Received: 14 December 2021 | Revised: 1 March 2022 | Accepted: 2 March 2022

DOI: 10.1111/zph.12940

SHORT COMMUNICATION

WILEY

Cluster of human *Puumala orthohantavirus* infections due to indoor exposure?—An interdisciplinary outbreak investigation

Christina Princk[1] | Stephan Drewes[2] | Kristin M. Meyer-Schlinkmann[1] | Marion Saathoff[3] | Florian Binder[2] | Jona Freise[3] | Beate Tenner[4] | Sabrina Weiss[4] | Jörg Hofmann[4] | Jutta Esser[5] | Martin Runge[3] | Jens Jacob[6] | Rainer G. Ulrich[2] | Johannes Dreesman[1]

[1]Public Health Agency of Lower Saxony, Hannover, Germany

[2]Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health, Institute of Novel and Emerging Infectious Diseases, Greifswald-Insel Riems, Germany

[3]Lower Saxony State Office for Consumer Protection and Food Safety, Oldenburg/Hannover, Germany

[4]Institute of Virology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

[5]Practice of Laboratory Medicine, Department of Dermatology, Environmental Medicine, Health Theory, University Osnabrück, Osnabrück, Germany

[6]Julius Kühn-Institute (JKI),, Federal Research Centre for Cultivated Plants, Institute for Plant Protection in Horticulture and Forests, Vertebrate Research, Münster, Germany

Correspondence
Johannes Dreesman, Public Health Agency of Lower Saxony (NLGA), Roesebeckstraße 4-6, 30449 Hannover, Germany.
Email: johannes.dreesman@nlga.niedersachsen.de

Present address
Christina Princk, Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany

Kristin M. Meyer-Schlinkmann, MVZ Labor Krone GbR, Bad Salzuflen, Germany

Sabrina Weiss, Centre for International Health Protection – Public Health Laboratory Support, Robert Koch-Institute, Berlin, Germany

Funding information
Bundesministerium für Bildung und Forschung, Grant/Award Number: 01KI1721D, 01KI1721A, 01KI2004A, 01KI1721C, 01KI1721E and 01KI1721H

Abstract

Puumala orthohantavirus (PUUV) is the most important hantavirus species in Europe, causing the majority of human hantavirus disease cases. In central and western Europe, the occurrence of human infections is mainly driven by bank vole population dynamics influenced by beech mast. In Germany, hantavirus epidemic years are observed in 2- to 5-year intervals. Many of the human infections are recorded in summer and early autumn, coinciding with peaks in bank vole populations. Here, we describe a molecular epidemiological investigation in a small company with eight employees of whom five contracted hantavirus infections in late 2017. Standardized interviews with employees were conducted to assess the circumstances under which the disease cluster occurred, how the employees were exposed and which counteractive measures were taken. Initially, two employees were admitted to hospital and serologically diagnosed with hantavirus infection. Subsequently, further investigations were conducted. By means of a self-administered questionnaire, three additional symptomatic

cases could be identified. The hospital patients' sera were investigated and revealed in one patient a partial PUUV L segment sequence, which was identical to PUUV sequences from several bank voles collected in close proximity to company buildings. This investigation highlights the importance of a One Health approach that combines efforts from human and veterinary medicine, ecology and public health to reveal the origin of hantavirus disease clusters.

KEYWORDS
Clethrionomys glareolus, hantavirus outbreak, occupational exposure, One Health initiative, *Puumala orthohantavirus*

1 | INTRODUCTION

Hantaviruses, family *Hantaviridae*, are rodent-, insectivore- and bat-borne pathogens (ICTV, 2022; Krüger et al., 2011; Laenen et al., 2019; Vapalahti et al., 1999). Human hantavirus infections are caused by rodent-borne orthohantaviruses, and the majority in Germany are caused by *Puumala orthohantavirus* (PUUV) transmitted by bank voles (*Clethrionomys glareolus*, syn. *Myodes glareolus*) (Faber et al., 2019).

In humans, PUUV causes a mild-to-moderate form of haemorrhagic fever with renal syndrome (HFRS), called nephropathia epidemica (NE), with mortality rates <1% (Avšič-Županc et al., 2019). Transmission occurs via inhalation of virus-containing aerosols originating from urine, faeces and saliva of chronically infected rodents (Reil et al., 2017). This way of transmission is assumed to be dominant in accidentally infected humans (Krüger et al., 2011), whereby the specific origin of infection is often unclear. After an incubation period of 1 to 6 weeks, NE starts with a sudden onset of high fever, accompanied by headache and back pain and, sporadically, gastrointestinal symptoms (Krüger et al., 2011; Plyusnina et al., 2012). Severe disease progression is associated with impaired renal function, occasionally requiring dialysis (Heyman et al., 2007). Due to a frequently unspecific or asymptomatic clinical course, many hantavirus infections remain undiagnosed, resulting in an underreporting of human cases (Drewes, Turni, et al., 2017).

Since 2001, hantavirus disease is subject to notification requirements in Germany under the Protection against Infection Act ('Infektionsschutzgesetz' [IfSG] in German) §§ 6,7 (Höhl, 2020). The incidence of notified cases shows strong temporal and spatial variations with endemic regions mainly in the German federal states Baden-Wuerttemberg, Bavaria, North Rhine-Westphalia, Lower Saxony and Hesse (Faber et al., 2019). Increased human case numbers were observed in the years 2007, 2010, 2012, 2017 and 2019 (Binder et al., 2020; Faber et al., 2019; Robert Koch-Institut, 2020). This variation is caused by massive beech fructification in a particular year ('mast' year) followed by a so called 'hantavirus epidemic year' with an increase in human cases (Krüger et al., 2013; Reil et al., 2015).

