Impact factor 5.49

Eurosurveillance

Europe's journal on infectious disease epidemiology, prevention and control

Vol. 19 | Weekly issue 13 | 03 April 2014

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Integrated surveillance for prevention and control of emerging vector-borne diseases in Europe

J C Semenza (Jan.semenza@ecdc.europa.eu)[1], H Zeller[1]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden

Citation style for this article:
Semenza JC, Zeller H. Integrated surveillance for prevention and control of emerging vector-borne diseases in Europe. Euro Surveill. 2014;19(13):pii=20757. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20757

Article submitted on 28 March 2014 / published on 3 April 2014

World Health Day, celebrated on 7 April, marks the anniversary of the founding of the World Health Organization (WHO) in 1948. This year, vector-borne diseases which are transmitted mainly by bites of vectors such as mosquitoes, ticks and sandflies are highlighted as a global public health priority. This issue of *Eurosurveillance* focuses on vector-borne diseases and their impact on public health in Europe and other parts of the world such as the recent outbreaks of Chikungunya fever in the Caribbean and Zika virus fever in the Pacific [1-6].

Mosquito-borne diseases

Dengue and malaria are important mosquito-borne viral diseases, often also referred to as 'tropical' diseases. Globally, dengue is the most common mosquito-borne viral disease, with an estimated 390 million infections per year and 40% of the world's population at risk [7]. While interventions to control mosquitoes have resulted in a decrease of malaria cases, WHO nonetheless estimates that 219 million individuals were infected in 2010, of which 660,000 died, predominantly in Africa [8].

Yet, vector-borne diseases are also a threat to public health in Europe. Mounting an effective public health response can counteract challenges posed by them and protect humans from infections; dedicated activities such as disease and vector surveillance as well as monitoring infectious disease drivers (e.g. environmental or climatic conditions) can help to anticipate and to respond to emerging vector-borne diseases [9, 10].

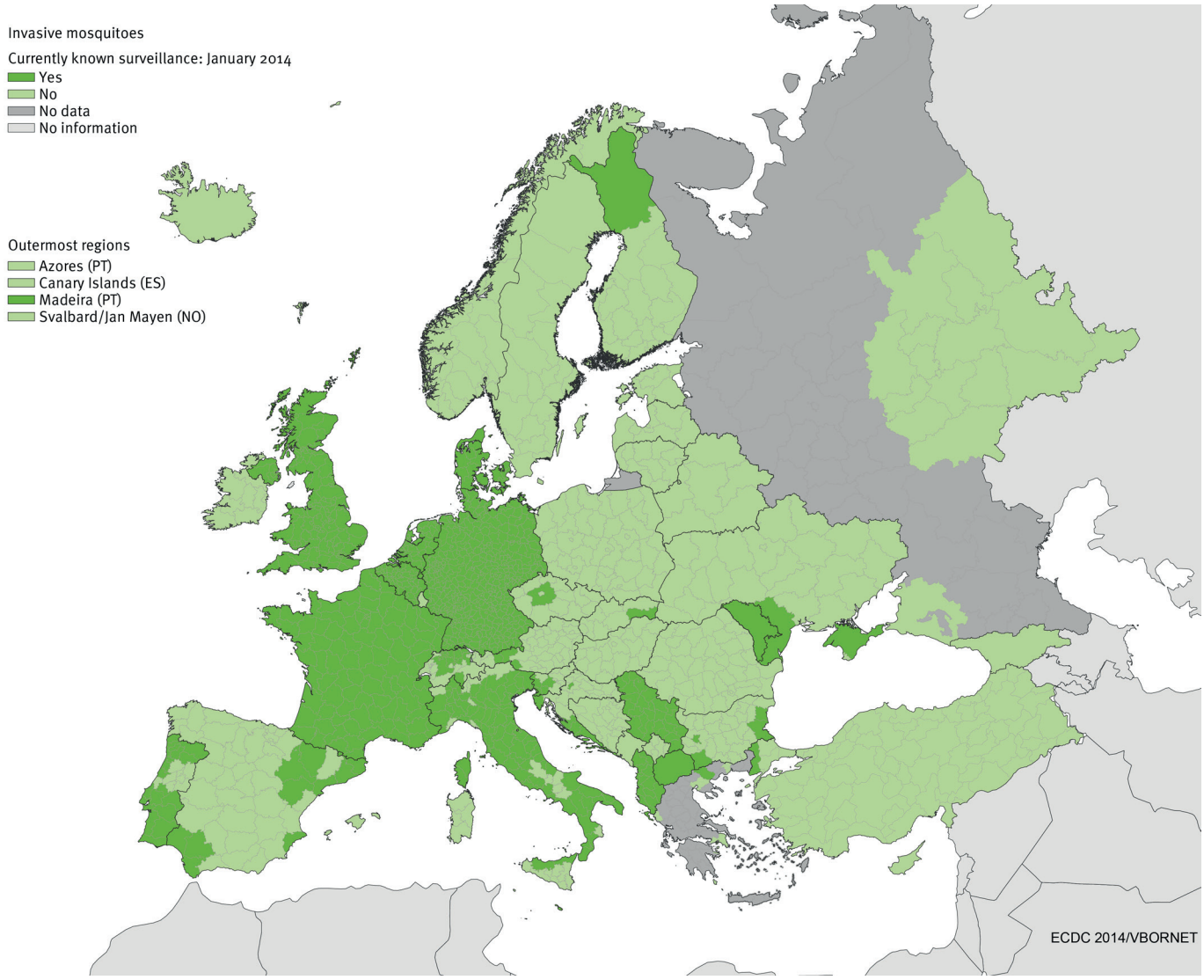
Globalisation and environmental change; social and demographic change; and health system capacity are three interacting drivers that can set the stage for novel vector-borne disease scenarios [11]. The changing dynamic of these drivers can potentially create new constellations of threats that challenge control measures. Pathogens and vectors are bound to disseminate rapidly through globalised transportation networks: over 100 million air travellers alone enter continental Europe annually, connecting it to international 'hot spots' of emerging infectious diseases [12]. A case-in-point is the importation, establishment and expansion of the Asian tiger mosquito (*Aedes albopictus*), first recorded in Albania in the 1970s and subsequently in Italy in the 1990s. The mosquito was imported in used car tires from the United States into Genova and Venice, both in Italy, from where the mosquito spread [13]. Dedicated vector surveillance activities (Figure 1) have documented that the vector has expanded due to permissive climatic and environmental conditions and is now established in numerous regions in Europe.

Astute surveillance activities were able to detect the autochthonous transmission of Chikungunya and dengue viruses by *Ae. albopictus* in Europe triggered by infected travellers returning from endemic areas [13, 14]. Through vector surveillance, *Ae. aegypti* mosquitoes, the main vectors of dengue, were first detected in Madeira, Portugal in 2005 where they dispersed across the southern coastal areas of the island. From September 2012 to January 2013, the island experienced a large dengue outbreak, affecting more than 2,100 individuals, including 78 cases exported to continental Europe; the responsible dengue virus serotype DEN-1 was traced back to a probable Central or South American origin [15].

In December 2013, public health surveillance confirmed the first local transmission of Chikungunya virus in the Caribbean. Within three months the virus spread from Saint Martin island to six other neighbouring islands and autochthonous transmission was even reported in French Guiana, South America. Cassadou et al. and Omarjee et al. in this issue describe the importance of proactive public health practice during such a vector-borne disease emergence [1]. Chikungunya infections were identified in a cluster of patients suffering from a febrile dengue-like illness with severe joint pain and who tested negative for dengue. The outbreak illustrates the importance of a preparedness plan with awareness of healthcare providers, adequate laboratory support for early pathogen identification, and

Figure

Currently known vector surveillance activities in Europe, January 2014



The surveillance activities include not only specific surveillance studies but also work done as part of on-going control activities, research projects and inventory studies.

Source: European Center for Disease Prevention and Control, 2014 [25].

appropriate response. Incidentally, in the past, several imported cases of Chikungunya fever were reported but did not result in local transmission or spread to surrounding islands.

Zika virus, transmitted by *Ae. aegypti* mosquitoes and originated from Africa and Asia emerged in French Polynesia in September 2013 and posed another health threat by *Ae. albopictus* mosquitos [16]. In this issue, Musso et al. report the first evidence of perinatal transmission of the Zika virus [2].

The parasitic mosquito-borne disease malaria was once common mainly in southern parts of Europe. While it had been eliminated largely via sanitary measures, local transmission has sporadically returned to Europe in recent years and cases from endemic countries continue to be routinely imported into Europe via travelers. In Greece, malaria had been eliminated in 1974 but starting in summer 2009 through 2012, locally acquired cases of *Plasmodium vivax* occurred in the summer months, mostly due to multiple re-introductions of the parasite [14]. The continuous spread of *P. vivax* by local anopheline mosquitoes raised the possibility of a sustained malaria transmission. In order to guide malaria control, areas with suitable environments for persistent transmission cycles were identified through multivariate modelling of environmental variables [17]. With information about this environmental fingerprint and using European Union (EU) structural funds, adequate measures could be taken and transmission in these areas was interrupted. Targeted epidemiological and entomological surveillance, vector abatement activities, and awareness raising among the

general public and health workers proved to be successful to this effect.

A further important viral vector-borne disease is West Nile fever (WNF). It was first recognised in Europe in the 1950s and re-emerged in Bucharest in 1996 and Volgograd in 1999 [13, 14]. Since then, several countries experienced limited outbreaks until 2010, when Europe witnessed an unprecedented upsurge in the numbers of WNF cases [18]. Ambient temperature deviations from a thirty year average during the summer months correlated with a WNF outbreak of over 1,000 cases in newly affected areas of south-eastern Europe [19]. Since the emergence of WNF in Greece in 2010, the disease has spread in the country reaching both rural and urban areas. In the subsequent summers from 2011 to 2013, the outbreaks did not subside in these areas. An article by Pervanidou et al. in the current issue describes the third consecutive year of autochthonous West Nile virus transmission in Greece [3]. It is a descriptive analysis of the 2012 outbreak, confirming risk factors such as advanced age, for severity of disease and medical risk factors such as chronic renal disease, for mortality from WNF.

Temperature determines viral replication rates, growth rates of vector populations and the timing between blood meals, thereby accelerating disease transmission [18]. With global climate change on the horizon, rising temperatures might be a climatic determinant of future WNV transmission that can be used as an early warning signal for vector abatement and public health interventions [13].

Tick-borne diseases

Tick-borne diseases are also of public health concern in Europe. Tick-borne encephalitis (TBE) is endemic in Europe and due to its medical significance was recently added to the list of notifiable diseases with a harmonised case definition focussing on neuroinvasive illness with laboratory confirmation [20]. The main vector of TBE, *Ixodes ricinus,* is widely distributed in Europe while TBE virus transmission is restricted to specific foci. Integrated surveillance is important to precisely determine these locations of active transmission to humans to better assess the risk and inform the public about adequate preventive measures which include protective clothing as well as vaccination. Schuler et al. in this issue describe the epidemiological situation of TBE in Switzerland over a five year period, showing the heterogeneity of the incidence according to cantons and the importance of the surveillance and vaccination as a preventive measure [4].

Tick activity is determined by ecological environmental conditions [21]. TBE incidence has been affected by both climatic and socio-demographic factors [13]. The political changes in the 1990s after the dissolution of the former Soviet Union, might have contributed to the transmission of TBEV in the Baltic countries (Estonia, Latvia and Lithuania) and in eastern Europe by increasing the vulnerabilities for some population subgroups. A case control study from Poland found that spending extended periods of time in forests harvesting forest foods such as mushrooms, being unemployed or employed as a forester significantly increased the risk for TBE infections [22]. In central Europe, climate change-related temperature rise has been linked to an expansion of TBE virus transmitting ticks into higher altitude [23].

Lyme borreliosis, another endemic tick-borne disease, is believed to be the vector-borne disease with the highest burden in Europe. Climate change may be affecting the risk of Lyme borreliosis in Europe [13]; it has already been demonstrated that Borrelia transmitting ticks have been associated with an expansion into higher latitudes in Sweden [24].

Collectively, these examples demonstrate that vector-borne diseases remain an important challenge to public health in Europe. Monitoring environmental and climatic precursors of vector-borne diseases linked to integrated surveillance of human cases and vectors can help counteract potential impacts [9, 10]. Certainly, raising awareness and increasing knowledge among the general public, public health practitioners, and policy makers about disease vectors and their relationship with infectious diseases remains a priority also. Exposure prevention through personal protection and vector abatement are important components of effective intervention strategies. In addition, integrated vector surveillance of invasive and endemic mosquito species is crucial for effective prevention and control of vector-borne diseases.

References

1. Cassadou S, Boucau S, Petit-Sinturel M, Huc P, Leparc-Goffart I, Ledrans M. Emergence of chikungunya fever on the French side of Saint Martin island, October to December 2013. Euro Surveill. 2014;19(13):pii=20752.
2. Besnard M, Lastère S, Teissier A, Cao-Lormeau VM, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014 . Euro Surveill. 2014;19(13):pii=20751.
3. Pervanidou D, Detsis M, Danis K, Mellou K, Papanikolaou E, Terzaki I, Baka A, Veneti L, Vakali A, Dougas G, Politis C, Stamoulis K, Tsiodras S, Georgakopoulou T, Papa A, Tsakris A, Kremastinou J, Hadjichristodoulou C. West Nile virus outbreak in humans, Greece, 2012: third consecutive year of local transmission. Euro Surveill. 2014;19(13):pii=20758.
4. Schuler M, Zimmermann H, Altpeter E, Heininger U. Epidemiology of tick-borne encephalitis in Switzerland, 2005 to 2011. Euro Surveill. 2014;19(13):pii=20756.
5. Van Bortel W, Dorleans F, Rosine J, Blateau A, Rousseau D, Matheus S, Leparc-Goffart I, Flusin O, Prat CM, Césaire R, Najioullah F, Ardillon V, Balleydier E, Carvalho L, Lemaître A, Noël H, Servas V, Six C, Zurbaran M, Léon L, Guinard A, van den Kerkhof J, Henry M, Fanoy E, Braks M, Reimerink J, Swaan C, Georges R, Brooks L, Freedman J, Sudre B, Zeller H. Chikungunya outbreak in the Caribbean region, December 2013 to March 2014, and the significance for the European Union. Euro Surveill. 2014;19(13):pii=20759.
6. Omarjee R, Prat CM, Flusin O, Boucau S, Tenebray B, Merle O, et al. Importance of case definition to monitor ongoing outbreak of chikungunya virus on a background of actively circulating dengue virus, St Martin, December 2013 to January 2014. Euro Surveill. 2014;19(13):pii=20753.
7. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature 2013; 496(7446): 504-7. http://dx.doi.org/10.1038/nature12060

8. World Health Organization (WHO). Factsheet on the World Malaria Report 2012. [Accessed 28 Mar 2014]. Available from: http://www.who.int/malaria/media/world_malaria_report_2012_facts/en/.
9. Semenza JC, Sudre B, Oni T, Suk JE, Giesecke J. Linking environmental drivers to infectious diseases: the European environment and epidemiology network. PLoS Negl Trop Dis 2013; 7(7): e2323. http://dx.doi.org/10.1371/journal.pntd.0002323
10. Nichols GL, Andersson Y, Lindgren E, Devaux I, Semenza JC. European Monitoring Systems and Data for Assessing Environmental and Climate Impacts on Human Infectious Diseases. Int J Environ Res Public Health 2014; 11 (forthcoming).
11. Suk JE, Semenza JC. Future infectious disease threats to Europe. Am J Public Health. 2011; 101(11): 2068-79. http://dx.doi.org/10.2105/AJPH.2011.300181
12. Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, et al. Global trends in emerging infectious diseases. Nature. 2008; 451(7181): 990-3. http://dx.doi.org/10.1038/nature06536
13. Semenza JC, Menne B. Climate change and infectious diseases in Europe. Lancet Infect Dis 2009; 9(6): 365-75. http://dx.doi.org/10.1016/S1473-3099(09)70104-5
14. Zeller H, Marrama L, Sudre B, Van Bortel W, Warns-Petit E. Mosquito-borne disease surveillance by the European Centre for Disease Prevention and Control. Clin Microbiol Infect. 2013; 19(8): 693-8. http://dx.doi.org/10.1111/1469-0691.12230
15. Alves MJ, Fernandes PL, Amaro F, Osorio H, Luz T, Parreira P, et al. Clinical presentation and laboratory findings for the first autochthonous cases of dengue fever in Madeira island, Portugal, October 2012. Euro Surveill. 2013;18(6):pii=20398.
16. Wong PS, Li MZ, Chong CS, Ng LC, Tan CH. Aedes (Stegomyia) albopictus (Skuse): a potential vector of Zika virus in Singapore. PLoS Negl Trop Dis. 2013; 7(8): e2348. http://dx.doi.org/10.1371/journal.pntd.0002348
17. Sudre B, Rossi M, Van Bortel W, Danis K, Baka A, Vakalis N, et al. Mapping environmental suitability for malaria transmission, Greece. Emerg Infect Dis. 2013; 19(5): 784-6. http://dx.doi.org/10.3201/eid1905.120811
18. Paz S, Semenza JC. Environmental drivers of West Nile fever epidemiology in Europe and Western Asia--a review. Int J Environ Res Public Health. 2013; 10(8): 3543-62. http://dx.doi.org/10.3390/ijerph10083543
19. Paz S, Malkinson D, Green MS, Tsioni G, Papa A, Danis K, et al. Permissive summer temperatures of the 2010 European West Nile fever upsurge. PLoS One. 2013; 8(2): e56398. http://dx.doi.org/10.1371/journal.pone.0056398
20. Amato-Gauci AJ, Zeller H. Tick-borne encephalitis joins the diseases under surveillance in the European Union. Euro Surveill. 2012;17(42):pii=20299.
21. Medlock JM, Hansford KM, Bormane A, Derdakova M, Estrada-Pena A, George JC, et al. Driving forces for changes in geographical distribution of Ixodes ricinus ticks in Europe. Parasit Vectors. 2013; 6: 1. http://dx.doi.org/10.1186/1756-3305-6-1
22. Stefanoff P, Rosinska M, Samuels S, White DJ, Morse DL, Randolph SE. A national case-control study identifies human socio-economic status and activities as risk factors for tick-borne encephalitis in Poland. PLoS One. 2012; 7(9): e45511. http://dx.doi.org/10.1371/journal.pone.0045511
23. Daniel M, Materna J, Honig V, Metelka L, Danielova V, Harcarik J, et al. Vertical distribution of the tick Ixodes ricinus and tick-borne pathogens in the northern Moravian mountains correlated with climate warming (Jeseniky Mts., Czech Republic). Cent Eur J Public Health. 2009; 17(3): 139-45.
24. Lindgren E, Talleklint L, Polfeldt T. Impact of climatic change on the northern latitude limit and population density of the disease-transmitting European tick Ixodes ricinus. Environ Health Perspect. 2000; 108(2): 119-23. http://dx.doi.org/10.1289/ehp.00108119
25. European Centre for Disease Prevention and Control (ECDC). Available from: http://www.ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx

