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Rise in the number of notified human hantavirus infections since October 2011 in Baden-Württemberg, Germany

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From October 2011 to April 2012, 852 human hantavirus infections were notified in Germany, of which 580 (68%) were in Baden-Württemberg. Case numbers started to rise earlier than they did before the previous outbreaks in 2007 and 2010, and are the largest ever reported in this state during October to April of any year. The early rise could be due to a beech mast year in 2011, followed by an early and massive reproduction of the reservoir bank vole populations during winter 2011 and spring 2012.

Outbreak description

From October 2011 to April 2012 (reporting weeks 40 2011 to week 17 2012, ending 27 April 2012), 852 cases of hantavirus infections meeting the national case definition [1,2] were notified in Germany (cumulative incidence: 1.04 per 100,000 population) [3]. Of these, 580 cases (68%) originated in the southern federal state of Baden-Württemberg (cumulative incidence: 5.4 per 100,000 population) (Table). This count exceeds the number of cases observed during the months October to April that preceded the outbreaks in 2007 (172 cases) and in 2010 (327 cases) in the same state (Table). We report on this ongoing outbreak in Baden-Württemberg, taking into consideration cases notified from October 2011 to April 2012.

Background

Puumala virus is the predominant human pathogenic hantavirus species in western, central and northern Europe [4]. It is transmitted to humans by exposure to excreta of its rodent reservoir, bank voles (*Myodes glareolus*) [5]. After an incubation period of usually two to four weeks [6], typical clinical manifestations include a sudden onset with fever, headache, back pain and gastrointestinal symptoms. Renal involvement is prominent and manifests initially as oliguria and later as marked polyuria (nephropathia epidemica)

[7]. Only 30% of Puumala virus infections occur with typical clinical signs, resulting in high under-reporting [8]. There is currently no specific antiviral treatment [4]. Recommended prevention measures focus on the avoidance of exposure and inhalation of potentially contaminated dust [9].

In Germany, laboratory-confirmed cases of hantavirus infections have been notifiable since 2001 [1,10]. Between 2001 and 2011, the number of annual notifications ranged from 72 to 447, with a median of 235, except for two outbreaks in 2007 (1,688 cases) and 2010 (2,107 cases) [11]. From November 2011 to February 2012, the Robert Koch Institute observed an increase in the number of cases notified in Germany compared with the mean in the same period in the five preceding years, from 2006/2007 to 2010/2011. Some 64% of these cases were reported from Baden-Württemberg [11].

Figure 1 represents the temporal distribution of cases in Baden-Württemberg from reporting week 40 in 2011 until reporting week 17 in April 2012, in comparison with the outbreak periods of 2006–2007 and 2009–2010. The current outbreak period 2011–2012 is characterised by an early increase of cases, which started already in October 2011. In the last reported week in 2012 (week 17), the number of cases (n=87) has almost reached the historical weekly maximum of the 2007 outbreak year (96 cases in week 22).

Figure 2 shows the geographical distribution of cases in Baden-Württemberg. Some 45% of all cases (n=580) were reported from five of the 44 counties of Baden-Württemberg. These counties are in the central part of the state, comprising the city of Stuttgart (n=65; incidence: 10.7 per 100,000 population), Tübingen (n=34; incidence: 15.4 per 100,000 population),

TABLE

Number and incidence of notified cases of hantavirus infection in each federal state, Germany, 2001–2012

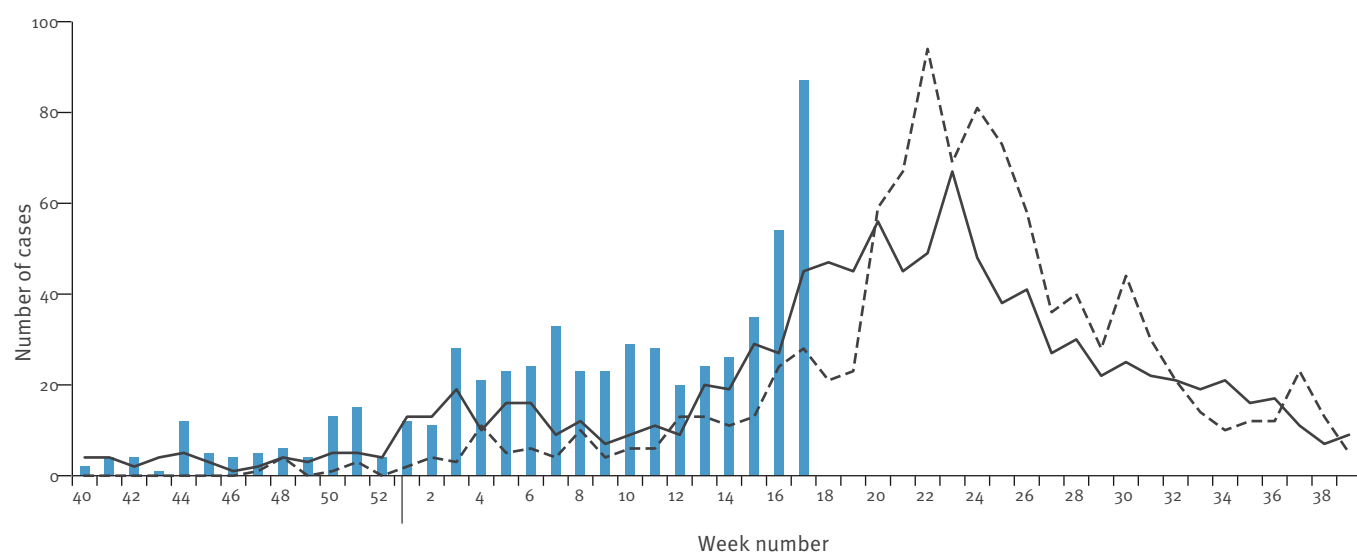
State	2001–2006		2007		2008	2009	2010		2011		2012	
	Median annual number of cases (range)	Median annual incidence (range)	Number of cases (incidence per 100,000 population)									
			Winter ^a	Annual	Annual	Annual	Winter ^a	Annual	Winter ^a	Annual	Winter ^a	2012 until week 17 ^b
Baden-Württemberg	87.5 (22–164)	1.02 (0.55–1.54)	172 (1.6)	1,090 (10.14)	74 (0.69)	83 (0.77)	327 (3.04)	998 (9.28)	61 (0.57)	128 (1.19)	580 (5.39)	501 (4.66)
Bavaria	23.5 (12–61)	0.24 (0.14–0.49)	38 (0.31)	296 (2.36)	41 (0.33)	21 (0.17)	86 (0.68)	437 (3.49)	45 (0.36)	46 (0.37)	65 (0.52)	43 (0.34)
Berlin	1 (0–2)	0.03 (0–0.06)	1 (0.03)	1 (0.03)	3 (0.09)	0 (0)	0 (0)	3 (0.09)	0 (0)	0 (0)	0 (0)	0 (0)
Brandenburg	0 (0–3)	0 (0–0.12)	1 (0.04)	4 (0.16)	3 (0.12)	0 (0)	0 (0)	2 (0.08)	2 (0.08)	6 (0.24)	4 (0.16)	0 (0)
Bremen	0 (0–1)	0 (0–0.15)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.15)	1 (0.15)	0 (0)	1 (0.15)	1 (0.15)
Hamburg	0 (0–1)	0 (0–0.06)	0 (0)	3 (0.17)	1 (0.06)	2 (0.11)	1 (0.06)	0 (0)	1 (0.06)	1 (0.06)	0 (0)	0 (0)
Hesse	10.5 (4–34)	0.21 (0.08–0.56)	3 (0.05)	27 (0.44)	12 (0.2)	4 (0.07)	31 (0.52)	174 (2.87)	10 (0.16)	13 (0.21)	23 (0.38)	19 (0.31)
Mecklenburg-Vorpommern	4 (1–8)	0.23 (0.23–0.46)	2 (0.12)	11 (0.65)	11 (0.66)	12 (0.73)	8 (0.48)	11 (0.67)	5 (0.3)	5 (0.3)	5 (0.3)	1 (0.06)
Lower Saxony	8 (3–75)	0.13 (0.04–0.94)	12 (0.16)	93 (1.17)	18 (0.23)	16 (0.2)	34 (0.43)	123 (1.55)	18 (0.23)	23 (0.29)	48 (0.6)	36 (0.45)
North Rhine-Westphalia	29.5 (18–143)	0.17 (0.11–0.79)	22 (0.12)	124 (0.69)	61 (0.34)	32 (0.18)	57 (0.32)	156 (0.87)	24 (0.13)	62 (0.35)	86 (0.49)	60 (0.34)
Rhineland-Palatinate	2.5 (2–10)	0.07 (0.05–0.25)	1 (0.02)	11 (0.27)	4 (0.1)	1 (0.02)	2 (0.05)	28 (0.7)	4 (0.09)	7 (0.17)	11 (0.27)	9 (0.22)
Saarland	0 (0–1)	0 (0–0.09)	0 (0)	2 (0.19)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	1 (0.1)	1 (0.1)
Saxony	1 (0–2)	0.02 (0–0.05)	0 (0)	5 (0.12)	1 (0.02)	0 (0)	2 (0.05)	3 (0.07)	1 (0.02)	3 (0.07)	7 (0.16)	6 (0.14)
Saxony-Anhalt	1.5 (0–3)	0.08 (0.04–0.12)	0 (0)	3 (0.12)	1 (0.04)	1 (0.04)	1 (0.04)	6 (0.26)	1 (0.04)	1 (0.04)	4 (0.17)	4 (0.17)
Schleswig-Holstein	1.5 (0–7)	0.04 (0–0.25)	3 (0.11)	10 (0.35)	6 (0.21)	9 (0.32)	6 (0.22)	11 (0.39)	7 (0.25)	6 (0.21)	3 (0.11)	1 (0.04)
Thuringia	2 (0–14)	0.12 (0.04–0.6)	1 (0.04)	8 (0.35)	7 (0.31)	0 (0)	4 (0.18)	63 (2.82)	4 (0.17)	4 (0.18)	14 (0.62)	11 (0.49)
Total	205 (72–447)	0.28 (0.17–0.54)	256 (0.31)	1,688 (2.05)	243 (0.3)	181 (0.22)	559 (0.68)	2,017 (2.47)	184 (0.23)	305 (0.37)	852 (1.04)	693 (0.85)