Mostly, hantavirus cases are notified as single cases and only a few could be epidemiologically linked to outbreaks. In Lower Saxony, only 16 out of 740 cases from 2001 to 2016 could be attributed to an outbreak (eight groups of two patients each), for example. Similar to the endemic regions of Germany, 2017 was one of the years with the highest notified case numbers to date in Lower Saxony, with 132 cases reported (NLGA, 2021). In December 2017, a highly focused outbreak of hantavirus cases was identified by a local public health authority after two hospitalized cases were reported, working in the same small company. Due to this rarely occurring and specific situation, we took this unique opportunity to conduct an interdisciplinary outbreak investigation at the affected company to determine the cause of infection and to identify potential transmission route(s).

Impacts

- The outbreak occurred in frequently used company buildings due to indoor exposure to bank voles.
- Using molecular techniques and an epidemiological approach the investigation provided a comprehensive picture of the outbreak.
- More attention should be given to such outbreak events as they provide valuable information on the epidemiology of the disease.

2 | MATERIALS AND METHODS

In the course of the outbreak investigation, detailed information was collected among all employees (a total of eight) of the affected company via a standardized self-administered questionnaire from January through February 2018. The questionnaire included questions on demographics, disease symptoms, tasks that were frequently performed at the workplace, places where work was carried out, rodent contact and measures taken to prevent rodent contact. The potential duration of exposure to PUUV was set from 1 October 2017, until the date of the survey. Participation in the questionnaire survey was voluntary; therefore, each participant did not necessarily provide responses to every question. Collected data were subjected to descriptive analysis using statistical software Stata/SE

TABLE 1 Number of bank voles trapped and results of serological and reverse transcription—quantitative polymerase chain reaction (RT-qPCR) analyses

		Number of positive/total number of tested voles (percentage)		
Trapping site	**Date**	**PUUV IgG-ELISA**	**PUUV S RT-PCR**	**PUUV real-time RT-PCR**
Inside company building	Jan 2018	n.a.[a]	n.a.	n.a.
	Mar 2018	n.a.	n.a.	n.a.
Subtotal		**n.a.**	**n.a.**	**n.a.**
Company premises	Jan 2018	2/10 (20%)	2/10 (20.0%)	2/10 (20.0%)
	Mar 2018	2/8 (25%)	2/8 (25.0%)	2/8 (25.0%)
Subtotal		**4/18 (22.2%)**	**4/18 (22.2%)**	**4/18 (22.2%)**
Closer surroundings	Jan 2018	0[b]/12 (0.0%)	1/12 (8.3%)	1/12 (8.3%)
	Mar 2018	7/18 (38.9%)	8/18 (44.4%)	9/18 (50.0%)
Subtotal		**7/30 (23.3%)**	**9/30 (30.0%)**	**10/30 (33.3%)**
Total	**2018**	**11/48 (22.9%)**	**13/48 (27.1%)**	**14/48 (29.2%)**

Note: Real-time RT-PCR: samples with ct values above 35 were treated as negative.

[a]n.a. = not applicable: no animals were trapped by the standard protocol used.

[b]One individual was tested equivocal in **Puumala orthohantavirus** (PUUV) IgG-ELISA.

15.1 (StataCorp, 2017) after data pseudonymization to ensure participants confidentiality.

As part of the initial diagnostic procedures, hospitalized patients were tested for hantavirus-specific IgG- and IgM antibodies in the regional laboratory medical practice Osnabrück using a commercial assay (recomLine HantaPlus IgG und IgM; Mikrogen, Munich, Germany). Furthermore, the positive patients' sera were sent to the national consiliary laboratory for hantaviruses at the Institute of Virology at Charité for S segment specific reverse transcription—quantitative polymerase chain reaction (RT-qPCR) and conventional L segment RT-PCR and sequencing (for details see Appendix S1).

Rodent collection was conducted via snap trapping during January and March 2018 in the company building, its premises and the nearby environment, a rural area on the edge of an industrial park nearby a small forest, with birch (*Betula* spec.), oak (*Quercus* spec.) and beech (*Fagus* spec.) trees as dominant species (for details see Appendix S1).

Rodent carcasses were transferred to the national reference laboratory for hantaviruses (veterinary medicine) at the Friedrich-Loeffler-Institut and dissected according to standard protocols (for details see Appendix S1).

Chest cavity lavages were tested by in-house PUUV IgG-ELISA (Mertens et al., 2011). Molecular analyses followed previously described protocols of one-step conventional and real-time S segment (Drewes, Sheikh Ali, et al., 2017; Essbauer et al., 2006; Schmidt et al., 2016) and L segment RT-PCR (Klempa et al., 2006) and dideoxy-chain termination sequencing. Comparison and phylogenetic analyses of bank vole- and patient-derived nucleotide L and S segment sequences followed a previously described workflow (for details, see Appendix S1).

Ethics approval was not required for the present outbreak investigation because it was conducted in the framework of the IfSG aimed to investigate the infection pathways and stop the further spread of infection.

