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# Global Warming and Epidemic Trends of an Emerging Viral Disease in Western-Europe: The Nephropathia Epidemica Case

J. Clement et al.<sup>1</sup>

*National Hantavirus Reference Centre, Clinical Virology, University Hospital Gasthuisberg & Rega Medical Research Institute, University of Leuven, Leuven, Belgium*

## 1. Introduction

Hantaviruses were first described in Korea in 1978, and are an important group of “new” pathogens, now constituting the most widely distributed zoonotic (i.e. transmitted from vertebrated animals to humans) viruses on earth. Hantaviruses are “emerging” viruses, and are now confirmed as being the only viral haemorrhagic fever agents with a worldwide distribution, including even the temperate Northern hemisphere (Clement et al. 2007a). They are spread by wild rodents (and perhaps also by insectivores), infecting man via their aerosolized but infectious excreta. So far, at least 23 different hantavirus species are officially recognized, each with its own main rodent reservoir, and hence specific geographical spread (Maes et al, 2009). The most important pathogens are *Hantaan* and *Seoul virus* in Asia, *Puumala* and *Dobrava virus* in Europe and West-Russia, and *Sin Nombre* and *Andes virus* in the Americas. American hantaviruses, discovered only in 1993, affect mainly the human lung and cause the “hantavirus cardio- pulmonary syndrome” (HCPS), with a fatality rate of about 35%. By contrast, all Old World hantaviruses are targeted mainly to the human kidney resulting in the “haemorrhagic fever with renal syndrome” (HFRS), an often epidemic form of acute kidney injury (AKI), resulting in a rapidly progressive, but ultimately self-remitting acute renal failure (Clement et al., 2007a, 2007b). Among hantaviral pathogens, the European *Puumala virus* (PUUV) is the least severe. It causes an infection, aptly named “nephropathia epidemica” (NE), which in fact is a mild form of HFRS, with a very low fatality rate of 0.5-0.1 %. However, more severe cases do occur, resulting in multi-organ involvement, necessitating sometimes live-saving acute haemodialysis and/or mechanical lung ventilation in intensive care settings (Clement et al., 1994a, 2007a, 2007b).

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<sup>1</sup>P. Maes<sup>1</sup>, M. Barrios<sup>2</sup>, W.W. Verstraeten<sup>2,3</sup>, S. Amirpour Haredasht<sup>2</sup>, Geneviève Ducoffre<sup>4</sup>, J-M Aerts<sup>2</sup> and M. Van Ranst<sup>1</sup>

<sup>1</sup> National Hantavirus Reference Centre, Clinical Virology, University Hospital Gasthuisberg & Rega Medical Research Institute,

<sup>2</sup> M3-BIORES, both of the University of Leuven, Leuven, Belgium,

<sup>3</sup> Royal Netherlands Meteorological Institute, Climate Observations Department, De Bilt & Eindhoven University of Technology, Fluid Dynamics Dept., Eindhoven, The Netherlands

<sup>4</sup> Epidemiology, Scientific Institute of Public Health, Brussels, Belgium

The reservoir and vector for PUUV is a member of the Cricetidae family, the bank vole (*Myodes glareolus*, formerly named *Clethrionomys glareolus*), one of the most common wild rodents in Europe and W.-Russia.

Since the early '80 s, Belgium has developed a pioneering and long-standing interest for hantaviruses in the country and in its neighbours. The presence of a PUUV-like antigen in Belgian bank voles (Van der Groen et al., 1983a), the earliest clinical description of three NE cases (Van Ypersele de Strihou et al., 1983), and a first sero-epidemiological study (Van der Groen et al., 1983b), were all published in 1983, the same year wherein the first NE cases were also published in France (Méry et al., 1983). From 1983 on, the serodiagnosis of NE was improved by the isolation in Belgium of a PUUV strain, CG 18-20, derived from a bank vole captured in Russia (Tkachenko et al., 1984). It allowed the seroconfirmation of early Belgian NE cases and even of the first "autochthonous" German case in 1985 (Zeier et al., 1986). In fact, the very first serodiagnosis of a human PUUV infection in Germany occurred already in January 1984, in a Belgian military working and living in Germany, and admitted with NE in the (then) Military Hospital in Cologne, Germany (Clement & van der Groen, 1987). CG 13891, the first autochthonous Belgian PUUV strain was isolated in 1985 (Verhagen et al., 1986)(Van der Groen et al., 1987). This local PUUV strain (later by French authors erroneously also called IPH 90-13) appeared more sensitive and more reliable for screening and diagnosing purposes in W.-European NE cases than the former Russian or Scandinavian reference PUUV strains (Saluzzo et al., 1990) (Le Guenno et al., 1994). Thus, the Belgian prototype strain CG 13891 was substantial in the serodiagnosis of the first Dutch NE case in 1986 (Koolen et al., 1989), the first NE outbreak in The Netherlands (1989, around Twente)(Osterhaus et al. 1989), the first NE outbreak in Germany (1990, around Ulm, Baden-Württemberg) (Clement et al., 1996), and the Belgian as well as the French cases in the first joint Franco-Belgian NE outbreak in 1993 (Clement et al., 1994b) (Le Guenno et al., 1994). Native or recombinant versions of CG 13891 were successfully used by the national hantavirus reference laboratory in Belgium, founded by one of us (JC), and form likewise the base for current NE serodiagnosis in France (Le Guenno et al., 1994) (Billecocq et al., 2003)(Clement et al., 2010). These novel screening antigens allowed between 1985-1987 a pioneer study on a total of 21,059 healthy Belgian blood donors, yielding 275 (1.30%) PUUV IgG seropositives, confirming hereby a past (but mostly asymptomatic) NE episode. However, a significantly higher PUUV seroprevalence was found in the densely forested south, versus the sparsely forested north of the country, thus demonstrating statistically and for the first time in W.-Europe an apparently profound impact of a forest biotope on this emerging pathogen (Clement & van der Groen, 1987). Moreover, with the use of these same PUUV screening antigens, we could demonstrate that all early European epidemics of NE were linked indeed to a significantly higher presence of PUUV antibodies in the blood and/or of PUUV antigen in the lungs of bank voles (*Myodes glareolus*), captured locally after such a first outbreak, respectively in Chimay (Belgium), Ulm (Germany) and Twente (The Netherlands) (Clement et al., 1993).