Emergence of chikungunya fever on the French side of Saint Martin island, October to December 2013

S Cassadou (sylvie.cassadou@ars.sante.fr)[1], S Boucau[2], M Petit-Sinturel[1], P Huc[3], I Leparc-Goffart[4], M Ledrans[1]
1. French Institute for Public Health Surveillance (InVS), Paris, France
2. Regional Health Agency of Guadeloupe, Saint Martin and Saint Barthélemy, France
3. Laboratory 'Biocaraïbes' – Saint Martin, France
4. French National Reference Centre for Arboviruses, Armed Forces Biomedical Research Institute (IRBA), Marseille, France

Citation style for this article:
Cassadou S, Boucau S, Petit-Sinturel M, Huc P, Leparc-Goffart I, Ledrans M. Emergence of chikungunya fever on the French side of Saint Martin island, October to December 2013. Euro Surveill. 2014;19(13):pii=20752. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20752

Article submitted on 20 February 2014 / published on 3 April 2014

On 18 November 2013, five residents of Saint Martin presented with severe joint pain after an acute episode of dengue-like fever. Epidemiological, laboratory and entomological investigations provided evidence of the first autochthonous transmission of chikungunya virus in the Americas. The event indicates a risk of epidemics in America and Europe through substantial passenger traffic to and from continental France. We describe detection and confirmation of the first six cases and results of the first weeks of surveillance.

On 16 and 18 November 2013, through health event intelligence, separate signals from two sources, a patient and a hospital practitioner, reached Public Health Nurse (PHN) and epidemiologists, respectively. Five residents of a Saint Martin district called Oyster Pond, which straddles the two sides of the island, presented with severe joint pain after an acute episode of dengue-like fever. Following the alerts, two investigations were carried out in Oyster Pond.

Detection and confirmation of the first six cases: health event activity

Epidemiological surveillance and health event activities on Saint Martin before the outbreak

Saint Martin and Sint-Maarten are parts of the same Caribbean island and are, respectively, French and Dutch overseas territories. Epidemiological surveillance and health event intelligence activities on the French side are performed through a network of health professionals including epidemiologists from the French Institute for Public Health Surveillance (Cire), public health nurses (PHN) from the Regional Agency for Health (ARS), hospital and general practitioners, local laboratory and professionals of vector control. This network has been in place for many years to monitor, for example, the epidemiology of dengue fever that is endemo-epidemic in the French West Indies [1].

Investigations following the first signal of the health event

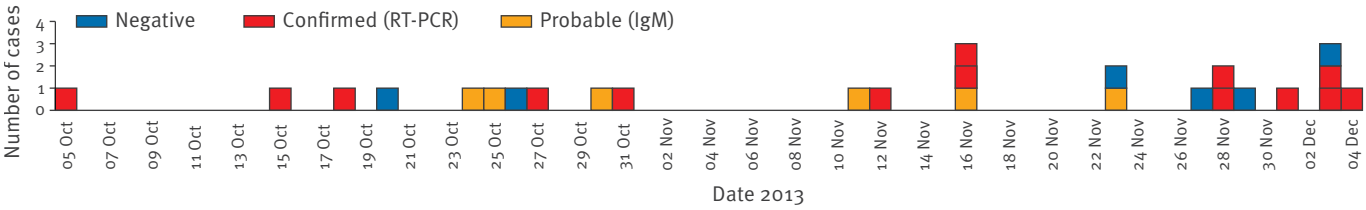
On 21 and 22 November 2013, standardised interviews and an entomological survey were conducted in the Oyster Pond district. In addition to the first five notified patients, three further patients were detected during the investigations in the district and, finally, eight patients were interviewed: five women and three men whose age ranged from 49 to 73 years. Their dates of symptom onset ranged from 15 October to 12 November; fever was acute, with a high temperature ranging from 38.8 to 39.5 °C. Five patients reported rashes (erythema, maculae, papules and, in one case, vesicles). All eight had incapacitating pain, most often in the joints of hands or feet, preventing day-to-day activities. Seven patients also had oedema in the painful joints. Available laboratory data suggested a viral infection because of a normal white cell blood count and a normal level of C-reactive protein, but the specific laboratory tests to confirm dengue fever were negative (IgM and NS1 test) [2-3]. None of the patients reported travelling to countries other than continental France, the Virgin Islands, the United States and Germany, all countries unaffected by chikungunya virus (CHIKV).

A dengue epidemic was ongoing on Saint-Martin at the time, and the vector (*Aedes aegypti*) was present on the island. The entomological investigation following the signal showed a higher density of these mosquitoes in the Oyster Pond district compared with other areas. This observation made a mosquito-borne disease plausible, but the negative laboratory tests suggested a cause other than dengue virus (DENV).

Blood samples of the eight patients were tested in the French National Reference Centre for Arboviruses in Marseille, mainland France. On 2 December 2013, serology results for two cases were positive for CHIKV (IgM). A first positive RT-PCR [4] result for another case was received on 5 December. Overall, six of the eight suspected cases could by laboratory-confirmed: four had positive IgM tests, one had a positive RT-PCR, one

Figure

Epidemic curve of chikungunya fever cases by date of symptom onset, Saint Martin, 5 October–4 December 2013 (n=26)



had positive results in both tests. The remaining two patients were negative in both tests. The six confirmed cases were classified as autochthonous, since they had no travel history to countries affected by CHIKV. Diagnostic tests for DENV were negative for all six.

The full-length viral RNA genome was characterised by the French National Reference Centre for Arboviruses, in Marseille. Importantly, the virus did not belong to the East Central South African genotype but to the Asian genotype, phylogenetically related to a number of strains recently identified in Asia (Indonesia 2007, China 2012 and the Philippines 2013) [5].

Detection of later cases

Improvement of surveillance

After the confirmation of virus circulation on Saint Martin, the following four objectives were established for future chikungunya surveillance: detect all new suspected cases in a timely manner, collect epidemiological data, confirm cases by laboratory tests and monitor the spread of the disease on the French side of Saint Martin. Collaboration with the Dutch side of the island was also enhanced with meetings and data exchange, although the preparedness plan did not specifically include such actions.

The definition for a suspected case of chikungunya fever was sent to all hospitals and general practitioners as follows: (i) a patient with onset of acute fever >38.5 °C and with at least one of the following symptoms (headache, retro-orbital pain, myalgia, arthralgia, lower back pain) and who had visited an epidemic or endemic area, or (ii) a patient with acute fever >38.5 °C and severe arthralgia of hands or feet not explained by another medical condition.

For laboratory confirmation, it was recommended that doctors request simultaneous tests for dengue and CHIKV for all patients fulfilling the case definition. The laboratory in charge of taking blood samples had to fill in a form including the date of symptom onset, date of sample, the address and phone number of the patient. These data were transmitted to epidemiologists and vector control staff. Spatial distribution of the cases was analysed using the addresses provided for all patients.

As for the first detected cases, all blood samples collected during this second phase of surveillance had to be sent to the National Reference Laboratory in Marseille, France. The laboratory results allowed classification of the clinical suspected cases as follows: invalidated case if all the tests were negative, probable case if only serology (IgM) was positive, confirmed case if RT-PCR was positive, confirmed co-infection if RT-PCR was positive for dengue and CHIKV in the same sample.

Overall results for all 26 suspected cases with laboratory test by 4 December 2013

The epidemic curve (Figure) summarises, by date of symptom onset, the first 26 patients tested between 5 of October and 4 December 2013. These include the first eight patients described above as well as a further 18 suspected cases with available laboratory test. Of those 26, 20 were identified as probable or confirmed cases. Seven probable or confirmed patients were male and 13 were female; the median age was 50 years (range 6–72 years). No patient had to be hospitalised. In addition to these 26 patients, 10 were seen by a doctor who considered that their symptoms fulfilled the criteria of a suspected case, but these patients, probably because of a mild condition, did not go to the laboratory for blood sample taking.

The period of approximately two weeks between the first confirmed case and the subsequent two confirmed cases is consistent with the time required for the contamination of a mosquito, the extrinsic cycle of the virus in this mosquito, the stinging of another patient by this infected mosquito and the incubation period in the new patient. This temporal pattern was repeated for the later groups of probable and confirmed cases occurring in November 2013.

Discussion and conclusion

Epidemiological, laboratory and entomological investigations of the first cases provided evidence for the first active transmission of CHIKV in the Americas.

At the time of the investigations, information available about the international epidemiological situation of chikungunya fever was scarce. During 2013, cases had been reported in Bali, Indonesia, Java, the Pacific Ocean (Micronesia, New Caledonia), the Philippines and Singapore [6]. Several states in India (Gujarat, Kerala, Nad, Odisha and Tamil) also reported an increased number of cases [7]. This is of relevance because of the substantial passenger traffic between the Indian community of Saint Martin and India, and indicates a risk of importing cases from India.

The timeliness of the alert, despite the simultaneous dengue fever epidemic, was made possible by three factors. The first was the health event intelligence system organised in the French West Indies, which aims to confirm and assess the risk of every unusual health signal transmitted (via telephone or email) by a health professional or a patient [8].

The second was the awareness of the risk of introduction and transmission of CHIKV on all Caribbean islands, since the major epidemic on Reunion Island in 2006 [9]. Between 2006 and 2009, nine travellers entering the French West Indies were diagnosed with confirmed CHIKV infection, one of them on Saint Martin [10]. Seven of them had arrived from Reunion Island and two from India. Vector control activities were implemented around each of these imported cases, and none led to local transmission. Although Girod and Coll confirmed vector competence of *Ae. aegypti* (the only vector mosquito genus present in the French West Indies) for CHIKV transmission [11], no indigenous transmission of this virus had been observed in the Americas since [12].

The third factor of timeliness was the chikungunya preparedness plan which is similar to that for DENV, integrating activities of surveillance, laboratory, communication, patient care and vector control. Following the alert of 2006 and the risk of virus spread from potential other imported cases, the Cire and ARS teams of all the French territories in the Americas had decided to implement a preparedness and response plan for CHIKV introduction. Suspected and confirmed case definitions were standardised, laboratory resources for confirmation identified in the region, and first response activities implemented. This plan ('Programme de Surveillance, d'Alerte et de Gestion' (Psage)), based on the Integrated Management Strategy recommended by the World Health Organization for DENV, included four phases of increasing epidemic risk. At the time of the outbreak in 2013, Saint Martin was in the first risk phase, which required reporting of suspected and confirmed cases of CHIKV by clinicians and diagnostic laboratories to the local Health Event-dedicated cell of the corresponding Regional Agency for Health (Martinique, Guadeloupe or French Guiana). Epidemiological and entomological investigations were to be conducted simultaneously in the neighbourhood of the reported cases.

This regional alert has a wider impact: if the epidemic continues to spread in the Caribbean region and the Americas during the coming months, imported cases in southern Europe may have the potential to cause local outbreaks during the summer season.

Conflict of interest

None declared.

Authors' contributions

Sylvie Cassadou and Martine Ledrans: management and coordination of the investigations. Severine Boucau: implementation of investigations. Marion Petit-Sinturel: data management. Patricia Huc: blood sample taking and management. Isabelle Leparc-Goffart: Chikungunya tests (RT-PCR and Serology).

References

1. Quénel P, Rosine J, Cassadou S, Ardillon V, Blateau A, Matheus S, et al. Épidémiologie de la dengue dans les Départements français d'Amérique. [Epidemiology of dengue in the French overseas departments of the Americas]. Bull Epidémiol Hebd. 2011;33-34:358-63. French. Available from: http://www.invs.sante.fr/content/download/18602/117933/version/5/file/BEH_33_34_2011.pdf
2. Dussart P, Petit L, Labeau B, Bremand L, Leduc A, Moua D, et al. Evaluation of two new commercial tests for the diagnosis of acute dengue virus infection using NS1 antigen detection in human serum. PLoS Negl Trop Dis. 2008;2(8):e280. http://dx.doi.org/10.1371/journal.pntd.0000280
3. Tricou V, Vu HT, Quynh NV, Nguyen CV, Tran HT, Farrar J, et al. Comparison of two dengue NS1 rapid tests for sensitivity, specificity and relationship to viraemia and antibody responses. BMC Infect Dis. 2010;10:150. http://dx.doi.org/10.1186/1471-2334-10-142
4. Marchand E, Prat C, Jeannin C, Lafont E, Bergmann T, Flusin O, et al. Autochthonous case of dengue in France, October 2013. Euro Surveill. 2013;18(50):pii=20661.
5. Leparc-Goffart I, Nougairede A, Cassadou S, Prat C, de Lamballerie X. Chikungunya in the Americas. Lancet. 2014;383(9916):514. http://dx.doi.org/10.1016/S0140-6736(14)60185-9
6. Institut de Veille Sanitaire (InVS). Bulletin hebdomadaire international no 428 du 27 novembre au 3 décembre. Paris: InVS; 2013. French. Available from: http://www.invs.sante.fr/fr/Publications-et-outils/Bulletin-hebdomadaire-international/Tous-les-numeros/2013/Bulletin-hebdomadaire-international-du-27-novembre-au-3-decembre-2013.-N-428
7. Cellule interrégionale d'épidémiologie (Cire) Océan Indien. Situation de la dengue et du chikungunya à la Réunion. [Situation of dengue and chikungunya on Reunion Island]. Point épidémiologique. 2013;46:1-2. French. Available from: http://www.invs.sante.fr/fr/Publications-et-outils/Points-epidemiologiques/Tous-les-numeros/Ocean-Indien/2013/Surveillance-des-arboviroses-a-la-Reunion.-Point-au-20-novembre-2013
8. Cellule interrégionale d'épidémiologie (Cire) Antilles-Guyane. Le nouveau dispositif de veille sanitaire des Antilles Guyane. [The new system for health event intelligence on the West Indies and French Guiana]. Bulletin de veille sanitaire. 2011;4:1-21. French. Available from: http://www.invs.sante.fr/fr/Publications-et-outils/Bulletin-de-veille-sanitaire/Tous-les-numeros/Antilles-Guyane/Bulletin-de-veille-sanitaire-Antilles-Guyane.-n-4-avril-2011
9. Renault P, Solet JL, Sissoko D, Balleydier E, Larrieu S, Filleul L, et al. A major epidemic of chikungunya virus infection on Réunion Island, France, 2005-2006. Am J Trop Med Hyg. 2007;77(4):727-31.
10. Cellule interrégionale d'épidémiologie (Cire) Antilles-Guyane. Surveillance et gestion du risqué d'émergence du virus Chikungunya d'émergence du virus Chikungunya aux Antilles et en Guyane Française. [Monitoring and management of the risk of emergence of chikungunya virus in the West Indies and French Guiana]. Bulletin d'Alerte et de Surveillance Antilles

Guyane. 2006;2:1-6. French. Available from: http://www.invs.sante.fr/publications/basag/basag2006-2.pdf

11. Girod R, Gaborit P, Marrama L, Etienne M, Ramdini C, Rakotoarivony I, et al. Viewpoint: High susceptibility to Chikungunya virus of Aedes aegypti from the French West Indies and French Guiana. Trop Med Int Health. 2011;16(1):134-9. http://dx.doi.org/10.1111/j.1365-3156.2010.02613.x
12. Pan American Health Organization (PAHO). Preparedness and Response for Chikungunya Virus: Introduction in the Americas. Washington, D.C.: PAHO; 2011. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=16984&Itemid

Importance of case definition to monitor ongoing outbreak of chikungunya virus on a background of actively circulating dengue virus, St Martin, December 2013 to January 2014

R Omarjee[1], C M Prat[1], O Flusin[1], S Boucau[2], B Tenebray[1], O Merle[1], P Huc-Anais[3], S Cassadou[4], I Leparc-Goffart (isabelle.leparcgoffart@gmail.com)[1]
1. IRBA, French National Reference Center for Arboviruses, Marseille, France
2. Affaires Sanitaires et Sociales (ARS), Délégation territoriale de Saint Martin et Saint Barthélemy, Saint Martin, France
3. Laboratory Saint-Martin Biologie Philippe Chenal, Saint Martin, France
4. French Institute for Public Health Surveillance, Paris France

Citation style for this article:
Omarjee R, Prat CM, Flusin O, Boucau S, Tenebray B, Merle O, Huc-Anais P, Cassadou S, Leparc-Goffart I. Importance of case definition to monitor ongoing outbreak of chikungunya virus on a background of actively circulating dengue virus, St Martin, December 2013 to January 2014. Euro Surveill. 2014;19(13):pii=20753. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20753

Article submitted on 24 March 2014 / published on 3 April 2014

Since 5 December 2013, chikungunya virus (CHIKV) has been demonstrated to circulate in the Caribbean, particularly on Saint Martin. This region is facing a concomitant dengue virus (DENV) outbreak. Of 1,502 suspected chikungunya cases, 38% were confirmed chikungunya and 4% confirmed dengue cases, with three circulating serotypes. We report in addition 2.8% CHIKV and DENV co-infections. This study highlights the importance of the case definition for clinicians to efficiently discriminate between DENV infection and CHIKV infection.

