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Urban habituation, ecological connectivity and epidemic dampening: the emergence of Hendra virus from flying foxes (*Pteropus* spp.)

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Anthropogenic environmental change is often implicated in the emergence of new zoonoses from wildlife; however, there is little mechanistic understanding of these causal links. Here, we examine the transmission dynamics of an emerging zoonotic paramyxovirus, Hendra virus (HeV), in its endemic host, Australian *Pteropus* bats (fruit bats or flying foxes). HeV is a biosecurity level 4 (BSL-4) pathogen, with a high case-fatality rate in humans and horses. With models parametrized from field and laboratory data, we explore a set of probable contributory mechanisms that explain the spatial and temporal pattern of HeV emergence; including urban habituation and decreased migration—two widely observed changes in flying fox ecology that result from anthropogenic transformation of bat habitat in Australia. Urban habituation increases the number of flying foxes in contact with human and domestic animal populations, and our models suggest that, in addition, decreased bat migratory behaviour could lead to a decline in population immunity, giving rise to more intense outbreaks after local viral reintroduction. Ten of the 14 known HeV outbreaks occurred near urbanized or sedentary flying fox populations, supporting these predictions. We also demonstrate that by incorporating waning maternal immunity into our models, the peak modelled prevalence coincides with the peak annual spill-over hazard for HeV. These results provide the first detailed mechanistic framework for understanding the sporadic temporal pattern of HeV emergence, and of the urban/peri-urban distribution of HeV outbreaks in horses and people.

Keywords: Hendra virus; *Pteropus*; flying fox; bat virus; connectivity; metapopulation disease model

1. INTRODUCTION

Emerging zoonoses from wildlife represent a significant and increasing threat to global public health [1]. There is evidence that anthropogenic changes are responsible for most zoonotic emerging infectious diseases [1–4]. However, very few studies have been able to identify mechanistic linkages between environmental drivers and disease emergence [5,6]. Bats are hosts of some of the most significant recently emerging zoonoses [7–9] and, since 1994, four novel human pathogens have emerged from bats of the genus *Pteropus* (fruit bats, known as flying foxes) alone [10,11]. Two of these, the paramyxoviruses Hendra and Nipah virus, have caused sporadic outbreaks in domestic animals and people, with extremely high case-fatality rates, and evidence of human-to-human transmission for Nipah virus [12–14]. The unprecedented emergence of four novel human pathogens from a single host genus in such a short period of time suggests that recent changes in host ecology may play a role in emergence [6]. However, despite their pandemic potential, and the lack of effective therapies or vaccines, little is known about what factors may have caused these bat-borne viruses to emerge.

Hendra virus (HeV) is lethal in humans and horses. Fourteen known outbreaks of HeV have occurred in Australia (see the electronic supplementary material, table S1), apparently with an increasing frequency (figure 1*a*), and a higher risk of spill-over from May to October (figure 1*b*). All 14 outbreaks involved transmission of virus from flying foxes to a primary case horse, and five events involved subsequent transmission to humans resulting in an illness or death (see the electronic

