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Hantavirus infections in The Netherlands: epidemiology and disease

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SUMMARY

A serological survey for the prevalence of hantavirus infections in The Netherlands was carried out on > 10000 sera, from selected human populations, and different feral and domestic animal species. Hantavirus-specific antibodies were found in about 1% of patients suspected of acute leptospirosis, 10% of patients with acute nephropathia, and in less than 0·1% haemodialysis and renal transplant patients. Among individuals with a suspected occupational risk, 6% of animal trappers, 4% of forestry workers, 2% of laboratory workers and 0·4% of farmers were seropositive. The majority of the seropositive individuals lived in rural and forested areas. The main animal reservoir of the infection was shown to be the red bank vole (*Clethrionomys glareolus*). Epidemiological, clinical and laboratory findings seen in serologically confirmed human cases were similar to those associated with nephropathia epidemica.

INTRODUCTION

The severity of haemorrhagic fever with renal syndrome (HFRS), caused by members of the genus *Hantavirus* (HV) of the family Bunyaviridae, is largely dependent on the serotype of the virus involved. So far at least four different subtypes of HV have been characterized [1, 2]. These subtypes are all closely associated with the genus of the reservoir host involved: *Apodemus* – Hantaan-like viruses; *Rattus* – Seoul-like viruses; *Clethrionomys* – Puumala-like viruses and *Microtus* – Prospect-Hill-like viruses. Recently a HV has been identified in the USA as the cause of a severe respiratory disease in humans with high mortality. This infection is transmitted to humans by the deer mouse (*Peromycus*

* Requests for reprints.

maniculatus) [3]. Infections with Hantaan-like, Seoul-like and Puumala-like viruses may cause renal failure in humans and are predominantly transmitted by the air-borne route. The clinical symptoms related to Hantaan- and Seoul-like virus infections are generally characteristic, whereas the symptoms associated with Puumala-like virus infections are more variable and often difficult to define as belonging to a disease entity [4]. As impairment of renal function of varying severity is a consistent feature of infection with Puumala-like viruses, the syndrome is referred to as nephropathia epidemica (NE). Seroepidemiological studies in Asia, Europe and the USA have demonstrated HV-specific antibodies in the sera of individuals, such as farmers and army personnel, at high risk of contact with feral rodents [5–10]. Recently, serological evidence of HV infection was also found in patients with chronic renal failure, haemodialysis patients, and in renal transplant candidates [11–13]. Furthermore, HV-specific serum antibodies have been found in individuals with acute respiratory disease and in patients suspected of acute leptospirosis [3, 6, 8]. The geographical distribution of HV infection in humans is usually focal probably due to the distribution of infected reservoir animals [9]. Although HV has been detected in a large variety of feral and domestic animals [14] the main reservoirs are rodent species. In 1984 we documented the first cases of HV infections in The Netherlands among laboratory workers of the National Institute of Public Health and Environmental Protection (RIVM), who had been in contact with infected laboratory Lou/M rats [5]. One of the laboratory workers suffered severe transient renal failure whereas the others showed milder clinical symptoms. Subsequently a number of serologically confirmed human cases of NE, not related to contacts with laboratory animals, was found in the eastern and southern parts of The Netherlands [6, 7]. In these areas we also identified HV-infected feral rodents [15]. We subsequently showed that the laboratory workers at the RIVM had been infected with Seoul-like viruses whereas the majority of the other seropositive human cases had been infected with Puumala-like viruses [15, 16].

In the present study we have investigated the geographical distribution of HV-specific serum antibodies in individuals in The Netherlands with or without a history of renal disease or suspected occupational risk. In addition, sera from a large collection of feral and domestic animals in The Netherlands were tested. Clinical and laboratory findings of the individuals with a history of serologically confirmed NE infection are presented.

MATERIALS AND METHODS

Human serum samples

Human serum samples were collected between 1972 and 1994 from 1783 individuals with renal diseases, including patients with suspected acute leptospirosis, established renal disease, haemodialysis and kidney transplant patients. Sera from 2172 individuals with suspected occupational risk of HV infection (laboratory workers, farmers, hunters, forestry workers, veterinary surgeons, zoologists, gardeners, trappers and military recruits) and 4474 sera from a control group consisting of office personnel and healthy blood donors in apparently enzootic areas (see below) were also collected. Samples were also collected from 463 military office personnel from all over the country. All sera were heat inactivated for 30 min at 56 °C directly after collection and stored at −20 °C until used.

