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- Author(s): Wang, Yingying X. G.; Voutilainen, Liina; Aminikhah, Mahdi; Helle, Heikki; Huitu, Otso; Laakkonen, Juha; Lindén, Andreas; Niemimaa, Jukka; Sane, Jussi; Sironen, Tarja; Vapalahti, Olli; Henttonen, Heikki; Kallio, Eva R.
- **Title:** The impact of wildlife and environmental factors on hantavirus infection in the host and its translation into human risk

Year: 2023

Version: Accepted version (Final draft)

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Please cite the original version:

Wang, Y. X. G., Voutilainen, L., Aminikhah, M., Helle, H., Huitu, O., Laakkonen, J., Lindén, A., Niemimaa, J., Sane, J., Sironen, T., Vapalahti, O., Henttonen, H., & Kallio, E. R. (2023). The impact of wildlife and environmental factors on hantavirus infection in the host and its translation into human risk. Proceedings of the Royal Society B : Biological Sciences, 290(1996), Article 20222470. https://doi.org/10.1098/rspb.2022.2470

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

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1 Abstract

Identifying factors that drive infection dynamics in reservoir host populations is essential in 2 understanding human risk from wildlife-originated zoonoses. We studied zoonotic Puumala 3 4 orthohantavirus (PUUV) in the host, the bank vole (Myodes glareolus), populations in 5 relation to the host population, rodent and predator community and environment related 6 factors and whether these processes are translated into human infection incidence. We used 5-7 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 8 9 with the abundance of red foxes, but this process did not translate into human disease 10 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 11 diversity were negatively associated with the abundance index of PUUV positive bank voles, 12 which, in turn, showed a positive association with human disease incidence. Our results 13 suggest certain predators, high proportion of young bank vole individuals, and a diverse 14 15 rodent community, may reduce PUUV risk for humans through their negative impacts on the abundance of infected bank voles. 16

17

18

19 Keywords

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

23 1. Introduction

24 Rodents are important wildlife hosts of many zoonotic pathogens [1], such as

orthohantaviruses (hereon called hantaviruses; family: Hantaviridae; genus: Orthohantavirus, 25 26 formerly genus Hantavirus). In humans, hantaviruses cause two diseases: Hantavirus 27 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 28 29 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 30 is the bank vole (Myodes glareolus) [5,6]. PUUV infection in the bank vole is asymptomatic 31 32 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 33 disease incidence globally, with 1000–3300 human PUUV infections diagnosed annually [9]. 34 It has been proposed that the risk posed by rodent-borne pathogens are in increase, as the 35 global loss of biodiversity is likely to increase the relative abundance of commensal rodents 36 37 [10]. Therefore, it is urgent to quantify the role of different mechanisms in driving the 38 infection dynamics in the reservoir host populations and identify whether these processes are translated into human infections. 39

40

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., 48 "encounter reduction"[15]). For instance, field vole (Microtus agrestis) has been suggested to 49 reduce PUUV infection rate in the reservoir host bank vole by reducing its abundance 50 through interspecific competition in autumn in Sweden [16]. Hantavirus dilution through 51 52 encounter reduction has also been suggested in several hantavirus-host systems, including 53 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 54 bank voles, likely through inhibition of encounter rates among bank voles or between bank 55 56 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]. 57 Meanwhile, a study in Northern Finland [20] reported that the total abundance of other small 58 mammals reduced PUUV seroprevalence in bank voles, but this effect was seasonal, found 59 only in spring (in the breeding season). 60

61

Besides (host density and) small mammal species interactions, hantavirus transmission may 62 63 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 64 influenced by population structure. Host individuals of different ages and reproductive 65 66 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 67 host population, the proportion of infected individuals, and therefore pathogen infection 68 69 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]. 70 An increasing number of individuals with maternal antibodies may decrease or delay 71 pathogen transmission, affecting the seasonal dynamics of the pathogen [25,28]. However, 72

despite the importance of population structure in pathogen transmission [21], it has not been 73 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 abundance of hosts, (ii) altering host behaviour, resulting in reduced host contact rate [29], or 77 (iii) selectively preying on infected hosts [16,30]. Only a few studies have examined the role 78 of predators in reducing hantavirus infection prevalence in rodent host populations (Sin 79 80 Nombre virus in the USA [31], PUUV seroprevalence in bank voles in northern Sweden [16,30]). Recent studies [16,30] indicate that Tengmalm's owl (Aegolius funereus), an avian 81 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 predators in decreasing hantavirus transmission and/or infection prevalence (reviewed by 84 [32]). 85

86

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

93

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

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.

