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Research Article

In All Things There is a Law of Cycles; Pathogen-host Interactions in Hantavirus Infections.

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Abstract

Hantaviruses are carried by rodents, insectivores and bats. Some serotypes are able to cause disease in humans, i.e. hemorrhagic fever with renal syndrome (HFRS) in Europe and Asia, and hantavirus cardio-pulmonary syndrome (HCPS) on the American continent. We examine the multiple factors that drive hantavirus outbreak occurrence in Europe like rodent population structure, habitat suitability and its changes, general climatic and local/temporal meteorological conditions, food availability in its various facets (hard, soft mast), predators, biodiversity and anthropogenic factors.

Keywords: Hantavirus; Climate; Rodent Population Dynamics; Pathogen-Host Relations

Introduction

In early attempts to understand pathogen-host relations, stable interaction patterns were suggested, and agreement existed that pathogens and their hosts evolve in such a way that would make the consequences of infection more benign [1], this concept has undergone major changes over the past decades. The idea that evolution aims to benefit the species, is indeed contradicted by the ever present or newly emerging highly virulent and apparently stable human and animal diseases. It was however also hypothesized that emerging pathogens made the species-jump sufficiently recent so that the expected evolutionary loss of virulence has not yet sufficiently progressed to be measurable [2].

Hantaviruses are a prime example of infectious agents that heavily rely on favorable environmental conditions for their distribution. They are carried by rodents, insectivores and bats, but so far only those carried by rodents cause disease in humans. There exist two dominant syndromes, i.e. Hemorrhagic Fever with Renal Syndrome (HFRS) in Europe and Asia, and Hantavirus Cardio-Pulmonary Syndrome (HCPS) on the American continent. Hantaviruses are usually associated with a single primary rodent host species, chronically infected, that is capable to infect humans that come into contact with the rodent or its infected excreta [3]. Great efforts have already been made to investigate the nature of the virus reservoir, its temporal and spatial dynamics, and its relation to the human population.

In the Four Corners regions in the United States, the overall risk for Sin Nombre virus (SNV, carried by Peromyscus maniculatus, (Wagner 1845) infection seems to be related to habitat structure, environmental changes of limited duration and certainly –as demonstrated by the 1992 to 1993 El Niño event, the precipitation pattern was associated with increased rodent populations in the Southwest of the USA. This led to the 1993 HCPS outbreak in the Four Corners region [4]. In South America, so-called “ratadas” (rodent population peaks) have been recorded since the Spanish conquest in the 16th century. Two types of ratadas were identified, namely the bamboo bloom-associated and rainfall-associated events. Bamboo blooms depend on the species and occur with 10- to 30 year intervals, while El Niño years were also found to be responsible for subsequent ratadas and higher risk for infection [5]. The transmission of HFRS in North-eastern China, the region with the highest HFRS incidence in the country, seems influenced by rainfall, land surface temperature, relative humidity and the El Niño Southern Oscillation index [6]. While HFRS cases in China occur throughout the year, an increase in both winter and spring was noted. The winter peaks result from Hantaan virus (HTNV) infections and the smaller spring epidemics are caused by Seoul virus (SEOV) infections. The three responsible rodent hosts, i.e., Apodemus agrarius coreae (Thomas, 1908) or Apodemus agrarius (Pallas, 1771), and Rattus norvegicus (Berkenhout, 1769), and their respective biological characteristics cause this seasonal effect [7]. In Fennoscandia the multiannual population oscillations of boreal and arctic small rodents (voles and lemmings) are driven by predation. Although sometimes criticized because the earliest views about predation and rodent dynamics were judged to be too simplistic, the predation hypothesis seems to apply throughout the boreal region, i.e. Fennoscandia, northern Japan and North America [8]. The similarity between common vole populations patterns in South-West France and Fennoscandian is however perhaps the geographical exception that confirms the rule [9]. It suggests that predation could also affect rodent population dynamics in temperate Europe. In Western and Central Europe a multi-factorial system involving food availability, climatic conditions, habitat and anthropogenic features drive rodent population dynamics and hantavirus epidemics [10] (Linard et al. 2007)[11]. Puumala virus (PUUV, carried by the bank vole Myodes glareolus, Schreber, 1780) is the prevailing serotype. The virus is present in most of Europe and also Turkey [12], and is known to cause clinical infection in thousands of individuals each year with a mortality less than 1% [12]. Dobrava virus (DOBV, carried by Apodemus agrarius, Pallas, 1771) is present in Middle and Eastern Europe and the Balkans region [13], up to Turkey [12]. The virus is responsible for several hundreds of infections per year with a mortality of around 10% [14].

Rodent population dynamics and their impact on public health depend -in various biomes and on different latitudes and climate zones- however not on one, but several parameters; population structure, habitat suitability and its changes, general climate and local/temporal meteorological conditions, food availability in its various facets (hard, soft mast, herbs, seeds, tree bark, insects), predators, biodiversity and last, but not least, anthropogenic factors. Here we aim to review a number of interacting parameters that can lead to the occurrence of Hantavirus outbreaks in Western Europe.

