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The impact of wildlife and environmental factors on hantavirus infection in host and its translation into human risk

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Abstract

Identifying factors that drive infection dynamics in reservoir host populations is essential in understanding human risk from wildlife-originated zoonoses. We studied zoonotic Puumala orthohantavirus (PUUV) in the host, the bank vole (*Myodes glareolus*), populations in relation to the host population, rodent and predator community and environment related factors and whether these processes are translated into human infection incidence. We used 5-year rodent trapping and bank vole PUUV serology data collected from 30 sites located in 24 municipalities in Finland. We found that PUUV seroprevalence was negatively associated with the abundance of red foxes, but this process did not translate into human disease incidence, which showed no association with PUUV seroprevalence. The abundance of weasels, the proportion of juvenile bank voles in the host populations and rodent species diversity were negatively associated with the abundance index of PUUV positive bank voles, which, in turn, showed a positive association with human disease incidence. Our results suggest certain predators, high proportion of young bank vole individuals, and a diverse rodent community, may reduce PUUV risk for humans through their negative impacts on the abundance of infected bank voles.

Keywords

Zoonotic Puumala orthohantavirus, Dilution effect, Top-down trophic interactions, Juvenile dilution effect.

1. Introduction

Rodents are important wildlife hosts of many zoonotic pathogens [1], such as orthohantaviruses (hereon called hantaviruses; family: *Hantaviridae*; genus: *Orthohantavirus,* formerly genus *Hantavirus*). In humans, hantaviruses cause two diseases: Hantavirus cardiopulmonary syndrome (HCPS) has a high case fatality rate (38%) and is caused by hantaviruses present in the New World [2] and milder hemorrhagic fever with renal syndrome (HFRS) in the Old World [3,4]. In Northern Europe, the most common HFRS is nephropathia epidemica (NE), caused by Puumala hantavirus (PUUV), which reservoir host is the bank vole (*Myodes glareolus*) [5,6]. PUUV infection in the bank vole is asymptomatic with fitness costs [7]. PUUV is horizontally transmitted among bank voles and to humans through direct contacts or contaminated environment [8]. Finland has the highest hantavirus disease incidence globally, with 1000–3300 human PUUV infections diagnosed annually [9]. It has been proposed that the risk posed by rodent-borne pathogens are in increase, as the global loss of biodiversity is likely to increase the relative abundance of commensal rodents [10]. Therefore, it is urgent to quantify the role of different mechanisms in driving the infection dynamics in the reservoir host populations and identify whether these processes are translated into human infections.

Previous studies of hantavirus–host systems have been largely focused on the role of small mammal community. For example, many studies aim to understand the relationship between hantavirus prevalence and the density of reservoir hosts. The direction of the relationship is inconsistent in the literature; positive relationship [5,11], negative relationship and an absence of a relationship have all been reported [12–14]. Some studies focused on the impact of other non-host small mammals on hantavirus prevalence with the consideration of the interspecific interactions (i) affecting density/abundance of hantavirus host (i.e., "susceptible

host regulation" [15]) and/or (ii) affecting contact rate of hosts through behaviour (i.e., "encounter reduction"[15]). For instance, field vole (*Microtus agrestis*) has been suggested to reduce PUUV infection rate in the reservoir host bank vole by reducing its abundance through interspecific competition in autumn in Sweden [16]. Hantavirus dilution through encounter reduction has also been suggested in several hantavirus–host systems, including PUUV in Belgium [12] and in Sweden [16] and Sin Nombre hantavirus in the USA [17–19]. The presence of wood mice (*Apodemus sylvaticus*) leads to reduced PUUV infection rate in bank voles, likely through inhibition of encounter rates among bank voles or between bank voles and virus-contaminated environment [12]. In addition, common shrews (*Sorex araneus*) dilute PUUV infection in bank voles, likely through its impact on bank vole behaviour [16]. Meanwhile, a study in Northern Finland [20] reported that the total abundance of other small mammals reduced PUUV seroprevalence in bank voles, but this effect was seasonal, found only in spring (in the breeding season).

Besides (host density and) small mammal species interactions, hantavirus transmission may also be hindered by other mechanisms, resulting in decreased/low infection prevalence or abundance of infected hosts. First, transmission within the host populations may be influenced by population structure. Host individuals of different ages and reproductive conditions differ in their behaviour and immunology (reviewed by [21,22]), which may be translated into differences in infection likelihood. When many juvenile individuals enter the host population, the proportion of infected individuals, and therefore pathogen infection prevalence, is decreased, resulting in a "juvenile dilution effect" [14,23,24]. Moreover, juveniles of infected mothers are protected against infection by maternal antibodies [25–27]. An increasing number of individuals with maternal antibodies may decrease or delay pathogen transmission, affecting the seasonal dynamics of the pathogen [25,28]. However,

73 despite the importance of population structure in pathogen transmission [21], it has not been
74 commonly considered in hantavirus–host dilution studies (but see [20]).