101

102 2. Material and Methods

103 (a) Rodent data

The bank vole is a habitat generalist species that prefers forests [35] but is also found in other 104 habitats like agricultural landscapes [36]. In this study, bank voles and other rodents (all 105 together eight rodent species; Table 1) were trapped at 30 study sites located in 24 106 municipalities across the Southern half of Finland (Figure 1). The study sites were located 107 along a route across the south part of Finland with circa 30 km intervals. At each site, in total 108 109 150 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 110 carried out during September - October from 2001 to 2005. In 2001, 2002, 2004 and 2005, 111 trappings were carried out for two continuous days (traps were set on day 1, checked and 112 reset on day 2 and checked and removed on day 3). In 2003, the trappings were only 113 114 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 115 processing. 116

117

118 (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

121	status. Organ and tissue samples were taken, and the heart was placed in a microtube with
122	200 μ l of PBS (phosphate buffered saline). The elution was used in immunofluorescence
123	assay (IFA) to detect antibodies against PUUV [37]. Out of 6111 recorded bank voles, 5155
124	were dissected, sampled and screened for PUUV antibodies (Figure S1). PUUV antibodies in
125	the infected bank voles persist life-long and infected individuals can shed PUUV for the rest
126	of their life [38]. Consequently, PUUV-seropositive individuals were interpreted as infected.
127	For each site and year, the PUUV seroprevalence is calculated as:
128	PUUV seroprevalence = the number of PUUV seropositive bank voles / the number of
129	PUUV antibody tested bank voles

131 Similarly, the abundance index of seropositive bank voles was calculated (for each site and132 year) as:

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

135

136 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 137 138 Infectious Diseases Register https://thl.fi/en/web/infectious-diseases-andvaccinations/surveillance-and-registers/finnish-national-infectious-diseases-register for each 139 of the 24 municipalities where the 30 rodent trapping sites were located (Figure 1). We used 140 the sum of cases over October, November and December in the trapping year and January of 141 the following year, which is the period when most of human infections take place [39]. The 142 143 number of human NE cases at municipality level is likely to be impacted by human 144 population size i.e., the number of inhabitants in a municipality. Thus, we included human

145 population size per municipality in our model as an offset to account for its impact.

146 Consequently, we examined human NE incidence using the number of diagnosed NE cases

147 after accounting for the human population size. Human population size of each municipality

148 in 2005 was extracted from Statistics Finland

149 (<u>http://www.stat.fi/org/avoindata/paikkatietoaineistot_en.html</u>) using ArcGIS.

150

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

152 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 wascalculated as:

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

157

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].

164

165 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.

167 We also considered the abundance index of each rodent species separately, which was

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

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

198

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).

202

203 (e) Environmental variables

Landscape variables: We calculated the percentage of different land cover types from 204 CORINE Land Cover 2006 project (https://www.syke.fi/fi). We used the data on the 205 percentage of forests and semi-natural areas, artificial surfaces, agricultural areas, wetlands, 206 and water bodies within each 5 km buffer zone around trapping sites from 2000 to 2005 207 (Table 1). We also considered habitat fragmentation, we first combined the forests and semi-208 natural areas and agricultural areas as suitable habitats for bank voles and then calculated 209 fragmentation, including the total area of habitat in question (CA), edge density (ED) of 210 211 habitat [45] within 5 km buffer zone around study sites.

212

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.

221

222 (f) Statistical analyses

223 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 224 NE incidence, we used Structural Equation Models (SEMs). SEMs is a multivariate, theory-225 226 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 227 [47]. Hence, first we listed all potentially relevant explanatory variables regarding to our 228 research questions (Table 1), and of those, we selected variables to be used in SEMs based on 229 a combination of single variable regression results and correlation tests (see Supplementary 230 231 methods and results).

232

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 preassumed 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 the abundance index of PUUV seropositive bank voles (SEM2).

241

239

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

253

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

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 R² 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].

269

270 **3. Results**

271 (a) PUUV in bank voles and humans

In total, 6111 bank voles were recorded in the study, of which 5155 were screened for PUUV 272 antibodies (Figure S1). PUUV seroprevalence in the bank voles, the abundance index of 273 seropositive bank voles and human NE incidence varied across sites and years (Figure S2, 274 275 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 276 2 per 100 trap nights, varying from 0.3 to 5 per 100 trap nights between sites (Figure S2b). 277 278 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. 279

280

281 (b) Drivers of PUUV seroprevalence in bank voles

282 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 ofweasels.

287

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

289 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).

292

293 (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.

