Appendix Six: Epidemiological interaction at the wildlife/livestock/human interface: can we anticipate emerging infectious diseases in their hotspots?

(Appendix reference: Caron, A., de Garine-Wichatitsky, M., Morand. 2012. Chapter 14: Epidemiological interaction at the wildlife/livestock/human interface: can we anticipate emerging infectious diseases in their hotspots? A framework for understanding emerging diseases processes in their hotspots. "New Frontiers of Molecular Epidemiology of Infectious Diseases". Morand, S., Beaudeau F., Cabaret J. (Eds).,Part 5, 311-332.)

Introduction

The incidence of Emerging Infectious Diseases (EIDs) in human and domestic species has increased in the last decades (Cleaveland et al. 2001, Taylor et al. 2001, Jones et al. 2008, Woolhouse 2008). Zoonoses constitute 60.3% of human EIDs of which 71.8% originate in a wildlife source with intermediate animal hosts often necessary (Jones et al. 2008). Following (Haydon et al. 2002), we define target species as those species receiving the bulk of sanitary surveillance: human and domestic species as well as a few wildlife flagship species. The sum of these target species represents a tiny fraction of the biodiversity. The bias induced by this focused surveillance hides the majority of EIDs events in the non-target species.

We have little insight about what is happening “in the wild”, where statistically most of pathogen evolution and transmission processes are underway. Our knowledge about EIDs processes is therefore limited and skewed in favour of a non-random sample of those occurring. Describing these processes and their common properties could benefit the surveillance and control of EID in target but also in non-target species, supporting global objectives of public and animal health and conservation as presented in the “One World, One Health” concept (Karesh and Deem 2000, Osofsky et al. 2008, Gibbs and Anderson 2009).

The origin of this increase in EIDs is complex. A relation with disturbed ecological processes is often assumed (Daszak et al. 2001). Massive changes in organism distribution and relations induced by global trends, such as increased anthropogenic footprint and climate change have triggered new host, pathogen and environment interactions. These new ecological interactions are not randomly geographically located and regions with a higher risk of emergence can be identified by plotting known emergence events on a map. According to Jones et al. 2008, hotspots of disease emergence are characterised by: 1) high densities in human and animal populations in systems under intensive health surveillance; 2) the wildlife/livestock/human interface in tropical ecosystems. Focusing on wildlife-linked EIDs, the integration of these two characteristics leads to a description of EIDs events as a two steps process: 1) emergence of the pathogen *sensu stricto* (defined as the interspecies spill-over from a non-target to a target species) (steps 1 and 2 in Childs et al. 2007); 2) amplification of the epidemic phase with higher host availability (provided by higher densities). Recent EIDs can be classified accordingly: Ebola in humans, originating from a potential bat reservoir has reached step 1 but not step 2 (Leroy et al. 2005); HPAI H5N1 in poultry with a wild bird origin has reached step 1 and 2 (Webster and Govorkova 2006); SARS in humans, originating in bats, as reached step 1 but had a limited step 2 in 2003 (Wang and Eaton 2007). In tropical and sub-tropical ecosystems, the degree of wildlife/livestock/human interface and biodiversity are high and offer numerous potential events of spill-over. However, low animal and human health surveillance decrease the detection probability. In ecosystems with artificially high host densities, less inter-species transmission events occur because of the physical and sanitary protection of these systems. Moreover, efficient surveillance systems in target species increase the detection probability of the emergence. This analysis could explain the global EID patterns observed.

In order to improve the efficiency and reduce the cost of health interventions, research should be implemented on step 1 in order to understand, predict and control emergence processes and to prevent amplification events (step 2) or prepare the health sector to control them (Barclay 2008). Step 1 requires focusing on the wildlife/livestock/human interface, which necessitates ecological, epidemiological as well as socio-economical information. This interface is characterised by: a) multi-host systems; b) managed and unmanaged animal populations ("managed" referring to the state of animal population when influenced by voluntary human intervention); c) natural and modified habitats; d) remote areas, where basic commodities are often lacking; e) unknown socio-economical system in marginalised human communities. The lack of baseline information which characterised these interfaces combined with the above particularities requires the development of theoretical and technological tools adapted to the study of EIDs in their hotspots (Morgan et al. 2006). However, studying EIDs in selected ecosystems raises any of the following challenges: a) looking for a still unknown pathogen; b) arriving after the emergence process, when one does not know if the spill-over process still occurs; c) looking for a pathogen which is not yet in the study site. In order to overcome this dilemma, a shift from a pathogen-centred to a process-centred approach is necessary. The process at stake is the pathogen spill-over in multi-hosts system at the wildlife/livestock/human interface.

We define epidemiological interaction (EI) as any ecological interaction resulting in the transmission of pathogen between two host populations (Chapter Three - Caron et al. 2010). This definition of EI is developed in the next sections of this chapter. We then present a research framework, process-orientated, using host and/or pathogen data for the inference of emergence risk in a given ecosystem. We describe a method to build EI network and present using an example how this network can be used to identify host populations or EI at risk for pathogen emergence.

Methods

Estimating transmission rate for pathogens shared between host populations

Standard approaches to study pathogen transmission rate in a single host population are pathogen-centred (Bordes and Morand 2009). In one host population, prevalence and incidence of the pathogen measured by serological or viral detection techniques can be used to calculate the transmission rate. Common index of this transmission rate are the R0 and β index and the force of infection (McCallum et al. 2001; see Real and Biek 2007 for a recent discussion of these parameters for wildlife zoonosis). These parameters are defined for a given pathogen in a defined host population. The data needed to estimate these parameters are the contact rate between hosts, the transmission probability resulting from these contacts and the infectiveness of the pathogen in the target host or the probability that such a contact occurs between an infected and a susceptible host (McCallum et al. 2001). Models of a shared pathogen between two hosts populations have been developed (see Tompkins et al. 2002 for some examples).

In an experimental situation using a domestic species, these parameters are accessible. *A posteriori*, after an outbreak, these parameters can be estimated if the relevant data has been timely collected. This data concerns repeated data collection on a pre-determined sample of the animal population and the setting-up of the appropriate environment in which the samples will be adequately stored until laboratory testing. Applied to the wildlife/livestock interface, estimating these parameters is difficult in free-ranging species (Morgan et al. 2006). Capture of wild species is often expensive, implemented in extreme conditions not suitable for sample conservation and unrealistic when the activity needs to be repeated in time on the same animals. Real & Biek (Real and Biek 2007) suggest a possible framework using telemetry (radio and satellite) on wild species combined with sampling survey on wild and domestic species. However they identify limits such as the underestimation of the quantity of contacts if the entire wild population is not marked. Richomme et al. 2006 estimated by direct observations the contact rate and exposure between a domestic ungulate and a wild mountain ungulate and discuss additional limits of such data for the inference of EIs because of the nocturnal behaviour of wild species which cannot be apprehended. The necessity to include in the study the respective sensibility of each species to the pathogen requires also an extrapolation from available data on closely-related species. The role of modelling has been and will be crucial in the estimation of the behaviour of transmission parameters and their interpretation (Lloyd-Smith et al. 2009). A model allows playing with variables to estimate outcomes impossible to observe in the field. They use the available data to test hypothesis which would be too complex or too costly to test in experimental conditions. Multi-host models have been developed under the form of meta-population pathogen diffusion process in the particular case of multi-host meta-population (Arino et al. 2005). Recently, transmission models of multi-strains with differential transmission pathways (with emphasis on the role of the environment) paved the way for multi-pathogen models (Roche and Rohani 2010). However, the integration of multi-host and multi-pathogen models has yet to be done. This step will be necessary in order to encompass the full complexity of transmission ecology at the wildlife/domestic interface.

The application of these different methods to the case of an unknown pathogen before its emergence in the ecosystem raises new issues. Here, the objective is to identify an unknown emerging pathogen to reach the target population. The emergence event *sensu stricto* that we are trying to detect is the spill-over of an unknown pathogen from an unknown source population to a known naive population. Which non-target host should be studied? For which pathogen should we test it? In this context where no target pathogen is identified, a pathogen-centred approach cannot be implemented.

