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**Title**

Heterogeneous Puumala orthohantavirus situation in endemic regions in Germany in summer 2019

**Running Title**

Puumala orthohantavirus in Germany in summer 2019

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## **SUMMARY**

Puumala orthohantavirus (PUUV) causes most human hantavirus disease cases in Europe. PUUV disease outbreaks are usually synchronized Germany-wide driven by beech mast-induced irruptions of its host (bank vole, *Myodes glareolus*). Recent data indicate high vole abundance, high PUUV prevalence and high human incidence in summer 2019 for some regions, but elsewhere values were low to moderate. This significant lack of synchrony among regions in Germany is in contrast to previous studies. Health institutions need to be informed about the heterogeneous distribution of human PUUV infection risk to initiate appropriate actions.

## **KEYWORDS**

bank vole; HFRS; emerging virus; infection risk; outbreak; Puumala orthohantavirus

## 1 INTRODUCTION

Hantaviruses are emerging pathogens that can cause human disease worldwide (Krüger, Figueiredo, Song, & Klempa, 2015). Puumala orthohantavirus (PUUV) is the most relevant hantavirus in Europe: It causes the majority of human hantavirus disease cases in Europe and is distributed in several parts of the continent. The number of human cases in Fennoscandia, Belgium, France and Germany oscillates among outbreak and non-outbreak years (Ettinger et al., 2012; Heyman et al., 2011; Olsson, Leirs, & Henttonen, 2010; Reil, Imholt, Eccard, & Jacob, 2015; Reil et al., 2017). Human PUUV infections lead to a mild to moderate course of symptoms called nephropathia epidemica (NE) characterized by an acute onset of high fever, headache, myalgias, gastrointestinal symptoms, and thrombocytopenia (Latus et al., 2015). Later, renal insufficiency or an acute renal failure may occur. Severe hemorrhagic fever with renal syndrome (HFRS) rarely appears in patients with PUUV infection (Heyman et al., 2009; Krüger, Ulrich, & Hofmann, 2013; Latus et al., 2015; Vaheri et al., 2013). The reservoir of PUUV is the bank vole (*Myodes glareolus*), which is a forest rodent distributed in most parts of Europe (Mitchell-Jones et al., 1999). PUUV, as all hantaviruses that are pathogenic for humans, is transmitted to humans by aerosols of dried rodent feces and urine or by biting via infectious saliva (Vaheri et al., 2013). Bank vole population abundance fluctuates more or less regularly across Europe (Jacob & Tkadlec, 2010) but the degree of regularity may vary depending on region and time. In temperate Europe, population peaks are driven by food supply available through tree seed mast in beech (*Fagus spec.*) and other forest trees (Clement et al., 2009). This provides ample food over winter resulting in early reproduction (Eccard & Ylönen, 2001) and population irruption in the following year (Reil et al., 2015).

In Germany, human NE cases are mainly restricted to the southern and western parts of the country (Drewes, Ali, et al., 2017) (Figure 1). This heterogeneous distribution of PUUV has been explained by postglacial recolonization of Central and Western Europe by the Western evolutionary lineage of the bank vole (Drewes, Ali, et al., 2017). There is considerable fluctuation in human hantavirus disease cases in Germany with outbreaks in the years 2007, 2010, 2012 and 2017. Outbreaks are usually spatially synchronized among endemic regions of Germany (Ettinger et al., 2012) (Figure 1). Human PUUV prevalence can be high in any endemic region but more people seem to be affected in the south. The variation in human PUUV prevalence in endemic regions of western Germany may be due to regional differences in forest structure (Magnusson et al., 2015; Voutilainen et al., 2012). This region exhibits the highest degree of landscape fragmentation in Germany (Walz, Krüger, & Schumacher, 2011), a more continuous forest cover in the south can increase human PUUV incidence (Drewes, Turni et al., 2017).

The objective of this study was to find out putative early predictors of a hantavirus outbreak year in Germany and to prove if these parameters and the human incidence data in 2019 indicate a homogenous outbreak pattern.

## 2 MATERIAL AND METHODS

Regular bank vole monitoring was conducted in several German federal states (Figure 2) following a standard snap trapping protocol (Drewes, Schmidt, Jacob, Imholt, & Ulrich, 2016). Trapped bank voles were stored frozen at -20°C until dissection. Data are reported as individuals per 100 trap nights (TN) to adjust for variation in trap success. Sites were selected because they are situated in or close to known endemic regions (see Drewes, Turni, et al., 2017; Ettinger et al., 2012; Faber et al., 2013; Reil et al., 2017; Weber de Melo et al., 2015).