3 | RESULTS

Seven out of eight company employees participated in our survey, three females and four males with a mean age of 35.3 years (range 29–47). At least one of the symptoms queried within the survey period was reported by five survey participants; one person reported no symptoms, and no data were provided by the remaining person. Symptoms most often mentioned were dizziness, sudden onset of fever (>38.5°C), muscle pain, headache, back pain and gastrointestinal symptoms such as nausea, vomiting and diarrhoea. In one case, impaired renal function was reported (Table S1). Two out of the five symptomatic employees were hospitalized, and their sera tested positive for PUUV-reactive IgG- and IgM antibodies regarding standard diagnostics (laboratory confirmation). The onset of symptoms of these two laboratory-confirmed cases was only 3 days apart (on 8 and 11 December 2017). For further laboratory confirmation during the outbreak investigation, a partial L segment sequence was amplified by RT-PCR and identified as PUUV sequence of the Central European (CE) clade. The conventional S and M segment RT-PCRs failed to detect specific products, and the qPCR showed a low viral load (4,073 copies/ml serum). Additionally, the remaining three symptomatic participants could be identified as cases by means of the survey, due to confirmation as clinical cases with epidemiological link according to IfSG. Therefore, for them no laboratory confirmation was performed.

More than half of the survey participants ($N = 4$) mentioned direct rodent contact inside the company building during the exposure period. They reported signs of rodent activity in offices, warehouses and the employee kitchen. The rodents present on the company

premises, and surrounding areas were identified as bank voles by the employees based on pictures of relevant rodent species (Table S1).

No bank voles or other rodents were caught inside the building, which suggests that the rodent control measures implemented after the first cases of human hantavirus disease were reported at the company had proven successful. In contrast, 18 bank voles (0.13 ind/trap night) were trapped on the company premises and 30 bank voles (0.5 ind/trap night) outside the premises indicating large populations at or exceeding outbreak density (Reil et al., 2015).

IgG-ELISA screening of the 48 bank voles resulted in the detection of eleven PUUV-seroreactive animals and one individual tested equivocal (Table 1). Conventional S segment RT-PCR revealed that these eleven seroreactive individuals were positive for hantavirus RNA. In addition, one serological negative and one equivocal bank vole tested positive in S segment RT-PCR. For seven out of 13 positive individuals, S segment sequences were generated (Table 1). The results of the PUUV S segment specific real-time RT-PCR of bank vole samples matched the results of the conventional S segment RT-PCR almost perfectly (Table 1).

The human-derived PUUV sequence was identical to eight of the nine bank vole-derived PUUV L segment sequences (Table S2). Phylogenetic analysis revealed that outbreak-related L segment sequences clustered together with other human-derived PUUV sequences from neighbouring geographic areas in Germany, but were distinct from sequences of other geographic origins (Figures 1 and 2). Bank vole-derived PUUV S segment sequences from the outbreak area formed a clade well separated from bank vole-derived sequences from the Netherlands, Belgium and France (Figure S1).

4 | DISCUSSION

During our interdisciplinary outbreak investigation, we were able to identify a total of five hantavirus disease cases, which corresponds to an infection rate of 62.5% for this company, and a high abundance of PUUV-infected bank voles on the company premises. Close collaboration of the public health and veterinary authorities at the local, federal and national level led to the identification of identical partial virus RNA sequences in a patient and bank voles, indicating the transmission of PUUV from bank voles to employees at the workplace.

A similar approach was done previously, comparing nucleotide sequences of human PUUV strains with those from bank voles trapped within putative areas of infection and describing it as an essential tool for 'case-investigations' (Plyusnin et al., 1999).

Occupational exposure to hantaviruses is well documented for persons working in agriculture, forestry or the military (Abu Sin et al., 2007; Clement et al., 1996; Jurke et al., 2015; Mertens et al., 2011; Ruo et al., 1994; Zöller et al., 1995). For example, in late 2017, a hantavirus-induced interstitial nephritis case due to Dobrava–Belgrade orthohantavirus (DOBV) was identified in Northern Germany related to occupational exposure (Mahmud et al., 2019). Although the described case was infected by DOBV, which has a differing seasonality compared with PUUV, the example shows that hantavirus infection should be considered also in winter if flu-like symptoms in combination with acute kidney failure are present. The occurrence of hantavirus infections during winter is well known from Finland, where the highest numbers of human NE cases are observed between November and January (Brummer-Korvenkontio et al., 1999; Kallio et al., 2009). However, the situation differs between the European countries: In countries with temperate climate like Germany, the bank vole dynamics is mainly driven by the food availability ('mast' years) and has its peak during summer, while in boreal climate, like in Finland, the vole dynamics is predominantly determined by their specialist mammalian predators (Kallio et al., 2009; Vaheri et al., 2013).

Occupational hantavirus cases unrelated to agriculture, forestry or the military are rarely described and occurred as isolated single cases. In 1996, one employee of a California utility company was shown to be infected at the workplace by Sin Nombre orthohantavirus, a hantavirus causing hantavirus cardiopulmonary syndrome in North America (Jay et al., 1996). In Germany, hantavirus disease has been included in the catalogue for recognized occupational diseases since 2003 (Bundesministerium für Gesundheit und Soziale Sicherung, 2003). For an audit of work-related cases, a polystyrene recycling company located in an endemic hantavirus region with a confirmed case of occupational disease was selected. During the audit in 2010, microbiological investigations of air and material samples, dust measurements and rodent trappings were performed on the premises of this company. PUUV was found in one-third of the bank voles collected on the company premises and was also diagnosed in the infected employee notified in 2008. As a consequence of this investigation, the authors suggested that appropriate preventive occupational medical examinations should be offered to all employees in hantavirus endemic regions with high prevalence of bank voles (Brenner et al., 2012). Our outbreak investigation provides additional evidence that occupational risk of hantavirus infection also exists in other businesses and is not restricted to agricultural, forestry or military settings.

Human PUUV cases often occur in close temporal and spatial association, but it is very rare that they meet the definition of being epidemiologically linked according to Robert Koch-Institute case definition for hantavirus disease. Our findings suggest that epidemiologically linked PUUV cases should be investigated in more detail in the future, since this allows identification of shared exposures and risks, and hence provides information where to implement preventive measures to mitigate transmission risk.