75

76 Second, predators can reduce PUUV risk for bank voles and humans through (i) reducing the
77 abundance of hosts, (ii) altering host behaviour, resulting in reduced host contact rate [29], or
78 (iii) selectively preying on infected hosts [16,30]. Only a few studies have examined the role
79 of predators in reducing hantavirus infection prevalence in rodent host populations (Sin
80 Nombre virus in the USA [31], PUUV seroprevalence in bank voles in northern Sweden
81 [16,30]). Recent studies [16,30] indicate that Tengmalm's owl (*Aegolius funereus*), an avian
82 predator of voles, can selectively prey on and limit the number of hantavirus-infected voles.
83 Indeed, there is still a considerable shortage of studies examining the potential role of
84 predators in decreasing hantavirus transmission and/or infection prevalence (reviewed by
85 [32]).

86

87 Third, many environmental factors (e.g., landscape structure, composition, and climate) can
88 also influence PUUV transmission. For example, landscape structure (e.g., patch size and
89 fragmentation) determines the habitat suitability and the population size of bank voles and
90 other mammals [33]. Consequently, landscape composition may affect pathogen transmission
91 [34] and, thus, the prevalence of PUUV. Meanwhile, temperature and precipitation can
92 directly influence the transmission of PUUV by affecting the survival of this virus [8].

93

94 Here, we integrate disease ecology and community ecology to better understand the
95 mechanisms potentially affecting PUUV infection in bank vole populations and identify
96 whether these are translated into human infections. Specifically, we study the role of host

abundance and host population structure, the community of rodents and predators, as well as potentially relevant environmental factors on PUUV in the host populations. Moreover, we examine how PUUV in the bank vole populations is translated into the PUUV risk for humans.

2. Material and Methods

(a) Rodent data

The bank vole is a habitat generalist species that prefers forests [35] but is also found in other habitats like agricultural landscapes [36]. In this study, bank voles and other rodents (all together eight rodent species; Table 1) were trapped at 30 study sites located in 24 municipalities across the Southern half of Finland (Figure 1). The study sites were located along a route across the south part of Finland with circa 30 km intervals. At each site, in total 150 snap traps were set with circa 10 meters intervals along 2-4 transects, which were located in forests and on the border between forests and agricultural fields. The trappings were carried out during September – October from 2001 to 2005. In 2001, 2002, 2004 and 2005, trappings were carried out for two continuous days (traps were set on day 1, checked and reset on day 2 and checked and removed on day 3). In 2003, the trappings were only performed at every second trapping site, lasting for only one day. All captured small mammals were frozen in dry ice in the field and later stored at -20 °C until further processing.

(b) PUUV infection data

PUUV infection data in bank vole: The captured bank voles were thawed and dissected, and their individual level data were recorded, including body mass, sex and reproductive

status. Organ and tissue samples were taken, and the heart was placed in a microtube with 200 µl of PBS (phosphate buffered saline). The elution was used in immunofluorescence assay (IFA) to detect antibodies against PUUV [37]. Out of 6111 recorded bank voles, 5155 were dissected, sampled and screened for PUUV antibodies (Figure S1). PUUV antibodies in the infected bank voles persist life-long and infected individuals can shed PUUV for the rest of their life [38]. Consequently, PUUV-seropositive individuals were interpreted as infected. For each site and year, the PUUV seroprevalence is calculated as:

PUUV seroprevalence = the number of PUUV seropositive bank voles / the number of PUUV antibody tested bank voles

Similarly, the abundance index of seropositive bank voles was calculated (for each site and year) as:

The abundance index of PUUV seropositive bank voles = the number of PUUV seropositive bank voles/number of trap nights (number of traps set × number of trapping days).

Human disease incidence data: Data on human NE cases between 2001 and 2005 were provided by the Finnish National Institute for Health and Welfare from the Finnish National Infectious Diseases Register https://thl.fi/en/web/infectious-diseases-and-vaccinations/surveillance-and-registers/finnish-national-infectious-diseases-register for each of the 24 municipalities where the 30 rodent trapping sites were located (Figure 1). We used the sum of cases over October, November and December in the trapping year and January of the following year, which is the period when most of human infections take place [39]. The number of human NE cases at municipality level is likely to be impacted by human population size i.e., the number of inhabitants in a municipality. Thus, we included human

population size per municipality in our model as an offset to account for its impact. Consequently, we examined human NE incidence using the number of diagnosed NE cases after accounting for the human population size. Human population size of each municipality in 2005 was extracted from Statistics Finland (http://www.stat.fi/org/avoindata/paikkatietoaineistot_en.html) using ArcGIS.

(c) **Bank vole population and rodent assemblage-related variables**

We considered the abundance index of bank voles (per site per year) to examine the impact of the density of reservoir host on PUUV seroprevalence in bank voles. Abundance index was calculated as:

Abundance index = the number of captured individuals/ numbers of trap nights (=number of traps set × number of trapping days).

