2020) Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science 368:860-868.

Klingberg E, Olerod G, Konar J, Petzold M, and Hammarsten O (2015) Seasonal variations in serum 25-hydroxy vitamin D levels in a Swedish cohort. Endocrine 49:800-808.

Klopmas M, Baker MA, and Rhee C (2020) Airborne transmission of SARS-CoV-2: theoretical considerations and available evidence. JAMA 324:441-442.

Knop E, Zoller L, Ryser R, Gerpe C, Hörmann J, and Fontaine C (2017) Artificial light at night as a new threat to pollination. Nature 548:206-209.

Kwiatkowski DP (2005) How malaria has affected the human genome and what human genetics can teach us about malaria. Am J Hum Genet 77:171-192.

Kyba CCM, Kuester T, Sánchez de Miguel A, Baugh K, Jechow A, Hölker F, Bennie J, Elvidge CD, Gaston KJ, and Guanter L (2017) Artificial light at night as a new threat to pollination. Science 360:550-562.

Lal A, Hales S, French N, and Baker MG (2012) Seasonality in human zoonotic enteric diseases: a systematic review. PLoS ONE 7:e31883.

Lalor MK, Ben-Smith A, Gorak-Stolinska P, Weir RE, Floyd S, Blitz R, Mvula H, Newport MJ, Branson K, and McGrath N (2009) Population differences in immune responses to Bacille Calmette-Guerin vaccination in infancy. J Infect Dis 199:795-800.

Lanham-New SA, Webb AR, Cashman KD, Buttriss JL, Fallowfield JL, Masud T, Hewison M, Mathers JC, Kiely M, Welch AA, et al. (2020) Vitamin D and SARS-CoV-2 virus/COVID-19 disease. BMJ Nutr Prev Health 3:106-110.

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KS, Lau EH, and Wong JY (2020a) Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 382:1199-1207.
Li Y, Wang X, and Nair H (2020b) Global seasonality of human seasonal coronaviruses: a clue for post-pandemic circulating season of severe acute respiratory syndrome coronavirus 2? J Infect Dis 222:1090-1097.

Lim AS, Klein H-U, Yu L, Chibnik LB, Ali S, Xu J, Bennett DA, and De Jager PL (2017) Diurnal and seasonal molecular rhythms in human neocortex and their relation to Alzheimer’s disease. Nat Commun 8:14931.

Lincoln G (2019) A brief history of circannual time. J Neuroendoctrinol 31:e12694.

Liu D, Fernandez BO, Hamilton A, Lang NN, Gallagher JM, Newby DE, Feelisch M, and Weller RB (2014) UVA irradiation of human skin vasodilates arterial vasculature and lowers blood pressure independently of nitric oxide synthase. J Invest Dermatol 134:1839-1846.

Lockett GA, Soto-Ramírez N, Ray MA, Everson TM, Xu CJ, Patil VK, Terry W, Kaushal A, Rezwan FI, and Ewart SL (2016) Association of season of birth with DNA methylation and allergic disease. Allergy 71:1314-1324.

Lowen AC and Steel J (2014) Roles of humidity and temperature in shaping influenza seasonality. J Virol 88:7692-7695.

Lowen AC, Mubareka S, Steel J, and Palese P (2007) Influenza virus transmission is dependent on relative humidity and temperature. PLoS Pathog 3:1470-1476.

Luca F, Perry GH, and Di Rienzo A (2010) Evolutionary adaptations to dietary changes. Annu Rev Nutr 30:291-314.

Luca GD, Kerckhove KV, Coletti P, Poletto C, Bossuyt N, Hens N, and Colizza V (2018) The impact of regular school closure on seasonal influenza epidemics: a data-driven spatial transmission model for Belgium. BMC Infect Dis 18:29.

Lutz C, Maher L, Lee C, and Kang W (2020) COVID-19 preclinical models: human angiotensin-converting enzyme 2 transgenic mice. Hum Genomics 14:20.

Mackenzie J, Gubler D, and Petersen LR (2004) Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses. Nat Med 10:98-109.