Our investigations revealed that bank voles enter buildings intensively used by humans, a behaviour suggested previously for largely uninhabited human dwellings during winter (Clement et al., 2009; Kallio et al., 2009; Khalil et al., 2014; Vaheri et al., 2013). In our study, bank voles were present in buildings in late autumn in unusually high numbers, probably because of food shortages in their natural habitat or first freezing, which occurred on 1 December. Such invasion into buildings is rare but likely to increase exposure of humans to PUUV (Reil et al., 2016; Xiang et al., 2018). PUUV prevalence in the bank voles trapped on company premises was about 23% and may have been similar to voles

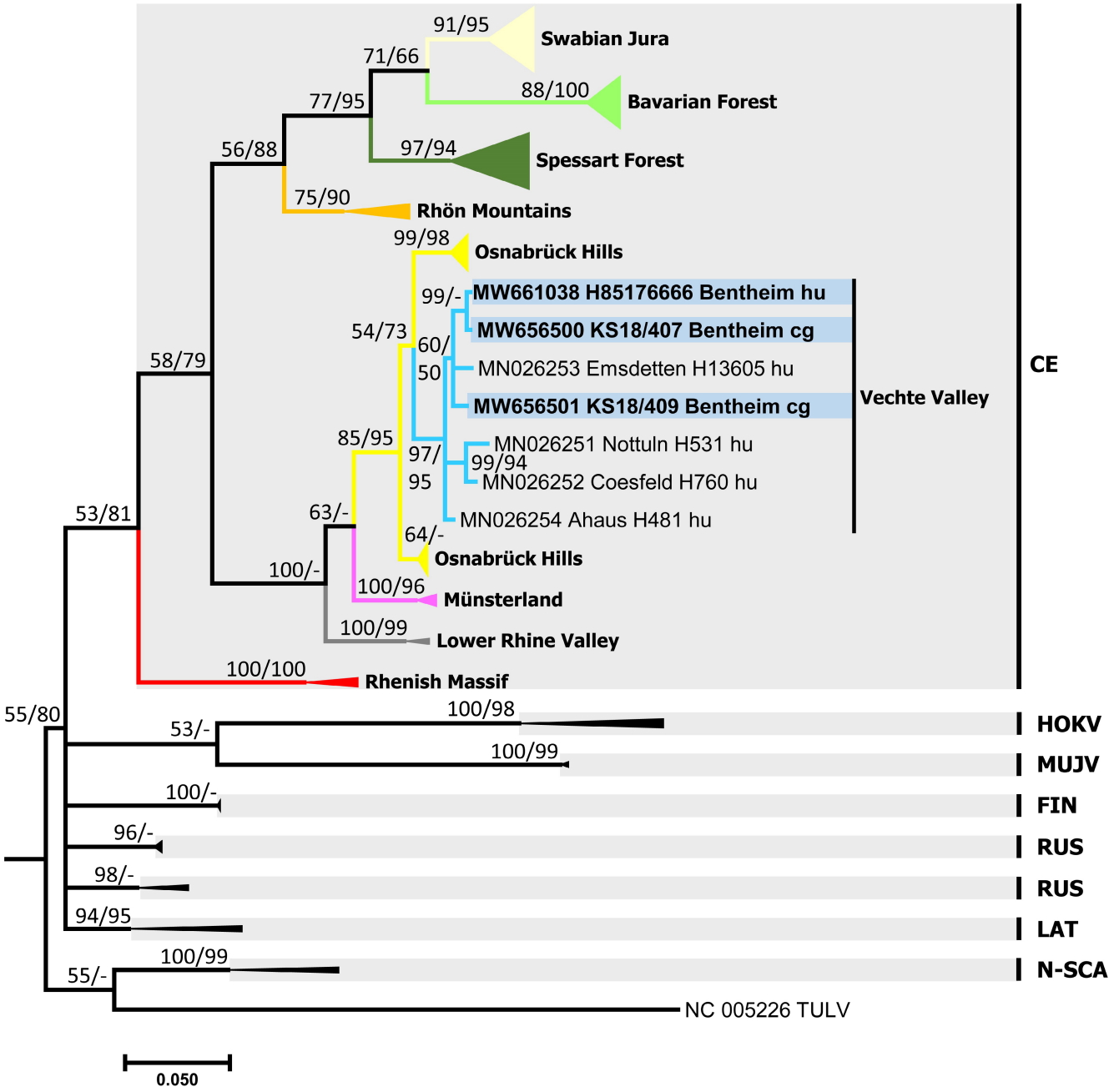

FIGURE 1 *1 Consensus phylogenetic tree of outbreak related Puumala orthohantavirus* (PUUV) L segment sequences with a length of 325 nt (with geographic reference "Bentheim") and other human-derived PUUV sequences from neighboring geographic areas (see Weiss et al., 2019) and bank-vole derived PUUV sequences. The consensus phylogenetic tree is based on Bayesian analyses with 8,000,000 generations and a burn-in fraction of 25% and on Maximum-Likelihood analyses with 1,000 bootstrap replicates. The Hasegawa, Kishino and Yano substitution model with invariant sites and a gamma distributed shape parameter (HKY+I+G) was used for Bayesian and the Jukes-Cantor including the categories model (JC+CAT) for Maximum-Likelihood tree reconstructions. Posterior probabilities are given in front and bootstrap values behind the slash if branches are supported with values above 50 and if branches of both trees were consistent. CE Central European lineage; cg *Clethrionomys glareolus*; FIN Finnish lineage; hu human; HOKV Hokkaido virus; LAT Latvian lineage; MUJV Muju virus; N-SCA North-Scandinavian lineage; RUS Russian lineage; TULV Tula orthohantavirus

that were present inside the building at the time of human infection. This value is similar to prevalences reported for bank voles in their natural habitat in spring of non-outbreak years in northwestern Germany (Reil et al., 2017) and seems to pose considerable risk of human infection at least in confined spaces. To mitigate the risk of zoonotic transmission, we recommend rodent-proof structures to prevent bank voles from entering buildings. This can be achieved by integrated preventive measures like reduction in food availability, reduction in shelters and limiting access to buildings. In case, rodents are present in buildings, additional rodent control measures must be taken. The use of snap traps is the first choice if bank voles manage to enter the building. At higher abundance, registered rodenticidal products might also be used. One disadvantage of rodenticides compared with traps is that rodents

