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Cyclic hantavirus epidemics in humans — Predicted by rodent host dynamics

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ABSTRACT

Wildlife-originated zoonotic diseases are a major contributor to emerging infectious diseases. Hantaviruses cause thousands of human disease cases annually worldwide, and understanding and predicting human hantavirus epidemics still poses unsolved challenges. Here we studied the three-level relationships between the human disease nephropathia epidemica (NE), its etiological agent Puumala hantavirus (PUUV) and the rodent host of the virus, the bank vole (*Myodes glareolus*). A large and long-term data set (14 years, 2583 human NE cases and 4751 trapped bank voles) indicates that the number of human infections shows both seasonal and multi-annual fluctuations, is influenced by the phase of vole cycle and time of the year, and follows vole abundance with a lag of a few months. Our results suggest that although human hantavirus epidemics are preceded by high sero prevalence in the host population, they may be accurately predicted solely by the population dynamics of the carrier species, even without any knowledge about hantavirus dynamics in the host populations.

Introduction

More than half of the known human pathogens are zoonotic, and the majority of these have their origin in wildlife species (Jones et al., 2008). A feature typical for wildlife-originated zoonoses is that the densities of their host populations tend to fluctuate. An example of this is small rodent populations, which typically show seasonal but often also multi-annual fluctuations in abundance (Davis et al., 2005; Korpimäki et al., 2004; Lambin et al., 2006; Stenseth, 1999; Stenseth et al., 1998). As the most specious and widely distributed mammalian group, rodents are the wildlife reservoir for many zoonoses (Mills and Childs, 1998; Ostfeld and Holt, 2004), characterized by considerable variation in ecology and life-history. Although high rodent abundance is assumed and predicted to increase the risk of human exposure to rodent-borne (robo-) diseases, direct evidence of this relationship is still scarce (Davis et al., 2005; Mills and Childs, 1998; Olsson et al., 2003b, 2009; Tersago et al 2009). Understanding the features involved in the transmission of robo-diseases to humans is thus an important challenge.

Hantaviruses represent a group of zoonotic robo-viruses (and increasing number of insectivore-borne viruses) distributed more widely in the world than any other known viruses carried by wildlife animals (Nemirov et al., 2004). They are a good example of pathogens that circulate in their rodent host species in nature and are accidentally transmitted to humans with several of them causing human diseases of varying severity (Vaheri et al., 2008).

Puumala virus (PUUV, genus *Hantavirus*, family *Bunyaviridae*) is carried by the bank vole (*Myodes glareolus*) (Brummer-Korvenkontio et al., 1980) and infection in bank voles is chronic and asymptomatic (Bernshtein et al., 1999; Meyer and Schmaljohn, 2000; but see Kallio et al., 2007). PUUV virus is transmitted horizontally via direct or indirect contacts between the bank voles and to humans (e.g. Gavrilovskaya et al., 1990; Kallio et al., 2006a; Niklasson et al., 1995; Hardestam et al., 2008). In humans, PUUV causes nephropathia epidemica (NE), which is a mild form of hemorrhagic fever with renal syndrome (HFRS) with thousands of diagnosed cases annually in Europe and European Russia (Vapalahti et al., 2003). Human NE epidemics have been observed to reflect the fluctuations in bank vole populations, with a high number of human cases when bank voles are abundant (e.g. Brummer-Korvenkontio et al., 1982; Heyman et al., 2001; Niklasson et al., 1995; Olsson et al., 2003b; 2009; Rose et al., 2003).

The bank vole, the carrier of PUUV, is a common rodent species in most of Europe. However, the population dynamics of the bank vole differ greatly in various parts of Europe. Seasonal fluctuations with

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occasional mast-driven outbreak characterize temperate Europe, while in Northern Fennoscandia, bank vole populations show multi-annual cyclic fluctuations. These bank vole cycles are three to five years in length and of high amplitude. They occur simultaneously with other sympatric vole species and are synchronous over large areas (Hansson and Henttonen 1988; Korpimäki et al., 2005). These variations in the dynamics are well-reflected in human NE epidemiology. Therefore, to understand the human epidemics, it is essential to study dynamical dependencies in various biomes in Europe.

