A five-year perspective on the situation of haemorrhagic fever with renal syndrome and status of the hantavirus reservoirs in Europe, 2005–2010

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Hantavirus infections are reported from many countries in Europe and with highly variable annual case numbers. In 2010, more than 2,000 human cases were reported in Germany, and numbers above the baseline have also been registered in other European countries. Depending on the virus type human infections are characterised by mild to severe forms of haemorrhagic fever with renal syndrome. The member laboratories of the European Network for diagnostics of Imported Viral Diseases present here an overview of the progression of human cases in the period from 2005 to 2010. Further we provide an update on the available diagnostic methods and endemic regions in their countries, with an emphasis on occurring virus types and reservoirs.

Introduction

Hantaviruses (family *Bunyaviridae*, genus *Hantavirus*) are enveloped RNA viruses that have rodents and insectivores as hosts and are transmitted by aerosols of host excreta or by direct contact to humans. At least five hantaviruses, Puumala (PUUV), Dobrava (DOBV), Saaremaa (SAAV), Tula (TULV) and Seoul virus (SEOV), circulate in Europe. The most prominent and most widely occurring hantavirus in Europe is PUUV, transmitted by the bank vole (*Myodes glareolus*). PUUV causes a mild form of haemorrhagic fever with renal syndrome (HFRS), called nephropathia epidemica (NE). DOBV is transmitted by the yellow-necked field mouse (*Apodemus flavicollis*) and is known to cause more severe HFRS [1,2]. SAAV, which is closely related to DOBV, is carried by the striped field mouse (*A. agrarius*). It should be noted that the hantavirus strains associated with *A. agrarius* in central Europe and Russia have been shown to be phylogenetically distinct from the north-eastern European SAAV strains as well as from strains associated with *A. flavicollis* (DOBV-Af lineage) or the strains associated with the

Table 1

Carrier species, endemic regions and diagnostic tools for hantaviruses, Europe (n=30 ENIVD member countries)

	Carrier species for								
	Puumala virus	Tula virus	Seoul virus	Dobrava virus	Saaremaa virus	Laihia virus	Asikkala virus	Seewis virus	
Austria	*Myodes glareolus*	*Microtus arvalis*							
Belgium	*Myodes glareolus*	*Microtus arvalis*	*Rattus norvegicus*						
Bosnia and Herzegovina	*Myodes glareolus*			*Apodemus flavicollis*					
Bulgaria	*Myodes glareolus*			*Apodemus flavicollis*					
Cyprus									
Czech Republic	*Myodes glareolus*	*Microtus arvalis*		*Apodemus flavicollis*					
Denmark	*Myodes glareolus*								
Estonia	*Myodes glareolus*				*Apodemus agrarius*				
Finland	*Myodes glareolus*	*Microtus arvalis*			*Apodemus agrarius*	*Neomys fodiens*	*Sorex minutus*	*Sorex araneus*	
France	*Myodes glareolus*	*Microtus arvalis*	*Rattus norvegicus*						
Germany	*Myodes glareolus*	*Microtus arvalis* *Microtus agrestis*		*Apodemus flavicollis*	*Apodemus agrarius*			*Sorex araneus*	
Greece				*Apodemus flavicollis*					
Hungary	*Myodes glareolus*	*Microtus arvalis*		*Apodemus flavicollis*	*Apodemus agrarius*				
Italy									
Ireland	*Myodes glareolus*		*Rattus norvegicus*						
Lithuania	*Myodes glareolus*	*Microtus arvalis*		*Apodemus flavicollis*	*Apodemus agrarius*				
Luxembourg	*Myodes glareolus*								
the Netherlands	*Myodes glareolus*	*Microtus arvalis*							
Norway	*Myodes glareolus*								
Poland	*Myodes glareolus*			*Apodemus flavicollis*					
Portugal			*Rattus norvegicus*						
Romania	*Myodes glareolus*			*Apodemus flavicollis*					
Russia	*Myodes glareolus*	*Microtus arvalis*	*Rattus norvegicus*	*Apodemus flavicollis*	*Apodemus agrarius*				
Slovakia	*Myodes glareolus*			*Apodemus flavicollis*	*Apodemus agrarius*				
Slovenia	*Myodes glareolus*	*Microtus arvalis*, *Microtus agrestis*, *Microtus subterraneus*		*Apodemus flavicollis*	*Apodemus agrarius*				
Spain									
Sweden	*Myodes glareolus*								
Switzerland									
Turkey	*Myodes glareolus*			*Apodemus flavicollis*					
United Kingdom									

ELISA: enzyme-linked immunosorbent assay; ENIVD: European Network for diagnostics of Imported Viral Diseases; IFA: immunofluorescence assay; RT-PCR: reverse transcription polymerase chain reaction.