On 5 December 2013, the first confirmed autochthonous cases of chikungunya virus (CHIKV) infection were reported in the Caribbean, on the island of Saint Martin, by the French National Reference Center for Arboviruses (IRBA, Marseille) [1]. Before that time, only imported cases of Chikungunya had been detected in the Americas.

CHIKV is a mosquito-transmitted virus (arbovirus) of the *Togaviridae* family and Alphavirus genus. It was first isolated from humans and mosquitoes in 1952/53 during an epidemic of febrile polyarthralgia in Tanzania [2]. CHIKV is endemic in some parts of Africa and causes recurrent epidemic waves in Asia and on the Indian subcontinent.

The Caribbean region, with tropical climate and the presence of *Aedes aegypti* mosquito vectors is endemic for dengue virus (DENV), another arbovirus. Since the re-emergence of dengue in the Caribbean subregion in the 1970s and the first dengue outbreak identified on Saint Martin in 1977, this arbovirus has been responsible for multiple waves of outbreaks on this island [3]. The latest epidemic of DENV on the island started in January 2013.

Both chikungunya and dengue disease have similar clinical symptoms, which makes the clinical diagnosis complex, although differences exist. In the context of an emerging virus in a region where another arbovirus is already endemic and actively circulating, the case definition (Table 1) is crucial to follow the dynamics of the new outbreak. This report shows the efficiency of the established case definition in the chikungunya outbreak on Saint Martin, and presents the incidence of co-infection of DENV and CHIKV.

Virological findings during the chikungunya and dengue outbreak

The French National Reference Centre for Arboviruses in Marseille received all samples from Saint Martin fitting the CHIKV case definition. However, both DENV and

Table 1

Case definition for clinical suspected chikungunya and dengue cases, Saint Martin, 2013

Chikungunya virus infection	Dengue virus infection
Fever higher than 38.5 °C of sudden onset	Fever higher than 38.5 °C of sudden onset
Articular pain in extremities	At least one of the following clinical signs: headache, arthralgia, myalgia, back pain, retro-orbital pain, musculo-articular pain
Absence of other aetiological causes	Absence of other aetiological causes

Table 2

Strategy for laboratory diagnosis of chikungunya and dengue virus infection, Saint Martin, 2013

Period between start date of clinical symptoms and sample date	Laboratory tests performed
<5 days	Real-time RT-PCR
Between 5 and 7 days	Real-time RT-PCR and serology
>7 days	Serology

CHIKV diagnosis was done on every sample because of the local epidemiological context and the clinical similarities between the two diseases. According to the date of clinical symptoms onset and the sampling date, viral genome and/or IgM and IgG detection techniques were performed following the strategy described in Table 2, by using, respectively, real-time RT-PCR described previously [4,5] and in-house ELISA (MAC ELISA for IgM and indirect IgG ELISA) [6]. The samples were mostly early samples, with 87% of samples taken less than seven days after the onset of symptoms.

The virological results are presented in Figure 1. A total of 1,502 suspected chikungunya cases samples were received between week 43 of 2013 (4 December 2013) and week 05 of 2014 (31 January 2014). Of those, 570 were confirmed chikungunya cases (38%), and 65 were confirmed dengue cases (4%). Confirmed cases were defined as patients with RT-PCR-positive or IgM- and IgG-positive samples. The median age of confirmed chikungunya cases was 39 (range: 10 days–73) and 60% were female. There were only three severe cases which required hospitalisation.

In Saint Martin, three serotypes of DENV co-circulated during this outbreak: DENV1, DENV2 and DENV4, with serotype 1 predominating. The proportion of the different DENV serotypes detected during this period is presented in Figure 2.

There were an additional 16 patients with confirmed co-infection of CHIKV and DENV (not included in Figure 1), i.e. with both viral genomes detected in the same blood sample. Those cases corresponded to the clinical case definition (Table 1) and were not severe cases. The co-infecting DENV was predominantly serotype 1, following the distribution observed in the mono-infected patients with 10 DENV1, two DENV2 and four DENV4 infections. Of these co-infected cases, four patients were two pairs of relatives living at the same address.

Discussion

The Caribbean region is currently facing an epidemic of CHIKV that started on Saint Martin and spread to Saint Barthelemy, Martinique, Guadeloupe and the Virgin Islands within a few weeks. This is the first time that CHIKV circulation has been demonstrated in the Caribbean area and, more generally, the Americas. The genome of this circulating CHIKV strain was sequenced and belongs to the Asian genotype, suggesting Asia as the probable origin for the circulating virus [7].

The concomitant presence of DENV on this island leads to a difficult differential diagnosis for clinicians because both infections have similar clinical signs. Here, shortly after the start of the outbreak, an efficient case definition was set up that allowed monitoring of the emerging CHIKV outbreak on the background of actively circulating DENV.

A non-negligible proportion of co-infections were identified. Patients co-infected with CHIKV and DENV were previously reported in India, South-East Asia and Africa [8-10]. During the chikungunya epidemic in Gabon in 2007, a total of 3% of CHIKV-infected patients were also infected with DENV, both viruses being detected by RT-PCR. The CHIKV strain in Gabon belonged to the East Central South African genotype, contrary to the present Saint Martin virus, which belongs to the Asian

Figure 1

Confirmed chikungunya (n=570) and dengue (n=65) cases, Saint Martin, 4 December 2013–31 January 2014

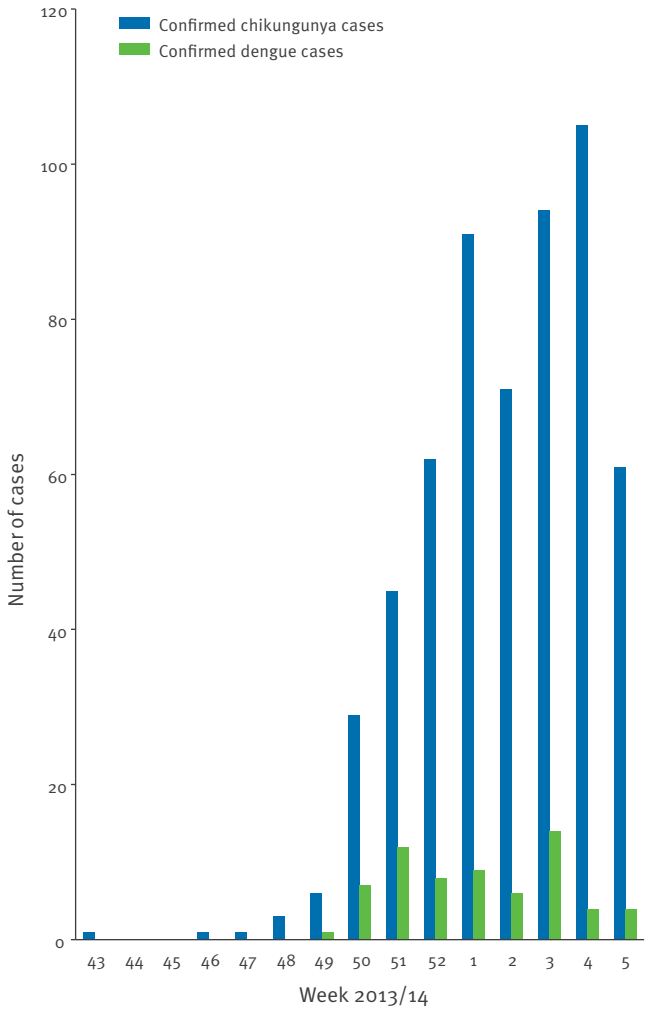
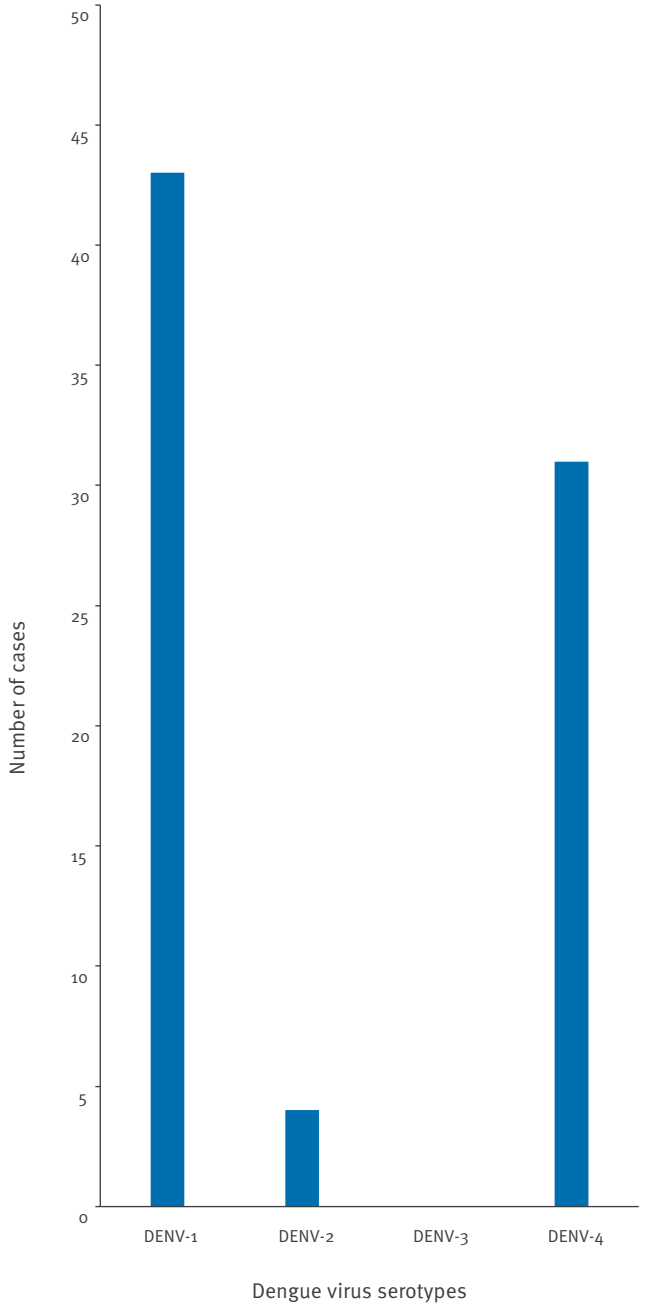


Figure 2

Distribution of circulating dengue virus serotypes, Saint Martin, 4 December 2013 to 31 January 2014 (n=78)



genotype. However, the number of co-infected cases in this current outbreak follows the same pattern, with 2.8% of CHIKV-infected patients also infected by DENV.

This study documents the importance of a clear case definition set up for clinicians to efficiently discriminate between DENV infection and CHIKV infection, thereby allowing good monitoring of the emerging outbreak by health authorities. With the presence of Aedes mosquitos in most of the Americas, and intense circulation of the human population in this area, it is predicted that CHIKV will spread, and most probably in DENV-endemic areas.

Both emergences of dengue virus in France in 2010 and 2013 started with the arrival of a viraemic patient from the French Caribbean, which reflects the considerable exchange between Europe and the Caribbean [11,12]. The current chikungunya outbreak in the Caribbean likewise presents a threat of emergence of this disease in European countries, where the vector Aedes albopictus is already established.

Authors' contributions

RO, CMP, OF, SB, BT, OM, PH-A, SC and ILG participate to the study; RO, CMP, OF, ILG wrote the manuscript; PH-A and SC reviewed the manuscript.

Conflict of interest:

None declared.

References

1. Cassadou S, Boucau S, Petit-Sinturel M, Huc P, Leparc-Goffart I, Ledrans M. Emergence of chikungunya fever on the French side of Saint Martin island, October to December 2013. Euro Surveill. 2014;19(13):pii=20752.
2. Robinson M. An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952–53. I. Clinical features. Trans R Soc Trop Med Hyg. 1955;49(1):28-32. http://dx.doi.org/10.1016/0035-9203(55)90080-8
3. Van der Sar A, Woodall JP, Temmer LE. The dengue epidemic in the Leeward Islands of the Netherlands Antilles: Saba, St. Eustatius, and St. Martin, 1977. In: PAHO Scientific pub. Dengue in the Caribbean. Washington, DC: Pan American Health Organization; 1977. p. 55-9.
4. Pastorino B, Bessaud M, Grandadam M, Murri S, Tolou HJ, Peyrefitte CN. Development of a TaqMan RT-PCR assay without RNA extraction step for the detection and quantification of African Chikungunya viruses. J Virol Methods. 2005;124(1-2):65-71. http://dx.doi.org/10.1016/j.jviromet.2004.11.002
5. Leparc-Goffart I, Baragatti M, Temmam S, Tuiskunen A, Moureau G, Charrel R, et al. Development and validation of real-time one-step reverse transcription-PCR for the detection and typing of dengue viruses. J Clin Virol. 2009;45(1):61-6. http://dx.doi.org/10.1016/j.jcv.2009.02.010
6. Marchand E, Prat C, Jeannin C, Lafont E, Bergmann T, Flusin O, et al. Autochthonous case of dengue in France, October 2013. Euro Surveill. 2013;18(50):pii=20661.
7. Leparc-Goffart I, Nougairede A, Cassadou S, Prat C, de Lamballerie X. Chikungunya in the Americas. Lancet. 2014;383(9916):514. http://dx.doi.org/10.1016/S0140-6736(14)60185-9
8. Chahar HS, Bharaj P, Dar L, Guleria R, Kabra SK, Broor S. Co-infections with hikungunya virus and dengue virus in Delhi, India. Emerg Infect Dis. 2009;15(7):1077-80. http://dx.doi.org/10.3201/eid1507.080638
9. Leroy EM, Nkoghe D, Ollomo B, Nze-Nkogue C, Becquart P, Grard G, et al. Concurrent chikungunya and dengue virus infections during simultaneous outbreaks, Gabon, 2007. Emerg Infect Dis. 2009;15(4):591-3. http://dx.doi.org/10.3201/eid1504.080664
10. Chang SF, Su CL, Shu PY, Yang CF, Liao TL, Cheng CH, et al. Concurrent Isolation of Chikungunya Virus and Dengue Virus from a Patient with Coinfection Resulting from a Trip to Singapore. J Clin Microbiol. 2010;48(12):4586-9. http://dx.doi.org/10.1128/JCM.01228-10
11. La Ruche G, Souarès Y, Armengaud A, Peloux-Petiot F, Delaunay P, Desprès P, et al. First two autochthonous dengue virus infections in metropolitan France, September 2010. Euro Surveill. 2010;15(39):pii=19676.
12. Marchand E, Prat C, Jeannin C, Lafont E, Bergmann T, Flusin O, et al. Autochthonous case of dengue in France, October 2013. Euro Surveill. 2013;18(50):pii=20661.

Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014

M Besnard[1], S Lastère[1], A Teissier[2], V M Cao-Lormeau[2], D Musso (dmusso@ilm.pf)[2]
1. Centre hospitalier de Polynésie française, Hôpital du Taaone, Tahiti, French Polynesia
2. Institut Louis Malardé, Tahiti, French Polynesia

Citation style for this article:
Besnard M, Lastère S, Teissier A, Cao-Lormeau VM, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014 . Euro Surveill. 2014;19(13):pii=20751. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20751

Article submitted on 20 March 2014 / published on 3 April 2014

A Zika virus (ZIKAV) outbreak started in October 2013 in French Polynesia, South Pacific. We describe here the clinical and laboratory features of two mothers and their newborns who had ZIKAV infection as confirmed by ZIKAV RT-PCR performed on serum collected within four days post-delivery in date. The infants' infection most probably occurred by transplacental transmission or during delivery. Attention should be paid to ZIKAV-infected pregnant women and their newborns, as data on the impact on them are limited.

Since October 2013, French Polynesia has experienced the largest outbreak of Zika virus (ZIKAV) infection ever reported, with an estimate of 28,000 ZIKAV infections in early February 2014 (about 11% of the population) [1,2]. We report here evidence of perinatal transmission of ZIKAV in French Polynesia in December 2013 and February 2014.

Clinical and laboratory description

Case 1

In December 2013, a woman in her early 30s (Mother 1), who presented at hospital at 38 weeks' gestation, vaginally delivered a healthy newborn (Apgar score 10/10) (Newborn 1), who was immediately breastfed. The mother had a mild pruritic rash without fever that had started two days before delivery and lasted up to two days post-delivery (day 2). Clinical examination of the infant remained unremarkable from birth to five days after delivery, when the infant was discharged. The infant evolved favourably and the mother recovered favourably.

Case 2

In February 2014, a woman in her early 40s (Mother 2), who had been monitored for gestational diabetes and intrauterine growth restriction diagnosed during the second trimester of pregnancy, presented at hospital at 38 weeks' gestation for delivery. She underwent a caesarean section due to pregnancy complications. Her newborn (Newborn 2) had severe hypotrophy and Apgar score 8/9/9. Enteral nutrition with formula milk for premature newborns was started due to hypoglycaemia and breastfeeding was started, in addition, from the third day post-delivery (day 3). On day 3, the mother presented a mild fever (37.5–38 °C) with pruritic rash and myalgia. The following day, after a three-hour ultraviolet light session for neonatal jaundice, the newborn presented transiently an isolated diffuse rash. Both mother and infant evolved favourably.

