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Geographic variation in seasonality and its influence on the dynamics of an infectious disease

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Seasonal changes in environmental drivers – such as temperature, rainfall, and resource availability – have the potential to shape infection dynamics through their reverberating effects on biological processes including host abundance and susceptibility to infection. However, seasonality varies geographically. We therefore expect marked differences in infection dynamics between regions with different seasonal patterns. By pairing extensive Avian Influenza Virus (AIV) surveillance data – 65 358 individual bird samples from 12 species of dabbling ducks sampled at 174 locations across North America – with quantification of seasonality using remote sensed data indicative for primary productivity (normalised differenced vegetation index, NDVI), we provide evidence that seasonal dynamics influence infection dynamics across a continent. More pronounced epidemics were seen to occur in regions experiencing a higher degree of seasonality, and epidemics of lower amplitude and longer duration occurred in regions with a more protracted and lower seasonal amplitude. These results demonstrate the potential importance of geographic variation in seasonality for explaining geographic variation in the dynamics of infectious diseases in wildlife.

Synthesis

Infectious diseases regularly exhibit marked seasonal dynamics, yet these dynamics often vary between geographic regions. Several biological mechanisms are thought to alter infection dynamics and, crucially, these biological mechanisms are intimately linked to seasonal variation in temperature, rainfall and resource availability. As a result, the underlying seasonal dynamics of the environment may enable us to both understand and predict geographic variation in infection dynamics. To test this hypothesis we explicitly quantify seasonal dynamics across regions with varying seasonality and demonstrate that the dynamics of avian influenza virus in its wild bird reservoir conform to our predictions on a macroecolgical scale. Our results demonstrate the potential importance of geographic variation in seasonality for explaining variation in the dynamics of infectious diseases.

Conspicuous seasonal dynamics, characterised by predictable annual peaks and troughs in disease incidence, have been demonstrated for a wide range of infectious diseases in humans. Childhood infections such as measles (Fine and Clarkson 1982), waterborne infections such as cholera (Pascual et al. 2002), aerosol-borne infections such as influenza (Dushoff et al. 2004), and vector-borne infections such as malaria (Hoshen and Morse 2004) have all been shown to exhibit marked seasonal oscillations. Although fewer examples exist for wildlife systems, similar dynamics have been demonstrated suggesting that seasonality in infectious disease may be a general pattern (Altizer et al. 2006). Mechanisms that underpin the seasonal dynamics of infectious diseases are also increasingly well established. Seasonal changes in day length and solar intensity typically induce seasonality in extrinsic environmental drivers such as temperature, rainfall and resource availability. Those, in turn, have the potential to induce seasonal variation in so called intrinsic drivers that fundamentally shape infection dynamics such as susceptibility to infection, host density and contact rate (Hosseini et al. 2004, Koelle and Pascual 2004), as well as pathogen survival and viability (Stallknecht et al. 1990, Herrick et al. 2013).

Seasonal changes in the density of susceptible individuals are one of the most widely accepted biological drivers, and almost universally observed in wildlife. The vast majority of animal populations show marked seasonal variation in the timing of birth, resulting in a pulsed influx of immunologically naïve (i.e. susceptible) individuals into the population (Hosseini et al. 2004, Begon et al. 2009a). Such seasonal birth pulses have been shown to both precede annual peaks in infection prevalence in wildlife (van Dijk et al. 2014), and to be fundamental to producing these dynamics in empirically validated models (Hosseini et al. 2004, He 2005, Begon et al. 2009b). Seasonal changes in the susceptibility of the standing population may also occur, as a result of resource-based tradeoffs. Although immune responses to pathogen invasion have the potential to reduce susceptibility,

these responses depend on resources that may be important to sustain other individual requirements, such as growth, reproduction, and survival (Ilmonen et al. 2000, Prendergast et al. 2004). As a result, immune function, and hence susceptibility, is thought to be subjected to tradeoffs with other resource-intensive activities (Martin et al. 2008). For instance, the energetic demands of reproduction are known to result in lower antibody production and cell-mediated immunity in several bird species (Hillgarth and Wingfield 1997, Moreno et al. 2001).

Critically, the extent of seasonality varies markedly across the globe. Seasonal variation in day length is greatest towards the poles, becoming negligible near the equator. As a result, seasonal changes in temperature and resource availability also show geographical variation, with resource availability having sharper peaks of shorter duration towards the poles, becoming progressively more uniform towards the equator. Crucially, these broad latitudinal patterns are further modified by topography, proximity to oceans, and rainfall, together defining the 'degree of seasonality' of a given location. Thus, explicit consideration of seasonality, rather than assuming latitude as a proxy, is essential to investigating the seasonal dynamics of infectious diseases.