Food

Food preference

The availability or absence of food is probably the most important feature that drives hantavirus infections worldwide. This is however is in turn dependent on besides food, a pleiade of other parameters influence

Hantavirus outbreaks. Bank voles are granivorous/folivorous with a strong preference for forest habitats with heavy understory [15]. This allows defining them as a food generalist but habitat specialist species. They eat a vast variety of nutrients, in sub-optimal habitats they are also able to adapt to almost every available food source. Voles in an oak-hornbeam forest eat evidently what the season provides, but mainly green vegetative parts of plants and a rather significant percentage of insects [16]. Voles in a Northern Finnish spruce forest on the other hand feed for up to 50% of their diet on lichen [17]. Although bank voles share their habitat with the wood mouse (Apodemus sylvaticus, Linnaeus, 1758), the wood mouse is to a great extent more specialized on seeds [18].

Rodents also frequently cause significant damage to forests, according to Borowski and colleagues, European larch (Larix decidua, Miller), European ash (Fraxinus excelsior. Linnaeus, 1758), beech (Fagus sylvatica, Linnaeus, 1758) and maple (Acer sp., Linnaeus, 1758) are the tree species that from which small rodents preferred the fruits the most. Birch (Betula sp., Linnaeus, 1758), Norway spruce (Picea abies, Linnaeus, 1758), Scots pine (Pinus sylvestris, Linnaeus, 1758) and black alder (Alnus glutinosa, Linnaeus, 1758) were the least preferred [19]. Small rodents also influence forest regeneration and forest health and composition therefore regulate to a certain extent their very population dynamics. A considerable amount of bark damage can be found on young trees (20%) in spring after the peak abundance of field voles (Microtus agrestis, Linnaeus, 1761) in combination with a long winter with heavy snowfall. In contrast, little damage to young trees was noted under high densities of bank voles with a lower snow cover the following winter. The bark of deciduous trees was shown to be more attractive to voles (22% damaged) than conifers (8%). Young trees originating from natural regeneration were apparently less damaged compared to planted trees. The main factors influencing the impact of rodent species on tree regeneration comprise open, grassy habitat conditions, a higher variety and abundance of vole species, tree species preferences- and snow-cover conditions. Natural regeneration is preferable over artificial plantings which suffer more, probably due to the abundance of young trees in the latter case [20].

Mast hypothesis

Attempts to explain rodent population dynamics are plentiful throughout the past 80 years and recently a renewed focus on mast events as driving phenomenon is emerging [21-24]. The debate regarding the mast hypothesis is however not new [25]. In 1997, Selás linked population cycles to cyclic seed cropping, i.e. mast events and he introduced the so-called "mast hypothesis" [26]. In 1998, Hansson criticized the conclusions and already concluded "one factor is not enough" to explain rodent population fluctuations [27]. It became in the past decade increasingly clear that in-depth examination of this one parameter -however interesting - does not sufficiently explain epizoonotic events and we should think further. Beech mast records for Germany, Denmark, The Netherlands, England and Sweden from 1800 until 2001 suggested not only variable mast production on a multi-annual base, but also a geographical and even a tree-to-tree variation [28].

The responses of rodent populations to acorn mast were found different depending on the acorn type (related to the oak species, Quercus sp., Linnaeus, 1758), e.g. high tannins, fat and protein content and consequently energy rich (sometimes coined as type 1 acorns), or high tannins but low fat and protein content (type 2 acorns), or low tannins and intermediate fat and protein levels (type 3 acorns). Rodents also respond differently to acorn mast depending on their feeding habits and the nutritional characteristics of acorns. Granivorous rodent species show different responses to acorn mast while granivory/herbivory showed positive responses to mast of type 3 acorns. An herbivorous rodent response to mast of any of the three acorns types was not reported.

These findings emphasize that a rodent-acorn mast relationship should not be generalized [29]. Quercus robur (pedunculate oak) acorns, native to Western Europe, belong to the type 1 category, whereas rodents generally prefer type 3 in their staple food [30]. It should however be noted that - in view of efforts made in the past three decades to convert oak forest to beech standings - acorns have been for centuries an essential part of the human diet in Europe and oak trees were thus carefully cultivated [31]. From the rodent point of view the human usage of acorns came in handy. The use of acorns dates back to prehistoric times and are still a food source for pigs in rural Spain. They are also used in the preparation of human food and as a coffee substitute and a number of beneficiary effects on human health are attributed to them [32].

Intriguing and so far unexplained is the fact that although bank voles and PUUV are supposed to have co-evolved for millions of years, are described in W-Europe since the Middle Ages and –logically- also mast years took place for millennia. Hantavirus outbreaks on the other hand, causing Nephropathia epidemica (NE) and Acute Renal Failure (ARF), were not reported before the twentieth century. Even in the absence of diagnostic tools the syndrome caused by Hantavirus infection should have been noticed and reported by clinicians.

As far as beech mast is concerned, Belgian data show that Hantavirus epidemics only relate to mast years in the period between 1995 and 2007. After 2007 i.e. 2008, 2009, 2010 were no mast years but hantavirus activity was nevertheless high. Only the 1993, 1996 and 2005 epidemics correlate with a previous oak and/or beech mast event, 2001 should have been an epidemic year but was not, after the oak-beech mast event of the year 2000. All years after 2005 -six in total- were epidemic years in the absence of oak and/or beech mast years [10]. Not only beech or oak mast triggers outbreaks, masting of various other tree species can have the same effect and virtually any mast event could provide sufficient food for rodent populations to peak and induce a Hantavirus epidemic in the next year.