Human hantavirus epidemics have often been explained by rodent host abundance (Heyman et al., 2001; Mills and Childs, 1998; Niklasson et al., 1995; Olsson et al., 2003b, 2009; Rose et al., 2003) although solid data supporting this are scarce. The explanation is based on the assumption that higher host densities increase both the number of infected individuals and the infection prevalence, as is expected with density-dependent pathogen transmission (Adler et al., 2008; Davis et al., 2005; Escutenaire et al., 2000; Mills et al., 1999; Olsson et al., 2003a). However, field studies have not consistently demonstrated this density-dependent relationship. For example, in some, PUUV hantavirus prevalence shows direct or delayed density dependence on the abundance of bank vole (Niklasson et al., 1995; Olsson et al., 2002). However, Olsson et al. (2005) concluded that PUUV transmission among rodents is independent of bank vole density. Studies on non-cyclic bank vole populations in temperate areas have demonstrated a threshold density below which PUUV does not persist in the host populations but above which no clear relationship between prevalence and bank vole density is apparent (Escutenaire et al., 2000; Tersago et al., 2008). Hence, further studies are needed to verify how the circulations of rodent-borne pathogens in their natural host populations are transformed into human epidemics.

The aim of this study is to investigate how PUUV hantavirus infection dynamics in rodents are translated into human epidemics using three-level data from human NE epidemics, bank vole population dynamics and PUUV dynamics in bank vole populations in an endemic area in Finland.

Materials and methods

Human data

The Finnish National Institute for Health and Welfare maintains the National Infectious Disease Registry (http://www3.ktl.fi/), into which laboratory-confirmed diagnoses of PUUV infection have been reported since 1995. In this study, the data are the number of human NE cases that have been collected from the health-care district of Central Finland from July 1995 to December 2008 (data updated 17.2.2009) (Fig. 1). This health-care district covers an area of 19763 km^2. Of the land area (~86% of the total area), 80% is covered by forest habitats. In 2004, there were 270701 inhabitants in the area, or 16 persons per km^2 (http://www.keskisuomi.fi/). The total number of diagnosed human NE cases in the area was 2583 during the study.

Bank vole data

Voles were trapped in the Konnevesi area in Central Finland (628379 N, 268209 E, Fig. 1) four times per year from July 1995 to October 2008. The first trapping session (spring) was carried out in early breeding season in May. The second (summer) was conducted typically during the first week of July, in the middle of the breeding season. The third (late summer) was typically in late August, and the fourth (late autumn) was carried out in late October–early November, after the breeding season typically just before the first snowfall.

There were 20 permanent trapping sites, in each of which four Ugglan Special multiple-capture live traps (Grahnab, Hillerstorp, Sweden) were situated at the corners of a 15-meter square (Mappes et al., 2008). The trapping plots were situated in coniferous forest dominated by Scots pine (*Pinus sylvestris*), Norway spruce (*Picea abies*) and various shrubs (e.g. *Calluna* sp., *Vaccinium* spp.) and the plots were chosen to be all in a similar habitat. Before each trapping session the traps were prebaited with sunflower (*Helianthus annuus*) seeds for two days, after which they were set for two consecutive days and nights and checked daily (altogether 160 trapping nights/session). The results for bank vole abundance are based on the pooled data from the trapping sites. As the 20 trapping sites were distributed over an area of approximate size 100 km^2, this estimate should be robust. It also conforms closely to a larger multi-annual pattern of voles in South-Central Finland during 1995–2008 (The National Vole Monitoring by the Finnish Forest Research Institute, in Finnish, http://www.metla.fi/).

From May 2002, captured voles were taken to the laboratory where a blood sample was taken from retro-orbital sinus with 18 μl capillary tubes (Haematocrit capillaries, Hirschmann Laborgeräte, Germany). In July 2006 only, the captured animals were euthanized and stored at −20 °C and later dissected, and the heart and visible frozen blood gathered and dissolved in PBS and this suspension was used to detect PUUV antibodies (see below).

Monthly indices of bank vole abundance were computed so that they could be related to the monthly human NE data. For this, the number of bank voles captured during each trapping session was used. The spring trapping each year was carried out when few newborn individuals existed or were trappable (<2% individuals trapped weighed less than 17 g) and the late autumn trapping was performed after the breeding season (<5% individuals weighed less than 13.5 g). Typically, the highest numbers of voles were captured during the late summer trapping session in August. Therefore, our trappings can be presumed to have coincided with the annual minimum and maximum sizes of the local bank vole populations and linear interpolation