Marcogliese D (2008) The impact of climate change on the parasites and infectious diseases of aquatic animals. Rev Sci Tech 27:467-484.

Martinez ME (2016) Preventing Zika virus infection during pregnancy using a seasonal window of opportunity for conception. PLoS Biol 14:e1002520.

Martinez ME (2018) The calendar of epidemics: seasonal cycles of infectious diseases. PLoS Pathog 14:e1007327.

Martinez-Bakker M and Helm B (2015) The influence of biological rhythms on host-parasite interactions. Trends Ecol Evol 30:314-326.

Mathis D (2013) Immunological goings-on in visceral adipose tissue. Cell Metab 17:851-859.

McCabe GJ, Betancourt JL, and Feng S (2015) Variability in the start, end, and length of frost-free periods across the conterminous United States during the past century. Int J Climatol 35:4673-4680.

Meyer C, Muto V, Jaspar M, Küssé C, Lambot E, Chellappa SL, Degueldre C, Balteau E, Luxen A, and Middleton B (2016) Seasonality in human cognitive brain responses. Proc Natl Acad Sci U S A 113:3066-3071.

Millet S, Bennett J, Lee KA, Hau M, and Klasing KC (2007) Quantifying and comparing constitutive immunity across avian species. Dev Comp Immunol 31:188-201.

Mills EL, Ryan DG, Prag HA, Dikovskaya D, Menon D, Zaslona Z, Jedrychowski MP, Costa AS, Higgins M, and Hams E (2018) Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1. Nature 556:113-117.

Moan JE, Lagunova Z, Bruoland Ø, and Juzeniene A (2010) Seasonal variations of cancer incidence and prognosis. Dermatoendoctrinol 2:55-57.

Moltchanova E, Schreier N, Lammi N, and Karvonen M (2009) Seasonal variation of diagnosis of Type 1 diabetes mellitus in children worldwide. Diabet Med 26:673-678.

Monto AS, DeJonge P, Callare AP, Bazzi LA, Capriola S, Malosh RE, Martin ET, and Petrie JG (2020) Coronavirus occurrence and transmission over 8 years in the HIVE cohort of households in Michigan. J Infect Dis 222:9-16.

Moore SE, Collinson AC, Fulford AJ, Jalil F, Siegrist CA, Goldblatt D, Hanson LÅ, and Prentice AM (2006) Effect of month of vaccine administration on antibody responses in The Gambia and Pakistan. Trop Med Int Health 11:1529-1541.

Moratelli R and Calisher CH (2015) Bats and zoonotic viruses: can we confidently link bats with emerging deadly viruses? Mem Inst Oswaldo Cruz 110:1-22.

Moriyama M, Hugentobler WJ, and Iwasaki A (2020) Seasonality of respiratory viral infections. Annu Rev Virol 7:83-101.

Naumova EN (2006) Mystery of seasonality: getting the rhythm of nature. J Pub Health Policy 27:2-12.

Nelson RJ, Demas GE, Klein SL, and Kriegsfeld LJ (1995) Minireview the influence of season, photoperiod, and pineal melatonin on immune function. J Pineal Res 19:149-165.

Nelson RJ, Demas GE, Klien SL, and Kriegsfeld LJ (2002) Seasonal patterns of stress, immune function and disease. Cambridge (UK): Cambridge University Press.

Nguyen HT, Dharan NJ, Le MTQ, Nguyen NB, Nguyen CT, Hoang DV, Tran HN, Bui CT, Dang DT, Pham DN, et al. (2009) National influenza surveillance in Vietnam, 2006-2007. Vaccine 28:398-402.

Nguyen JL, Schwartz J, and Dockery DW (2014) The relationship between indoor and outdoor temperature, apparent temperature, relative humidity, and absolute humidity. Indoor Air 24:103-112.