The degree of seasonality for any given location can be broadly described by two features: seasonal amplitude, describing the severity of the seasonal variation; and seasonal duration, describing the length of the period in which a certain biological process may take place. Many biological processes, including those fundamental to infection dynamics, therefore reflect the seasonal dynamics of the underlying landscape (Fig. 1). Given the importance of seasonal variation in host density, susceptibility and contact rate to infection dynamics (Hosseini et al. 2004, Altizer et al. 2006, Begon et al. 2009b), the seasonal dynamics of infectious diseases are likely to show marked differences between regions, according to their degree of seasonality (Fig. 1). For instance, it has long been recognized that the length of the breeding season of many northern hemisphere organisms contracts with greater proximity to the Arctic (MacArthur 1964), resulting in a short duration, high intensity birth pulse (Fig. 1). Similarly, although seasonal birth pulses in humans have been shown in almost all populations worldwide, they tend to be more pronounced in regions with extreme seasonal variation in day length and primary productivity (Becker 1991). Critically, recent theoretical studies have shown that species or locations experiencing seasonal birth pulses of higher amplitude experience greater variation in prevalence and higher peak prevalence throughout the year (Dorelien et al. 2013, Martinez-Bakker et al. 2014, Peel et al. 2014). Seasonal modulation of immune function, and hence susceptibility, may also be more distinct in regions experiencing more pronounced seasonality (Adelman et al. 2010). In terms of resource allocation, animals experiencing greater seasonality (short duration, high amplitude seasons) are thought to benefit from their well-defined temporal segregation of different life history stages, such as breeding and moult, to avoid resource tradeoffs between resource-demanding stages (Wingfield 2008). Consequently, any potential tradeoff between immune function and other resource-intensive activities, such as reproduction, is likely to differ among populations according to the degree of seasonality they experience (Fig. 1).

Social behaviour and host aggregation can also be forced by extrinsic seasonal factors, and may thus play an additional role in the seasonality of infectious disease dynamics. Host species might congregate around critical resources, be it nesting sites in colonial breeders, water during the dry season, or sites providing particularly high food availability. Such aggregations could lead to higher contact rates and increased incidence of infection (e.g. rabies in skunks during the winter months: Gremillion-Smith and Woolf 1988; avian influenza during migratory stopover: Krauss et al. 2010). However, host aggregations occur in some species and not others, and the timing of these aggregations within the annual cycle is highly species and location dependent. For instance, migratory waterfowl aggregate in high densities in autumn at sites near their breeding grounds, in winter on their non-breeding grounds, and for finite periods during autumn and/or spring at intervening stop-over sites en route. In contrast, the intrinsic biological drivers discussed above, including seasonal birth pulses and allocation to pathogen defense, have the potential to underpin macro-ecological patterns in the dynamics of infectious diseases (Fig. 1).