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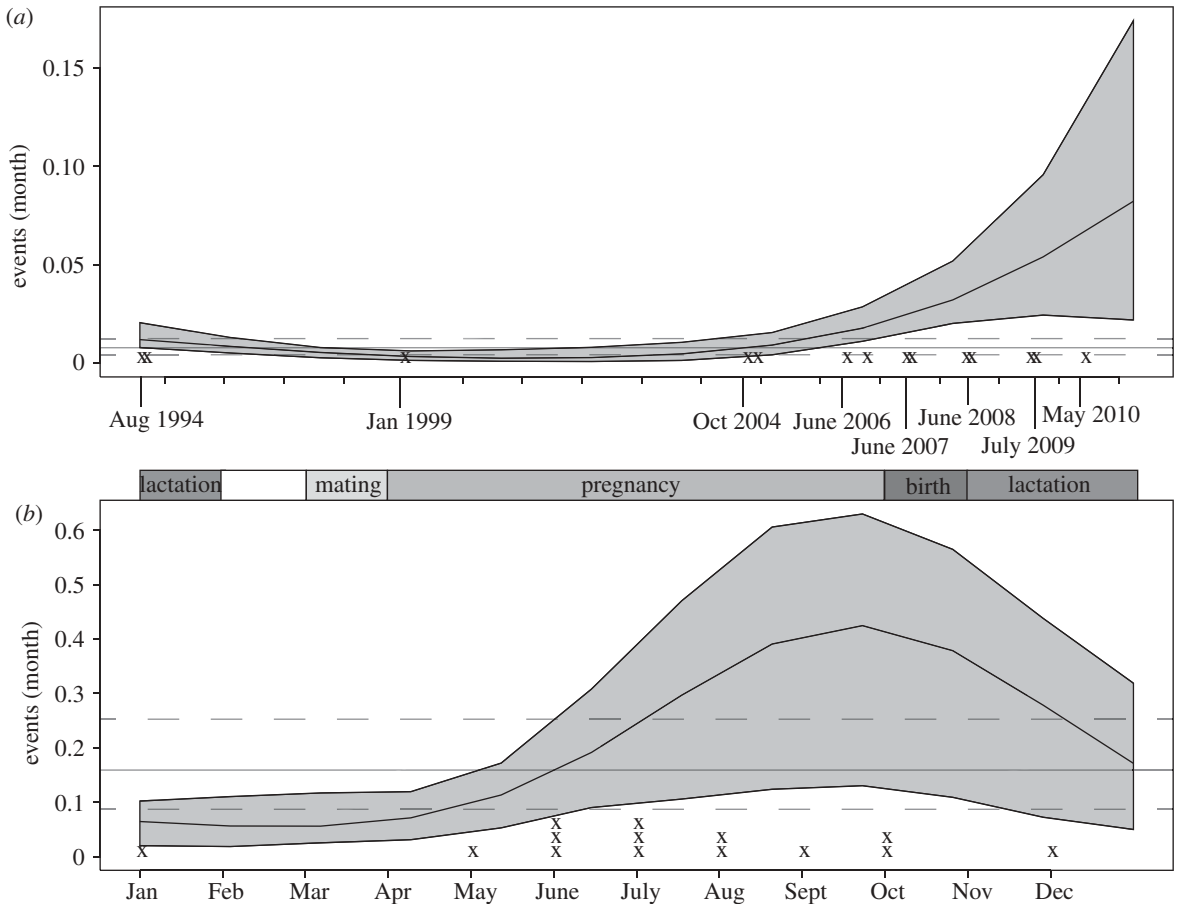

Figure 1. Epidemic hazard rates for HeV spill-over events. (*a*) Bayesian posterior epidemic hazard rate for Hendra virus (HeV) spill-over from 1994 to 2010. The grey region is bounded by the 2.5th and 97.5th posterior percentiles for the hazard rate. The grey horizontal line is the flat prior used, bound by the middle 95% of the prior distribution (see the electronic supplementary material, methods). Crosses represent spill-over events. (*b*) Bayesian monthly posterior epidemic hazard rate for HeV. Crosses indicate spill-over events within the labelled month. The approximate peak timing of life-history events for *P. alecto* and *P. poliocephalus* in South Queensland [15–18] is indicated at the top of the plot.

supplementary material, table S1). Experimentally infected flying foxes exhibit a short infectious period with no apparent clinical disease, and viral excretion in urine, saliva, faeces and placental fluids [19,20]. Transmission from flying foxes to horses is presumed to be via ingestion of pasture, feed or water contaminated with these products [13,21].

Flying foxes depend on nectar and fruit food sources that are irregular, ephemeral and patchily distributed in native forests, so only frequent migration over large areas of intact habitat can ensure a continuous food supply [15,17,22–24]. As natural food resources decline with the loss of up to 75 per cent of the once contiguous forest cover on the east coast of Australia [25], flying foxes have sought an alternative food source in urban gardens. Urban flowering resources are abundant, reliable and available year-round, decreasing the requirement for energy-expensive, long-distance foraging and migration. In response, an increasing proportion of flying fox populations are becoming urbanized, and an increasing proportion of these urban flying foxes are ceasing to migrate (figure 2 and the electronic supplementary material, figure S1) [16,23,30,31,33–36]. Today, all of Australia's major east coast cities, and many major towns, contain continuously occupied flying fox camps (daytime roosts), which were not historically present (figure 2; the electronic supplementary material, figures S1 and S2). In addition to this distributional shift, ongoing urban and rural residential development in critical flying fox habitat [22,37] may increase the overlap between human, horse and flying fox populations. These recent changes probably have important consequences for the metapopulation dynamics of HeV, and disease transmission between flying foxes and people.