To determine the PUUV infection rate in bank voles, lung tissue was sampled from 249 of the 375 bank voles trapped. A pin head-sized piece was minced, RNA isolated and tested by conventional standard RT-PCR targeting the small (S) segment (Drewes, Ali, et al., 2017). RT-PCR products were sequenced for PUUV detection by dideoxy-chain termination method using BigDye Terminator v1.1 Kit (Applied Biosystems, Darmstadt, Germany).

Beech fructification intensity was estimated between July and August 2018 as the percentage of fruiting beech trees older than 49 years, classified in absent, scarce, common and abundant fructification. Beech fructification is assessed annually by State Forest Authorities and reported as a mean value for each Federal State (Reil et al., 2015).

Human PUUV incidence was retrieved from SurvStat@RKI 2.0, <https://survstat.rki.de> and is reported as cases per 100,000 inhabitants (data status 30.08.2019). These data are reported to the national register irrespective of the hantavirus species. The vast majority of human hantavirus infections in Germany is caused by PUUV, whereas Dobrava-Belgrade virus (DOBV, genotype Kurkino) infections are largely restricted to the east of Germany where the reservoir species, the striped field mouse (*Apodemus agrarius*) is present (Faber et al., 2019; Hofmann et al., 2014; Krüger et al., 2013). Therefore, we use the reported incidence data as a proxy for human infection with PUUV and use the term “PUUV infection” throughout, since our analyzed data comes from the southern and western part of Germany rather than the eastern part where DOBV mostly occur.

To test for differences between human PUUV incidence patterns in 2019 and the mean pattern of previous outbreak years, we conducted a multiple linear regression analysis with incidence as the dependent variable and the respective week and year (2019 *versus* mean outbreak) as well as their interaction as explanatory variables. Non-significant interaction terms indicated no difference in the slope between 2019 and outbreak years.

### 3 RESULTS AND DISCUSSION

Beech fructification intensity (Table 1) varied in 2018 from 18 to 65% indicating medium to abundantly fruiting trees. Beech mast has been reported to be highly synchronous but may differ regionally in some years (Reil et al., 2015). Bank vole abundance in spring 2019 varied strongly between regions (Table 1). Particularly high abundance was recorded in districts Steinfurt (northwest) and Göppingen (south) but elsewhere abundance was low (central) to moderate (regionally in the northwest) and was highly variable between regions and plots (Table 1).

PUUV RNA detection rate generally followed beech mast intensity with high values in the south, regionally high-moderate values in the northwest and no evidence for PUUV RNA in bank voles from the central region but data were scarce for the latter. This pattern was roughly mirrored by human PUUV incidence (cumulative incidence of calendar weeks 1-33 in 2019) in these regions (Table 1). For comparison, incidence data for PUUV outbreak years (2007, 2010, 2012, 2017) and intermittent non-outbreak years (2011, 2013-2016, 2018) are presented in Table 1.

Beech fructification in 2018 in the northwest and south was mainly at levels that can trigger bank vole population irruptions (Reil et al., 2015). This was well reflected in several locations where high bank vole abundance was recorded in spring 2019 but not everywhere. Especially in parts of the northwest, bank vole abundance was not particularly high. The high abundance values were in the range found during PUUV outbreaks in Germany in previous years (Reil et al., 2015). The regional and local differences in abundance might be explained by heterogeneous beech fructification and little beech fructification in the central region but there is no regional information available for beech mast intensity (Table 1; Lower Saxony Ministry of Food, Agriculture and Consumer Protection, 2018; Thuringian Ministry for Infrastructure and Agriculture, 2018). Despite the overwhelming effect of beech mast on bank vole population dynamics it is possible that other factors such as local interaction in the food web or diseases have caused heterogeneous abundance of bank voles.