We also included the proportion (%) of juveniles in bank vole population (per site per year) to test the juvenile dilution effect. We defined juveniles as young individuals that have not started breeding, as they are similar in their behaviour and physiology [21]. As the breeding condition was not reliably detected in late autumn for all individuals, we used body mass as a proxy to separate juveniles from adults (that have been breeding) [40]. Specifically, we defined juveniles as individuals with a body mass ≤15.5 grams [40].

To test the dilution effect associated with the rodent assemblage, we calculated *species richness (SR), Shannon diversity* and *Simpson diversity* [41] of rodents for each site and year. We also considered the abundance index of each rodent species separately, which was

168 calculated per site per year as described above for the bank vole.

169

170 **(d) Predator assemblage data and related variables**

171 **Predator data:** Predator data were obtained from snow track index data collected within the
172 Finnish Wildlife Triangle Scheme, by Natural Resources Institute Finland (LUKE) [42,43].
173 The scheme is a long-term, large–scale monitoring of game species in boreal forests across
174 Finland, which provides annual estimates of the distribution and estimated abundance of
175 game species (https://www.riistakolmiot.fi). The abundance of a species in a triangle count is
176 measured with a snow track index [42,43], which is the number of snow tracks reported per
177 distance of the transect surveyed (unit 10 km) per day since the last snowfall (defining the
178 time during which new tracks have accumulated; details in
179 https://opendata.luke.fi/dataset/wildlife-triangle).

180

181 We used the snow track index data from 2001 to 2005 for red fox (*Vulpes vulpes*), stoat
182 (*Mustela erminea*), weasel (*Mustela nivalis*), European pine marten (*Martes martes*) and
183 raccoon dog (*Nyctereutes procyonoides*) (Table 1). Since European badgers (*Meles meles*) are
184 in torpor over winter and the species was not observed in the snow track monitoring, it was
185 not included in the predator data. Based on the snow track data, we made a heat map for each
186 species for each year (2001–2005), using the Kriging method (i.e., ordinary kriging) [44] for
187 interpolation. As rodent data (including PUUV seroprevalence data in bank vole) were
188 collected within a small (< 5ha) area at each trapping site, we extracted the mean interpolated
189 snow track index for 5 km buffer zones around each of the 30 trapping sites. Raccoon dogs
190 often hibernate during winter, due to which the snow track data might be not reliable for this
191 species. Thus, we also used raccoon dog hunting data to estimate the abundance of raccoon

dogs in study regions (details in the supplement). In addition, the snow track data collections for predators were conducted in winter (January to February), whereas rodent data were collected in autumn (September–October). We used predator data from the winter of the same year (approximately 6–8 months earlier than rodent trappings in September–October) to test the impact of predators on PUUV seroprevalence in bank vole populations and the abundance of seropositive bank voles.

To test top-down trophic interaction, we considered species richness (SR), Shannon diversity and Simpson diversity of predators, and the abundance of predator species, each species separately, based on snow track data and hunting data from 2001 to 2005 (Table 1).

(e) Environmental variables

Landscape variables: We calculated the percentage of different land cover types from CORINE Land Cover 2006 project (https://www.syke.fi/fi). We used the data on the percentage of forests and semi-natural areas, artificial surfaces, agricultural areas, wetlands, and water bodies within each 5 km buffer zone around trapping sites from 2000 to 2005 (Table 1). We also considered habitat fragmentation, we first combined the forests and semi-natural areas and agricultural areas as suitable habitats for bank voles and then calculated fragmentation, including the total area of habitat in question (CA), edge density (ED) of habitat [45] within 5 km buffer zone around study sites.

Climate variables: We calculated seasonal average temperatures and precipitation within each 5 km buffer zone from 2001 to 2005 based on monthly air temperature and precipitation

from the Finnish Meteorological Institute (https://en.ilmatieteenlaitos.fi/climate–statistics) (Table 1). Seasons were defined following [46] as *"winter*" (January, February, March), "*spring*" (April and May), "*summer*" (June, July and August) and "*autumn*" (October, November and December). September was excluded because it differs largely from summer and autumn months [46]. We used climate variables from the current year as explanatory variables.

(f) Statistical analyses

To decompose the role of different variables in PUUV seroprevalence and in the abundance of PUUV seropositive bank voles and, subsequently, whether they are translated into human NE incidence, we used Structural Equation Models (SEMs). SEMs is a multivariate, theory-driven analytical approach to test and evaluate the direct and indirect effects on pre-assumed relationships [47]. Selecting appropriate variables is the first step in the application of SEMs [47]. Hence, first we listed all potentially relevant explanatory variables regarding to our research questions (Table 1), and of those, we selected variables to be used in SEMs based on a combination of single variable regression results and correlation tests (see Supplementary methods and results).

Once the potentially relevant explanatory variables for (i) the prevalence of PUUV in bank voles, (ii) the abundance index of infected bank voles were selected (Table 1), SEMs was used to unite the relationships between multiple explanatory and response variables in a single network. In other words, SEMs allows us to simultaneously evaluate multiple pre-assumed relationships within a single network [48]. We constructed two piecewise SEMs [48] to examine the link between selected explanatory variables and human NE incidence at

239 municipality level through either (i) the PUUV seroprevalence in bank vole (SEM1), or (ii)
240 the abundance index of PUUV seropositive bank voles (SEM2).