^a Winter is used to describe the period from week 40 of the preceding year to week 17, a period that coincides with the annual influenza season in Germany.^b Ending 27 April 2012.

Source: Robert Koch Institute [2], as of 16 May 2012.

FIGURE 1

Cases of hantavirus infection by week of reporting, Baden-Württemberg, Germany, October (week 40) 2011–April (week 17) 2012 and weeks 1–39 for outbreak years 2007 and 2010, and from week 40 in 2006 and 2009 (years preceding outbreaks)

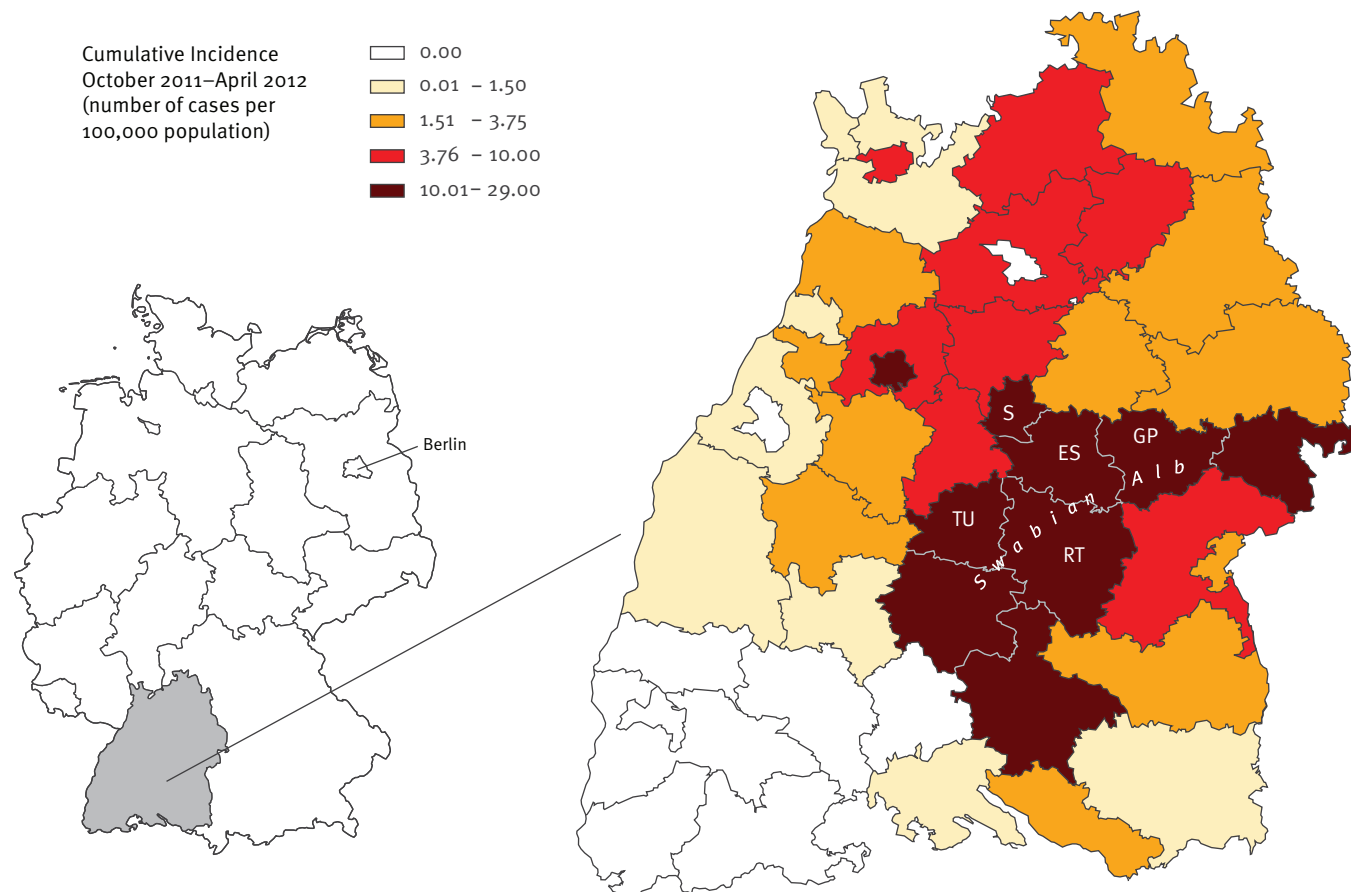


The bars show the number of cases reported during 3 October 2011 to 27 April 2012 (n=580). The broken line shows the number of cases from week 40 2006 to week 39 2007. The continuous line shows the number of cases from week 40 2009 to week 39 2010.

Source: Robert Koch Institute [2], as of 16 May 2012.

FIGURE 2

Geographical distribution of cases of hantavirus infection, by county and cumulative incidence, Baden-Württemberg, Germany, 3 October (reporting week 40) 2011–27 April (week 17) 2012 (n=580)



ES: Esslingen; GP: Göppingen; RT: Reutlingen; S: Stuttgart; TU: Tübingen.