## 2. The mast hypothesis: of mast, mice and men

As demonstrated in the Introduction, Belgium has a pioneer NE registration history, spanning now well over 28 years (1983-2010), an exceptionally long observation period for an emerging viral illness, virtually unknown before in Europe. During this 28-years registry, a total of 2,790 Belgian and clinically symptomatic NE cases were seroconfirmed. Bearing in

mind that probably less than 20% of all PUUV infections are actually registered as such (Brummer-Korvenkontio et al., 1999), the real number of PUUV infections may well have been in fact 5 times higher. Looking at the yearly NE numbers over this long time scale (Fig. 1), the lower results in the first 10 years, i.e. up to 1993, can be ascribed to a lower medical awareness and less performing laboratory capacity to seroconfirm suspected cases. However, these same arguments could not be maintained to explain the cyclic occurrence of ever increasing NE peaks noted since 1993, first with a 3-years, and later even with a 2-years interval (Fig. 1).

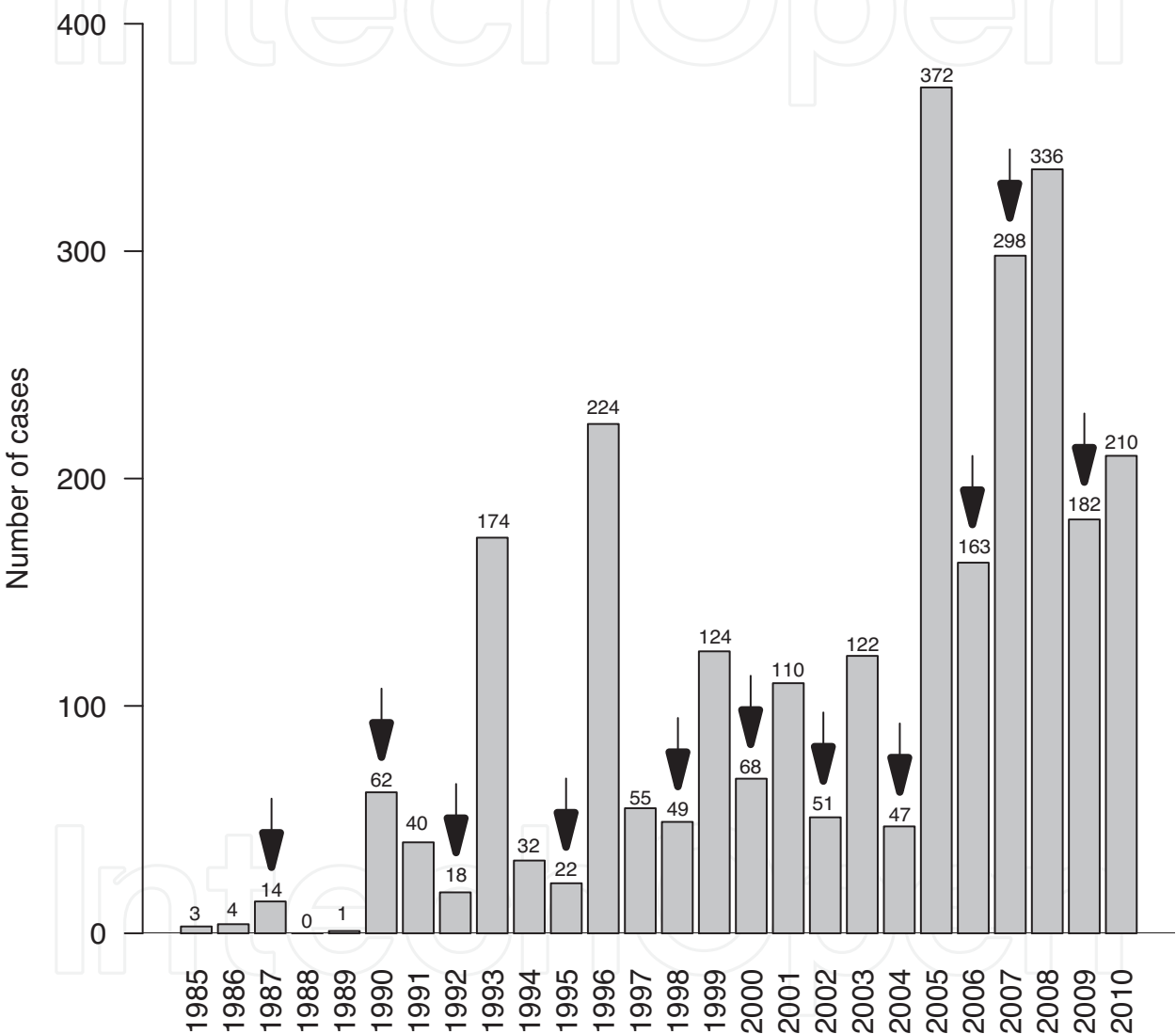


Fig. 1. Evolution of the number of NE cases officially registered in Belgium, 1985-2010. Black arrows indicate a “mast year”. Note that from 1992 on, each mast year is followed by a NE peak. Moreover, since 2005, an almost continuous epidemic trend is maintained.

With these elements, an underlying ecologic mechanism related to changing climatological conditions was suspected, formulated in 2005 as the “mast hypothesis” (Clement et al., 2005). “Mast” is the common denomination for the seeds of deciduous broad-leaf trees, in this case mainly beechnuts, and to a lesser degree also acorns. Mast constitutes the main staple food for bank voles, and it was suggested since 1994 (Clement et al., 1994b) that a

higher food supply in autumn (called further in the text “heavy masting”) might promote a better winter survival and earlier spring breeding in voles, leading to rodent densities up to 20 times the norm starting at the next spring. Thus, after such a heavy “mast year”, human population could be confronted from the next spring on with an ensuing “mice year”, leading to NE outbreaks, and explaining also the observed NE cyclicity. From the 1992 on, it is striking that each mast year in the subsequent 19 years was followed indeed by a more or less marked NE peak in Belgium (Fig. 1). The difference between the low NE numbers in mast years, and the high NE numbers one year later (i.e. the NE peaks) is highly significant (Clement et al., 2009).

Of note, even under the most favourable conditions, a deciduous broad-leaf tree is biologically not able to produce maximal crop during two subsequent years, as confirmed by the annual registry of beechnuts and acorns by the Walloon Forestry Department in the South of Belgium (Table 1). However, an alternation of heavy beech masting, followed by heavy acorn masting the next year is exceptionally possible, as we witnessed in 2006, respectively in 2007.