Fields with symbols indicate that the method is in use (x) or not in use (-).

The question marks refer to the presence of an unidentified hantavirus. In Portugal, the Algerian mouse (*Mus spretus*), the house mouse (*Mus musculus*) and the wood mouse (*Apodemus sylvaticus*), species that are so far not known to harbour a hantavirus, were found positive for hantaviral antibodies. No identification of the infecting hantavirus serotype has been achieved until now.

Data as reported by ENIVD members. This list compiles only the obtained information by means of the 2010 questionnaire and not the current state of the literature.

				Deaths (number)	Endemic region	Diagnostic methods			
	?	?	?			IFA	ELISA	RT-PCR	Sequencing
	Shrews			Yes (n=1)	95% in the south-east (Styria, Carinthia, Burgenland) 5% in the north-west (Upper Austria)	x	x	x	x
				No	Nationwide; 85% in the south, 15% in the north	x	x	x	x
				Yes (n=1)	Central and north-east	x	x	x	x
				No	South and south-west	x	x	x	x
				No	-	-	-	-	-
				No	DOBV (northern Moravia) PUUV (southern Bohemia)	x	x	x	x
				No	-	x	x	x	x
				No	North, east and couth-east	x	x	x	x
				< 0,1%	Nationwide except northern Lapland	x	x	x	x
				No	North-east, Jura	x	x	x	x
				No	DOBV: north-east PUUV: almost nationwide with hotspots in North Rhine-Westphalia, Lower Saxony, Bavaria and Baden-Württemberg	x	x	x	x
				No	North and north-west	x	x	x	x
				Yes (n=1)	Nationwide	x	x	x	x
				No	None	x	x	x	x
				No	-	x	x	x	x
				-	-	x	x	x	x
				No	Nationwide	x	x	x	x
				No	South-east, bordering Germany	x	x	x	x
				Yes (n=1,in 1998)	Hedmark and Oppland, Agder, Nordland	x	x	x	x
				-	East and south-east	x	x	x	x
	Mus musculus	*Mus spretus*	*Apodemus sylvaticus*	-	Central and south	x	x	x	x
				Yes (n=1 probable)	Cases diagnosed in Arad, Sibiu, Nemt, Iaşi and Vrancea counties	x	x	x	x
				-	-	x	x	x	x
				No	Kosicky and Presovsky (south-east) provinces and DOBV in the central part	x	x	x	x
				Yes (n=4)	Nationwide; most in north-east, south and central	x	x	x	x
				No	None	x	x	x	x
				No	North of the Limes norrlandicus	x	x	x	x
				No	-	x	x	x	x
				Yes	Provinces bordering the Black Sea	x	x	x	x
				No	-	-	-	-	-

Black Sea field mouse (*A. ponticus*) (DOBV-Ap lineage). It is from an epidemiological point of view currently impossible to distinguish between the lineages by routine diagnostics when the viral RNA sequence is not available [3,4]. TULV is transmitted by the common vole (*Microtus arvalis*), the field vole (*M. agrestis*) and the southern vole (*M. levis*, also known as *M. rossiaemeridionalis*). This virus has not definitely been linked to human disease. SEOV, transmitted by the brown and black rat (*Rattus norvegicus* and *R. rattus*), causes mild HFRS in Asia and in many harbour cities worldwide. In Europe, it has so far only been identified once as a human pathogen, in an unpublished case in France that was confirmed by focus reduction neutralisation test [1]. During the past decade several hantaviruses have been discovered that have insectivores as carriers. In Europe these are Laihia, Asikkala and Seewis virus, transmitted, respectively, by the Eurasian water shrew (*Neomys fodiens*), the Eurasian pygmy shrew (*Sorex minutus*) and the common shrew (*Sorex araneus*) (Table 1).

In the past decade (2000-2009) oscillations in the number of hantavirus infections have been reported [5]. The unusually high number of hantavirus infections in Germany in 2010, with 327 cases between January and April in Baden-Württemberg [6], prompted the European Centre for Disease Prevention and Control (ECDC) to request an update on the hantavirus situation in Europe from the European Network for diagnostics of Imported Viral Diseases (ENIVD) and its Collaborative Laboratory Response Network (CLRN). The present article summarises the current knowledge on the occurrence of hantaviruses based on a survey in 30 European countries.