Source: Robert Koch Institute [2], as of 16 May 2012.

Esslingen (n=53; incidence: 10.3 per 100,000 population), Reutlingen (n=62; incidence: 22.1 per 100,000 population) and Göppingen (n=71; incidence: 28.1 per 100,000 population). The last four counties are located in a hantavirus-endemic area lining the Swabian Alb, a low limestone mountain range covered by small forests and fields. Within all five counties, the cases were clustered in several municipalities (data not shown).

Of all the cases notified in Baden-Württemberg, 72% were male (418 of 578 cases with information on sex reported). The highest incidences were observed among persons between 20 and 59 years (Figure 3).

On the basis of preliminary data, the most common symptoms reported were fever (86%), renal impairment (75%), headache (51%) and back pain (23%). Some 69% of all cases were hospitalised. Where indicated (in 52% of the hospitalised cases), the median length of stay in hospital was five days (range: 1–20). No deaths were reported.

Information related to potential exposure was available for 39% of the cases. Most frequently mentioned were cutting and piling wood, spending time in a forest for leisure (hiking, hunting) or forestry work, contact with rodents or rodent excreta, especially during cleaning in barns, sheds, attics, cellars, garden houses, garages, etc.

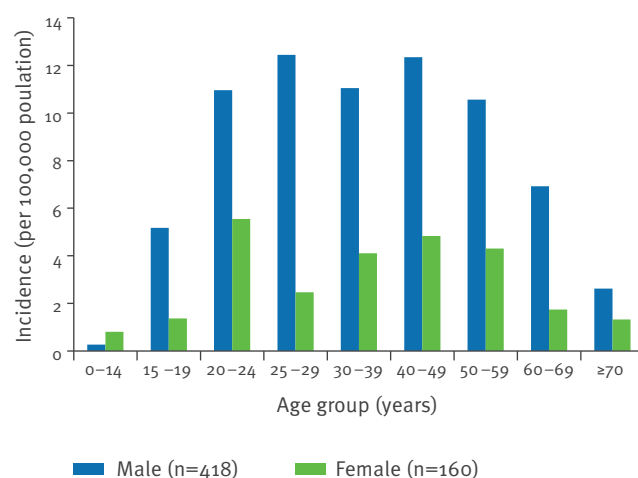
Discussion

Previous outbreaks of hantavirus infection in Baden-Württemberg in 2007 and in 2010 started in the first months of the year and peaked from May to June [11]. The early and intense increase in case numbers since October 2011 is without precedence. Early in 2012, the public was informed of the outbreak and recommended prevention measures [12,13] via media releases published state-wide on 13 January and 9 March 2012. Updated releases were also disseminated to local community-based media and physicians. However, data on the public's knowledge and the effectiveness of preventive measures against Puumala virus infections are lacking and are the subject of a separate study.

The causes for the early increase of case numbers remain unclear. Current hypotheses relate the rising incidence of Puumala virus infections to changes in the population density of bank voles, due to climatic factors [12] and possibly to the beech mast in 2011. During mast years, deciduous trees produce exceptionally high quantities of seeds, an important food source for bank voles [14]. Mast years and hantavirus outbreaks appear to be associated [15,16]. In Baden-Württemberg, the beech mast years of 2006 and 2009 were followed by outbreaks of human hantavirus infections in 2007 and 2010. Last year (2011) was again an exceptional mast year [17], followed by a remarkably mild winter [18]. This may have promoted winter survival and reproduction of bank vole populations.

FIGURE 3

Cumulative incidence of cases of hantavirus infection by age group and sex, Baden-Württemberg, Germany, 3 October (reporting week 40) 2011–27 April (week 17) 2012 (n=578)^a



^a Cases with information on sex reported.

Source: Robert Koch Institute [2], as of 16 May 2012.

Since spring 2010, the Julius Kühn-Institute (Federal Research Centre for Cultivated Plants) and Friedrich-Loeffler-Institute (Federal Research Institute for Animal Health) have been conducting monitoring studies in an area of Böblingen County, Baden-Württemberg, an endemic region for hantavirus. Trapping results showed a peak mean bank vole population density of 63 ± 46 individuals per hectare ($N \pm$ standard error/ha) in October 2011. In April 2012, the mean bank vole population density had increased to 76 ± 23 /ha (D. Reil, unpublished data). This study indicated considerable recruitment of bank voles, either through winter reproduction or migration. Serological and molecular studies in bank voles from this monitoring site demonstrated a continuous presence of Puumala virus during 2010 and 2011 and an increased Puumala virus seroprevalence in spring 2012 (U.M. Rosenfeld, unpublished data).

We anticipate a further increase in cases numbers during summer 2012. This necessitates additional public service information on prevention measures. Further studies have been initiated to correlate habitat factors of the bank vole reservoir with human exposure and behavioural data, to better understand the reasons for this early increase in case numbers. They will also examine possibilities for preventive measures that can be more efficiently communicated – and are at the same time effective and acceptable – to the population at risk.

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Increased number of cases of haemorrhagic fever with renal syndrome in Slovenia, January to April 2012

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Haemorrhagic fever with renal syndrome is endemic in parts of Slovenia. Since 1999, in January to April each year, the number of notified cases has generally been low ($n=0-6$). A high number of cases ($n=26$) in the first four months of 2012 has been observed, similar to that seen in the same period in 2008 ($n=14$). Given the increase in the number of cases at the start of 2012, we can expect a high number of cases this year.

Situation at the beginning of 2012

From 1 January to 18 April 2012, 26 cases of haemorrhagic fever with renal syndrome (HFRS) were notified in Slovenia: 7 in January, 6 in February, 3 in March and 10 in April. The patients (19 male, 7 female) ranged in age from 21 years to 75 years (interquartile range: 33–57 years). This number of cases for the four-month period is unusually high and may herald an increased number of cases this year.

Background

Viruses of the genus *Hantavirus*, family *Bunyaviridae*, are the causative agents of HFRS. They are most commonly acquired from inhalation of aerosolised excreta from acute and chronically infected rodent hosts [1]. The disease is characterised clinically by the triad of fever, haemorrhage and renal insufficiency. A person with mild disease presents non-specific symptoms: headache, back and abdominal pain, fever, chills and nausea. Severe disease might involve severe pulmonary impairment, disseminated encephalomyelitis and renal dysfunction; in cases with severe disease, the case fatality rate is high, varying from less than 1% to 12%, depending on the causative viruses [2].

The disease was first reported in Slovenia in 1954 [3]. Since then, cases have occurred sporadically or in small epidemics [3]. Mandatory reporting of laboratory-confirmed HFRS cases is enforced by the Contagious Diseases Act issued in 1995. Both mild and severe clinical courses of the disease have been observed, with an overall mortality rate of 3.3% [4].

Dobrava and Puumala viruses – two hantaviruses that cause HFRS – have been shown to coexist in Slovenia

[3]. There are considerable differences in disease severity as well as mortality due to infection with these viruses: all fatal HFRS cases in the country to date have been caused by infection with Dobrava virus, giving an 8.3% mortality rate for Dobrava virus-associated HFRS [4]. Infection with Puumala virus usually results in a milder disease course [5].

Since 1999, all HFRS cases have been laboratory confirmed at the National Reference Laboratory (at the Institute of Microbiology and Immunology, in the Faculty of Medicine at the University of Ljubljana): the laboratory notifies clinicians of the cases (immediately), as well as the regional epidemiologist (within three days) and the National Institute of Public Health (on a weekly basis).

Although HFRS patients have been found throughout the country, most of them have been reported in the endemic regions of Novo Mesto, Murska Sobota and Ljubljana. The Figure shows the mean annual incidence of notified HFRS cases from 1999 to 2011 by region.