Feral animal serum and organ samples

Feral animal samples were collected between 1984 and 1993 from 829 animals from 20 different species. Rodents were trapped between 1987 and 1993 at several places in The Netherlands, around houses surrounded by forests and fields, and on camp sites. The rodent species were identified, blood was collected and lung suspensions were prepared (for survey see Table 1). A separate group of rats was obtained from Rotterdam Harbour from an animal pest control service. Bats suspected of rabies were obtained from the Central Veterinary Institute in Lelystad. Serum samples from other feral mammals (Table 1; hare, roe deer, fox and wild boar) were collected between 1992 and 1993 during the hunting season.

Serum samples from domestic animals

Serum samples were collected from 2025 domestic animals, representing 14 species, at several locations in The Netherlands between 1984 and 1992. Sera from lagomorphs and rodents (Table 1) were obtained from a veterinary clinic, where the animals had been admitted with a variety of clinical symptoms. Serum samples from dogs with a history of acute gastrointestinal disease and from cats routinely examined for feline leukaemia virus infection were collected through veterinary practitioners throughout the country. Sera from cows, sheep and pigs were collected from different slaughter-houses.

Serology and antigen detection

Hantavirus-specific antibodies against Puumala-like virus (strain Hällnäs) were detected by a previously described indirect enzyme-linked immunosorbent assay (ELISA) [16]. For the detection of antibodies of species for which no species-specific conjugates were available (members of the families Talpidae, Sciuridae, Cricetidae, Castoridae, Chinchillidae, Caviidae, Capromyidae, Vespertilionidae and Dasyproctidae) a protein-A peroxidase conjugate (Amersham International, Amersham, UK) was used. The specificity and sensitivity of this conjugate for immunoglobulins of different animal species had been evaluated previously [17]. OD 450 values were obtained by subtracting the OD 450 values of control antigen-coated wells from corresponding viral antigen-coated wells. Values > 0·2 were tested in a confirmatory indirect immunofluorescence test (IFA) at a 1/16 dilution, using drop slides fixed with Vero E6 cells infected with HV strain Hällnäs [16]. Results were considered positive when a characteristic dot-like immunofluorescence pattern was observed in the cytoplasm of infected cells.

HV antigen in lung tissues of feral animals was detected by a previously described antigen capturing ELISA [16]. For this purpose 10% lung suspensions were prepared in a glass grinder in phosphate buffered saline (PBS) containing 1% Triton X-100 and used as antigen.

Clinical and laboratory findings

The medical records of the 27 hospitalized and seropositive NE patients obtained from three hospitals in The Netherlands were reviewed for clinical chemistry, haematological, clinical findings and epidemiological data. These data

Table 1. *Prevalence of HV specific serum antibodies in feral and domestic animals in The Netherlands*

