THESIS INTRODUCTION

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1. Abstract

ABSTRACT. Pathogens make up a huge proportion of global diversity and their role in disease strongly affects human disease, economics and development as well as having an important ecological role. However, the factors that control the number of pathogen species are poorly understood.

The patterns of contacts between individuals — in both human and animal populations — are nonrandom and depend on the density of individuals. Population structure and density have important epidemiological consequences, but their role in the control of pathogen richness is unknown.

It is still unknown whether population structure and density controls pathogen richness in bats. Furthermore, the specific mechanisms by which structure might influence pathogen richness have not been studied.

In this thesis I have studied how population structure and density control pathogen richness using bats as a case study. I have used epidemiological simulations and comparative analyses of data from wild bat populations to show that population structure does not have a strong affect on pathogen richness. Using further simulations I have shown that the interaction between population density and population structure is an important consideration. Finally, I have created a model for estimating bat densities — previously an incredibly challenging task — using acoustic data. Together, these studies clarify the relative roles of population density and structure and facilitate further study of population density in bats as a driver of pathogen richness.

While theory previously predicted that population structure should increase pathogen richness, the expectation in the ecological literature was that population structure would decrease pathogen richness. My studies support neither of these views, instead suggesting that population structure does not have a strong affect in either direction.

2. Introduction

The diversity of pathogens is huge and largely unknown [1]. Recent large studies have found tens [2] or even hundreds of virus species in a single host species [3]. This suggests the number of mammalian viruses globally is of the order of hundreds of thousands of virus species [2] while only three thousand species of virus, across all host groups, are currently described [4]. Recent large databases include nearly 2,000 pathogens from approximately 400 wild animal hosts [5]. Given that there are nearly 4,000 named mammal species [6], the undiscovered diversity of pathogens is likely huge.

This diversity of pathogens presents a risk to human health. 60% of newly emerged disease are zoonotic (acquired from animals) with wild animals being the predominant source [7]–[9]. Zoonotic diseases can be extremely virulent: viruses such as Nipah [10], Ebola [11] having case fatality rates over 50%. Furthermore these pathogens can have large economic costs (e.g. SARS is estimated to have cost $40 billion [12]). In particular these impacts can have huge affects on developing economies. For example the 2014 ebola epidemic caused both Liberia and Guinea to fall from positive to negative per capita growth rates [13], [14]. In general we can expect competition between pathogens. Competition between pathogens can occur by different mechanisms: immunological mechanisms such as cross-immunity or shared immune respone [15] and ecological mechanisms such as removal of susceptable hosts by death [16] or competition for

internal host resources [17]. Like ecological systems this competition leads us to expect competitive exclusions [18]–[22] so the diversity of parasites needs an explanation.

Surveillance of zoonotic diseases is crucial. In particular we want to categorise diseases before they spillover into humans (SARS was not identified until months into the pandemic for example [23]) and we want to anticipate outbreaks. If we know there is an increased number of infections in host species, increased numbers of a species that is a known reservoir of a high risk zoonotic disease, or increased contacts between humans and a pathogen reservoir, we can prepare for a potential outbreak in that area. However, funds for zoonotic surveillance are limited and so efforts must be optimised. Knowing which species are likely to have many pathogens allows us to sample and identify potentially zoonotic viruses efficiently. Suggested factors that might control pathogen richness include individual traits (body mass [24]–[26] and longevity [27], [28]) as well as environmental factors such as latitude [24], [29]. Further population level traits that affect the dynamics of disease spread have also been studied (animal density [24], [25], [27], sociality [28], [30]–[32], population structure [33]–[36] and species range size [24], [27]). This understanding provides a basis for predicting which species will have high pathogen richness and should be prioritised for sampling and surveillance. Furthermore, given a good mechanistic understanding of how pathogen richness is created and maintained we can start to predict how pathogen richness (and zoonotic disease risk) will respond to global change.