This is supported by the bank voles dietary variations as described earlier in this paragraph. The variation of epidemic years in neighboring countries also does not support the mast theory. Tree mast is considered to take place on a large scale, even on sub-continental level [23]. In Belgium tree mast does not seem present at the same time in all regions; the 2011 mast of oak-beech was present in the Flanders region, the North and South -but not in the middle part- of the Wallonia region. In Belgium, we followed the mast production for a limited number of oak and beech trees of approximately the same age since 2001 up to present and noted similar tree-to-tree differences. It should however be noted that, to our knowledge, no statistically confirmed model (Vseed = Venv(i) + V mast - Vconst) is available in Belgium [25]. We also already stressed that oak/beech mast only correlated with hantavirus outbreaks for a rather short period, i.e. 1995-2005, and that mast events of other tree species also had its influence [10].

Competitors

Inherent to hard mast is the competition for this type of food between rodents, birds and large grazers. In Western Europe, roe deer (Capreolus capreolus, Linnaeus, 1758) and fallow deer (Dama dama, Linnaeus, 1758) are the main wild large grazers. Increases of their populations influence rodent populations in two main ways; a/ the increased competition for food they impose, and b/ the habitat changes they produce by removal through grazing and foraging on understory species and removal of groundcover and scrub. Removal of high quantities of staple food is reported to reduce the population peaks in rodent populations and the lack of groundcover provoked reduction of the bank vole population because it enhances the hunting success of birds of prey (e.g. owls [33] and specialist predators (e.g. Mustelidae) [34]. Sheep grazing activity, for instance, negatively impacts field vole populations but not bank voles [35].

Wild boar (sus scrofa, Linnaeus, 1758) consume a variety of vegetable food categories like mast (acorns, beechnuts, chestnuts, pine seeds, but also olives and grapes), roots, green plant matter and agricultural crops [36], but also animal foods like insects, earthworms, birds and mammals - more particularly rodents - discovered during grubbing (rooting pastures), and also even amphibians and reptiles [37]. They may impact revival and population growth of rodent species considerably as wild boar may actively look for hoards of hard mast collected by small mammals [38].

Biodiversity

When a predator, prey or plant species is eradicated from an environment that system can fail to function optimally, this in turn reduces productivity, resource availability and habitat quality. In the long term this results in lesser species richness and reduced biodiversity. Human interference then typically tries to mediate by protecting their "favored" mammals and non-vertebrates (the cuddly and esthetical ones) at the expense of the "less" favorite and annoying ones (those considered harmful or scary, a definition that is in most cases totally undeserved). Corrective hunting disguised as "nature management" is the prime example…

Although in the EU species extinction is not occurring as rapidly as on other continents, the percentage of species under pressure or threatened with extinction is still high. According to the EU 2010 biodiversity baseline 25 % of marine mammals and 15 % of terrestrial mammals, 22 % of amphibians, 21 % of reptiles, 16 % dragonflies, 12 % of birds and 7 % of butterflies are threatened with extinction at EU level. Only 17 % of the habitats and species were evaluated as 'favorable', 65 % and 52 % of habitats and of species assessments were 'unfavorable' respectively, while the percentage of habitats and species whose status is "unknown' is relatively high, i.e. 18 % and 31 % respectively [39,40]. Generalist species like bank voles adapt –as said earlier- easily to a wide range of food sources, especially when anthropogenic interferences result in deterioration of the environment. A short-term effect is the extinction of specialist species, while the population density of opportunistic species increases due to the decrease of competitive pressure. Decreased rodent species richness subsequently means lesser interspecies encounters and more efficient spread of the virus amongst conspecifics. Hantaviruses are thus transmitted and spread most efficiently within low diversity environments.

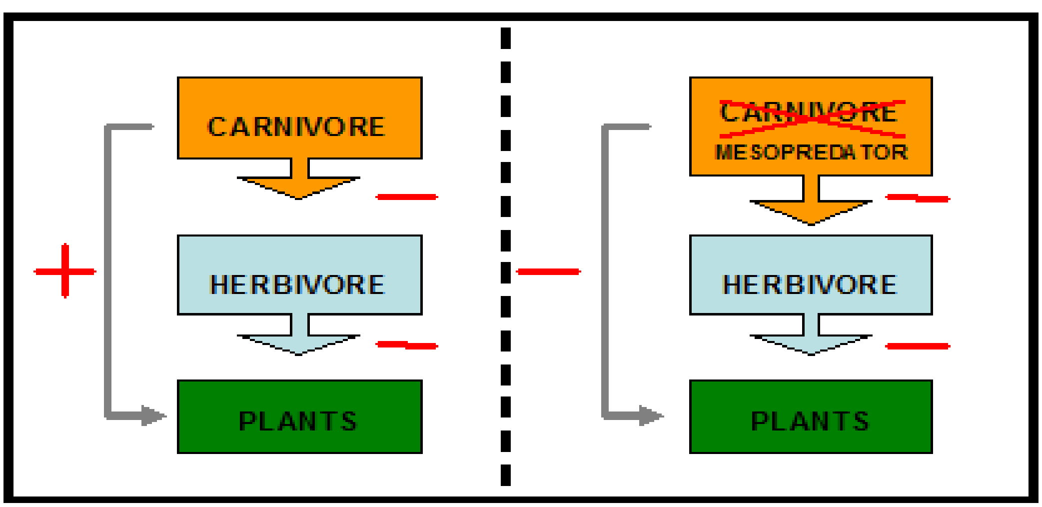
The biodiversity decrease thus facilitates transmission events because of an increase in encounters between infected and susceptible hosts [41] (Matt and Gebser 2011). Keesing and co-workers [42] suggested in certain cases the introduction of a predator or competitor species in order to control the pathogen carrying species. Whether or not this is - in view of experiences in the past (see the paragraph Invasive species further) - a good idea, should probably be evaluated case by case.