Group	Order	Family	Species	Common name	Year	Positive/ numbers tested	%
Feral	Insectivora	Talpidae	*Talpa europaea*	Common mole	89	0/33	0
		Soricidae	*Crocidura russula*	Common shrew	89	1/66*	1·5
	Rodentia	Cricetidae	*Ondata zibethia*	Muskrat	89	0/192	0
			Microtus arvalis	Field vole	89	1/68	1·5
			Clethrionomys glareolus	Red bank vole	84–89	12/111†	10·8
		Muridae	*Apodemus sylvaticus*	Wood mouse	89	0/56	0
			Rattus norvegicus	Norway rat	89	0·12	0
			Rattus rattus	Black rat	89	0/4	0
			Mus musculus	House mouse	89	0/12	0
	Lagomorpha	Leporidae	*Lepus capensis*	Hare	93	0/63	0
	Carnivora	Canidae	*Vulpes vulpes*	Red fox	93	0/62	0
		Mustelidae	*Meles meles*	Badger	93	0/3	0
	Artiodactyla	Bovidae	*Capreolus capreolus*	Roe	92	0/80	0
		Suidae	*Sus scrofa*	Wild boar	92	0/10	0
	Chiroptera	Vespertilionidae	*Pipistrellus pipistrellus*	Pipistrelle bat	93	0/31	0
			Epitesicus serotinus	Common brown bat	93	0/17	0
			Plecotus auritus	Common long-eared bat	93	0/6	0
			Pipistrellus nathusii	Pipistrelle bat	93	0/1	0
			Nyctalus noctula	Red bat	93	0/1	0
			Myotis dasycneme	Pond bat	93	0/1	0
Domestic	Lagomorpha	Leporidae	*Oryctolagus cuniculus*	European rabbit	92	0/113	0
	Rodentia	Sciuridae	*Sciurus carolinensis*	Grey squirrel	92	0/1	0
		Cricetidae	*Cricetus cricetus*	Hamster	92	0/2	0
		Castoridae	*Castor fiber*	Beaver	92	0/4	0
		Chinchillidae	*Chinchilla laniger*	Chinchilla	92	0/14	0
			Dolichotis patagona	Mara	92	0/3	0
		Caviidae	*Cavia porcellus*	Guinea pig	92	0/59	0
		Capromyidae	*Mycocastor coypus*	Nutria	92	0/2	0
		Dasyproctidae	*Myoprocta acouchy*	Agouti	92	0/1	0
	Carnivora	Canidae	*Canis familiaris*	Dog	91	0/585	0
		Felidae	*Felis catus*	Cat	84	0/200	0
	Artiodactyla	Bovidae	*Bos taurus*	Cow	91	0/579	0
			Ovis aries	Sheep	91	0/254	0
		Suidae	*Sus scrofa*	Pig	84	0/208	0
Total			34 species		84–93	14/2854	0·4

* Animal HV antigen positive and HV antibody negative.
† Two of the positive animals: no serum available and tested for HV antigen.

were compared with the published findings of NE cases in neighbouring countries [18, 19].

RESULTS

Prevalence of HV-specific antibodies in human sera

Between 1972 and 1994, 8892 serum samples from 1783 patients with renal disease, 2172 individuals with suspected occupational risk of HV infection and from 4937 individuals without apparent symptoms of renal disease or risk of HV infection were tested for the presence of HV-specific serum antibodies. In the first group 33/1783 patients (2%) were HV seropositive (Table 2). No HV-specific serum antibodies were found in 284 renal transplant patients and only 1/358 haemodialysis patient (0·3%) was seropositive. Five of the 865 leptospirosis suspected individuals (0·7%) were seropositive. All the seven serum samples collected retrospectively from patients who had been diagnosed with NE on clinical grounds between 1974 and 1988 were seropositive. In the years between 1989 and 1992 HV seropositivity in clinically suspected NE cases ranged from 4 to 11% (Table 2). In the period January–June 1993 7/33 suspected NE cases (21%) were HV seropositive. The geographical distribution of all the clinically documented and serologically confirmed cases is shown in Fig. 1.

Among the 2172 individuals with suspected occupational risk of HV infection, HV-specific serum antibodies were found in 4/180 laboratory workers (2·2%) who had worked with contaminated laboratory rodents, in 3/679 farmers (0·4%), 4/68 trappers (6%) and in 6/151 sera from forestry workers (4%). No HV-specific antibodies were found in hunters, zoologists, military personnel, gardeners or veterinarians. The geographical distribution of HV seropositive laboratory workers, farmers, animal trappers and forestry workers is indicated in Fig. 1. Of the 4474 serum samples from individuals in the control groups collected in apparently endemic areas between 1989 and 1992, 33 (0·7%) had HV-specific serum antibodies. No antibodies were found in 151 sera from army office personnel collected at several locations in The Netherlands.

Prevalence of HV-specific antibodies or HV antigen in animal samples

Sera from 2855 feral and domestic animals collected between 1984 and 1994 were tested for the presence of HV antibodies. Among 829 sera from feral animals (Table 1) representing 20 different species, HV-specific antibodies were detected in 10/111 (9%) red bank voles (*Clethrionomys glareolus*) and in 1/68 (1%) field voles (*Microtus arvalis*). HV antigen was detected in the lungs of one common shrew (*Crocidura russula*) and two red bank voles by ELISA from which no serum was available. No evidence of HV serum antibodies was found in the members of the Muridae, Leporidae, Canidae, Mustelidae, Bovidae, Suidae and Vespertilionidae families (Table 1). No HV antibodies could be demonstrated in the 2025 sera of domestic animals from 14 different species (Table 1). The geographical distribution of all the HV positive animals is shown in Fig. 1.