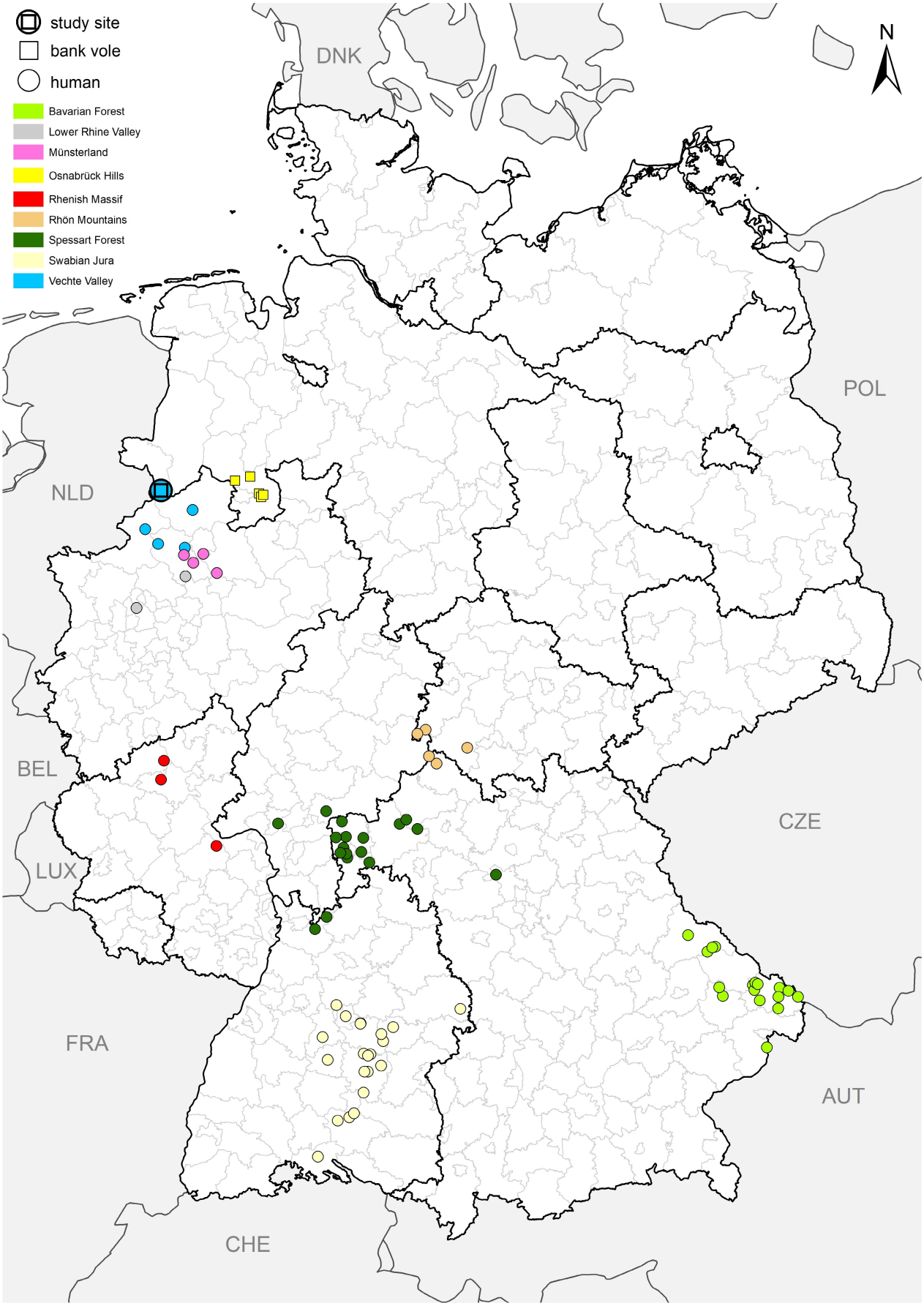

FIGURE 2 Map showing the locations where the samples from the phylogenetic tree in Figure 1 were collected (see Weiss et al., 2019). The outbreak site is represented by the top-left dot

survive for a longer time inside buildings, which leads to more contamination as it is known that shedding of the virus is lifelong after infection and that PUUV remains infectious outside the host for two weeks at room temperature (Kallio et al., 2006; Voutilainen et al., 2015). In any case, care must be taken to minimize potential risk for non-target small mammals (Walther et al., 2021).

ACKNOWLEDGEMENTS

The authors would like to specially thank Stefan Fischer for his help during rodent dissection, to Martin Oskamp and staff members and employees of the health department of the Grafschaft Bentheim district for their support in carrying out the questionnaire survey, and Patrick Wysocki and Daike Lehnau (Institute of Epidemiology, FLI) for generating Figure 2. Likewise, we would like to thank the affected company and its employees for their assistance during the outbreak investigation. The investigations were supported within the network of zoonotic infectious diseases by the Bundesministerium für Bildung und Forschung (BMBF; grants 01KI1721D to CP, KMMS and JD 01KI2004D to JD, 01KI1721A and 01KI2004A to RGU, 01KI1721C and 031L0096B to SW, 01KI1721E and 01KI2004E to JJ and 01KI1721H to JF).