PUUV RNA detection rate in the bank vole varied considerably with a peak at about 60% in the south and parts of the northwest, almost reaching values observed during previous PUUV outbreaks. For instance, PUUV RNA detection rate in district Osnabrück in spring of previous outbreak years was 86% (2010) and 75% (2012) (Weber de Melo et al., 2015). However, in other regions in the northwest and in central Germany PUUV RNA detection rate was low and did not reach prevalence values reported for previous outbreaks of PUUV in Germany (Reil et al., 2017). Although the relationship between abundance and RNA detection rate/seroprevalence varies seasonally and demographically (Reil et al., 2017), it is highly likely that some combination of bank vole abundance and RNA detection rate is an important risk factor for human PUUV infection. The snap-shot data from a limited selection of districts makes it difficult to draw firm conclusions in this regard, but earlier reports support this assumption (Drewes, Turni, et al., 2017).

A pattern similar to PUUV RNA detection rate in voles was found for the cumulative human PUUV incidence up to calendar week 33 (mid-August 2019). For some districts in the northwest and in the south it reached or even exceeded values known from former outbreaks. However, PUUV incidence until mid-August 2019 in other districts in the northwest and in the central region was lower than the mean in outbreak years. In fact, only the curves for human PUUV incidence in Stuttgart ( $p = 0,937$ ) and Osnabrück ( $p = 0.201$ ) were similar to the mean outbreak curves (Figure 3), while this was not the case in all other districts ( $p < 0.001$ ) indicating a typical outbreak situation in 2019 in two districts only. In Borken and Steinfurt, the curves for 2019 were different from the mean outbreak curve because the values in 2019 in these districts were higher than in the mean outbreak scenario. In all other districts, weekly cumulative PUUV incidence values until the mid-August 2019 were in between PUUV incidences of outbreak and non-outbreak years. These observations indicate a heterogeneous situation in 2019 in Germany and possibly the neighboring countries in the west and south where PUUV occurs.

Temporal trends of cumulative human PUUV incidence appeared mostly consistent. In comparison to outbreak years, the temporal trends until mid-August 2019 show similar patterns of a steady increase with an initial flat rise and a steeper rise from spring on (Figure 3). This seems to be a promising feature for the development of district scale prediction of human risk based on PUUV incidence early in the year.

The lack of synchrony within and among regions contrasts earlier findings (Ettinger et al., 2012) and may be a new pattern. However, a similar phenomenon can occur at larger spatial scale: in 2005, a small outbreak was reported that seemingly affected only the western part of Germany and neighboring countries (Mailles et al., 2005). Physicians and public health institutions should be aware of the potential scenario of more localized outbreaks. The abundance of PUUV-infected bank voles is a major risk factor

for human infection (Reil et al., 2015; Vanwambeke et al., 2019). It therefore seems reasonable to use information about vole abundance and PUUV prevalence in addition to data of human infections to assess human risk. Robust predictive models can aid such an approach but so far are only available at country (Tersago et al., 2009) or district scale (Reil et al., 2018) and the pathogen transmission system is still complex (Vanwambeke et al., 2019).

Physicians should consider hantavirus disease as differential diagnosis in patients to avoid false diagnoses, especially in risk groups that are prone to contract diseases with similar symptoms such as leptospirosis. Public health institutions can provide information on prevention of rodent infestations and other actions to minimize hantavirus infections focusing on regions with higher risk for infections. Future investigations should evaluate the reasons for the lack of synchrony of outbreaks. This could include modeling population abundance of bank voles based on interactions with food, predators and landscape factors. Future studies might explore the effect of the ongoing drought in Central Europe on tree mast synchrony as well as the subsequent effects on spatial and temporal bank vole dynamics.

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#### **ETHICS STATEMENT**

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. All relevant guidelines for the use of animals in scientific studies were followed.

#### CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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**Table 1** Beech fructification per region, bank vole trap success (individuals per 100 trap nights) per plot in spring 2019, PUUV RNA detection rate in bank voles in spring 2019 and human PUUV incidence in 2019 and in PUUV outbreak (2007, 2010, 2012, 2017) and non-outbreak years (2011, 2013-16, 2018) (cumulative for calendar weeks 1-33). Incidence values are values per district (2019) or means of districts across outbreak and non-outbreak years. Variance: standard deviation.