The distribution of the locations where the red bank voles, apparently the main HV reservoir in The Netherlands, were trapped is shown in Table 3. In five of the nine locations where HV seropositive or HV antigen positive animals were

Table 2. *Prevalence of hantavirus-specific serum antibodies in selected human populations in The Netherlands*

Selected groups	Individuals	Year	Number	Positive	%
Renal disease	Kidney transplants	72–84	284	0	0
	Suspected acute leptospirosis	84–9	865	5	0·7
	Suspected NE	74–88*	7	7	100
		89	27	3	11·1
		90	60	3	5·0
		91	81	4	4·9
		92	68	3	4·4
		93	33	7	21·2
	Haemodialysis	93	358	1	0·3
Suspected occupational risk	Laboratory workers	81–4	180	4	2·2
	Farmers	93	679	3	0·4
	Hunters	89	455	0	0
	Foresters	89–90	151	6	4·0
	Zoologists	91	17	0	0
	Trappers	91–3	68	4	5·8
	Military	92	460	0	0
	Gardeners	92	60	0	0
	Veterinary surgeons	93	102	0	0
Control	Office personnel†	89–90	151	1	0·7
	Healthy blood donors†	92	4323	32	0·7
	Army office personnel‡	92	463	0	0
Total		74–93	8892	83	0·9

* Retrospective.
† Sera collected in endemic areas.
‡ Sera collected at different barracks all over the country.

detected, the incidence in red bank voles ranged from 25 to 60 % per positive area. In four of the five areas where HV infected animals had been identified, clinically and serologically confirmed human cases of NE had been documented.

Epidemiological, clinical and laboratory findings in NE patients

Epidemiological and clinical findings of 27 HV seropositive individuals who had suffered from NE between January 1974 and June 1993 are shown in Fig. 2. Symptoms were observed more frequently in males (74 %), with a peak between 30 and 40 years in 12/27 (44 %) and no cases in children under 9 years. HV infections were observed in all seasons with a slight peak in the summer 11/27 (41 %). Mapping of the residences of the clinical NE cases showed that 26/27 (96 %) of the confirmed cases lived in rural and forested areas located in the eastern and southern regions of The Netherlands (Fig. 1).

The most pronounced symptoms found in hospitalized patients were: abdominal and/or flank pain in 24/25 patients, followed by fever (body temperature > 38·0 °C) in 25/27 patients, vomiting in 14/25, nausea in 17/25, headache in 12/25 and myopia in 4/27 patients. Myopia may have been overlooked in some patients, because it is easily missed during clinical examination. Duration of illness, defined as from the first day of illness till discharge from hospital ranged from 11 to 41 days (mean 17 days).