CONFLICT OF INTEREST

The authors declare that no conflict of interest exists.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Christina Princk https://orcid.org/0000-0001-9265-8480
Stephan Drewes https://orcid.org/0000-0003-1240-147X
Beate Tenner https://orcid.org/0000-0002-9435-359X
Sabrina Weiss https://orcid.org/0000-0002-4835-3695
Rainer G. Ulrich https://orcid.org/0000-0002-5620-1528

REFERENCES

Abu Sin, M., Stark, K., Van Treeck, U., Dieckmann, H., Uphoff, H., Hautmann, W., Bornhofen, B., Jensen, E., Pfaff, G., & Koch, J. (2007). Risk factors for Hantavirus infection in Germany, 2005. *Emerging Infectious Diseases*, *13*(9), 1364.

Avšič-Županc, T., Saksida, A., & Korva, M. (2019). Hantavirus Infections. *Clinical Microbiology and Infection*, *21S*, e6–e16. https://doi.org/10.1111/1469-0691.12291

Binder, F., Drewes, S., Imholt, C., Saathoff, M., Below, D. A., Bendl, E., Conraths, F. J., Tenhaken, P., Mylius, M., Brockmann, S., Oehme, R., Freise, J., Jacob, J., & Ulrich, R. G. (2020). Heterogeneous *Puumala orthohantavirus* situation in endemic regions in Germany in summer 2019. *Transboundary and Emerging Diseases*, *67*(2), 502–509. https://doi.org/10.1111/tbed.13408

Brenner, B., Endrich, A., Pawlitzki, B., Trani, M., Tuschak, C., Schneider, C. K., Daniels, H., Osterberg, A., Eßbauer, S., & Herr, C. (2012). Infektionsgefährdung durch Hantavirus und Leptospiren beim Styroporrecycling. *Arbeitsmedizin, Sozialmedizin, Umweltmedizin*, *47*(8), 441.

Brummer-Korvenkontio, M., Vapalahti, O., Henttonen, H., Koskela, P., Kuusisto, P., & Vaheri, A. (1999). Epidemiological study of nephropathia epidemica in Finland 1989–96. *Scandinavian Journal of Infectious Diseases*, *31*(5), 427–435. https://doi.org/10.1080/00365549950163941

Bundesministerium für Gesundheit und Soziale Sicherung (2003). *"Merkblatt zu der Berufskrankheit Nr. 3102 der Anlage zur Berufskrankheiten-Verordnung (BKV): 'Von Tieren auf Menschen übertragbare Krankheiten.'"*. https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Berufskrankheiten/pdf/Merkblatt-3102.pdf?__blob=publicationFile&v=3

Clement, J., Underwood, P., Ward, D., Pilaski, J., & LeDuc, J. (1996). Hantavirus outbreak during military manoeuvres in Germany. *Lancet*, *347*(8997), 336. https://doi.org/10.1016/S0140-6736(96)90519-X

Clement, J., Vercauteren, J., Verstraeten, W. W., Ducoffre, G., Barrios, J. M., Vandamme, A.-M., Maes, P., & Van Ranst, M. (2009). Relating increasing Hantavirus incidences to the changing climate: The mast connection. *International Journal of Health Geographics*, *8*(1), 1–11. https://doi.org/10.1186/1476-072X-8-1

Drewes, S., Sheikh Ali, H., Saxenhofer, M., Rosenfeld, U. M., Binder, F., Cuypers, F., Schlegel, M., Röhrs, S., Heckel, G., & Ulrich, R. G. (2017). Host-associated absence of human Puumala virus infections in Northern and Eastern Germany. *Emerging Infectious Diseases*, *23*(1), 83–86. https://doi.org/10.3201/eid2301.160224

Drewes, S., Turni, H., Rosenfeld, U. M., Obiegala, A., Straková, P., Imholt, C., Glatthaar, E., Dressel, K., Pfeffer, M., Jacob, J., Wagner-Wiening, C., & Ulrich, R. G. (2017). Reservoir-driven heterogeneous distribution of recorded human Puumala virus cases in South-West Germany. *Zoonoses and Public Health*, *64*(5), 381–390.

Essbauer, S., Schmidt, J., Conraths, F. J., Friedrich, R., Koch, J., Hautmann, W., Pfeffer, M., Wölfel, R., Finke, J., Dobler, G., & Ulrich, R. (2006). A new puumala Hantavirus subtype in rodents associated with an outbreak of nephropathia epidemica in South-East Germany in 2004. *Epidemiology and Infection*, *134*(6), 1333–1344. https://doi.org/10.1017/S0950268806006170

Faber, M., Krüger, D. H., Auste, B., Stark, K., Hofmann, J., & Weiss, S. (2019). Molecular and epidemiological characteristics of human puumala and Dobrava-Belgrade Hantavirus infections, Germany, 2001 to 2017. *Eurosurveillance*, *24*(32), 2–11. https://doi.org/10.2807/1560-7917.ES.2019.24.32.1800675

Heyman, P., Cochez, C., Ducoffre, G., Mailles, A., Zeller, H., Abu Sin, M., Koch, J., van Doornum, G., Koopmans, M., Mossong, J., & Schneider, F. (2007). Haemorrhagic fever with renal syndrome: An analysis of the outbreaks in Belgium, France, Germany, the Netherlands and Luxembourg in 2005. *Eurosurveillance*, *12*(5), 15–16. https://doi.org/10.2807/esm.12.05.00712-en

Höhl, N. (2020). *Infektionsschutzgesetz: Mit Trinkwasserverordnung* (8th ed.). Siegburg: Verlag W. Reckinger GmbH & Co. KG.