Table 2

Human cases of hantavirus infection in Europe, 2005-2010 (n=30 ENIVD countries)

	2005[a]	2006	2007	2008	2009	2010[c]	**Total[d]**
Austria	16	12	78	33	29	13	**351**
Belgium	372	163	298	336	182	161	**2,845**
Bosnia and Herzegovina	21	26	8	25	19	8	**732**
Bulgaria	5	0	2	4	5	2	**56**
Cyprus	0	0	NA	NA	NA	NA	**0**
Czech Republic	3	2	4	5	7	4	**43**
Denmark	0	0	NA	NA	NA	0	**0**
Estonia	NA	e	7	11	17	4	**39**
Finland	2,526	1,863	1,743	3,259	1,919	326	**31,919**
France	253	24	127	84	62	100	**1,913**
Germany	447	72	1,688	243	181	1,527	**4,956**
Greece	5	4	5	1	4	3	**52**
Hungary	6	NA	16	6	11	7	**342**
Italy	0	0	0	0	0	0	**0**
Ireland	NA	0	0	0	0	0	**0**
Lithuania	NA	0	NA	NA	NA	NA	**9**
Luxembourg	17	11	10	7	3	10	**60**
The Netherlands	3	3	32	32	12	14	**133**
Norway	64	22	76	50	21	8	**1234**
Poland	NA	NA	17	3	6	5	**31**
Portugal	1	4	2	4	0	NA	**37**
Romania	1	1	2	4	9	4	**21**
Russia	7,256	7,157	NA	NA	NA	NA	**173,652**
Slovakia			22	3	11	6	**42**
Slovenia	24	5	14	46	5	8	**294**
Spain	0	0	0	1[b]	0	0	**1**
Sweden	330	213	2,195	569	53	138	**7,198**
Switzerland	0	0	1	0	0	0	**2**
Turkey	NA	NA	NA	NA	23	NA	**23**
United Kingdom							**6**

ENIVD: European Network for diagnostics of Imported Viral Diseases; NA: data not made available.

[a] Previous years: see [7].

[b] Imported case.

[c] Up to 31 August 2010.

[d] Total of diagnosed hantavirus cases since start of surveillance in the specified country.

In general HFRS is characterised by high fever for up to four days and unspecific symptoms at the onset of the disease such as headache, thrombocytopenia and influenza-like symptoms, followed by nausea, abdominal pain and vomiting. After four to 10 days renal manifestations characterised by oliguria and transient renal failure and later polyuria may occur [1,2].