241

242 SEM1 consisted of three component models. Model (component) 1 evaluated human NE
243 incidence in relation to PUUV seroprevalence in bank voles using a generalised linear mixed
244 model (GLMM) with a negative binomial family. The human population size in the
245 municipality was included as an offset. Model 2 evaluated PUUV seroprevalence in bank
246 vole populations in relation to the selected variables (Table 1, SEM1: the abundances of bank
247 vole, red fox and weasel and the percentage of wetland) using GLMM with binomial family
248 and the number of screened bank voles were included as "weights" in the model, to take into
249 account the difference in the numbers of screened individuals. Model 3 was constructed to
250 examine the effect of red fox and weasel abundance on the abundance index of bank voles
251 using a linear mixed model (LMM). We accounted for the random effect for years and sites
252 for the three component models.

253

254 SEM 2 consisted of two component models. Model 1 evaluated the response of human NE
255 incidence to the abundance index of seropositive bank voles using a GLMM (as in SEM1).
256 Model 2 evaluated the relationship between the abundance index of PUUV seropositive bank
257 voles and the selected variables (Table 1, SEM2: the abundances of red fox and weasel and
258 percentage of wetland, the proportion of juveniles and Simpson diversity of rodents) using a
259 linear mixed model (LMM). We accounted for the random effect for years and sites for the
260 two component models.

261

The overall fit of the piecewise SEMs was evaluated by Fisher's C statistic, which indicates whether there are any missing paths. All SEMs were fitted with the *piecewiseSEM* package [49]. GLMMs, LMMs for SEMs and single-variable regressions were fitted with lme4 package [50]. We report the standardised coefficients for SEMs for each path in each model (Figure 2). We also report conditional and marginal R^2 values, which measure the variation explained by fixed and random factors or fixed factors only, respectively (Table S3-S5). All statistical analyses were conducted in R (4.2.1) [51].

3. Results

(a) PUUV in bank voles and humans

In total, 6111 bank voles were recorded in the study, of which 5155 were screened for PUUV antibodies (Figure S1). PUUV seroprevalence in the bank voles, the abundance index of seropositive bank voles and human NE incidence varied across sites and years (Figure S2, S3). The mean PUUV seroprevalence in bank voles (over 5 years) per site was 14%, varying from 3% to 27%. The mean abundance of seropositive bank voles (over 5 years) per site was 2 per 100 trap nights, varying from 0.3 to 5 per 100 trap nights between sites (Figure S2b). The mean human NE incidence (over 5 years) was 23 per 100,000 human population per municipality, varying from 0 to 119 per 100,000 human population.

(b) Drivers of PUUV seroprevalence in bank voles

PUUV seroprevalence in the bank vole populations was negatively associated with the abundance of red foxes (Figure 2a). We did not find significant associations between PUUV seroprevalence in bank voles and the abundance of weasels, percentage of wetland, and bank

vole abundance. Bank vole abundance was negatively associated with the abundance of weasels.

(c) Drivers of the abundance index of seropositive bank voles

We found that the abundance index of PUUV seropositive bank voles was negatively associated with the proportion of juvenile bank voles, Simpson diversity index of rodents, the abundance of weasels, and positively related to the percentage of wetland (Figure 2b).

(d) NE incidence in humans

NE incidence in humans was not associated with PUUV seroprevalence in bank voles (Figure 2a) but rather, the abundance index of seropositive bank voles (Figure 2b). The abundance of seropositive bank voles was negatively associated with weasel abundance, the proportion of juvenile bank voles and rodent diversity (Simpson), and these negative impacts were translated into human NE incidence (Figure 2b). The percentage of wetland was positively associated with human NE incidence through its positive association with the abundance of seropositive bank voles.

4. Discussion

We studied PUUV seroprevalence in bank vole populations in autumn samples and NE incidence in humans in autumn – early winter during five years across 30 trapping sites within 24 municipalities in southern Finland, where PUUV is highly endemic. Our results show a negative association between the abundance index of PUUV seropositive bank voles and weasels and a positive association between the abundance index of PUUV seropositive

bank voles and human NE incidence. Thus, our findings suggest that such predator(s) may reduce human infection risk by controlling the abundance of infectious hosts in the environment (i.e., top-down trophic interactions). In addition, our results suggest that a high proportion of juveniles and rodent diversity can also reduce the abundance of PUUV seropositive bank voles and subsequently reduce the human NE incidence (i.e., juvenile dilution effect and dilution effect associated with rodents). Interestingly, the association with human NE incidence was detected only with the abundance index of PUUV seropositive bank voles, not with PUUV seroprevalence in bank vole populations.

(a) Bank vole population structure and PUUV in bank voles and in humans.