301

302 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 308 reduce human infection risk by controlling the abundance of infectious hosts in the 309 310 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 311 seropositive bank voles and subsequently reduce the human NE incidence (i.e., juvenile 312 dilution effect and dilution effect associated with rodents). Interestingly, the association with 313 314 human NE incidence was detected only with the abundance index of PUUV seropositive bank voles, not with PUUV seroprevalence in bank vole populations. 315

316

317 (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 318 abundance of seropositive bank voles. In autumn, after the breeding season, rodent 319 320 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. 321 Young individuals are typically not infected with PUUV as it is a horizontally transmitted 322 pathogen, and the infection likelihood increases with age [53]. Furthermore, the offspring of 323 infected mothers are transiently (up to 2.5 months of age) protected by maternal antibodies 324 325 (MatAbs) against PUUV infection, transiently decreasing the proportion of susceptible individuals and thus delaying the transmission [25,27]. Hence, the lack of association 326 between bank vole abundance and PUUV seroprevalence in bank voles in autumn may be 327 explained by the juvenile dilution effect, together with the delay in susceptibility caused by 328 MatAb. 329

330

331 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, 332 both PUUV transmission and infection detection may be delayed, explaining the lack of 333 positive association between bank vole density and PUUV seroprevalence in autumn. Indeed, 334 most of the seroconversions take place in late autumn/winter, leading to the highest PUUV 335 seroprevalence in spring, when the host density is at its lowest [28]. As our rodent trappings 336 were carried out only in the autumn, we were not able to examine whether PUUV 337 seroprevalence would have shown delayed density dependence with bank voles as shown by 338 some other studies [14,55]. 339

340

341 (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 342 caused by small mammals in some hantavirus-host systems [12,16–19,56,57], the generality 343 of the relationship between small mammal diversity (i.e., species richness, Shannon diversity 344 and Simpson diversity) and seroprevalence in host species needs to be solved. For example, a 345 review concluded a consistent negative association between diversity of small mammals and 346 infection prevalence across 13 hantavirus-host studies system [22], whereas a recent meta-347 analysis [58] including 22 publications on the associations of hantavirus infection and 348 349 community diversity, found no general patterns for seroprevalence of hantaviruses.

350

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.

357

We found a negative association between the Simpson diversity of rodents and the abundance 358 index of PUUV seropositive bank voles, which may result from a negative association 359 between rodent diversity and the abundance of bank voles. This is in line with [18], which 360 showed negative relationship between the diversity of rodents and deer mice abundance. The 361 negative association may also result from other species causing encounter reductions among 362 bank voles, as shown by other hantavirus-host systems [17,18]. Unfortunately, the current 363 data do not enable examining the contact rates between individuals and thus, the mechanism 364 of the dilution caused remains unsolved. 365

366

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

368 Our results suggest that red foxes may reduce PUUV seroprevalence in the hosts when the 369 abundance of the host was controlled for. This result indicates that red foxes reduce PUUV 370 seroprevalence in the hosts through encounter reduction caused by behavioural changes in 371 bank voles. For example, rodents are known to move less when predators are abundant 372 [59,60], which reduces contact rates.

373

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).

386

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].

390

391 (d) The important role of environmental factors

Small-scale landscape characteristics (i.e., wetlands) play an important role in explaining 392 393 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 394 with wet habitats [68,69], and rainy (snowy) winters and/or high soil moisture increase 395 396 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]. 397 Interestingly, we did not find an association between precipitation and PUUV infection in 398 bank vole, which has been reported earlier [71]. This may be due to the difference in the 399 timing: Sipari et al [71] found that PUUV prevalence in bank vole in spring is positively 400 associated with precipitation in previous November, whereas we studied PUUV 401 seroprevalence in autumn. Nevertheless, both precipitation and wet habitats may affect rodent 402 behaviour increasing aggregation and thus contacts between individuals, affect host condition 403

and the survival of PUUV in the environment [8,71]. In addition, wet habitat is likely to have
more persistent effect than precipitation. Indeed, another study highlighted the role of microhabitat in spatial patterns of PUUV and found that PUUV maintenance and transmission is
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 between viral particles shed by infected bank voles and humans [73,74]. The abundances of 411 412 infected bank voles depend on bank vole abundance and their PUUV seroprevalence. Thus, we expected that the abundance index of seropositive bank vole and PUUV seroprevalence in 413 bank voles are positively associated with human NE incidence. Despite the reported positive 414 associations between human infection incidence and Sin Nombre hantavirus seroprevalence 415 in deer mice [75,76], we did not find a significant impact of PUUV infection prevalence on 416 human NE incidence. Instead, our results showed that the abundance index of PUUV 417 seropositive bank voles is an important predictor for human NE incidence. A higher number 418 of infected voles shed more virus into the environment, thus increasing PUUV risk for 419 humans [14,77]. Our finding is in line with the earlier findings [78], showed that abundance 420 of bank voles (which is correlated with at the abundance of positive bank voles), rather than 421 seroprevalence is translated into human infections. 422