Region	District	Beech fructification 2018	Bank vole trap success (plots)	PUUV RNA Detection rate (plots, total number of voles)	human PUUV incidence		
					2019 (districts)	Outbreak (years, districts)	Non-outbreak (years, districts)
North-west	OSN	48%	5.3 ±3.1 (8)	63 ±13% (5,75)	14.2 (1)	12.2±1.3 (4, 1)	1.2 ±1.0 (6, 1)
	STE	ca. 45%	15.4 ±14.8 (3)	18 ±19% (3,24)	4.7 (1)	3.0 ±2.2 (4, 1)	1.7 ±1.4 (6, 1)
	COE/BOR	ca. 45%	7.6 ±4.57 (9)	18 ±23% (9,80)	2.8-4.9 (2)	4.2 ±0.9 (4, 2)	1.9 ±1.2 (6, 2)
Central	WAK/UHE	18%	2.5 ±4.0 (15)	0.0 (1,11)	0-4.1 (2)	8.9 ±5.2 (4, 2)	1.4 ±1.9 (6, 2)
South	GÖP	ca. 65%	70 (1)*	57% (1,7)	17.9 (1)	31.2 ±14.2 (4, 1)	3.2 ±4.8 (6, 1)
	STU	ca. 65%	2.9 (1)*	63% (1,52)	15.2 (1)	15.6 ±10.9 (4, 1)	2.1 ±2.7 (6, 1)

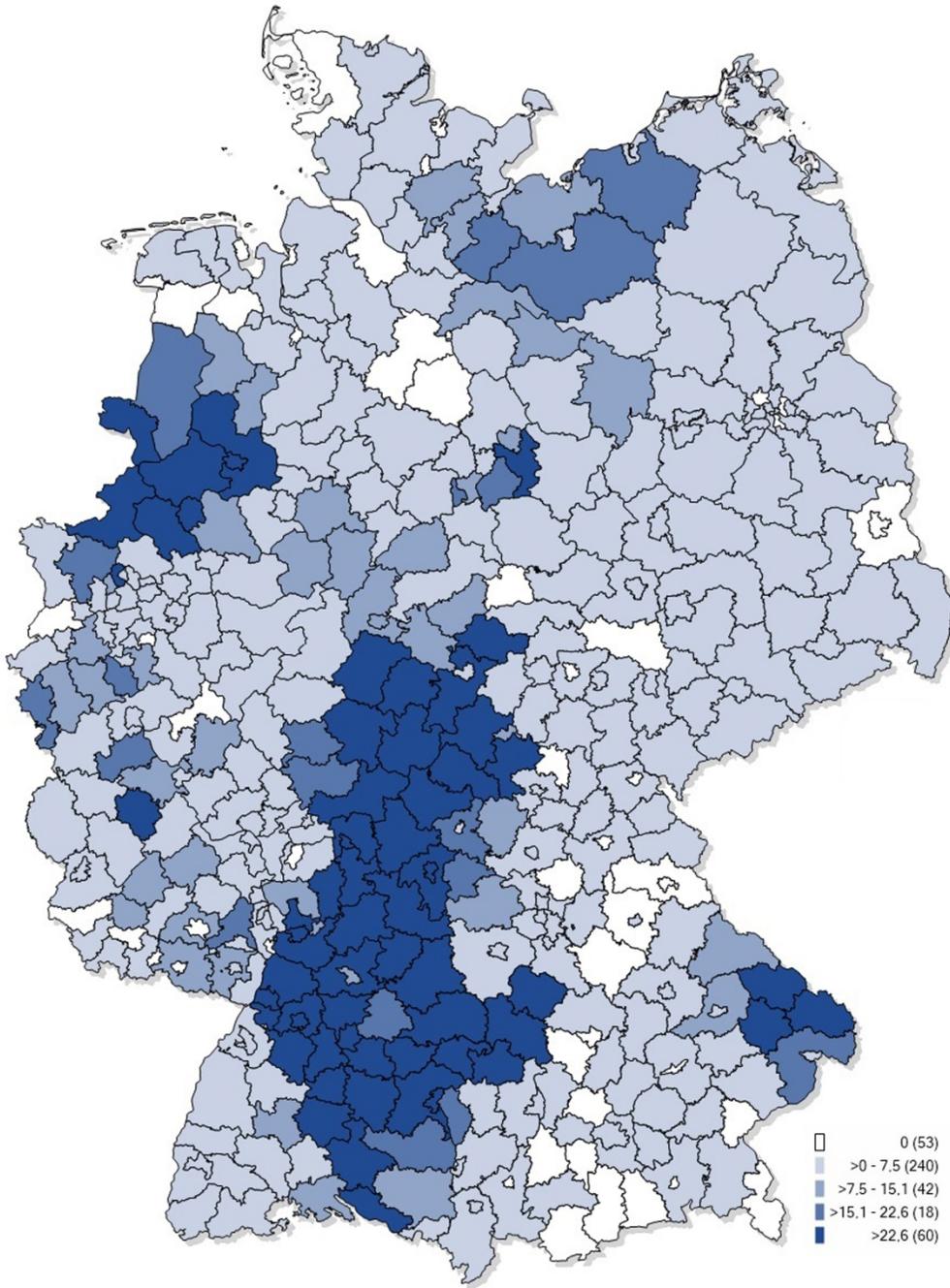
Districts: OSN – Osnabrück; STE – Steinfurt; COE – Coesfeld; BOR – Borken; WAK – Wartburgkreis; UHE – Unstrut-Hainich-Kreis; GÖP – Göppingen; STU – Stuttgart; \*trapping in GÖP and STU did not follow the protocol of Drewes, Schmidt, Jacob, Imholt, & Ulrich (2016).