Rating		Year
Native oak	Beech	
+++	+++	1995
0	0	1996
0	0	1997
+++	++	1998
0	0	1999
+++	+++	2000
0	0	2001
0	+++	2002
0	0	2003
+++	+++	2004
0	0	2005
+	+++	2006
+++	+	2007
0	0	2008
+	+	2009

+++ = very good year, ++ = good year, + = moderate year, 0 = weak or absent seed production.

Table 1. Rating of beech and native oak mast production 1995-2009 in the Ardennes, forested South of Belgium. Note that maximal seed crop production during two consecutive years by the same tree species is biologically impossible. Source: Le Comptoir Forestier-Région Wallonne (From: Barrios et al., 2010).

3. The rodent reservoir and its biotope: the role of the beech

Overall, NE remains an epidemic (or sporadic) kidney disease prevalent almost exclusively west of the Ural Mountains, i.e. in a part of Europe wherein two entirely different biotopes predominate: the northern coniferous forest or taiga, and the more southern temperate

broadleaf forest. A third very bare biotope, the tundra, is much less important and present only in the far-North region of the current Russia. Bank voles prefer a habitat with trees for protection from the air, a thick protective ground layer of fallen coniferous needles or deciduous leaves, and sufficient moisture, the so-called “wet habitat”, in which they thrive best (Verhagen et al., 1986). So, the favourite biotope of bank voles are the temperate forests of W.-and C.-Europe, and the boreal forests in Fenno-Scandia. This simple but often overlooked fact explains why NE is virtually absent from most of the South of Europe, whose predominant biotope, the “Mediterranean shrub”, is much drier, has less trees, and offers less protective ground layer.

As far as the temperate broadleaf forests are concerned, and from 1992 on, we noted that most NE cases occurred in the Ardennes (forested South of Belgium), on both sides of the Franco-Belgian border around the river Meuse, and particularly in very limited areas wherein beechnuts were abundant, and not so much acorns. That is, areas with a dense coverage of the same deciduous broad-leaf tree species, the European beech (*Fagus sylvatica*) seemed to predispose to an abundance of local bank voles, and consequently to outbreaks of NE (Clement et al., 1994b). Later on, with increased assessment of the spread of NE in temperate Europe, it became clear that the W.-European regions with the highest endemicity of NE, were exactly corresponding to the regions with a dense beech tree coverage, i.e. not only the French and Belgian Ardennes, but also the whole North-East of France, and the South of Germany (Skjøth et al., 2008). Of note, another important European broad-leaf tree, the European native oak (*Quercus robur* and *Q. petraea*), is clearly present in most of South-Europe, including Portugal and South- & Central- Spain (Skjøth et al., 2008), regions where the bank vole is totally absent, and where, not surprisingly, not a single NE case has hitherto been documented.