Surveillance data show that in 1999–2007 and 2009–2011 the number of cases was low ($n=0-6$) in the first four months of each year (Table). In 2008 [6] and 2012, the number of cases in the first four months of the year was higher (14 and 26, respectively).

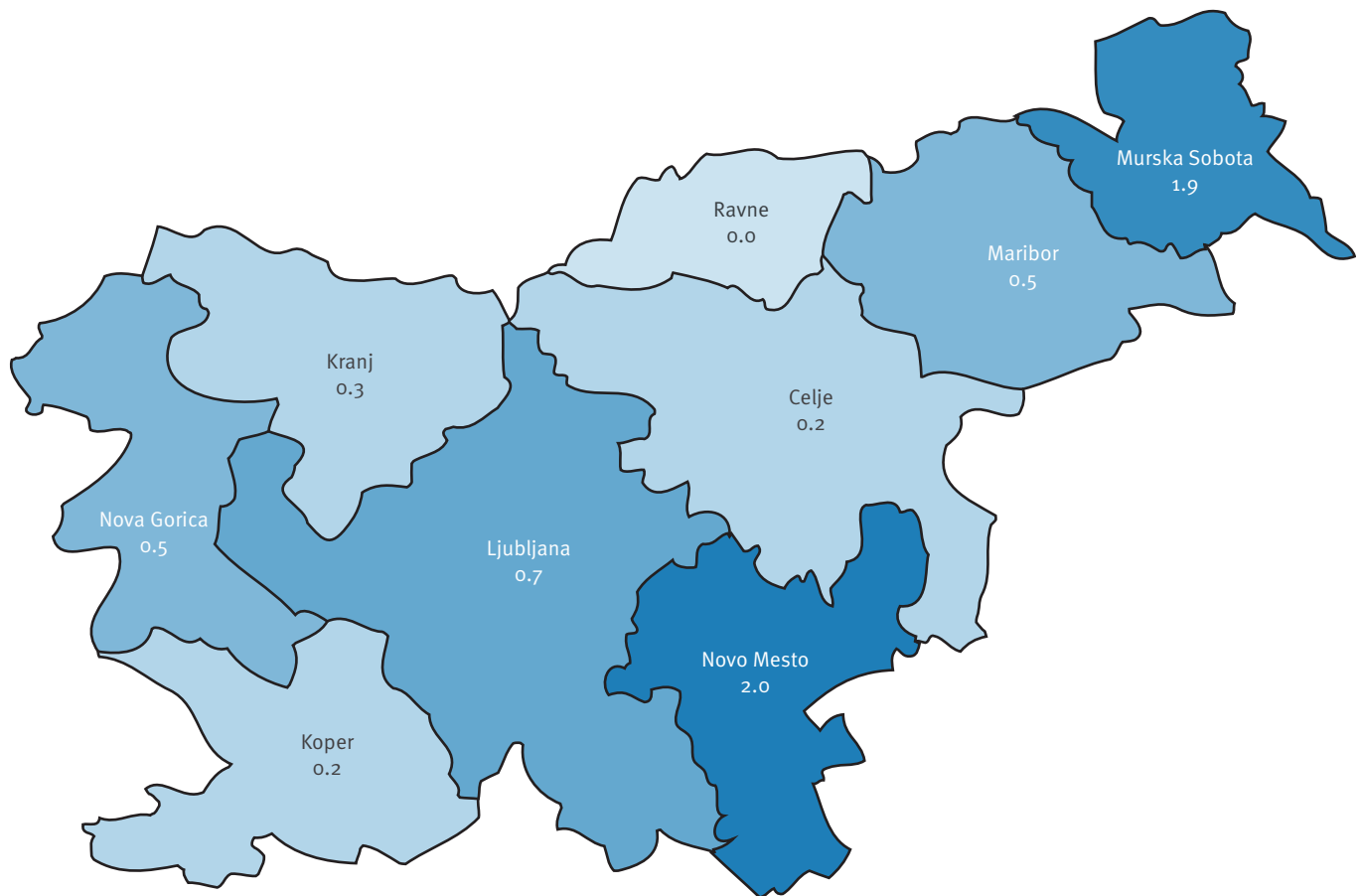
Epidemiological investigation of cases notified in 2012

All notified HFRS cases in 2012 were hospitalised. The infections were laboratory confirmed by indirect immunofluorescent antibody (IFA) test for detection of serum IgG antibodies and by enzyme-linked immunosorbent assay (ELISA) for detection of serum IgM antibodies [4]. The tests were performed by the National Reference Laboratory: the diagnostic procedures carried out have not changed since 1999.

In all 26 cases, the infectious agent was Puumala virus: it was identified in blood samples taken during the acute phase of disease by reverse transcription-PCR followed by direct sequencing of the PCR product [7,8].

FIGURE

Mean annual incidence of notified cases of haemorrhagic fever with renal syndrome, by region, Slovenia, 1999–2011 (n=182)



Mean annual incidence per 100,000 population per region is shown. The shading illustrates the regional variation in incidence.

Epidemiological investigation of the 26 cases involved visiting and interviewing them using a standardised questionnaire on exposure possibilities (including demographic data, epidemiological exposure history, sign and symptoms, laboratory tests, complications and outcome). This revealed that the work activities carrying potential risk for 18 of the patients living in the countryside were cleaning and working in barns and woodsheds, stocking corn and woodcutting. The work activities carrying potential risk for eight patients living in urban areas were cleaning basements and gathering firewood.

Eight of the patients (in rural and urban areas) reported having seen mice excreta.

Discussion

Since 1999, with the exception of 2008, the majority of HFRS cases each year have been reported in late spring and summer. Probable reasons for the increase in the number of HFRS cases in the first four months of 2012,

as in 2008, are the mild winter and an abundance of available oak and beech seeds in the preceding summer and autumn. The bank vole (*Myodes glareolus*), the principle vertebrate host for Puumala virus, and the yellow-necked field mouse (*Apodemus flavicollis*), the principle vertebrate host for Dobrava virus, are predominantly seed eaters [9].

Given the viral hosts and mode of transmission, one of the most important preventive measures is rodent control (use of traps, deratisation) in and around human dwellings [10]. In addition, minimising food available to rodents around residential areas is known to effectively reduce the rodent population [10]. To date, no systematic deratisation has been necessary.

Information on the increased occurrence of HFRS cases in 2012 has been provided to general practitioners, infectologists and nephrologists by regional epidemiologists by email.

TABLE

Notified cases and annual incidence of haemorrhagic fever with renal syndrome, by month, Slovenia, 1 January 1999–18 April 2012 (n=208)

Year	Month												Total	Annual incidence ^a per 100,000 population
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec		
1999	0	0	0	0	2	2	0	1	0	0	0	0	5	0.3
2000	1	0	1	1	2	1	1	1	0	0	0	0	8	0.4
2001	1	0	0	1	1	0	0	2	0	0	0	0	5	0.3
2002	1	1	0	4	3	8	5	3	1	1	0	0	27	1.4
2003	1	0	0	0	0	0	0	1	0	0	1	1	4	0.2
2004	2	0	0	2	1	1	2	3	0	1	0	2	14	0.7
2005	1	0	2	1	2	2	7	2	2	1	0	0	20	1.0
2006	1	0	0	0	1	0	0	0	0	0	0	1	3	0.1
2007	0	0	0	2	1	1	2	1	5	2	0	0	14	0.7
2008	2	1	5	6	6	11	6	4	1	3	0	0	45	2.2
2009	0	0	0	1	1	2	0	0	0	0	1	0	5	0.2
2010	2	0	0	0	1	1	2	2	5	1	1	2	17	0.8
2011	0	0	0	0	1	1	2	1	1	3	4	2	15	0.7
2012	7	6	3	10	–	–	–	–	–	–	–	–	26	1.3
Total	19	8	11	28	22	30	27	21	15	12	7	8	208	–

^a For 2012, from 1 January to 18 April only.