## Figure Legends

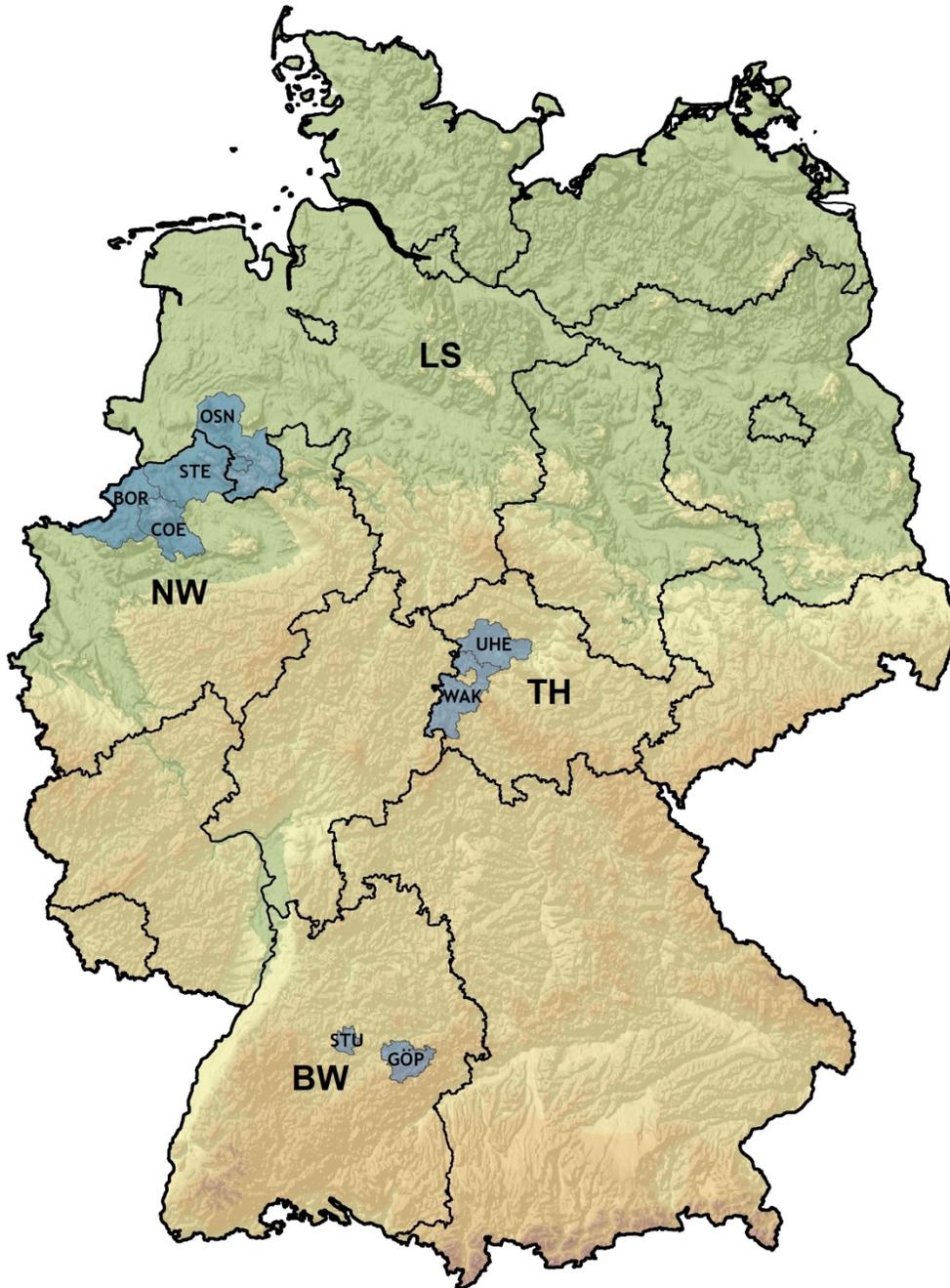
**Figure 1:** Spatial distribution of cumulative incidence classes of notified human hantavirus disease cases per district per 100,000 inhabitants for the years 2001-2018. The number of districts per class is stated in parentheses. Map and data retrieved on 30<sup>th</sup> August 2019, Robert Koch-Institute, SurvStat@RKI 2.0, <https://survstat.rki.de>.

