

HAEMORRHAGIC FEVER WITH RENAL SYNDROME: AN ANALYSIS OF THE OUTBREAKS IN BELGIUM, FRANCE, GERMANY, THE NETHERLANDS AND LUXEMBOURG IN 2005

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This article aims to describe the Haemorrhagic Fever with Renal Syndrome (HFRS) situation in 2005 in five neighbouring countries (Belgium, France, Germany, the Netherlands and Luxembourg) and define the most affected areas. The 2005 HFRS outbreaks in these countries were the most significant in the region since 1990, with a total of 1,114 confirmed cases. The main feature of the epidemic was the extension of the known endemic area in several of the affected countries, with the involvement of urban areas for the first time. A significant increase in the number of cases was noted for the first time in the province of Liège in Belgium and in the Jura department in France.

Introduction

Hantaviruses (family *Bunyaviridae*, genus *Hantavirus*) are rodent-borne, zoonotic, lipid-enveloped RNA viruses, and comprise the aetiological agents of HFRS. HFRS occurs in Europe and Asia, and infection with these viruses can cause a disease characterised by fever, headache, gastrointestinal symptoms and renal dysfunction, the more severe forms with haemorrhagic manifestations [15,20]. Nephropathia epidemica (NE), the mildest form of HFRS, caused by Puumala virus (PUUV), the most common hantavirus, is present in most countries in north-western Europe. Dobrava (DOBV), Tula (TULV), Seoul (SEOV) and Saaremaa viruses also circulate in the region; the first three have been described as causing human disease (DOBV in Germany, Austria and the Balkans region). NE due to PUUV infection has an abrupt onset with fever and myalgias, thrombopenia and sometimes myopia. An acute renal failure occasionally requiring dialysis can occur. The incubation period varies from a few days up to 41 days. The outcome is favourable in most patients and mortality is lower than 0.1%. DOBV causes severe HFRS with a reported mortality rate of up to 20% [20].

The epidemiology of hantaviruses is closely linked to the ecology of their principal hosts. The bank vole is a polyphagous animal that eats seeds, fruits of trees and bushes, and green plants. The multi-annual bank vole population dynamics are therefore directly influenced by the seed production of trees, especially oak, beech and acorn. Years with increased seed production (mast years), mediated by favourable climatic conditions (mild winter), give

rise to increased rodent population densities in the following year. The bank vole (*Myodes glareolus*) acts as the main reservoir for PUUV, while the yellow-necked mouse (*Apodemus flavicollis*), the common vole (*Microtus arvalis*), the striped field mouse (*Apodemus agrarius*) and the brown rat (*Rattus norvegicus*) carry and transmit respectively DOBV, TULV, SAAV and SEOV. Transmission of the viruses to man occurs through inhalation of infected animal excreta, i.e. urine, faeces and saliva. Working with wood piles and cleaning long abandoned buildings seem to significantly increase the risk for hantavirus infection.

Outbreaks of hantavirus infections in humans occurred in western Europe in 1985, 1990, 1993, 1996, 1999, 2001 (Belgium only) and in 2003 [4,8,13]. Most cases occurred between March and November, with a peak from August to September. A preliminary report regarding Belgium, France and Germany was published in *Eurosurveillance Weekly* in June 2005 [11].

Methods

Case definitions in the five affected countries match, as do diagnostic tools (IFA and ELISA are the only validated systems available), so we have compared the data below, with the countries listed separately in alphabetical order.

