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Incidence of hantavirus infections in Belgium

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Abstract

Over the last two decades, and from the moment that serological detection was possible, human hantavirus infections have been documented in most European countries. This paper summarises the available data on hantavirus cases in Belgium. These data enable the demonstration of the existence of a 3-year epidemic cycle in Belgium, which is apparently linked to rodent population dynamics. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The members of the genus hantavirus are carried and spread by wild rodent or insectivore species. The prototype virus (*Hantaan*) was isolated from *Apodemus* agrarius coreae and described for the first time in 1978 by Lee et al. (1978). The first human cases in Western Europe were detected in personnel of animal facilities in the 80s (Desmyter et al., 1983). The increasing significance of hantaviruses is best demonstrated by the observation that in 1978 only one serotype was known (*Hantaan*), this increased to seven serotypes by 1994, whereas today 31 serotypes have been described. Thirteen of these are human

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pathogens. Often, as demonstrated during epidemics in Bosnia, Argentina, the United States and Russia, two or more serotypes were responsible, or suspected to be responsible for human disease (Elliott et al., 1994; Rollin et al., 1995; Levis et al., 1997; Lundkvist et al., 1997; Alexeyev et al., 1998). In Belgium, we have noted 873 human cases since 1976, with increasing numbers of human infections during epidemic and non-epidemic years in the last few years. We also found evidence for a 3-year epidemic cycle, i.e. the years 1987, 1990, 1993, 1996 and 1999 were characterised by a significantly higher number of human cases.

2. The virus

The hantavirus genus consists of a group of antigenically and structurally related viruses in the family *Bunyaviridae* (Schmaljohn et al., 1985). The virus contains a lipid envelope with two surface glycoproteins and an RNA-genome. This genome is composed of three segments; short (S), medium (M) and long (L). They code respectively for the nucleocapsid protein (N), the two envelope proteins, G1 and G2, and a polymerase. The N protein induces the cellular immune response, the glycoproteins, G1 en G2, induce neutralising antibodies. Because of their lipid envelope, hantaviruses are susceptible to inactivation by detergents and chemical disinfectants (e.g. bleach solution).

3. The reservoir

Rodent reservoirs for hantaviruses belong to the *Murinae*, Arvicolinae and *Sigmodontinae* subfamilies within the *Muridae* family. During or after viraemia, virus is detectable in blood, tissue, saliva, urine and faeces in infected rodents. In the host species hantavirus infection is apparently persistent for life and seems not to affect the health of the rodent in any way (Yanagihara et al., 1985; Gavrilovskaya et al., 1990). Several factors are considered to play a role in transmission of the virus amongst rodents; exposure to the virus in the nests through contact with infected excreta, sexual contact and wounding through fighting and biting between rodents of the same species might maintain the enzootic cycle (Mills et al., 1997, 1998).

There are indications of a relationship between rodent densities, the subsequent increase in seroprevalence in rodent populations and the number of human cases at a given time (LeDuc, 1987; Niklasson and LeDuc, 1987; Parmenter and Vigil, 1993). High densities of rodent populations are very often related to extrinsic ecological factors such as an abundant food supply and favourable living conditions. The explosion of rodent populations induces an increase in the frequency of contacts between members of the species and thus increases the risk of transmission of the virus.

Clethrionomys glareolus (red bank vole) is the natural host of PUU in Europe. The importance of Clethrionomys glareolus in the transmission of hantavirus infection to humans in Belgium was studied in detail from 1996 to 1999. High rodent densities associated with a high prevalence of PUU virus infection in red bank voles were also recorded during the 1996 and 1999 epidemic years (Escutenaire et al., 2000). Moreover, in fall 1996, an apparent widespread distribution of the virus was observed among the bank vole populations located in the southern epidemic region of Belgium (Escutenaire et al., 2000). In spring 1999, an increased red bank vole population was noticed in the investigated area and a seroprevalence reaching 47.7% (189/396) was recorded (Escutenaire et al., 2000). During the non-epidemic years, i.e. in 1997 and 1998, no eruption in rodent densities was observed; prevalence rates of hantavirus infection were low in rodent communities and the virus was only found focally in the studied area (Escutenaire et al., 2000). Fig. 1 shows the relationship between the occurrence of human cases in Belgium and the prevalence of PUU virus infection in red bank voles from 1996 to 1999. The prevalence in fall 1997 was significantly lower ($P < 0.01$) than in fall 1996 while the seroprevalence in spring 1999 was significantly higher ($P < 0.01$) than in spring 1998. No apparent relationship did exist between the dynamics of infection and population density in the rodents