We found evidence for a juvenile dilution effect for human NE incidence through the abundance of seropositive bank voles. In autumn, after the breeding season, rodent populations are typically dominated by young individuals [52]. A high proportion of young individuals were negatively associated with the abundance of PUUV seropositive bank voles. Young individuals are typically not infected with PUUV as it is a horizontally transmitted pathogen, and the infection likelihood increases with age [53]. Furthermore, the offspring of infected mothers are transiently (up to 2.5 months of age) protected by maternal antibodies (MatAbs) against PUUV infection, transiently decreasing the proportion of susceptible individuals and thus delaying the transmission [25,27]. Hence, the lack of association between bank vole abundance and PUUV seroprevalence in bank voles in autumn may be explained by the juvenile dilution effect, together with the delay in susceptibility caused by MatAb.

Moreover, there is a delay in the detection of PUUV infection by using serological assays

(the antibodies are detectable approximately one month after the infection [20,54]). Thus, both PUUV transmission and infection detection may be delayed, explaining the lack of positive association between bank vole density and PUUV seroprevalence in autumn. Indeed, most of the seroconversions take place in late autumn/winter, leading to the highest PUUV seroprevalence in spring, when the host density is at its lowest [28]. As our rodent trappings were carried out only in the autumn, we were not able to examine whether PUUV seroprevalence would have shown delayed density dependence with bank voles as shown by some other studies [14,55].

(b) The effect of rodent assemblage on PUUV risk for bank voles and humans

While previous studies provide some evidence for the dilution effect on infection prevalence caused by small mammals in some hantavirus-host systems [12,16–19,56,57], the generality of the relationship between small mammal diversity (i.e., species richness, Shannon diversity and Simpson diversity) and seroprevalence in host species needs to be solved. For example, a review concluded a consistent negative association between diversity of small mammals and infection prevalence across 13 hantavirus-host studies system [22], whereas a recent meta-analysis [58] including 22 publications on the associations of hantavirus infection and community diversity, found no general patterns for seroprevalence of hantaviruses.

In this study, we did not detect the dilution effect related to rodent assemblage on PUUV seroprevalence in bank voles suggested by [20], which showed that a high density of other small mammals (other vole species and *Sorex* shrews) decreased PUUV seroprevalence in bank vole populations. The reason might be that the impact of other rodents on voles was seasonal and observed only in spring when all animals were breeding and more or less

territorial, whereas no such association was detected in autumn on nonbreeding, docile voles.

We found a negative association between the Simpson diversity of rodents and the abundance index of PUUV seropositive bank voles, which may result from a negative association between rodent diversity and the abundance of bank voles. This is in line with [18], which showed negative relationship between the diversity of rodents and deer mice abundance. The negative association may also result from other species causing encounter reductions among bank voles, as shown by other hantavirus-host systems [17,18]. Unfortunately, the current data do not enable examining the contact rates between individuals and thus, the mechanism of the dilution caused remains unsolved.

(c) The effect of predator assemblage on PUUV in bank voles and in humans

Our results suggest that red foxes may reduce PUUV seroprevalence in the hosts when the abundance of the host was controlled for. This result indicates that red foxes reduce PUUV seroprevalence in the hosts through encounter reduction caused by behavioural changes in bank voles. For example, rodents are known to move less when predators are abundant [59,60], which reduces contact rates.

We found that the abundance index of bank voles was negatively associated with weasels, which is consistent with previous studies [61–63]. The weasel preys on bank vole and is one of the most important factors in driving vole population dynamics in Northern Fennoscandia [61,62]. Meanwhile, we found a negative association between weasels and the abundance index of PUUV seropositive bank voles, suggesting that weasels may selectively prey on infected bank voles and thus reduce human NE incidence. Recent studies [16,30] have shown

that Tengmalm's owl, an avian predator of voles, can selectively prey on and limit the number of hantavirus-infected voles [16,30]. Moreover, avian predators, including owls, have been suggested to influence the activity of the prey [64]. We assume that predators that largely focus on bank voles, like owls and weasels, can potentially reduce human infection risk by controlling the abundance of infectious hosts in the environment (i.e., top-down trophic interactions).

Moreover, our findings that, predator abundance in the previous winter was negatively associated with PUUV infections in autumn may also result from predator-induced maternal stress. For example, predation risk on mother can influence offspring behaviour [65–67].

(d) The important role of environmental factors

Small-scale landscape characteristics (i.e., wetlands) play an important role in explaining human NE incidence. Our results are in line with previous studies showing that the number of infected bank voles (i.e., the abundance of seropositive bank voles) is positively associated with wet habitats [68,69], and rainy (snowy) winters and/or high soil moisture increase human NE incidence [13,70]. Humid conditions are expected to improve the survival of the virus outside the host [8], facilitating virus transmission in the host population [68]. Interestingly, we did not find an association between precipitation and PUUV infection in bank vole, which has been reported earlier [71]. This may be due to the difference in the timing: Sipari et al [71] found that PUUV prevalence in bank vole in spring is positively associated with precipitation in previous November, whereas we studied PUUV seroprevalence in autumn. Nevertheless, both precipitation and wet habitats may affect rodent behaviour increasing aggregation and thus contacts between individuals, affect host condition

404 and the survival of PUUV in the environment [8,71]. In addition, wet habitat is likely to have
405 more persistent effect than precipitation. Indeed, another study highlighted the role of micro-
406 habitat in spatial patterns of PUUV and found that PUUV maintenance and transmission is
407 higher in wet habitats [72].