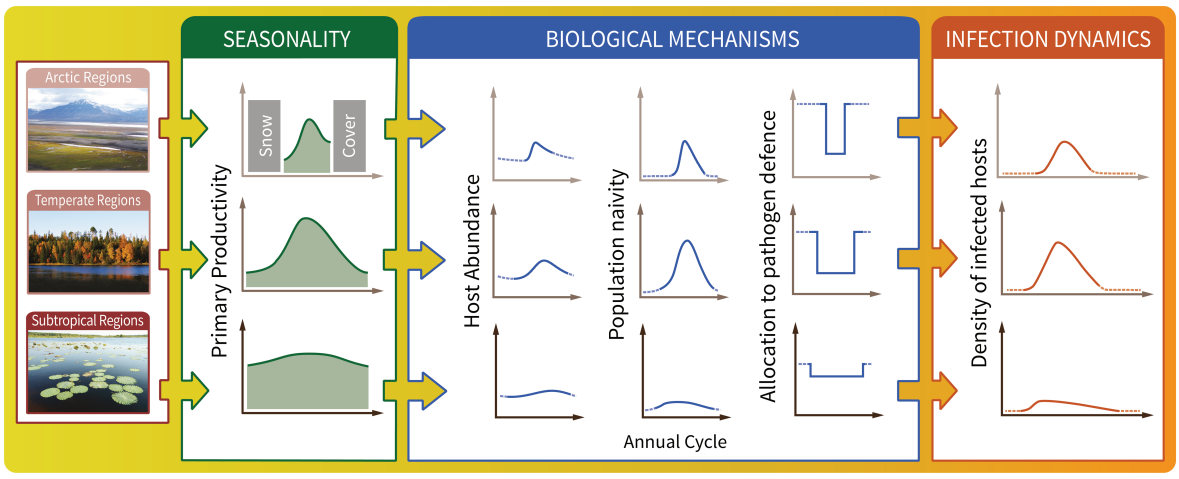

Figure 1. Variation in underlying seasonality (exemplified by three generalized macro-ecological regions) can be expected to influence the seasonal dynamics of an infectious disease through changes to the amplitude and duration of intrinsic biological drivers, such as the density and susceptibility of the host population (Photos: BJH).

Here, we evaluate the influence of the degree of seasonality on infectious disease dynamics using a globally distributed, intensively investigated, multi-host–pathogen system – avian influenza virus (AIV) in wild birds. Several studies from north-temperate regions have shown that AIV infections in the reservoir community, which notably consists of dabbling ducks (Olsen et al. 2006), show annual epidemics with a distinct seasonal signature (Hinshaw et al. 1985, Krauss et al. 2004, van Dijk et al. 2014). The pulsed entry of naïve juveniles and seasonal changes in host abundance have been proposed as important drivers of these infection dynamics (Hinshaw et al. 1985, Olsen et al. 2006, Munster et al. 2007), which were recently examined on a single site within the north-temperate zone (van Dijk et al. 2014). Given that these intrinsic drivers are expected to vary with the amplitude and duration of seasonality (Fig. 1), we hypothesize that the timing, duration, and amplitude of annual epidemics will also vary with the seasonal amplitude and duration. Specifically, we anticipate more pronounced epidemics in regions experiencing a higher degree of seasonality, and epidemics of lower amplitude and longer duration in regions with more protracted, lower-amplitude dynamics (Fig. 1). To test this hypothesis, we utilize continent-wide AIV surveillance in dabbling ducks from North America together with remotely-sensed data indicative for primary productivity as a proxy for seasonal progression of the environment.

Material and methods

Classification of seasonality

Remotely-sensed normalized difference vegetation index (NDVI) was used to characterize seasonal variation in primary productivity across the North American continent. Raw weekly NDVI data (16 × 16 km grid cells) from NOAA STAR AVHRR Vegetation Health dataset (<www.star.nesdis.noaa.gov/smcd/emb/vci/VH/vh_ftp.php>) for 2005–2013 were downloaded, and grid-cells overlapping the coastline removed to avoid artefacts of ocean reflectance. Seasonal amplitude ($s_{amp\ [NDVI]}$) and duration ($s_{dur\ [weeks]}$) were calculated for each grid cell based on annual maximum (max_{NDIV}) and minimum (min_{NDVI}) NDVI values (further details in Supplementary material Appendix 1).

Infection data

Individual-level AIV infection data for dabbling ducks sampled across North America was obtained from the NIAID influenza research database (Squires et al. 2012) on 2 February 2016. Due to the low number of samples prior to 2005 and the potential for incomplete reports after 2013 (Supplementary material Appendix 2), we used only samples collected from 2005 to 2013. All records lacking spatial information, or from birds that were not live and free-living at the time of sampling, were removed, resulting in 65 358 records from individual birds representing 12 species sampled across 174 sites (sites within a radius of 50 km were treated as one site). Records were dominated by samples from mallard duck (43%), followed by blue-winged teal (14%) and the northern pintail (13%) all other species were represented with less than 10%. For detailed information in species composition see Supplementary material Appendix 3.

Seasonal dynamics for each site were defined by calculating the mean s_{amp} and s_{dur} across all constituent NDVI cells within a 350-km radius of the centre of the site to reflect the predominant seasonal parameters of the area. In order to assess the influence of seasonality on infection dynamics on a regional scale we clustered the sampling locations on the basis of their respective seasonal parameters (s_{dur} and s_{amp}) using a partitioning method (*pam* in R package *cluster* [14]; Fig. 2a). Three clusters (k = 3) led to the highest homogeneity in sample size between regional clusters (Supplementary material Appendix 3) and to the best spatial spread of sampling efforts within the period of peak AIV incidence (week 24 (15 July) to 47 (20 November)).