Baden-Württemberg in the South of Germany is densely covered with beech trees. More than two thirds of all current German NE cases are localized in Baden-Württemberg, the same region where indeed the first NE outbreak was noted already in 1990 (Clement et al., 1996). Endemic NE in this “Land” is now by far the highest in W.-Europe. Its population (10.7 million) is comparable to that of Belgium (11 million), but the 2007 NE incidence was 3.6 times higher ( $10.1/10^5$ ) than the record 2005 incidence ( $2.8/10^5$ ) for Belgium. (Piechotowski et al., 2008)(Schwarz et al., 2009). It is striking that in Baden-Württemberg, districts with the highest beech forest cover (15% or more) correlate significantly with the highest district NE incidences ( $50/10^5$ ). Moreover, for each 5% increase in beech coverage per district, risk for NE is almost doubled (Schwarz et al., 2009). Thus, the prerequisite for an appropriate biotope for bank voles to generate W.-European NE epidemics can be summarized as the presence of deciduous broad-leaf forests with a predominance of beech trees, and a sufficient degree of humidity.

#### **4. Russia and Fenno-Scandia, two other regions in Europe highly endemic for NE**

Of the three regions endemic for NE, being Russia, Fenno-Scandia and W.-Europe, we will discuss in depth only the latter, because the new insights in some ecological mechanisms might be only relevant for W.-Europe, and not applicable in the two former regions. However in Russia alone, 68,612 HFRS cases, most of which NE, were registered (i.e. often hospitalized) between 1978 and 1992, peaking in 1985 with 11,413 cases (WHO, 1993).



Moreover, an even higher total number of 76,000 HFRS cases, the vast majority again being NE, was registered in a subsequent shorter study period of only 9 years (1999-2008). Of these Russian HFRS cases, 87% occurred on the forested foothills of the Ural mountains, or in the steppe-forest regions around Volga river, i.e. in the European part of the country, resulting in a high average annual incidence of 20/10<sup>5</sup>. (Tkachenko et al., 2010). The reasons for this apparent increase of European-Russian NE incidence are not entirely clear, and a possible impact of global warming has not been studied systematically. However, cyclic NE peaks have also been noted during a 1973-2002 study period, linked to cyclic peaks in local bank vole populations every 2-4 years (mostly 3 years). These “mice years” started with higher reproduction of voles under the snow during winter, and were correlated ( $R=0.86$ ) with abundant linden harvest during previous autumn (Bernshtein et al., 2010).

With around 1,000 NE cases/year, Finland has reported between 1979 and 2010 more than 70% of all cases registered within W.-Europe. Again, an increasing trend was noted in the last decade, with peaks of 2,300 cases in 1999, 2,603 in 2002, 2,526 in 2005 and an all-time high of 3,259 cases in 2008 (National Public Health Institute of Finland, 2011). With its population of 5.2 million, the 2008 Finnish incidence thus reached 62.6/10<sup>5</sup>, the highest in the world. In Sweden, NE has been registered from 1989 on. Incidence averaged between 200-400/year, but peaked suddenly to 2,195 in 2007, and again to 1,483 in 2008 (Olsson et al., 2009). Winter NE peaks are characteristic for Fenno-Scandia, in contrast to the summer peaks in W.-Europe. Global warming during wintertime has been incriminated somewhat paradoxically for an increased contact between humans and voles, since the decreased protective snow cover in Fenno-Scandia is supposed to favour bank voles' entry into human dwellings, in search for food and shelter. Overall, the 3-yearly NE peaks in Fenno-Scandia are ascribed to predator-prey cycles, a mechanism very different from the one operative in temperate Europe (Olsson et al., 2009).

Indeed, the vegetation type that covers most of Norway, Sweden and Finland is another difference, since the boreal forest or taiga consists mainly of pine trees, in contrast to the temperate forest in the rest of Europe, wherein deciduous broad-leaf trees predominate.

## 5. The role of global warming in the NE surge of four W.-European countries

If our “mast hypothesis” could explain recurrent NE outbreaks in Belgium as showed in chapter 2, it could not explain the noticeable increase of NE cases during last years, nor the smaller interval between subsequent NE peaks, recently every 2 years instead of every 3 years previously (Fig. 1). Indeed, from 2005 on, an epidemic trend of NE in Belgium was heralded, resulting in a record total of 1,554 cases for the last six years (2005-2010) or a robust mean of 259.0 cases/year, versus a mean of only 56.18 cases/year for the previous 22 years, totalling 1,236 cases. This difference between recent and former NE is statistically highly significant ( $p<0.001$ ,  $\alpha=0.05$ ), and again cannot be explained by increased medical awareness alone. As recently noted for other, mostly tropical, infections, an influence of global warming was suspected. It was known that broad-leaf trees reacted with increased bud formation as a survival strategy when confronted with prolonged heat during summertime, particularly if this is enforced by marked drought (Pucek et al., 1993). Moreover, tree flower formation in spring can be stimulated by higher spring temperatures, particularly during the month of April (Piovesan et al., 2001). Higher bud formation in year-1, especially if combined with higher flower formation in the year 0, can result in a (much) higher seed crop harvest in autumn of the same year 0, or “heavy masting” (Bennet et al.,

2009). However plausible this approach might appear, it should be supported by hard data and convincing statistics, not available until recently in Europe. For this purpose, a 2009 study was started in Belgium. In a second step, conclusions found for Belgium were matched against NE data registered in its neighbouring countries, France, The Netherlands, and Germany.