EI network and selection of host and pathogen community to predict pathogen emergence

The human species, a domestic species (e.g. livestock) or a flagship wild species (e.g. mountain gorilla) can be the target species under study. The unknown pathogen emerging in a given ecosystem will be transmitted to the target species by an unknown non-target species, through direct and/or indirect contacts (Figure A6.1). The main assumption of the research framework is that the emerging pathogen will use contacts between hosts which have already been used by other pathogens. The higher the intensity of EI, the higher the probability of the emerging pathogen to use it. If the EI network can be built between different host populations, prediction on the likelihood of emergence through a particular EI can be made.

Network Analysis (NA) developed primarily in the context of social sciences is increasingly used in health ecology (Luke and Harris 2007). It has been applied to explore relations between cattle movement data (Heath et al. 2008) or human populations patterns (Bansal et al. 2007) and disease spread. A network is a set of different entities defined by "nodes" linked by "edges". Nodes and edges have several properties (Figure A6.2). Nodes are host populations, and edges represent EIs. Nodes can be linked with characteristics of the host population (ecological or epidemiological) defined by the type of data used to build the network. Edges have two properties: 1) intensity, defined by the number of contacts between host populations, or the proportion of pathogens shared between the two host populations; this property can be graphically represented by the width of the link between 2 nodes; 2) directionality, uni- or bidirectional depending on the transmission possibilities between the two host populations; an arrow at the extremity of the edge represents this property. If interested in the temporal variation of EIs, different networks can be built or different colour for different temporal windows can be used, based on temporal series. Once nodes and edges have been characterised given their attributes, the network illustrates the principal edges-EIs between the target species and non-target species.

Figure A6.1: *a) Theoretical contact network including wild, domestic and human populations; in the remaining figures, the same network when the human population (b), a domestic population (c) or a flagship wildlife species (d) is considered as the target species. Depending on the target population selected, the contact network potentially leading to the spill-over of a pathogen from non-target populations change. For example, wildlife population 2 does not play a role in (b) and (c) whereas it is considered as a potential source of pathogen in case (d). Relevant epidemiological interactions in the system change in case (b), (c) and (d).*

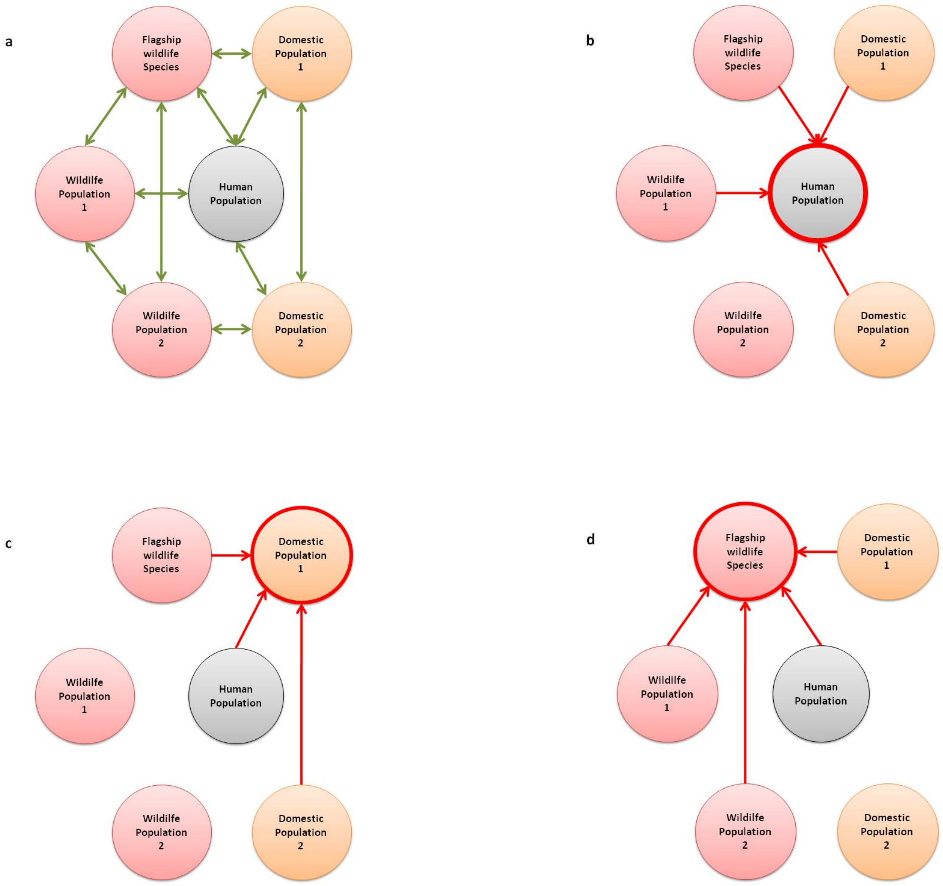
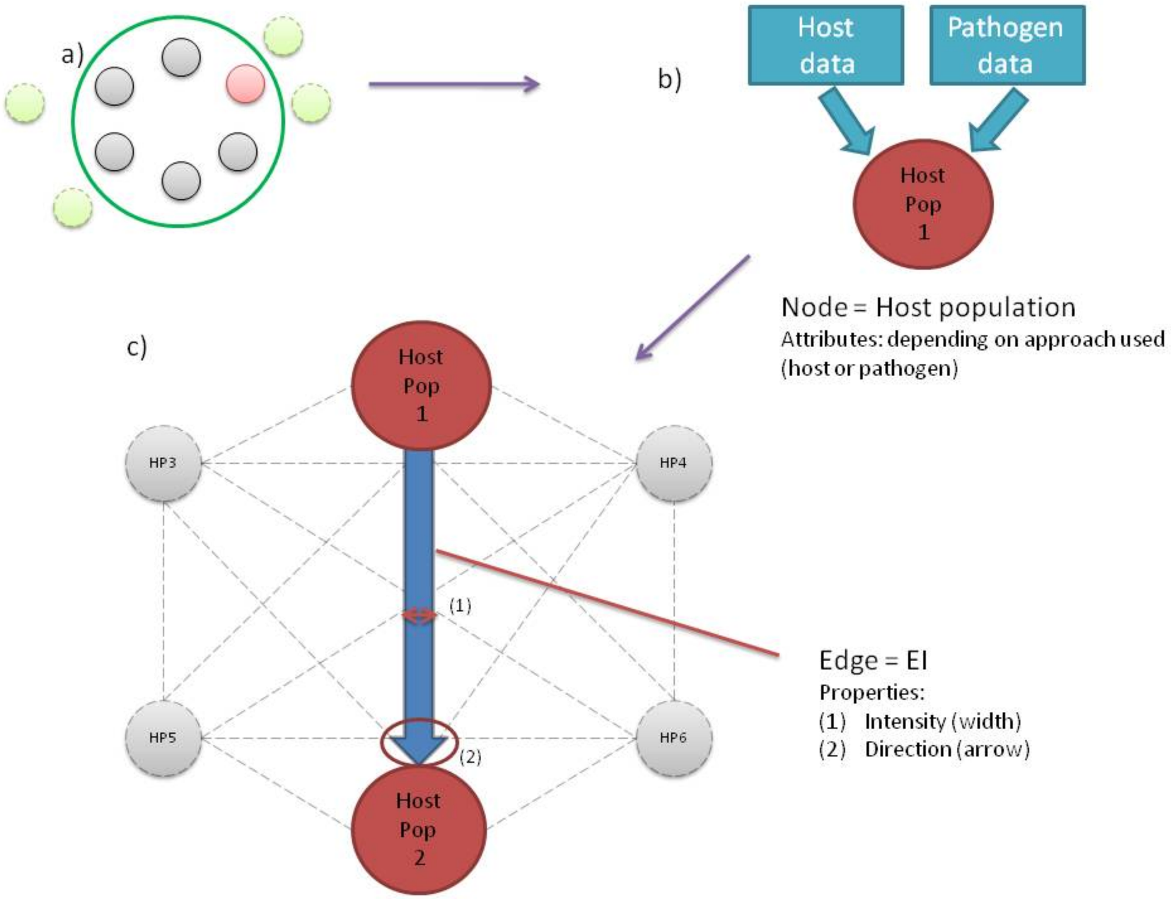


Figure A6.2: *Three-step process to build a EI network and its schematic representation: a) Six Host populations (HP; target – in red- and non-target) are selected in the ecosystem; b) Characterisation of the attributes of the nodes of each HP based on host or pathogen data; c) Zoom on 2 nodes which properties can be decided according to available information (see Box A6.1) and one edge characterised by its 2 properties: (1) Intensity represented by the width of the edge; (2) Direction represented by an arrow which could uni- or bidirectional.*



The EI network can be build using two different sources of data: host data or pathogen data. The host data consists in estimates of directs and indirect contacts between host populations. The pathogen data consists in the community of pathogens shared by different host populations. In the former case, the host contacts will be used as estimation of future pathogen spill-over and this approach can be called *a priori*. In the later case, pathogen transmissions that have already occurred will be used to estimate the potential pathways for future pathogen spill-over and the approach is in that case *a posteriori*.