Information on general hygiene and how to avoid contact with rodent urine, droppings, saliva and nesting materials, and the safety measures to be followed when cleaning rodent-infested areas has been widely spread through the local media and Internet [11].

In the light of our experience since 1999 – and in particular, the increased number of HFRS cases in 2008, with 14 cases in the first four months and a total of 45 cases at the end of the year – we can also expect a high number of cases by the end of 2012.

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W135 invasive meningococcal infections imported from Sub-Saharan Africa to France, January to April 2012

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From January to April 2012, 16 cases of W135 invasive meningococcal infection were reported in France. Of these, eight were linked to a recent travel history to Sub-Saharan Africa. These cases were reported in France concomitantly with the meningitis epidemic season in Sub-Saharan Africa. Considering the high number of travellers between France and West-African countries belonging to the so-called meningitis belt, the French recommendations for travellers stress the importance of vaccination before travelling to these countries.

In mid-February 2012, two W135 invasive meningococcal disease (IMD) cases were reported in two French regions (Pays de la Loire and Rhône-Alpes) in persons having recently returned from Senegal. The first case had arrived in France on 12 February and was hospitalised three days later. The second case arrived on 19 February and was hospitalised on the same day. No connection could be established between the two cases but they had both visited the same region in Senegal (near Mbour) and they were both working with non-governmental organisations (NGOs).

In France, the annual mean incidence of IMD varies between 0.9 and 1.5 cases per 100,000 population. Cases are mainly due to serogroup B and C meningococci (65% and 27% respectively for the last 10 years). Serogroup W135 is rare in France; sporadic cases were reported in the 1990s (less than five cases per year) and they mainly belonged to the clonal complexes ST-11 and ST-22 (French National Reference Centre for Meningococci (NRCM), unpublished data). However, this serogroup underwent a clonal expansion in France and other European countries in 2000, during the first reported multinational outbreak of serogroup W135 *Neisseria meningitidis* infections belonging to a particular clone of the ST-11 clonal complex. This outbreak started among pilgrims to Mecca and their contacts [1] and then affected Sub-Saharan countries (mainly Burkina Faso) [2,3]. Following a peak of incidence in 2002 with 42 reported cases, the incidence of W135 (ST-11) IMD cases decreased in France and the W135

cases were most frequently due to isolates belonging to the clonal complex ST-22 representing in 2011 less than 3% of the cases with known serogroup (14/542) (NRCM, unpublished data).

Investigation of W135 meningitis cases in 2012

In 2012, the epidemic meningitis season, which coincides annually with the dry season between December and June, had already started in the so-called meningitis belt when the two W135 cases imported from Senegal were notified. Therefore we collected information regarding recent travel for all the W135 IMD cases that occurred in France since the beginning of the year.

Between 1 January and 1 April 2012, a total number of 16 IMD cases were notified in France. This is an important increase if compared to the previous five years when only four to eight W135 cases were reported each year during the first five months.

All 16 cases reported this year were laboratory-confirmed through isolation of *N. meningitidis*, positive PCR or detection of *N. meningitidis* antigens. The median age of cases was 45 years (range: 2 months to 89 years) and the M:F ratio was 9:7. None of the 16 cases had been vaccinated with a tetravalent A/C/Y/W135 meningococcal polysaccharide vaccine.

For eight of the 16 cases, a link to Sub-Saharan Africa was identified: two had returned from Senegal in February, one had arrived from Mali four days before the disease onset and one arrived from Senegal 15 days before the disease onset. The other four cases did not travel during their incubation period but a recent travel history was found for their close contacts: to Benin for one case, to Mali for two cases and to Senegal for one case with dates of return to France within the three weeks before the disease onset of the case. The purpose of travel was visiting friends and relatives for six cases or contacts and working for NGOs for two.

Considering an incubation period of 10 days, the dates of arrival in France and onset of the disease, three of

the eight cases could be considered as imported. The remaining five cases may have been infected by asymptomatic contacts carrying an imported strain. However, strains were not investigated among contacts.

Among the eight cases, four cases presented with meningitis, two with pneumonia and septicaemia, one with arthritis, and one with pericarditis. No death was registered among the cases.

As of 24 May 2012, no other W135 IMD case has been notified since 1 April 2012.

All eight 'possibly import-related' W135 IMD cases were caused by the same strain, characterised at the NRCM in Paris by multilocus sequence typing, *PorA* variable regions (VR1 and VR2), *penA* and *fetA* genes. The antigenic formula was W135:2a:P1-5,2, the genetic typing showed *porA* VR1=5, VR2=2, *fetA*=F1-1, *penA*=1, and the strains were ST-11.

Conclusions

The increase of serogroup W135 meningococcal disease incidence in France in early 2012 was concomitant to the meningitis epidemic season in Sub-Saharan Africa. From 1 January to 15 April 2012, almost 15,000 meningitis cases have been reported in West Africa to the World Health Organization. In some countries (e.g. Burkina Faso, Côte d'Ivoire, Ghana, Mali, Niger) the serogroup W135 was predominant among cases for which *N. meningitidis* has been identified whereas serogroup A was predominant in other countries like Chad [4]. Serogroup W135 has increased in Niger in 2010 [5]. No laboratory results were available from Senegal.

The French NRCM typed eight isolates from Côte d'Ivoire. These bacteria were isolated in February 2012 in three different districts of the country. All the isolates from France and Côte d'Ivoire shared the same tested markers (*porA* VR1=5, VR2=2, *fetA*=F1-1, *penA*=1, ST-11) (unpublished data). Eight other cases of W135 cases were also isolated in France during the same period but they reported no travel history during the previous three months. All these isolates also showed different markers (unpublished data).

Further investigations are required including typing isolates from other countries within the meningitis belt and comparing results with isolates from the previous years in order to help understanding this recent re-emergence of W135/ST-11 isolates. A long-lasting establishment of this serogroup in sub-Saharan African countries may prompt re-considering the vaccination strategies in the belt upon the introduction of the conjugate vaccine against serogroup A [6].

In the meantime, specific surveillance should be enhanced in Europe and recommendations for travellers who have contacts with population in high-incidence countries should be updated taking into account that

non-pilgrimage-related travel is rarely associated with transmission and that the purposes of travel described above for the cases themselves or their asymptomatic contacts were visits to family members and friends or work for NGOs [7]. Since there are frequent travellers between France and West-African countries belonging to the meningitis belt, the French recommendations for travellers insist on the importance of vaccination with a quadrivalent A/C/Y/W135 vaccine (preferably a conjugate vaccine) when travelling to these countries [8].

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Emergence of West Nile virus infections in humans in Turkey, 2010 to 2011

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In 2010, 47 human cases of West Nile virus (WNV) infection, including 12 laboratory-confirmed and 35 probable cases, were identified in Turkey. These were the first cases detected during routine surveillance. The patients were from 15 provinces, mainly located in the western part of the country. Incidence was 0.19/100,000 with a maximum of 1.39 in Sakarya province. Forty of the total 47 cases showed neuroinvasive manifestation. Median age was 58 years with a range of four to 86. Ten of the patients died. Enhanced surveillance in humans and animals and mosquito control measures were implemented. The WNV infections were included in the national notifiable diseases list as of April 2011. In 2011, three probable and two confirmed cases of WNV infection were diagnosed in provinces where infections had been detected in the previous year, supporting a lower activity than 2010. However, detection of WNV infections in humans in 2010 and 2011 consecutively, may indicate that WNV has become endemic in the western part of Turkey. Field epidemiological studies were undertaken to understand more about the nature of infection in Turkey.

