REVIEW

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

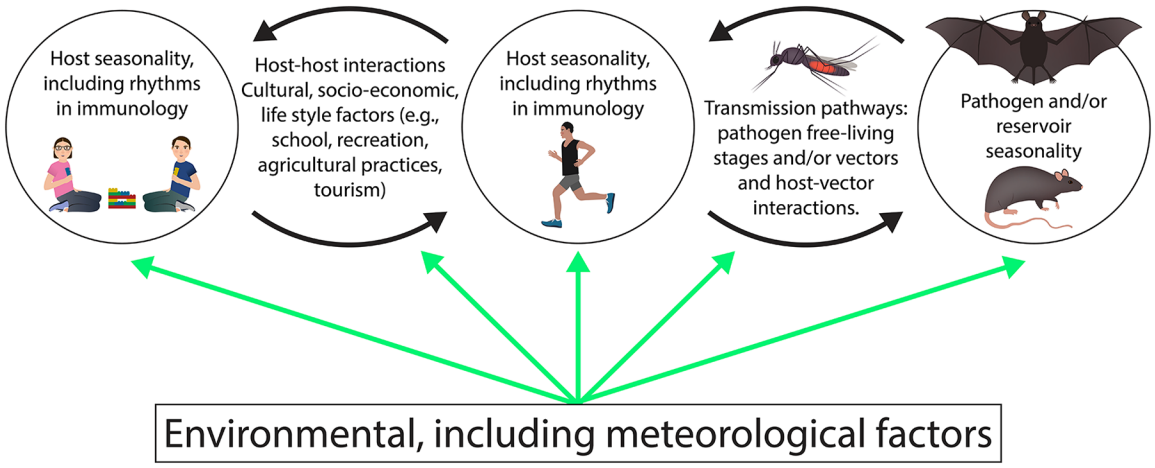

Figure 1. Candidate drivers of disease seasonality. Circles show organisms implicated in disease transmission, black arrows indicate their interactions, and green arrows indicate the influence of environmental factors. Color version is available online.

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 nonhuman) and vectors, frequency of pathogen-host interactions (cultural, socioeconomic, linked to life style), 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

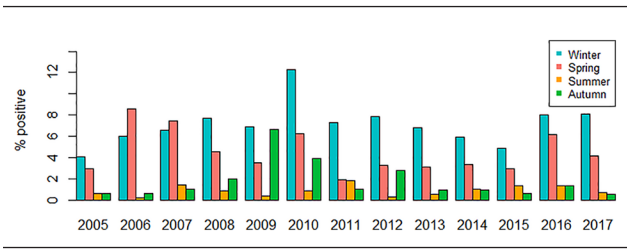

Figure 2. Seasonality of endemic human coronaviruses (CoV-OC43, CoV-NL63, and CoV-229E species) detected in a large urban patient population. The percentage (%) of human coronaviruses detected during routine real-time multiplex RT-PCR diagnostic testing of 84,957 episodes of respiratory illness in NHSGGC (primary and secondary care services), Scotland, UK, by calendar month categories from 2005 to 2017. Winter = December-February; Spring = March-May; Summer = June-August; Autumn = September-November. Note: Years 2009 and 2010 must be viewed with caution as only influenza-negative patients at risk of severe illness were tested for human coronaviruses in NHSGGC during the three waves of the influenza A/H1N1 pandemic in the United Kingdom; see also Nickbakhsh et al. (2020). Abbreviations: CoV = coronaviruses; NHSGGC = NHS Greater Glasgow and Clyde; RT-PCR = reverse transcription polymerase chain reaction.

cold/temperate areas. Temperature impinges upon metabolism across taxa, and while temperature swings in theory could weaken or strengthen the immune system (Shampo and Kyle, 1987), several negative consequences are apparent. Temperature drops of 5 °C in the nose can weaken antiviral defenses and have been linked to a higher likelihood of catching a cold virus (Foxman et al., 2015). Temperature swings also tend to be associated with spending more time indoors, which can facilitate viral transmission at a higher rate than during time spent outdoors (Jayaweera et al., 2020), especially if using public transport or during social events.

Other aspects of weather and the environment may also affect behavior and immune responses. For instance, vitamin D levels are influenced by exposure to sunlight. They tend to be higher during the summer (Klingberg et al., 2015) and could bolster the immune system when fighting viral infections. The impact of weather on infection is understudied in tropical and subtropical regions compared to temperate regions. Some locations experience regular outbreaks coinciding with rainy seasons, often with multiple peaks (Bloom-Feshbach et al., 2013), while other locations under similar climatic conditions experience low year-round variability in disease incidence (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* mosquitos are required for the malaria parasite to conclude 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 annual as well as on diel time-scales (Borrmann 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 blastogenic 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).