HeV has probably circulated in flying fox populations for long periods of evolutionary time [9] but cases have only recently been described in horses and humans. Cases of HeV in humans and horses also appear to be seasonal and cyclical. It is important to determine what factors account for the spatio-temporal trends and HeV's modern-day persistence, emergence and spill-over. Our study used data and modelling approaches to evaluate a set of probable contributory mechanisms underlying HeV emergence in urban and peri-urban locations in eastern Australia. Likely mechanisms consistent with the data that include: (i) An increase in urban flying fox populations allows for increased contact with humans and horses; (ii) a decrease in migratory behaviour of urban flying foxes reduces viral transmission, leading to a decline in herd immunity, and a consequent increase in the intensity of HeV outbreaks when infection is re-introduced; and (iii) synchrony of stressors on individual bats and some demographic factors, including seasonal

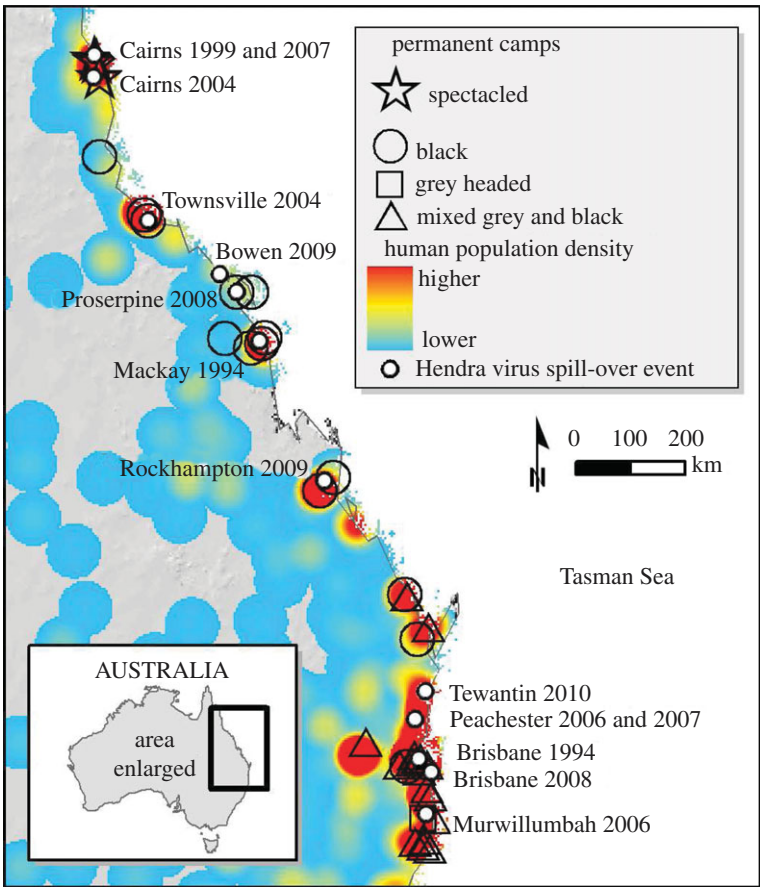

Figure 2. Continuously occupied flying fox camps and HeV spill-over locations in relation to human population density. 'Spectacled', 'black' and 'grey headed' refer to flying fox species ([26–32]; P. Eby 2004, unpublished data; L. Shilton & D. Westcott 2009, personal communication).

aggregation, pregnancy, birth and waning maternal immunity in pups, could drive annual temporal clustering of HeV outbreaks. We use computational models, parametrized by field and laboratory data, to investigate the factors driving temporal oscillations in HeV outbreaks and the predicted impact of urban habituation and decreased flying fox migration on HeV dynamics and emergence.

2. METHODS

The population structure of flying foxes—notably the distinct camps in which bats aggregate, with low levels of movement between camps—provides an ideal configuration for viral metapopulation dynamics. We developed a spatial SEIR (susceptible, exposed, infectious, recovered) model to approximate the stochastic behaviour of HeV transmission in this spatially structured flying fox metapopulation. Our model includes precise information about quantitative dynamics within local populations (camps) as well as between-population coupling and explicit metapopulation structure. Models with heterogeneous infectious periods or transmission rates and a model with waning maternal immunity (phenomena proposed for henipaviruses) were also explored to account for alternative mechanisms of persistence within flying fox populations (see the electronic supplementary material, 'methods').

Demographic parameters including birth rate, death rate and seasonality were estimated from captive and field studies of *Pteropus poliocephalus* and *Pteropus alecto* (grey-headed and black flying foxes) ([38]; P. Eby 2004, unpublished data), while epidemiological parameters were estimated from experimental, field and captive data on *P. poliocephalus* and *P. alecto* (table 1). Direct empirical estimates of transmission rates (β) have thus far been impossible to obtain, hence we estimated a range of β values from field seroprevalence data (table 1), assuming equilibrium at γ/β susceptibles [40,41]. Lifelong immunity to HeV in *P. poliocephalus* and *P. alecto* was assumed on the basis of long-lived detectable antibodies in captive flying foxes ([39]; H. Field 2005, unpublished data), and long-lived immunity induced by other paramyxoviruses [42–44]. The period over which maternal immunity wanes was estimated from field and captive serosurveys [21,39].