408

409 **(e) PUUV risk for humans**

410 PUUV risk for humans is determined by the number of infected bank vole and contact
411 between viral particles shed by infected bank voles and humans [73,74]. The abundances of
412 infected bank voles depend on bank vole abundance and their PUUV seroprevalence. Thus,
413 we expected that the abundance index of seropositive bank vole and PUUV seroprevalence in
414 bank voles are positively associated with human NE incidence. Despite the reported positive
415 associations between human infection incidence and Sin Nombre hantavirus seroprevalence
416 in deer mice [75,76], we did not find a significant impact of PUUV infection prevalence on
417 human NE incidence. Instead, our results showed that the abundance index of PUUV
418 seropositive bank voles is an important predictor for human NE incidence. A higher number
419 of infected voles shed more virus into the environment, thus increasing PUUV risk for
420 humans [14,77]. Our finding is in line with the earlier findings [78], showed that abundance
421 of bank voles (which is correlated with at the abundance of positive bank voles), rather than
422 seroprevalence is translated into human infections.

423

424 **5. Conclusions**

425 We investigated how the factors that impact pathogen transmission in wildlife hosts can be
426 important for predicting human disease outbreaks. Our study highlights several essential
427 points that may have been overlooked previously. First, our results suggest that the

428 proportion of juveniles in bank vole population, through a negative impact on the number of
429 infected bank vole, can reduce disease incidence in humans. Second, our results suggest that
430 even though rodent diversity may not impact hantavirus prevalence in the host population, it
431 can still reduce disease incidence in humans through its negative impact on the number of
432 seropositive bank vole. Third, our results suggest some mammalian predator species (e.g., red
433 foxes and weasels) can reduce PUUV risk for bank voles and humans. A growing body of
434 literature, indeed, indicates that predators can impact prey behaviour and/or fitness [59,60]
435 and thus potentially impact pathogen transmission within the prey population. However, it
436 remains largely unknown how the effects of predators are translated into seroprevalence in
437 prey populations. Experimental studies are warranted to quantify predator impacts, especially
438 trans-generational and behavioural effects, on infection dynamics. In addition, including
439 other predators that prey on the hosts, such as avian predators, would be required to expand
440 our understanding of the effects of predators on infection dynamics. Our results supply
441 evidence that PUUV risk for humans and wildlife are interlinked and understanding the
442 disease epidemiology requires knowledge of wildlife composition, wildlife interactions, and
443 the contributing environmental factors.