Laboratory features

All available samples collected from Mother 1 and Newborn 1 until day 3 and from Mother 2 and Newborn 2 until day 13 were tested for ZIKAV and dengue virus (DENV). No other pathogens were tested for, given the co-circulation of DENV (serotypes 1 and 3) [3] and ZIKAV.

The test for ZIKAV was real-time reverse-transcription (RT) PCR using two primers/probe amplification sets specific for ZIKAV [4]: results were reported positive when the two amplifications occurred (threshold cycle less than 38.5). A standard curve using serial dilutions of known concentrations of a ZIKAV RNA synthetic transcript was included within the RT-PCR run to estimate the RNA loads. Both mothers and both newborns had ZIKAV infection confirmed by positive RT-PCR result on at least one serum sample.

Breast milk samples from both mothers were inoculated on Vero cells in order to detect replicative ZIKAV and were also tested by RT-PCR. The samples gave positive RT-PCR results, but no replicative ZIKAV particles were detected in cell culture. Blood cell counts were in the normal range, except for Newborn 2, who displayed a low platelet count from day 3 (65×10^9/mL) to day 7 (106×10^9/mL) (norm: $>150 \times 10^9$/mL) and an elevated level of total bilirubin on day 3 (247 µmol/L) (norm: <200 µmol/L); total protein and C-reactive protein levels were within the normal range.

All samples tested by ZIKAV RT-PCR were also tested for DENV using a multiplex RT-PCR [5]: all were negative.

Table

Biological features of mothers and newborns with evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014

Number of days from delivery	Clinical picture				Zika virus RT-PCR and culture			
	Mother 1	Newborn 1	Mother 2	Newborn 2	Mother 1	Newborn 1	Mother 2	Newborn 2
–2	Rash	–	–	–	–	–	–	–
0	Delivery	Breastfeeding	Delivery	Enteral nutrition	–	–	–	Serum RT-PCR: Neg
1	Rash	–	–	–	–	–	Serum RT-PCR: Pos (59×10^4 copies/mL)	–
2	Rash	–	–	–	Serum RT-PCR: Pos (7.0×10^4 copies/mL) Saliva RT-PCR: Pos[a]	–	–	–
3	–	–	Rash, mild fever (37.5–38°C)	Breastfeeding	Breast milk RT-PCR: Pos (205×10^4 copies/mL) Breast milk culture: Neg	Serum RT-PCR: Pos (65×10^4 copies/mL) Saliva RT-PCR: Pos[a]	–	Serum RT-PCR: Neg
4	–	–	–	Rash	–	–	–	Serum RT-PCR: Pos (62×10^4 copies/mL)
5	–	–	–	–	–	–	Serum RT-PCR: Pos (2.6×10^4 copies/mL)	–
7	–	–		–	–	–	–	Serum RT PCR: Pos (69×10^4 copies/mL)
8	–	–	–	–	–	–	Serum RT-PCR: Neg Breast milk RT-PCR: Pos (2.9×10^4 copies/mL) Urine RT-PCR: Pos (16×10^4 copies/mL) Breast milk culture: Neg	Urine RT-PCR: Pos (20×10^4 copies/mL)
11	–	–	–	–	–	–	Serum RT-PCR: Neg	Urine RT-PCR: Neg
13	–	–	–	–	–	–	Serum RT-PCR: Neg	–

Neg: negative; Pos: positive; RT: real-time reverse-transcription.

[a] Viral load was not determined on saliva samples.

Detailed laboratory results for ZIKAV PCR and culture are reported in the Table.

Ethics approval

Informed written consent was obtained from the two mothers and publication of data related to ZIKAV infections was approved by the Ethics Committee of French Polynesia (reference 66/CEPF).

Background

ZIKAV, first isolated in 1947 from a rhesus monkey in Zika Forest, Uganda, is an arthropod-borne virus (arbovirus) belonging to the *Flaviviridae* family and the *Flavivirus* genus [6]. Since the 1960s, human cases have been sporadically reported in Asia and Africa [7], but the first large documented outbreak occurred in 2007 in Yap Island, Micronesia, in the North Pacific, where physicians reported an outbreak characterised by rash, conjunctivitis and arthralgia [8].

ZIKAV is transmitted by mosquitoes, especially *Aedes* species [7]. Direct inter-human transmission, most likely by sexual intercourse, has been described [9]. As little is known about ZIKAV transmission, we investigated other possible modes of transmission. The cases studied provide the first reported evidence of perinatal transmission of ZIKAV.

Discussion

Perinatal transmission of arbovirus has been reported for DENV [10-14], chikungunya virus (CHIKV) [15,16], West Nile virus (WNV) [17,18] and yellow fever virus (YFV) [19,20]. Breast milk transmission has been reported for DENV [14] and WNV [18] and has been suspected for the vaccine strain of YFV [20]. Severe consequences of arbovirus materno–fetal transmission have been reported, notably for CHIKV (encephalopathy and haemorrhagic fever) [16] and DENV (preterm delivery, fetal death, low birth weight, fetal anomalies, prematurity and acute fetal distress during labour) [10,12].

The possible routes of perinatal transmission are transplacental, during delivery, during breastfeeding and by close contact between the mother and her newborn. The sera from the mothers were RT-PCR positive within two days post-delivery and those of their newborns within four days post-delivery. The observation that Mother 1 had displayed a rash two days before delivery and was confirmed ZIKAV RT-PCR positive on two days post-delivery suggests that she was viraemic before and during delivery. Mother 2's serum was RT-PCR positive the day after delivery, suggesting that she was viraemic or at least incubating ZIKAV at the time of delivery. As there are no firm data on the delay necessary for ZIKAV to become detectable by RT-PCR in serum after exposure, the observation that ZIKAV RNA was detectable as early as three and four days post-delivery in the newborns does not provide evidence of transplacental transmission rather than contamination during delivery. Evidence of transplacental transmission would have been the delivery of a viraemic newborn, but the serum sample collected the day of delivery from Newborn 2 was RT-PCR negative; no sample was available on the delivery day for Newborn 1.

In November 2013, a first case of perinatal transfusion of ZIKAV was suspected in French Polynesia: the newborn displayed a maculopapular rash at delivery and the mother reported a ZIKAV infection-like syndrome two weeks before (data not shown). Unfortunately, however, virological investigations were not performed.

The detection of ZIKAV RNA by PCR in breast milk samples in our study raises the question of possible transmission by breastfeeding. The fact that replicative ZIKAV was not found in breast milk samples makes contamination by this route unlikely. The finding that RT-PCR on Newborn 2's serum was positive the day following the start of breast feeding can reasonably exclude this route of contamination for this infant. The ZIKV RNA load reported in the two breast milk samples (2.9×10^4 and 205×10^4 copies /mL) were higher than the DENV RNA load reported in a suspected case of DENV breast milk transmission ($>0.01 \times 10^4$ and $>0.1 \times 10^4$copies /mL) in New Caledonia in 2012 [14]. Of interest, CHIKV RNA was not detected from 20 milk samples collected from breastfeeding viraemic mothers during an outbreak of CHIKV infection in Réunion Island in 2005–06 [16].

As saliva samples from Mother 1 and Newborn 1 gave positive RT-PCR results, contamination by close contact cannot be excluded. However, it is currently unknown whether saliva actually contains replicative ZIKV.

Contamination of the newborns as a result of being bitten by an infected mosquito bite seems fairly improbable because of the air-conditioned rooms in the hospital.

Even though the newborns had similar ZIKAV RNA loads (about 60 x 10^4 copies/mL) in serum, Newborn 1 remained asymptomatic, whereas Newborn 2 displayed a maculopapular rash and thrombocytopenia. This newborn also had low birth weight but we do not have data to suggest this was due to ZIKAV infection, especially as there was intrauterine growth restriction from the second trimester of pregnancy and gestational diabetes.

During this large outbreak, many pregnant women could have been infected by ZIKAV, but we did not register any increase in the number of fetal deaths or premature births.

Conclusions

Given the severe neonatal diseases reported with other arbovirus infections, such as chikungunya [16] and dengue [10,12], we recommend close monitoring of perinatal ZIKAV infections. Due to the high ZIKAV RNA load detected in breast milk, and even though no replicative

ZIKAV particles were detected, ZIKAV transmission by breastfeeding must be considered.

Zika fever has been reported in tourists returning from French Polynesia to Japan in 2013–14 [21]. An outbreak of ZIKAV infection was also declared in February 2014 in New Caledonia, in the South Pacific [22]. Patients living in or returning from ZIKAV-endemic or epidemic areas presenting with a 'dengue-like' syndrome but testing negative for DENV should be tested for ZIKAV, with attention paid to infected pregnant women and their newborns, as data on the impact of the infection on them are limited.

Acknowledgements

We acknowledge Ms Claudine Roche for helpful technical support.

Conflict of interest

None declared.

Author's contributions

MB, SL, VM CL and DM wrote the manuscript. AT performed laboratory investigations.

References

1. Cao-Lormeau VM, Roche C, Teissier A, Robin E, Berry AL, Mallet HP, et al. Zika virus, French Polynesia, South Pacific. 2013. Emerg Infect Dis. Forthcoming 2014.
2. European Centre for Disease prevention and Control (ECDC). Zika virus infection outbreak, French Polynesia. 14 February 2014. Stockholm: ECDC; 2014. Available from: http://www.ecdc.europa.eu/en/publications/Publications/Zika-virus-French-Polynesia-rapid-risk-assessment.pdf
3. Cao-Lormeau VM, Roche C, Musso D, Mallet HP, Dalipana T, Dofai A, et al. Dengue virus type-3, South Pacific Islands, 2013. Emerg Infect Dis. Forthcoming 2014.
4. Lanciotti RS, Kosoy OL, Laven JJ, Velez JO, Lambert AJ, Johnson AJ, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis. 2008;14(8):1232-9. http://dx.doi.org/10.3201/eid1408.080287
5. Johnson BW, Russell BJ, Lanciotti RS. Serotype-specific detection of dengue viruses in a fourplex real-time reverse transcriptase PCR assay. J Clin Microbiol. 2005;43(10):4977-83. http://dx.doi.org/10.1128/JCM.43.10.4977-4983.2005
6. Kirya BG. A yellow fever epizootic in Zika Forest, Uganda, during 1972: Part 1: Virus isolation and sentinel monkeys. Trans R Soc Trop Med Hyg. 1977;71(3):254-60. http://dx.doi.org/10.1016/0035-9203(77)90020-7
7. Hayes EB. Zika virus outside Africa. Emerg Infect Dis. 2009;15(9):1347-50. http://dx.doi.org/10.3201/eid1509.090442
8. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009;360(24):2536-43. http://dx.doi.org/10.1056/NEJMoa0805715
9. Foy BD, Kobylinski KC, Chilson Foy JL, Blitvich BJ, Travassos da Rosa A, Haddow AD, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis. 2011;17(15):880-2. http://dx.doi.org/10.3201/eid1705.101939
10. Tan PC, Rajasingam G, Devi S, Omar SZ. Dengue infection in pregnancy: prevalence, vertical transmission, and pregnancy outcome. Obstet Gynecol. 2008;111(5):1111–7. http://dx.doi.org/10.1097/AOG.0b013e31816a49fc
11. Pouliot SH, Xiong X, Harville E, Paz-Soldan V, Tomashek KM, Breart G, et al. Maternal dengue and pregnancy outcomes : a systematic review. Obstet Gynecol Surv. 2010;65(2):107-18.
12. Basurko C, Carles G, Youssef M, Guindi WE. Maternal and foetal consequences of dengue fever during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2009;147(1):29-32. http://dx.doi.org/10.1016/j.ejogrb.2009.06.028
13. Adam I, Jumaa AM, Elbashir HM, Karsany MS. Maternal and perinatal outcomes of dengue in PortSudan, Eastern Sudan. Virol J. 2010;7:153. http://dx.doi.org/10.1186/1743-422X-7-153
14. Barthel A, Gourinat AC, Cazorla C, Joubert C, Dupont-Rouzeyrol M, Descloux E. Breast milk as a possible route of vertical transmission of dengue virus? Clin Infect Dis. 2013;57(3):415-7. http://dx.doi.org/10.1093/cid/cit227
15. Fritel X, Rollot O, Gerardin P, Gauzere BA, Bideault J, Lagarde L, et al. Chikungunya virus infection during pregnancy, Reunion, France, 2006. Emerg Infect Dis. 2010;16(3):418-25. http://dx.doi.org/10.3201/eid1604.091403
16. Gérardin P, Barau G, Michault A, Bintner M, Randrianaivo H, Choker G, et al. Multidisciplinary prospective study of mother-to-child chikungunya virus infections on the island of La Réunion. PLoS Med. 2008;5(3):e60. http://dx.doi.org/10.1371/journal.pmed.0050060
17. Stewart RD, Bryant SN, Sheffield JS. West nile virus infection in pregnancy. Case Rep Infect Dis. 2013;2013:351872.
18. Center for Disease Control and prevention. Possible West Nile virus transmission to an infant through breast-feeding--Michigan, 2002. Morb Mortal Wkly Rep. 2002;51(39):877-8.
19. Bentlin MR, de Barros Almeida RA, Coelho KI, Ribeiro AF, Siciliano MM, Suzuki A, et al. Perinatal transmission of yellow fever, Brazil, 2009. Emerg Infect Dis. 2011;17(9):1779-80. http://dx.doi.org/10.3201/eid1709.110242
20. Kuhn S, Twele-Montecinos L, MacDonald J, Webster P, Law B. Case report: probable transmission of vaccine strain of yellow fever virus to an infant via breast milk. CMAJ. 2011;183(4):E243-5. http://dx.doi.org/10.1503/cmaj.100619
21. Kutsuna S, Kato Y, Takasaki T, Moi M, Kotaki A, Uema H, et al. Two cases of Zika fever imported from French Polynesia to Japan, December 2013 to January 2014. Euro Surveill. 2014;19(4):pii:20683.
22. Direction des Affaires Sanitaires et Sociales de Nouvelle Caledonie (DASS-NC). Epidemie de Zika. [Zika epidemic]. Nouméa : DASS-NC; 27 Mar 2014. French. Available from: http://www.dass.gouv.nc/portal/page/portal/dass/alertes

Chikungunya outbreak in the Caribbean region, December 2013 to March 2014, and the significance for Europe

W Van Bortel (wim.vanbortel@ecdc.europa.eu)[1], F Dorleans[2], J Rosine[2], A Blateau[2], D Rousset[3], S Matheus[3], I Leparc-Goffart[4], O Flusin[4], C M Prat[4], R Césaire[5], F Najioullah[5], V Ardillon[6], E Balleydier[7], L Carvalho[6], A Lemaître[8], H Noël[8], V Servas[9], C Six[10], M Zurbaran[8], L Léon[8], A Guinard [11], J van den Kerkhof[12], M Henry[13], E Fanoy[12,14,15], M Braks[12], J Reimerink[12], C Swaan[12], R Georges[16], L Brooks[17], J Freedman[18], B Sudre[1], H Zeller[1]

1. European Centre for Disease Prevention and Control, Stockholm, Sweden
2. French Institute for Public Health Surveillance, Fort-de-France, Martinique
3. National Reference Centre, Institut Pasteur de la Guyane, Cayenne, French Guiana
4. National Reference Centre, IRBA, Marseille, France
5. University Hospital Laboratory of virology, Fort-de-France, Martinique
6. French Institute for Public Health Surveillance, Cayenne, French Guiana
7. French Institute for Public Health Surveillance, Saint-Denis, La Réunion
8. French Institute for Public Health Surveillance, Paris, France
9. French Institute for Public Health Surveillance, Bordeaux, France
10. French Institute for Public Health Surveillance, Marseille, France
11. French Institute for Public Health Surveillance, Toulouse, France
12. National Institute for Public Health and the Environment, Bilthoven, The Netherlands
13. Section General Public Health of the Department of Collective Prevention Services, Sint Maarten
14. European Programme for Intervention and Epidemiology Training, Stockholm, Sweden
15. Public Health Service Region of Utrecht, Zeist, the Netherlands
16. Ministry of Health and Social Development, British Virgin Islands
17. Ministry of Social Development, Government of Anguilla
18. Public Health England, United Kingdom

Citation style for this article:
Van Bortel W, Dorleans F, Rosine J, Blateau A, Rousseau D, Matheus S, Leparc-Goffart I, Flusin O, Prat CM, Césaire R, Najioullah F, Ardillon V, Balleydier E, Carvalho L, Lemaître A, Noël H, Servas V, Six C, Zurbaran M, Léon L, Guinard A, van den Kerkhof J, Henry M, Fanoy E, Braks M, Reimerink J, Swaan C, Georges R, Brooks L, Freedman J, Sudre B, Zeller H. Chikungunya outbreak in the Caribbean region, December 2013 to March 2014, and the significance for Europe. Euro Surveill. 2014;19(13):pii=20759. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20759

Article submitted on 01 March 2014 / published on 3 April 2014

On 6 December 2013, two laboratory-confirmed cases of chikungunya without a travel history were reported on the French part of the Caribbean island of Saint Martin, indicating the start of the first documented outbreak of chikungunya in the Americas. Since this report, the virus spread to several Caribbean islands and French Guiana, and between 6 December 2013 and 27 March 2014 more than 17,000 suspected and confirmed cases have been reported. Further spread and establishment of the disease in the Americas is likely, given the high number of people travelling between the affected and non-affected areas and the widespread occurrence of efficient vectors. Also, the likelihood of the introduction of the virus into Europe from the Americas and subsequent transmission should be considered especially in the context of the next mosquito season in Europe. Clinicians should be aware that, besides dengue, chikungunya should be carefully considered among travellers currently returning from the Caribbean region.