Population and metapopulation characteristics of flying foxes (table 1) were estimated using data from biannual synchronized surveys of *P. poliocephalus* populations [26–29] and regional surveys of *P. alecto* populations [30,31]. Although the ecology of these two species differ, field and laboratory studies of HeV have not been able to distinguish significant differences in host-viral dynamics; furthermore, roost sharing [30,45,46] and identical isolates from both species [47] imply frequent interspecific transmission. Therefore, for the purpose of this paper, we grouped populations of the two species together. Qualitative assessments of long-term changes to flying fox populations were obtained by comparing historic literature [48–50] to current assessments [26–29,31] and expert opinion. Connectivity estimates from radio and satellite telemetry studies of *P. poliocephalus* [15,36] and radio telemetry studies of *P. alecto* [51,52] differed substantially, hence, we explored HeV dynamics over the entire range of the connectivity parameter, c, for which

Table 1. Model parameters.

parameter		estimate or range	source
transmission rate	β	2E − 5–5E − 5	γ/β susceptibles, estimate from field data
infectious period	$1/\gamma$	7 (95% CI: 4, 10) days	K. Halpin *et al.* (2005), unpublished data
incubation period	$1/\sigma$	6 (95% CI: 4, 9) days	K. Halpin *et al.* (2005), unpublished data
mean seroprevalence		0.5	estimate from data in Field [39]
standard deviation of seroprevalence		0.3	estimate from data in Field [39]
local population (camp) size	N_0	10 000	mean estimated from [26–30]
birth rate average	b	max 0.40	P. Eby (2004), unpublished data
mortality rate	d	1/10 years	[38]
carrying capacity	K	$K = N_0/(1 - d/b)$	calculated for equilibrium value
duration of breeding season		12 weeks Oct–Dec	[38]
number of local populations	h	200–800 (two species)	[26–30]
urban cluster size	s	0–40	current maximum is 20 camps [31].
rate at which transmission declines with distance	$c*d$	(0–0.25)*30	range of c values for which simulations persisted
duration of maternal immunity		182 days (six months)	[6,21,39]

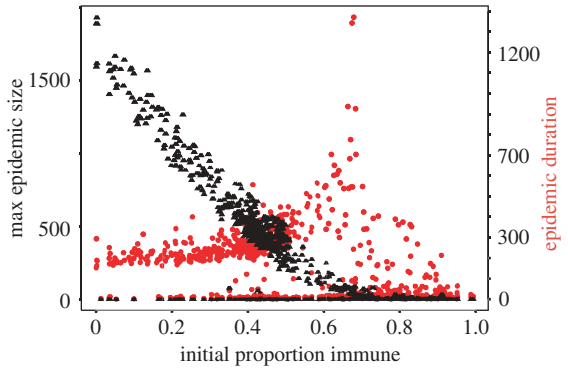

Figure 3. Herd immunity and epidemic size. Relationship between initial herd immunity, epidemic amplitude (black triangles) and epidemic duration (red circles) in a stochastic metapopulation simulation ($N_0 = 10\,000$, $\beta = 4.76\text{E} - 05$, $\gamma = 0.143$, $h = 200$, $c = 0.16$). The deterministic threshold number of susceptibles required for disease invasion in this model system is approximately 3000 (initial proportion immune = 0.7). When virus is introduced into a population with initial herd immunity approaching the threshold for invasion, low amplitude, persistent smouldering epidemics may result. When virus is introduced into a more susceptible population, high amplitude, shorter epidemics may result.

simulations persisted (see the electronic supplementary material, methods).

3. RESULTS

(a) *Local and metapopulation dynamics*

Local populations (camps) within the model flying fox–HeV system experienced periodic epidemics that depleted the susceptible pool, leading to local viral extinction after which susceptibles were replenished via births, followed by reinfection via spatial transmission. The size and the duration of each local epidemic were critically dependent on the local herd immunity (proportion of immune animals) at the start of the each epidemic (figure 3) [53,54]. Therefore, given heterogeneous herd immunity across local populations in an endemic host, an ensemble of epidemic types occurred across the metapopulation—from large explosive short-lived epidemics to slow 'smouldering' epidemic dynamics. Viral persistence depended on a small number of highly persistent smouldering epidemics to maintain infection through global troughs, as well as classic asynchronous metapopulation dynamics.

