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MULTIDISCIPLINARY STUDIES, SYSTEMS APPROACHES AND PARASITE ECO-EPIDEMIOLOGY: SOMETHING OLD, SOMETHING NEW

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Summary:

Parasite requires an understanding of complex transmission systems where individual, population and environmental factors and their interactions can hardly been considered separately. Moreover, the importance of space and time in host population and parasite transmission processes is increasingly recognised. The present review illustrates how epidemiology and transmission ecology have evolved in a multidisciplinary framework to a systems approach that includes both spatial and temporal dimensions. Focusing on population processes, three significant challenges are discussed: (i) integration of landscape ecology concepts and modelling across time-space scales, (ii) development of molecular methods that permits easy parasite/host identification and process tracking (e.g. host and parasite movements), and (iii) integration of sociology methods to estimate zoonotic risk and exposure.

KEY WORDS : landscape ecology, molecular epidemiology, sociology, multi-scale parasite transmission.

Understanding parasite transmission requires knowledge of the ecological conditions that regulate their population dynamics. This transmission concerns both parasite life cycles and human exposure, especially for zoonotic species, and presents the challenge of understanding the complexity of a life-cycle with a systems approach which must address multiple levels of biological organisation. Euzet and Combes popularized the concept of meeting and compatibility "filters" (or 'screens') to symbolise the mechanisms responsible for sustainable transmission of a parasite (Combes, 2001). The "compatibility" screen relates to host recognition by the parasite and host resistance/susceptibility and is generally studied at cellular, individual and population levels. The "meeting" screen relates to parasite-host encounters at the organism level and is studied in terms of population distributions, dispersion and interactions. Systems characterised by physiologically susceptible hosts populations that are dynamic in time and space require that transmission studies focus also on the "meeting" screen. Understanding how a parasite passes the "meeting" screen involves various fields of ecology: landscape and community ecology, population dynamics (with important modelling components), ethology and ecophysiology. It should also involve sociology as long as human parasites are concerned. Thus, several fields of science are obviously required at each level of organisation. Moreover, to understand parasite transmission in the real world means to understand a complex transmission system where individual, population and environmental factors can hardly be considered separately (Sholthof, 2007). Although many fields of science contribute to parasitology, the number of articles addressing the complexity of transmission systems in itself and syntheses on this subject is relatively low compared to more specialised issues of parasitology. Furthermore, even fewer addressing complexity are based on multidisciplinary studies. For instance, a query of the Scopus data base on parasite/parasitology identifies 497 articles also indexed on complexity from 1973 to 2006 while only 66 were indexed on multidisciplinary over the same period. In both cases 50 % of them were

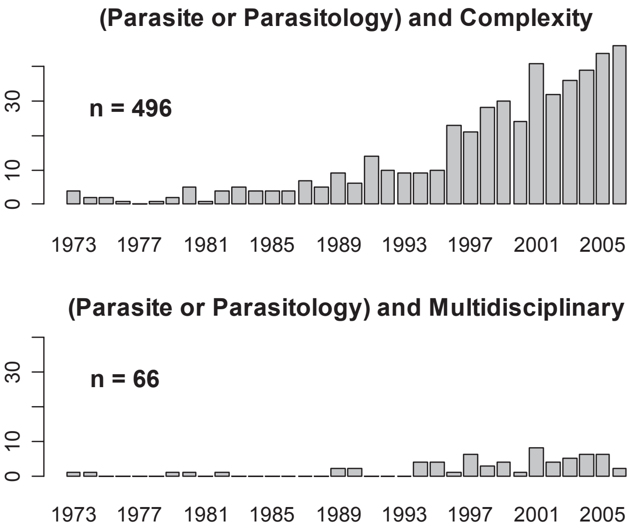

Fig. 1. – Number of articles from 1973 to 2006 indexed on Parasite, Parasitology, Complexity and Multisciplinary (Scopus© database).