The first step in the building of the EI network is to select which host and which pathogens are included in the study. The non-target host populations represent a range of wild and domestic species living in the same environment as the target species, and potentially acting as candidate source of pathogen. As it is usually impossible to obtain relevant data for all wild species in an area for practical and financial reasons, the selection of potential hosts can be prioritised, using available information: 1) Phylogenetic proximity (e.g. apes most closely related to human or wild bovids species most related to livestock species) is a known criteria to increase the chance of pathogen spill-over between two host species (Davies and Pedersen 2008); 2) Ecological knowledge on host species present in the study site; 3) Epidemiological information can orientate as well the selection process,. For example, bats species represent 25% of all mammal species despite being under-studied from an ecological point of view. They can be in contact for behavioural reasons – feeding, roosting - with different host species. They have also been involved in recent human EIDs epidemiology, notably in haemorrhagic fever events (Wang and Eaton 2007). If the target species is the human species, including bats in the study seems relevant if they occur in the ecosystem. Usually, as most studies focus on a specific or a group of pathogens, the selection of host populations is based on the available knowledge on the pathogen's host range. Caron et al. (submitted) have presented a framework for this selection process based on epidemiological functional groups of hosts. This framework offers a systematic step by step process to consider and select all potential hosts in a given ecosystem. In this selection process, available data about host contact (e.g. questionnaire-based) or pathogen prevalence (available through national studies) should be used to fine-tune the choice of host populations for the network.

*Estimating epidemiological interactions using host data (*a priori *approach)*

Estimates of contacts between the target population and one or more non-target populations can be used to build the EI network. Host movements and contacts can be monitored using different field techniques adapted to the level of study: individual, population or community.

Few empirical studies have considered contacts at the wildlife/livestock interface. At the individual host level, direct observation or telemetry can detect and quantify these contacts. For example, the development of satellite telemetry and the increase capacity of miniature batteries allow the study of animal movements with a large range of body sizes: up to a few grams for birds (Gaidet et al. 2008) at a very fine time-scale (up to a point every 5mn) for long periods (a year or more). Recent examples combining telemetry and density or visual observation techniques have successfully determined contact rate of individuals at the wildlife/livestock interface (Bohm et al. 2009, Perkins et al. 2009). The main weakness of these studies is the underestimation of contacts as it can never been assumed that the entire non-target population has been followed. This weakness can be partially controlled by objective or subjective knowledge of the study site but can never be completely addressed.

At the population or community level, estimates of overlaps in habitat used by different host populations or species (Ezenwa 2003, Kilpatrick et al. 2009) can be utilised as a proxy of interspecies contacts at different seasons. Data collected during road-counts or counts focusing on key resources or habitat (such as waterholes) on both sides of the interface, as well as trapping data (Caley and Hone 2004) provide a quantitative estimate of interspecies interactions which can be used to build an EI network. . A recent study attempted to estimate EIs in avian communities using bird count data in wild and domestic sites to predict the risk of Avian Influenza transmission at the wildlife/domestic interface (Chapter Three - Caron et al. 2010). Finally, local community questionnaire-based studies can also produce contact rate between host populations, paying particular attention in the design of the questionnaire and treating the information as perceptions and not facts (Brook et al. 2009).

The field of molecular epidemiology has experienced recent and major developments (Gupta et al. 2009). The amount of genetic data on host and pathogen species is produced at an exponential rate (Holmes 2007). Recent years have seen the development of powerful molecular tools to characterize specific pathogens and hosts. This host information supports the characterisation of the genetic distance between and among host species or populations (Nieberding and Olivieri 2007). Host population dynamics estimated by gene flow will be a particular case of population-level study to estimate contacts (see in this book Chevillon et al. 2011, Charbonnel et al. 2011). Molecular tools in this field have been developed and can give indication as fine as the parental relationship between individuals. This genetic data can provide fine information to build an EI network between populations of the same species, giving information on the intensity (or width) of edges as well as the direction of edges.

Most of host contact studies to estimate probabilities of pathogen transmission have been developed in the context of a specific pathogen. Our objective is to use the same tools to qualify and/or quantify EI with no *a priori* on the pathogen under study. As presented in Figure A6.2, after the first step of host selection, each node, representing a host population or species will be attributed characteristics: species and/or population information; and the number of host of the network in contact with the focal species/population (through habitat, resource overlap or direct contact). Edge intensity will be proportional to the estimation of the contact between the two hosts. Edge direction is usually not indicated except in particular circumstances. For example, species A only transiting in a particular habitat will not be infected in this habitat while species B feeding in this habitat could be infected through environmental contamination. Finally, successive EI networks can be built in order to account for temporal variability of contacts (e.g. seasons). The EI network will have to be interpreted with the same limits as the initial contact data: e.g. contacts between populations will be under-estimated.

*Estimating epidemiological interactions using the pathogen level (*a posteriori *approach)*

In the previous paragraph, we presented how host movement and contact data can be used to build an EI network. In the following paragraph, we will show how epidemiological data can also be used to build EI networks using an *a posteriori*, allowing the most likely pathways for the future emergence of new pathogens.

For each pathogen infecting more than one host population, we can estimate EIs; accumulating data on an array of different pathogens will strengthen the network. In other words, gathering epidemiological data on numerous pathogens in an ecosystem in different wild and domestic populations can structure the EI network between these populations and predict to a certain extent (discussed below) the behaviour of an outsider pathogen. The type of data referred to here as already been collected in various studies, albeit not used for this purpose. Jolles et al. 2008 collected data on micro- and macroparasite species in buffaloes in South Africa to investigate potential ecological interactions (competition, synergies) between pathogens in a single host. In another study, Ezenwa 2003 looked at macroparasite richness in sympatric wild and domestic ungulates, and analysed their variations according to habitat overlap between host species. Other studies dealing with the health status of some endangered species, a parameter increasingly investigated in species conservation, can also produce relevant information on free-ranging species (Philippa et al. 2008).

Parasite community ecology is a subset of community ecology focusing on the distribution of parasites between host populations. Large datasets of parasites (mostly macroparasite) in multi-hosts systems have been collected in the course of these studies (see (Poulin 2007 for a review). Several indices have been used to compare parasite communities between host populations (Poulin 2003, 2010). The Jaccard index (Jaccard 1912) uses presence-absence data of parasites in different host populations to give an indicator of the similarity of these communities. Other indices, more sophisticated, use prevalence data to compare parasite community (Boyle et al. 1990, Poulin 2007). In the context of host populations from the same ecosystem, the geographic distance between the host populations is controlled (geographic distances usually looked at in parasite community ecology are of the order of hundreds or thousands of kilometres). If the phylogenetic distance between host populations can be controlled, the similarities measured can estimate the EI between these host populations. These indices can therefore be used to build EI network as the value of the index between two parasite communities shared by two host populations (their similarity). Analytical tools to control for phylogentic distances between hosts are already used and new ones are under development incorporating sophisticated statistical analyses (Adams 2008; Hadfield and Nakagawa, 2010).

History of contacts between host populations is another variable to be considered (see discussion). The type of the epidemiological data that one can gather varies depending on the pathogens targeted and the investment of the scientific and private community into the development of specialised diagnostic tools. Presence-absence data are the simplest data that one can gather on pathogen epidemiology in a singular host, and is often the only available information from the literature. Prevalence data (direct through pathogen detection or indirect through antibody detection) provides the percentage of hosts in each population which have been or are in contact with the pathogens. As mention above, this type of data can be included in the calculation of similarity indices borrowed from community ecology (Boyle et al. 1990, Poulin 2007).