In recent decades bats have been implicated in a number of high profile zoonotic outbreaks including Nipah [37], Ebola [38], SARS [39] and Hendra [37]. This has lead to much research on whether bats are a particular source of zoonotic disease [40]–[42] and examinations of factors, such as flight, social living and longevity, that might predispose them to being reservoires of zoonotic viruses [43]–[45]. Given that bats are the second largest order of mammals [6], we may expect them to be the source of many viruses simply through weight of numbers [40]. The broad conclusions are that while bat do host more zoonotic viruses than other groups [40] they do not host more virus species in general [41]. Questions remain as to why bat viruses have a tendency to have such high zoonotic potential.

Many factors of bat populations make them epidemiologically interesting. Firstly, the population density of most bat species is largely unknown. As they are small, noctornal and difficult to identify on the wing, estimating there density is incredibly difficult without distruptive and time consuming roost surveys. Secondly they have highly varied and sometimes complex social structures. While some species are largely solitary or live in very small groups (e.g. *Lasiurus borealis* [46]) some species live in colonies of millions of individuals (e.g. *Pteropus scapulatus* [47]). These groups can be very stable. Further complexity arises due to their propensity for seasonal migration [] and seasonally changing social organisation including maternity roosts, hibernation roosts and swarming sites []. Finally, their ability to fly means populations can be well mixed across vast distances [48] but this is highly variable with some species have limited dispersal [].

Define. Simple count of pathogens across whole species. Ignores heterogeneity in prevalence, across space and time.

REFERENCES

[1]   R Poulin, "Parasite biodiversity revisited: frontiers and constraints," *International journal for parasitology*, vol. 44, no. 9, pp. 581–589, 2014. DOI: 10.1016/j.ijpara.2014.02.003.

[2]   SJ Anthony, JH Epstein, KA Murray, I Navarrete-Macias, CM Zambrana-Torrelio, A Solovyov, R Ojeda-Flores, NC Arrigo, A Islam, SA Khan, P Hosseini, TL Bogich, KJ Olival, MD Sanchez-Leon, WB Karesh, T Goldstein, SP Luby, SS Morse, JAK

Mazet, P Daszak, & WI Lipkin, "A strategy to estimate unknown viral diversity in mammals," *MBio*, vol. 4, no. 5, e00598–13, 2013.

[3] SJ Anthony, A Islam, C Johnson, I Navarrete-Macias, E Liang, K Jain, PL Hitchens, X Che, A Soloyvov, AL Hicks, R Ojeda-Flores, C Zambrana-Torrelio, W Ulrich, MK Rostal, A Petrosov, J Garcia, N Haider, N Wolfe, T Goldstein, SS Morse, M Rahman, JH Epstein, JK Mazet, P Daszak, & WI Lipkin, "Non-random patterns in viral diversity," *Nature communications*, vol. 6, 2015. DOI: 10.1038/ncomms9147.

[4] AM King, MJ Adams, & EJ Lefkowitz, *Virus taxonomy: classification and nomenclature of viruses: Ninth Report of the International Committee on Taxonomy of Viruses*. San Diego, CA: Elsevier, 2011, vol. 9, ISBN: 978-0123846846.

[5] M Wardeh, C Risley, MK McIntyre, C Setzkorn, & M Baylis, "Database of host-pathogen and related species interactions, and their global distribution," *Scientific data*, vol. 2, 2015. DOI: 10.1038/sdata.2015.49.

[6] DE Wilson & DM Reeder, *Mammal species of the world: a taxonomic and geographic reference*. JHU Press, 2005, vol. 12, ISBN: 9780801882210.

[7] KE Jones, NG Patel, MA Levy, A Storeygard, D Balk, JL Gittleman, & P Daszak, "Global trends in emerging infectious diseases," *Nature*, vol. 451, no. 7181, pp. 990–993, 2008. DOI: 10.3201/eid0903.020336.

[8] ME Woolhouse & S Gowtage-Sequeria, "Host range and emerging and reemerging pathogens," in *Ending the War Metaphor:: The Changing Agenda for Unraveling the Host-Microbe Relationship-Workshop Summary*, National Academies Press, vol. 192, 2006.