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published after 2000, indicating that complexity and multidisciplinary are issues of increasing interest recently (Fig. 1). Of course the validity of picturing the scarcity of multidisciplinary studies in this manner is debatable since studies on complexity that may be intrinsically multidisciplinary may well not have been indexed with these key words. However, the pattern does provide a striking illustration of recent climatic change within the scientific community by revealing a recent augmentation of interest among scientists for such studies.

Furthermore, the importance of space and time in population processes is increasingly recognised. In many cases sub-populations of interest do not exist in isolation but interact, *via* dispersal, with other conspecific sub-populations across a larger region. In this case, the inadequacy of traditional (*e.g.* non-spatial) approaches to determining population and transmission dynamics is obvious. In 1970, Richard Levins coined the term *metapopulation* for a set of population patches within larger areas of space, with long-term survival of the species depending on a shifting balance between local extinctions and recolonizations in the patchwork (Hanski, 1998, 1999). Landscape ecology incorporates metapopulation concepts and focuses on the spatial relationships among landscape elements, the population dynamics of species among the elements, and the ecological dynamics of the landscape mosaic through time. It also provides a challenging framework for the study of host – parasite interactions.

Describing patterns and disclosing processes over large areas and long time periods are undoubtedly targets shared by both human/veterinary epidemiologists and population/community ecologists. In doing so, they combine information provided by molecular biologists, immunologists, clinicians, veterinarians, wildlife biologists, geographers and sociologists in various kinds of models (not all mathematical) and aim at integrating heterogeneous data in a consistent framework.

The aim of this paper is to illustrate, based on some examples, how such eco-epidemiological approaches have been used to help understand parasite transmission systems, and to discuss some forthcoming challenges where both spatial and temporal dimensions must be specifically taken into account.

BRIEF HISTORICAL PERSPECTIVE

The combination of several heterogeneous observations to disclose the mechanisms of infectious organism transmission is not really new. The discovery of the route for anthrax transmission by Louis Pasteur, Charles Chamberland and Emile Roux at the "*Champs maudits*" (doomed fields), in the Chartres countryside of France, was of this kind (Gascar, 1986). There, local peasants made the relationship between places where ground colour between grasses was not exactly normal and the fact that animals bred in those pastures often died from disease. In August 1878, Roux and Chamberland, sent by Pasteur, walked slowly and tirelessly across fields and remarked that those areas were spotted with small earth twists expelled by earthworms. Microscopic examination showed the bacteria. However, it did not explain how sheep could be infected (experimental infection of naive animals did not lead them to get anthrax): new enigma! Thorough examination of animals that died from anthrax showed small mouth lesions provoked by chewing thistles or sharp edged grasses. Most of the elements of a multidisciplinary study were gathered in this story. Transmission was studied in a systems approach, and this study was based on collecting empirical data in the real world (*Les champs maudits*) where epidemics occurred, to reassemble them into a consistent theory (nowadays, one would read "conceptual model"). Pasteur was a chemist, Chamberland a biologist and physicist and Roux a medical physician. Information coming from common people having faced the disease for years was not neglected but acted upon and augmented with complementary information gleamed from systematic observation. These observations then helped form hypotheses which were then subjected to experimental investigation. Negative results formed a basis for new empirical observations and so on. This scheme has been the starting point of the success story of the "Pastorians" in their early years which also encompassed the discovery of the mechanisms of plague transmission by Alexandre Yersin, of malaria, suspected by Emile Marchoux then formally confirmed by Ronald Ross, of typhus by Charles Nicolle, etc. The common traits of those approaches were: *i)* to take natural complex systems as a whole, and to reassemble empirical data from these systems to build hypothesis models and to organise them holistically; *ii)* to test models by experimentation and to reorganise hypotheses via a continuous exchange between theory, observations and experimental results. At every moment of a specific experiment the system as a whole was in mind.