Regional infection dynamics

To quantify annual infection dynamics within each cluster and using a restricted maximum likelihood (REML) approach, we fitted a generalized additive model (GAM with cubic spline and binomial response) using the R Package *mgcv* (Maechler et al. 2014) to weekly infection data and calculated the area under this infection curve as a quantitative measure for the total number of cases of infection over time (Galsworthy et al. 2011). Given the small number of clusters (n = 3) that prevented any quantitative tests of the association between the environmental seasonality and the infection dynamics, we compared patterns of means in the AUC and the seasonal dynamic of the environment (s_{amp}, s_{dur}) between clusters.

Annotated R code for NDVI data manipulation, clustering of sampling locations and AIV infection analysis is available at: <https://github.com/slisovski>.

Results

Seasonality

Of the three regional clusters based on similarities in underlying seasonality (s_{amp}, s_{dur}), cluster 1 had a high degree of seasonal variation ($s_{amp} = 0.33$; Fig. 2b–c) and the shortest productive season ($s_{dur} = 21.9$), encompassing locations in Alaska, the Canadian prairies and Baffin Island. Cluster 2 contained sampling locations along the upper Mississippi basin, the Great Lakes region, and the central and northern East coast, and was characterized by typical 'temperate' dynamics – a high degree of seasonal variation (the highest s_{amp}; 0.44; Fig. 2b–c) over a relatively long productive season ($s_{dur} = 30.5$). Cluster 3 was characterized by the lowest average s_{amp} (0.21; Fig. 2b–c) and longest s_{dur} (34.1), and included locations in the lower Mississippi basin, along the Gulf coast and throughout California.

Regional infection dynamics

The empirical infection data, revealed seasonal dynamics in infection incidence within all three clusters, with a rapid increase in incidence followed by a gradual decline towards the annual nadir. All clusters reached their peak prevalence (21–36%) in the post-breeding period (July–September; Fig. 2d). The onset of these dynamics was earliest in cluster 3 (lower Mississippi basin, Gulf coast, California) and latest in cluster 1 (Alaska, Canadian prairies, Baffin Island;