[9] LH Taylor, SM Latham, & E Mark, "Risk factors for human disease emergence," *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, vol. 356, no. 1411, pp. 983–989, 2001. DOI: 10.1093/acprof:oso/9780198525738.003.0035.

[10] SP Luby, MJ Hossain, ES Gurley, BN Ahmed, S Banu, SU Khan, N Homaira, PA Rota, PE Rollin, JA Comer, *et al.*, "Recurrent zoonotic transmission of Nipah virus into humans, Bangladesh, 2001–2007," *Emerging infectious diseases*, vol. 15, no. 8, p. 1229, 2009. DOI: 10.3201/eid1508.081237.

[11] A Lefebvre, C Fiet, C Belpois-Duchamp, M Tiv, K Astruc, & LA Glélé, "Case fatality rates of Ebola virus diseases: a meta-analysis of World Health Organization data," *Médecine et maladies infectieuses*, vol. 44, no. 9, pp. 412–416, 2014. DOI: 10.1016/j.medmal.2014.08.005.

[12] S Knobler, S Lemon, A Mack, L Sivitz, & K Oberholtzer, *Learning from SARS: Preparing for the Next Disease Outbreak: Workshop Summary*. National Academies Press Washington, DC, USA: 2004. DOI: 10.1016/j.socscimed.2006.08.004.

[13] World Bank, *Update on the economic impact of the 2014 Ebola epidemic on Liberia, Sierra Leone, and Guinea*, Washington, DC, 2014. DOI: 10.1211/pj.2014.20066832. [Online]. Available: http://documents.worldbank.org/curated/en/2014/12/20454884/update-economic-impact-2014-ebola-epidemic-liberia-sierra-leone-guinea.

[14] ——, "World Development Indicators: Size of the economy," [Online]. Available: http://wdi.worldbank.org/table/1.1.

[15] A Fenton & SE Perkins, "Applying predator-prey theory to modelling immune-mediated, within-host interspecific parasite interactions," *Parasitology*, vol. 137, no. 06, pp. 1027–1038, 2010. DOI: 10.1017/s0031182009991788.

[16] P Rohani, C Green, N Mantilla-Beniers, & B Grenfell, "Ecological interference between fatal diseases," *Nature*, vol. 422, no. 6934, pp. 885–888, 2003. DOI: 10.1038/nature01542.

[17]   EC Griffiths, AB Pedersen, A Fenton, & OL Petchey, "Analysis of a summary network of co-infection in humans reveals that parasites interact most via shared resources," *Proceedings of the Royal Society of London B: Biological Sciences*, vol. 281, no. 1782, p. 20 132 286, 2014. DOI: 10.1098/rspb.2013.2286.

[18]   HJ Bremermann & H Thieme, "A competitive exclusion principle for pathogen virulence," *Journal of mathematical biology*, vol. 27, pp. 179–190, 1989. DOI: 10.1007/BF00276102.

[19]   M Martcheva & XZ Li, "Competitive exclusion in an infection-age structured model with environmental transmission," *Journal of Mathematical Analysis and Applications*, vol. 408, no. 1, pp. 225–246, 2013. DOI: 10.1016/j.jmaa.2013.05.064.

[20]   AS Ackleh & LJ Allen, "Competitive exclusion and coexistence for pathogens in an epidemic model with variable population size," *Journal of mathematical biology*, vol. 47, no. 2, pp. 153–168, 2003. DOI: 10.1007/s00285-003-0207-9.

[21]   AS Ackleh & PL Salceanu, "Robust uniform persistence and competitive exclusion in a nonautonomous multi-strain SIR epidemic model with disease-induced mortality," *Journal of mathematical biology*, no. 1-2, pp. 453–475, 2014. DOI: 10.1007/s00285-012-0636-4.

[22]   K Turner & G Garnett, "The impact of the phase of an epidemic of sexually transmitted infection on the evolution of the organism," *Sexually transmitted infections*, vol. 78, pp. i20–i30, 2002. DOI: 10.1136/sti.78.suppl_1.i20.