444

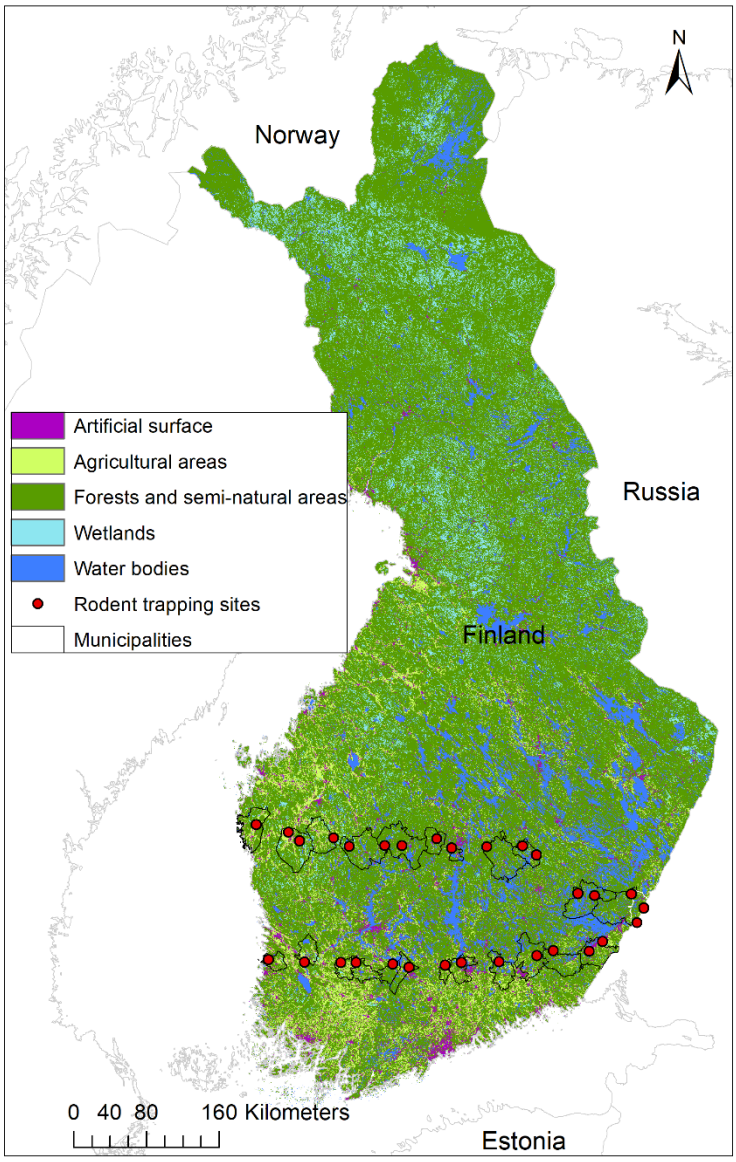
Tables

Table 1. Variables (with category) used in the analyses with units, sources, and the corresponding SEMs in which the variable is included. An entry of "n/a" is used to indicate when a variable has no units. / indicate that variables are not included in SEM1 or SEM2.

Category	Variable	Unit	SEMs	Sources
Bank vole population variables	Bank vole abundance	Number of captured bank vole per trap night	SEM1	Rodent trapping data from this study
	Proportion of Juvenile	%	SEM2	
Rodent assemblage	Species richness of rodents	n/a	/	
	Shannon diversity of rodents	n/a	/	
	Simpson diversity of rodents	n/a	SEM2	
Abundance of rodent species	Non-host rodents	Number of captured individuals per trap night	/	
	Field mouse *(Apodemus agrarius*)		/	
	Yellow-necked wood mouse (*Apodemus flavicollis*)		/	
	European water vole (*Arvicola amphibius*)		/	
	Harvest mouse *(Micromys minutus*)		/	
	Field vole *(Microtus agrestis*)		/	
	Common vole *(Microtus arvalis*)		/	
	House mouse *(Mus musculus*)		/	
	Brown rat *(Rattus norvegicus*)		/	
Predator assemblage	Species richness of predators	n/a	SEM2*	Snow tracking data from LUKE
	Shannon diversity of predators	n/a	/	
	Simpson diversity of predators	n/a	/	
Abundance of predator species	Red fox (*Vulpes vulpes*)	Number of snow tracks reported per 10 km	SEM1 and 2	
	Stoat (*Mustela erminea*)		/	
	Weasel (*Mustela nivalis*)		SEM1 and 2	
	European pine marten (*Martes martes*)		/	
	Raccoon dog (*Nyctereutes procyonoides*) (from snow tracking data)		/	
	Raccoon dog (*Nyctereutes procyonoides)* (from hunting data)	Number of hunted individuals	/	Hunting data from LUKE
Landscape related variables	total area of habitat in question (CA)	ha	/	Corine land cover
	habitat fragmentation measured by edge density (ED)	m/ha	/	
	Percentage of artificial land	%	/	
	Percentage of agricultural land	%	/	
	Percentage of forests	%	/	
	Percentage of wetland	%	SEM1 and 2	
	Percentage of water	%	/	
Climate related variables	Winter precipitation	mm	/	Finnish Meteorological Institute
	Spring precipitation	mm	/	
	Summer precipitation	mm	/	
	Autumn precipitation	mm	/	
	Winter temperature	°C	/	
	Spring temperature	°C	/	
	Summer temperature	°C	/	
	Autumn temperature	°C	/	

Note: * Alternative SEM2 in supplements (Table S5)

451 **Figures**



452

453 Figure 1. Rodent trapping sites (red dots) in Finland. Municipalities (black boundaries) for

454 the human NE incidence data overlapped the rodent trapping sites.

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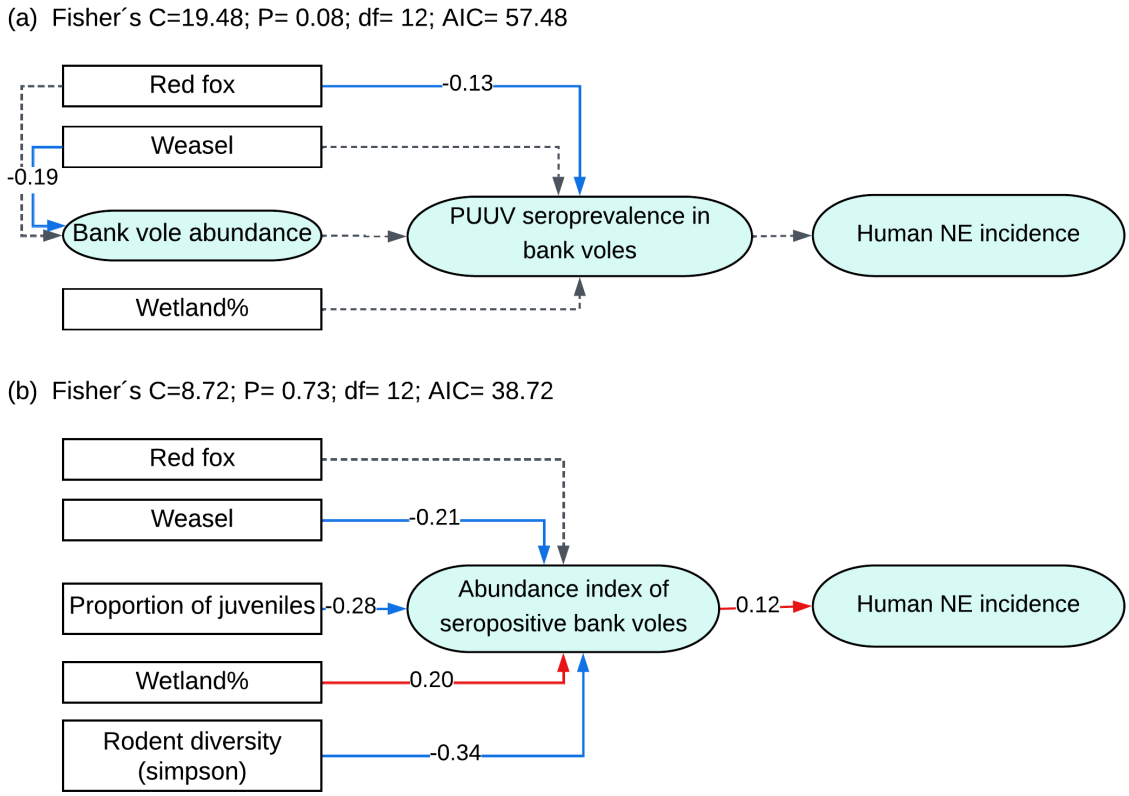