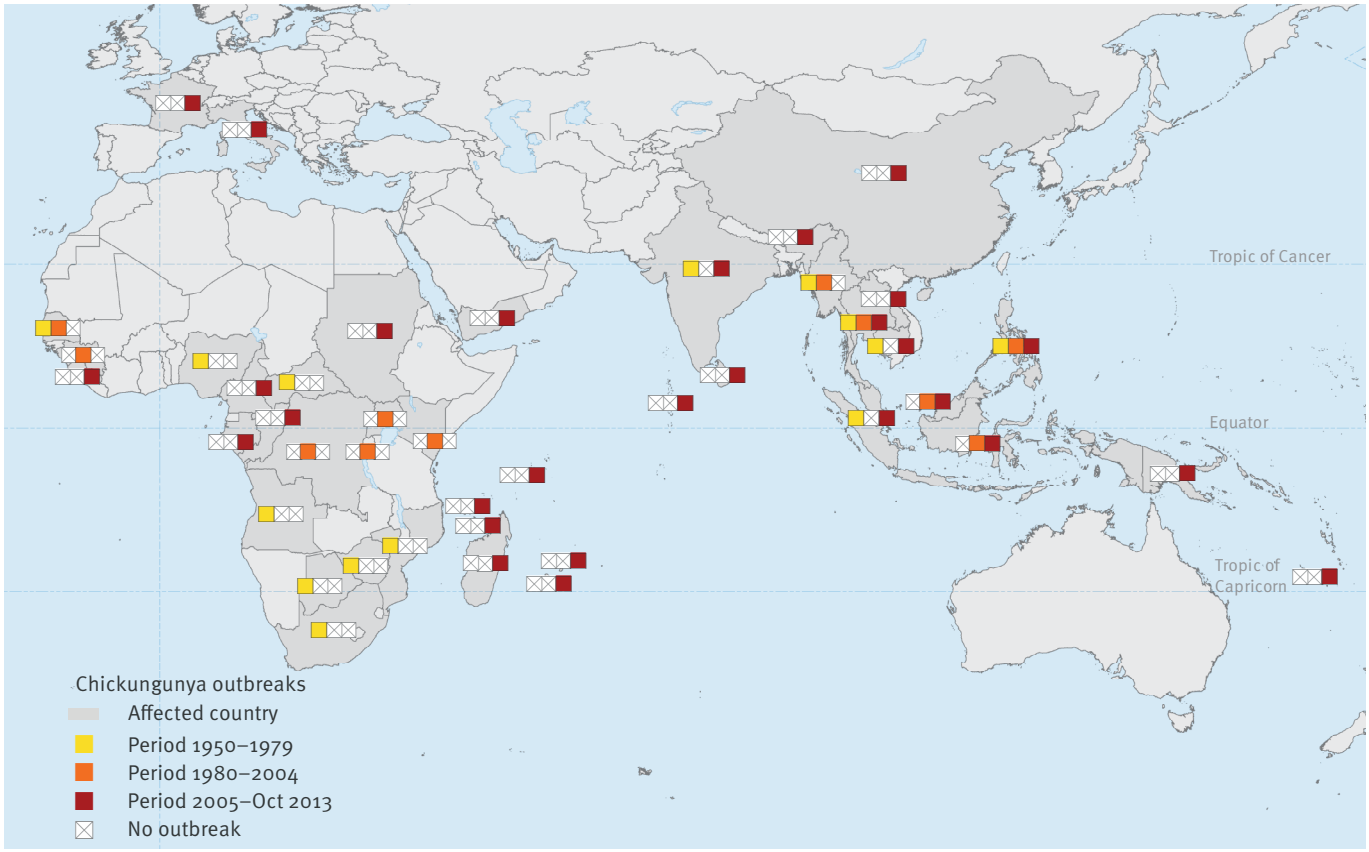
Introduction

Chikungunya is a mosquito-borne viral disease caused by an alphavirus from the Togaviridae family. The virus is transmitted by the bite of *Aedes* mosquitoes, primarily *Aedes aegypti* and *Aedes albopictus*. The typical clinical signs of the disease are fever and severe arthralgia, which may persist for weeks, months or years after the acute phase of the infection [1]. General complications include myocarditis, hepatitis, ocular and neurological disorders [2]. The detection and diagnosis of the disease can be challenging especially in settings where dengue is endemic. It was estimated that three to 25% of infected individuals are asymptomatic. Blood-borne transmission is possible [3,4] and mother-to-child transmission has also been reported in newborns of viraemic women who developed the disease within the week prior to delivery [5,6].

Chikungunya has been, up to 2005, found to be endemic in parts of Africa, south-east Asia and on the Indian subcontinent (see historical overview: Figure 1). Prior to 2005, outbreaks occurred mainly in the well-known endemic areas. From 2005 to 2006, large chikungunya outbreaks were reported from Comoros, Mauritius, Mayotte, Réunion and various Indian states (Figure 1). In 2013, chikungunya outbreaks occurred in a variety of geographic locations within India (Gujarat, Tamil Nadu, Kerala, Odisha states), Indonesia (East Jakarta, East Java), Micronesia (Yap), the Philippines archipelago, including the city of Manila, as well as Singapore, and the first evidence of autochthonous transmission

Figure 1

Historical overview of the chikungunya outbreaks prior to the emergence of the chikungunya virus in the Caribbean in December 2013



The Figure is based on references [29-81]. The detection of the chikungunya virus in the Caribbean in December 2013 constitutes the first finding of the virus in the Americas, therefore this region of the world is not shown on the map. Each square represents a particular period: the left square represents period 1950–1979, the middle square period 1980–2004 and the right square period 2005–October 2013. The squares are coloured yellow, orange and red respectively when an outbreak was reported in the literature. Otherwise the square is white-crossed.

in New Caledonia and Papua New Guinea was reported in June 2012 (Figure 1 and [7]). Autochthonous transmission in continental Europe was first reported from Emilia-Romagna, Italy, in August 2007 with more than 200 confirmed cases [8] and subsequently in 2010 in the Var, France with two confirmed cases [9]. In both areas the vector *Ae. albopictus* is established [10].

Three different genotypes of chikungunya virus, namely Asian, West African, and East/Central/South African (ECSA), have been identified. The acquisition of an A226V mutation in the envelope protein E1 of ECSA chikungunya virus, as observed in Réunion in 2005, increased the transmissibility of the virus by the widely distributed *Ae. albopictus* mosquitoes [11]. This mutated virus spread from the Indian Ocean to East Africa and Asia and was involved in the chikungunya outbreak in Italy [8]. Phylogenetic analysis proved that the chikungunya virus responsible for autochthonous cases in France belonged to the ECSA strain, but without the mutation at position 226 [9].

On 6 December 2013, two laboratory-confirmed cases of chikungunya without a travel history were reported on the French part of the Caribbean island of Saint Martin in the context of a dengue outbreak occurring on this island [12] and the virus spread since then to other islands in the Caribbean. This is the first documented outbreak of chikungunya with autochthonous transmission in the Americas. This paper aims to review the current epidemiological situation of chikungunya in the Caribbean region, to assess its significance for both the region and the European Union (EU) and to provide an historical overview of the geographical emergence of chikungunya.

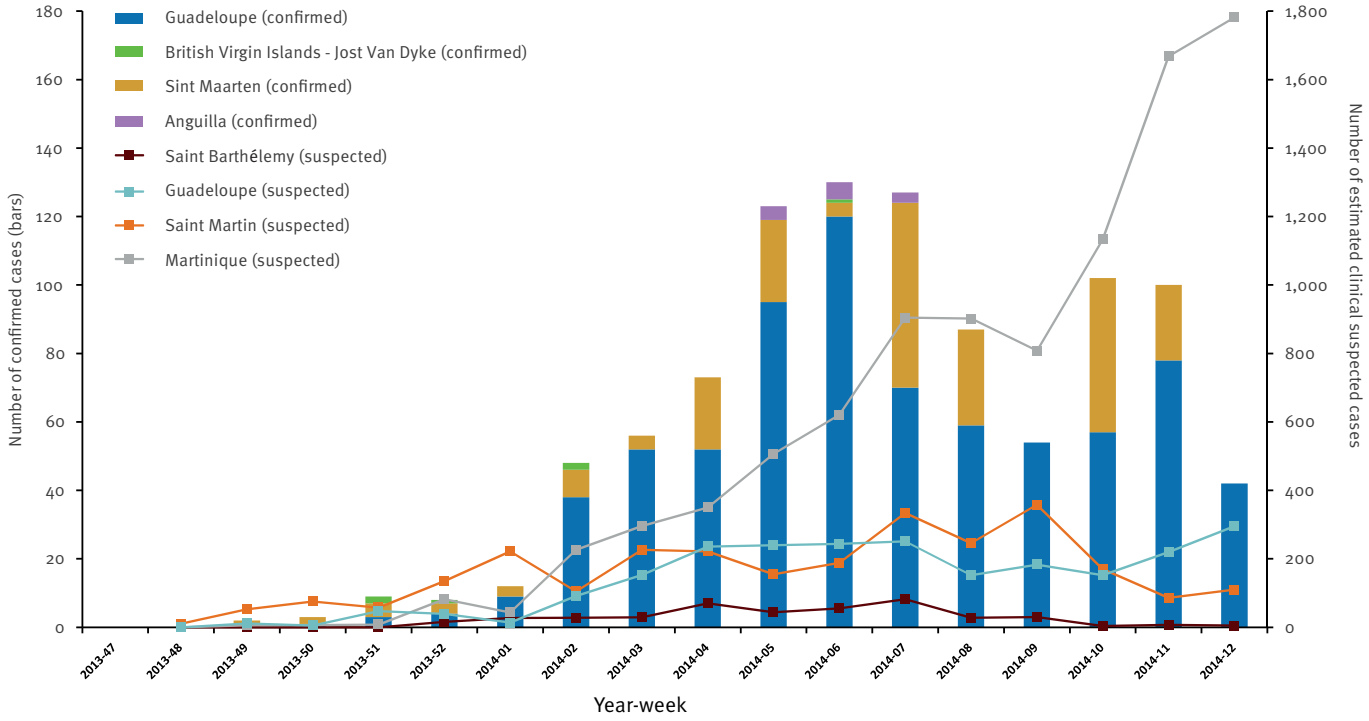
Epidemiology of chikungunya in the Caribbean

The Caribbean French overseas territories: French Guiana, Guadeloupe, Martinique, Saint Barthélemy and Saint Martin

The Caribbean French overseas territories include the islands Guadeloupe, Martinique, Saint Barthélemy

Figure 2

Number of confirmed and estimated suspected chikungunya cases reported in the Caribbean by week of sampling, 1 December 2013–23 March 2014



The period 1 December 2013–23 March 2014 corresponds to week 48 2013–week 12 2014. From week 5 2014 onwards the expert committee for emerging and infectious diseases of Martinique, Saint Barthélemy and Saint Martin recommended to focus the laboratory diagnostics on patients for which laboratory confirmation is needed to support case management. From then, the systematic confirmation of cases was ceased on these islands. Therefore the confirmed cases (bars) are only shown for Anguilla, Guadeloupe, Jost Van Dyke and Sint Maarten. Estimated numbers of suspected clinical cases (lines) are respectively provided for Guadeloupe, Martinique, Saint Barthélemy, and Saint Martin.

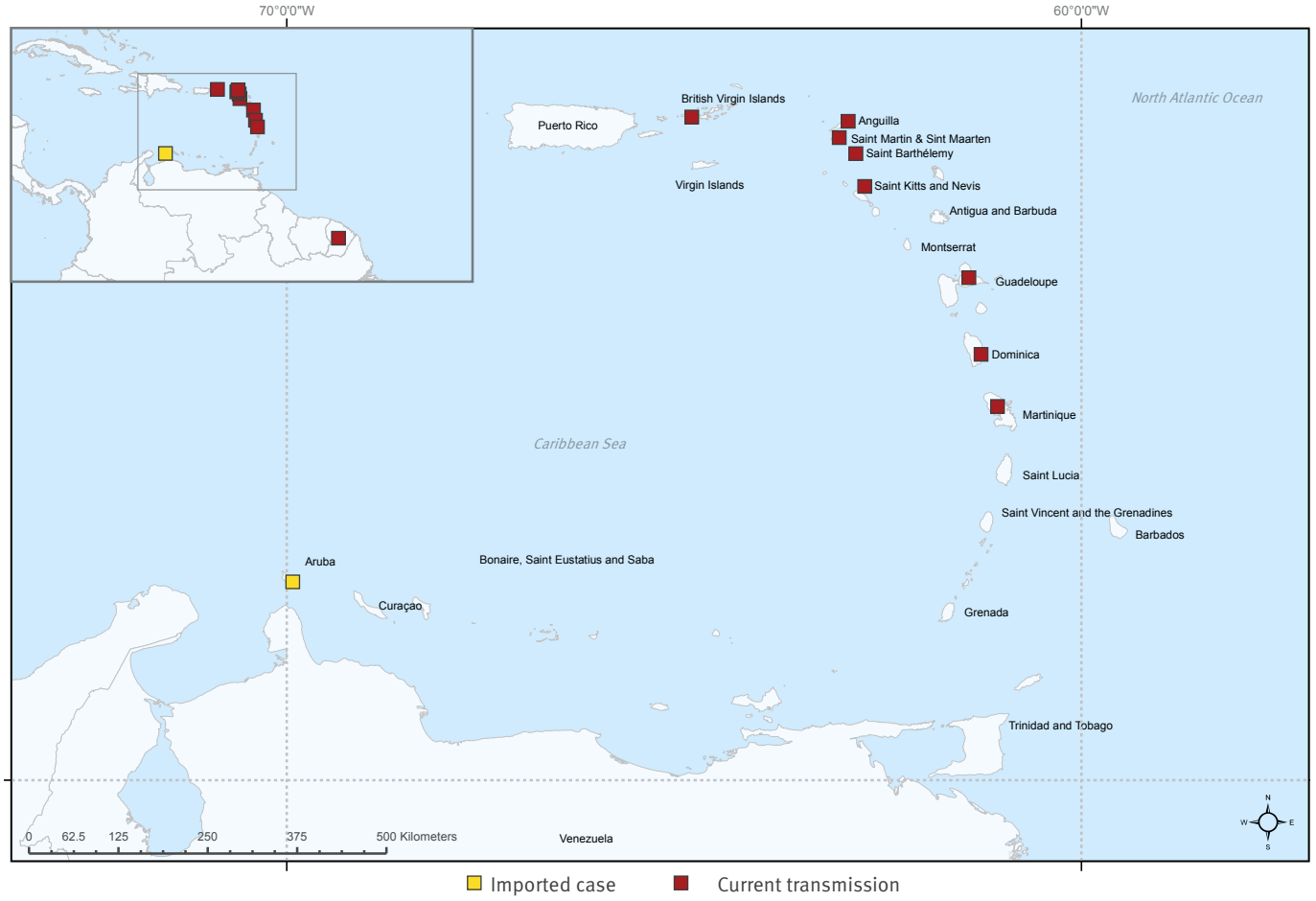
and Saint Martin, and French Guiana on the South American continent. Dengue surveillance and control are well established on the Caribbean French overseas territories.

In mid-November 2013, the suspicion of autochthonous transmission of chikungunya virus on the island of Saint Martin was brought to the attention of the local health authorities. On 6 December 2013, a first suspected case of chikungunya occurring in the French part of the island was laboratory confirmed and an outbreak phase was declared the same day for Saint Martin.

Following this confirmation, enhanced surveillance for chikungunya cases was implemented not only in Saint Martin but also in the other Caribbean French overseas territories, because intense travel of people occurs between the affected island and these neighbouring territories. Based on the phase of the outbreak in the different territories – each territory declares the outbreak-phase based on their assessment/context – the following components of the surveillance system were either implemented or strengthened to achieve the early detection of suspected chikungunya cases and to monitor the evolution of the epidemic. (i) During the pre-outbreak phase, i.e. when the first autochthonous cases are detected and laboratory confirmed, the surveillance focussed on systematic confirmation of cases. Therefore, general practitioners and medical microbiologists were invited to report all clinical suspected cases of chikungunya using a specific notification form. A clinical suspected case was defined as any individual with sudden onset of fever (›38.5°C) with arthralgia and without any other aetiology. Laboratory investigations were systematically conducted on all clinical suspected cases. A confirmed case was defined as a clinical suspected case with laboratory confirmation, either a positive reverse transcription-polymerase chain reaction (RT-PCR) or a positive detection of IgM and IgG or both; (ii) once the outbreak was declared by the local authorities, i.e. the outbreak phase, the surveillance was performed through the weekly notification of clinical suspected cases by the sentinel network of general practitioners; in Saint Martin, all general practitioners and one paediatrician were asked to report the number of clinical suspected cases. Further all hospitals in the territories had to weekly notify emergency room visits for suspected cases, and hospital admissions for confirmed cases. The systematic

Figure 3

Local chikungunya transmission and imported cases in the islands of the Caribbean region and in French Guiana, 1 December 2013–23 February 2014



The period 1 December 2013–23 February 2014 corresponds to week 48 2013–week 8 2014.

laboratory confirmation of all suspected cases was ceased in week 5 2014 in Martinique, Saint Barthélemy and Saint Martin to prevent overloading the laboratories performing the diagnosis.