### 5.1 The Belgian study

Base elements for this 1996-2007 study period (Clement et al., 2009) were monthly NE data for Belgium delivered from 1996 on by the Scientific Institute of Public Health (SIPH), Brussels, and the daily and monthly data of mean temperature (in degrees Celsius) and precipitation (in mm), delivered by the Royal Meteorological Institute (RMI), situated in the centre of the country in Ukkel (Brussels). This station is considered to be representative for the Belgian territory, despite regional variations.

In a first approach, we tried to correlate climatological 1996-2007 data to the seasonal NE data of the same 12 years. Annual average daily temperature in this period was with  $11.4^{\circ}\text{C}$  significantly higher than in the previous decade 1985-1995 with only  $10.7^{\circ}\text{C}$  ( $p=0.0001$ ), but annual average daily rainfall was not (2.37 versus 2.30 mm,  $p=0.5461$ ). Harsh winters with mean monthly temperatures below  $0^{\circ}\text{C}$  were completely absent in the 1996-2007 study period, whereas monthly mean winter temperatures below  $0^{\circ}\text{C}$  were still noted begin 1985 through 1987 (Clement et al., 2009).

As known already before this study, each NE peak was preceded since 1993 by a mast year (Fig. 1), resulting in significantly higher NE case numbers during these peaks (Spearman  $R = -0.82$ ;  $P = 0.034$ ). NE peaks were significantly related to warmer autumns the year before ( $R = 0.51$ ;  $P < 0.001$ ), hotter summers two years before ( $R = 0.32$ ;  $P < 0.001$ ), but also to colder ( $R = -0.25$ ;  $P < 0.01$ ) and more moist summers ( $R = 0.39$ ;  $P < 0.001$ ) three years before. The correlation improved even when only July was selected as the most representative summer month. Autumn mast production was particularly heavy in 2004 and to a lesser degree in 2007 (Table 1), resulting each time a year later in the two highest NE peaks ever registered to date in Belgium. The summer 2003 had mean temperatures of the months June, July and August consecutively on or above  $20^{\circ}\text{C}$  (mean summer temperature in Belgium  $19.7^{\circ}\text{C}$ , normal only  $17^{\circ}\text{C}$ ), resulting in what was estimated to be the hottest summer in Europe since 1540. This stimulated flower bud initiation in oaks and even more in beeches, thus paving the way in autumn 2004 for the heaviest masting ever recorded in the country (Table 1), which in turn resulted in 2005 in the most important NE outbreak (372 cases) observed in Belgium to date (Fig. 1).

The next NE peak in 2007, third highest with 293 cases, is less obvious to explain, since it appeared to be a acorn mast year by itself (Fig. 1)(Table 1). However, beech mast production end 2006 was also fairly pronounced (Table 1), and we suppose this food supply for voles was optimized again by very warm autumn temperatures (mean September  $18.4^{\circ}\text{C}$ , and October  $14.2^{\circ}\text{C}$ ), and one of the mildest winters since decades, allowing early winter breeding in voles and a denser rodent population early 2007, as indicated by the high NE incidence during the first months of 2007 (Clement et al., 2009).

In contrast to winter temperatures or rainfall parameters, showing only very weak or negative correlations, a positive and strong ( $R = 0.51$ ) highly significant correlation was found for autumn temperatures, the year before NE occurrence, or year-1. Fall climate



factors cannot influence any more mast formation of the same year itself, but still can influence favourably other vegetal food sources and the bank vole population itself. Higher staple food availability during increased tree seed production in autumn may allow higher bank vole survival not only during the subsequent winter, but also already in the (late) autumn of the mast year itself, particularly if this is accompanied by milder temperatures as observed during last years (see hereunder). In this hypothesis, human population is already at risk for higher NE incidence during late autumn and early winter of a mast year, as observed indeed in Belgium (Clement et al., 2009). Moreover, “late winter NE peaks” subsequent to heavy autumn masting may ensue the following year, hereby announcing already very early an important NE peak that same year: the record number of 22 Belgian NE cases in February 2005 was heralding the most important summer NE peak ever recorded in Belgium, and an even higher February 2008 record with 28 cases announced the second highest (336 cases) peak that same year (Clement et al., 2009).

A recent similar study, relying on the same Belgian 1995-2007 NE registry, came independently to exactly the same conclusions: NE outbreaks are favoured by hot summers two years before, and warm autumns one year before the facts (Tersago et al., 2009).