THE EARLY YEARS

Systems approaches in transmission studies were reactivated in the second half of the twentieth century. One such study was initiated by French medical doctors whose training at that time had included zoology and botany (ecology was not taught as an organized discipline during that epoch). Golvan & Rioux (1961, 1963) showed that plague epidemics in the Iranian Kurdistan were due to a resistant stable populations of gerbils (*Meriones persicus)*, living in rocky areas, and serving as a stable reservoir, that transfer the bacillus (*Yersinia pestis)* to an unstable sensitive populations of *Meriones vinogradovi* living in farmland. During population surges of the latter, dispersal of some individuals from farmland to suboptimal rocky habitats was found to open the meeting screen between *M. vinogradovi* and fleas of *M. persicus* giving rise to fresh waves of infection and a new epizootic in *M. vinogradovi* population leading to sharp declines in numbers leading to virtual extinction. During the high density phases of the population cycle, crop damage was severe and people compensated for losses by digging up the caches of cereals gathered by gerbils (several kilos per den). This practice, and the subsequent "imprudent handling of dead gerbils", increased the risk for human contamination (Combes, 2001). In this case most of the key-issues challenging current research were already present: the importance of space (transmission is explained by species movements between habitats), importance of time (disease transmission dynamics depends on host population temporal dynamics), importance of species sensitivity (plague is stable there because one population is resistant), importance of human behaviour (which explains human exposure). However, reading the original paper, it is striking to see that most of the current tools of modern epidemiology were absent (*e.g.* GIS, mathematical modelling, molecular taxonomy, etc.).

The term "landscape epidemiology" was coined in early works of Pavlowski (1964). Later, Darling (1970) contributed to the field by highlighting some of the interfaces between ecology and medicine. This theme was pursued by Rioux who studied: intestinal schistosomiasis in Guadeloupe (Rioux *et al.*, 1977), leishmaniases in Southern France (Rioux *et al.*, 1969) and North Africa (Rioux *et al.*, 1977) and mosquitoes ecology for control in Southern France (Rioux *et al.*, 1967). In those works he conceptualized how ecological and epidemiological concepts and methods could be combined to ground parasite transmission studies and control programmes (Rioux *et al.*, 1981). He coined the term "eco-epidemiology" for systems approaches integrating methods inherited from both ecology and epidemiology and his approach focused on the definition of a spatial risk, a temporal risk and a population risk (related to population age structure, immunology, etc.). He also stressed the importance of spatial and temporal scales relative to transmission issues (Rioux *et al.*, 1990). His approach was mostly grounded on ecological strata defined from composite maps elaborated from both existing maps (topography, soils, vegetation, etc.) and field data (vector population densities, etc.). Again at that time, GIS, map algebra and sophisticated spatial statistics were still not popular. The link with the Zuricho-Montpellieran phytosociology school which was at its peak was obvious. Vegetation maps seen as indicators of ecological conditions were the elective support for example to identifying e.g. vector areas (Fig. 2) and to refer transmission systems to explicit spatial scales (local and regional, in general). Furthermore, multivariate exploratory analysis methods, which were popular in phytosociology to analyse "habitats x species" matrices, were used for the analysis of insect vector distribution in a multivariate context (Rioux *et al.*, 1997; Rioux, 2001). Epidemiology and ecology concepts were integrated as were the modelling and statistical approaches already adopted within the two disciplines.