Strengthened surveillance enabled the detection of confirmed cases of chikungunya on French territories other than Saint Martin. Data were collected at the local level and regional level (i.e. the Regional Office of the French Institute for Public Health Surveillance, Fort-de-France, Martinique) in order to follow the progression of the virus in the different territories (French Guiana, Guadeloupe, Martinique, Saint Barthélemy, Saint Martin), to coordinate the activities and to harmonise common tools (questionnaires, templates, protocols) used during the pre-outbreak and outbreak management phases.

Epidemiological situation

Since the introduction of the chikungunya virus in Saint Martin and subsequent implementation of enhanced surveillance, the first cases in Martinique, Guadeloupe, Saint Barthélemy and French Guiana were confirmed on 18, 24, 30 December 2013 and 19 February 2014 respectively. Since the start of the outbreak the number of suspected and confirmed cases increased indicating continuous transmission of the virus in all affected territories (Figure 2).

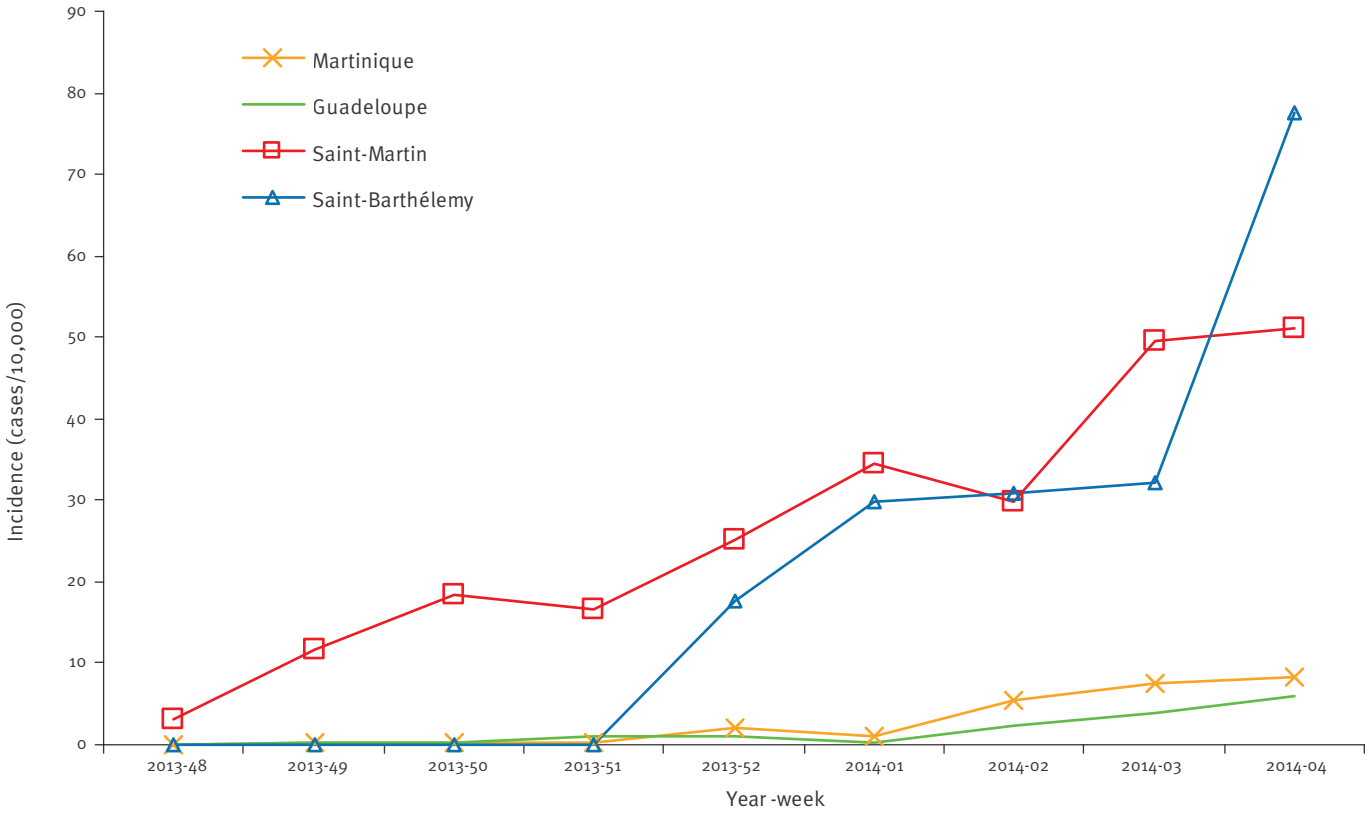
As of 27 March 2014, the estimated number of clinical suspected cases of chikungunya in Saint Martin was 2,750 and the number of confirmed cases was 784 (week 48 2013 to 12 2014).Three deaths indirectly related to chikungunya were reported.

A total of 435 clinical suspected cases were estimated on the island of Saint Barthélemy and 134 infections have been confirmed (week 50 2013 to 12 2014).

In Martinique, 9,340 clinical suspected cases of chikungunya were estimated (week 49 2013 to 12 2014) and 1,207 cases were identified as laboratory-confirmed

Figure 4

Weekly incidence of the estimated suspected cases of chikungunya by the sentinel network in Guadeloupe, Martinique, Saint Barthélemy and Saint Martin, 1 December 2013–26 January 2014



The period 1 December 2013–26 January 2014 corresponds to the weeks 48 2013–4 2014.

cases. Two deaths were reported in Martinique in hospitalised patients: one death was classified as indirectly linked with chikungunya; the second death is under investigation.

In Guadeloupe, a total of 2,270 clinical suspected cases were estimated to have occurred (week 52 2013 to 12 2014) and 734 cases were confirmed for the infection in this island (Figures 2 and 3).

A rapid increase of the weekly incidence was observed in the smaller islands Saint Martin (population: 36,029) and Saint Barthélemy (population: 9,035) compared to the larger islands Martinique (population: 392,290) and Guadeloupe (population: 404,640) (Figure 4).

Since the beginning of the outbreak, 11 cases from Saint Martin and Martinique were imported in French Guiana. The first autochthonous cases in French Guiana were reported on 19 February, with a total of 24 autochthonous laboratory-confirmed cases in week 11 2014.

In Saint Martin, all areas of the island have been affected by the virus, a predominant number of confirmed cases occurred in Sandy Ground, Concordia and Quartier d'Orléans. In Martinique, the outbreak is geographically generalised. The main city, Fort-de-France, had the highest attack rate (estimated from the weekly number of notifications of clinical suspected cases) followed by, La Trinité, Case Pilote, Schoelcher, Saint-Pierre, and Les Anses d'Arlet. The main cluster identified in Guadeloupe was located in Baie-Mahault and in other municipalities of the windward shore of Basse Terre. In total, 27 of 32 municipalities had at least one confirmed case.

Microbiological investigation

Before the outbreak phase, laboratory confirmation was requested for every clinical suspected case of chikungunya. The diagnostic algorithm was intended to be followed by practitioners and microbiological laboratories. The samples were processed according to the date of the onset of symptoms and the date of sample collection. When the sample was taken between the first and fifth day after symptom onset, the sample was processed by RT-PCR. When the sample was taken between the fifth and the seventh day after symptoms onset, the sample was processed both by RT-PCR and detection of IgM and IgG, for the remainder only IgM and IgG detection was performed.

Because both dengue and chikungunya viruses are currently circulating, dengue diagnostic was systematically performed parallel to chikungunya laboratory tests. The microbiological analysis strategy was adapted according to the respective outbreak situation. In the territories where there was evidence of wide virus spread, only at-risk patients (when laboratory confirmation was needed to support the case management) and uncommon forms of the infection were targeted for laboratory confirmation (Martinique, Saint Barthélemy and Saint Martin, from week 5 2014). Local, regional and national capacities support the diagnostic strategy of the region (National Reference Laboratories and hospital-based microbiological laboratories).

On 10 December 2013, five days after the detection of the first autochthonous cases in Saint Martin, the complete chikungunya virus sequence showed that this virus belongs to the Asian genotype and the information was shared with the relevant public health authorities [13].

Control measures

All houses and work places of confirmed cases were targeted by vector control measures as scheduled in the Management, Surveillance and Alert of chikungunya outbreak Programme, which was implemented as a result of the outbreak. Epidemiological and entomological investigations were conducted simultaneously in the neighbouring environment of the suspected and confirmed cases (during pre-outbreak and outbreak phases) as well as interventions on the whole territory (outbreak phase), to identify possible clusters of cases and to implement vector control targeting adult mosquitoes and their breeding sites.

Public education was established through radio spots, television, distribution of flyers and posters with prevention messages in public areas, airports, private practitioner's offices, hospitals and clinics. The health authorities also implemented a specific programme preventing possible shortage of healthcare capacities due to the high burden of patients on emergency, hospital and outpatient capacities.

Overseas territories of the Netherlands

The overseas territories of the Netherlands in the Caribbean region comprise six islands grouped in three smaller Windward Islands in the north, and three larger Leeward Islands in the south, just north of the Venezuelan coast. The total population of these islands is 320,000 and ranges from 2,000 (Saba) to over 147,000 (Curaçao). The three islands with a larger population, Aruba, Curaçao, and Sint Maarten, are independent states within the Netherlands, the other three islands (Bonaire, Sint Eustatius and Saba), the so-called BES islands, have the status of special municipalities within the Netherlands. Sint Maarten (close to 40,000 inhabitants) is the southern part of the island of which the Northern part is formed by Saint Martin.

Epidemiological situation

The first report of laboratory-confirmed autochthonous chikungunya case in the overseas territories of the Netherlands was received by section General Public Health of the Department of Collective Prevention Services in Sint Maarten on 22 December 2013. The case had had onset of illness on 6 December 2013. Since the start of the outbreak, the total number of confirmed patients diagnosed with chikungunya on Sint Maarten has been 234 (up to week 11 2014), including one hospitalised case. The Dutch case definition for confirmed cases is fever (›38.5°C) and joint pain in a person who has a positive polymerase chain reaction (PCR) and/or specific positive IgM antibody test. The proportion of test-positive samples increased from 29% (2/7) in December 2013 up to 69% (77/111) at the end of March 2014. The Caribbean Public Health Association (CARPHA) is, amongst other activities, assisting the countries and territories in the Caribbean region in the surveillance of communicable diseases. In this context they operate a syndromic surveillance system. Data from the surveillance showed for Sint Maarten an average and stable number of patients with undifferentiated fever since December 2013. Since the end of January 2014, start of week 5, the syndromic surveillance showed a consistently higher number of cases of undifferentiated fever compared to the historical average, generally below five cases per week based upon four years of data. Since week 5, cases vary between two and 34 per week (an average of 13 per week between week 5 and 12). Although there has been an ongoing dengue outbreak during this period, the increase is likely to be due to chikungunya, given that dengue season started well before January.

The number of confirmed cases on Sint Maarten (n=234) is much lower than on Saint Martin (n= 784) although the number of inhabitants of both parts of the island is comparable (ca. 40,000). Because of intense traffic occurs between the two parts of the island and ecological barriers are absent, there is no obvious reason why the disease would be more prominent in the northern than in the southern part of this small island (87 km^2). More likely, the difference in the number of reported cases is due to the difference in the availability of diagnostic testing and under-reporting. Twelve patients from Sint Maarten were diagnosed by general practitioners from Saint Martin. From the epidemiological data currently available, the residencies of most patients cannot be identified in a reliable manner.

The other two Dutch Windward islands, Saba and Sint Eustatius, have small populations (2,000 and 3,900) of which no patients have been diagnosed so far. The syndromic surveillance on these islands shows a low and stable number of patients with undifferentiated fever since December 2013. A rise in these figures could be an early signal for emergence of chikungunya. In the Dutch Leeward Islands, Aruba, Bonaire and Curaçao, no autochthonous cases have been identified so far. One imported confirmed case returning from Saint

Martin was reported on the island of Aruba in the first week of February 2014 (Figures 2 and 3).

Microbiological investigation

The first three patients from Sint Maarten were diagnosed by the French National reference laboratory (CNR-IRBA Marseille) using RT-PCR testing. On January 2014, serum samples from Sint Maarten were sent to the virological laboratory of the National Institute for Public Health and the environment (RIVM) in Bilthoven, which made diagnostic testing available. Reference materials were obtained from the laboratory in Marseille (CNR-IRBA). Due to a lack of information about the date of onset of illness, all samples were tested by RT-PCR and for chikungunya-specific IgM and IgG-antibodies when RT-PCR was negative. Because transport of samples is both expensive and time consuming, the RIVM assists the local laboratories of Sint Maarten and Curaçao to implement serological testing indirect fluorescent-antibody (IFA) from the second quarter of 2014.

Control measures

Mosquito control services are present on Sint Maarten and routine measures are the same as for the control of dengue fever: fogging with adulticides (Evoluer 4-4; active ingredient: permethrin/piperonyl butoxide), removal of breeding sites, application of larvicides in water containers and health education on prevention of mosquito bites. Upon arrival, tourists, which are paramount for the regional economy of the islands, are informed of the ongoing outbreak of chikungunya and advised to take personal protection measures against mosquito bites. The local authorities make use of the preparedness and response plan of the United States (US) Centers for Disease Control and Prevention (CDC) for introduction of chikungunya virus in the Americas, which was introduced during two workshops in 2012 hosted by Pan American Health Organization (PAHO) [14]. Specialists from the CARPHA and the PAHO have provided expert advice concerning control in January 2014 by means of a work visit to Sint Maarten. General practitioners have been informed of the presence of the disease and an intensified surveillance has been initiated by the Public Health Authority of Sint Maarten. The ministry of Health has initiated procedures in order to make chikungunya cases notifiable for the BES islands. General practitioners and specialists on all other overseas territories in the Netherlands have been informed of this emerging epidemic, and have been advised concerning diagnostic testing since the end of December 2013.

Overseas territories of the United Kingdom

The overseas territories of the United Kingdom (UK) in the Caribbean region comprise five territories of which three (Anguilla, British Virgin Islands and Montserrat) are located within the Lesser Antilles east of Puerto Rico and two (Cayman Islands and Turks and Caicos Islands) in the western Caribbean in the Greater Antilles. The total population of these territories is around 136,000 and ranges from just over 5,000 (Montserrat) to around 53,200 (Cayman Islands). All are internally self-governing UK overseas territories.

A standard case reporting form is used to collect information on chikungunya cases (based on the case definition). Reports from undifferentiated fever (›38.5°C), which might include chikungunya cases, are collected on a weekly basis from sentinel sites.

Epidemiological situation

British Virgin Islands: three cases of chikungunya were confirmed by CAPHA on Jost Van Dyke island in the British Virgin Islands on 13 January 2014 (Figures 2 and 3). The cases had onset of symptoms on the 15, 17 and 25 December 2013. The symptom profile of the three cases consisted of fever (›38.5°C) and severe arthralgia. Retro-orbital pain, back pain, and rash were not present. There was no history of travel. These three cases tested positive for chikungunya and were negative for dengue by PCR. As of 27 March 2014, a total of seven autochthonous cases have been confirmed in the British Virgin Islands, all from Jost Van Dyke island; the most recent case with onset of illness on 5 February 2014 (week 6 2014).

Anguilla: On 31 January 2014, one case of chikungunya, believed to be imported from Saint Martin was diagnosed in Anguilla and confirmed by CARPHA in Trinidad. As of 27 March, a total of 14 confirmed cases (13 autochthonous and one imported) have been reported in Anguilla with onsets of illness between 27 January and 16 February 2014.

The case definition used is in line with the one provided by CARPHA: a suspected case is a patient with acute onset of fever ›38.5°C and severe arthralgia or arthritis not explained by other medical conditions, and who resides or has visited epidemic or endemic areas within two weeks prior to the onset of symptoms; a probable case is defined as a suspected case with a positive result for chikungunya by IgM enzyme-linked immunosorbent assay (ELISA); and a confirmed case is a suspected case with a positive result for chikungunya by viral isolation, RT-PCR or four-fold increase in chikungunya virus specific antibody titres (samples collected at least 2 to 3 weeks apart).

Microbiological investigation

Molecular PCR testing for chikungunya is undertaken by CARPHA in Trinidad and the first positive samples in British Virgin Islands were sent to the US CDC for verification, as these were the first cases confirmed by the Trinidad laboratory.

Control measures

The vector control unit of the Environmental Health Division of the British Virgin Islands performed control activities and monitoring as well as house to house inspections and education at the time of the initial reports. They have been monitoring mosquito indices on Jost Van Dyke. Surveillance activities have

been increased. The Ministry of Health and Social Development in Anguilla continues to work in collaboration with the relevant agencies to ensure that the appropriate preventative measures are implemented to reduce and contain the spread of the virus. Measures include mass education of the public to raise awareness of symptoms and prevention, fogging in areas where confirmed or suspected cases of chikungunya have been reported and engaging with port health teams at sea and airports in order to implement appropriate controls.