As presented in the previous section, the molecular epidemiology revolution has changed the field of parasite ecology and new genetic information is providing the ground for major advances in pathogen research, evolutionary ecology and population dynamics of pathogens. The characterisation of HIV strains from different human and great apes populations or even from different human individuals has brought important development on our knowledge about the origin and the spread of this pathogen across the world (Heeney et al. 2006, Cohen 2007, Gilbert et al. 2007). Another example is the abundant recent literature on phylogenetic analyses of HPAI H5N1 strains across the globe linking animal and human outbreaks (see Wang et al. 2008, Cattoli et al. 2009 for HPAI H5N1 and Nelson et al. 2007, Liu et al. 2009 for AIV). Other important pathogens have benefited from these technological advances (for some examples on multi-host utilisation (Bastos et al. 2003, Vosloo et al. 2006, Foster et al. 2009). The level of accuracy to detect single nucleotide change in parasite genomes of these molecular tools is increasing and their use at the ecosystem level can pick-up recent transmission events including their direction. Biek et al. 2006 have used the Feline Immunodefficiency virus (FIV) to track the population dynamics of one of its host (*Puma concolor*). Haagmans et al. 2009 highlight this point with another angle and suggest to compare the outcomes of an EIDs outbreak with “closely related pathogens in different but related host species (...)”. The evolution of parasites is often faster than the evolution of their hosts (Nieberding and Olivieri 2007). Recent host population dynamics not detected in the host genetic material can be captured by the faster genetic evolution of its parasites. Applied to our context, a phylogenetic tree of the same parasites detected in different host populations in the same ecosystem can reveal connexions between these host populations and give an estimate of the EIs between these host populations for this specific pathogen. The molecular tools can be used to characterise EIs. It is likely that in the coming years additional data on genetic of parasites and new analytical methods will provide more power in the estimation of EIs between host populations. Transmission pathways between host populations and EI network will be strengthened by these advances (Chevillon et al. 2011).

Replicating the multi-step process developed in Figure A6.2 and in the previous section, once the host selection has been implemented in the ecosystem, each node representing a host population can be characterised by the total number of parasite species harboured (nodes property represented by its size) and other attributes (e.g. in Box A6.1, the colour of the node is used to indicate in which habitat the host species is mainly occurring). To estimate the intensity of the edge (its width), we use the value of the index calculating the proportion of the parasites shared between two host populations/species. In very rare occasions where knowledge about the epidemiology of some parasites exists, the direction of the EI could be known: e.g. when a species known to be susceptible but not capable of maintaining a parasite is infected by a known reservoir of the parasite. Molecular data can potentially inform EIs on both their properties: intensity, as molecular data can be used as prevalence data (e.g. prevalence for different strains of parasites); direction, the evolution of a parasite strain between two host populations can be tracked back and the donor population can be distinguished from the receptor population. Finally, if time series data is available different network can estimate the variation of EIs across seasons (time series used to infer transmission dynamics between hosts see Begon et al. 1999.

So far, the use of these epidemiological and molecular tools has been limited to one target pathogen and only a few articles have referred to the extension of their use to several pathogens, to host population dynamics, or to contacts between hosts (Poss et al. 2002). At an ecosystem level, it is the combined use of presence-absence, prevalence and molecular data on multiple pathogens which will define EI networks. The integration of different type of data for different parasite species will be a challenge in the framework of this approach. Prevalence data will give more fine-scale details about the shared community of pathogens than presence/absence data as for each host population, the estimated percentage of individuals in the population infected by the parasite will be taken into account in the index. Molecular data can give even more details about how long ago the parasite strain was transmitted form one host to the other. To our knowledge, the only possibility to integrate this data in one network is to weight each type of data (e.g. giving more weight to molecular, then prevalence and finally presence/absence data). The more data gathered on various pathogens, the more detailed the hypotheses on future EIDs epidemiological pathways.

For example, de Garine-Wichatitsky et al. 2010 (Appendix Three) have recently detected the first case of bovine tuberculosis (bTB) in African buffaloes in a Zimbabwean national park and discussed the outcomes of this emergence at the country level. How will the pathogen behave in this ecosystem? Will it spill-over to the communal cattle populations? To other wildlife species? To the human population? Data on circulating diseases (zoonoses and others) in this area (e.g. foot-and-mouth disease, brucellosis, rift valley fever etc.) can bring information on the structure of the EI network. The network and other epidemiological knowledge about parasites can be used to prioritize the nodes or edges at risk. One can consider interventions on the nodes (host) of the network for surveillance and/or control but also on the edges (EIs) to “break” the transmission pathways and limit the potential for emergence. If not detailed here, the relation between an EI network and a spatially explicit approach can be done.

Discussion

The discussion will mainly address the pathogen approach as the host approach is at advance stage of development in the literature.

From an epidemiological perspective, usually investigating one epidemiological cycle at a time, the EI network approach that we present makes no sense. The epidemiology of each disease is different and one cannot draw inferences on a pathogen using data from another. However, from an ecological perspective, the line of thoughts is logical even if challenging. There is not an infinite opportunities for a pathogen to be transmitted between two host populations and new pathogens will use routes already used by other pathogens with a higher probability. Identifying common pathways between host populations will therefore increase the knowledge about future probable emergence pathways in this system. This pathogen approach does not refer to a specific pathogen and focuses on the hosts' direct and indirect contacts but only the ones resulting in pathogen transmission. The utility of such an approach is obvious in the surveillance of EIDs in a hotspot: with an EI network, one can assess the probability of future spill-over processes between specific populations and target surveillance and/or control. In a limited-resource environment (true everywhere but even more in most EID hotspots), EI networks will point at most probable transmission pathways between host populations which can be acted upon to reduce the probability of transmission/emergence.

Box A6.1 (adapted from Chapter Six) gives an example of an EI network built using presence-absence data of macro- and micro- parasites in 14 rodent species and the human species. The data has been gathered from the literature. Using a simple method to describe the parasite communities shared by each pair of host populations, the EI network illustrates the intensity of each edge proportional to its width, the parasite species richness per host and the main habitat where each host occurs. Eco-epidemiological information such as which rodent host shares a high proportion of its parasite species with humans are visually explicit and new hypotheses about key-rodent species are presented. These observations suggest that the EI network is representative of the level of contacts between the human species and the rodent species. Finally, combining this (crude) epidemiological and ecological information in a single analysis provide more information about the system than a simple juxtaposition of single parasite information.

***<u>Box A6.1</u>**: Epidemiological Interaction Network for 14 rodent species and the human species*

In this example, the human species is our target species and we explore the EIs between the human species and several rodent species present in particular ecosystems of Southeast Asia represented by different habitats (dry and irrigated agricultural areas, forests, and villages).

From the literature (Chaisiri et al. 2010, Herbreteau et al. unpublished), we obtained presence-absence data on 14 rodent species. Information about 34 macroparasite species and 8 microparasite species were collected for these 14 rodent species and susceptibility to these parasites for the human species were taken from Chaisiri et al. (2010) and Herbreteau et al. (unpublished) (Table A6.1). A 42 parasites*15 hosts matrix was built (and filled with “1” or “0” for occurrence of infection and absence respectively in each host species. This matrix was used to calculate the Jaccard Index (=number of parasite species present in both host populations/sum of parasite species present in each host populations) displayed in Table A6.2. The Jaccard index value varies therefore between “0” for no parasite species shared and “1” for all parasite species shared.

We used the Jaccard index as a proxy of the epidemiological interactions (EIs) between each host population and built the corresponding EI network (Figure A6.3).