Methods

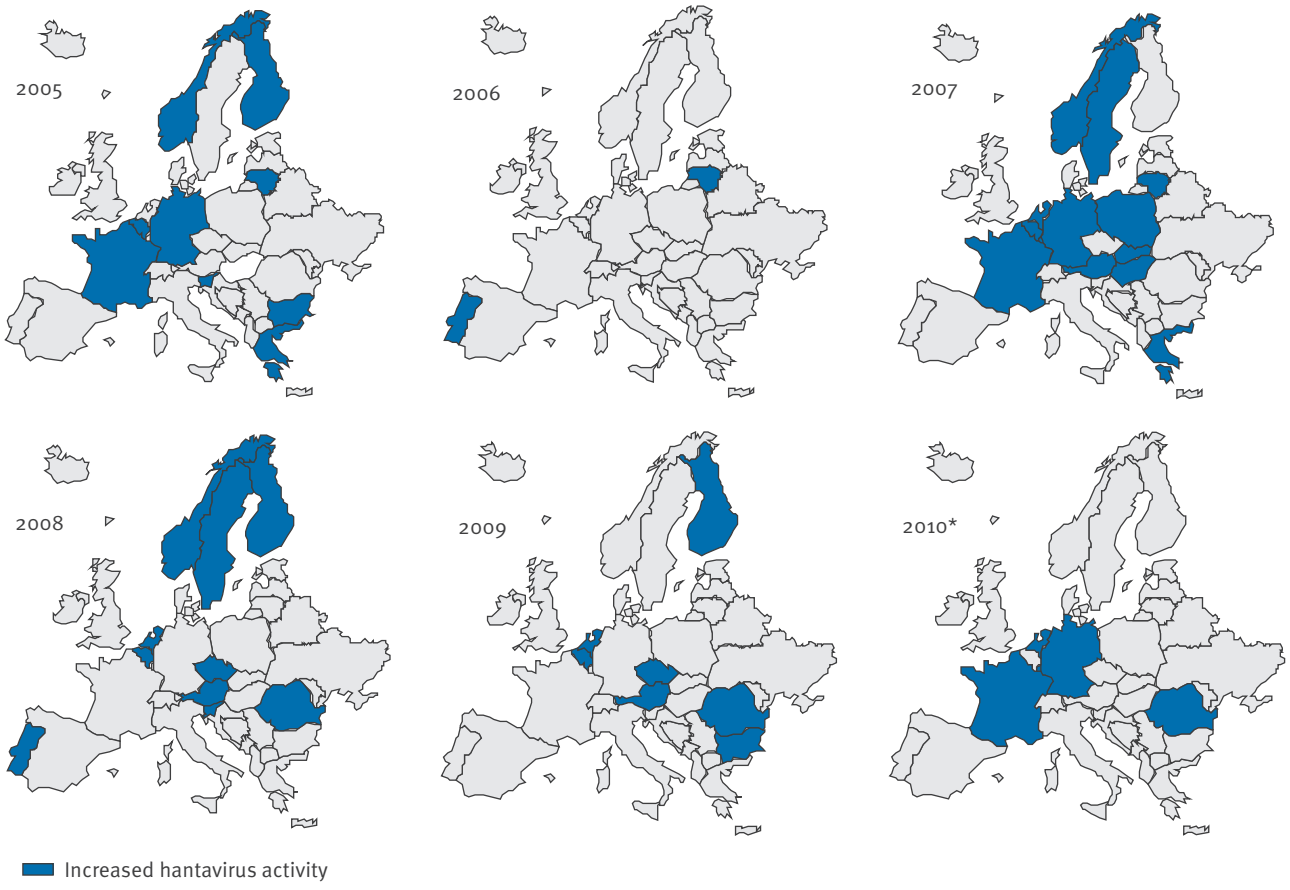
The ENIVD hantavirus working group sent a questionnaire to all ENIVD members (N=30, see Table 1) requesting information on the occurrence of clinically apparent cases of hantavirus infection according to the ENIVD case definition during the period from January 2006 to end of August 2010, fatalities due to hantavirus infection, the hantavirus carrier species present in the country and available diagnostic methods. The questionnaire was similar to the one used in 2006 [7], and was intended to update the information already available up to 2006. In addition, the average numbers of clinically apparent cases reported annually by ENIVD collaborating countries were calculated for the two decades 1990–1999 and 2000–2009 and were used to assess the reported country case numbers in the individual years. A year was regarded as a normal year when the number of cases matched the average case numbers, plus or minus 10% recorded for the respective country during the decade ending in the respective year. Case numbers 10–50% higher than the 10-year average were considered moderate activity, numbers 50-100% higher were considered slightly elevated and numbers at least 100% higher than the average number were considered increased activity.

Results

The annual number of cases diagnosed per country in the years 2006 to 2009 and 2010 up to end of August is summarised in Table 2. The year 2005 is added in order to facilitate the transition between this report and the previous one published in 2008 [7]. 2005 was a year with increased hantavirus activity, with approximately twice as many cases as in the ten previous years in Belgium, Finland, France, Luxembourg, Norway and some regions in Germany, especially North Rhine Westphalia, Lower Saxony and Baden-Württemberg [8]. In the year 2007 Belgium and Norway reported more human infections than the annual average of clinically apparent infections calculated for the decade 2000–2009. In the same year, France, Austria, Germany and Hungary reported between three- and

Figure 1

Countries with increased (over the previous year) hantavirus activity, Europe, 2005–2010 (n=30 ENIVD countries)



ENIVD: European Network for diagnostics of Imported Viral Diseases.
* The epidemic situation for 2010 is depicted up until the 31 August 2010.

five-fold elevated case numbers, and Sweden 10-fold elevated numbers compared with the annual average of the decade. These were the highest numbers of hantavirus infections ever seen in Germany and Sweden. The year 2008 was again an epidemic year in Belgium, with 336 reported cases, and also in Finland, where a record number of 3,259 cases were observed. All other European countries that had data available (Table 2) noted normal hantavirus activity in 2008. In 2009, all European countries had case numbers that corresponded to the annual average of the past decade. In 2010 it became clear already in February that the hantavirus activity in Germany was high, which was confirmed by the number of diagnosed cases up to August 2010 that reached 2.017 [9]. In bordering countries, i.e. Belgium, France, Luxembourg and The Netherlands, the hantavirus activity was normal or moderately elevated in comparison to the annual average of the past decade. In Austria, the Czech Republic, Denmark, Poland and Switzerland the hantavirus activity in 2010 remained low (Table 2 and Figure 1).