Population Dynamics

Trophic cascades

Since man –the very top of the food chain- appeared on earth, he has tried to eradicate apex predators, like the big canidae and felidae but also hominidae, simply because they meant competition for -often hard to obtain- food resources. In more recent times apex predator eradication was a technique applied to maintain and increase the availability of game species for hunters and to reduce losses in livestock [43]. In general, a (terrestrial) trophic cascade event occurs when a change in the food availability in an ecosystem has an impact farther down the chain, or as George Orwell (pen name for Eric Arthur Blair, British writer and journalist, 1903-1950) wrote ‘‘All animals are equal, but some animals are more equal than others.’’. Food-web ecology mainly focuses on interactions between three main trophic levels, i.e. predators (the top of the natural food chain), eat prey animals situated one trophic level lower. These prey animals consume plants, the lowest level of the ecosystem [44] (Figure 1).

(Figure 1): Simplified version of a trophic cascade in which only 3 levels are affected



Left, when the carnivore is present, there is an overall positive effect on the growth of plants. This is because the carnivore has a negative effect on the herbivore, which normally has a negative effect on the vegetation.

Right, where the top predator has been eliminated and mesopredators occur, there is an overall negative effect, also on vegetation.

This pattern is however nearly always more complicated due to direct and indirect secondary interactions, inter-species (mesopredators) or intra-species hierarchy in a trophic level, and by omnivorous species that affect multiple trophic levels simultaneously. The mesopredator release hypothesis (MRH), coined by Soulé and colleagues in 1988 [45], suggests that by removal of the top predators, a surge in mesopredator numbers (cats, raccoons, badgers, snakes, etc.) occurs which leads to increased predation on prey species. Apex predators can thus be indirectly beneficial to prey populations by suppressing the mesopredators. Mesopredators have important advantages over apex predators as they require smaller habitats and are therefore less affected by habitat loss Habitat fragmentation and urbanization increase also increases the resources available to mesopredators (garbage, pet food, etc.) qualify much more as food resources to mesopredators than to apex predators [46]. Important to note is that mesopredators nevertheless have restrictions as they cannot replace and take over the role of the apex predator. Elk for instance modify their foraging behaviour depending on the presence or absence of wolves [47], mesopredators are often however not able to impose this behavioural change [48]. Trophic cascades can also have important indirect or side effects. The alteration of the system's intermediary activity (herbivory) and the relative abundance of plants in a system also increases the fuel mass (dry grasses, leafs, etc) available for wildfires. In unprepared regions this can have disastrous long-term effects [49]. The general effect of climate change on forest environments is an earlier onset of spring and increased summer temperatures are now evident [50].

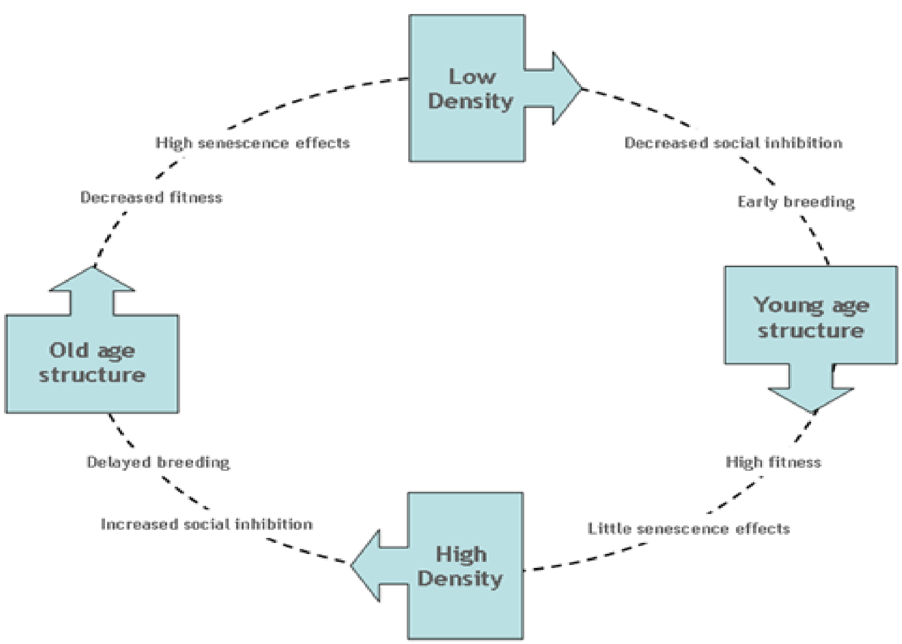
The island syndrome, habitat fragmentation