(b) *Decreased migratory behaviour and urban aggregation*

We simulated the effects of two changes in the structure and dynamics of the flying fox–HeV metapopulation: decreased migratory behaviour and greater aggregation of flying foxes in urban areas. Decreased migratory behaviour (a reduction in the probability of animals moving between populations—synonymous with decreasing population connectivity) had a significant impact on viral metapopulation dynamics. As connectivity decreased, epidemics (i) increased in size and, when combined with urban aggregation of flying foxes, (ii) diverged in amplitude and frequency in urban and rural environments (figure 4*a*,*b*).

The inverse relationship between outbreak size and connectivity can be explained by the change in inter-epidemic intervals. As fewer individuals migrate, the probability of infected hosts moving between local populations decreases—thereby lowering the probability of camps becoming reinfected after local viral extinction—and increasing the time over which flying fox populations can recruit susceptible individuals via birth (figure 4*c*). The resulting decline in herd immunity across the metapopulation shifts disease dynamics towards sporadic, shorter and more intense local epidemics with a higher epidemic amplitude, and larger number of individuals infected (figure 3). However, the total number of infected individuals within a metapopulation over a 20 year simulation decreased with declining connectivity (figure 4*d*). When we simulated changing flying fox population structure—towards clusters of urban camps, spanning to linear arrays of rural camps—the total number of infectious individuals, and therefore the force of infection, was notably higher in the urban clusters, compared with the rural arms (figure 5).

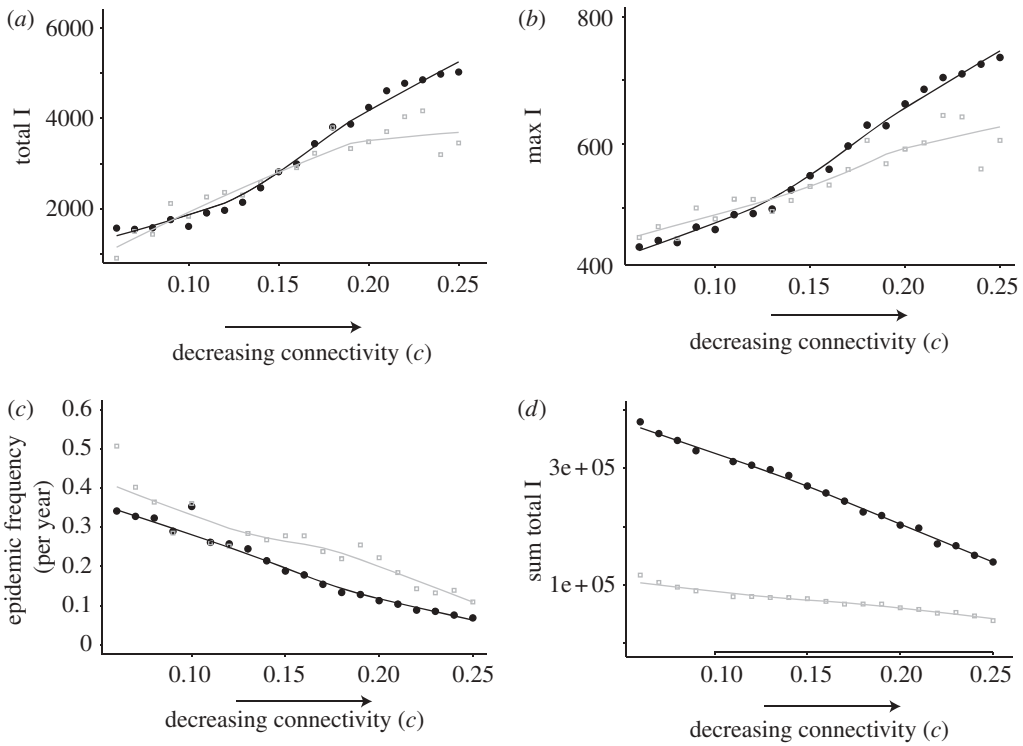

Figure 4. The effect of decreasing connectivity on viral dynamics. Grey squares, urban populations within the central cluster; black circles, linear rural populations outside the central urban cluster. As connectivity between local populations decreases: (*a*) the median total number of individuals infected per local epidemic increases; (*b*) the median maximum amplitude of local epidemics increases; (*c*) while the median epidemic frequency decreases; (*d*) the sum of infected individuals in the metapopulation over a 20 year simulation.