Introduction

On 12 August 2010, the Manisa Provincial Health Directorate and the Ministry of Health in Turkey were informed about an increase in the number of hospitalised patients with encephalitis-like symptoms of unknown etiology. A preliminary case definition based on the clinical picture, and a case management algorithm were immediately set up by a Scientific Commission at national level, consisting of experts from universities and from the Ministry of Health (MOH), and sent to provincial health facilities. A viral infection including possibly West Nile virus (WNV) was suspected. According to the case management algorithm, the blood and cerebrospinal fluid (CSF) samples of suspected cases were sent to national reference laboratories, Refik Saydam

National Public Health Agency (RSNPHA) and Ankara University Faculty of Veterinary Medicine, for further analysis. Of 12 suspected cases from Manisa province, three tested positive for WNV infection by serology and neutralisation, while another showed a WNV-specific antibody response in a serum sample. These were the first acute human WNV infection cases documented in Turkey. Prior to this first cluster of WNV cases, WNV infections were not notifiable in Turkey. Neuroinvasive cases were probably diagnosed as 'viral meningitis' and not investigated further.

At the time when the first cluster of human WNV cases was determined in Turkey, human cases were also reported from Greece, Russia and Israel as well as equine cases from Morocco [1,2]. In 2010, human WNV infection epidemics in Europe occurred in Greece, Italy and Romania. In Greece, 262 probable and confirmed cases were reported, including 197 neuroinvasive cases and 33 deaths [2]. In Romania, a total of 57 cases of WNV infection (54 with neuroinvasive infection and three febrile cases) were identified between July and October 2010 [3]. In Italy, human cases of WNV infection, including three confirmed cases of neuroinvasive disease and three confirmed cases of West Nile fever were identified in the north-eastern part of country and they were detected through the enhanced regional surveillance plan for West Nile fever [4]. In 2010, WNV infections in humans were also reported from other European countries, such as Hungary (15 cases), Portugal (1 suspected case) and Spain (1 confirmed case) [5].

The 2011 West Nile virus season started in July in Europe, with 96 confirmed human cases reported by the end of the season (November). As of 24 November 2011, 93 confirmed human cases of West Nile fever had been reported in the European Union: 69 cases

in Greece, 14 in Italy and 10 in Romania. In the neighbouring countries, 189 cases had been declared: two in Albania, four in the Former Yugoslav Republic of Macedonia, 33 in Israel, 136 in the Russian Federation, three in Tunisia, three in Turkey and eight cases in Ukraine [6,7].

This study describes the human WNV infection cases identified in Turkey between July 2010 and December 2011.

Methods

Surveillance

In August 2010, following the detection of seven cases with encephalitis-like symptoms including one fatal case, the Ministry of Health issued an alert and strengthened the surveillance by formulating a case definition, and case and laboratory management algorithms. The initial case definition set up by the Scientific Commission was highly sensitive including non-neuroinvasive features such as skin rash. Once WNV infection had been established as cause, the case definition was revised and structured on identifying neuroinvasive disease. A standardised reporting form was developed including information on basic demographic characteristics, clinical manifestations and findings, main risk factors and underlying conditions.

In April 2011, WNV infections were included in the national notifiable diseases list with a case definition adapted from the European Union case definition for reporting communicable diseases to the Community network [8].

In addition to the national routine surveillance in the 2011 season, starting in July, the Health Directorates of Edirne, Manisa, Sakarya and Mugla provinces implemented active surveillance with an enlarged case definition including influenza-like illness to detect asymptomatic or subclinical cases of WNV infection.

Seropositivity study

Following the peak of WNV season, in October 2010, a seropositivity study was conducted on people living in close proximity to cases, in three provinces which showed high incidence. The aim of the study was to collect serum samples from persons who shared similar ecological conditions with WNV infection cases.

Case definition

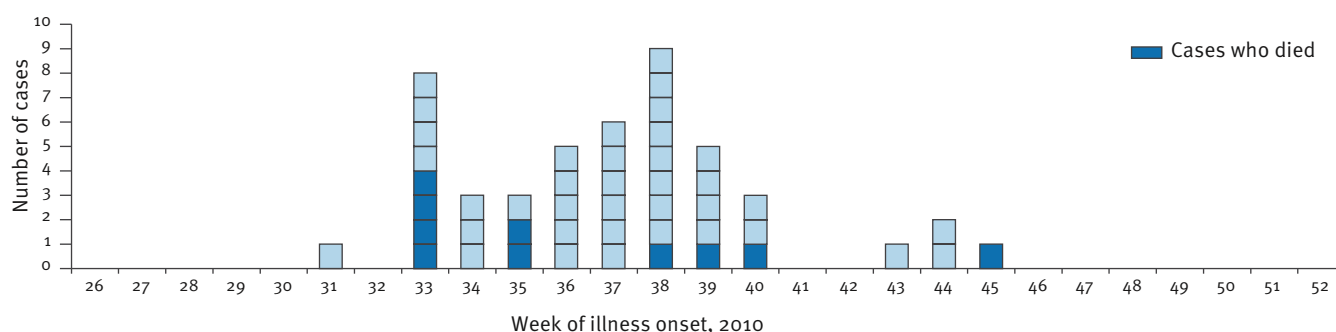
People presenting fever with unknown etiology and at least one of the clinical signs or findings of meningitis or encephalitis or meningoencephalitis or myelitis, such as sudden alteration of mental status, acute signs of central or peripheral neurological dysfunction, stiffness of neck, acute flaccid paralysis or cranial and peripheral neuritis, other neuropathies including Guillain–Barré syndrome were considered ‘suspected’ and tested for WNV-specific IgM and IgG antibodies with enzyme-linked immunosorbent assay (ELISA) or immunofluorescence test (IFA). The first 12 positive cases by IFA were analysed with plaque-reduction neutralisation test (PRNT) which was used for confirmation.

A case was considered as ‘probable’ if WNV-specific antibody response was demonstrated in their serum sample by ELISA and IFA, and ‘confirmed’ if PRNT was positive or specific IgM antibodies were detected in the CSF or an increasing titre of WNV-specific IgM was demonstrated in their serum sample. The cases presenting clinically with meningitis/encephalitis or meningoencephalitis were considered as having neuroinvasive disease.

An exception in diagnosis was made for a deceased patient where the sample was negative in ELISA and IFA. It was further analysed with PRNT as there was no chance of assessing seroconversion. The patient was accepted as a confirmed case, as PRNT was found positive.

FIGURE 1

Reported cases of West Nile virus infections by onset of illness, Turkey, 28 June–31 December 2010 (n=47)



TABLE

Number and incidence of reported cases of West Nile virus infections by age group and province of residence, Turkey, July–November 2010 (n=47)

Characteristic	Number of cases	Incidence (per 100,000 population)
Age group (years)		
<20	8	0.10
20–29	3	0.07
30–39	1	0.03
40–49	6	0.19
50–59	8	0.33
60–69	4	0.28
70–79	12	1.29
≥80	5	1.63
Province of residence		
Ankara	1	0.02
Adana	1	0.05
Antalya	1	0.05
Kocaeli	1	0.06
Afyon	1	0.14
Konya	3	0.15
Manisa	2	0.15
Izmir	8	0.21
Isparta	1	0.24
Balikesir	3	0.26
Diyarbakir	4	0.26
Aydin	4	0.41
Karaman	1	0.43
Mugla	4	0.50
Sakarya	12	1.39
Total	47	0.19

Laboratory methods

Acute and convalescence period serum samples were collected from all suspected cases upon the first day of hospitalisation, within 8 to 14 days and at 21 days after the onset of illness to be tested by ELISA and IFA to find IgG and IgM antibodies against WNV, and by PRNT to detect specific neutralising antibodies. The samples were transported at +4°C and stored at -25°C until testing. Serological tests were performed by the national reference laboratory (RSNPHA), Virology Reference Laboratory, Novel and Dangerous Pathogens Unit in Ankara. Samples were analysed by using West Nile virus ELISA and IFA tests (anti-West Nile virus ELISA IgG and IgM Euroimmun, Lübeck Germany; IIFT Flavivirus Mosaic 1 IgG ve IgM Euroimmun, Lübeck Germany). Tests were performed according to the protocol of the manufacturer.