Discussion

Chikungunya is endemic in Africa, south-east Asia and on the Indian subcontinent with outbreaks occurring beyond the well-known endemic areas from 2005 (Figure 1). Compared to this historical occurrence, this is the first documented outbreak of chikungunya in the Americas. The virus in the Caribbean belongs to the Asian genotype [13]. It might have been introduced by travellers from Asia where outbreaks were reported in 2013. With the increased transmission of chikungunya in Asia and Africa in the last decade, the Caribbean region has been considered highly vulnerable [14]. The primary vector, *Ae. aegypti*, is widespread in the region [15], but also *Ae. albopictus* is found in the Americas and on a number of Caribbean islands [16]. The latter species has not been found in French Guiana, the French Caribbean islands nor the Dutch Caribbean territories but the climate suitability model revealed that the area is highly suitable for this vector species [15-17]. The presence of a human population naïve to the chikungunya virus, competent vectors in the region and the intense movement of people into and between islands are factors that most likely contributed to the extension of the virus circulation. Indeed, contacts between the islands are high as exemplified by the increased traffic between Saint Martin/Sint Maarten and the British Virgin Islands as a consequence of a boat show in the British Virgin Islands in December 2013. Besides the reported affected areas of the French, Dutch and British overseas territories, confirmed cases were reported from Dominica and Saint Kitts and Nevis (Figure 3 and [18,19]) and the first autochthonous transmission on the continent was confirmed in French Guiana 11 weeks after the first confirmed case on Saint Martin (week 8 2014). The establishment of autochthonous transmission following importation of viraemic patients in other territories of the Americas is expected and will likely have a significant public health impact in the region. Surveillance in the region, which is well established for dengue, has been intensified and laboratory testing has been strengthened in collaboration with regional or international reference laboratories. Further, a close follow-up of the situation and co-ordinated surveillance and control within the regions is still needed.

The vulnerability of Europe for the transmission of chikungunya virus and other arboviruses was recognised prior to 2007 [20] and confirmed with the first chikungunya outbreak in Italy in 2007 [8,21,22]. For onward transmission to occur, the introduction of this virus into Europe would need to coincide with high vector abundance and activity i.e. during the summer season in the EU. Hence, chikungunya outbreaks in the northern hemisphere are of bigger concern for the EU than those in the southern hemisphere [23]. During the period from 2008 to 2012, 475 imported chikungunya cases have been reported by 22 EU/European Economic Area (EEA) countries [7]. Most cases originated from Asia (one third from India, otherwise Indonesia, Maldives, Sri Lanka and Thailand) and Africa (including islands from the Indian Ocean). Temporal clusters of chikungunya cases imported in the EU are largely synchronous with large outbreaks in endemic countries as reported for Germany [24]. The occurrence and possible establishment of chikungunya in the Caribbean region adds an additional possible source of introduction of the virus. Because of the relatively intensive traffic between the overseas territories and the EU, introduction of chikungunya in Europe can be anticipated and blood safety measures could be considered [25]. It should be noted that both autochthonous dengue cases in France in 2010 and 2013 followed the introduction of a viraemic patient from the French Caribbean overseas territories. The introduction of chikungunya viraemic persons will most likely not lead to onwards transmission in Europe during the winter season as the vectors are not active during this season. However, vigilance is needed if the outbreak in the Caribbean region continues and overlaps with the mosquito vector season in areas where *Ae. albopictus* is established in continental Europe.

Firstly reported in Europe in 1979 in Albania [26], the mosquito vector *Ae. albopictus* has continuously expanded its distribution in the EU. To date this species has colonised almost all Mediterranean countries and has been found introduced, without establishment in Austria, Belgium, Czech Republic, in more northern localities in France, and the Netherlands, [10]. *Ae. albopictus* can reach high densities from July to September around the Mediterranean where it is established [27]. *Ae. aegypti* has recently established on Madeira and is found around the Black Sea coast. The A226V mutation of ECSA chikungunya virus has increased the transmissibility of the chikungunya virus by *Ae. albopictus* [11] and vector competence studies using *Ae. albopictus* populations from France showed that both the mutated and non-mutated ECSA chikungunya strains can be transmitted by local mosquito populations [28]. The chikungunya strain currently circulating in the Caribbean region does not belong to the ECSA genotype but to the Asian genotype. The strain is related to strains recently identified in Indonesia, China and the Philippines [13]. The competence of the European population of *Ae. albopictus* to transmit this chikungunya strain needs investigation.

In conclusion, spread and establishment of the disease in the Caribbean and other regions in the Americas can be anticipated given the high connectivity between the affected and non-affected areas and the widespread

occurrence of efficient vectors. Also, the risk of introduction of the disease to the EU from the affected territories in the Caribbean should be considered especially in the context of the next mosquito season in Europe. Clinicians should be aware that, besides dengue, chikungunya should be considered among travellers currently returning from the Caribbean region. The clinical picture of both infections can be similar and might be a challenge for clinicians that are not familiar with the clinical presentation of these infections.

Acknowledgements

We would like to thank the CVAGS in French Guiana, Guadeloupe, Martinique, Saint Barthélemy and Saint Martin, the microbiologists and the staff of the National Reference Laboratories (CNR in Irba Marseille, CNR in IPG Cayenne, RIVM-IDS in Bilthoven) and the public hospital microbiological laboratory of virology for their high commitment. We are also grateful to the sentinel doctors from Guadeloupe, Martinique, Saint Barthélemy, Saint Martin, and Sint Maarten, and the infectious diseases specialists working at the hospital Centres in the different territories and the private microbiological laboratories.

Conflict of interest

None declared.

Authors' contributions

Wim Van Bortel coordinated and drafted the manuscript, and reviewed final document for accuracy; Frédérique Dorleans coordinated and drafted the part of the manuscript on the French Caribbean territories and reviewed the different versions of the MS / Permanent member of the outbreak team management in Martinique; Jacques Rosine and Alain Blateau are permanent members of the outbreak management team in Martinique and permanent member of the regional outbreak management team (French Caribbean territories) and responsible for the data collection management and interpretation; Dominique Rousset form the French National Reference Center for Arboviruses is head of the associated lab for the French departments of the Americas and involved in virological diagnosis and manuscript proofreading; Fatiha Najioullah of the University Hospital Laboratory of virology, Fort-de-France, Martinique manages the molecular virological diagnosis and in involved in virological diagnosis and manuscript proofreading ; Raymond Césaire Head of the virology laboratory of the University Hospital Laboratory of virology, Fort-de-France, Martinique was involved in the implementation of virological diagnosis; Séverine Matheus of the French National Reference Center for Arboviruses is deputy head of the associated laboratory for the French departments of the Americas and involved in virological diagnosis and manuscript proofreading; Isabelle Leparc-Goffart Head of the French National Reference Center for Arboviruses and coordinating all French territories is involved in virological diagnosis and participated to the writing of the manuscript; Olivier Flusin of the French National Reference Center for Arboviruses, is involved in virological diagnosis and editing of the manuscript; Christine M Prat of the French National Reference Center for Arboviruses is involved in virological diagnosis and editing of the manuscript; Vanessa Ardillon is a permanent member of the outbreak management team in French Guyana and member of the regional outbreak management team (French Caribbean territories) and responsible for management, data collection and interpretation; Elsa Balleydier is temporary member of the outbreak management team in Guadeloupe, Saint Martin and Saint Barthélemy and is involved in the data collection, management and interpretation; Luisiane Carvalho is a permanent member of the outbreak management team in French Guyana and member of the regional outbreak management team (French Caribbean territories) and responsible for management, data collection, and interpretation; Audrey Lemaître is a temporary member of the outbreak management team in Saint Martin and Saint Barthélemy and involved in the data collection, management and interpretation; Lucie Léon is a temporary member of the outbreak management team in Saint Martin and Saint Barthélemy and involved in the data collection, management and interpretation; Harold Noël, Véronique Servas, Caroline Six and Manuel Zurbaran are temporary members of the outbreak team management in Saint Martin and Saint Barthélemy and responsible for data collection, management and interpretation; Anne Guinard from the French Institute for Public Health Surveillance, Toulouse, France was involved in data collection and interpretation; Hans van den Kerkhof coordinates the international aspects of control for the Netherlands, and coordinating author of the Netherlands contribution to the Euro Roundup Chikungunya ; Ewout Fanoy is responsible for the registration of cases, epidemiological analysis and reviewing manuscript; Marieta Braks is an entomologist at the RIVM and advisor/trainer for mosquito control programmes on Sint Maarten. She was involved in the editing and proof reading of the manuscript; Johan Reimerink is a senior staff in the virological Laboratory in RIVM, and responsible for Diagnostic Testing of outbreak samples; Maria Henry is in charge of surveillance and control activities Sint Maarten and reviewed the manuscript; Corien Swaan coordinates the international aspects of control for the Netherlands and contributed to the writing of the manuscript; Ronald Georges provided epidemiological information from the British Virgin Islands and reviewed manuscript; Lynrod Brooks: provided epidemiological information from Anguilla and reviewed manuscript; Joanne Freedman: provided the UK background, coordinated the contribution of additional epidemiological information from the UK overseas territories and reviewed final document for accuracy; Bertrand Sudre coordinated and developed the historical overview and the transmission map and reviewed final document ; Herve Zeller, head of the emerging and vector borne disease programme of ECDC, reviewed final document for accuracy. All authors have read and approved the manuscript.

References

1. Pialoux G, Gaüzère B-A, Jauréguiberry S, Strobel M. Chikungunya, an epidemic arbovirosis. Lancet Infect Dis. 2007;7(5):319-27. http://dx.doi.org/10.1016/S1473-3099(07)70107-X
2. Farnon EC, Sejvar JJ, Staples JE. Severe disease manifestations associated with acute chikungunya virus infection. Crit Care Med. 2008;36(9):2682-3. http://dx.doi.org/10.1097/CCM.0b013e3181843d94
3. Bianco C. Dengue and Chikungunya viruses in blood donations: risks to the blood supply? Transfusion. 2008;48(7):1279-81. http://dx.doi.org/10.1111/j.1537-2995.2008.01806.x
4. Appassakij H, Khuntikij P, Kemapunmanus M, Wutthanarungsan R, Silpapojakul K. Viremic profiles in asymptomatic and symptomatic chikungunya fever: a blood transfusion threat? Transfusion. 2013;53(10 Pt 2):2567-74. http://dx.doi.org/10.1111/j.1537-2995.2012.03960.x
5. Ramful D, Carbonnier M, Pasquet M, Bouhmani B, Ghazouani J, Noormahomed T, et al. Mother-to-child transmission of Chikungunya virus infection. Pediatr Infect Dis J. 2007;26(9):811-5. http://dx.doi.org/10.1097/INF.0b013e3180616d4f
6. Gerardin P, Barau G, Michault A, Bintner M, Randrianaivo H, Choker G, et al. Multidisciplinary prospective study of mother-to-child chikungunya virus infections on the island of La Reunion. PLoS Med. 2008;5(3):e60. http://dx.doi.org/10.1371/journal.pmed.0050060

7. European Centre for Disease Prevention and Control (ECDC). Rapid Risk Assessment. Autochthonous cases of chikungunya fever on the Caribbean island, Saint Martin. 11 December 2013. Stockholm: ECDC;2013.
8. Angelini R, Finarelli AC, Angelini P, Po C, Petropulacos K, Macini P, et al. An outbreak of chikungunya fever in the province of Ravenna, Italy. Euro Surveill. 2007;12(36):pii:3260.
9. Grandadam M, Caro V, Plumet S, Thiberge JM, Souares Y, Failloux AB, et al. Chikungunya virus, southeastern France. Emerg Infect Dis. 2011;17(5):910-3. http://dx.doi.org/10.3201/eid1705.101873
10. European Centre for Disease Prevention and Control (ECDC). VBORNET - Network of medical entomologists and public health experts. Mosquito maps. Stockholm: ECDC; [Accessed 28 Feb 2014]. Available from: http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx
11. Vazeille M, Moutailler S, Coudrier D, Rousseaux C, Khun H, Huerre M, et al. Two Chikungunya isolates from the outbreak of La Reunion (Indian Ocean) exhibit different patterns of infection in the mosquito, Aedes albopictus. PloS one. 2007;2(11):e1168. http://dx.doi.org/10.1371/journal.pone.0001168
12. Alerte "chikungunya" dans les Antilles. Point Epidemiol Cire Antilles Guyane. 2013; 2. French.
13. Leparc-Goffart I, Nougairede A, Cassadou S, Prat C, de Lamballerie X. Chikungunya in the Americas. Lancet. 2014;383(9916):514. http://dx.doi.org/10.1016/S0140-6736(14)60185-9
14. Pan-American Health Organization (PAHO). Preparedness and Response Plan for Chikungunya Virus Introduction in the Caribbean sub-region. Washington, DC: PAHO; 2013.
15. European Centre for Disease Prevention and Control (ECDC). E3 Geoportal: Aedes aegypti environmental suitability model Stockholm: ECDC; 2014. [Accessed 14 Feb 2014]. Available from: https://e3geoportal.ecdc.europa.eu/SitePages/Aedes%20aegypti%20Suitability%20Map.aspx
16. European Centre for Disease Prevention and Control (ECDC). E3 Geoportal: Aedes albopictus (tiger mosquitoes) environmental suitability model Stockholm: ECDC; 2014. [Accessed 14 Feb 2014]. Available from: https://e3geoportal.ecdc.europa.eu/SitePages/Aedes%20albopictus%20Suitability%20Map.aspx
17. European Centre for Disease Prevention and Control (ECDC). The climatic suitability for dengue transmission in continental Europe. Stockholm: ECDC, 2012.
18. Pan-American Health Organization (PAHO) – World Health Organization (WHO). Epidemiological update. Chikungunya fever, 21 February 2014. PAHO-WHO. [Accessed 28 Feb 2014]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=24318&Itemid=
19. Caribbean Public Health Agency (CARPHA). Chikungunya Updates: Caribbean Public Health Agency. CARPHA; 2014. [Accessed 31 Mar 2014]. Available from: http://carpha.org/What-We-Do/Public-Health-Activities/Chikungunya
20. European Centre for Disease Prevention and Control (ECDC). Consultation on Chikungunya risk assessment for Europe. Stockholm: ECDC; 2006.
21. Rezza G, Nicoletti L, Angelini R, Romi R, Finarelli AC, Panning M, et al. Infection with chikungunya virus in Italy: an outbreak in a temperate region. Lancet. 2007;370(9602):1840-6. http://dx.doi.org/10.1016/S0140-6736(07)61779-6
22. Angelini R, Finarelli AC, Angelini P, Po C, Petropulacos K, Silvi G, et al. Chikungunya in north-eastern Italy: a summing up of the outbreak. Euro Surveill. 2007;12(47):pii=3313.
23. Charrel RN, de Lamballerie X, Raoult D. Seasonality of mosquitoes and chikungunya in Italy. Lancet Infect Dis. 2008;8(1):5-6. http://dx.doi.org/10.1016/S1473-3099(07)70296-7
24. Frank C, Schoneberg I, Stark K. Trends in imported chikungunya virus infections in Germany, 2006-2009. Vector-Borne Zoonotic Dis. 2011;11(6):631-6. http://dx.doi.org/10.1089/vbz.2010.0269
25. Petersen LR, Stramer SL, Powers AM. Chikungunya virus: possible impact on transfusion medicine. Transfus Med Rev. 2010;24(1):15-21. http://dx.doi.org/10.1016/j.tmrv.2009.09.002
26. Medlock JM, Hansford KM, Schaffner F, Versteirt V, Hendrickx G, Zeller H, et al. A Review of the Invasive Mosquitoes in Europe: Ecology, Public Health Risks, and Control Options. Vector-Borne Zoonotic Dis. 2012;12(6):435-47. http://dx.doi.org/10.1089/vbz.2011.0814
27. Tran A, L'Ambert G, Lacour G, Benoit R, Demarchi M, Cros M, et al. A rainfall- and temperature-driven abundance model for Aedes albopictus populations. Int J Environ Res Public Health. 2013;10(5):1698-719. http://dx.doi.org/10.3390/ijerph10051698
28. Vega-Rua A, Zouache K, Caro V, Diancourt L, Delaunay P, Grandadam M, et al. High efficiency of temperate Aedes albopictus to transmit chikungunya and dengue viruses in the Southeast of France. PloS one. 2013;8(3):e59716. http://dx.doi.org/10.1371/journal.pone.0059716
29. McIntosh BM, Harwin RM, Paterson HE, Westwater ML. An Epidemic of Chikungunya in South-Eastern Southern Rhodesia. Cent Afr J Med. 1963;43:351-9.
30. Jadhav M, Namboodripad M, Carman RH, Carey DE, Myers RM. Chikungunya disease in infants and children in Vellore: a report of clinical and haematological features of virologically proved cases. Indian J Med Res. 1965;53(8):764-76.
31. Myers RM, Carey DE, Reuben R, Jesudass ES, De Ranitz C, Jadhav M. The 1964 epidemic of dengue-like fever in South India: isolation of chikungunya virus from human sera and from mosquitoes. Indian J Med Res. 1965;53(8):694-701.
32. Moore DL, Reddy S, Akinkugbe FM, Lee VH, David-West TS, Causey OR, et al. An epidemic of chikungunya fever at Ibadan, Nigeria, 1969. Ann Trop Med Parasitol. 1974;68(1):59-68.
33. Khai Ming C, Thain S, Thaung U, Tin U, Myint KS, Swe T, et al. Clinical and laboratory studies on haemorrhagic fever in Burma, 1970-72. Bull World Health Organ. 1974;51(3):227-35.
34. Filipe AF, Pinto MR. Arbovirus studies in Luanda, Angola. 2. Virological and serological studies during an outbreak of dengue-like disease caused by the Chikungunya virus. Bull World Health Organ. 1973;49(1):37-40.
35. Tomori O, Fagbami A, Fabiyi A. The 1974 epidemic of Chikungunya fever in children in Ibadan. Trop Geogr Med. 1975;27(4):413-7.
36. Morrison JG. Chikungunya fever. Int J Dermatol. 1979;18(8):628-9. http://dx.doi.org/10.1111/j.1365-4362.1979.tb04677.x
37. Padbidri VS, Gnaneswar TT. Epidemiological investigations of chikungunya epidemic at Barsi, Maharashtra state, India. J Hyg Epidemiol Microbiol Immunol. 1979;23(4):445-51.
38. Saluzzo JF, Gonzalez JP, Herve JP, Georges AJ. [Epidemiological study of arboviruses in the Central African Republic: demonstration of Chikungunya virus during 1978 and 1979]. Bull Soc Pathol Exot Filiales. 1980 Jul-Aug;73(4):390-9. French.
39. Brighton SW, Prozesky OW, de la Harpe AL. Chikungunya virus infection. A retrospective study of 107 cases. S Afr Med J. 1983;63(9):313-5.
40. Saluzzo JF, Cornet M, Digoutte JP. [Outbreak of a Chikungunya virus epidemic in western Senegal in 1982]. Dakar Med. 1983;28(3):497-500. French.
41. Centers for Disease Control (CDC). Chikungunya fever among U.S. Peace Corps volunteers--Republic of the Philippines. MMWR Morb Mortal Wkly Rep. 1986;35(36):573-4.
42. Rodhain F, Carteron B, Laroche R, Hannoun C. [Human arbovirus infections in Burundi: results of a seroepidemiologic survey, 1980-1982]. Bull Soc Pathol Exot Filiales. 1987;80(2):155-61.
43. Rodhain F, Gonzalez JP, Mercier E, Helynck B, Larouze B, Hannoun C. Arbovirus infections and viral haemorrhagic fevers in Uganda: a serological survey in Karamoja district, 1984. Trans R Soc Trop Med Hyg. 1989;83(6):851-4. http://dx.doi.org/10.1016/0035-9203(89)90352-0
44. Dash AP, Bhatia R, Sunyoto T, Mourya DT. Emerging and re-emerging arboviral diseases in Southeast Asia. J Vector Borne Dis. 2013;50(2):77-84.
45. Ivanov AP, Ivanova OE, Lomonosov NN, Pozdnyakov SV, Konstantinov OK, Bah MA. Serological investigations of Chikungunya virus in the Republic of Guinea. Ann Soc Belg Med Trop. 1992;72(1):73-4.
46. Thaikruea L, Charearnsook O, Reanphumkarnkit S, Dissomboon P, Phonjan R, Ratchbud S, et al. Chikungunya in Thailand: a re-emerging disease? Southeast Asian J Trop Med Public Health. 1997;28(2):359-64.
47. Lam SK, Chua KB, Hooi PS, Rahimah MA, Kumari S, Tharmaratnam M, et al. Chikungunya infection--an emerging disease in Malaysia. Southeast Asian J Trop Med Public Health. 2001;32(3):447-51.
48. Muyembe-Tamfum JJ, Peyrefitte CN, Yogolelo R, Mathina Basisya E, Koyange D, Pukuta E, et al. [Epidemic of Chikungunya virus in 1999 and 200 in the Democratic Republic of the Congo]. Med Trop. 2003;63(6):637-8. French.
49. Porter KR, Tan R, Istary Y, Suharyono W, Sutaryo, Widjaja S, et al. A serological study of Chikungunya virus transmission in Yogyakarta, Indonesia: evidence for the first outbreak since 1982. Southeast Asian J Trop Med Public Health. 2004;35(2):408-15.