From the available information it was possible to calculate the yearly average number of diagnosed cases in Europe. For the 10-year period 1990 to 1999 this annual average was 1,671 cases, calculated for those countries from which reliable data on human infections were available, i.e. Belgium, Finland, France, Hungary, the Netherlands, Norway, Portugal, Slovenia and Sweden, as well as those countries from which apparently not all cases had been reported, i.e. Austria, Bosnia-Herzegovina, the Czech Republic and Greece. However, for the period 2000 to 2009 the annual average was significantly higher, namely 3,138 cases, including available data for further countries. It is at present impossible to state whether there is a real increase in hantavirus cases in Europe or whether the observation is influenced by increased awareness and better use of diagnostic tools. It is noteworthy that in the period 1990 to 1999, the years 1995, 1998 and 1999 were above the calculated arithmetic mean of 1.671 cases (Figure 2), and in the period between 2000 and 2010 the years 2002, 2005, 2007, 2008 and 2010 showed more than average activity, i.e. above the arithmetic mean of 3,138 cases (Figure 3). This is in accordance with already recognised epidemic years in different European countries (Table 2).

Further information we obtained on the carrier species present in the participating countries and the viruses detected in those rodents is summarised in Table 1. It confirmed earlier observations regarding the prominent role of PUUV and DOBV in Europe. Hantaviruses transmitted by insectivores were only found in Finland and Austria in this survey (see Table 1). No link to human disease has been shown so far for these viruses. Given the established role of the rodent-borne viruses PUUV, DOBV and possibly SAAV as human HFRS pathogens in Europe, it seems unlikely that insectivore-borne hantaviruses play a major role as pathogens.

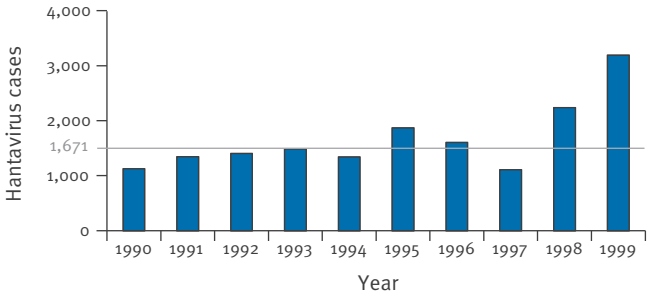
Fatal cases due to hantavirus infection are rare in Europe and mostly linked to DOBV infection. Although some fatal cases have been linked to PUUV infection, the mortality rate due to this virus remains lower than 0.1%.

Discussion

Data on human hantavirus infections have been registered in 30 European countries since 2005. Our knowledge of the disease, virus geno- and serotypes, hosts and diagnostic capacities has increased over the past decade. However, there seem to be large regional differences in the case numbers. The update on endemic regions in the participating countries confirmed the focal aspect of hantavirus infections (see Table 1). In the majority of countries, the endemic regions are forested areas that provide sufficient shelter and food for rodent populations.

Figure 2

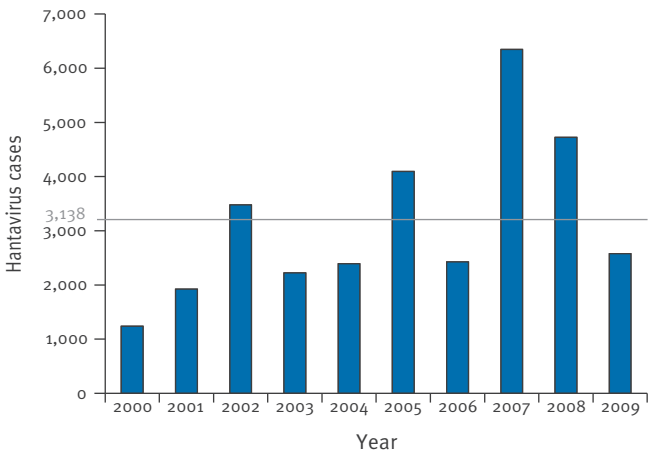
Annual number of human cases of hantavirus infection in Europe, 1990–1999 (n=29 ENIVD countries, excluding Russia)



ENIVD: European Network for diagnostics of Imported Viral Diseases.
Grey line: Average number of diagnosed cases per year: 1,671.