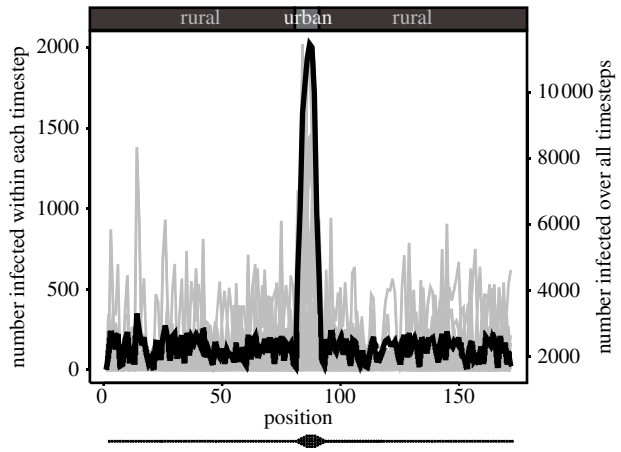

Figure 5. The total number of infected flying foxes in urban versus rural environments. The graphic below the plot shows the spatial structure of the model flying fox metapopulation with a central urban cluster with linear arms expanding on each side. 'Position' is an indicator of population *x*-coordinates. Infected individuals are tallied over all populations at a given *x*-coordinate, within each time step (grey line) and over all time steps (black line).

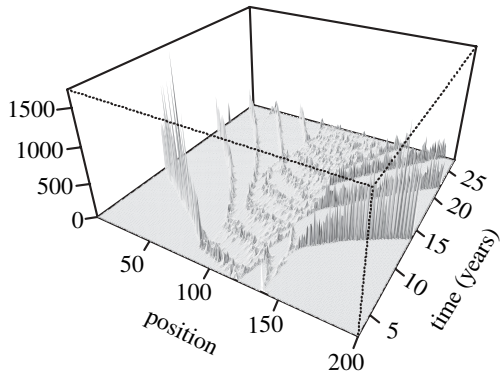

Figure 6. Simulated HeV dynamics in urban and rural flying fox populations. Populations in position 80–120 are within an urban cluster (a 4×5 matrix with tapering edges—see bottom of figure 5). The linear arms are in position 1–79 and 121–200. Urban populations experience smaller, more frequent epidemics which occasionally seed travelling waves of infection through the rural linear populations ($h = 200$, $\beta = 4.76\text{E} - 05$, $N_0 = 10\,000$, $c = 0.1$, $s = 20$).

When decreased migratory behaviour was imposed on the clustered flying fox population structure, the resulting establishment of a spatial hierarchy set up the conditions [55] that allowed HeV dynamics in urban and rural environments to diverge. Even at low rates of flying fox migration, HeV was more likely to persist within clusters of proximate urban camps, thereby periodically sparking spatio-temporal waves of infection through rural populations (figure 6).

(c) *Connectivity and persistence*

Connectivity had a profound effect on viral persistence. As we decreased migratory rates below levels of connectivity optimal for persistence, movement eventually became insufficient to allow reinfection of patches, resulting in concerted viral extinction. Thus, the same conditions that promoted larger epidemics eventually led to viral extinction, rendering the system vulnerable to a large synchronized outbreak.

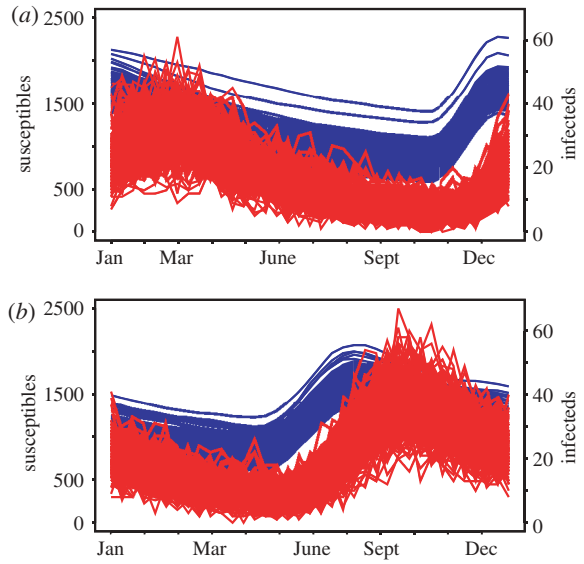

Figure 7. Temporal dynamics of HeV prevalence over an 18 month period. (*a*) Temporal dynamics of infected individuals (red) in 200 populations following the spring birth pulse (blue are susceptibles); (*b*) temporal dynamics when maternal immunity wanes after six months. Note the spike in prevalence is delayed by six months. ($h = 200$, $\beta = 4.76\text{E} - 05$, $N_0 = 10\,000$, $c = 0.1$, 1/100 infected individuals were infected for 365 days).