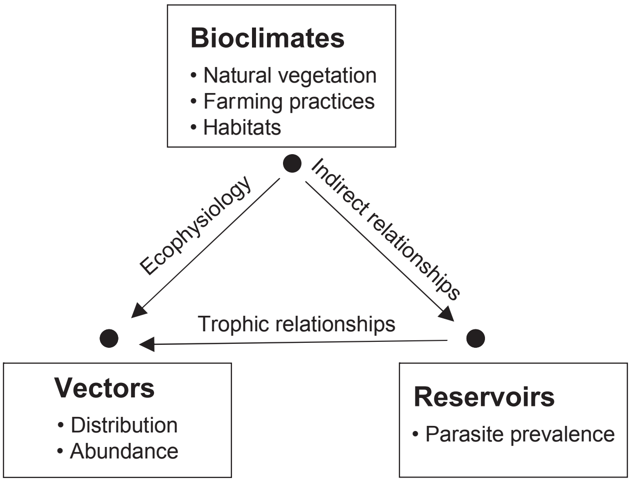


Fig. 2. – Triangular conceptual model of circum-mediterranean leishmaniasis transmission. Bioclimats are revealed from plant species association analysis. Plant associations are correlated to vector distribution and abundance and indirectly determine population reservoir infection (here dogs or small mammals). After Rioux *et al.* (1997)

CURRENT CHALLENGES

Understanding and predicting the effect of anticipated global changes is currently one of the big challenges of science and this concern is arguably less present in the examples mentioned above (however see Rioux *et al.*, 1997)). The principal concern lying at the interface of parasite transmission and epidemiological systems is to understand how environmental events, such as habitat alteration, loss of biodiversity, biological invasion, climate change and pollution, alter the risks of emergence and transmission of parasites (see *e.g* the Millennium Ecosystem Assessment reports, http://www.millenniumassessment.org). How can epidemiology be more innovative in this context? Probably in cultivating more cross-links with other disciplines especially ecology and molecular biology and in draining renewed computing and modelling capacities from mathematics and statistics. An additional challenge will be to use and develop concepts and high tech methods that have the potential to *live for themselves* within a whole-systems epidemiology.

That is to harness the power of technical advances, perhaps in highly specialised sub-disciplines, but keeping the whole system in mind and providing real contributions to a global understanding. Figure 3 shows how the view of the zoonotic cestode, *Echinococcus multilocularis*, has evolved during the recent years and stresses the importance of a system view with consideration of spatial and temporal scales and processes. However, this growing recognition of the importance of scale issues has still not led to an operative approach permitting to handle/model parasite transmission at multiple temporal and spatial scales, integrating processes up and down across scales while still retaining a view on the whole system.

Ecologists have attempted to theorize and describe the way processes are organized in nested hierarchies long since Allen & Starr (1982). They have recognised that to carry out investigations at several scales simultaneously it is essential to understand the full set of constraints that determine observed patterns and processes. Indeed, the spatial and temporal scales of investigations determine the range of patterns and processes that may be detected and therefore the level of understanding and explanation that can be achieved. Observations made within one scale may even have limited power to explain patterns and processes observed even at this scale (see *e.g.* Giller & Gee, 1987). For instance, in the parasite world, observing transmission intensity on a small time span of some months can be misleading in areas where multi-annual intermediate host population cycles occur. *E. multilocularis* transmission can be provisory interrupted during the low density phases of small mammal intermediate host population cycles, which may contrast with high prevalence rates observed at the same time in humans in the same area (human infection observed at population level at a given time, is the result of cumulative events that occurred during preceding decades) (Craig *et al*., 2000; Giraudoux *et al*., 2002). Furthermore, after the early insights provided by island biogeography about the effect of space on community processes (MacArthur & Wilson, 1967), landscape ecology specifically addresses how a range of ecological processes interact in space and time. This approach mainly concerns a high level of biological organisation such as large ecosystems and spatial arrays of interacting communities (Wiens *et al*., 2007) and thus also applies to complex parasite transmission systems. One of the