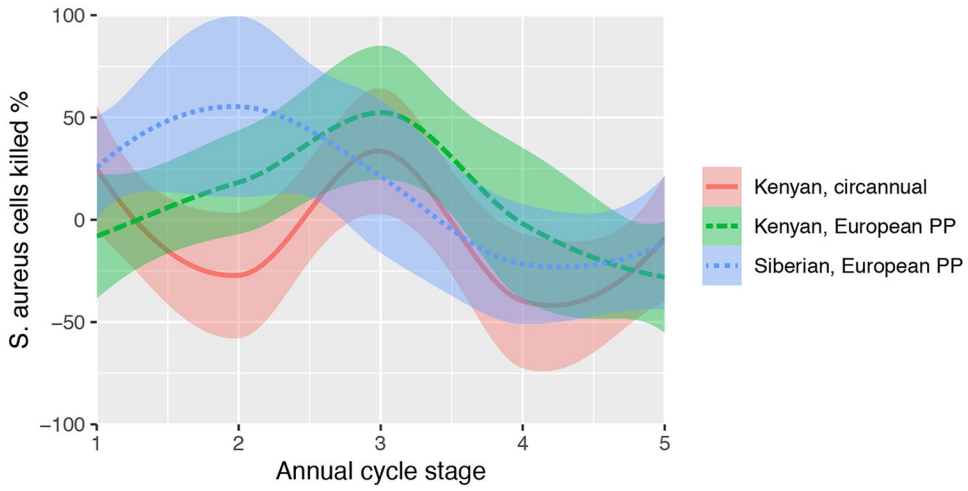

Figure 3. Annual and circannual cycle in an immune parameter. The capacity of whole blood to kill cultures of *Staphylococcus aureus* is shown for 3 experimental groups of songbirds, stonechats (genus *Saxicola*). Siberian (blue) and Kenyan (green) stonechats were kept in a common garden setup of annually changing European photoperiod (PP) over 1 year, where they showed distinct, population-specific annual cycles (Versteegh et al., 2014). Groups were measured per life cycle stage because the populations differed in duration of phases such as migration or molt (annual cycle stages 1-5: spring migration; breeding season; molt; autumn migration; winter). An additional Kenyan (red) group (Versteegh, Tieleman & Helm, unpubl.) that was kept under constant photoperiod showed similar, circannual cycles; curves indicate loess smoothing. Color version is available online.

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

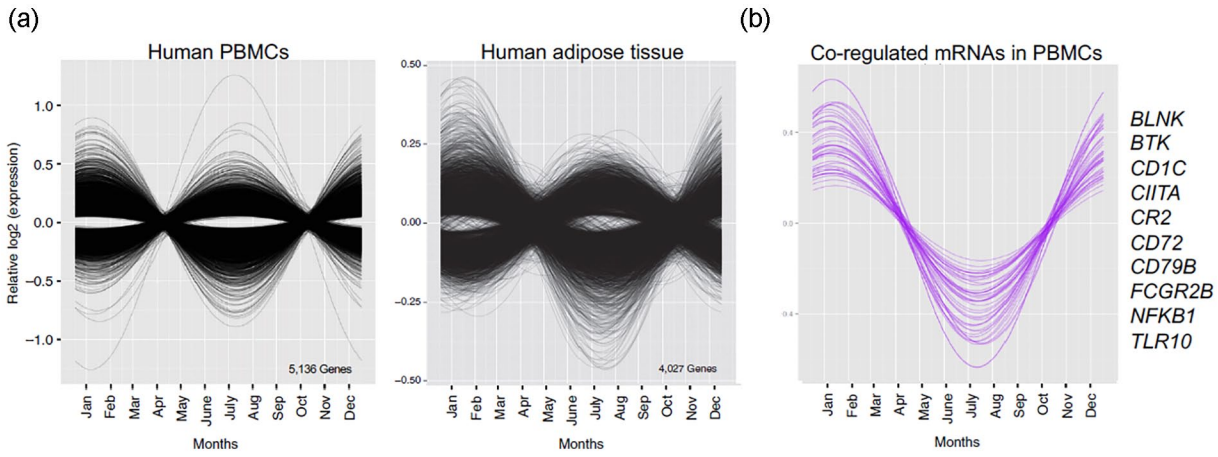

Figure 4. Seasonal gene expression changes in humans. (a) Peripheral white blood cells (PBMCs, from children) and subcutaneous adipose tissue (adults). (b) A group of 68 coregulated messenger RNAs (mRNAs) with winter tropism in the human immune system, enriched for genes associated with B-lymphocyte activation (KEGG). A cosinor model was used to analyze seasonality in mRNA expression (Dopico et al., 2015). Abbreviation: PBMC = peripheral blood mononuclear cell.