423

424 **5.** Conclusions

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

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

445 Tables

- 446 Table 1. Variables (with category) used in the analyses with units, sources, and the corresponding SEMs
- 447 in which the variable is included. An entry of "n/a" is used to indicate when a variable has no units. /
- 448 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	2
Rodent	Species richness of rodents	n/a	/	-
assemblage	Shannon diversity of rodents	n/a	/	
	Simpson diversity of rodents	n/a	SEM2	
Abundance	Non-host rodents		/	
of rodent	Field mouse (Apodemus agrarius)	Number of	/	
species	Y ellow-necked wood mouse (<i>Apodemus</i>	captured	/	
	European water vole (Arvicola amphibius)	individuals per	/	
	Harvest mouse (Micromvs minutus)	trap night	/	
	Field vole (Microtus agrestis)		/	
	Common vole (Microtus arvalis)		/	
	House mouse (Mus musculus)		/	
	Brown rat (Rattus norvegicus)		/	
Predator	Species richness of predators	n/a	SEM2*	Snow
assemblage	Shannon diversity of predators	n/a	/	tracking
	Simpson diversity of predators	n/a	/	data from
Abundance	Red fox (Vulpes vulpes)	Number of	SEM1 and 2	LUKE
of predator	Stoat (Mustela erminea)	snow tracks	/	
species	Weasel (Mustela nivalis)	reported per 10	SEM1 and 2	
	European pine marten (Martes martes)	km	/	
	Raccoon dog (<i>Nyctereutes procyonoides</i>) (from snow tracking data)		/	
	Raccoon dog (Nyctereutes procyonoides) (from	Number of	/	Hunting
	hunting data)	hunted		data from
		individuals		LUKE
Landscape	total area of habitat in question (CA)	ha	/	Corine
related variables	habitat fragmentation measured by edge density (ED)	m/ha	/	land cover
	Percentage of artificial land	%	/	
	Percentage of agricultural land	%	/	
	Percentage of forests	%	/	
	Percentage of wetland	%	SEM1 and 2	
c1'	Percentage of water	%	/	E ¹ 1
Climate	Winter precipitation	mm	/	Finnish
related	Spring precipitation	mm	/	Meteorolo
variables	Autumn precipitation	mm	/	gical
	Winter temperature	°C	/	msmule
	Spring temperature	°C	/	
	Summer temperature	°Č	/	
	Autumn temperature	°Č	/	

449 Note: * Alternative SEM2 in supplements (Table S5)



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.



(a) Fisher's C=19.48; P= 0.08; df= 12; AIC= 57.48

457

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

466	Acknowledgements
467	We thank Saana Sipari, Anni Hämäläinen, Phillip Watts, and people from "the vole group"
468	who offered helpful comments that improved the manuscript. We thank Yanjie Xu for the
469	help with GIS.
470	Conflicts of interest
471	The authors declare no conflict of interest.
472	Authors contributions
473	Design (ERK, HHenttonen), fieldwork (ERK, LV, HHelle JN), laboratory analyses (ERK,
474	LV, JN, JL, TS, OV), data acquisition (ERK, LV, JL, JN, OH, AL, MA, JS), data analyses
475	(YW), writing (YW, ERK, HH) with the help of all authors.
476	Funding
477	This research was funded by EU FP5 project QLRT-2001-01358 and European Commission
478	Project GOCE-CT-2003-010284 EDEN to Henttonen and Academy of Finland (329332 and
479	329308, 335651 to Eva R. Kallio).
480	
481	Data accessibility
482	The rodent trapping data, including PUUV infection data in bank vole, data on game species,
483	human population size, land use and climate used and/or analysed during the current study
484	are available from https://doi.org/10.5061/dryad.bg79cnpfh [79]. Original data on game spe-

- 485 cies from Resources Institute Finland (LUKE) are available from <u>https://www.riistakol-</u>
- 486 <u>miot.fi</u>. Human NE cases from the Finnish National Institute for Health and Welfare from

- 487 the Finnish National Infectious Diseases Register are available from <u>https://thl.fi/en/web/in-</u>
- 488 <u>fectious-diseases-and-vaccinations/surveillance-and-registers/finnish-national-infectious-dis-</u>
- 489 <u>eases-register</u>. 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.

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

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 <u>registers/finnish-national-infectious-diseases-register/</u>) without any individual level data.
- 507 Hence, no ethical permission is needed for the use of the human data.

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510

512 **References**

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731 Figure legends

- 732 Figure 1. Rodent trapping sites (red dots) in Finland. Municipalities (black boundaries) for
- 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
- indirect effects of predictors on human NE incidence through (a) PUUV seroprevalence in bank
- 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
- 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.