(d) *Alternative models: waning immunity and superspreaders*

Incorporating waning maternal immunity shifted the annual pulse in disease incidence by six months (figure 7*a*,*b*), to approximately coincide with the peak in HeV spill-over hazard (figure 1*b*). When the infectious period was allowed to vary, so that a small fraction of individuals became 'super-long-shedders' (see the electronic supplementary material, methods), local populations became permanently infected, with synchronous annual fluctuations in incidence driven by the influx of susceptibles. The shift in peak prevalence, driven by waning maternal immunity, was more pronounced in the 'super-long shedder' model compared with the acute homogeneous model where local populations were in frequently infected.

When we simulated decreased migratory behaviour, and urban aggregation with super-long-shedder, and 'super-high-shedder' models (see the electronic supplementary material, methods), the sum of infected individuals within urban aggregations was still greater than in the rural linear positions (see the electronic supplementary material, figure S3), however rare super-long-shedders maintained herd immunity so that declining connectivity did not impact epidemic size (see the electronic supplementary material, figure S4). The super-high-shedder model generated very similar dynamics to the acute homogeneous model (electronic supplementary material, figure S4).

4. DISCUSSION

Our study provides a number of viable mechanistic explanations for the recent emergence, and pattern of continued but sporadic spill-over, of HeV near densely populated areas of eastern Australia. Our models suggest that changes in host ecology, behaviour and movement, driven by anthropogenic environmental change, may have provided critical conditions for HeV emergence; while seasonal changes associated with reproduction may drive annual temporal trends in viral dynamics within bat populations.

(a) *Increasing urban aggregation is a likely driver of emergence*

The risk of pathogen emergence from a reservoir host to a new host species is affected by the number of reservoir hosts infected, the encounter rate between reservoir and novel hosts, and the infection dynamics and transmission biology of the pathogen [21,56–58]. The increasing number of flying foxes in urban settings should increase the encounter rate between flying foxes and urban/peri-urban horse populations as the pattern of domestic horse distribution and density closely follows that of humans on the east coast of Australia (R. McFarlane 2009, unpublished data). In addition, urban aggregation of flying foxes increases the absolute number of infected flying foxes in urban clusters, regardless of whether flying foxes are changing their migratory behaviour.

The finding that nine out of 14 known HeV spill-over events have been within the foraging radius of continuously occupied urban camps is consistent with the hypothesis that human/bat overlap in peri-urban environments contributes to HeV spill-over. A further one of these 14 outbreaks occurred near a continuously occupied non-urban camp, but is unusual in occurring where abundant food resources in northern New South Wales sustain permanently occupied camps regardless of human population density. The other four spill-overs occurred near seasonally occupied camps with large aggregations of flying foxes at the time of spill-over (H. Field 2011, unpublished data), with two of these in areas of high human (and horse) density. Although, the pattern of spill-over is consistent with our findings, 14 spill-over events is a limited sample size, and biases may exist within this sample (e.g. reporting bias in urban areas). Thus, prospective exploration of urban and non-urban HeV dynamics, as well as more rigorous identification, and investigation of future outbreaks is essential to confirm or reject this hypothesis.

(b) *Changing migratory behaviour may also drive spill-over events*

Our model showed that, in the absence of a rare super-long-shedder state, epidemics become larger, but less frequent when migration declines. However, over entire, multiple-decade simulations of highly connected metapopulations, in which virus was predicted to be continuously present at low incidence, the overall numbers of infected individuals were comparable to, or even higher than, the sporadic, explosive outbreaks in fragmented metapopulations. Therefore, the critical question is—which scenario increases the risk of spill-over: a continuous, low-level force of infection or an infrequent but high force of infection from flying foxes?

Data show that flying fox populations have either declined, shifted into urbanized environments, or both

[16,22,30,34,59], since early surveys by Ratcliffe [49,50] and Nelson [48]. Historically, more numerous and more connected flying fox populations probably favoured smouldering, low-incidence epidemic dynamics in nearly contiguous east coast forest, and an overall larger number of infected individuals. Therefore, we hypothesize that high-intensity epidemics, a possible consequence of reducing flying fox population connectivity, could facilitate spill-over to horses, and therefore explain the increasing hazard of HeV outbreaks, despite our prediction that the global number of infected flying foxes has declined. If large epidemics happen to coincide spatially with areas of high human and horse density, or temporally with periods of putative increased risk for horses (e.g. pregnancy; [60]) or flying foxes (e.g. nutritional stress or pregnancy; [21]), the risk of spill-over from intense but infrequent epidemics may be enhanced. Although the fact that 10 out of 14 HeV outbreak sites were near continuously occupied flying fox camps, which we assume contain non-migratory animals ([16,36,61]; P. Eby 2008, unpublished data), supports this hypothesis, detailed temporal surveys of urban flying foxes demonstrating declining herd immunity before HeV outbreaks in horses, will be necessary to confirm this hypothesis.