## 5.2 The case of France, Germany and the Netherlands

In a second study, we examined if our “mast hypothesis” was also valid for three neighbouring countries with registered NE data, being France, Germany, and the Netherlands. Mast years are simultaneous in most countries of W.-Europe, including even the British Isles (Bennett et al., 2009), but exceptions can occur due to regional climatological differences. Thus, for the sake of simplicity, we maintained in this international study the same mast years, and even the same mean temperatures for summer and autumn as for Belgium, with the exception however of the years 2006 and 2009, in which beech masting in (South-)Germany appeared to be much stronger than in the three other considered countries (Fig. 2). Indeed, it seems admissible that climatological differences between (South-)Belgium and its direct neighbours (North-East France and The Netherlands) might be less pronounced as to the more distant South-Germany, where the vast amount of NE cases are situated (see chapter 3).

In France, a total of 2,036 cases were reported in 28 years (1983-2010) (Institut National de Veille Sanitaire, France, 2007) with yearly fluctuations surprisingly similar to those in neighbouring Belgium, i.e. often after a mast year (Fig. 4). It is striking that the highest French NE peak (253 cases) so far, was also recorded in 2005, likewise after heavy masting in 2004, itself a consequence of the infamous summer 2003, which in France had been even hotter than in Belgium.

The same phenomenon, but in a much dampened form was observed in the Netherlands, where a total of 121 NE cases was recorded in 16 years (1995-2010) (National Institute for Public Health and the Environment [RIVM], Bilthoven, 2011). (Fig. 4). The mostly very modest numbers of NE cases in this country are probably due to a lack of dense coverage by beech trees. In Germany, official NE registration started only in 2001, but showed a similar cyclic pattern with rising incidences, resulting in a record total of 4,880 cases in 10 years (2001-2010) (Robert Koch Institut, Berlin, 2011). Thus, the four studied countries together passed in 2005 for the first time the mark of more than 1,000 cases (total 1,019) of an until then underdiagnosed and ill-known emerging infection, a rare example of tree ecology having an impact on a human kidney disease. Germany is recently confirming itself as the

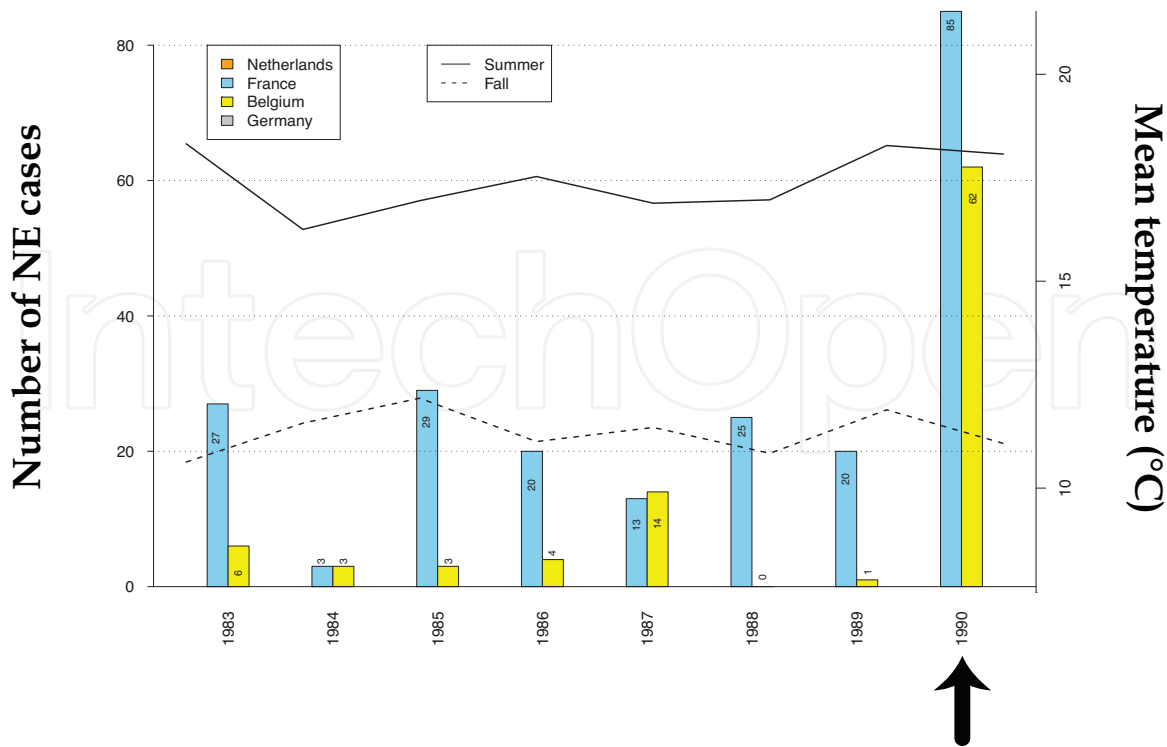


Fig. 2. NE cases 1983-1990 in France and Belgium. The black arrow indicates a possible mast year. Exact 1983-1989 mast data are lacking. Full line indicates mean summer temperatures, dotted line indicates mean autumn temperatures, both in Belgium.