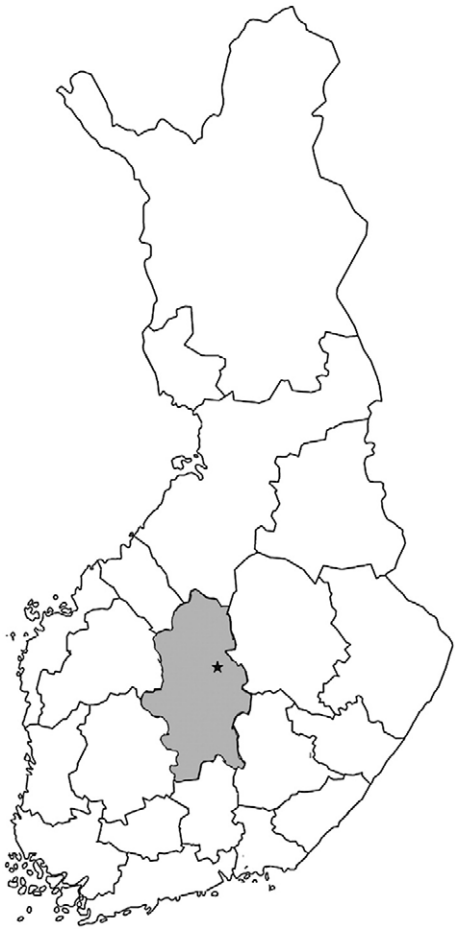

Fig. 1. The location of health-care district of Central Finland (grey) and the Konnevesi study area (dot).

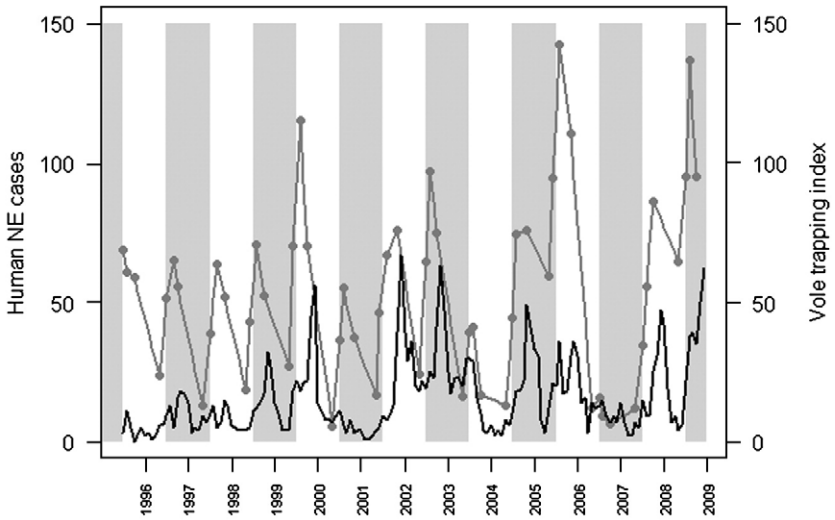

Fig. 2. Monthly numbers of human NE cases in Central Finland (black line) and the density index of bank voles (grey line) at Konnevesi in 1995–2008 (vole trapping index = captured individuals / 100 trap nights, monthly data are interpolated from the trappings carried out four times per year, trappings are indicated with dots). Biological years (see Materials and methods) are marked with open and shaded bars.

between the actual trapping sessions may give reliable approximations for the bank vole abundances for the non-trapped months, although it is known that the timing of a population crash in the decline phase may vary from mid winter to spring.

Puumala virus data

PUUV antibodies were screened from the bank vole blood samples collected from spring 2002 until late autumn 2008 using an immunofluorescence assay (IFA) (Vapalahti et al., 1995). The whole blood samples were diluted 1:10 in PBS for the IFA. Although PUUV-specific antibodies are transferred from an infected female to its offspring (Kallio et al., 2006b) and they are detected as positive results using IFA, it was not possible in this study to separate individuals that were carrying maternal antibodies from those in which antibodies were induced by genuine infection. Therefore all seropositive individuals are assumed to reflect PUUV infection, although a substantial number of young individuals may carry maternal antibodies when the infection prevalence in reproducing females is high (typically in late summer of vole peak year, when one third of seropositivity may be of maternal origin (our unpublished data)). Because seroprevalence is influenced by several independent biological factors (PUUV transmission as well as demographic processes in the host population), we did not interpolate the PUUV data. Hence, in all analyses where PUUV data are used as explanatory variables, the data are restricted to the actual trapping periods during 2002–2008.

Statistical analyses

Time series analyses of human NE data and monthly bank vole data were carried out using autocorrelation analysis and cross-correlation analysis to characterize and describe the seasonal and multi-annual patterns in the data sets. For these analyses the data were detrended in two ways. To highlight the seasonal fluctuations, the monthly number of human cases and voles were subtracted from the annual mean (calculated over the time from July to following June) of human cases and voles, respectively. This 'biological year' was based on the changes in bank vole population sizes: due to the seasonal breeding, bank vole abundance may increase only during summer, whereas the population size during the rest of the year is determined by the population size at the end of the breeding season and mortality. In our data, young individuals were first observed typically during the summer trapping (July) and hence July was determined to start the biological year. To highlight the multi-annual fluctuations, the data were detrended by subtracting the monthly values from the overall mean (over the whole study period).