(c) *Spatio-temporal clustering of spill-over events: epidemic waves*

The spatio-temporal clustering of some spill-over events (e.g. Cairns and Townsville in 2004, Peachester and Murwillumbah in 2006), the isolation of identical strains of HeV from separate locations (e.g. Mackay and Brisbane in 1994; [62,63]), and the sporadic nature of HeV outbreaks could be explained by wave-like spatio-temporal behaviour. Our models show that epidemic waves of HeV, sparked by urban epidemics and travelling progressively through non-urban populations, are a possible consequence of changing flying fox spatial population structure. Similarly, spatial heterogeneity in host population structure has been hypothesized to account for travelling waves of measles virus in England and Wales [55] and dengue haemorrhagic fever in Thailand [64], with larger communities periodically sparking waves in incidence through small communities. Monitoring of HeV in Australian flying foxes will be necessary to determine whether HeV exhibits these patterns of spatial spread.

(d) *Seasonal clustering of spill-over events: birth pulses, pregnancy, aggregation and 'stress synchrony'*

Seasonal changes in reproductive behaviour, birth rates, aggregation patterns and host susceptibility can drive pulses in disease incidence [65,66] and annual peaks in epidemic frequency [65]. Seasonal factors almost certainly apply to flying foxes, with the annual birth pulse, pregnancy, seasonal aggregation and cyclical environmental stressors being several distinct mechanisms that could contribute to the seasonal (winter–spring) increase in HeV spill-over hazard.

Seasonal births provide an influx of immunologically naive hosts, lowering herd immunity and increasing the risk of infection for all susceptibles [67,68]. In the absence of maternal immunity, our models predicted that a pulse in disease incidence should follow the birth pulse. Waning maternal immunity shifted the recruitment of susceptibles by six months, and delayed the spike in prevalence to coincide with the peak in HeV spill-over hazard. Seasonal forcing was a dominant feature of the super-long-shedder model, where seasonal effects were synchronous across the persistently infected local populations. When local infection was sporadic, as in the acute homogeneous model, seasonality could only drive dynamics within populations that happened to be infected during the recruitment of susceptibles, and specific local epidemic history was a more dominant influence on local force of infection. Temporal studies of HeV prevalence and seroprevalence are required to investigate the role of waning maternal immunity and to assess outputs from the superspreader and homogeneous models.

A delayed pulse of susceptibles could potentially interact with an increased risk of infection during pregnancy, as demonstrated in *P. scapulatus* [21], or other, as yet unknown factors, such as recrudescent infection [69]. Host aggregation during reproduction [23,30,48,49] or periods of resource concentration [15,22] are other potential drivers of transmission that need further investigation. Finally, environmental stress could drive geographical 'stress synchrony'. Elevated seroprevalence was associated with nutritional stress in *P. scapulatus* [21], suggesting that processes that alter flying fox food sources—such as drought and climate change—could both increase and synchronize the risk of HeV spill-over. As synchronous stressors affect bats, synchronous stressors on horses, (e.g. foraging stress or pregnancy) or conditions that promote pathogen survival in the environment, could exacerbate the potential for spill-over. Identifying the mechanism linking seasonal host factors with HeV emergence is critical to aid in forecasting outbreaks and developing control strategies.

5. CONCLUSION

Our work suggests multiple factors in the changing landscape of Australia and the demography of flying foxes contribute to HeV dynamics in bats and spill-over hosts. Our models predict that urban habituation of flying foxes increases the epidemiological linkage between flying foxes and horses, providing plausible scenarios for the recent apparent increased frequency of HeV outbreaks in Australia. We present alternative models of HeV persistence, including an acute homogeneous metapopulation model, where explosive infrequent outbreaks may drive the sporadic pattern of emergence; and a locally persistent model of HeV dynamics with seasonal oscillations in incidence coinciding with increased risk of HeV emergence. Field data are critically needed to distinguish between these alternative models for HeV persistence and spill-over, along with laboratory investigations that improve our interpretation of serology. Furthermore, we describe a counterintuitive 'epidemic dampening' effect, where decreasing reservoir host population connectivity can favour a sporadic, high force of infection that may facilitate pathogen emergence into an aberrant host. We propose that future work on the drivers of emergence of other zoonotic disease systems test this theoretical framework that may have important conservation and public health implications. Finally, our results suggest that anthropogenically driven changes to

flying fox ecology may result in more intense, sporadic, lethal outbreaks of HeV in livestock and people.

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