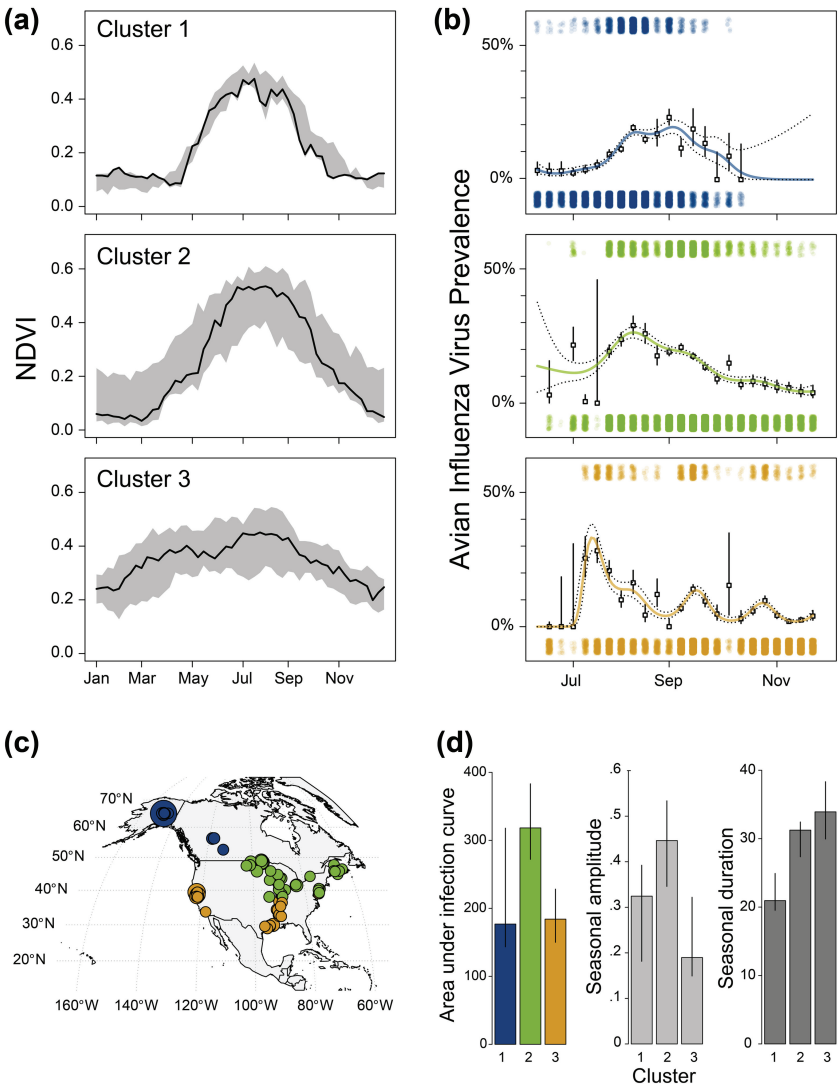

Figure 2. (a) Underlying environmental seasonality quantified using remote sense data (NDVI) indicative for primary productivity; median primary productivity (black line) with upper and lower 2.5 percentile (grey polygon) across each cluster based on NDVI from 2005 to 2013. (b) AIV infection dynamics from mid-June to mid-November within each cluster (unfilled squares represent raw estimates of Avian Influenza Virus prevalence across weekly pools, ± 95% CI; coloured bars represent individual samples jittered around AIV negative (bottom) and AIV positive (top)). Solid lines represent the model prediction (GAM) with ± 95% CI (dashed lines). (c) Locations of sampling for avian influenza virus (AIV) across North America (2005–2013) reported via Influenza Research Database (<www.ird.org>). Circle diameter indicates the relative number of samples (individual ducks); colours denote clusters. (d) Area under the infection curve (± 95% CI of model prediction) and seasonal amplitude and duration (error bars indicate 95% of data range) for each cluster.

Fig. 2d). Area under the curve (AUC) corresponded with regional seasonality in the productive season: low AUC in cluster 1 (high amplitude, short duration seasonality) and 3 (low amplitude, long duration), and high AUC in cluster 2 (high amplitude, long duration productive season; Fig. 2b). The GAM models fit resulted in highly significant smoothing terms ($p > 0.001$) for all three clusters and similar R^2-values (cluster 1: 0.02, cluster 2: 0.02, cluster 3: 0.04).

Discussion

Seasonality is recognized as a key driver in the dynamics of a wide range of infectious diseases (Fine and Clarkson 1982, Altizer et al. 2006). Although geographic variation in seasonality, for instance between the tropics and the Arctic, is also widely recognized, remarkably few studies specifically assess the effect of geographic variation in extrinsic seasonality on the dynamics of infectious diseases across large spatial scales. For example, studies that have used subsets of the analysed here have all found a correlation between the annual peak prevalence and latitude, with peak prevalence seen to increasing from south to north (Farnsworth et al. 2012, Bevins et al. 2014, Nallar et al. 2015); although these studies were limited to the lower 48 states, and therefore excluded data from higher latitudes, including Canada and Alaska. These studies have proposed that non-seasonal mechanisms, including annual minimum temperatures (see also Viboud et al. 2006 Herrick et al. 2013), as well as potentially higher numbers of migratory waterfowl in higher latitudes may drive this latitudinal trend in peak-prevalence. And yet most studies, including our analysis, have demonstrated that peak prevalence in AIV across North American occurs during periods prior to fall migration (Fig. 2d), which corresponds

to the warmer ambient temperatures. Moreover, prevalence was seen to increase far earlier in the more southern regions (with lower amplitude and longer duration in the environmental seasonality), yet any effect of migration or low ambient temperatures would be expected to manifest in these regions after, rather than before, it has been seen in more seasonal (higher latitude) regions. Therefore, we suggest that a more robust understanding of infectious disease dynamics may be achieved by considering that the same drivers may manifest vastly different infection dynamics depending on the underlying seasonality of a region (Fig. 1).

One of the major advances of this study is arguably the use of remotely sensed data as a proxy for primary productivity in order to directly quantify the underlying seasonality of each of the 174 sampling locations. By then drawing on an extensive surveillance database and including data from across a continent (where Canada and Alaska show different seasonal dynamics the lower United States), we demonstrate a macro-ecological coupling between the degree of seasonality and the dynamics of infection. Conceptually, this link operates in three dimensions: firstly, the onset of the annual infection epidemic correlates with the onset of the productive season; secondly, the amplitude of the annual infection epidemic correlates with the amplitude of the inter-seasonal variation in primary productivity; and thirdly, the duration of the infection epidemic correlates with the length of the productive season. We found initial evidence for all three of these dimensions (Fig. 2). While all clusters showed a similar level of peak prevalence, this was achieved far earlier, and decreased rapidly, in the cluster with the lowest seasonal amplitude. The link between infection dynamics and underlying seasonality can be illustrated by integrating the duration and amplitude and assessing the area under the infection curve. This showed that the total number of infected birds was highest in cluster 2, which had the highest degree of seasonality, whereas clusters 1 and 3 showed similar, smaller, AUC corresponding to the shorter duration and lower amplitude, respectively, of the infection curves and underlying seasonal dynamics (Fig. 2b). These patterns may also have implications for the potential risk of AIV spill-over from the wild bird reservoir into domestic poultry. Based on our findings, risk of spill-over is likely to be considerably higher during late summer and early autumn, in regions with high amplitude and medium-to-long-duration seasonal dynamics.