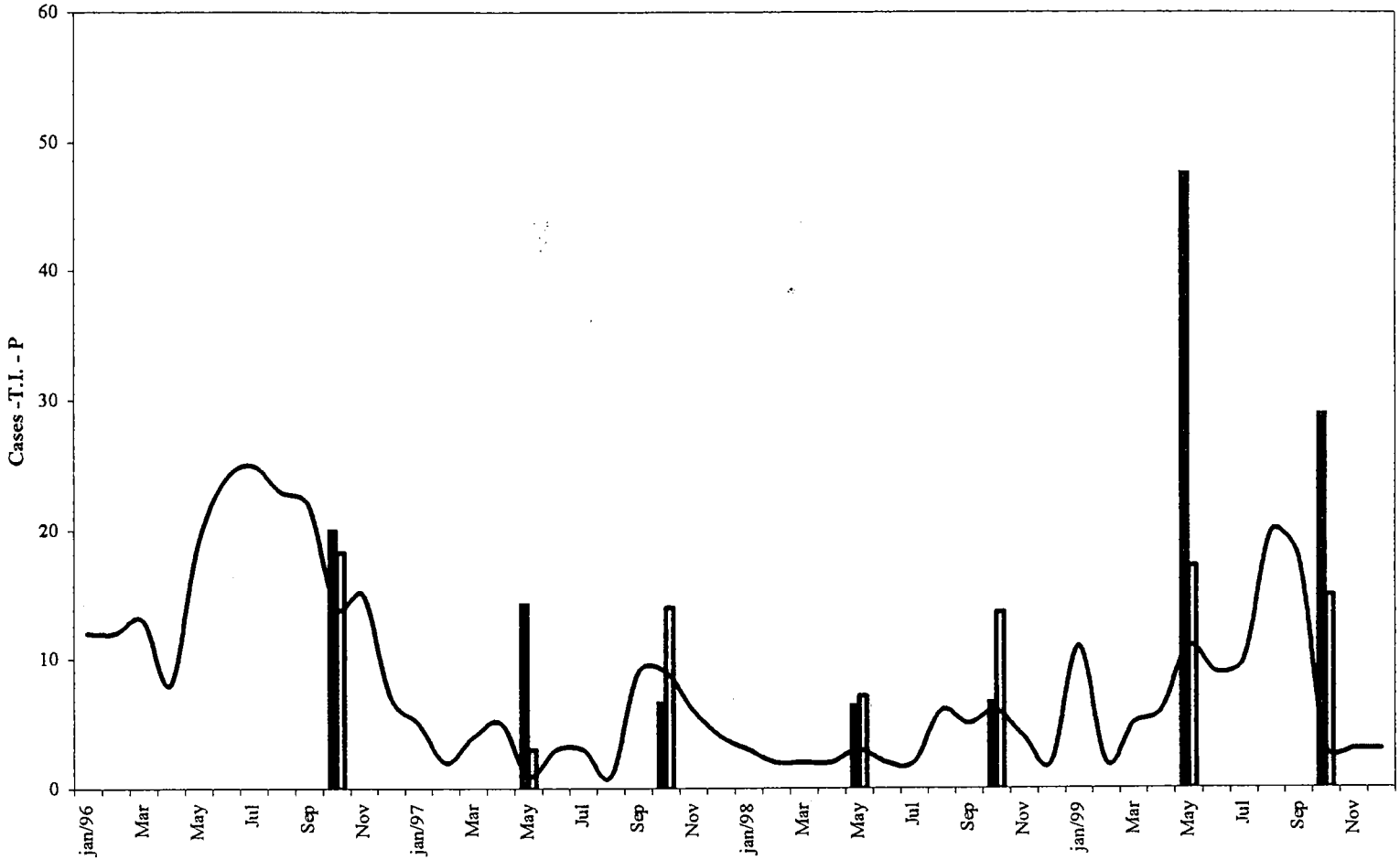

Fig. 1. Relationship between the number of NE (*n* cases NE) cases recorded monthly in Belgium between 1996 and 1999 and the trapping index (T.I.) and prevalence (P) of hantavirus infection in red bank voles (C. gl.) trapped in the southwestern epidemic region. Line, human cases; Black columns, prevalence percentages; White columns, Trapping indexes.

and the appearance of human cases in the non-epidemic years 1997 and 1998.