457

458 **Figure 2.** Path diagram of a piecewise Structural Equation Models (SEMs) showing direct and
459 indirect effects of predictors on human NE incidence through (a) PUUV seroprevalence in bank
460 vole (SEM1) and (b) the abundance index of seropositive bank voles (SEM2). Variables with green
461 backgrounds were the response variable of each component model in SEMs. Solid red arrows
462 represent positive effects ($p < 0.05$), solid blue arrows represent negative effects ($p < 0.05$), and dotted
463 grey arrows represent non-significant effects ($p > 0.05$). We report the path coefficients as
464 standardised effect sizes next to arrows.

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Conflicts of interest

The authors declare no conflict of interest.

Authors contributions

Design (ERK, HHenttonen), fieldwork (ERK, LV, HHelle JN), laboratory analyses (ERK, LV, JN, JL, TS, OV), data acquisition (ERK, LV, JL, JN, OH, AL, MA, JS), data analyses (YW), writing (YW, ERK, HH) with the help of all authors.

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Data accessibility

The rodent trapping data, including PUUV infection data in bank vole, data on game species, human population size, land use and climate used and/or analysed during the current study are available from https://doi.org/10.5061/dryad.bg79cnpfh [79]. Original data on game species from Resources Institute Finland (LUKE) are available from https://www.riistakolmiot.fi. Human NE cases from the Finnish National Institute for Health and Welfare from

487 the Finnish National Infectious Diseases Register are available from https://thl.fi/en/web/in-
488 fectious-diseases-and-vaccinations/surveillance-and-registers/finnish-national-infectious-dis-
489 eases-register. Human abundance data from Statistics Finland is available
490 fromhttp://www.stat.fi/org/avoindata/paikkatietoaineistot_en.html. Land cover data from
491 CORINE Land Cover 2006 project is available from https://www.syke.fi/fi.

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494 **Ethics approval**

495 Ethical statement: According to the Finnish Act on the Use of Animals for Experimental
496 Purposes (62/2006) and a further decision by the Finnish Animal Experiment Board (16th
497 May, 2007), the animal capture technique, i.e., using traps that instantly kill the animal, is not
498 considered an animal experiment and therefore requires no animal ethics license from the
499 Finnish Animal Experiment Board. All animal trapping took place with permissions from
500 land owners. A permit (23/5713/2001) for capturing protected species (*Sorex spp.* and
501 *Myopus schisticolor*) was granted by the Finnish Ministry of the Environment. Other species
502 captured in this study are not protected in Finland and none of the captured species are
503 included in the Red List of Finnish Species.

504 Human infection data includes only the number of laboratory diagnosed infections per month
505 per municipality (https://thl.fi/en/web/infectious-diseases-and-vaccinations/surveillance-and-
506 registers/finnish-national-infectious-diseases-register/) without any individual level data.
507 Hence, no ethical permission is needed for the use of the human data.

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731 **Figure legends**

732 **Figure 1**. Rodent trapping sites (red dots) in Finland. Municipalities (black boundaries) for
733 the human NE incidence data overlapped the rodent trapping sites.

734 **Figure 2.** Path diagram of a piecewise Structural Equation Models (SEMs) showing direct and
735 indirect effects of predictors on human NE incidence through (a) PUUV seroprevalence in bank
736 vole (SEM1) and (b) the abundance index of seropositive bank voles (SEM2). Variables with green
737 backgrounds were the response variable of each component model in SEMs. Solid red arrows
738 represent positive effects ($p < 0.05$), solid blue arrows represent negative effects ($p < 0.05$), and dotted
739 grey arrows represent non-significant effects ($p > 0.05$). We report the path coefficients as
740 standardised effect sizes next to arrows.