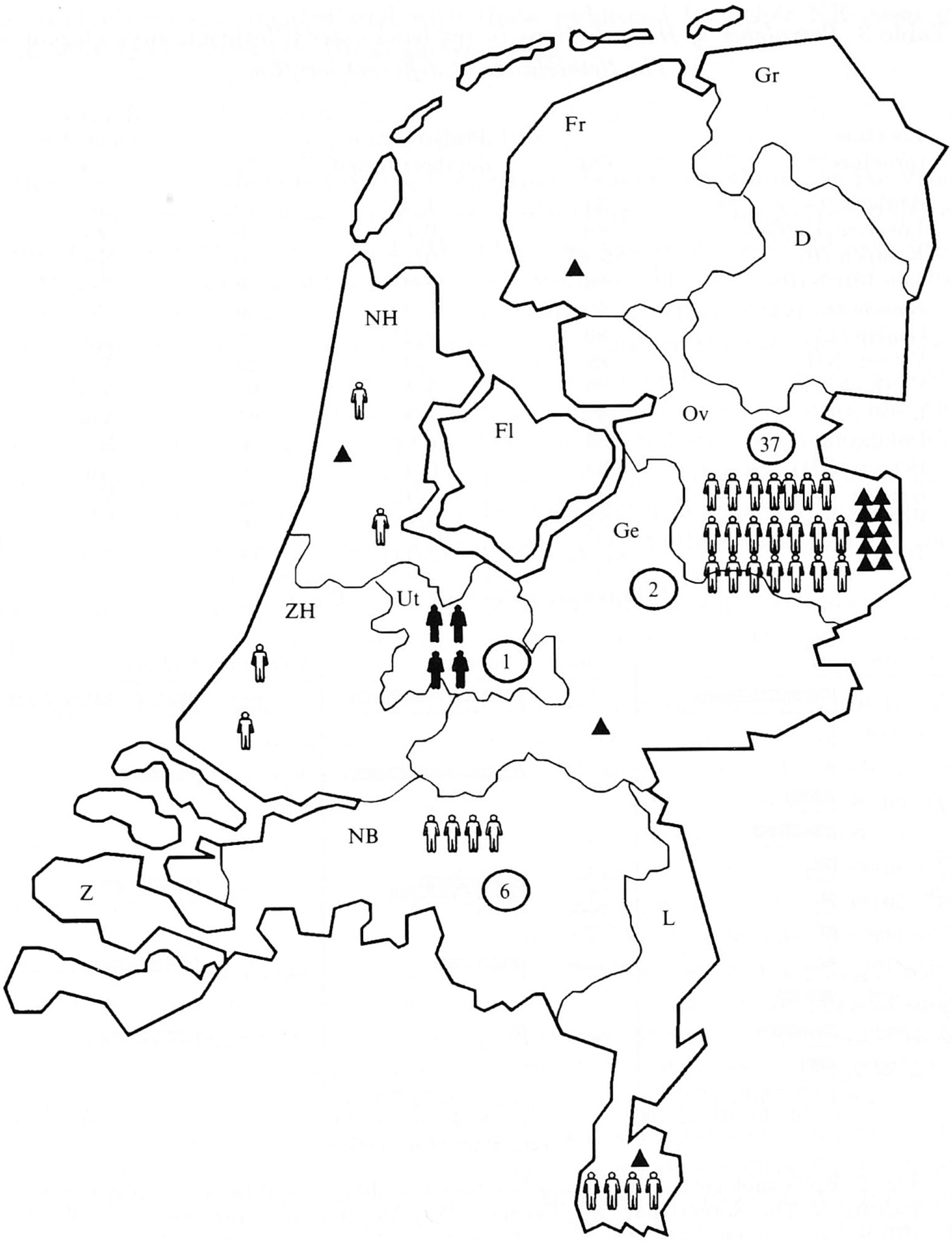

Fig. 1. Geographic distribution of hantavirus infections in The Netherlands; [symbol], seropositive laboratory workers; [symbol], serologically confirmed human cases of NE; ⊙, numbers of seropositive individuals in the province indicated; ▲, HV sero- or antigen-positive rodents. (Letters indicate the different provinces; (Fr), Friesland; (Gr), Groningen; (D), Drenthe; (Ov), Overijssel; (Ge), Gelderland; (Ut), Utrecht; (Fl), Flevoland; (NH), Noord-Holland; (ZH), Zuid-Holland; (Z), Zeeland; (NB), Noord-Brabant; (L), Limburg.

Table 3. *Prevalence of HV infections in red bank voles* (Clethrionomys glareolus) *in The Netherlands at different locations*

Location (province)*	Year	Positive mice/ numbers tested	%	Reported human NE case
Arnhem (Ge)	84	1/4	25	No
Loenermark (Ge)	86	0/5	0	No
Kempen (B)	86–87	0/22	0	No
Den Bosch (B)	88	0/1	0	Yes
Linschoten (Ut)	89	0/11	0	No
Geulen (L)	89	0/21	0	No
Velsen (NH)	89	1/4	25	No
Volthe (Ov)	89	3/5	60	Yes
Lutte (Ov)	89	1/4	25	Yes
Doldersum (D)	93	0/12	0	No
Bergen (NH)	93	0/4	0	No
Rossum (Ov)	93	3/12	25	Yes
Boekelo (Ov)	93	3/6	50	Yes
Total	84–93	12/111	11	5/9

* Provinces abbreviated as in Fig. 1.