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). Coronaviruses 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,

1991), and vitamin D metabolism (Norman, 1998). Amazingly, UV skin exposure cues skin nitric oxide synthase (NOS)–independent nitrate metabolism, reducing blood pressure (Liu et al., 2014), which is itself associated with inflammation (Chae et al., 2001). How the mammalian immune system aligns itself with whole-organism metabolic needs and processes, and at different times, is largely unknown at the molecular level.

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 seasonal-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 (Brassey 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 R_0 by 0.0383 and 0.0224, respectively (where the base reproduction number R_0 of SARS-CoV-2 is estimated to fall between 1.5 and 3.5 (Brassey 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., 1600:0800 h light:dark schedule to 0800:1600 h 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),

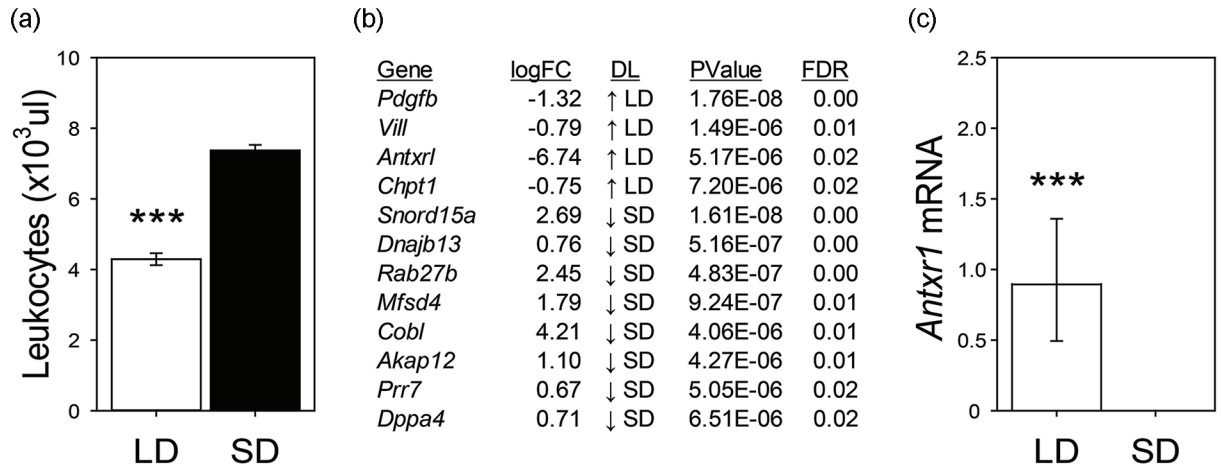

Figure 5. Photoperiodic regulation of Siberian hamster blood leukocytes. Siberian hamsters housed in summer-like long-day (LD) photoperiods have lower levels of circulating leukocytes compared to winter-like short-day (SD) housed animals. (a) Unpublished RNA sequencing of blood leukocytes revealed several transcripts that are differentially expressed between LD and SD conditions. (b) Adult male hamsters were kept in LD (15L:9D) or SD (9D:15L) for 12 weeks. At the termination of the study, leukocytes were obtained from a retroorbital sample and cells were separated as described previously (Stevenson et al., 2014). Illumina sequencing and statistical analyses were conducted using the same procedures described in Bao et al. (2019). In LD, hamster leukocytes express the anthrax receptor 1 transcript, whereas there is a complete absence of its expression in SD. (c) Asterisks denote $p < 0.001$. Abbreviations: Pdgfb = Platelet-Derived Growth Factor Subunit B; Vill = Villin-like; Antxr1 = Anthrax receptor 1; Chpt1 = Choline Phosphotransferase 1; Snord15a = Small Nucleolar RNA, C/D Box 15A; Hsp40 = DnaJ Heat Shock Protein Family; Dnajb13 = Member B13; Rab27b = RAB27B Member RAS Oncogene Family; Mfsd4 = Major facilitator superfamily domain–containing protein 4; Cobl = Cordon-Bleu WH2 Repeat Protein; Akap12 = A-Kinase Anchoring Protein 12; Prr7 = Proline Rich 7 Synaptic; Dppa4 = Developmental Pluripotency Associated 4; DL = daylength; FDR = false discovery rate. ***$p < 0.005$.

Figure 6. Drivers of emerging infectious disease events during 1940-2003. Data from Jones et al. (2008).