Belgium:

In Belgium, the National Reference Laboratory for Hantavirus Infections and the Scientific Institute of Public Health (IPH) sentinel laboratory network report data to the IPH. The National Reference Laboratory for Hantavirus Infections applies IgG and IgM ELISA for PUUV and HTN routinely but can if necessary also test for SEOV and DOBV IgG and IgM as well as apply species-specific RT-PCR (traditional or real-time) for the four forenamed serotypes. An HFRS case is considered to be confirmed when the following conditions are fulfilled: detection of IgM antibodies and evidence of seroconversion in a follow-up sample, or detection of hantavirus nucleic acid in a sequenced RT-PCR from blood or urine sediment. Since 1980, more than 1,600 cases have been diagnosed in Belgium. The total number of cases from the 2005 outbreak was 372, which is the so far the most significant epidemic

since the 1996 epidemic. Statistically, an average epidemic year would account for more than 158 cases. The available information on human cases suggests that, in Belgium, a three-year epidemic cycle existed until 1999, after which there was a two-year cycle [6,7]. The reason for this pattern change is not known but could be influenced by changes in the climate.

France:

In France, the Centre National de Référence des Fièvres Hémorragiques (National Reference Laboratory for Viral Haemorrhagic Fevers, CNRFH) is responsible for the surveillance of hantavirus infections in humans [15]. Diagnoses are based on single sera if presence of IgM and IgG (IFA and ELISA) or on paired serum samples if detection of IgM without IgG on the first serum sample. Diagnosis is done in several laboratories (at least three in France) but it is mandatory to send all positive or borderline samples from local laboratories to the CNRFH for confirmation. Only confirmed specimens were included in the study. The total number of cases for the 2005 outbreak was 253 and, as for Belgium, this was the most important outbreak since 1996.

Germany:

In Germany, hantavirus infection became a notifiable disease in 2001. Reports of laboratory-confirmed symptomatic hantavirus infections are transferred to the Robert Koch Institute based on a case definition [17]. The laboratory diagnosis of an HFRS case is considered confirmed when one of the following conditions is fulfilled: detection of IgM- or IgA-antibodies confirmed by IgG-antibodies or marked rise of IgG-antibodies in a paired sample or detection of hantavirus nucleic acid in a sequenced RT-PCR from blood. The average incidence for hantavirus infections over the time period 2001-2004 was 0.25 per 100,000 inhabitants, with an average annual total number of 200 cases. During this period, increased numbers of hantavirus infections were reported in 2002 and 2004. In both those years, the increase was due to outbreaks in a known endemic area of Baden Württemberg in southwestern Germany, the Swabian Alb. In 2004, there was also an outbreak with 38 cases in Lower Bavaria [10].

The Netherlands:

In the Netherlands, hantavirus infections are diagnosed in two laboratories, and data are aggregated for passive surveillance by the Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and Environment, RIVM). With the initial reports of enhanced hantavirus activity in the summer of 2005, regional health services, medical microbiologists and nephrologists were informed actively and were asked to consider hantavirus infections in the differential diagnosis of cases with the appropriate clinical picture. In total, 27 cases were detected. A case is considered confirmed when IgM antibodies are detected and evidence of seroconversion is found in a follow-up sample, or by detection of hantavirus nucleic acid in a sequenced RT-PCR from blood or urine sediment.

Luxembourg:

In Luxembourg, laboratory-based hantavirus surveillance began in September 2003 and the Laboratoire National de Santé is the only laboratory in the country carrying out hantavirus serodiagnosis. There was one confirmed case in 2003 equating to a yearly incidence of 0.22 per 100,000 inhabitants. A case is considered confirmed when the following conditions are fulfilled: detection of IgM antibodies and evidence of seroconversion in a follow-up

sample, or detection of hantavirus nucleic acid in a sequenced RT-PCR from blood or urine sediment.