Mainland populations are geographically defined as "populations living on continents" and as "populations living on connected habitats without firm boundaries". Island populations can be defined as strictly "populations living on an island surrounded by water" or as "populations living in a habitat with firm boundaries". These latter populations often display differences in morphology, reproduction, demography and behavior what is called the Island syndrome. The observed differences include changes in dispersal, often decreased reproduction, increased body mass, reduced aggressiveness, stable and increased population densities in time and increased survival [51]. More recently arguments against a generalized island syndrome were brought forward. In certain cases larger and more elaborate datasets show that there is no evidence for the existence of the island rule when phylogenetic comparative methods are applied and the specific species biology and the biotic and abiotic characteristics of the different islands are taken into account. More specifically it was shown that heteromyid rodents (kangaroo rats, kangaroo mice, pocket mice) and artiodactyls (even-toed ungulates) and carnivores typically display smaller size on islands while murid rodents (mice and rats) are usually larger. As such, the island rule was coined an artefact of comparing distantly related groups with clade-specific responses to isolation [52].

Senescence and Disease

Ogden Nash (American poet, 1902 – 1971) coined senescence as “the day your descendants outnumber your friends”, and this is not different for rodents. Senescence is probably also often overseen as a factor of influence to multi-annual rodent population fluctuations (cycles). The age structure shifts that inevitably occur in a rodent (but not only rodent) population, i.e. a fluctuating breeding volume, shifting age structure contributes to the temporal population fluctuation(s). [53]. (Figure 2).

(Figure 2):



Attempts have also been made to quantify the impact of infectious diseases on population dynamics, more particularly on the population decline. Although rather scarce, the available information points out that intestinal parasite infestation contribute to the autumn population crashes in white footed mice (Peromyscus leucopus, Rafinesque 1818) and deer mice (P. maniculatus, Wagner 1845) [54]. Smith and colleagues produced a model for the impact of infectious diseases in European microtine populations and found that disease-induced population crashes lead to multi-year population cycles [55].

Invasive species

Invasive species are able to radical changes in habitat and biodiversity. In case their "candidate" predators were on beforehand eliminated from a system by biodiversity loss, the system is vulnerable for invasion by the non-native species. Invasive species can either reduce native species populations through predation, competition, parasitism or disease [56,57] or native predators reduce invader populations resulting in an increase their own biomass/number [58]. An increase in predator population may in turn result in a decrease in native prey biomass.

In some cases the invasive species can become a (meso) predator or possess efficient defenses against native predators. A particular example was the introduction in Australia in 1935 of the cane toad (Rhinella marinus, Linnaeus, 1758)) as a biological control agent against the cane beetle (Dermolepida albohirtum, Waterhouse, 1875), a pest of sugar cane (Saccharum officinarum Linnaeus, 1758). The amphibian has been migrating westward across northern Australia and it has been since implicated -due to its poisonous skin- in the widespread decline of many native frog-eating predators and can even be a treat for humans that manipulate it [59]. An additional mechanism that can occur is that -if the native predators successfully predate on invasive species- the predator population increases and inflicts a negative impact on the its original native prey species [58].

Climate change

As Hantavirus disease outbreaks have been associated with changes in rodent population densitie and rodent population dynamics are often weather and/or climate related. In the case of hantaviruses, there seems to be a rather important influence of climatological changes (short- or long term). In more arid conditions (e.g. the Four corners region in the USA in 1993), periods with increased rainfall positively influence rodent populations and trigger hantavirus epidemics. In more moderate climatic conditions (e.g. most of Europe and Asia), rainfall is probably less important, but mild winters favor winter survival and an early start of the breeding season, resulting in higher rodent densities in autumn. This, in turn, results in more human infections in that season [60, 10]. Dervović and coworkers suggested that -in Bosnia and Herzegovina- changing climatic conditions and flooding contribute to triggering hantavirus epidemics [61]

Human impact

The anthropogenic impact on terrestrial [62], but also to an even greater extend on marine, ecosystems is increasingly important [63,64]. Although this review focuses on rodents, is good to remember that about 99% of all animals are invertebrates that are probably even more vulnerable to human interference as demonstrated by coral reef destruction [65], species shift and overfishing in Northern oceans and seas and the subsequent detrimental effect on the food supply of marine birds and mammals [66], together with a multitude of other negative effects recognized in the past few decades. Human activities have altered both form and function of terrestrial ecosystems by urbanization of natural landscapes [67] and introducing floral and faunal species far beyond their natural boundaries and by altering carbon and nitrogen cycles which most probably led to global warming. Despite (hesitating…) attempts to initiate corrective measures, it will most probably be difficult to remediate ecosystems and it will certainly take generations to stop the downward environmental spiral [68].

Public Health Implications

All above discussed parameters have, in varying degree, an indirect impact on public health because of their direct influence on the risk for infection for humans [69].

With the increasing importance of zoonotic diseases worldwide, elaborate systems have been put in place by CDC, ECDC, WHO and other organizations to control this kind of events. There is however still little doubt that zoonotic diseases have -and will continue to have- an important impact on human health worldwide.