4. Geographical distribution of human cases in Belgium

The distribution of human cases by postal code indicated that the vast majority was recorded along the French–Belgian border, i.e. in the provinces of Hainaut, Namur and Luxembourg as well as the adjacent French Départements Ardennes, Picardie, Haute-Marne, Lorraine and Franche-Comté. This was particularly true in non-epidemic years. In epidemic years however, cases were also recorded in other provinces, i.e. Liège, Antwerp, Brabant and Flanders.

Observed changes in previously described endemic areas indicate that the presence of foci might be influenced by ecological events like changes in biotope (the aging of woods), rodent migration, human activities in forested area and agricultural activities (Lahdevirta, 1971). This suggests that the 'endemic area' could have its own dynamic and temporal features and is by no means a stable entity.

5. Infection mechanism, disease characteristics and treatment

Humans are infected with hantaviruses by inhalation of infectious, aerosolised particles of fresh rodent excreta. At present there are no data available on the survival time of the virus in nature after being shed by the rodent. Human-to-human transmission was not recorded in Europe, evidence of horizontal transmission was obtained during the 1995-epidemic in Argentina (Wells et al., 1997).

The prevalent serotype in Belgium, *Puumala* (PUU) virus, as well as other serotypes present in Europe, i.e. *Seoul* (SEO) and *Dobrava* (DOB), have the kidney as main target organ whereas the American serotypes, *Sin Nombre* (SNV) and SNV-related viruses mainly affect the lungs (Duchin et al., 1994; Colson et al., 1995). Most PUU infections are probably asymptomatic and if any (in 5–10% of the cases), symptoms most often appear as ARF (acute renal failure) and to a far lesser extend involve the respiratory tract. American serotypes primarily show cardiac involvement and adult respiratory distress syndrome (ARDS). ARF and ARDS can however occur in Europe as well as in the Americas (Stuart et al., 1996). There is no specific treatment for hantavirus infections. Ribavirin, that is known to inhibit RNA-virus replication in vivo, can favourably influence the clinical course of infections with HTNV when administered early. Actual treatment is supportive and in critical cases, includes cardio-supportive intensive care, mechanical ventilation, peritoneal or hemodialysis and extracorporeal membrane oxygenation (ECMO). With proper medical care, fatality rates for PUU are $< 1\%$ (Colson et al., 1995), 47% for SNV and SNV-related infections (Duchin et al., 1994), 10–20% for DOB (Avsic Zupanc et al., 1989), 5–10% for HTN (Chen and Qiu, 1993) and for 3–7% SEO (Song et al., 1982).

6. Epidemic features

The monthly distribution of NE cases in Belgium from 1990 to 1999 is depicted in Fig. 2. The seasonal distribution of the cases, observed during epidemic years, i.e. a major summer peak between June and September and a minor winter peak from January to March. The mean seasonal distribution over the 10-year period confirms this finding.

The mean age of the patients was around 40 years, on average 75% of the human infections were recorded in the male population group and, on the age distribution curve, the 20–40-year age group is most at risk (Heyman et al., 1999). The highest incidence was recorded in the provinces of Hainaut, Namur and Luxembourg. However, human cases were noted all over the country, especially in the vicinity of forested areas (Heyman et al., 1999). On average, eighty-five percent of the cases are located in the southern and eastern part of the country, and the remaining 15% in the north and the west. The respective curves during the 1995–1996 epidemic show a different distribution in time (Fig. 3), the south-east region curve

showed peaks in the months November 1995 and February, June, August and November 1996 while the north-west region curve showed peaks in the months October 1995, January, March, May, July and October 1996. This observation could indicate that registration of cases by postal code, i.e. the residence of the patients, does not reflect the actual place of infection, i.e. their work place or occasional residence for holidays. Because the northwest part of Belgium is mainly industrial and urban, infection might be acquired during visits (holiday periods) of inhabitants of this part of the country to the south-eastern part, which is mainly rural and forested. It also demonstrates the relation between human activities (holiday periods, recreation) and acquiring hantavirus infection, at least for residents from the north and west of the country. Shifted peaks in the monthly distribution curve between the south-eastern and north-western part of the country could however also be due to differing rodent population dynamics under the influence of different climatic and living conditions in the respective Belgian regions.