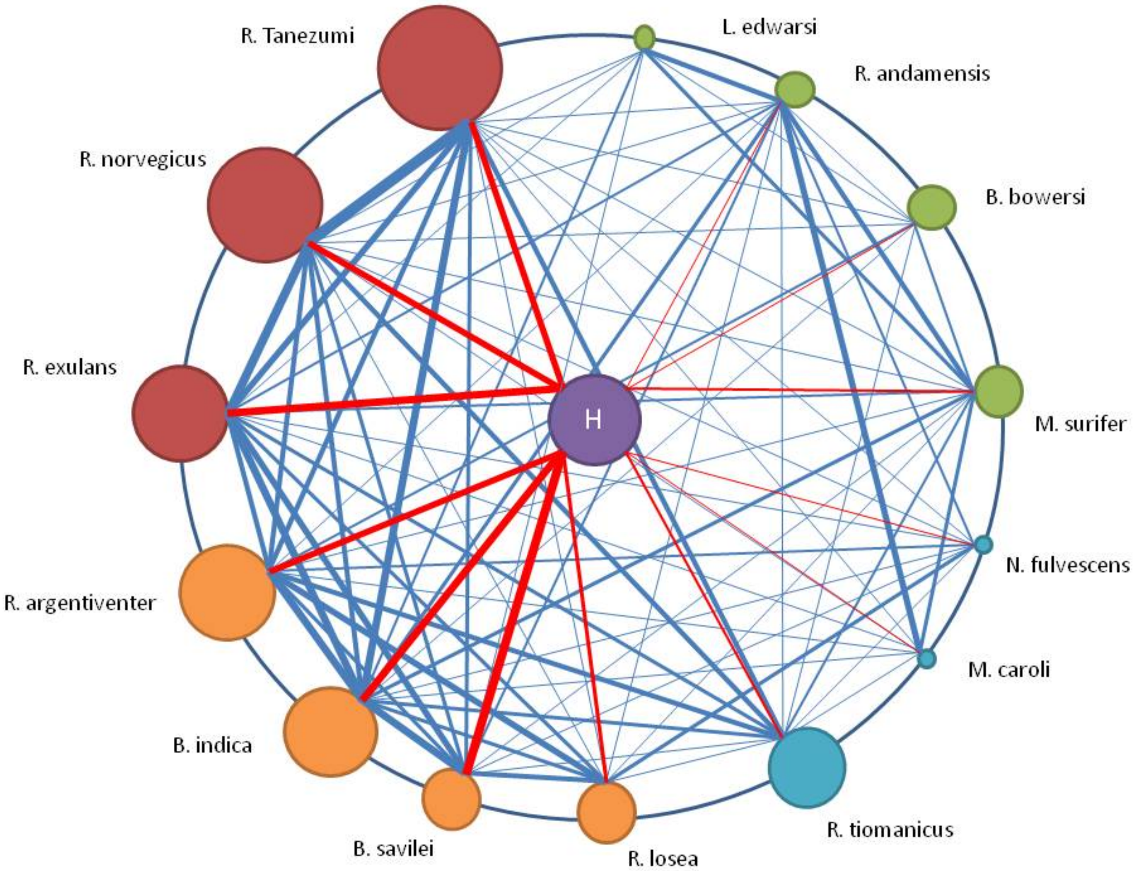
Table A6.1: *Host and parasite species used*

Target sp.	*Homo sapiens*
Rodent sp.	*Bandicota indicata (Bi), Bandicota savilei (Bs), Verylmys bowersi (Bb), Leopoldamys edwardsi (Le), Maxomys surifer (Ms), Mus caroli (Mc), Niviventer fulvescens (Nf), Rattus andamanensis (Ran), Rattus argentiventer (Rar), Rattus exulans (Re), Rattus losea (Rl), Rattus norvegicus (Rn), Rattus tanezumi (Rta), Rattus tiomanicus (Rti)*
Macroparasite sp.	*Hymenolepis nana, Rodentolepis sp., Taenia sp., Taenia taeniaeformis, Ascaris sp., Gnathostoma malaysiae, Ganguleterakis spumosa, Citellina levini, Syphacia muris, Physaloptera sp., Rictularia sp., Rictularia tani, Gongylonema neoplasticum, Mastophorus muris, Protospiura-Mastophorus sp., Cyclodontostomum purvisi, Strongyloides ratti, Strongyloides sp., Nippostrongylus brasillensis, Nippostrongylus sp., Orientostrongylus tenorai, Echinostoma ilocanum, Echinostoma malayanum, Notocotylus sp., Quinqueseralis quinqueseralis, Gastrodiscoides hominis, Centrocestus sp.*
Microparasite sp.	Leptospira, scrub typhus, Bartonella, hanta virus, herpes virus, LCM virus, Trypanosoma, rabies virus.

Table A6.2*: Matrix of Jaccard index for all pairs of host populations; habitat type for rodent species is mentioned: 1=in human settlements; 2=in rice fields; 3=in modified forest and dry agricultural areas; 4=in primary forest; the number of parasite species (Nb of para) per host is also indicated.*

	Nb Para	**Bi**	**Bs**	**Bb**	**Le**	**Ms**	**Mc**	**Nf**	**Ran**	**Rar**	**Re**	**Rl**	**Rn**	**Rta**	**Rti**	**Hs**
Bi	**16**															
Bs	**9**	0,47														
Bb	**7**	0,15	0,00													
Le	**3**	0,12	0,09	0,11												
Ms	**8**	0,20	0,06	0,15	0,22											
Mc	**2**	0,06	0,00	0,00	0,00	0,25										
Nf	**2**	0,06	0,10	0,00	0,00	0,00	0,00									
Ran	**5**	0,24	0,17	0,09	0,33	0,30	0,40	0,17								
Rar	**17**	0,43	0,24	0,14	0,00	0,09	0,06	0,12	0,10							
Re	**18**	0,48	0,35	0,00	0,11	0,13	0,05	0,05	0,15	0,30						
Rl	**9**	0,19	0,29	0,00	0,00	0,06	0,00	0,22	0,08	0,37	0,23					
Rn	**23**	0,34	0,23	0,03	0,04	0,07	0,04	0,09	0,08	0,33	0,52	0,19				
Rta	**32**	0,45	0,24	0,11	0,06	0,14	0,03	0,06	0,09	0,32	0,47	0,17	0,72			
Rti	**13**	0,26	0,05	0,05	0,00	0,17	0,07	0,07	0,06	0,36	0,24	0,10	0,33	0,36		
Hs	**15**	0,48	0,50	0,05	0,06	0,21	0,06	0,06	0,18	0,28	0,43	0,20	0,41	0,42	0,17	

__Figure A6.3__: *Epidemiological Interaction Network for 14 rodent species and the human species in the Southeast Asian ecosystems based on presence-absence data for 34 macroparasite species and 8 microparasite species. Each node represents a host species, the size of the node is proportional to the number of parasite species harbored by the host and the color of the circle represents the habitat in which the host species is mostly found (except for human): red=in human settlements; orange=in rice fields; blue=in modified forest and dry agricultural areas; green=in primary forest. Each edge between two nodes represents the shared parasite community and its width is proportional to the Jaccard index. We placed the human species in the centre of the figure and its edges in red for visual comfort.*



The analysis of this network leads to the following observations:

- Interpreting the size of the nodes, the three rodent species with the highest parasite diversity are occurring in human settlements. The three rodent species with the lowest parasite diversity occur in primary or secondary forests and dry agricultural land.

- The size of the human species node indicates that we share 15 parasite species with rodent species studied here.

- Interpreting the width of the edges at the network level, there is a higher density of large-width edges on the left of the network, indicating that rodent species in human settlements and rice-fields share a higher proportion of their parasite diversity than rodent species in the remaining habitats.

- Interpreting the width of the edges concerning the human species, Bi and Bs have the highest Jaccard index values (0.48 and 0.5 respectively), followed by Re, Rta and Rn (0.43, 0.42, 0.41 respectively).

- The nodes of Bi, Ran, Rn and Rta have the maximum number of edges (n=14) possible in this network. They all occur in human settlements, rice fields except for Ran occurring in primary forest. The nodes of Bb, Le and Mc have the lowest number of edges in the network (n=9) and they all belong to primary and secondary forest or dry agricultural areas.

- The node of the human species has 13 edges close to the maximum of 14.

The method of calculus of the index needs to be kept in mind: the observation that Bi and Bs share more parasites with the human species than Rta and Rn is wrong. The human species shares more parasite species with Rn and Rta than with Bi and Bs (11, 14, 10, 8 respectively). The difference is due to the high parasite species richness of Rn and Rta. Other indices can be used to address this kind of issue but no index is perfect. The highest intensities of EI are found in rodent species present in heavily disturbed habitat (human settlement and rice fields) and the highest intensities of EI linking the human species with rodent species are also found with rodent species living in these same habitats. This observation suggests that humans are more at risk of contracting new pathogens from rodents present in the human settlement compared to rodents present in primary forest. The availability and patchiness of resources in human modified environment could explain the higher EI intensity in rodent species living in these environments.

This first network can orientate surveillance protocols towards the most interesting host species to be included in order to answer the question at stake: if the question is the probability of EID from rodent host in this ecosystem, the surveillance protocol will target species living in the human settlements (and a ranking can be done on this species) and in the rice fields with maybe Rti being an interesting sentinel species to look at as a bridge species between pristine and modified environment. To our knowledge, this species is never mentioned as a potential source of infectious disease or as a sentinel in the literature. If one is more interested in the potential emergence of pathogens in rodent species, Ran which shares parasite species with all the other rodent species and humans and lives mostly in primary forests should be considered as a potential source.