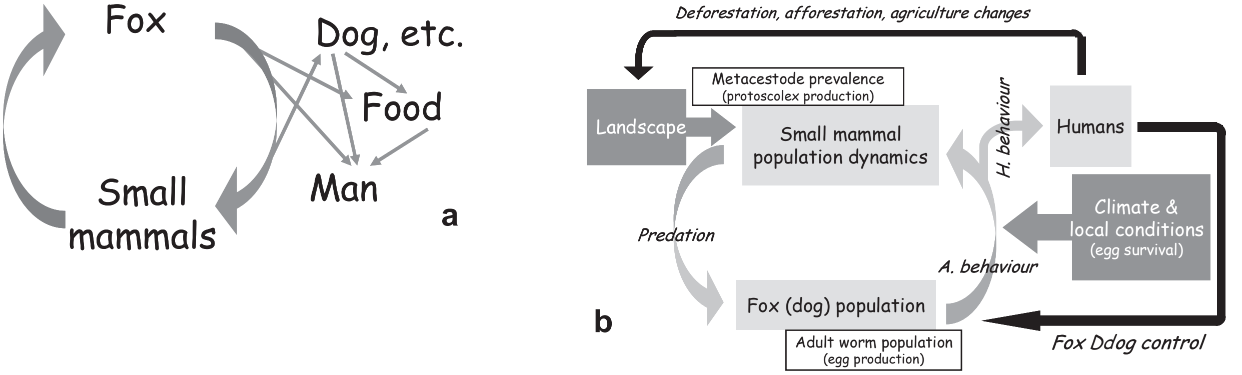
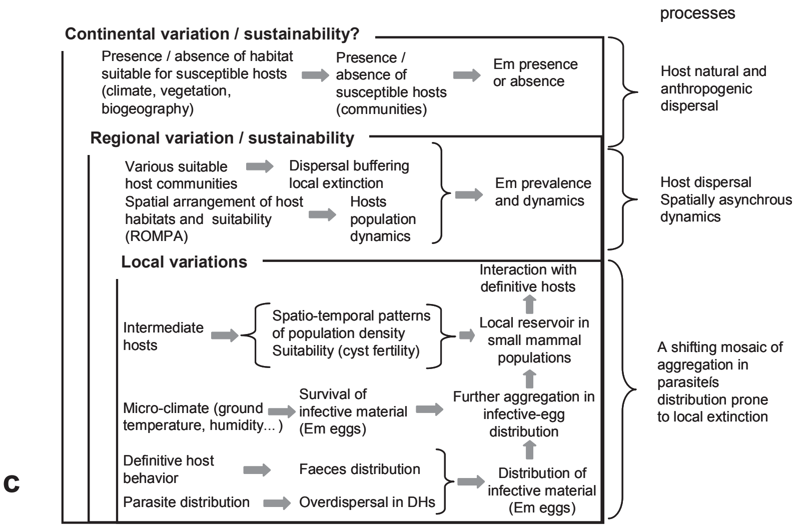


Fig. 3. – Evolution of *E. multilocularis* transmission picturing. The "classical" parasitological cycle of the 90s (a) has shifted to a more complex box system explicitly featuring population and ecological direct and indirect processes governing transmission (b). Adding an explicit reference to the nested hierarchy of spatial scales at which various processes occur (c) makes the conceptual model much more complex, although temporal dimension is not represented. After Giraudoux *et al*. (2003, 2006).



big forthcoming challenges is likely to be how to better link concepts and methods emerging from the fields of ecology, population dynamics and epidemiological studies in parasite transmission (Kitron, 1998; Holdenrieder *et al.*, 2004; Ostfeld *et al.*, 2005).

A number of new methods and technologies have become widely adopted since the mid 1990s and these hold the potential to renew eco-epidemiological approaches of parasite transmission within this conceptual framework.