Conclusion

Rodent-borne diseases are prime examples regarding cyclic occurrences and the above discussed parameters apply particularly to hantavirus infection outbreaks. Hantavirus infections are still considered emerging, despite the discovery already 50 years ago of the first serotype (Tottapalayam virus (TMPV) in India in the 1960ties (Carey et al. 1971)). It is foreseeable that the number of hantavirus species, the variety of their reservoir species and their geographical distribution will increase in the future and complicate the overall picture [70]. The described parameters influence

Hantaviruses through impacts on the ecology of their reservoir and host populations. In Western and Central Europe as well as in Scandinavia, the Americas and Asia climatic, while anthropogenic factors have been implicated in hantavirus outbreaks, although with different outcomes [71]. In an attempt to compare the driving characteristics for Hantavirus outbreaks in Belgium, France and Germany - three countries with common borders and common endemic regions for sHantavirus infections - we found only partial evidence for common outbreaks. The most puzzling were the isolated outbreaks in the three countries while the rodent food situation and climatic conditions did not differ significantly. We also noted that, for instance oak/beech mast events, held responsible Hantavirus epidemics in the recent past, were sometimes absent the year before an outbreak in the last decade [10]. Lacking in many European countries are long-term and comparable data series on hard mast, anthropogenic impact assessments and other parameters discussed above. Loyal to the very nature of a zoonotic disease, i.e. an event for which we usually only observe the proverbial "top of the iceberg" at the peak of the outbreak and the full extent on hindsight, it seems extremely difficult to predict outbreaks. It can however be anticipated that hantaviruses will remain a significant public health threat in the years to come [14].

Acknowledgements

"In all things there is a law of cycles" Publius Cornelius Tacitus (56 – 117 AD).
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References

1. May RM, Anderson RM (1983) Parasite–Host Coevolution. In Coevolution, D.J. Futuyma and M. Slatkin, 186–206. Sunderland, M.A.: Sinauer Associates.
2. Dieckman U (2002) Adaptive Dynamics of Pathogen–Host Interactions. In: Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management, eds. Dieckmann U, Metz JAJ, Sabelis MW & Sigmund K, 39-59. Cambridge University Press.
3. Vapalahti O, Mustonen J, Lundkvist A, et al. (2003) Hantavirus Infections in Europe. The Lancet Infectious Diseases; 3(10): 653-661.
4. Engelthaler DM, Mosley DG, Cheek JE, et al. (1999) Climatic and Environmental Patterns Associated with Hantavirus Pulmonary Syndrome, Four Corners Region, United States. Emerg Infect Dis; 5(1): 87–94.
5. Jaksic FM, Lima M (2003) Myths and Facts on Ratadas: Bamboo Blooms, Rainfall Peaks and Rodent Outbreaks in South America. Austral Ecology; 28(3): 237-251.

6. Zhang WL, Guo WD, Fang LQ, et al. (2010) Climate Variability and Hemorrhagic Fever with Renal Syndrome Transmission in Northeastern China. Environ Health Perspect; 118(7): 915-920.
7. Yan L, Fang LQ, Huang HG, et al. (2007) Landscape Elements and Hantaan Virus–Related Hemorrhagic Fever with Renal Syndrome, Peoples Republic of China. Emerg Infect Dis; 13(9): 1301-1306.
8. Hanski I, Henttonen H, Korpimaki E, et al (2001) Small-Rodent Dynamics and Predation. Ecology; 82(6): 1505-1520.
9. Lambin X, Bretagnolle V, Yoccoz NG (2006) Vole Population Cycles in Northern and Southern Europe: Is There a Need for Different Explanations for Single Pattern? J Anim Ecol; 75(2): 340-349.
10. Heyman P, Thoma BR, Marié JL, et al. (2012) In Search for Factors That Drive Hantavirus Epidemics. Front Physiol; 3: 1-23.
11. Tersago K, Verhagen R, Vapalahti O, et al. (2011) Hantavirus Outbreak in Western Europe: Reservoir Host Infection Dynamics Related to Human Disease Patterns. Epidemiology and Infection 139(3): 381–390.
12. Heyman P, Cochez C, Korukluoglu G, et al. (2011) Bridging Continents; Hantaviruses of Europe and Asia Minor. [Kitalararasi Köprü; Avrupa ve Küçük Asyanin Hantavirüsleri]. Turk Hij Den Biyol Derg. 68(1): 41–48.
13. Avsic-Zupanc, T, Xiao SY, Stojanovic R, et al. (1992) Characterization of Dobrava Virus: A Hantavirus from Slovenia, Yugoslavia. J Med Virol; 38(2): 132-137.
14. Heyman P, Vaheri A, Lundkvist A, et al. (2009) Hantavirus Infections in Europe: From Virus Carriers to a Major Public-Health Problem. Expert Rev Anti Infect Ther; 7(2): 205-217.
15. Wereszcynska AM, Nowakowski WH (2004) What Food Allows Bank Voles to Stay Fit in Spring? EJPAU; 7(2): 1-10.
16. Gebczynska Z (1976) Food Habits of the Bank Vole and Phonological Phases of Plants in an Oak-Hornbeam Forest. Acta Theriologica; 21(16): 223-236.
17. Viro P, Sulkava S (1985) Food of the Bank Vole in a Northern Finnish Spruce Forest. Acta Theriologica 30(15): 259-266.
18. Jensen SP (1993) Temporal Changes in Food Preferences of Wood Mice (Apodemus Sylvaticus L.). Oecologica; 97(1): 76-82.
19. Borowski Z (2007) Damage Caused by Rodents in Polish Forests. Int J Pest Management; 53(4): 303-310.
20. Heroldova M, Bryja J, Janova E, et al (2012) Rodent Damage to Natural and Replanted Mountain Forest Regeneration. The Scientific World Journal; 1: 1-6.