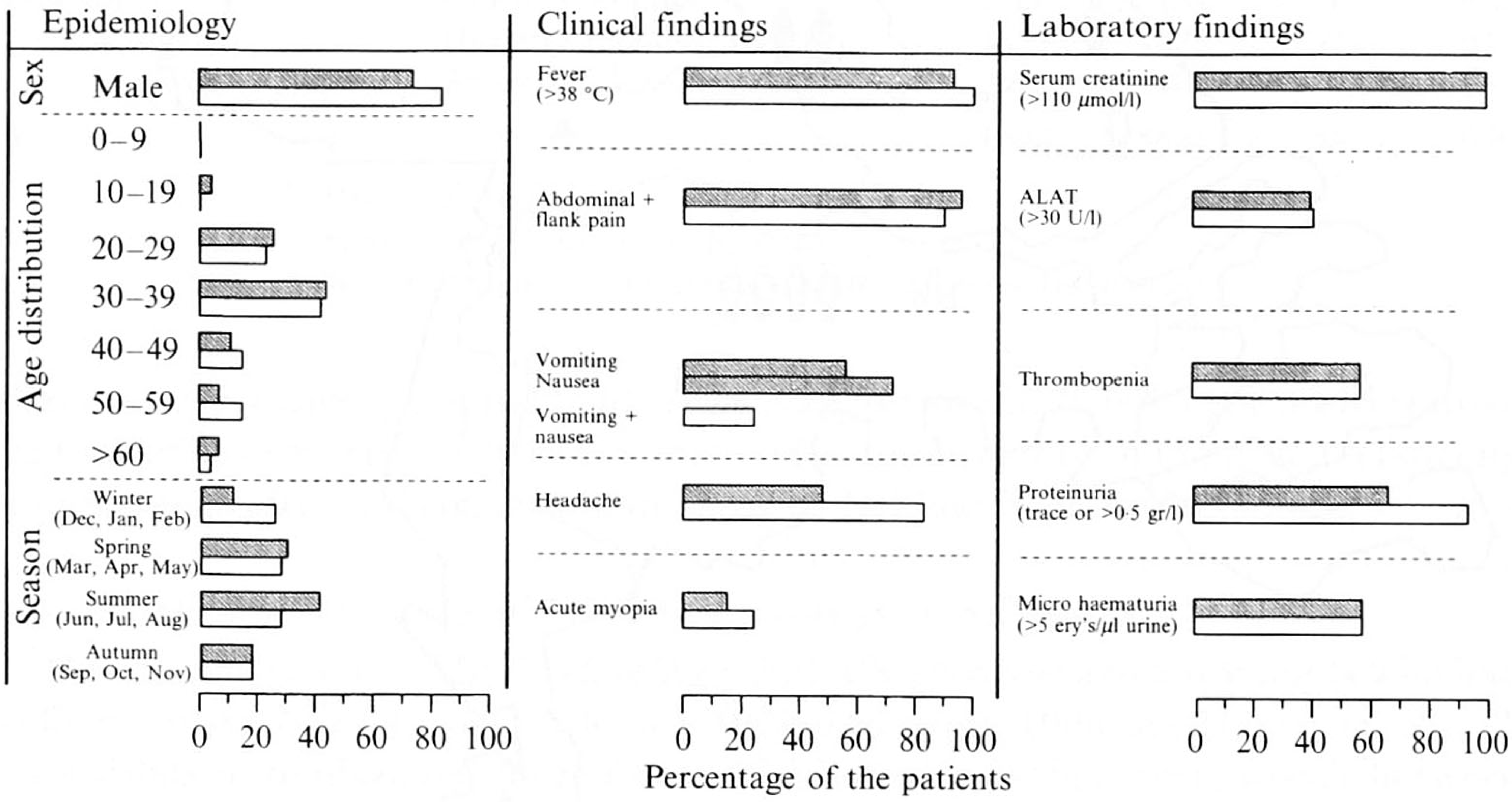

Fig. 2. Epidemiological, clinical and laboratory findings of hantavirus nephropathy patients in The Netherlands (▨), Germany [18], Belgium and northern France [19] (☐).

Laboratory findings showed that the serum creatinine was increased (> 110 μmol/l) in all 27 patients, ranging from 140 to 1300 μmol/l with a mean value of 537 μmol/l. Four of the 27 patients had to be given haemodialysis. Thrombocytopenia was found in 10/24 patients. Alanine aminotransferase (ALAT) was increased in 11/27 patients, ranging from 31 to 168 U/l. Protein was detected in the urine of 18/27 patients; in 14/27 the amount of protein was more than 0·5 g/l and in 4 of the 27 only a trace protein was detected. Microscopic haematuria, defined as > 5 erythrocytes/μl urine, occurred in 14/27 patients. All the data observed coincided well with those published for other NE cases in neighbouring countries [18, 19] as shown in Fig. 2.