7. Evolution of human hantavirus cases in Belgium in time

Hantaviruses are archaic viruses that have cohabited with their respective hosts for probably millions of years. There are indications that the PUU virus host, *C. glareolus*, has been present in Europe for at least 7000 years in its present distribution range. The first reliable descriptions in Europe of a disease that shared features with hantavirus disease as we know it, date from the World War I period (Ameuille, 1916; Bradford, 1916; Brown, 1916). The first hard evidence of human hantavirus disease in Belgium, by means of serology, dates from the 1970s (van Ypersele de Strihou and Mery, 1989). Due to the rareness of the diagnostics in those days, published data are scarce and only focused on outbreaks or unusual clinical findings.

A literature search shows that, between 1978 and 1986, 76 cases were reported in France and Belgium, 19 of which occurred in Belgium (van Ypersele de Strihou and Mery, 1989). Furthermore, sporadic cases were described in 1986 (van

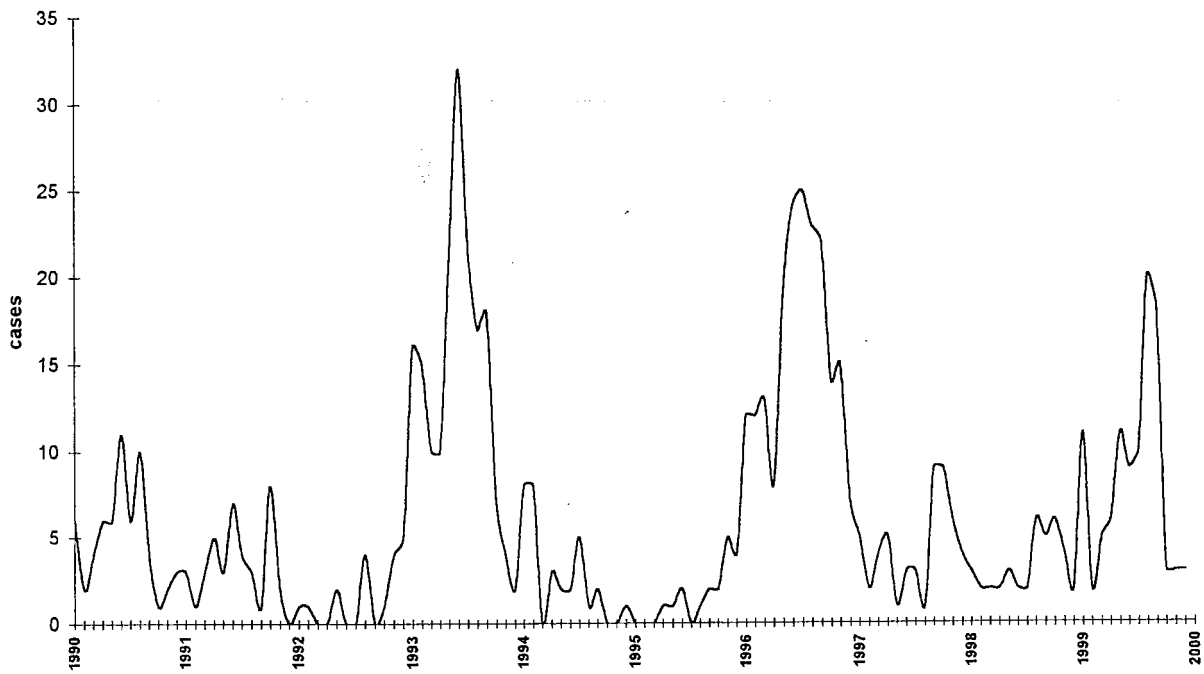

Fig. 2. Monthly distribution of human hantavirus cases from 1990 to 1999.