21. Bozinovic F (1997) Diet Selection in Rodents; an Experimental Test of the Effect of Dietary Fiber and Tannins on Feeding Behavior. Revista Chilena de Historia Natural; 70: 67-71.
22. Olsson GE, Leirs H, Henttonen H (2010) Hantaviruses and Their Hosts in Europe: Reservoirs Here and There, but Not Everywhere? Vector Borne Zoonotic Dis; 10(6): 549-561.
23. Kelly D, Koenig WD, Liedhold AM (2008) An Intercontinental Comparison of the Dynamic Behavior of Mast Seeding Communities. Popul Ecol; 50(4): 329–342.
24. Schwarz AC, Ranft U, Piechotowski I, et al. (2009) Risk Factors for Human Infection with Puumala Virus, Southwestern Germany. Emerg Infect Dis; 15(7): 1032-1039.
25. Kelly D (1994) The Evolutionary Ecology of Mast Seeding. Tree; 9(12): 465–470.
26. Selás, V (1997) Cyclic Population Fluctuations of Herbivores as an Effect of Cyclic Seed Cropping of Plants: The Mast Depression Hypothesis. Oikos; 80(2): 257-268.
27. Hansson L (1998) Mast Seeding and Population Dynamics of Rodents: One Factor Is Not Enough. Oikos; 82(3): 591-594.
28. Hilton GM, Packham JR (2003) Variation in the Masting of Common Beech (Fagus Sylvatica L) in Northern Europe over Two Centuries (1800-2001). Forestry; 76(3): 319-328.
29. Takuya S, Takashi S (2006) Re-Evaluation of the Relationship between Rodent Populations and Acorn Masting: A Review from the Aspect of Nutrients and Defensive Chemicals in Acorns. Population Ecology; 48(4): 341-352.
30. Rakic S, Povrenovic D, V Tesevic, et al. (2006) Oak Acorn, Polyphenols and Antioxidant Activity in Functional Food. Journal of Food Engineering 74(3): 416-423.
31. Feijen JM (2003) Oak, King or Villein? Forest Ecology and Forest management, Wagenningen, The Netherlands: Wageningen University.
32. Deforce K, Bastiaens J, Van Calster H, et al. (2009) Iron Age Acorns from Boezinge (Belgium): The Role of Acorn Consumption in Prehistory. Archaol. Korrespondenzbl; 39(3): 381-392.
33. Heyman P, Cochez C, Simons L, et al. (2013) Breeding Success of Barn Owls Reflects Risk of Hantavirus Infection. Vet Rec; 172(11): 290.
34. Flowerdew JR, Ellwood SA (2001) Impacts of Woodland Deer on Small Mammal Ecology. Forestry; 74(3): 277-287.
35. Steen H, Mysterud A, Austrheim G (2005) Sheep Grazing and Rodent Populations:

Evidence of Negative Interactions from a Landscape Scale Experiment. Oecologia; 143(3): 357-364.

36. Fournier-Chambrillon Ch, Maillard D, Fournier P (1995) Diet of the Wild Boar (Sus Scrofa L) Inhabiting the Montpellier Garrigue. IBEX JME; 3: 174-179.
37. Schley L, Roper TJ (2003) Diet of Wild Boar Sus Scrofa in Western Europe, with Particular Reference to Consumption of Agricultural Crops. Mammal Review 33(1): 43-56.
38. Focardi S, Capizzi D, D Monetti (2000) Competition for Acorns among Wild Boar (Sus Scrofa) and Small Mammals in a Mediterranean Woodland. Journal of Zoology; 250(3): 329-334.
39. De Vries W, Reinds GJ, Van Dobben H, et al. (2002) Intensive Monitoring of Forest Ecosystems in Europe, 2002. Technical Report UN/ECE 2002. Brussels, Geneva: EC.
40. EU 2010 Biodiversity Baseline. 2010 Technical Report 12/2010. Brussels: European Environment Agency.
41. Peixoto, ID, Abramson G (2006) The Effect of Biodiversity on the Hantavirus Epizootic. Ecology; 87(4): 873-879.
42. Keesing F, Belden LK, Daszak P, et al. (2010) Impacts of Biodiversity on the Emergence and Transmission of Infectious Diseases. Nature; 468: 647-652.
43. Sterner RT, Shumake SA (2001) Coyote Damage Control Research: A Review and Analysis. In Coyotes: Biology, Behavior, and Management., Bekoff M, 297–325. Blackburn Press.
44. Hairston NG, Smith FE, Slobotkin LB (1960) Community Structure, Population Control and Competition. American Naturalist; 94(879): 421-425.
45. Soulé ME, DT Bolger, AC Alberts, et al. (1988) Reconstructed Dynamics of Rapid Extictions of Chaparral-Requiring Birds in Urban Habitat Islands. Conservaton Biology 2(1): 75–92.
46. Prugh LR, Stoner CJ, Epps CW, et al. (2009) The Rise of the Mesopredator. BioScience; 59(9): 779-791.
47. Beschta RL (2003) Cottonwoods, Elk, and Wolves in the Lamar Valley of Yellowstone National Park. Ecological Applications; 13(5): 1295-1309.
48. Gehrt SD, Clark WR (2003) Raccoons, Coyotes and Reflexions on Mesopredator Release Hypothesis. Wildlife Society Bulletin; 31(3): 836-842.
49. Direct Observations of Recent Climate Change. 2007 IPCC, AR4 Working Group 1.
50. Sommers WT, Coloff SG, Conard SG (2009) Synthesis of Knowledge: Fire History and Climate Change. Final Report to the Joint Fire Science Program, JFSP Project 09-02-1-09. JFSP.