DISCUSSION

Here we have documented that HV infections caused by a Puumula-like virus occur in eastern and southern rural and forested areas in The Netherlands, in addition to laboratory-associated HV infections caused by a Seoul-like virus [15, 16]. As in neighbouring Germany and Belgium, the main reservoir of this infection is the red bank vole (*Clethrionomys glareolus*), which in a limited survey in the apparently enzootic areas showed a seroprevalence of HV-specific antibodies of 25–60%. Evidence of sporadic infection was also found in two animal species, the common shrew (*Crocidura russula*) in an apparently enzootic area and the common vole (*Microtus arvalis*). No evidence of HV infection was found in the other feral mammalian species investigated. These included bats, which have recently been shown to be a reservoir for HV infection in Korea [20]. Screening of the most common domestic mammalian species in The Netherlands indicated that domestic animals including the cat do not play an important role in the transmission of HV disease to humans. In the United Kingdom, however, cats have been shown to have a relatively high prevalence of HV-specific serum antibodies [21].

Evidence for HV infection in humans was predominantly found in apparently enzootic areas in individuals with typical signs of NE. In contrast to reports from other countries which demonstrated serological evidence of HV infections in individuals with chronic renal disease [9–13], we only found evidence for HV infection in 1 out of 642 haemodialysis and renal transplant patients. Furthermore, the seroprevalence of HV infections in patients suspected of leptospirosis (1%) was slightly lower than the incidence of acute leptospirosis in this group (3%), which indicates the relative importance of the HV infection in The Netherlands. HV seropositive individuals were more frequently identified amongst laboratory workers (2%), foresters (4%) and animal trappers (6%) than in the population at large (< 0·5%), which indicates that the majority of these individuals run an occupational risk for acquisition of HV infections. It is of interest to note that the majority of the seropositive individuals identified in these studies had no history of clinically apparent renal disease, indicating that subclinical or non-typical HV infection may occur. The clinical signs of the serologically-confirmed human NE cases in The Netherlands are quite similar to those observed in neighbouring countries, with abdominal or flank pain, elevated levels of serum creatinine and proteinuria as most prominent features. Although most of the non-laboratory associated HV infections run a relatively mild course, more severe cases have been diagnosed. Recently we also investigated a patient with Guillain–Barré syndrome in association with HV infection [22]. The predominance of cases in males between 30 and 40 years of age, living in rural or forested areas, is also quite characteristic for NE cases observed in western Europe [6, 7, 10, 18, 23]. As in Germany, Belgium and France, NE cases occur throughout the year with a slight increase in the summer months. This is probably due to the mild climate, which largely allows rodents to survive outside the direct human environment. This is in contrast to the situation in Scandinavian countries, where rodents tend to seek human shelters in the autumn and winter [24]. Consequently the disease incidence peaks in these seasons. It is difficult to determine whether the recent increase in diagnosed cases of NE in The Netherlands is due to an increased awareness of the disease amongst the medical profession, or to an increased exposure of humans to infected rodents [3, 23, 25]. The recent outbreak of a previously unrecognized HV disease in the USA with a case fatality rate exceeding 60%, probably due to an increased exposure of humans to infected deer mice [3], stresses the need for a monitoring system for HV infections in humans and potential host animals.