ICTV (2022). *Virus taxonomy: 2020 release*. (https://talk.ictvonline.org/

Jay, M., Hjelle, B., Davis, R., Ascher, M., Baylies, H. N., Reilly, K., & Vugia, D. (1996). Occupational exposure leading to Hantavirus pulmonary syndrome in a utility company employee. *Clinical Infectious Diseases*, *22*(5), 841–844. https://doi.org/10.1093/clinids/22.5.841

Jurke, A., Bannert, N., Brehm, K., Fingerle, V., Kempf, V. A. J., Kömpf, D., Lunemann, M., Mayer-Scholl, A., Niedrig, M., Nöckler, K., Scholz, H., Splettstoesser, W., Tappe, D., & Fischer, S. F. (2015). Serological survey of *Bartonella* Spp., *Borrelia burgdorferi*, *Brucella* Spp., *Coxiella burnetii*, *Francisella tularensis*, *Leptospira* Spp., *Echinococcus*, Hanta-, TBE- and XMR-virus infection in employees of two forestry enterprises in North Rhine-Westphalia. *International Journal of Medical Microbiology*, *305*(7), 652–662.

Kallio, E. R., Begon, M., Henttonen, H., Koskela, E., Mappes, T., Vaheri, A., & Vapalahti, O. (2009). Cyclic hantavirus epidemics in humans—predicted by rodent host dynamics. *Epidemics*, *1*(2), 101–107. https://doi.org/10.1016/j.epidem.2009.03.002

Kallio, E. R., Klingström, J., Gustafsson, E., Manni, T., Vaheri, A., Henttonen, H., Vapalahti, O., & Lundkvist, Å. (2006). Prolonged

survival of puumala Hantavirus outside the host: Evidence for indirect transmission via the environment. *The Journal of General Virology*, *87*(Pt 8), 2127–2134. https://doi.org/10.1099/vir.0.81643-0

Khalil, H., Olsson, G., Ecke, F., Evander, M., Hjertqvist, M., Magnusson, M., Ottosson Löfvenius, M., & Hörnfeldt, B. (2014). "The importance of bank vole density and rainy winters in predicting nephropathia epidemica incidence in Northern Sweden" edited by C. A. Stoddart. *PLoS One*, *9*(11), e111663. https://doi.org/10.1371/journal.pone.0111663

Klempa, B., Fichet-Calvet, E., Lecompte, E., Auste, B., Aniskin, V., Meisel, H., Denys, C., Koivogui, L., ter Meulen, J., & Krüger, D. H. (2006). Hantavirus in African wood mouse, Guinea. *Emerging Infectious Diseases*, *12*(5), 838–840. https://doi.org/10.3201/eid1205.051487

Krüger, D. H., Schönrich, G., & Klempa, B. (2011). Human pathogenic Hantaviruses and prevention of infection. *Human Vaccines*, *7*(6), 685–693. https://doi.org/10.4161/hv.7.6.15197

Krüger, D. H., Ulrich, R. G., & Hofmann, J. (2013). Hantaviruses as zoonotic pathogens in Germany. *Deutsches Aerzteblatt Online*, *110*(27–28), 461–467. https://doi.org/10.3238/arztebl.2013.0461

Laenen, L., Vergote, V., Calisher, C. H., Klempa, B., Klingström, J., Kuhn, J. H., & Maes, P. (2019). Hantaviridae: Current classification and future perspectives. *Viruses*, *11*(9), 788. https://doi.org/10.3390/v11090788

Mahmud, M., Winkelmann, C., & Harendza, S. (2019Fulminantes akutes Nierenversagen nach Cholezystektomie bei einer 45-jährigen Patientin. *Internist (Berl)*, *60*(4), 390–395. https://doi.org/10.1007/s00108-018-0494-2

Mertens, M., Kindler, E., Emmerich, P., Esser, J., Wagner-Wiening, C., Wölfel, R., Petraityte-Burneikiene, R., Schmidt-Chanasit, J., Zvirbliene, A., Groschup, M. H., Dobler, G., Pfeffer, M., Heckel, G., Ulrich, R. G., & Essbauer, S. S. (2011). Phylogenetic analysis of puumala virus subtype Bavaria, characterization and diagnostic use of its recombinant nucleocapsid protein. *Virus Genes*, *43*(2), 177–191. https://doi.org/10.1007/s11262-011-0620-x

NLGA (2021). *Hantavirus-Erkrankungen in Niedersachsen*. https://www.nlga.niedersachsen.de/startseite/infektionsschutz/weitere_themen_projekte/projekt_robopub/hantavirus_erkrankungen_in_niedersachsen/hantavirus-erkrankungen-176063.html

Plyusnin, A., Mustonen, J., Asikainen, K., Plyusnina, A., Niemimaa, J., Henttonen, H., & Vaheri, A. (1999). Analysis of puumala Hantavirus genome in patients with nephropathia epidemica and rodent carriers from the sites of infection. *Journal of Medical Virology*, *59*(3), 397–405. https://doi.org/10.1002/(SICI)1096-9071(199911)59:3<397:AID-JMV21>3.0.CO;2-#