51. Adler GH, Levins R (1994) The Island Syndrome in Rodent Populations. Q Rev Biol; 69(4): 473-490.
52. Meiri S, Cooper N, Purvis A (2008) The Island Rule: Made to Be Broken? Proc Biol sci;. 275(1631): 141–148.
53. Boonstra R (1994) Population Cycles in Microtines: The Senescence Hypothesis. Ecol Evol; 8(2): 196-219.
54. Pedersen AB, Greives TJ (2008) The Interaction of Parasites and Resources Cause Crashes in a Wild Mouse Population. J Anim Ecol 77(2): 370-377.
55. Smith MJ, White A, Sherratt JA, et al. (2008) Disease Effects on Reproduction Can Cause Population Cycles in Seasonal Environments. J Anim Ecol 77(2): 378-389.
56. Sakai A, Allendorf FW, Holt JS, et al. (2001) The Population Biology of Invasive Species. Annual Reviews of Ecology and Systematics 32: 305-332.
57. Kirchner JW, Roy BA (2002) Evolutionary Implications of Host–Pathogen Specificity: Fitness Consequences of Pathogen Virulence Traits. Evol Ecol Res 4: 27-48.
58. Noonburg EG, Byers JE (2005) More Harm than Good: When Invader Vulnerability to Predators Enhances Impact on Native Species. Ecology 86(10): 2555-2560.
59. Doody JS, Green B, Rhind D, et al. (2009) Population-Level Declines in Australian Predators Caused by an Invasive Species. Animal Conservation; 12(1): 46–53.
60. Heyman P, Ceianu CS, Christova I, et al. (2011) A Five-Year Perspective on the Situation of Haemorrhagic Fever with Renal Syndrome and Status of the Hantavirus Reservoirs in Europe, 2005-2010. Euro Surveillance: Bulletin Européen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin; 16(36): 977-986.
61. Dervović E, Salimović-Bešić I, Šeremet M, et al. (2015) EV1083: The Potential Impact of Climate Conditions and Catastrophic Floods in Bosnia and Herzegovina on Expanding Hantavirus Infection during April-September 2014. Dervović E, Salimović-Bešić I, Šeremet M, Knežević Z, Dedeić-Ljubović A, Hukić M. In . 25th ECCMID, Copenhagen, Denmark.
62. Heimann M, Reichstein M (2008) Terrestrial Ecosystem Carbon Dynamics and Climate Feedbacks. Nature; 451: 289-292.
63. Mather J. (2013) Marine Invertebrates: Communities at Risk. Biology; 2(2): 832–840.
64. Halpern BS, Walbridge S, Selkoe KA, et al. (2008) A Global Map of Human Impact on Marine. Science; 319(5865): 948-952.

65. Bellwood DR, Hughes TP, Folke C, et al. (2004) Confronting the Coral Reef Crisis. Nature; 429: 827-833.
66. Perry AL, PJ Low, JR Ellis, et al. (2005) Climate Change and Distribution Shifts in Marine Fishes. Science; 308(5730): 1912-1915.
67. McKinney ML (2002) Urbanization, Biodiversity, and Conservation: The impacts of urbanization on native species are poorly studied, but educating a highly urbanized human population about these impacts can greatly improve species conservation in all ecosystems. BioScience; 52(10): 883–890.
68. Corvalan C, Hales S, McMichael A (2005) Ecosystems and Human Well-Being : Health Synthesis : A Report of the Millennium Ecosystem Assessment. WHO.
69. Burroughs T, Knobler S, Lederberg J (2002) The Emergence of Zoonotic Diseases- Understanding the Impact on Animal and Human Health. Washington D.D., USA: National Academy Press.
70. Carey DE, Reuben R, Panicker KN, et al. (1971) Thottapalayam Virus: A Presumptive Arbovirus Isolated from a Shrew in India. Indian J Med Res; 59(11): 1758-1760.
71. Klempa B (2009) Hantaviruses and Climate Change. Clin Microbiol and Infect; 15(6): 518-523.
72. Catherine L, Lamarque P, Heyman P, et al. (2007) Determinants of the Geographic Distribution of Puumala Virus and Lyme Borreliosis Infections in Belgium. International Journal of Health Geographics 6: 15.
73. Matt F, Gebser R (2010) Biodiversity Decline Can Increase the Spread of Infectious Diseases. TEEB. www.TEEBweb.org.
74. Woods M, McDonald RA, Harris S (2003) Domestic Cat Predation on Wildlife. Mammal Review; 33(2): 174-188.