Further statistical analyses addressed several issues. First, the monthly numbers of human NE (natural log-transformed) cases were investigated in relation to bank vole abundance (including interpolated values) with lags. Optimal models were selected using criteria (see below) for which the sample size needs to remain constant for all possible models (Burnham and Anderson, 2002). Because the bank vole abundances (natural log-transformed) in preceding months (up to 6 months earlier) were used as continuous predictors for the human cases, and since the first vole abundance data were collected in July 1995, the analysis was limited to the period between January 1996 and October 2008. Second, NE cases during the annual peak month (the month showing the highest number of human cases during the biological year) were studied in relation to bank vole trapping data (no interpolated values). In these analyses, the data contained human cases up to December 2008 and bank vole abundance from each trapping session. Third, human cases were studied in relation to the PUUV data, which were available from spring 2002 until late autumn 2008.

The categorical fixed effects in the models were the month and the phase of the vole cycle. Years (July to next June) were classified into four vole cycle categories according to the peak bank vole density attained *within* a year, and the peak density attained in the preceding and succeeding year. For example, a low year is a year peaking typically at less than 100 captured individuals per trapping session (vole trapping index (= captured individuals/100 trapping nights) <62.5), preceded by a year peaking at more than 150 captured individuals (high year, vole trapping index >93.75) and followed by a year peaking at 100–150 individuals (increase year). From summer 1995 until summer 1998 the bank vole abundance varied only seasonally in our study area (Fig. 2). Consequently, there were four vole cycle phases: stable years (until June 1998), low years (2000/2001, 2003/2004 and 2006/2007), increase years (1998/1999, 2001/ 2002, 2004/2005 and 2007/2008), and high years (1999/2000, 2002/2003, 2005/2006 and 2008 (until December 31)).

Analyses of the monthly number of human NE cases (natural log-transformed) were conducted using linear mixed-effect models (LMM) with year (varying intercept) as a random effect, using the R statistical software package (http://www.r-project.org). Starting from a maximum model, models were restricted using, separately, both AIC and BIC (Akaike and Bayesian information criteria), the latter penalizing complex models more strongly (Johnson and Omland, 2004), with terms being eliminated if they did not reduce the AIC or BIC by more than 2 units when included (Burnham and Anderson, 2002). Models were