Results

Belgium:

The current endemic area in Belgium is situated in the southeast of the country (the provinces of Luxembourg, Liège, Namur and Hainaut). The most affected provinces during the 2005 epidemic were the Luxembourg province (87 cases, incidence 33.8 per 100,000 inhabitants), the Liège province (83 cases, incidence 8.1 per 100,000 inhabitants), the Namur province (78 cases, 17.1 per 100,000 inhabitants) and the Hainaut province (76 cases, incidence 5.9 per 100,000 inhabitants). The 2005 epidemic was the first in which the Liege province (22.3% (83/372) of the cases in 2005) figured as a hot-spot for hantavirus infections. Traditionally, the Belgian hyperendemic area was composed of the provinces Hainaut, Namur and Luxembourg. Based on the residence of the patients, the Flanders region accounted for 7.4% of the total number of cases, while the Walloon region and the Brussels Capital region respectively accounted for 90.1% and 2.5% of the cases. The male-female ratio was 2.4. The median age of the patients was 41.3 years (3-85 years). During the last decade the endemic area, comprising the Hainaut-Namur-Luxembourg provinces has extended substantially and includes now the province of Liège. A significant increase in *Myodes glareolus* (bank vole) population densities was observed in the fall of 2004, coinciding with a beech mast, and during the first 10 months of 2005. In Belgium, *M. glareolus* population density was five to six times higher in April-October 2005 than during the same period in 2004 and seroprevalences in populations that were sampled (P. Heyman, personal communication).

France:

The endemic area is situated in the north-east of the country, along the Belgian and German borders [12,14]. Most cases were noted in the Ardennes district (97 cases, 32.7/100,000), the Aisne district (32 cases, 6.0/100,000), the Nord district (22 cases, 0.9/100,000), the Oise district (15 cases, 2.1/100,000) and the Jura district with 30 cases (12.0/100,000). In the latter district, clusters of hantavirus infection were not observed before and this suggests, as in Belgium, an enlargement of the endemic area. The five most affected districts (see above) in France account for 77.5% of the total number of cases. The male-female ratio was 2.6. The median age of the patients was 42.5 years (11- 81 years).

Germany:

In 2005, the incidence for hantavirus infections increased to 0.54/100,000 persons and in contrast to previous years, the annual number of cases doubled (2005: 448 cases). The weekly number of cases peaked earlier than in the previous years. The season ran from the beginning of May until the end of July. During this time, 15 to 23 infections were reported weekly and nearly half of the cases of 2005 occurred during this period. From mid-October, the weekly number of cases reached the values of the last years. In Germany the hantavirus outbreak of 2005 was mainly due to an increase of cases in several federal states north of the river Main such as Lower Saxony (75 cases, 0.9/100,000), North Rhine Westphalia (143 cases, 0.8/100,000), Hesse (34 cases, 0.6/100,000) and Thuringia (14 cases, 0.6/100,000). In contrast to previous epidemiological findings that hantavirus infections were obtained in rural areas in North Rhine-Westphalia and to a lower extent in also in Lower Saxony, infections were mainly acquired in

urban regions. As in previous years, the highest incidence rate was measured in Baden Württemberg, a known endemic area. In 2005, 110 cases were reported (incidence 1.0 per 100,000 inhabitants) which did not differ much from the previous year (120 cases). In Germany, where the surveillance includes the virus species, most infections were caused in 2005 by the hantavirus species Puumala (n=388; 87%), 7 infections (1.6%) were caused by Dobrava, 1 Hantaan infection was imported from China and for 52 cases the causative virus was not specified (11.5%) [18,19,21]. The male-female ratio was 2.6. The median age of the patients was 41.0 years (6-76 years). The hantavirus outbreak of 2005 was mainly caused by an increase of the reservoir rodent population. According information from experts of agriculture and forestry the reservoir density, especially bank voles, began to rise already in fall 2004 and its increase continued during 2005.

The Netherlands:

In total, 27 cases were detected. One person had become ill while on vacation in Finland, and was considered to have acquired the infection abroad. In all, 78% of cases lived in a region of the country that is known to be endemic for Puumala virus [3,4]. The number of cases was in the same range as has been seen in the

past five years, with the exception of 2003, when only 12 cases were diagnosed.