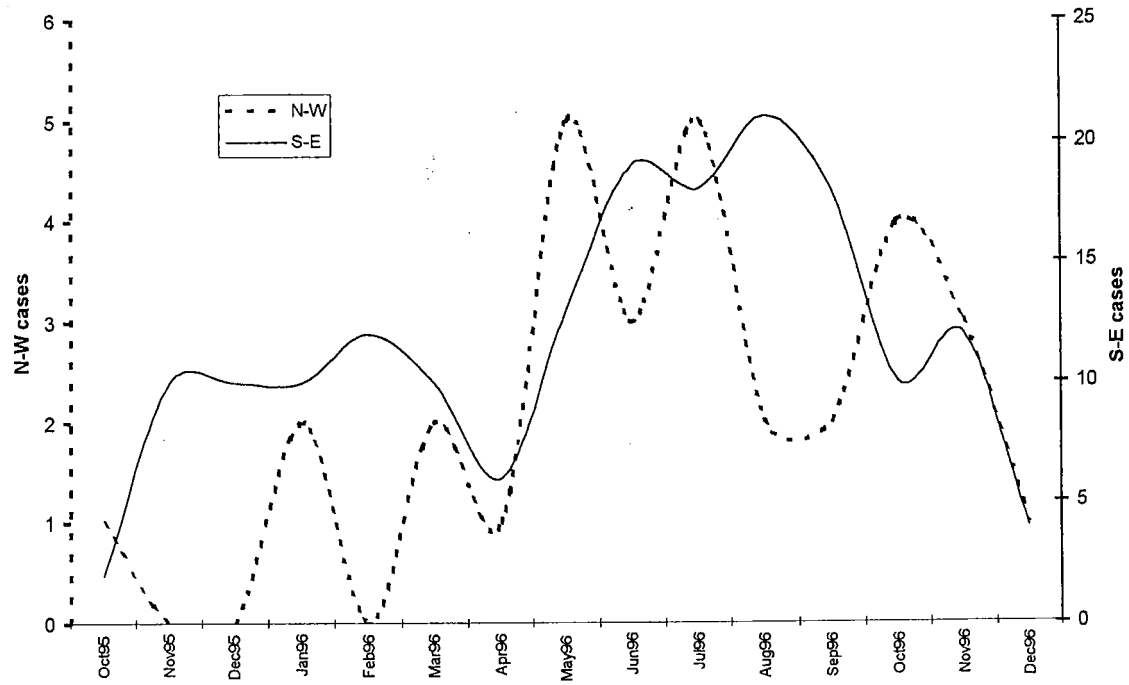

Fig. 3. Distribution of hantavirus cases in the south-eastern and north-western part of Belgium in 1995–1996.

Ypersele de Strihou et al., 1983). In 1983, three cases of ARF originating in 1981, and 39 cases with serological signs of early or past infection were documented among staff handling laboratory animals (Desmyter et al., 1983). Three cases were described in 1987, originating from the South of Belgium (Buysschaert et al., 1987).

Available data show that in 1990, 1991, 1992 and 1993, respectively 61, 40, 18, and 174 cases were detected. In 1994 only 32 cases were reported, 1995 proved to be the onset year of the 1995–96 outbreak although only 18 cases were found. In 1996 a record of 224 cases occurred while in 1997 and 1998, 52 and 55 cases were reported, respectively (Ducoffre, 1997). In 1999, 159 cases were recorded. The available data on hantavirus cases from 1976 to 1999, which account for a total of 873 cases, were depicted in Fig. 4. It shows five major peaks of human cases in Belgium, respectively in 1987, 1990, 1993, 1996 and 1999. Each peak is followed by 2 years with significantly less observed cases. Assuming we are in an open (non-immunized) human population, we can apply a Poisson regression model on the data. So far, we have observed on average a 2.30 times increase every 3 years ($P < 0.0001$).