Nguyen JL, Yang W, Ito K, Matte TD, Shaman J, and Kinney PL (2016) Seasonal influenza infections and cardiovascular disease mortality. JAMA Cardiol 1:274-281.
Nguyen KD, Fentress SJ, Qiu Y, Yun K, Cox JS, and Chawla A (2013) Circadian gene Bmal1 regulates diurnal oscillations of Ly6C(hi) inflammatory monocytes. Science 341:1483-1488.

Nickbakhsh S, Ho A, Marques DF, McMenamin J, Gunson RN, and Murcia PR (2020) Epidemiology of seasonal coronaviruses: establishing the context for the emergence of coronavirus disease 2019. J Infect Dis 222:17-25.

Nickbakhsh S, Mair C, Matthews L, Reeve R, Johnson PCD, Thorburn F, von Wissmann B, Reynolds A, McMenamin J, Gunson RN, et al. (2019) Virus-virus interactions impact the population dynamics of influenza and the common cold. Proc Natl Acad Sci U S A 116:27142-27150.

Norman AW (1998) Sunlight, season, skin pigmentation, vitamin D, and 25-hydroxyvitamin D: integral components of the vitamin D endocrine system. Oxford (UK): Oxford University Press.

Olival KJ, Hosseini PR, Zambrana-Torrelio C, Ross N, Bogich TL, and Daszak P (2017) Host and viral traits predict zoonotic spillover from mammals. Nature 546:646-650.

Onishi KG, Maneval AC, Cable EC, Tuohy MC, Scasny AJ, Sterina E, Love JA, Riggle JP, Malamut LK, Mukerji A, et al. (2020) Circadian and circannual timescales interact to generate seasonal changes in immune function. Brain Behav Immun 83:33-43.

Paludan SR, Pradeu T, Masters SL, and Mogensen TH (2020) Constitutive immune mechanisms: mediators of host defence and immune regulation. Nat Rev Immunol. Epub ahead of print August. doi:10.1038/s41577-020-0391-5.

Pedersen B (2007) IL-6 signalling in exercise and disease. London (UK): Portland Press.

Peruzzotti-Jametti L, Bernstock JD, Vicario N, Costa AS, Kwok CK, Leonardi T, Booty LM, Bicci I, Balzarotti B, and Volpe G (2018) Macrophage-derived extracellular succinate licenses neural stem cells to suppress chronic neuroinflammation. Cell Stem Cell 22:355-368. e313.

Planelles D, Hernández-Godoy J, Montoro A, Montoro J, and González-Molina A (1994) Seasonal variation in proliferative response and subpopulations of lymphocytes from mice housed in a constant environment. Cell Prolif 27:333-341.

Plowright RK, Parrish CR, McCallum H, Hudson PJ, Ko AI, Graham AL, and Lloyd-Smith JO (2017) Pathways to zoonotic spillover. Nature Rev Microbiol 15:502-510.

Prendergast BJ, Baille SR, and Dhabhar FS (2008) Gonadal hormone-dependent and -independent regulation of immune function by photoperiod in Siberian hamsters. Am J Physiol Regul Integr Comp Physiol 294:R384-R392.

Price RHM, Graham C, and Ramalingam S (2019) Association between viral seasonality and meteorological factors. Sci Rep 9:929.
models poorly mimic human inflammatory diseases.

Proc Natl Acad Sci U S A 110:3507-3512.

Shaman J and Kohn M (2009) Absolute humidity modulates influenza survival, transmission, and seasonality.

Proc Natl Acad Sci U S A 106:3243-3248.

Shampo MA and Kyle RA (1987) Hyperthermia (Kneippism). Mayo Clin Proc 62:929.

Shi J, Wen Z, Zhong G, Yang H, Wang C, Huang B, Liu R, He X, Shuai L, and Sun Z (2020) Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. Science 368:1016-1020.

Shivatcheva TM and Hadjioloff AI (1987) Seasonal involution of gut-associated lymphoid tissue of the European ground squirrel. Dev Comp Immunol 11:791-799.

Sia SF, Yan L-M, Chin AW, Fung K, Choy K-T, Wong AY, Kaewpreeedee P, Perera RA, Poon LL, and Nicholls JM (2020) Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. Nature 583:834-838.