Plyusnina, A., Razzauti, M., Sironen, T., Niemimaa, J., Vapalahti, O., Vaheri, A., Henttonen, H., & Plyusnin, A. (2012). Analysis of complete puumala virus genome, Finland. *Emerging Infectious Diseases*, *18*(12), 2070–2072. https://doi.org/10.3201/eid1811.120747

Reil, D., Imholt, C., Drewes, S., Ulrich, R. G., Eccard, J. A., & Jacob, J. (2016). Environmental conditions in favour of a Hantavirus outbreak in 2015 in Germany? *Zoonoses and Public Health*, *63*(2), 83–88. https://doi.org/10.1111/zph.12217

Reil, D., Imholt, C., Eccard, J. A., & Jacob, J. (2015). "Beech fructification and bank vole population dynamics - combined analyses of promoters of human Puumala virus infections in Germany" edited by. J. Waldenström. *PLoS One*, *10*(7), e0134124. https://doi.org/10.1371/journal.pone.0134124

Reil, D., Rosenfeld, U. M., Imholt, C., Schmidt, S., Ulrich, R. G., Eccard, J. A., & Jacob, J. (2017). Puumala Hantavirus infections in bank vole populations: Host and virus dynamics in central Europe. *BMC Ecology*, *17*(1), 9. https://doi.org/10.1186/s12898-017-0118-z

Robert Koch-Institut (2020). *"SurvStat@RKI 2.0 Web-Basierte Abfrage der Meldedaten gemäß Infektionsschutzgesetz (IfSG).".* https://survstat.rki.de

Ruo, S. L., Li, Y. L., Tong, Z., Ma, Q. R., Liu, Z. L., Tang, Y. W., Ye, K. L., Xu, Z. Y., McCormick, J. B., & Fisher-Hoch, S. P. (1994). Retrospective and prospective studies of hemorrhagic fever with renal syndrome in rural China. *Journal of Infectious Diseases*, *170*(3), 527–534. https://doi.org/10.1093/infdis/170.3.527

Schmidt, S., Saxenhofer, M., Drewes, S., Schlegel, M., Wanka, K. M., Frank, R., Klimpel, S., von Blanckenhagen, F., Maaz, D., Herden, C., Freise, J., Wolf, R., Stubbe, M., Borkenhagen, P., Ansorge, H., Eccard, J. A., Lang, J., Jourdain, E., Jacob, J., … Ulrich, R. G. (2016). High genetic structuring of Tula Hantavirus. *Archives of Virology*, *161*(5), 1135–1149. https://doi.org/10.1007/s00705-016-2762-6

StataCorp. (2017). *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC.

Vaheri, A., Henttonen, H., Voutilainen, L., Mustonen, J., Sironen, T., & Vapalahti, O. (2013). Hantavirus infections in Europe and their impact on public health. *Reviews in Medical Virology*, *23*(1), 35–49. https://doi.org/10.1002/rmv.1722

Vapalahti, K., Paunio, M., Brummer-Korvenkontio, M., Vaheri, A., & Vapalahti, O. (1999). Puumala virus infections in Finland: Increased occupational risk for farmers. *American Journal of Epidemiology*, *149*(12), 1142–1151. https://doi.org/10.1093/oxfordjournals.aje.a009769

Voutilainen, L., Sironen, T., Tonteri, E., Tuiskunen Bäck, A., Razzauti, M., Karlsson, M., Wahlström, M., Niemimaa, J., Henttonen, H., & Lundkvist, Å. (2015). Life-long shedding of Puumala Hantavirus in Wild Bank Voles (*Myodes glareolus*). *The Journal of General Virology*, *96*(Pt 6), 1238–1247. https://doi.org/10.1099/vir.0.000076

Walther, B., Geduhn, A., Schenke, D., Schlötelburg, A., & Jacob, J. (2021). Baiting location affects anticoagulant rodenticide exposure of non-target small mammals on farms. *Pest Management Science*, *77*(2), 611–619. https://doi.org/10.1002/ps.5987

Weiss, S., Klempa, B., Tenner, B., Krüger, D. H., & Hofmann, J. (2019). Prediction of the Spatial Origin of Puumala Virus Infections Using L Segment Sequences Derived from a Generic Screening PCR. *Viruses*, *11*(8), 694. https://doi.org/10.3390/v1108069

Xiang, J., Hansen, A., Liu, Q., Tong, M. X., Liu, X., Sun, Y., Cameron, S., Hanson-Easey, S., Han, G.-S., Williams, C., Weinstein, P., & Bi, P. (2018). Impact of meteorological factors on hemorrhagic fever with renal syndrome in 19 cities in China, 2005–2014. *Science of the Total Environment*, *636*, 1249–1256. https://doi.org/10.1016/j.scitotenv.2018.04.407

Zöller, L., Faulde, M., Meisel, H., Ruh, B., Kimmig, P., Schelling, U., Zeier, M., Kulzer, P., Becker, C., Roggendorf, M., Bautz, E. K. F., Krüger, D. H., & Darai, G. (1995). Seroprevalence of Hantavirus antibodies in Germany as determined by a new recombinant enzyme immunoassay. *European Journal of Clinical Microbiology and Infectious Diseases*, *14*(4), 305–313. https://doi.org/10.1007/BF02116523

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Princk, C., Drewes, S., Meyer-Schlinkmann, K. M., Saathoff, M., Binder, F., Freise, J., Tenner, B., Weiss, S., Hofmann, J., Esser, J., Runge, M., Jacob, J., Ulrich, R. G., & Dreesman, J. (2022). Cluster of human *Puumala orthohantavirus* infections due to indoor exposure?—An interdisciplinary outbreak investigation. *Zoonoses and Public Health*, *69*, 579–586. https://doi.org/10.1111/zph.12940