8. Establishing an early warning system

With the present knowledge, i.e. the 3-year cycle of human epidemics and the relation between rodent population densities versus rodent hantavirus prevalence versus human infection rate, an attempt could be made to establish an early warning system for hantavirus epidemics. The most convenient method for W-Europe would be to monitor the harvest of beech- and oak trees, because the rodent population fluctuations appear to be directly related to the amount of available food sources during the winter period. This would allow assessing the probability of an increased- or decreased-incidence of hantavirus infection in humans in the year to come. Also, sufficient time would be available to issue a warning to clinicians in the endemic area and popula-

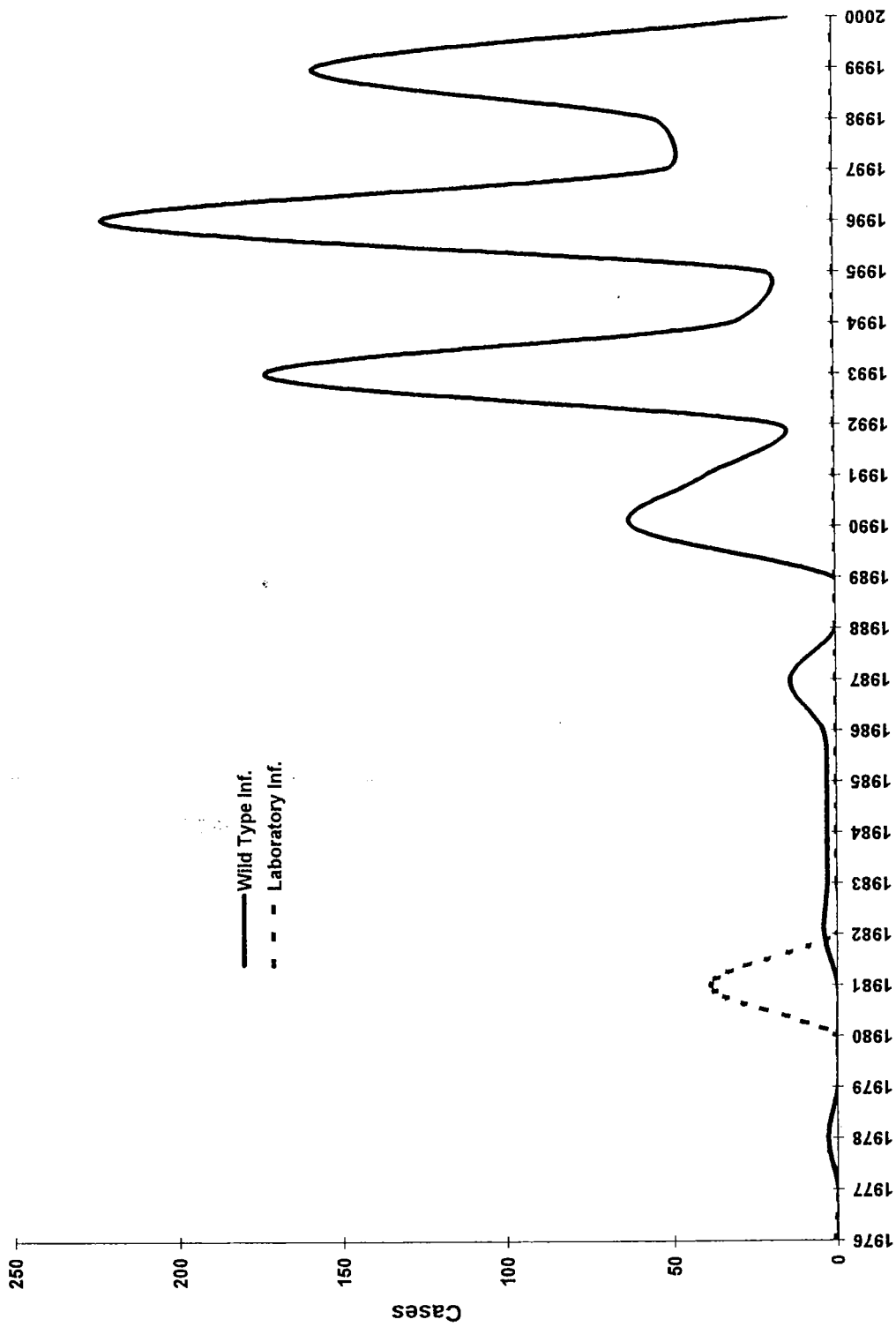

Fig. 4. Human hantavirus cases from 1976 to 1999.

tions at risk, i.e. forest workers, farmers, wood workers. Guidelines for the general public (information leaflets) exist and could be distributed as a reminder.