Singh RK, Chang H-W, Yan D, Lee KM, Ucmak D, Wong K, Abrouk M, Farahnik B, Nakamura M, and Zhu TH (2017) Influence of diet on the gut microbiome and implications for human health. J Transl Med 15:73.

Singh V, Pattanaik AK, Goswami T, and Sharma K (2013) Effect of varying the energy density of protein-adequate diets on nutrient metabolism, clinical chemistry, immune response and growth of Muzaffarnagar lambs. Asian-Australas J Anim Sci 26:1089-1101.

Smith E (2019) The effect of potential climate change on infectious disease presentation. J Nurse Pract 15:405-409.

Stefan N, Birkenfeld AL, Schulze MB, and Ludwig DS (2020) Obesity and impaired metabolic health in patients with COVID-19. Nat Rev Endocrinol 16:341-342.

Stevenson TJ and Prendergast BJ (2015) Photoperiodic time measurement and seasonal immunological plasticity. Front Neuroendocrinol 37:76-88.

Stevenson TJ, Onishi KG, Bradley SP, and Prendergast BJ (2014) Cell-autonomous iodothyronine deiodinase expression mediates seasonal plasticity in immune function. Brain Behav Immun 36:61-70.

Stevenson TJ, Visser ME, Arnold W, Barrett P, Biello S, Dawson A, Denlinger DL, Dominoni D, Elton S, et al. (2015) Disrupted seasonal biology impacts health, food security and ecosystems. Proc Biol Sci 282:20151453.

Stone EL, Harris S, and Jones G (2015) Impacts of artificial lighting on bats: a review of challenges and solutions. Mamm Biol 80:213-219.

Stuart P, Paredis L, Hendtonen H, Lawton C, Torres CAO, and Holland CV (2020) The hidden faces of a biological invasion: parasite dynamics of invaders and natives. Int J Parasitol Parasites Wildl 50:111-123.

Tay MZ, Poh CM, Rénia L, MacAry PA, and Ng LF (2020) The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 20:363-374.

Taylor K, Das S, Pearson M, Kozubek J, Pawlowski M, Jensen CE, Skowron Z, Møller GL, Strivens M, and Gardner S (2020) Analysis of genetic host response risk factors in severe COVID-19 patients. medRxiv. https://www.medrxiv.org/content/10.1101/2020.06.17.2034015v2.

Ter Horst R, Jaeger M, Sneekens SP, Oosting M, Swertz MA, Li Y, Kumar V, Diavatopoulos DA, Jansen AF, and Lemmers H (2016) Host and environmental factors influencing individual human cytokine responses. Cell 167:1111-1124. e1113.

Thackeray SJ, Sparks TH, Frederiksen M, Burthe S, Bacon PJ, Bell JR, Botham MS, Breton TM, Bright PW, and Carvalho L (2010) Trophic level asynchrony in rates of phenological change for marine, freshwater and terrestrial environments. Glob Change Biol 16:3304-3313.

Thysen AH, Rasmussen MA, Kreiner-Møller E, Larsen JM, Følsgaard NV, Bønneleykke K, Stokholm J, Bisgaard H, and Brix S (2016) Season of birth shapes neonatal immune function. J Allergy Clin Immunol 137:1238-1246. e1213.

Tostanoski LH, Wegmann F, Martinot AJ, Loos C, McMahan K, Mercado NB, Yu J, Chan CN, Bondoc S, and Starke CE (2020) Ad26 vaccine protects against SARS-CoV-2 severe clinical disease in hamsters. Nat Med 26:1694-1700.

Ucar D, Márquez EJ, Chung C-H, Marches R, Rossi RJ, Uyar A, Wu T-C, George J, Stitzel ML, and Palucka AK (2017) The chromatin accessibility signature of human immune aging stems from CD8+ T cells. J Exp Med 214:3123-3144.