[23]   C Drosten, S Günther, W Preiser, S Van Der Werf, HR Brodt, S Becker, H Rabenau, M Panning, L Kolesnikova, RA Fouchier, *et al.*, "Identification of a novel coronavirus in patients with severe acute respiratory syndrome," *New England Journal of Medicine*, vol. 348, no. 20, pp. 1967–1976, 2003. DOI: 10.1056/NEJMoa030747.

[24]   T Kamiya, K O'Dwyer, S Nakagawa, & R Poulin, "What determines species richness of parasitic organisms? A meta-analysis across animal, plant and fungal hosts," *Biological Reviews*, vol. 89, no. 1, pp. 123–134, 2014. DOI: 10.1111/brv.12046.

[25]   P Arneberg, "Host population density and body mass as determinants of species richness in parasite communities: comparative analyses of directly transmitted nematodes of mammals," *Ecography*, no. 1, pp. 88–94, 2002. DOI: 10.1034/j.1600-0587.2002.250110.x.

[26]   R Poulin, "Phylogeny, ecology, and the richness of parasite communities in vertebrates," *Ecological Monographs*, pp. 283–302, 1995. DOI: 10.2307/2937061.

[27]   CL Nunn, S Altizer, KE Jones, & W Sechrest, "Comparative tests of parasite species richness in primates," *The American Naturalist*, vol. 162, no. 5, pp. 597–614, 2003. DOI: 10.1086/378721.

[28]   VO Ezenwa, SA Price, S Altizer, ND Vitone, & KC Cook, "Host traits and parasite species richness in even and odd-toed hoofed mammals, Artiodactyla and Perissodactyla," *Oikos*, vol. 115, no. 3, pp. 526–536, 2006. DOI: 10.1111/j.2006.0030-1299.15186.x.

[29]   R Poulin, "Latitudinal gradients in parasite diversity: bridging the gap between temperate and tropical areas," *Neotropical Helminthology*, vol. 4, no. 2, pp. 169–177, 2010.

[30]   F Bordes, DT Blumstein, & S Morand, "Rodent sociality and parasite diversity," *Biology letters*, vol. 3, no. 6, pp. 692–694, 2007. DOI: 10.1098/rsbl.2007.0393.

[31]   ND Vitone, S Altizer, & CL Nunn, "Body size, diet and sociality influence the species richness of parasitic worms in anthropoid primates," *Evolutionary Ecology Research*, vol. 6, no. 2, pp. 183–199, 2004.

[32]   S Altizer, CL Nunn, PH Thrall, JL Gittleman, J Antonovics, AA Cunnningham, AP Dobson, V Ezenwa, KE Jones, *et al.*, "Social organization and parasite risk

in mammals: integrating theory and empirical studies," *Annual Review of Ecology, Evolution, and Systematics*, pp. 517–547, 2003. DOI: 10.1146/annurev.ecolsys.34.030102.151725.

[33] A Nunes, MT da Gama, & M Gomes, "Localized contacts between hosts reduce pathogen diversity," *Journal of theoretical biology*, vol. 241, no. 3, pp. 477–487, 2006. DOI: 10.1016/j.jtbi.2005.12.010.

[34] GD Maganga, M Bourgarel, P Vallo, TD Dallo, C Ngoagouni, JF Drexler, C Drosten, ER Nakouné, EM Leroy, & S Morand, "Bat distribution size or shape as determinant of viral richness in african bats," *PloS one*, vol. 9, no. 6, e100172, 2014. DOI: 10.1371/journal.pone.0100172.

[35] N Gay, KJ Olival, S Bumrungsri, B Siriaroonrat, M Bourgarel, & S Morand, "Parasite and viral species richness of Southeast Asian bats: Fragmentation of area distribution matters," *International Journal for Parasitology: Parasites and Wildlife*, vol. 3, no. 2, pp. 161–170, 2014. DOI: 10.1016/j.ijppaw.2014.06.003.