In several practical situations, scientists and managers will be concerned by the possible emergence of a specific pathogen in a given ecosystem and for a specific target species. In that case, they should target closely related pathogens or some with similar behaviour (transmission pathways, host range) in order to delineate a more specific EI network. This step can be done by creating a sub-network with the selected pathogens or by weighting the influence of some pathogens in the network. Other *a priori* conditions could be a research question targeting a type of emerging pathogen to look for (e.g. haemorrhagic fevers). For example, several authors have argued that future EIDs will concern in majority RNA virus-type pathogens, due to inherent viral characteristics such as high mutation rate (Poss et al. 2002, Holmes and Rambaut 2004, Cleaveland et al. 2007). The design of a research framework focusing on emerging RNA viruses will select pathogens with similar mode of transmission (other RNA viruses for example) which should use the same EIs. This could be done by focusing the EI network with information from parasites phylogenetically related to the potentially emerging parasite of interest (e.g. separating viruses, bacteria, macroparasites, etc.) and/or sharing the same mode(s) of transmission. The later seems to bear more power than the former, but this will need to be tested. This approach is process orientated and the modes of transmission of parasite will be crucial in determining the transmission pathways between host populations. Groups of parasite with direct, environmental or vector-born transmission could *a priori* produce different EI networks. Three outcomes emerge from empirical data: 1) each EI network is specific for each parasite species and the EI network approach is somehow useless; 2) they are functional groups of parasite sharing a similar EI network (e.g. based on their modes of transmission); 3) EI network are general and produce a transmission framework for all parasite species given that the network is fed with data from enough parasite species. In the case study of Box A6.1, sub-network could be explored comparing macro- and microparasites EI network or regrouping parasite by modes of transmission and comparing the corresponding sub-network.

Another argument in favour of the inclusion of all types of parasites in the building of EI network using the *a posteriori* approach is that there is no independence between the parasite data from various hosts (Jolles et al. 2006). Each parasite species is in struggle with the host immunity system and in ecological interaction (e.g. direct competition, synergy or indirect through the host immune system) with the other parasites. The community of parasites in the ecosystem will have its own ecological interactions defined by host and parasite presence and densities (Booth and Dunne 2004, Bordes and Morand 2009). Despite some interesting recent results (Graham 2008, Jolles et al. 2008), co-infections of parasites in host populations have not been much explored. The patterns of co- occurrence or exclusion between parasites in hosts are *de facto* included in EI networks and will not create issues for their interpretation. Developing EI network will provide more information on parasite interaction in hosts.

Host populations in the same ecosystem for long periods of time should share more parasites than host populations which have recently come into contact. Here, “recently” refers to a period of time during which host populations did not have time to exchange most of their parasite species. Evolutionary processes should be close to equilibrium in co-evolved host-pathogen interaction (e.g. for Low Pathogenic Influenza viruses and waterfowl, Webster et al. 1992) and the EI network identified quite robust. As time since hosts have been in contact increases, potential transmission events with low probability will statistically increase. In the EID hotspots considered, the time since first contact between a target and a non-target population should be small: human and great apes due to hunting or tourism; livestock and wild ungulates in pristine areas recently colonised; intensive poultry production units recently installed in proximity of wetlands used by wild birds. In EIDs hotspots, by definition, (human-induced) changes disturb ecological interactions in communities. In this context, the EI identified could be instable (Alitzer et al. 2003, Thomson 2005) and prone to change leading to an evolving EI network. In this context, the *a priori* approach, using host movements and contacts could be used. The *a posteriori* approach will be more difficult to implement in extremely recent interface. However, a few years should be enough for the shared community of parasites to reach a relative equilibrium.

More information could be added in the EI network presented in Box A6.1. First, some of the parasites used, mainly microparasites such as Leptospira or Hanta viruses, have benefited from molecular tools able to track minute changes in their genetic load. As mentioned already microparasites are fast evolving organisms compared to their hosts (Poss et al. 2002, Holmes and Rambaut 2004). This can be useful in tracking the origin of infection between different populations, capturing the history of spill-over process at a fine scale. A phylogenetic tree of the parasites strains detected in different host populations could bring information on the directionality of some EI and indicates rodent species as source or reservoir for the rest of host community (for an example see Cottam et al. 2008). Secondly, data from the host population, as presented previously, such as home range or telemetry data could be included to incorporate potential direct and indirect contact between host populations and related to EI identified in the pathogen approach. This would combine the host and pathogen approaches.

Conclusion

After presenting how the use of host data can shed light on transmission pathways between host populations, we developed a multi-pathogen approach, process-centred, to infer epidemiological interaction at the wildlife/livestock/human interface. Theoretical and technical tools for this approach have already been developed but they are used with a different angle here. Epidemiological data on various pathogens are integrated in a network to predict the behaviour of EIDs, in particular before the emergence event. The reflexion about this approach comes from an empirical point of view, from experiences in areas of limited resources (financial and available data) and tries to answer practical questions of surveillance and control of EIDs where we know that they have a high probability to happen (EID hot spots). The scale of study – the community level – is extremely complex but we suggest that we could benefit from this scale in a resource limited environment.

Albeit empirical, this reflexion links with the modelling approach by concentrating on processes of transmission. The data produced should feed some models (e.g. Arino and van den Driessche 2006) and maybe push the building of models towards including multi-pathogen data to construct EI networks. Network-based modelling can be an entry point with the potential to include social data, facilitating the inclusion of human/animal transmission processes (Perkins et al. 2009, Van Kerkhove et al. 2009).

The context of EIDs in developing countries is an environment where usually little epidemiological data is available except for key diseases, important for government services: if existing data on a pathogen brings light on contacts between two host species, this builds a starting point in the EI network. The gathering of ecological and epidemiological information available for the ecosystem under study, obtained from different sources (e.g. literature, veterinary services, conservation NGOs) can be included in a preliminary EI network which could identify the first surveillance priorities to protect the target species following for example a risk analysis process. The inclusion of the epidemiology of several pathogens in the analysis should explore the results of shared prevalence or strains in relation to the specific modes of transmission. If molecular data exists for a pathogen, the comparison of this data across host populations can say a lot about the history of contacts between these hosts and about the intensity and the frequency of contacts (Real et al. 2005, Biek et al. 2006).

From a more practical point of view, one could argue that such an approach would be too costly to be funded mainly due to the multiplicity of diagnostic tests which can peak quickly when gene sequencing is needed. The cost of sampling wildlife species in remote areas is high. Specialised team working on particular diseases will be more than willing to collaborate and contribute in terms of laboratory cost in order to access such rare samples. This requires prior communication and agreement with interested teams and logistical arrangements for the right samples to be collected and delivered to laboratories. The accumulation of such collaborations will increase the multi-pathogen data and strengthen the EI network. Multidisciplinarity inter- and intra- research team is a prerequisite for this approach.

Finally, if the EI concept survives the test of empirical data, it means that it exists epidemiological "tubes" between different host populations identifying the "highways" of transmission of parasites, ready to be used by the next EIDs. Exploration of this concept can bring new insights in the ecology of disease transmission.

Literature Cited

Adams, D.C. (2008). Phylogenetic meta-analysis. Evolution 62, 567–572.

Alitzer, S., D. Harvell, and E. Friedle. 2003. Rapid evolutionary dynamics and disease threats to biodiversity. Trends in Ecology and Evolution **18**:589-596.

Arino, J., J. R. Davis, D. Hartley, R. Jordan, J. M. Miller, and P. van den Driessche. 2005. A multi-species epidemic model with spatial dynamics. Mathematical Medecine and Biology **22**:129-142.

Arino, J., and P. van den Driessche. 2006. Disease Spread in Metapopulations. Pages 1-12 Fields Institute Communications.

Bansal, S., B. T. Grenfell, and L. A. Meyers. 2007. When individual behaviour matters: homogeneous and network models in epidemiology. Journal of the Royal Society Interface **4**:879-891.

Barclay, E. 2008. Predicting the next pandemic. Lancet **372**:1025-1026.

Bastos, A. D., E. C. Anderson, R. G. Bengis, D. F. Keet, H. K. Winterbach, and G. R. Thomson. 2003. Molecular epidemiology of SAT3-type foot-and-mouth disease. Virus Genes **27**:283-290.