**Figure 2:** Regions in the northwest, center and south of Germany, where vole abundance was recorded, samples for PUUV RNA detection were collected and matching information for human incidence was available. Map origin: Federal Agency for Cartography and Geodesy. Federal States: LS – Lower Saxony; NW – North Rhine-Westphalia; TH – Thuringia; BW – Baden-Wuerttemberg. Districts: OSN – Osnabrück; STE –Steinfurt; COE – Coesfeld; BOR – Borken; WAK – Wartburgkreis; UHE – Unstrut- Hainich-Kreis; GÖP – Göppingen; STU – Stuttgart.

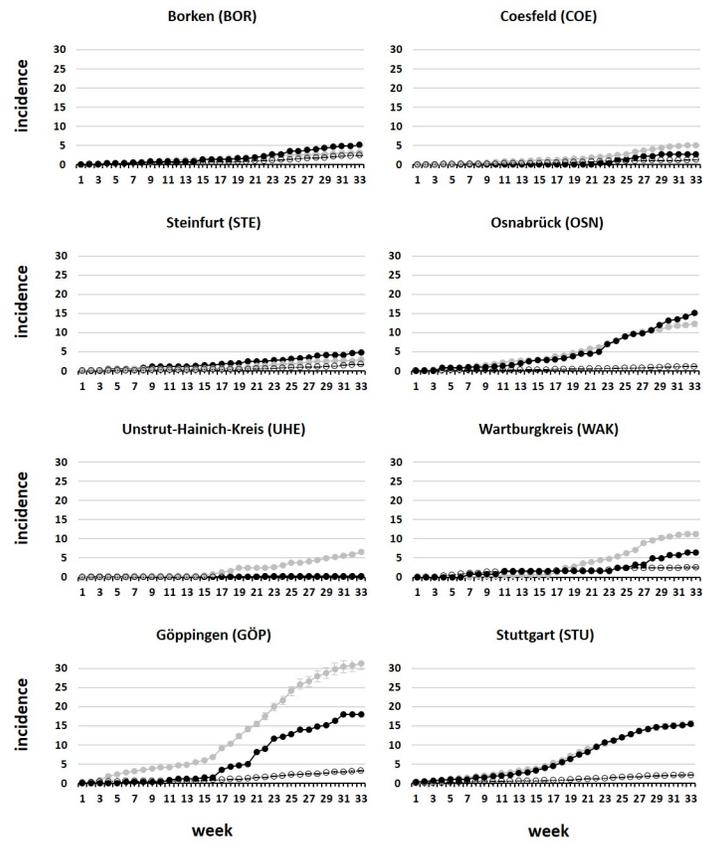
**Figure 3:** Weekly cumulative hantavirus incidence from 1<sup>st</sup> January until 18<sup>th</sup> August per district for 2019 (black line/dots), mean values for outbreak years (2007, 2010, 2012, 2017 – medium grey line/dots) and non-outbreak years (2011, 2013-2016, 2018 – dotted black line/dots). Data retrieved on 30<sup>th</sup> August 2019, Robert Koch-Institute, SurvStat@RKI 2.0, <https://survstat.rki.de>. 95% confidence intervals for the cumulative incidence of human infections in outbreak and non-outbreak years are given as error bars in the corresponding line color.



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