Luxembourg:

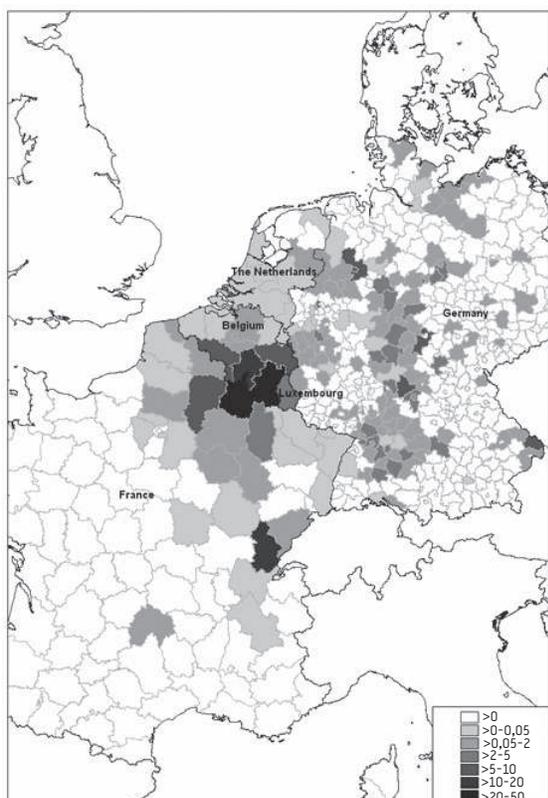
There were 14 laboratory-confirmed cases in Luxembourg in 2005 [16]. Two of these patients lived in Belgium and France, close to the border with Luxembourg. The other 12 patients were clustered in the rural region of Mullerthal and surrounding areas in the east of the country, which suggests that the outbreak in Luxembourg was fairly localised. The Mullerthal is an area characterised by beech forests and sandstone formations. The yearly incidence in 2005 of Luxembourg residents was 2.6 per 100,000 persons.

Discussion

The 2005 HFRS epidemic in Belgium, France, Germany, the Netherlands and Luxembourg resulted in a grand total of 1,114 cases. Belgium, France, Germany, the Netherlands and Luxembourg were respectively responsible for 31.4%, 22.7%, 40.2%, 2.5% and 1.2% of the cases according to their respective population sizes (Belgium: 10,263,400; France: 59,039,700; Germany: 82,192,600; the Netherlands: 15,987,100; and Luxembourg: 445,000), the national incidence was 3.6/100,000 for Belgium, 0.4/100,000 for France, 0.6/100,000 for Germany, 0.2/100,000 for the Netherlands and 3.2/100,000 for Luxembourg. Figure 1 displays in more detail the geographical distribution of the incidence.

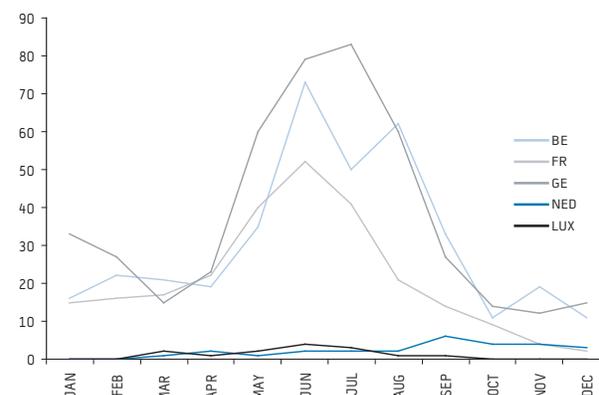
The main feature of the 2005 epidemic was the extension of the known endemic area in, at least, Belgium, France and Germany. In Belgium, Liège province figured as a new hot-spot, in the Jura region in France a significant increase of human hantavirus cases was noted. In Germany the increase of hantavirus infections was observed in urban regions and areas where hantaviruses were not known to be endemic. The monthly distribution of the cases showed a moderate activity during the first four months of 2005, but the main peak occurred from May to August/September. From October on, the monthly number of cases returned to normal. Exception to this rule were the Netherlands where the majority of the cases occurred in the last four months of the year and where the total number of cases did not significantly increase in 2005 (Figure 2).