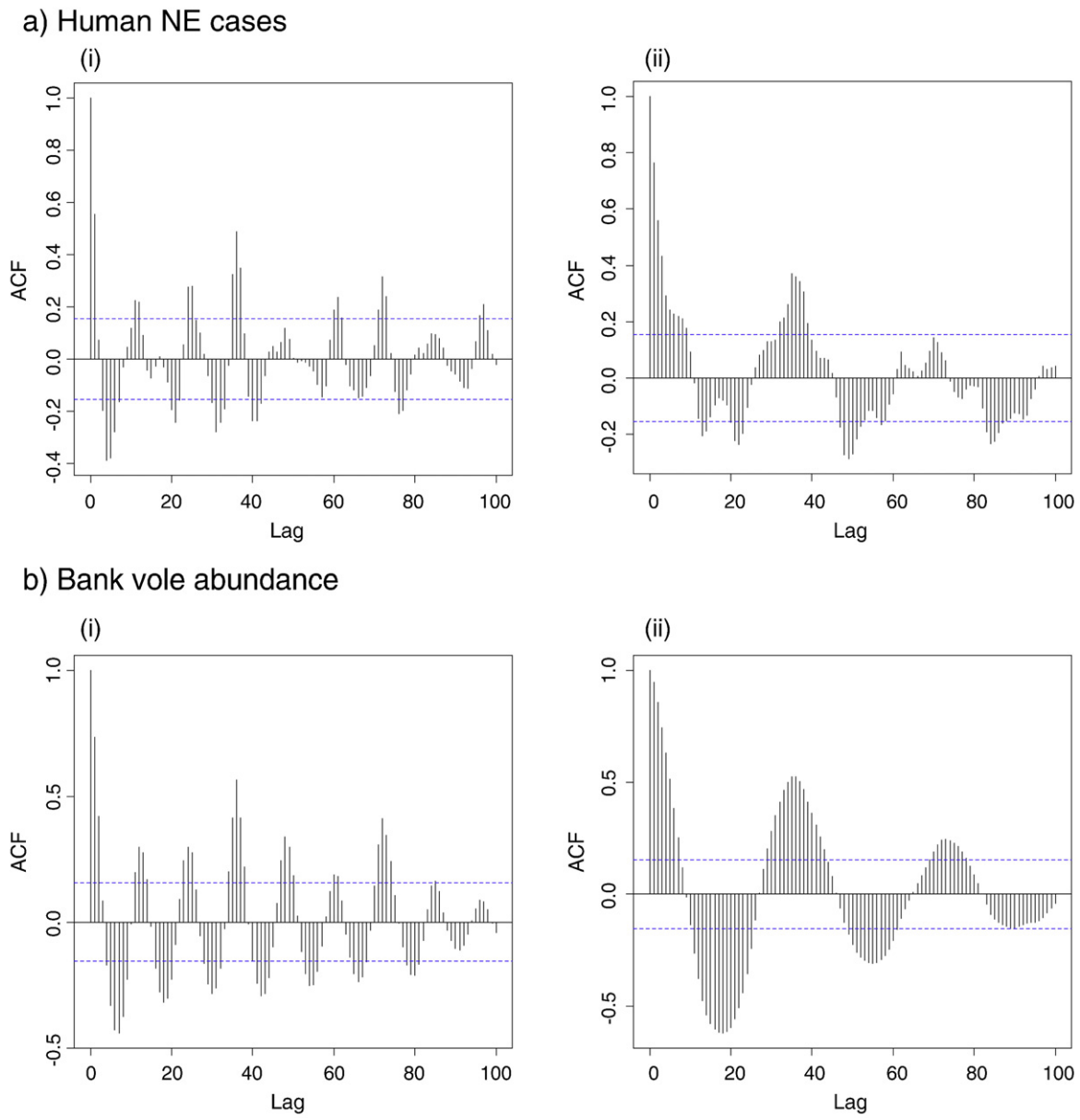

Fig. 3. Autocorrelation functions (ACFs) for time series of (a) human NE cases in Central Finland and (b) bank vole abundances at Konnevesi at time lags of 0–100 months. Bars that cross the dashed horizontal lines (95% confidence interval) indicate significant evidence for fluctuations in (i) multi-annual and (ii) in seasonal manner with a period length equal to the number of lags on the *x*-axis. For detrending the original values see Materials and methods.

included in the final set of 'supported models' if their AIC (or BIC) was within 2 of the model receiving the strongest support and they were not more complex than the best-supported model. The maximum likelihood (ML) method was used during the model selection procedure. The parameter coefficients for the most important variables were estimated by 'restricted maximum likelihood' (REML) methods.

Other questions were implemented using standard statistical techniques using SPSS version 14.0 (SPSS Inc., Chicago, IL).

Results

Monthly human NE cases and bank vole abundance

The dynamics of the human NE cases ($n = 2583$) and bank voles ($n = 4751$) over the 14-year study period in Central Finland are shown in Fig. 2. During the first three years of the study (from July 1995 to June 1998), the bank vole populations showed only seasonal fluctuations and the monthly number of human cases remained relatively stable compared to later years. Thereafter, bank vole abundances started to fluctuate in a multi-annual manner, reaching a first high phase of the cycle in 1999/2000, such that the previous biological year was designated an increase year. The number of human cases was also higher in 1999, reaching its peak slightly after the bank vole population density peak. Later, both the bank vole abundance and the number of human NE cases showed seasonal and multi-annual fluctuations (Figs. 2 and 3). In most years the numbers of human NE cases reached their peak after the voles reached their highest annual abundance. However, the obvious difference in bank vole abundances between increase and high years is not reflected in the human epidemics. In fact, human peaks were slightly higher in the increase (2001 and 2004) than in the high (2002 and 2005) phase of vole cycles.

Autocorrelation analyses

Autocorrelation analyses showed clear annual fluctuations both for the human cases and vole abundance, having significant negative