Indispensable features would be, apart from monitoring the food supply, the constant monitoring of the density of rodent populations and the seroprevalence in endemic and non-endemic areas, centralised reporting of human cases and immediate epidemiological interpretation and reverse-reporting of these data. Extrapolation of the data in relation to the information of previous epidemics could give an estimate of the magnitude of the hantavirus problem for the near future.

9. Conclusion

Already in 1983, van der Groen et al. reported hantavirus antibody prevalences in the Belgian population ranging from 0.7 to 2.2%. On the same occasion, sera submitted to hantavirus serology in order to exclude leptospirosis infection, showed an IgG seroprevalence of 3.8% (van der Groen et al., 1983).

These data indicate that hantavirus infection was present, but under-diagnosed, in the 70 and the 80s and probably before. The mild course of the disease and the absence of reliable, easily accessible diagnostic methods have probably contributed to this situation. Hantavirus infected cell lines for IFA (Immunofluorescence assay) and antigen preparations for ELISA (enzym linked immuno sorbent assay) only became readily available in the 1980s.

The question for how long hantavirus disease has been occurring in Belgium is difficult to answer. As previously mentioned, there are indications that the virus infected humans long before we were able to detect it efficiently. Hantavirus epidemics probably occurred in Europe early in the 20th century. During WW I, a condition called 'Néphrite de guerre', 'Feldnephritis' or 'Trench nephritis', depending on the military source, was described that resembled the present symptoms (Ameuille, 1916; Bradford, 1916; Brown, 1916). In Sweden, the symptoms were described by Myhrman (Myhrman, 1934). During WW II, German troops in Northern Europe suffered from the same problem (Stuhlfauth, 1943). Van Ypersele-De Strihou et al. report a peak incidence during the summer of 1983 in France and Belgium (van Ypersele de Strihou and Mery, 1989). From 1990 on, an increase in the number of cases in epidemic years was noted until 1996. This is however not necessarily an indication that hantavirus disease is an increasing public health problem because we should take into account the increased knowledge about the disease and the increased awareness of clinicians for the problem, which has led to more demands for specific serology. Statistically however, it was possible to obtain evidence for the existence of a 3-year cycle for human epidemics.

An unusually high number of human cases was recorded in Belgium in 1996 when major epidemics also occurred in Bosnia, France, Germany and South America. In Germany, human hantavirus infection due to *Dobrava* serotype was detected for the first time during this period, while in South America, new and previously unknown serotypes (*Andes*, *Lechiguanas*, *Oran*) were held responsible for the first time for human disease (Wells et al., 1997). The 1993 outbreak took place in Belgium at the same time as the previously unknown Sin Nombre virus emerged as causal agent for the first hantavirus epidemic in North America (Khan et al., 1996). Retrospectively, the virus could be traced back as far as 1959, again indicating that lack of diagnostic tools hampered detection (Frampton et al., 1995). To our knowledge, no attempts were made in Belgium to trace back hantavirus infection in humans in time. Such investigations would provide additional knowledge regarding the 'origin' of this type of disease.

The increased awareness of health care providers and the advances in serological and molecular biology tools for detection of hantaviruses have improved the level of detection of the disease in humans. Although still mainly 'home-made', the specificity and sensitivity of hantavirus serology diagnostics has greatly improved during the past 5 years. Standardisation with regard to protocols, antigens, etc. now remains the first issue to be solved.

The collected data indicate that hantavirus infection in Belgium was, is and most likely will be in the future, a health problem that has to be taken into account in areas where the virus is known to be endemic. The available data from the last 10 years indicate that the number of cases that can be expected in an epidemic year is 157 (range 86–222) on average; in non-epidemic years the annual total would be around 36 (range 20–47) cases on average. The increasing numbers of cases in the epidemic years from 1987 to 1996, most likely only reflects the increased awareness of healthcare providers and the optimisation of laboratory detection.

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