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REFERENCES

1. Sugiyama K, Morikawa S, Matsuura Y, et al. Four serotypes of haemorrhagic fever with renal syndrome viruses identified by polyclonal and monoclonal antibodies. J Gen Virol 1987; **68**: 979–87.
2. Lee PW, Gibbs CJ, Gajdusek DC, Yanagihara R. Serotypic classification of hantavirus by indirect immunofluorescent antibody and plaque reduction neutralization test. J Clin Microbiol 1985; **22**: 940–4.
3. Childs JE, Rollin PE. Emergence of hantavirus disease in the USA and Europe. Curr Op Inf Dis 1994; **7**: 220–4.
4. Pether JVS, Lloyd G. The clinical spectrum of human hantavirus infection in Somerset, UK. Epidemiol Infect 1993; **111**: 171–5.
5. Osterhaus ADME, Spijkers I, Steenis G, Van der Groen G. Hantavirus infections in The Netherlands. Ned Tijdschr Geneeskd 1984; **128**: 2461–2.
6. Osterhaus ADME, Groen J, UytdeHaag FCGM, et al. Hantavirus nephropathy in the Netherlands. Lancet 1989: **5**: 338–9.
7. Jordans JGM, Groen J, Clement J, Lefevré A, Harolddottir V, Osterhaus ADME. Hantavirusinfecties in Twente. Ned Tijdschr Geneeskd 1991; **18**: 796–8.
8. Nuti M, Amaddeo D, Autorino GL, et al. Seroprevalence of antibodies to hantaviruses and leptospires in selected Italian population groups. Eur J Epidemiol 1992; **8**: 98–102.
9. Yanagihara R. Hantavirus infection in the United States: epizootiology and epidemiology. Rev Infect Dis 1990; **12**: 449–57.
10. Nuti M, Amaddeo D, Crovatto M, et al. Infections in an Alpine environment: antibodies to hantaviruses, leptospira, rickettsiae, and *Borrelia burgdorferi* in defined Italian populations. Am J Trop Med Hyg 1993; **48**: 20–5.
11. Glass GE, Childs JE, Watson AJ, LeDuc JW. Association of chronic renal disease, hypertensia, and infection with a rat-borne hantavirus. Arch Virol 1990; **[Suppl 1]**: 69–80.
12. Glass GE, Watson AJ, LeDuc JW, Kelen GD, Quinn TC, Childs JE. Infection with a rat-borne hantavirus in US residents is consistently associated with hypertensive renal disease. J Infect Dis 1993; **167**: 614–20.
13. Tsianos EV, Dalekos GN, Elisaf M, Zervou E, Siamopoulos KC. High frequency of antibodies to Hantaan virus and hepatitis C virus in chronic haemodialysis patients: coincidence or cross-reaction? J Int Med 1993; **234**: 607–10.

14. Clement J, McKenna P, Leirs H, et al. Hantavirus infections in rodents. In: Osterhaus ADME, ed. Virus infections of rodents. Amsterdam: Elsevier, (Horzinek M, ed. Virus infections of vertebrates: Vol 5.), 1994; 293–316.
15. Groen J, Osterhaus ADME, Avsic-Zupanc T, et al. Different Hantavirus serotypes in Western-Europa. Lancet 1991; **337**: 621–2.
16. Groen J, Jordans HGM, Clement JP, et al. Identification of hantavirus serotypes by testing of post-infection sera in immunofluorescence and enzyme-linked immunosorbent assays. J Med Virol 1991; **33**: 26–32.
17. Kelly PJ, Tagwira M, Matthewman L, Mason PR, Wright P. Reactions of sera from laboratory domestic and wild animals in Africa with protein A and A recombinant chimeric protein AG. Comp Immun Microbiol Infect Dis 1993; **6**: 299–305.
18. Pilaski J, Ellerich C, Kreutzer T, et al. Endemisches Vorkommen des Hämorrhagischen Fiebers mit renalem Syndrom (HFRS) in der Bundesrepublik Deutschland. Z Ärztl Fortbild 1991; **85**: 869–74.
19. Van Ypersele De Strihou C. Clinical features of hemorrhagic fever with renal syndrome in Europe. Kidney Intern 1991; **40 (Suppl 35)**: 80–3.
20. Kim GR, Lee YT, Park CH. A new natural reservoir of hantavirus: isolation from lung tissues of bats. Arch Virol 1994; **134**: 85–95.
21. Bennet M, Lloyd G, Jones N, et al. Prevalence of antibody to hantavirus in some cat populations in Britain. Vet Rec 1990; **127**: 548–9.
22. Esselink RAJ, Gerding MN, Brouwers PJAM, et al. Gullain–Barré syndrome associated with hantavirus infection. Lancet 1994; **343**: 180–1.
23. Clement J, McKenna P, Colson P, et al. Hantavirus epidemic in Europe, 1993. Lancet 1994; **343**: 114.
24. LeDuc JW. Epidemiology of Hantaan and related viruses. Lab Anim Sci 1987; **37**: 413–18.
25. Gerding MN, Jordans JGM, Groen J, Osterhaus ADME. Haemorrhagic fever with renal syndrome. Lancet 1993; **342**: 495.