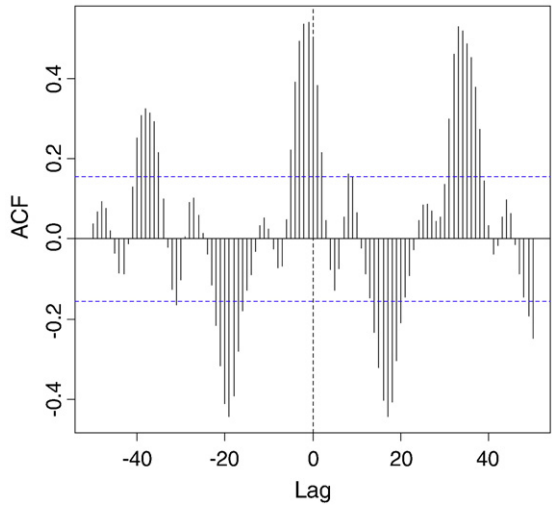

Fig. 4. Cross-correlation function (CCF) for the time series of the number of human NE cases and bank vole abundances in 1995–2007, at time lags of 0–100 months, in Central Finland. Bars that cross the dashed horizontal lines (95% confidence interval) indicate significant evidence for correlation between the two time series. Highest correlation was between human cases at time (lag = 0, vertical dashed line) and bank vole abundance 1 to 3 months earlier (lag = 1 to 3).

correlation with, for example, a lag of approximately six months (Fig. 3) and significant positive correlation with time lag of approximately twelve months. The human cases and bank vole abundances also fluctuated with three years cycles (Fig. 3). Cross-correlation analysis between the vole and human NE case time series (Fig. 4) indicated that the human cases followed the bank vole abundance with a 1 to 3 month lag.

Linear mixed models

The monthly number of human NE cases was studied further using linear mixed models. The best model based on AIC included the variables month and phase of cycle, and their interaction term, and bank vole abundance five months earlier (N_{t-5}) (Table 1 and Table 2). Using BIC, the best model included only season and phase of cycle without their interaction (Table 1). Among the other supported models, bank vole abundance in another of the previous six months was included within 2 AIC units of the best. Hence there was strong support for including month and the phase of the rodent cycle in the optimal predictive model of the current number of human cases (Table 2) and some support, too, for including past bank vole abundance. The number of human cases was lowest during low phase of vole cycle and when the host population was not showing cyclic fluctuations and highest during rodent peaks. The months differed from one another, with the highest number of human cases occurring during November and December and the lowest number during February–June (Table 2).

Table 1
Results from model selection procedures to explain the number of human nephropathia epidemica cases using variables *month* and *phase of vole cycle* as well as the *bank vole abundance* during current (N_t) and previous months (N_{t-1}–N_{t-6}).

a) Model	AIC	ΔAIC	No. of parameters
Month * Phase of cycle + Voles (N_{t-5})	259.75	–	51
Month * Phase of cycle + Voles (N_{t-6})	261.13	1.38	51
Month * Phase of cycle + Voles (N_{t-1})	261.55	1.80	51
Month * Phase of cycle + Voles (N_{t-3})	261.66	1.91	51
Month * Phase of cycle + Voles (N_t)	261.69	1.94	51
b) Model	BIC	ΔBIC	No. of parameters
Month + Phase of cycle	337.49	–	17

a) indicates the best set of models selected using AIC, and b) shows the model selected using BIC.

Table 2
Parameter coefficients for the variables *month* and *phase of cycle*, which were supported as important predictors for the number of human NE cases of a month both using AIC and BIC (Table 1).

Monthly human NE cases	Parameter estimate	SE	*t*-value
Intercept	2.16209	0.21626	9.998
Month			
February	−0.57018	0.21549	−2.646
March	−0.90078	0.21549	−4.180
April	−1.09483	0.21549	−5.081
May	−0.55792	0.21549	−2.589
June	−0.34732	0.21549	−1.612
July	−0.01583	0.21604	−0.073
August	0.09116	0.21604	0.422
September	−0.21591	0.21604	−0.999
October	0.09330	0.21604	0.432
November	0.38036	0.22063	1.724
December	0.40008	0.22063	1.813
Cycle			
Low	−0.21486	0.20318	−1.057
Increase	0.80898	0.18738	4.317
High	1.02453	0.20050	5.110
Random effect: year	$\sigma^2 = 0.056$; sd = 0.237		

Intercept indicates non-cyclic bank vole population and month is January. σ^2 = the variance attributable to random effect. sd = standard deviation of σ^2.

Highest month for human cases

The peak month in the year (July to the following June) in human NE cases during the study period was always reached either in summer (July or August) or in late autumn (November or December), except for one vole peak year (2005), which had the same maximum number of human NE cases in both (see Fig. 2). Summer peaks in human NE cases were significantly lower than those in late autumn (mean ± SD: Summer: 16.5 ± 8.5, Autumn: 45.4 ± 19.5, two-sample *t*-test, $t_{11} = -2.80$, $p = 0.017$).