Begon, M., S. M. Hazel, D. Baxby, K. Bown, R. Cavanagh, J. Chantrey, T. Jones, and M. Bennett. 1999. Transmission dynamics of a zoonotic pathogen within and between wildlife host species. Proceedings of the Royal Society Series B **266**:1939-1945.

Biek, R., J. Alexei, J. Drummond, and M. Poss. 2006. A Virus Reveals Population Structure and Recent Demographic History of Its Carnivore Host. Science **311**:538-541.

Bohm, M., M. R. Hutchings, and P. C. White. 2009. Contact networks in a wildlife-livestock host community: identifying high-risk individuals in the transmission of bovine TB among badgers and cattle. PLoS One **4**:e5016.

Booth, M., and D. W. Dunne. 2004. Spatial awareness in parasite immuno-epidemiology. Parasite Immunology **26**:499-507.

Bordes, F., and S. Morand. 2009. Parasite diversity: an iverlokked metric of parasite pressures? Oikos **118**:801-806.

Boyle, T. P., G. M. Smillie, J. C. Anderson, and D. R. Beeson. 1990. A sensitivity analysis of nine diversity and seven similariry indices. Research Journal of the Water Pollution Control Federation **62**:749-762.

Brook, R. K., S. J. Kutz, A. M. Veitch, R. A. Popko, B. T. Elkin, and G. Guthrie. 2009. Fostering community-based wildlife health monitoring and research in the Canadian North. EcoHealth **6**:266-278.

Caley, P., and J. Hone. 2004. Disease transmission between and within species, and the implications for disease control. Journal of Applied Ecology **41**:94-104.

Caron, A., M. de Garine-Wichatitsky, N. Gaidet, N. Chiweshe, and G. S. Cumming. 2010. Estimating dynamic risk factors for pathogen transmission using community-level bird census data at the wildlife/domestic interface. Ecology and Society **15**:25.

Caron, A., M. de Garine-Wichatitsky, and S. Morand. (submitted). The ecology of emerging disease transmission in multi-host systems.

Cattoli, G., I. Monne, A. Fusaro, T. M. Joannis, L. H. Lombin, M. M. Aly, A. S. Arafa, K. M. Sturm-Ramirez, E. Couacy-Hymann, J. A. Awuni, K. B. Batawui, K. A. Awoume, G.

L. Aplogan, A. Sow, A. C. Ngangnou, I. M. El Nasri Hamza, D. Gamatie, G. Dauphin, J. M. Domenech, and I. Capua. 2009. Highly pathogenic avian influenza virus subtype H5N1 in Africa: a comprehensive phylogenetic analysis and molecular characterization of isolates. PLoS ONE **4**:e4842.

Chaisiri, K., W. Chaeychomsri, J. Siruntawineti, F. Bordes, V. Herbreteau, and S. Morand. 2010. Human-dominated habitats and helminth parasitism in Southeast Asian murids. Parasitology Research.

Childs, J. E., J. A. Richt, and J. S. Mackenzie. 2007. Introduction: Conceptualizing and Partitioning the Emergence Process of Zoonotic Viruses from Willdife to Humans. Pages 1-31 *in* J. E. Childs, J. S. Mackenzie, and J. A. Richt, editors. Wildlife and Emerging Zoonotic Diseases: The Biology, Circumstances and Consequences of Cross-Species Transmission. Springer, Heidelberg.

Cleaveland, S., D. T. Haydon, and L. Taylor. 2007. Overview of Pathogen Emergence: Which Pathogens Emerge, When and Why? Pages 85-111 *in* J. E. Childs, J. S. Mackenzie, and J. A. Richt, editors. Wildlife and Emerging Zoonotic Diseases: The Biology, Circumstance and Consequences of Cross-Species Transmission. Springer, Heidelberg.

Cleaveland, S., M. K. Laurenson, and L. H. Taylor. 2001. Diseases of humans and their domestic mammals: Pathogen characteristics, host range and the risk of emergence. Proceedings of the Royal Society of London Series B **356**:991-999.

Cohen, J. 2007. Reconstruction of the origins of the AIDS epidemic from archived HIV isolates. Science **318**:731.

Cottam, E. M., G. Thebaud, J. Wadsworth, J. Gloster, L. Mansley, D. J. Paton, D. P. King, and D. T. Haydon. 2008. Integrating genetic and epidemiological data to determine transmission pathways of foot-and-mouth disease virus. Proceedings of the Royal Society of London Series B **275**:887-895.

Daszak, P., A. A. Cunningham, and A. D. Hyatt. 2001. Anthropogenic environmental change and the emergence of infectious diseases in wildlife. Acta Tropica **78**:103-116.

de Garine-Wichatitsky, M., A. Caron, A. Gomo, C. Foggin, K. Dutlow, D. Pfukenyi, E. Lane, S. Le Bel, M. Hofmeyr, T. Hlokwe, and A. Michel. 2010. Bovine tuberculosis in Buffaloes, Southern Africa. Emerging Infectious Diseases **16**:884-885.

Ezenwa, V. O. 2003. Habitat overlap and gastrointestinal parasitism in sympatric African bovids. Parasitology **126**:379-388.

Foster, J. T., S. M. Beckstrom-Sternberg, T. Pearson, J. S. Beckstrom-Sternberg, P. S. Chain, F. F. Roberto, J. Hnath, T. Brettin, and P. Keim. 2009. Whole-genome-based phylogeny and divergence of the genus Brucella. Journal of Bacteriology **191**:2864-2870.

Gaidet, N., G. Cattoli, S. Hammoumi, S. H. Newman, W. Hagemeijer, J. Y. Takekawa, J. Cappelle, T. Dodman, T. Joannis, P. Gil, I. Monne, A. Fusaro, I. Capua, S. Manu, P. Micheloni, U. Ottosson, J. H. Mshelbwala, J. Lubroth, J. Domenech, and F. Monicat. 2008. Evidence of Infection by H5N2 Highly Pathogenic Avian Influenza Viruses in Healthy Wild Waterfowl. PLoS Pathogens **4**:e1000127.

Gibbs, E. P. J., and T. C. Anderson. 2009. 'One World - One Health' and the global challenge of epidemic diseases of viral etiology. Veterinaria Italiana **45**:35-44.

Gilbert, M. T. P., A. Rambaut, G. Wlasiuk, T. J. Spira, A. E. Pitchenik, and M. Worobev. 2007. The emergence of HIV/AIDS in the Americas and beyond. Proceedings of the National Academy of Sciences of the USA **104**:18566-18570.

Goldberg, T. L., T. R. Gillespie, I. B. Rwego, E. L. Estoff, and C. A. Chapman. 2008. Forest fragmentation as cause of bacterial transmission among nonhuman primates, humans, and livestock, Uganda. Emerging Infectious Diseases **14**:1375-1382.

Graham, A. L. 2008. Ecological rules governing helminth-microparasite coinfection. Proceedings of the National Academy of Sciences of the USA **105**:566-570.

Gupta, R., M. H. Michalski, and F. R. Rijsberman. 2009. Can an infectious disease genomics project predict and prevent the next pandemic? PLoS Biology **7**:e1000219.

Haagmans, B. L., A. C. Andeweg, and A. D. Osterhaus. 2009. The application of genomics to emerging zoonotic viral diseases. PLoS Pathogens **5**:e1000557.

Haydon, D. T., S. Cleaveland, L. H. Taylor, and M. K. Laurenson. 2002. Identifying Reservoirs of Infection: A Conceptual and Practical Challenge. Emerging Infectious Diseases. **8**:1468-1473.

Heath, M. F., M. C. Vernon, and C. R. Webb. 2008. Construction of networks with intrinsic temporal structure from UK cattle movement data. BMC Veterinary Research **4**.

Heeney, J. L., A. G. Dalgeish, and R. A. Weiss. 2006. Origins of HIV and the evolution of resistance to AIDS. Science **313**:462-466.

Holmes, E. C. 2007. Viral Evolution in the Genomic Age. PLoS Biology **5**:e278.

Holmes, E. C., and A. Rambaut. 2004. Viral evolution and the emergence of SARS coronavirus. Proceedings of the Royal Society of London Series B **359**:1059-1065.

Jaccard, P. 1912. The distribution of the flora in the alpine zone. New Phytologist **11**:37-50.

Jolles, A. E., R. S. Etienne, and H. Olff. 2006. Independent and Competing Disease Risks: Implications for Host Populations in Variable Environments. The American Naturalist **167**:745-757.