IFA test contained antigens to Flavivirus Mosaic 1 (Euroimmun, Lübeck Germany), tick-borne encephalitis virus (TBEV), yellow fever virus (YFV), West Nile virus (WNV) and Japanese encephalitis virus (JEV).

In order to detect and/or discriminate WNV specific neutralising antibodies, PRNT was performed as a confirmation test by the Virology Department in the Faculty of Veterinary Medicine, Ankara University. The test was carried out as previously described by Ozkul et al, 2006 [9], using WNV/NY99 strain (200 plaque forming units (PFU) per reaction). Serum samples that neutralised the challenge virus > 70% were regarded as seropositive.

Data analysis

Data were analysed using SPSS 15.0 software package, CHICAGO, IL, RSHMB 9887381. Incidence was calculated using 2009 Address Based Population Registration System from the Turkish Statistical Institute as denominator [10]. Towns with more than 20,000 inhabitants were considered as urban areas while others were considered as rural, according to the definitions of the Turkish Statistical Institute. Information on animal health was gathered from the surveillance data of the Ministry of Food, Agriculture and Husbandry.

Results

Surveillance data 2010

From July to November in 2010, 47 cases of WNV infection were detected, 40 with central nervous system manifestations, seven with non-neuroinvasive symptoms. Of these 47 cases, 35 were probable, 12 were confirmed. The overall incidence of WNV infections was 0.19 cases per 100,000 population, with the maximum of 1.39 in Sakarya province.

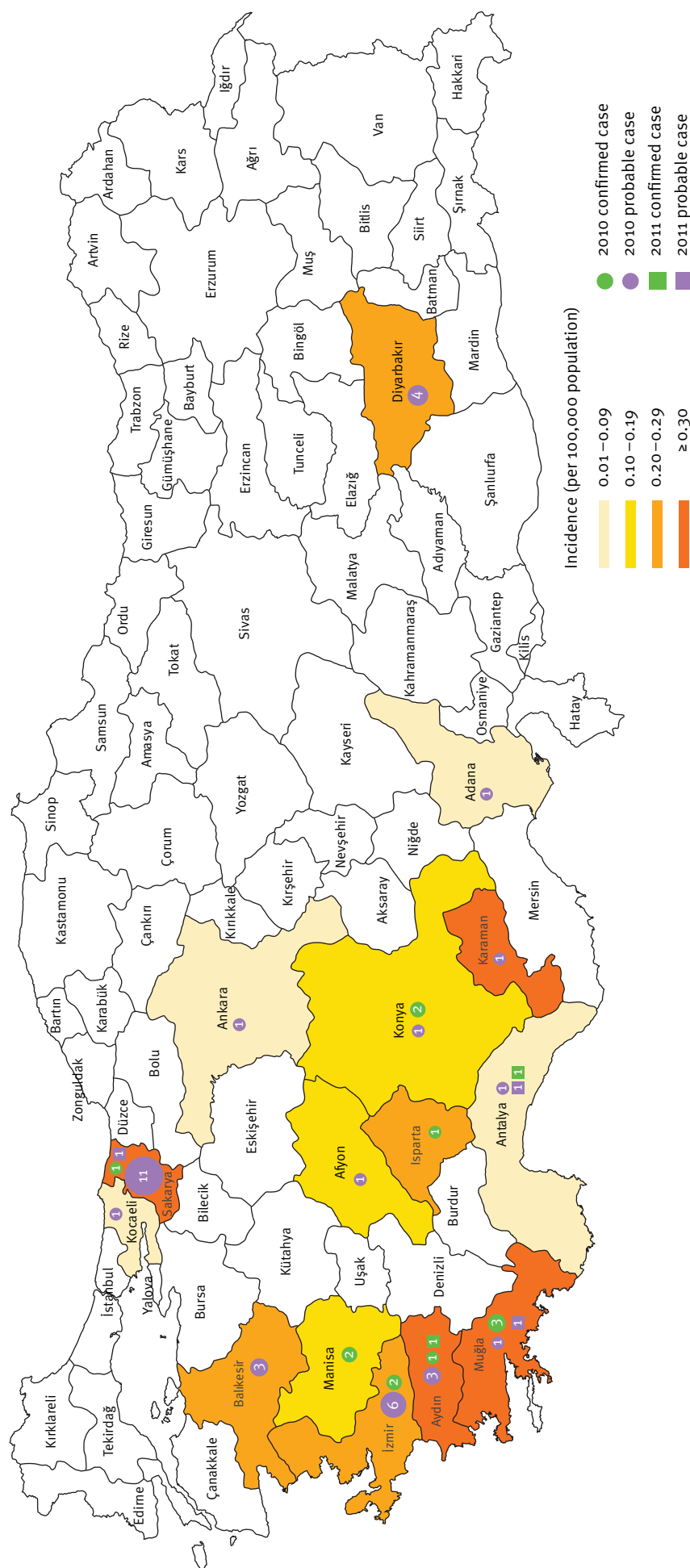
The first cases of WNV infection had onset of symptoms in late July and early August in 2010 (Figure 1). The cases cumulated between the second week of August and last week of September. The last case had onset of illness in the second week of November.

Some characteristics of reported WNV infection cases are shown in the Table. The median age of WNV infections cases was 58 years and the range four to 86 years, with most (n=17) aged 70 years or older. The highest incidence was in the age group of 80 years or older and was 1.63 cases per 100,000 population. Of all WNV infection cases, 32 were males.

The place of residence of WNV infection cases is presented in the Table and in Figure 2. The WNV cases were from 15 provinces, mainly from the western part of the country. The highest incidence was in Sakarya province with 1.39 cases per 100,000 population, followed by Mugla, Karaman and Aydin provinces with incidences ranging from 0.4 to 0.5 cases per 100,000 population. The incidence was higher in the western part of the country except for Diyarbakir province which is located in the south-east of Turkey. The incidences of urban and rural areas were 0.22 and 0.27 (per 100,000) respectively.

FIGURE 2

Number of West Nile virus cases in 2010 (n=47) and 2011 (n=5) and incidence in 2010 according to province of residence in Turkey, 2010–2011



All WNV infection cases were hospitalised while four of them needed to be treated in intensive care units. The first attended service was mainly the emergency unit (58%). The average length of stay in hospital was 19.6±21.5 days (range: 2–120 days).

The most common symptoms were fever (n=40), headache (n=34) and nausea/vomiting (n=30). The alteration of consciousness (n=23), convulsion (n=6) and fainting (n=5) were also observed.

Of the 47 cases, 10 died. Case fatality rate was 21%. The median age was 76 in deceased patients with the range of 25 to 86. Four of the fatal cases were residing in rural areas and six had underlying conditions such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease and psychiatric diseases.

WNV-specific IgM antibodies were detected in all 47 sera, while WNV-specific IgG antibodies were detected in 36 of 47 serum samples. The CSF samples could only be obtained from 10 of the patients whose serum samples were positive for IgM antibodies, but none of the CSF samples demonstrated positivity. The initial 12 serum samples that demonstrated WNV-specific antibody positivity with ELISA and IFA were tested with PRNT and all of them were found positive.