The timing of the human peak was associated with the phase of the rodent cycle. Thus, in the low phase (high abundance in the previous autumn) the annual human peak was always reached (three occasions) during summer (July or August), whereas in the increase and peak phases this always occurred (seven occasions) in late autumn (November or December) (Fisher's exact test: $p = 0.008$; 2005 excluded and 2008 until December included in the analysis).

The peak in human NE cases was also studied in relation to the actual vole trappings that were carried out. The number of bank voles captured in the preceding year's late autumn was higher when the annual peak in the human NE cases was reached in summer than in late autumn, though the difference was not quite significant (mean of bank voles ± SE: autumn peak 78.4 ± 13.7, summer peak 136.3 ± 20.5, $t_{3.98} = 2.353$, $p = 0.079$). When the annual peak in the human NE cases was reached in late autumn, the numbers of bank voles trapped were higher during that year's late autumn, late summer and (not quite significantly) spring than when the peak was reached during summer (mean of bank vole ± SE: late autumn trapping: autumn NE peak 113.3 ± 8.0, summer NE peak 47.8 ± 18.6, $t_{4.17} = -3.240$, $p = 0.030$; late summer trapping: autumn peak 132.4 ± 14.7, summer peak 66.5 ± 18.4, $t_{6.98} = -2.806$, $p = 0.026$; spring trapping: autumn peak 37.9 ± 8.6, summer peak 18.0 ± 8.5, $t_{9.87} = -1.999$, $p = 0.074$).

Human NE cases and PUUV in bank vole populations

The PUUV data, collected over the years 2002–2008, contained altogether 2481 blood samples from 2571 bank voles, of which 820 were PUUV seropositive. The number of PUUV seropositive bank voles

in the late autumn of the same year was higher when the peak in human NE cases was reached in late autumn than in summer (mean of PUUV seropositives ± SE: autumn peak 34.0 ± 7.1, summer peak 3.5 ± 2.5, $t_{3.63} = -4.073$, $p = 0.018$). During other trapping sessions, neither the number of PUUV seropositives, nor PUUV seroprevalence in bank voles differed between the human NE summer-peak and autumn-peak years ($p \geq 0.1$).

Also, the relationships were studied between the PUUV data during each trapping session and the numbers of human NE cases then and during following nine months. The numbers of human NE cases one to six months after the trapping were positively correlated (Pearson correlations, all $r \geq 0.41$, $p < 0.05$) with the number of PUUV-infected bank voles. However, since high numbers of infected individuals were correlated with the high total numbers of bank voles ($r = 0.78$, $p < 0.001$), which in turn were positively correlated with the number of human cases (see above), this result is perhaps inevitable. In addition, though, PUUV seroprevalence correlated positively with the NE cases five to seven months ahead (all $r \geq 0.43$, $p < 0.05$; for all other months $p > 0.3$).

Discussion

Our results clearly demonstrate that human nephropathia epidemica epidemics in Northern Europe are well predicted by the cyclic phase of the bank vole fluctuations, together with the time of the year and earlier bank vole abundance, even without any knowledge about PUUV dynamics in the bank vole populations. In contrast to earlier studies which provide related evidence (e.g. Brummer-Korvenkontio et al 1982; Niklasson et al., 1995; Olsson et al., 2003b, 2009; Rose et al., 2003), our study period (14 years) covered full three-year cycles and years when the bank vole populations did not fluctuate in a multi-annual manner. As a consequence, it was possible to detect an association between human cases and vole abundance at two scales, i.e. immediate past vole abundance but also the phase of the voles' multi-annual abundance cycle.

Earlier studies on the relationship between human cases and bank vole abundance have shown contradictory results on the delay between the two time series. Niklasson et al. (1995) found a positive correlation between human cases and rodent population size six months earlier. However, their rodent data were 'snapshots' taken twice per year, and so did not allow shorter time delays to be observed. Olsson et al. (2003b) found that human cases during autumn (pooled data over October–December) correlated positively with September bank vole abundance, whereas human cases in winter (January–March) showed no such consistent relationship with September rodent abundance, indicating a time delay shorter than six months. However, their data did not allow fine scale evaluation of the time delay between human NE cases and rodent population size. In the present study, for the first time, the data contain monthly estimates for both human NE cases and for bank vole abundances. The trapping sessions were timed to cover both the lowest and the highest annual population densities (Fig. 2). Thus, although the linear interpolation between these inevitably smoothes the changes in bank vole population size, we contend that the data represent the monthly bank vole abundances very well. Therefore, we also contend that the observed lag, centred around three months (Fig. 4), reliably describes the interaction between human cases and bank vole abundances. Such a lag may also readily be interpreted biologically: the signs of symptoms and the antibody responses in humans take two to six weeks from the actual infection time (Vapalahti et al., 2003; Kramski et al., 2008).