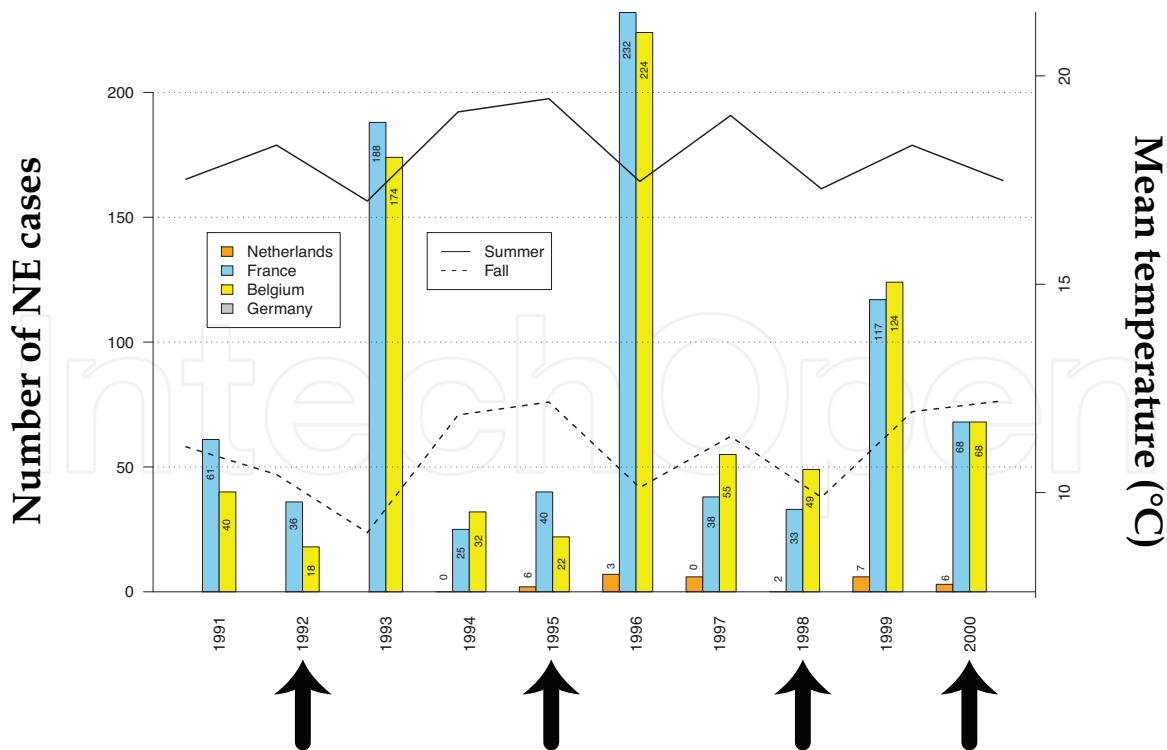


Fig. 3. NE cases 1991-2000 in France, Belgium, and The Netherlands. Black arrows indicate mast years in Belgium. Note that each mast year is followed by NE peaks, the latter often 2 years after warmer summers.