The use of remote sensing and multi-layered composite data sets using GIS to detect correlations between environmental factors and disease prevalence has, after thirty years of maturation, become a well established practice (Hay *et al.*, 2000; Beck *et al.*, 2002; Durr & Gattrel, 2004; Brooker *et al.*, 2006). GIS has been successfully used for studying vector borne parasite distribution and to design subsequent control interventions including land management. Indeed, invertebrate vectors are extremely sensitive to changes in temperature and humidity conditions, which can be indirectly measured from soil/vegetation reflectance. The increased availability of satellite data and spatial databases has allowed the production of improved environmental maps and to confront them to ecological, human or veterinary data collected on the ground. For instance, a large number of studies have been achieved on the distribution of trypanosomiasis in Africa, some on a multiscale basis (*e.g.* Rogers, 2000; Hendrickx *et al.*, 2001; de La Rocque *et al.*, 2005) and this has led to management recommendations (de La Rocque *et al.*, 2001). GIS and satellite imagery have also been used for studying, among others, malaria (Hay *et al.*, 1998; Malone *et al.*, 2006; Rogers, 2002), *Triatoma infestans*, the vector of *Trypanosoma cruzi* (Cecere *et al.*, 2004), American visceral leishmaniasis (Bavia *et al.*, 2005), Old world cutaneous leishmaniasis (Cross *et al.*, 1996), *Biomphalaria* spp., the snail-host of *Schistosoma* spp. and *Fasciola* spp (Kristensen *et al.*, 2001; Yang *et al.*, 2005), onchocerciasis (Gebre-Michael *et al.*, 2005), *Echinococcus multilocularis* (Danson *et al.*, 2004; Pleydell *et al.*, 2004; Danson *et al.*, 2006), Old World screwworm myiasis (Siddig *et al.*, 2005), and Bancroftian filariasis (Hassan, 2004), not to mention the many studies conducted on virus vector-borne diseases (blue tongue, Hanta, La Crosse, West Nile, Sin Nombre, Rift Valley fever and tick-borne viruses, etc.) and some bacteria (*e.g.* cholera and leprosy).