The number of human NE cases was highest between November and January (early–mid winter when rodents enter human dwellings) and lowest between February and June, even after variations in vole abundance had been accounted for. This suggests there is variation in the transmission rate (perhaps the encounter rate) between voles and humans. However, the peak in human cases in any given year occurred either during late autumn–early winter (November–December) or during the summer (July or August), though these summer peaks were significantly lower than those occurring in late autumn. The summer peaks followed relatively high abundances of bank voles in the previous late autumn (rather than being associated with high vole abundance in the current year) and occurred with the incubation time lag time after most people had their summer vacations in the countryside during July (Brummer-Korvenkontio et al., 1999).

Recent studies emphasize the difference between the boreal and temperate patterns in human NE epidemics. In contrast to the high risk to humans in Finland in late autumn–winter, the highest numbers of NE cases in Western Europe (Belgium) occur during summers in years when bank vole abundance is high, where high epidemic years are predicted by climate and tree seed production, masting (Clement et al., 2009; Tersago et al., 2009). A high summer temperature induces the formation of flower buds of deciduous forest trees (oak and beech), and in the next year the seed production is abundant. Acorn and beechmast fall down in autumn, contributing to the high winter survival and early breeding of rodents, consequently leading to high rodent densities and numbers of human NE cases in summer (Clement et al., 2009; Tersago et al., 2009). In this scenario, there is a two year time lag between high summer temperature and human outbreak (Clement et al., 2009; Tersago et al., 2009). In the boreal zone, like in Finland, primarily coniferous forests do not provide significant mast production, so the vole cycles are determined predominantly by interactions between voles and their specialist mammalian predators and winter food resources (Hansson and Henttonen 1988; Hanski et al., 1991; Huitu et al. 2007; Korpimäki et al., 2005).

Interestingly, in two cases, higher numbers of NE cases were observed during the increase phase of the vole cycle than in the following peak phase (biological years 2001/2002 and 2004/2005) (Fig. 2). An association with the increase phase is understandable: a large number of new susceptible individuals in the host population should support a high transmission rate for PUUV, and consequently a high number of bank voles should become infected and shed the virus, increasing the risk to humans (Davis et al., 2005; Mills et al., 1999; Sauvage et al., 2006). Why, though, is the number of human cases not higher during the following peak phase when the vole density is higher? One explanation could be that PUUV transmission is limited despite the high density during the peak phase. Although PUUV causes a chronic infection in bank voles, individuals apparently secrete the virus only during a limited time of the infection (Hardestam et al., 2008). If most individuals become infected during, say, late autumn or early winter in the increase phase, their infectivity may be relatively low during the next (high phase) breeding season. Restricted transmission may also be caused by maternal antibodies if infection prevalence is high in the beginning of breeding season (Kallio et al., 2006b). Because our PUUV data were collected from May 2002 onward, we are not able to study these suggestions statistically. However, it is worth mentioning that in late autumn 2004 (increase phase with higher human NE peak than in the following vole peak phase) there were more PUUV seropositive individuals (42 positives out of 121) than during the following year's late autumn trapping (38 positives out of 177).

The number of PUUV seropositive bank voles and the PUUV seroprevalence in the host population correlated with the subsequent number of human NE cases when all trapping seasons were investigated simultaneously. This indicates that in addition to the population dynamics of the carrier species, hantavirus dynamics could be used to predict human hantavirus epidemics. According to our knowledge, this kind of evidence is currently lacking, and certainly deserves careful attention. However, as our current analyses cannot take into account the variation in age-structure of bank vole populations between the trapping seasons, the results should be interpreted with caution.

Our results suggest that characteristics of the bank vole population related to the cyclic phase in addition to the mere abundance, may be correlated with human risk. However, our results, relating the human incidence to the numbers of PUUV seropositive voles or overall PUUV seroprevalence in bank voles, received only weak statistical support. Accordingly, human hantavirus epidemics in an endemic area could be predicted solely by the population dynamics of its carrier species. Nonetheless, in order to evaluate and predict the risk to humans of becoming infected by zoonotic pathogens, it is necessary not only to examine correlation patterns between human and reservoir data sets, but to also understand the transmission dynamics of the pathogen in its host species (e.g. Mills and Childs, 1998; Davis et al., 2005; Adler et al., 2008). To summarize, we demonstrated that in the northern boreal zone, the cyclic phase of the bank vole population, together with season and earlier bank vole abundance, even without any knowledge about PUUV dynamics in the bank vole populations, accurately predicts the human epidemics.

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