Jolles, A. E., V. O. Ezenwa, R. S. Etienne, W. C. Turner, and H. Olff. 2008. Interactions between macroparasites and miccroparasites drive infection patterns in free-ranging African buffalo. Ecology **89**:2239-2250.

Jones, K. E., N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman, and P. Daszak. 2008. Global trends in emerging infectious diseases. Nature **451**:990-994.

Karesh, W. B., and S. L. Deem. 2000. Conservation medicine: a veterinary perspective. Conservation Biology **14**:336-337.

Kilpatrick, A. M., C. M. Gillin, and P. Daszak. 2009. Wildlife-livestock confllict: the risk of pathogen transmission from bison to cattle outside Yellowstone National Park. Journal of Applied Ecology **46**:476-485.

Leroy, E. M., B. Kumulungui, X. Pourrut, P. Rouquet, A. Hassanin, P. Yaba, A. Délicat, J. T. Paweska, J.-P. Gonzalez, and R. Swanepoel. 2005. Fruit bats as reservoirs of Ebola virus. Nature **438**:575-576.

Liu, S., K. Ji, J. Chen, D. Tai, W. Jiang, G. Hou, J. Chen, J. Li, and B. Huang. 2009. Panorama phylogenetic diversity and distribution of Type A influenza virus. PLoS ONE **4**:e5022.

Lloyd-Smith, J. O., D. George, K. M. Pepin, V. E. Pitzer, J. R. C. Pulliam, A. P. Dobson, P. J. Hudson, and B. T. Grenfell. 2009. Epidemic dynamic at the human-Animal interface. Science **326**:1362-1367.

Luke, D. A., and J. K. Harris. 2007. Network analysis in public health: history, methods, and applications. Annual Review of Public Health **28**:69-93.

McCallum, H., N. Barlow, and J. Hone. 2001. How should pathogen transmission be modelled? Trends in Ecology and Evolution **16**:295-300.

Morgan, E. R., M. Lundervoldb, G. F. Medleyb, B. S. Shaikenovc, P. R. Torgersond, and E. J. Milner-Gullande. 2006. Assessing risks of disease transmission between wildlife and livestock: The Saiga antelope as a case study. Biological Conservation **131**:244-254.

Nelson, M. I., L. Simonsen, C. Viboud, M. A. Miller, and E. C. Holmes. 2007. Phylogenetic Analysis Reveals the Global Migration of Seasonal Influenza A Viruses. PLoS Pathogens **3**:e131.

Osofsky, S. A., H. M. Cumming, and M. D. Kock. 2008. Transboundary Management of Natural Resources and the Importance of a "One Health" Approach.*in* E. Fearn, editor. State of the Wild: A global Portrait of Wildlife, Wildlands, and Oceans. Island Press.

Perkins, S. E., F. Cagnacci, A. Stradiotto, D. Arnoldi, and P. J. Hudson. 2009. Comparison of social networks derived from ecological data: implications for inferring infectious disease dynamics. Journal of Animal Ecology **78**:1015-1022.

Philippa, J., C. Fournier-Chambrillon, P. Fournier, W. Schaftenaar, M. van de Bildt, R. van Herweijnen, T. Kuiken, M. Liabeuf, S. Ditcharry, L. Joubert, M. Bégnier, and A. Osterhaus. 2008. Serologic survey for selected viral pathogens in free-ranging endangered European Mink (Mustela lutreola) and other mustelids fro the South-Western France. Journal of Wildlife Diseases **44**:791-801.

Poss, M., R. Biek, and A. Rodrigo. 2002. Viruses as Evolutionary Tools to Monitor Population Dynamics. Pages 118-129 *in* A. A. Aguirre, R. S. Ostfeld, G. M. Tabor, C. House, and M. C. Pearl, editors. Conservation Medicine: ecological health in practice. Oxford University Press, Oxford.

Poulin, R. 2003. The decay of similiraty with geographical distance in parasite communities of vertebrate hosts. Journal of Biogeography **30**:1609-1615.

Poulin, R. 2007. Evolutionary Ecology of Parasites. 2nd edition. Princeton University Press, Princeton.

Poulin, R. 2010. Decay of similiraty with host phylogenetic distance in parasite faunas. Parasitology **137**:733-741.

Real, L. A., and R. Biek. 2007. Infectious Disease Modeling and the Dynamics of Transmission. Pages 33-50 *in* J. E. Childs, J. S. Mackenzie, and J. A. Richt, editors. Wildlife and Emerging Zoonotic Diseases: The Biology, Circumstance and Consequences of Cross-Species Transmission. Springer, Heidelberg.

Real, L. A., J. C. Henderson, R. Biek, J. Snaman, T. L. Jack, J. E. Childs, E. Stahl, L. Waller, R. Tinline, and S. Nadin-Davis. 2005. Unifying the spatial population dynamics and molecular evolution of epidemic rabies virus. Proceedings of the National Academy of Sciences of the USA **102**:12107-12111.

Richomme, C., D. Gauthier, and E. Fromont. 2006. Contact rates and exposure to inter-species disease transmission in mountain ungulates. Epidemiology and Infection **134**:21-30.

Roche, B., and P. Rohani. 2010. Environmental transmission scrambles coexistence patterns of avian influenza viruses. Epidemics **2**: 92-98.

Rwego, I. B., G. Isabirye-Basuta, T. R. Gillespie, and T. L. Goldberg. 2008. Gastrointestinal bacterial transmission among humans, mountain gorillas, and livestock in Bwindi impenetrable National Park, Uganda. Conservation Biology **22**:1600-1607.

Taylor, L. H., S. M. Latham, and M. E. J. Wolhouse. 2001. Risk Factors for human disease emergence. Proceedings of the Royal Society of London Series B **356**:983-989.

Thomson, J. N. 2005. Coevolution: The Geographic Mosaic of Coevolutionary Arms Races. Current Biology **15**:992-994.

Tompkins, D. M., A. P. Dobson, P. Arneberg, M. E. Begon, I. M. Cattadori, J. V. Greenman, J. A. P. Heesterbeek, P. J. Hudson, D. Newborn, A. Pugliese, A. P. Rizzoli, R. Rosà, F. Rosso, and K. Wilson. 2002. Parasites and host population dynamics. Pages 45-62 *in* P. J. Hudson, A. Rizzoli, B. T. Grenfell, H. Heesterbeek, and A. P. Dobson, editors. The ecology of wildlife diseases. Oxford University Press, Oxford.

Van Kerkhove, M. D., S. Vong, J. Guitian, D. Holl, P. Mangtani, S. San, and A. C. Ghani. 2009. Poultry movement networks in Cambodia: implications for surveillance and control of highly pathogenic avian influenza (HPAI/H5N1). Vaccine **27**:6345-6352.

Vosloo, W., A. D. Bastos, and C. I. Boshoff. 2006. Retrospective genetic analysis of SAT-1 type foot-and-mouth disease outbreaks in southern Africa. Archive of Virology **151**:285-298.

Wang, G., D. Zhang, L. Li, F. Lei, B. Liu, D. Liu, H. Xiao, Y. Feng, J. Li, B. Yang, Z. Yin, X. Song, X. Zhu, Y. Cong, J. Pu, J. Wang, J. Liu, G. F. Gao, and Q. Zhu. 2008. H5N1 avian influenza re-emergence of Lake Qinghai: phylogenetic and antigenic analyses of the newly isolated viruses and roles of migratory birds in virus circulation. Journal of General Virology **89**:697-702.

Wang, L.-F., and B. T. Eaton. 2007. Bats, Civets and the Emergence of SARS Pages 325-344 *in* J. E. Childs, J. S. Mackenzie, and J. A. Richt, editors. Wildlife and Emerging Zoonotic Diseases: The Biology, Circumstance and Consequences of Cross-Species Transmission. Springer, Heidelberg.

Webster, R. G., W. J. Bean, O. T. Gorman, T. M. Chambers, and Y. Kawaoka. 1992. Evolution and Ecology of Influenza A Viruses. Microbiological Reviews **56**:152-179.

Webster, R. G., and E. A. Govorkova. 2006. H5N1 Influenza - Continuing Evolution and Spread. The New England Journal of Medecine **355**: 2174-2177

Woolhouse, M. E. 2008. Emerging diseases go global. Nature **451**:898-899.