Versteegh MA, Helm B, Kleynhans EJ, Gwinner K, and Tielemans BI (2014) Genetic and phenotypically flexible components of seasonal variation in immune function. J Exp Biol 217:1510-1518.

Visscher T and Seidell J (2004) Time trends (1993-1997) and seasonal variation in body mass index and waist circumference in the Netherlands. Int J Obes 28:1309-1316.

Visser ME and Gienapp P (2019) Evolutionary and demographic consequences of phenological mismatches. Nat Ecol Evol 3:879-885.

Visser ME, Caro SP, van Oers K, Schaper SV, and Helm B (2010) Phenology, seasonal timing and circannual rhythms: towards a unified framework. Philos Trans R Soc Lond B Biol Sci 365:3113-3127.

Wasserberg G, Abramsky Z, Kotler B, Ostfeld R, Yarom I, and Warburg A (2003a) Anthropogenic disturbances enhance occurrence of cutaneous Leishmaniasis in Israel deserts: patterns and mechanisms. Ecol Appl 13:868-881.

Wasserberg G, Yarom I, and Warburg A (2003b) Seasonal abundance patterns of the sandfly Phlebotomus papatasi in climatically distinct foci of cutaneous leishmaniasis in Israeli deserts. Med Vet Entomol 17:452-456.

Wehr TA (2001) Photoperiodism in humans and other primates: evidence and implications. J Biol Rhythms 16:348-364.
Weil ZM, Borniger JC, Cisse YM, Salloum BAA, and Nelson RJ (2015) Neuroendocrine control of photoperiodic changes in immune function. Front Neuroendocrinol 37:108-118.

Weisel FJ, Mullett SJ, Elsner RA, Menk AV, Trivedi N, Luo W, Wikenheiser D, Hawse WF, Chikina M, and Smita S (2020) Germinal center B cells selectively oxidize fatty acids for energy while conducting minimal glycolysis. Nature Immunol 21:331-342.

West AC and Wood SH (2018) Seasonal physiology: making the future a thing of the past. Curr Opin Physiol 5:1-8.

West AP, Khoury-Hanold W, Staron M, Tal MC, Pineda CM, Lang SM, Bestwick M, Duguay BA, Raimundo N, and MacDuff DA (2015) Mitochondrial DNA stress primes the antiviral innate immune response. Nature 520:553-557.

White RJ and Razgour O (2020) Emerging zoonotic diseases originating in mammals: a systematic review of effects of anthropogenic land-use change. Mam Rev 50:336-352. https://doi.org/10.1111/mam.12201

World Health Organization (1995) Factors affecting the immunogenicity of oral poliovirus vaccine: a prospective evaluation in Brazil and The Gambia. J Infect Dis 171:1097-1106.

Wyse C, O'Malley G, Coogan A, and Smith D (2020) Seasonal and daytime variation in multiple immune parameters in humans: evidence from 329,261 participants of the UK Biobank cohort. medRxiv. https://www.medrxiv.org/content/10.1101/2020.10.23.20218305v1.full

Yoshimura h (1958) Seasonal changes in human body fluids. Jpn J Physiol 8:165-179.

Young BE, Ong SWX, Kalimuthdin S, Low JG, Tan SY, Loh J, Ng O-T, Marimuthu K, Ang LW, and Mak TM (2020) Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 323:1488-1494.

Zandkarimi F, Vanegas J, Fern X, Maier C, and Bobe G (2018) Metabotypes with elevated protein and lipid catabolism and inflammation precede clinical mastitis in prepartal transition dairy cows. J Dairy Sci 101:5531-5548.

Zhou S, Cagampang FR, Stirland JA, Loudon AS, and Hopkins SJ (2002) Different photoperiods affect proliferation of lymphocytes but not expression of cellular, humoral, or innate immunity in hamsters. J Biol Rhythms 17:392-405.

Zimmet P, Alberti K, Stern N, Bilu C, El-Osta A, Einat H, and Kronfeld-Schor N (2019) The circadian syndrome: is the metabolic syndrome and much more! J Intern Med 286:181-191.