[36] AS Turmelle & KJ Olival, "Correlates of viral richness in bats (order Chiroptera)," *EcoHealth*, vol. 6, no. 4, pp. 522–539, 2009. DOI: 10.1007/s10393-009-0263-8.

[37] H Field, P Young, J Yob, J Mills, L Hall, & J Mackenzie, "The natural history of Hendra and Nipah viruses," *Microbes and infection*, vol. 3, no. 4, pp. 307–314, 2001. DOI: 10.1016/S1286-4579(01)01384-3.

[38] EM Leroy, B Kumulungui, X Pourrut, P Rouquet, A Hassanin, P Yaba, A Délicat, JT Paweska, JP Gonzalez, & R Swanepoel, "Fruit bats as reservoirs of Ebola virus," *Nature*, vol. 438, no. 7068, pp. 575–576, 2005.

[39] W Li, Z Shi, M Yu, W Ren, C Smith, JH Epstein, H Wang, G Crameri, Z Hu, H Zhang, J Zhang, J McEachern, H Field, P Daszak, BT Eaton, S Zhang, & LF Wang, "Bats are natural reservoirs of SARS-like coronaviruses," *Science*, vol. 310, no. 5748, pp. 676–679, 2005. DOI: 10.1126/science.1118391.

[40] AD Luis, DTS Hayman, TJ O'Shea, PM Cryan, AT Gilbert, JRC Pulliam, JN Mills, ME Timonin, CKR Willis, AA Cunningham, AR Fooks, CE Rupprecht, JLN Wood, & CT Webb, "A comparison of bats and rodents as reservoirs of zoonotic viruses: are bats special?" *Proceedings of the Royal Society B: Biological Sciences*, vol. 280, no. 1756, p. 20 122 753, 2013. DOI: 10.1098/rspb.2012.2753.

[41] KJ Olival, CC Weekley, & P Daszak, "Are bats really "special" as viral reservoirs? What we know and need to know," in *Bats and Viruses: A New Frontier of Emerging Infectious Diseases*, LF Wang & C Cowled, Eds., New Jersey: Wiley, 2015, pp. 281–294. DOI: 10.1002/9781118818824.ch11.

[42] L Wang, P Walker, & L Poon, "Mass extinctions, biodiversity and mitochondrial function: are bats 'special' as reservoirs for emerging viruses?" *Current Opinion in Virology*, 2011. DOI: 10.1016/j.coviro.2011.10.013.

[43] C Calisher, J Childs, H Field, K Holmes, & T Schountz, "Bats: important reservoir hosts of emerging viruses," *Clinical Microbiology Reviews*, vol. 19, no. 3, pp. 531–545, 2006. DOI: 10.1128/CMR.00017-06.

[44] TJ O'Shea, PM Cryan, AA Cunningham, AR Fooks, DT Hayman, AD Luis, AJ Peel, RK Plowright, & JL Wood, "Bat flight and zoonotic viruses," *Emerging infectious diseases*, vol. 20, no. 5, p. 741, 2014. DOI: 10.3201/eid2005.130539.

[45] AP Dobson, "What links bats to emerging infectious diseases?" *Science*, vol. 310, no. 5748, pp. 628–629, 2005. DOI: 10.1126/science.1120872.

[46] KA Shump & AU Shump, "Lasiurus borealis," *Mammalian species*, pp. 1–6, 1982. DOI: 10.2307/3503843.

[47] P Birt, M McCoy, & C Palmer, "Little Red Flying-fox, *Pteropus scapulatus*," in *The mammals of Australia*, S Van Dyck & R Strahan, Eds., 3rd ed., Sydney, Australia: Reed New Holland, 2008, pp. 446–447.

[48]   AJ Peel, DR Sargan, KS Baker, DT Hayman, JA Barr, G Crameri, R Suu-Ire, CC Broder, T Lembo, LF Wang, *et al.*, "Continent-wide panmixia of an African fruit bat facilitates transmission of potentially zoonotic viruses," *Nature communications*, vol. 4, 2013. DOI: 10.1038/ncomms3770.