However, one of the big limits in studies of parasite cycles including a wildlife component, is the fact that population biologists do not have fully reliable tools for estimating host and parasite populations in terms of absolute densities with high precision over large areas, which is required for deterministic models. This most often leads to the use of estimates of relative abundance (*e.g.* grounded on indirect indices of real densities), which are supposed to be robust enough to allow comparisons. Therefore two conflicting goals are faced designing such studies. On the one hand, it would be nice to have very narrow confidence intervals on density or prevalence estimates in (space and time) locations. The collection of such data is demanding and thus time-consuming. On the other hand to focus heavily on a small number of locations means one can never see the bigger picture (which may reveal e.g. spatial trends or local clusters) and will probably fail to understand transmission at other extremely informative places. Probably the key advantage in spatial approaches and statistics over classical statistics is that one can reach a kind of compromise. One no longer needs to focus all attention on a small number of locations so that single location-level confidence intervals are small. The reason is because with a spatial/temporal model when one estimates a confidence interval at a location all the data from neighbouring location is also used to help tighten that confidence interval. This is of great value because it means one is freer than before to sample a greater number of locations without risking loosing too much statistical power in any one location. Also from the point of view of an eco-epidemiology study it is good to remember that when it comes to analysing landscape effects on epidemiological data it is desirable to have a dataset which includes as much variation in landscape and locations as possible, so a large number of sampled locations is desirable. Thus, spatial modelling and statistics are probably one of the fields of science that can provide improved exploratory tools to eco-epidemiologists. Beyond their proven power for disclosing distribution patterns, it would be essential, focusing on processes, to better link landscape metrics (that can be obtained from remote sensing data) to population dynamics and landscape processes (requiring long term monitoring) in order to better understand how the variation in parasite transmission intensity may be linked to variations in host populations over space and time. For instance, population dynamics of small mammal populations (thus their density variations over time) not only respond to the availability of suitable habitats to a focal species, but also to the ratio of its optimal habitat to the total land area and by the effects of neighbouring sub-optimal habitats (Lidicker, 2000). This can impact tranmission processes in systems where various small mammal communities in contrasted landscapes are key-reservoirs for parasites such as *Echinococcus multilocularis* (Giraudoux *et al.*, 2003). Furthermore, to upscale results obtained on the limited areas where human population and animal community data can actually be collected to larger areas across scales is still an open challenge. Whether modelling tools will be enough to enable population biologists and epidemiologists to make a better use of scarce and imperfect data at a given scale to upscale to larger areas is still an open debate and ongoing research should help answer this important question (Hendrickx *et al.*, 2001; Giraudoux *et al.*, 2007). Molecular methods have also changed the way people are working in ecology and epidemiology especially improving diagnostic and parasite classification systems (Traub *et al.*, 2005; de Meeûs *et al.*, 2007). This is also the case for host studies especially in countries or regions where host taxonomy is not well characterized and where classical taxonomy capabilities have critically decreased to a small number of people where they still exist. Molecular methods have also helped understand how host genetics may increase the risk of infection (Godot *et al.*, 2000; Yang *et al.*, 2006). No less than 5,597 articles, among them 984 reviews, came out with the key word "molecular epidemiology" in PubMed© to date. However, only 89 of them (21 reviews) were indexed on "parasite" and still fewer studies were grounded on a spatially explicit approach to parasite and host distributions (but see Kyes *et al.*, 1997). This maybe a gross underestimation due to improper indexing, however, it may also reflects the fact that molecular tools that can relevantly address transmission issues in a spatial context are still at the development stage and that the ones available may be still underused by landscape epidemiologists. For instance, as far as transmission processes are dependent on individual movements of hosts (a general case are metapopulations), to know the distance at which host may disperse and the patterns in such dispersal remains a critical issue. These parameters are not accessible to classical methods of ecology (*e.g.* capture – mark – recapture of animals) essentially due to the fact that the probability of recapturing an animal marked decreases with the square of the distance to where it has been released, preventing any recapture at far distance (not to mention the uncertainty about its behaviour after release...). O'Loughlin *et al.* (2007) have recently shown how the genetic structure of populations of the malarian vector *Anopheles scanloni* reveals that the population is actually made of discrete subpopulations limited to limestone-karst habitats with restricted gene flow. Another example can be provided regarding *E. multilocularis* transmission in China where understanding the ways in which discrete foci within a variety of small mammal communities may be linked at continental scale remains a key challenge. For obvious technical and logistic reasons it is unlikely that this issue can be addressed directly *via* the study of definitive host dispersal (fox and dog). An alternate solution however is to investigate the spatial variation in genetic structure of georeferenced samples of parasite and host populations from different regions. Thus, it is expected that further advances in parasite and transmission ecology will come from molecular markers and methods that may be developed for exploring a fine grain polymorphism of parasite and host population in a spatial context (Giraudoux *et al.*, 2006).

Finally, systems approaches of anthropozoonoses transmission should also incorporate the variability of human behaviour. For instance, studies on *E. multilocularis* in China have identified landscape patterns and ecological processes that may be conducive to more intensive transmission and human exposure (Giraudoux *et al.*, 2003; Danson *et al.*, 2006). However, the large variability (0-15 %) of human alveolar echinococcosis among villages in areas of high endemicity remained unexplained and may well be due to undisclosed behavioural differences between villages. Indeed, classical epidemiology (*e.g.* epidemiological questionnaires and case control studies) carried out by scientists who are often culturally far from their studied communities is likely to miss important details of life traits that may hold hidden keys to understanding exposure. For example, data quality is not always guaranteed with questionnaires designed in the absence of in depth knowledge of cultural traditions and habits. Such uncertainties can escalate when language barriers necessitate one or more translations at which juncture it becomes hard to verify certain information. Thus, the inclusion of social sciences and their articulation to other studies on transmission systems is required although examples of such integration within a systems approach remain scarce to date if even done at all (Cohen *et al.*, 2007) and indeed how to do that whilst keeping a global view on the whole multi-scale transmission system remains an open question.

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