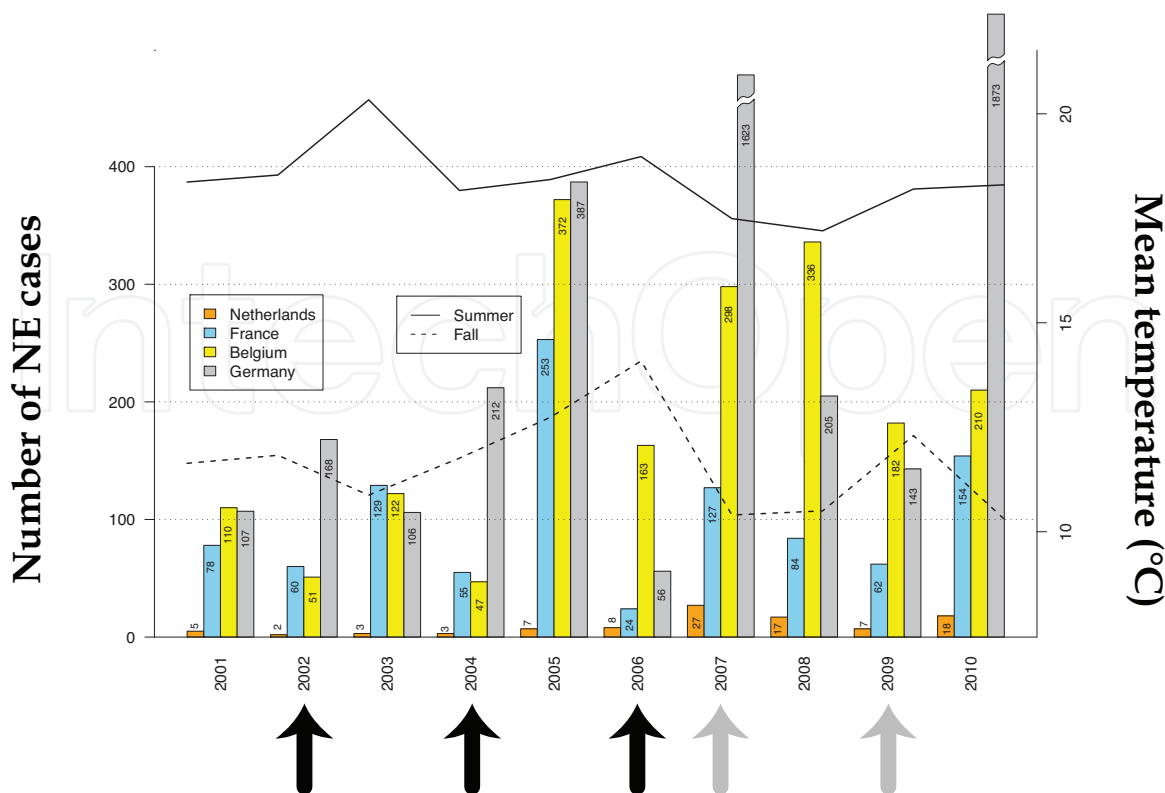


Fig. 4. NE cases in four W.-European countries. Black arrows indicate beech mast years in Belgium. The gray 2007 arrow indicates a heavy oak mast year. The gray 2009 arrow indicates a weak mast year in Belgium, but a heavy beech mast year in (South)-Germany. Note the high 2003 summer temperature, inducing the major joint 2005 NE peak in the four countries.

most endemic country for NE, presenting however some regional aspects different from its neighbours. In contrast to France, and apparently even more pronounced than in Belgium, it witnessed heavy beech masting in autumn 2006, leading to a record 1,623 NE cases in 2007. This record year was preceded by the mildest winter ever recorded in Germany, a very warm spring 2007, and confirmed by a noticeable increase in local bank vole population begin 2007 (Piechotowski et al., 2008). Of note, the Netherlands witnessed in 2007 also their highest NE peak (27 cases). However, the German record 2007 year was surpassed another time in 2010, with an all-time high of 1,873 cases (Fig. 4), again after strong local beech masting in autumn 2009, which in Belgium was much less pronounced (Table 1). It is also noticeable that the two highest German NE peaks were preceded each time by a clear surge in mean autumn temperatures in 2006, respectively in 2009 (Fig. 2), which seems to confirm our statistically significant correlation with warmer autumns found previously in Belgium (chapter 5.1). The role of warmer winters is less clear, although a 7-years (2001-2007) NE risk factor study in Baden-Württemberg concluded that a combination of a mild winter and prior heavy masting constitute the greatest risk for a subsequent NE outbreak (Schwarz et al., 2009). This seems now somewhat in contradiction with the fact that the record 2010 peak was preceded in Germany by a harsh 2009-2010 winter, as in many other European countries. Thus, the impact of low winter temperatures as a separate NE risk factor needs further study, the more so since it is known from Scandinavian countries that a constant winter cover with snow can have a rather protective effect on vole populations (Olsson et al., 2009). All by all, heavy beech masting seems to imply in temperate Europe the greatest

risk, since it appeared in the same 2001-2007 NE risk factor study in Baden-Württemberg that an abundant supply of beechnuts conferred by itself already a significant risk ratio of 2.86 (95% confidence interval 1.81-4.50) (Schwarz et al., 2009).

## 6. Other approaches in the future-and already in the present

Since vegetation characteristics are an important mechanism for understanding and even for predicting NE outbreaks, exhaustive new vegetation monitoring techniques, such as remote sensing by satellite, can now offer valuable techniques and data sources. With the help of a team of bio-engineers, we started satellite monitoring of different vegetation indices and climatological parameters in a series of collaborative studies. A first preliminary finding was that during a 2001-2007 observation period at the same 10 different locations in Belgium and France, a significant increase of the forest “length of the growing season” was observed, most pronounced in the densely forested areas, being also NE hot foci (Barrios et al., 2010). Moreover, a mathematical so-called multiple input-single output (MISO) model was developed, in which the inputs were average measured monthly precipitation and temperature in Belgium, as well as the estimated “vole carrying capacity”, expressed as number of voles per hectare, and based mainly on the yearly mast production. The output was the yearly observed number of NE cases in Belgium over the same 12-years study period (1996 – 2007) (Amirpour Haredasht et al., 2011). Since the observed output could be fairly validated by the input calculations, the next step will be to verify if this MISO model will allow us to predict future NE outbreaks in Belgium and in its neighbouring countries.

## 7. Conclusion

Global warming is the most evident explanation for the epidemic trend of NE, an emerging rodent-borne hantaviral disease, targeting mainly the kidney in humans. The correlation between higher temperatures, mainly during summers and autumns of the last decade, and higher NE peaks was proven to be highly significant in Belgium. Since occurrence and evolution of NE peaks in three adjacent countries, France, Germany and The Netherlands, was very similar to the situation in Belgium, it can be assumed that similar temperature-driven ecological mechanisms were likewise operative in these countries. Consequently, NE is now established as the most frequent infectious cause of acute (but self-remitting) kidney injury (AKI) in W.-Europe, as it was already the case in the two other NE-endemic regions in Europe, W.-Russia and Fenno-Scandia.

In recent medical literature, global warming has been invoked mainly as a driving force behind some (sub)tropical arthropod-borne infections, such as malaria, dengue, and Congo-Crimean haemorrhagic fever (CCHF), via an expansion of the habitat of the responsible vectors, mostly mosquitoes or ticks. This is the first report on the influence of global warming on an “autochthonous” disease, via expansion of the local rodent population. To our knowledge, this study is also the first assessment of a “new” kidney disease by a mathematical formula, or indirectly even by satellite monitoring.

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Phone: +86-21-62489820  
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