Although we cannot assess the importance of specific intrinsic mechanisms, we assume that the pulsed entrance of naïve individuals (Peel et al. 2014) and potential seasonal variation in immune responses (Buehler et al. 2008) are in phase with extrinsic seasonal dynamics and collectively account for seasonal variation in infection dynamics across broad spatial scales. Migration-induced seasonal variation in host aggregation has the potential to further modify the infection dynamics on a local and potential regional scale. For instance, the aggregation of ruddy turnstones *Arenaria interpres* feeding on horseshoe crab eggs in Delaware Bay during spring migration has been shown to dramatically increase local prevalence during this period. Such intense aggregations, together with a high degree of spatial and temporal migratory connectivity within a species may result in high levels of pathogen transmission (Krauss et al. 2010, Bauer et al. 2016). It is noteworthy, however, that peak prevalence in Ruddy turnstones in Delaware Bay occurs during spring, a period when otherwise relatively low prevalence prevails at the macro-ecological scale (Fig. 2). This example illustrates the highly site-specific nature of aggregation behaviour, with any corresponding modification of the large-scale seasonal dynamics of infection likely to be similarly restricted in space and time.

Future work constructing a dynamic model with these major drivers may help to explain their relative importance in the infection dynamics within different seasonal habitats. However, such models would require detailed information on e.g. temporal demographic patterns like birth and migration that is not yet available for large scale such as continent wide comparisons.

Moreover, seasonal changes to host aggregation behaviour and contact rates are often species-specific: some aggregate to breed while others disperse; migratory animals often aggregate prior to and during migration; and yet other species aggregate around food resources during the colder months of the year (Newton-Fisher et al. 2000). Indeed, large-scale differences in intrinsic factors, such as the timing and duration of birth pulses, have been shown to be critical to the seasonal dynamics of infection, even in systems heavily influenced by seasonal changes in host contact rates (Hosseini et al. 2004). For example, although seasonal changes in host aggregation behaviour influence the dynamics of *Mycoplasma gallisepticum* infections in house finches *Carpodacus mexicanus* (Altizer et al. 2004), the seasonal dynamics of this infection, and latitudinal differences in these dynamics, could only be simulated with the inclusion of intrinsic factors (Hosseini et al. 2004). As a result, although seasonal variation in contact rates may modify the dynamics of infection on a local scale, they are unlikely to underpin variation in infection dynamics across broader spatial scales.

In conclusion, avian influenza virus is arguably one of the best studied wildlife diseases and elaborate surveillance of its occurrence in North American wild birds has produced a unique, continental-scale database. By combining the findings of this surveillance with remotely-sensed data reflecting primary productivity across the continent, we demonstrate that the dynamics of infection differ on the basis of regional variation in seasonality, in line with predictions founded on the seasonality of known intrinsic drivers of infection. These findings therefore provide an important development in the understanding and prediction of infectious disease dynamics. Our results clearly illustrate that although infection dynamics may show marked differences across broad spatial scales, these dynamics can be underpinned by the same mechanisms when these mechanisms are themselves influenced by variation in seasonality. While it is tempting to suggest that this could be the case for infectious diseases more generally, it is likely that the relative importance of different intrinsic and extrinsic drivers will differ between host–pathogen systems. For instance, human populations may be partially buffered against inter-seasonal variations in the biotic environment, and social factors such as school terms may dilute the effect of seasonal birth pulses for some diseases. However, given that AIV is a generalist pathogen, transmitted in a density-dependent manner through a vast multi-host community, our study suggests that the application of a seasonal approach, including understanding of spatial variation in seasonality and how this may modify both extrinsic and intrinsic drivers of infection, is likely to yield profound insights into other infectious disease systems.

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Supplementary material (available online as Appendix oik-03796 at <www.oikosjournal.org/appendix/oik-03796>). Appendix 1–3.