FIGURE 1
Geographical distribution of human hantavirus cases in 2005 for Belgium, France, Germany, the Netherlands and Luxembourg*



*Colour coding represents the incidence (cases per 100,000 inhabitants) per administrative entity (provinces for Belgium and the Netherlands, départements for France, cantons for Luxembourg, Kreise for Germany) for the respective countries

FIGURE 2
Monthly distribution of human hantavirus cases per month during 2005



BE : Belgium, FR : France, GE : Germany, NED : the Netherlands, LUX : Luxembourg

FIGURE 3

Distribution of human hantavirus cases per age group during 2005

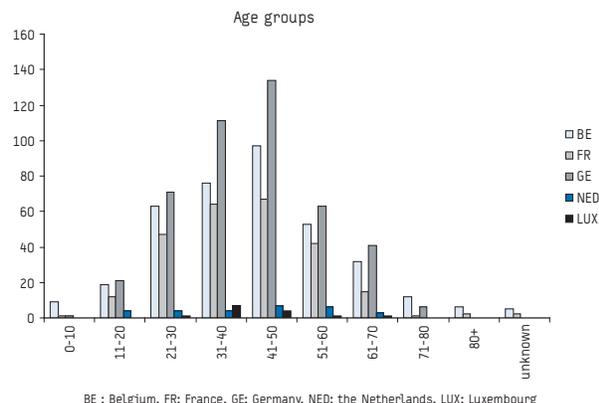


TABLE 1

Demographical data of human hantavirus cases during 2005

2005	Cases	M/F ratio	Median age (yrs)	Range (yrs)
Belgium	372	2.4	41.3	3-85
France	253	2.6	42.5	11-81
Germany	448	2.6	41.0	6-76
The Netherlands	27	2.9	42.5	11-68
GD-Luxembourg	14	1.8	37.8	21-70

The age distribution most affected in all five countries were in the range from 20 to 60 years, with the peak in the 41-50 years age group (Figure 3) – this is in line with published risk factors.

The epidemiology of hantavirus epidemics worldwide is determined by the interaction between rodents and humans. And as the rodent population dynamics are directly linked to abiotic factors such as more or less favourable climatic conditions and available food supplies, hantavirus epidemics are triggered by forenamed factors. Hantavirus epidemics in western Europe are not, as in northern Europe, truly cyclic events because of true cyclic rodent population dynamics; they occur after so-called mast years i.e. years in which trees produce more fruits than normal. These mast years normally occur, in western Europe, every four to seven years for oak trees and every three to five years for beech trees. A mast year for beech, oak or acorn will, as a rule, trigger a hantavirus epidemic, but the number of cases seems limited to the duplicate or triplicate of a non-epidemic year; “true” hantavirus epidemics occur when mast years of one or more tree species coincide and there is an abundance of food – and an abundance of various foods – available for rodents.

If this event is strengthened by favourable climatic conditions such as a mild winter, above zero Celsius dawn temperatures in early spring, moderately dry summer, etc. rodent population density may become very high in certain regions. The immediate result is an explosive spread of virus in the population and a significant increase of human cases in the months to follow. The above-described scenario took place in 2004-2005 and the most important

hantavirus epidemic ever recorded in western Europe was the result. To date, there exists no coordinated passive or active surveillance in the European for human hantavirus infections and a European early warning system is lacking, although efforts are being made to improve communication through reporting – via the European Network for diagnostics of Imported Viral Diseases (ENIVD) – to the European Centre for Disease Prevention and Control (ECDC). Standardization and evaluation of the available detection methods was done by means of a Quality Control by ENIVD [1,2]. Information on the epidemiology, clinical symptoms and case definition for HFRS can be found at: http://www.enivd.de/VHFDISEASES/fs_vhfdiseases.htm. Advice for the public is available from the websites and publications of the Public Health Institutions in most western European countries.

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