Surveillance data 2011

In 2011, three probable and two confirmed cases of WNV infections were identified in Turkey. The confirmed cases showed increasing titres of IgM WNV-specific antibodies. The probable cases were from Mugla, Sakarya and Antalya, the confirmed cases were from Aydın and Antalya Provinces, all of which had been affected in 2010. Two of the probable cases were identified through active surveillance that was conducted in Mugla and Sakarya in which influenza-like illness was included in the case definition. One of these two cases did not present any neurological manifestation. The WNV infection cases had an onset of illness between 5 and 25 August 2011. The places of residence of reported WNV infection cases are shown in Figure 2.

Seropositivity study in Mugla, Sakarya and Manisa provinces, October 2010

In addition to routine surveillance, a seropositivity study was conducted in three provinces (Mugla, Sakarya and Manisa) in October 2010, following the peak of epidemics. A total of 213 serum samples were collected, 40 from Mugla, 69 from Sakarya and 104 from Manisa provinces. The samples were analysed by ELISA and IFA in the national reference laboratory. Thirteen samples of 40 were seropositive in Mugla, 15 of 69 in Sakarya and four of 104 in Manisa (unpublished data from Refik Saydam National Public Health Agency).

Equine cases notified in 2010

Besides human cases, WNV infection was detected in two horses in Izmir province in September 2010. The equine cases were confirmed by neutralisation test performed by the Virology Department in the Faculty of Veterinary Medicine, Ankara University. These cases were notified by the Ministry of Food, Agriculture and Husbandry to the Ministry of Health. Both horses were from a private stud farm in Izmir Province, close to Manisa Province where the first cluster of human cases was determined. One of them died and the other one recovered without any complication. The Ministry of Food, Agriculture and Husbandry invited relevant sectors for an enhanced collaboration to reciprocally share information [11].

Discussion and conclusions

In Turkey, the first studies on the presence of arboviral infections in humans were carried out in the 1960s. In 1980, a study was performed in the western part of Turkey (Aegean) which presented 29.1% WNV seropositivity [12]. In recent studies from 2007 and 2010, WNV seropositivity was found to be 9.4% in the South-East and 0.56% in Central Anatolia for blood donors, while a 9.2% IgM and 3.4% IgG seropositivity were detected in patients with aseptic/viral meningitis/encephalitis [13–15].

Until 2010, WNV infections in humans had been subject to only field and clinical surveys in the country [12–15]. The infection had not been documented among routine health services until then. It was mainly because the infection was not a notifiable disease in Turkey. Other reasons are considered to be clinicians' lack of attention to most common forms of WNV infection which are asymptomatic or mild, and difficulties in laboratory diagnosis. As of April 2011, human WNV infections were included to the national notifiable diseases list.

The 2010 and 2011 cases of WNV infections in Turkey were observed in several provinces mostly in the western part. However, the previous studies had suggested that WNV infection was more widespread affecting other parts of the country such as Central Anatolia and the South-East [12–15]. Inclusion of WNV infections into national surveillance system covering the whole country and increasing awareness are expected to support the detection of cases in other regions of the country. On the other hand, detection of WNV infections in humans in 2010 and 2011 consecutively, may indicate that WNV has become endemic in the western part of Turkey.

The two cases of WNV infections in 2011 were identified through active surveillance conducted in four provinces. The case definition used in active surveillance included non-neuroinvasive symptoms in addition to neuroinvasive manifestations. As most human infections are asymptomatic and only 20% of infected WNV cases demonstrate clinical symptoms [16] it is

estimated that the number of cases was higher than that reported.

The veterinarian surveillance of WNV is limited in Turkey. There are few studies indicating WNV activity in animals. The first seroepidemiological evidence for the presence of arbovirus infections in animals was demonstrated in the 1960s. In 2005, Ozkul et al found presence of neutralising antibodies to WNV in a variety of mammalian species [9]. The detection of two equine cases in Izmir province which was very close to first cluster of human cases in 2010 was supportive of virus circulation in this part of country.

This is the first time that acute WNV infections in humans have been documented in Turkey. Capacity building activities, including surveillance and inter-sectoral collaboration have been put into practice. Enhanced surveillance in humans and animals and mosquito control measures with the support of municipalities were implemented. The Ministry of Health will communicate the arrangements regarding blood safety procedures due to results of surveys. Field epidemiological surveys in vectors and blood donors are still underway covering four provinces (Manisa, Mugla, Sakarya and Edirne) and a seroprevalence study has started in March 2012. These investigations will help to understand more about the nature of WNV infections in Turkey and to provide evidence-based recommendations for blood safety procedures.

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Letter to the editor: Australian immunisation registers: established foundations and opportunities for improvement

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To the editor:

In their recent article on the Australian immunisation registers [1] Chin et al. recognise the potential value of linking immunisation registers with healthcare outcome data for public health benefit by enabling rapid investigation of population-level vaccine safety and effectiveness. While the national Australian Childhood Immunisation Register (ACIR) has been linked on two occasions to examine vaccine safety, [2,3] it has not been linked to health outcome data to investigate vaccine effectiveness.

As Chin et al. mention, Queensland and the Northern Territory have separate jurisdiction-level immunisation registers. These registers, which are not subject to the same privacy legislation inhibiting linkage of ACIR data, have been used to calculate effectiveness for rotavirus [4,5], pneumococcal [6] and pertussis-containing vaccines (unpublished data) by linking immunisation with outcome data such as hospitalisations and disease notifications.

These studies demonstrate the usefulness of linking data from immunisation registers to assess vaccine effectiveness and the importance jurisdiction-level immunisation registers have played in allowing evaluation of large publicly-funded immunisation programmes.

Individual privacy must be protected. However, data linkage does not pose a significant threat to privacy and has the potential to contribute efficiently and substantially to public health. One could argue that the ethical obligation, seen from a population as well as individual perspective, is to ensure routinely-collected health information is efficiently and optimally used to achieve the greatest public benefit, while protecting the individual's privacy.

In setting up jurisdictional or national immunisation registers to achieve the greatest public benefit, we recommend thought be given to enabling easy linkage of data, in practical and legal terms, between immunisation and health outcome data.

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Authors' reply: Australian immunisation registers: established foundations and opportunities for improvement

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We welcome the insight of Sheridan et al. regarding the potential for the Australian Childhood Immunisation Register (ACIR) to be utilised for public health benefit in data linking, not only for examining vaccine safety, but also vaccine effectiveness. Jurisdictional studies have shown the value of this methodology in evaluating the effectiveness of a nationally-funded rotavirus programme within Queensland and Central Australia [1,2]. Gold et al. were also able to demonstrate the feasibility of ACIR data linkage in a single hospital study evaluating measles-mumps-rubella vaccine and thrombocytopenia [3].

In Australia, while federal and jurisdictional privacy laws are potential impediments, ethical arguments support data linking for vaccine surveillance as a public health imperative [4]. In addition, the vast majority of the public, when consulted, supported this process [5]. A computer-assisted telephone interview of randomly-selected rural and metropolitan households in South Australia in 2011 found 96.4% of respondents supported data linkage for post-licensure surveillance of vaccines. Notably, opt-out consent (40.4%) or no consent needed (30.6%) was favoured over opt-in consent (24.6%) [5].

In a country which traditionally has been an early adopter of vaccines, and allocates national programme funding based upon cost-effectiveness assessments, it is critical that both post-licensure safety and effectiveness can be assessed comprehensively and in a timely fashion [6]. This will maximise protection of vaccine recipients, confidence in the immunisation programme, and allow appropriate allocation of taxpayer resources. Linkage of national immunisation datasets with health outcome data offers a powerful public health resource.

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