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

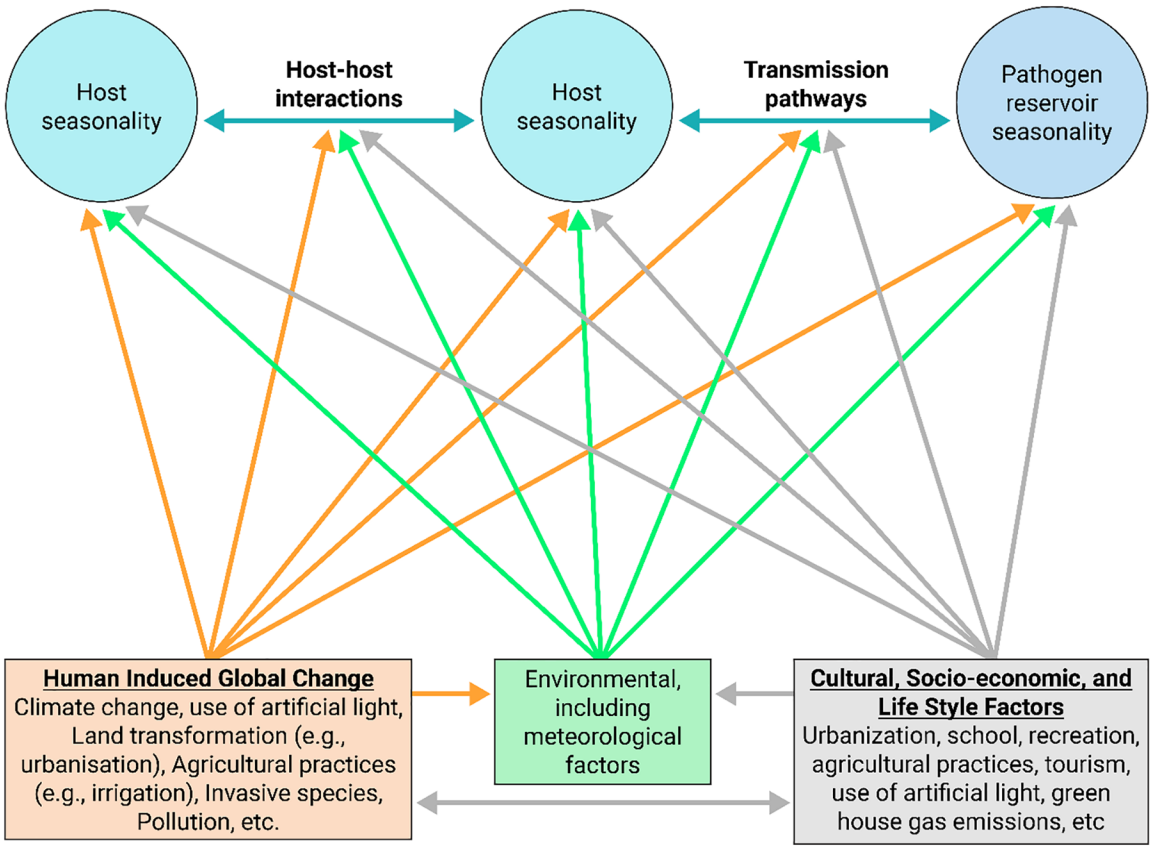

Figure 7. Effects of anthropogenic global changes on drivers of infectious disease seasonality. Global change of the environment (orange box and arrows), and cultural and socioeconomic changes (gray), can affect the seasonality of infectious diseases directly, but also indirectly through their effects on environmental conditions (green). Color version is available online.

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 a continental scale explaining latitudinal differences in the dynamics and seasonality of local epidemics, suggesting that temperature-driven increases to humidity may lead to a northward shift in the dynamic patterns observed (Baker et al., 2019).

In addition to effects of climate change, environmental cycles are also modified by changes in land use, including freshwater use, agricultural practice, and human settlement, which can affect the likelihood of transmission (e.g., Johnson et al., 2020; White and Razgour, 2020). For example, irrigation and other provision of year-round access to open water (Mackenzie et al., 2004; Govoetchan et al., 2014) may affect distributions, abundances, and phenology of species, including those that are disease vectors (Wasserberg et al., 2003a, 2003b). In areas where irrigation gives year-round access to open water, Japanese encephalitis is markedly increased (Mackenzie et al., 2004), and water containers have been shown to serve as dry-season refugia for Dengue vectors (Govoetchan et al., 2014). On the contrary, more than 50% of global wetlands have been lost in the past century (e.g., Davidson, 2014), groundwater overexploitation causes the disappearance of freshwater springs (e.g.,

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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