Figure 3

Annual number of human cases of hantavirus infection in Europe, 2000–2009 (n=29 ENIVD countries, excluding Russia)



ENIVD: European Network for diagnostics of Imported Viral Diseases.
Grey line: Average number of diagnosed cases per year: 3,138.

Epidemic peaks may be linked to times of favourable climatic conditions when an abundance of available food triggers a peak in the rodent population [8,10]. A relation between climate, high density of the rodent population and increased virus prevalence in rodent populations was also observed [4]. This puts humans at increased risk of contact with infected rodents and their excreta. According to preliminary findings, it was such a scenario that led to the spectacular increase in cases in Germany in 2010 [6]. Although mast events (increased seed production of various trees) seem to be of importance in triggering hantavirus epidemics, it should be remembered that only hantavirus epidemics in Atlantic and continental western Europe are mast-driven (although this seems not entirely true for Germany as in some years the country experienced very regional outbreaks), while other mechanisms drive these events in northern and eastern Europe [1,2].

The bank vole (*M. glareolus*), the principle vertebrate host for PUUV, is a generalist polyphagous species, i.e. eating seeds and fruits and occasionally invertebrates. It only acquires 50% of its energy intake from hard fruits and this only in the winter months. The yellow-necked field mouse (*A. flavicollis*), the principle vertebrate host for DOBV, is predominantly a seed eater, but the invertebrate portion of its diet can be considerably higher than for the bank vole. The diet of both *M. glareolus* and *A. flavicollis* varies considerably in different regions in Europe: in Atlantic western Europe (Belgium, France) oak and beech seed crops are instrumental [10,11], while in continental Europe (the Białowieża Primeval forest in Poland, for instance) oak (*Quercus petraea*) and hornbeam (*Carpinus betulus*) seed crops regulate population sizes of both species [12,13]. Both the bank vole and the yellow-necked field mouse prefer a forest environment. The third rodent species of interest, the striped field mouse (*A. agrarius*, carrier of SAAV), is typical of a mixed habitat of agricultural fields and forest, and its population dynamics thus relate not only to forest conditions but also to anthropogenic factors [14].

For all three species, winter survival is related to food availability in the preceding summer and autumn, spring numbers are dependent on winter mortality, which according to the rodent catchers is estimated to reach on average 70% of autumn numbers for voles and 85% for mice, and summer/autumn numbers are primarily related to vegetation biomass and temperature.

The hantavirus activity peaks indicated by our data did not in all years correlate with mast cycles. Although mast events are supposed to occur over large areas and even on sub-continental level, hantavirus epidemics in western Europe can probably not be related solely to mast events of one tree species, given the highly different levels of hantavirus activity in neighbouring countries in 2005, 2007, 2008 and 2010 (see Table 2) where mast events occur simultaneously. Unfortunately, detailed information about seed crops of the different endemic tree species, e.g. beech (*Fagus sylvatica*), oak (*Quercus sp.*) and hornbeam (*C. betulus*), that can significantly influence rodent winter survival rates are not always available in most countries.

At present, all European countries dispose of the same range of diagnostic tools (for a recent review, see [15]), i.e. IgG and IgM IFA and ELISA, classical or real-time RT-PCR methods targeting specific hantaviral sero-/genotypes followed by sequence analysis of the amplicons in order to study the molecular epidemiology of the circulating strains. Neutralisation tests are, due to the special requirements of these tests, only available in a few countries and are in general only used for research purposes.

Conclusions

Hantavirus infections continue to be a risk in the European Union. To our knowledge, notification systems have not changed in the past decade. In the past 10 years the annual number of diagnosed cases has significantly increased but it remains unclear whether this is due to higher awareness and better diagnostic tools or to a real increase in acquired infections. Epidemics occur locally and in foci, i.e. in regions where climatic, biotic and abiotic conditions pave the way for the carrier species to become abundant and humans to come in contact with the virus.

Infections caused by PUUV remain the most prevalent in Europe, and in regions where the virus is circulating, the number of infected individuals can reach hundreds or thousands per year, DOBV infections on the other hand are much less frequent, and important outbreaks are scarce. Incidence data on hantavirus infections are unfortunately not available.

The 2010 PUUV outbreak in Germany seems to be an isolated incident and is currently closely monitored by the local authorities. Further longitudinal studies are needed in Europe to better understand the factors that drive the oscillation of human cases on a local, regional and continental scale including a combination of landscape and land use, habitat, climate and geographical parameters.

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