50. Chastel C. [Chikungunya virus: its recent spread to the southern Indian Ocean and Reunion Island (2005-2006)]. Bull Acad Natl Med. 2005;189(8):1827-35. French.
51. Outbreak news. Chikungunya and dengue, south-west Indian Ocean. Wkly Epidemiol Rec. 2006;81(12):106-8.
52. Outbreak news. Chikungunya, India. Wkly Epidemiol Rec. 2006;81(43):409-10.
53. Bonn D. How did chikungunya reach the Indian Ocean? Lancet Infect Dis. 2006;6(9):543. http://dx.doi.org/10.1016/S1473-3099(06)70559-X
54. Josseran L, Paquet C, Zehgnoun A, Caillere N, Le Tertre A, Solet JL, et al. Chikungunya disease outbreak, Reunion Island. Emerg Infect Dis. 2006;12(12):1994-5. http://dx.doi.org/10.3201/eid1212.060710
55. Kalantri SP, Joshi R, Riley LW. Chikungunya epidemic: an Indian perspective. Natl Med J India. 2006;19(6):315-22.
56. Kumarasamy V, Prathapa S, Zuridah H, Chem YK, Norizah I, Chua KB. Re-emergence of Chikungunya virus in Malaysia. Med J Malaysia. 2006;61(2):221-5.
57. Seneviratne SL, Perera J. Fever epidemic moves into Sri Lanka. BMJ. 2006;333(7580):1220-1. http://dx.doi.org/10.1136/bmj.39051.725729.3A
58. Peyrefitte CN, Rousset D, Pastorino BA, Pouillot R, Bessaud M, Tock F, et al. Chikungunya virus, Cameroon, 2006. Emerg Infect Dis. 2007;13(5):768-71. http://dx.doi.org/10.3201/eid1305.061500
59. Beesoon S, Funkhouser E, Kotea N, Spielman A, Robich RM. Chikungunya fever, Mauritius, 2006. Emerg Infect Dis. 2008;14(2):337-8. http://dx.doi.org/10.3201/eid1402.071024
60. Gould LH, Osman MS, Farnon EC, Griffith KS, Godsey MS, Karch S, et al. An outbreak of yellow fever with concurrent chikungunya virus transmission in South Kordofan, Sudan, 2005. Trans R Soc Trop Med Hyg. 2008;102(12):1247-54. http://dx.doi.org/10.1016/j.trstmh.2008.04.014
61. Peyrefitte CN, Bessaud M, Pastorino BA, Gravier P, Plumet S, Merle OL, et al. Circulation of Chikungunya virus in Gabon, 2006-2007. J Med Virol. 2008;80(3):430-3. http://dx.doi.org/10.1002/jmv.21090
62. Ratsitorahina M, Harisoa J, Ratovonjato J, Biacabe S, Reynes JM, Zeller H, et al. Outbreak of dengue and Chikungunya fevers, Toamasina, Madagascar, 2006. Emerg Infect Dis. 2008;14(7):1135-7. http://dx.doi.org/10.3201/eid1407.071521
63. D'Ortenzio E, Grandadam M, Balleydier E, Dehecq JS, Jaffar-Bandjee MC, Michault A, et al. Sporadic cases of chikungunya, Reunion Island, August 2009. Euro Surveill. 2009;14(35):pii:19324.
64. Leo YS, Chow AL, Tan LK, Lye DC, Lin L, Ng LC. Chikungunya outbreak, Singapore, 2008. Emerg Infect Dis. 2009;15(5):836-7. http://dx.doi.org/10.3201/eid1505.081390
65. Leroy EM, Nkoghe D, Ollomo B, Nze-Nkogue C, Becquart P, Grard G, et al. Concurrent chikungunya and dengue virus infections during simultaneous outbreaks, Gabon, 2007. Emerg Infect Dis. 2009;15(4):591-3. http://dx.doi.org/10.3201/eid1504.080664
66. Theamboonlers A, Rianthavorn P, Praianantathavorn K, Wuttirattanakowit N, Poovorawan Y. Clinical and molecular characterization of chikungunya virus in South Thailand. Jpn J Infect Dis. 2009;62(4):303-5.
67. Yoosuf AA, Shiham I, Mohamed AJ, Ali G, Luna JM, Pandav R, et al. First report of chikungunya from the Maldives. Trans R Soc Trop Med Hyg. 2009;103(2):192-6. http://dx.doi.org/10.1016/j.trstmh.2008.09.006
68. Chua KB. Epidemiology of chikungunya in Malaysia: 2006-2009. Med J Malaysia. 2010;65(4):277-82.
69. Win MK, Chow A, Dimatatac F, Go CJ, Leo YS. Chikungunya fever in Singapore: acute clinical and laboratory features, and factors associated with persistent arthralgia. J Clin Virol. 2010;49(2):111-4. http://dx.doi.org/10.1016/j.jcv.2010.07.004
70. Chusri S, Siripaitoon P, Hirunpat S, Silpapojakul K. Case reports of neuro-Chikungunya in southern Thailand. Am J Trop Med Hyg. 2011;85(2):386-9. http://dx.doi.org/10.4269/ajtmh.2011.10-0725
71. Qiaoli Z, Jianfeng H, De W, Zijun W, Xinguang Z, Haojie Z, et al. Maiden outbreak of chikungunya in Dongguan city, Guangdong province, China: epidemiological characteristics. PloS one. 2012;7(8):e42830. http://dx.doi.org/10.1371/journal.pone.0042830
72. Singh P, Mittal V, Rizvi MM, Chhabra M, Sharma P, Rawat DS, et al. The first dominant co-circulation of both dengue and chikungunya viruses during the post-monsoon period of 2010 in Delhi, India. Epidemiol Infect. 2012;140(7):1337-42. http://dx.doi.org/10.1017/S0950268811001671
73. Wu D, Wu J, Zhang Q, Zhong H, Ke C, Deng X, et al. Chikungunya outbreak in Guangdong Province, China, 2010. Emerg Infect Dis. 2012;18(3):493-5. http://dx.doi.org/10.3201/eid1803.110034
74. Mombouli JV, Bitsindou P, Elion DO, Grolla A, Feldmann H, Niama FR, et al. Chikungunya virus infection, Brazzaville, Republic of Congo, 2011. Emerg Infect Dis. 2013;19(9):1542-3. http://dx.doi.org/10.3201/eid1909.130451
75. Wu D, Zhang Y, Zhouhui Q, Kou J, Liang W, Zhang H, et al. Chikungunya virus with E1-A226V mutation causing two outbreaks in 2010, Guangdong, China. Virol J. 2013;10:174. http://dx.doi.org/10.1186/1743-422X-10-174
76. Centers for Disease Control and Prevention (CDC). Chikungunya outbreak--Cambodia, February-March 2012. MMWR Morb Mortal Wkly Rep. 2012;61:737-40.
77. Soulaphy C, Souliphone P, Phanthavong K, Phonekeo D, Phimmasine S, Khamphaphongphane B, et al. Emergence of chikungunya in Moonlapamok and Khong Districts, Champassak Province,the Lao People's Democratic Republic, May to September 2012. Western Pac Surveill Response J. 2013;4(1):46-50. http://dx.doi.org/10.5365/wpsar.2012.3.4.017
78. Wangchuk S, Chinnawirotpisan P, Dorji T, Tobgay T, Dorji T, Yoon IK, et al. Chikungunya fever outbreak, Bhutan, 2012. Emerg Infect Dis. 2013;19(10):1681-4. http://dx.doi.org/10.3201/eid1910.130453
79. Zayed A, Awash AA, Esmail MA, Al-Mohamadi HA, Al-Salwai M, Al-Jasari A, et al. Detection of Chikungunya virus in Aedes aegypti during 2011 outbreak in Al Hodayda, Yemen. Acta Trop. 2012;123(1):62-6. http://dx.doi.org/10.1016/j.actatropica.2012.03.004
80. Ansumana R, Jacobsen KH, Leski TA, Covington AL, Bangura U, Hodges MH, et al. Reemergence of chikungunya virus in Bo, Sierra Leone. Emerg Infect Dis. 2013;19(7):1108-10. http://dx.doi.org/10.3201/eid1907.121563
81. Horwood PF, Reimer LJ, Dagina R, Susapu M, Bande G, Katusele M, et al. Outbreak of chikungunya virus infection, Vanimo, Papua New Guinea. Emerg Infect Dis. 2013;19(9):1535-8. http://dx.doi.org/10.3201/eid1909.130130

West Nile virus outbreak in humans, Greece, 2012: third consecutive year of local transmission

D Pervanidou (pervanidou@gmail.com)[1,2], M Detsis[1], K Danis[1,2], K Mellou[1], E Papanikolaou[1], I Terzaki[1], A Baka[1], L Veneti[1], A Vakali[1], G Dougas[1], C Politis[1], K Stamoulis[3], S Tsiodras[1,4], T Georgakopoulou[1], A Papa[5], A Tsakris[4], J Kremastinou[1], C Hadjichristodoulou[1,6]

1. Hellenic Center for Disease Control & Prevention, Athens, Greece
2. European Programme in Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
3. Hellenic National Blood Centre, Athens, Greece
4. Medical Faculty, University of Athens, Athens, Greece
5. Medical Faculty, University of Thessaloniki, Thessaloniki, Greece
6. Medical Faculty, University of Thessaly, Larisa, Greece

Citation style for this article:
Pervanidou D, Detsis M, Danis K, Mellou K, Papanikolaou E, Terzaki I, Baka A, Veneti L, Vakali A, Dougas G, Politis C, Stamoulis K, Tsiodras S, Georgakopoulou T, Papa A, Tsakris A, Kremastinou J, Hadjichristodoulou C. West Nile virus outbreak in humans, Greece, 2012: third consecutive year of local transmission. Euro Surveill. 2014;19(13):pii=20758. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20758

Article submitted on 09 July 2013 / published on 3 April 2014

In 2010, the first outbreak of West Nile virus (WNV) infection in Greece was recorded, the largest in Europe since 1996. After 2010, outbreaks continued to occur in different areas of the country. Enhanced surveillance was implemented during transmission periods (June to October). We investigated the 2012 outbreak to determine its extent and identify risk factors for severe disease using regression models. Of 161 cases recorded in 2012, 109 had neuroinvasive disease (WNND). Two outbreak epicentres were identified: the southern suburbs of Athens in July and a rural area in East Macedonia &Thrace in August–September. The case fatality rate of the WNND cases was 17% (18/109). A lower case fatality rate was recorded in the two epicentres (7% (2/28) and 9% (4/46)): the higher case fatality outside the two epicentres might reflect a diagnostic bias. Age above 74 years (adjusted risk ratio (RR): 7.0; 95% CI: 2.2–22) and chronic renal failure (adjusted RR: 4.5; 95% CI: 2.7–7.5) were independently associated with WNND-related death. In three PCR-positive samples, sequencing revealed WNV lineage 2 identical to the 2010 strain. The occurrence of human cases in three consecutive years suggests that WNV lineage 2 has become established in Greece. Raising awareness among physicians and susceptible populations (elderly people and persons with comorbidities) throughout Greece is critical to reduce the disease impact.

Introduction

West Nile virus (WNV) is one of the most widely distributed arboviruses in the world, with endemic foci in Africa, the Middle East, west Asia, North and Central America, parts of Europe and Australia [1]. Human cases have been reported from several countries since the 1960s; however, the frequency of reported outbreaks has increased over the last 15–20 years [2,3]. About 20% of persons infected with WNV develop a mild disease, usually referred to as West Nile fever (WNF). In less than 1% of the cases, the virus causes a neuroinvasive disease (WNND) with serious neurological manifestations, i.e. encephalitis, meningitis, meningoencephalitis or acute flaccid paralysis [4]. Among patients with severe illness, the case fatality rate varies (e.g. approximately 10% in the United States [5] and 12–18% during transmission periods during 2010 to 2011 in Greece [6]).

Two main WNV genetic lineages are known: lineage 1, identified in the majority of the outbreaks in humans and horses in Europe and the United States and lineage 2, which until 2004 had not been detected outside Africa, but since then has repeatedly appeared – initially in Hungary in 2004 [7] and 2005–09 [8], in Russia in 2007 [9] and in Austria in 2008–09 [8,10].

Before 2010, symptomatic human cases of WNV infection had not been documented in Greece. However, serosurveys in the early 60s, 80s and in 2007 suggest that WNV or a related flavivirus had been circulating at low levels in Greece at least since the 60s [11-13]. The first recorded outbreak of WNV infection in Greece was in 2010: this was the largest reported outbreak in Europe since 1996 [14], with 262 recorded cases. Of these, 197 developed WNND, of whom 33 (17%) died [15]. A seroprevelence study conducted after the 2010 outbreak (between 25 November to 22 December 2010) indicated that 1 in 140 people infected with WNV developed WNND [16].

The outbreak in 2010 was first detected in the Central Macedonia region, in northern Greece [15,17]. Surveillance in the blood donor population and post-transfusion information during the 2010 outbreak

showed that the estimated risk of infected blood donations in the affected areas, associated with collecting blood from asymptomatic donors (based on the method proposed by Biggerstaff and Petersen [18], which is recommended in the 2012 European Union (EU) preparedness plan for WNV and blood safety [19]) was 2.95 per 10,000 population. Transfusion-transmitted WNV infection was recorded in two of 369 thalassaemic patients in 2010 (incidence 1:2,397 transfused units of red cell concentrates), before the implementation of blood safety measures in this year [20,21].

In 2011, cases of WNV infection occurred in the same districts as in 2010. In addition, the virus dispersed southward to the region of Thessaly, and further south to Eastern Attica, in proximity to the metropolitan area of Athens [6]. Overall, 100 human cases were identified, 75 of whom had WNND and nine (12%) of the WNND cases died.

WNV lineage 2 sequences (strain Nea Santa-Greece-2010) were obtained from blood donors, mosquitoes and birds in the transmission period (June to October) of both years [22-27].

In 2012, cases of WNV infection were first reported to the Hellenic Center for Disease Control & Prevention in June. Here we present the analysed epidemiological data gathered during the 2012 transmission period in order to describe the outbreak in terms of time, place and person and identify possible factors associated with disease severity.

Methods

Surveillance

Following the 2010 outbreak, physicians (public and private sector) in Greece were asked to include WNV infection in their differential diagnosis during the transmission period and notify daily suspected and laboratory-diagnosed cases to the Hellenic Center for Disease Control & Prevention. In parallel, during this period, daily information exchange with the laboratories involved in the diagnosis of WNV infection was established for timely case identification and investigation.

Outbreak case definition

The 2008 European Union case definition for WNV infection [28] was used with a slight modification, i.e. the definition of probable cases included clinical and laboratory – but not epidemiological – criteria).

Data collection

We collected information regarding the demographic characteristics, clinical manifestations, underlying chronic diseases and laboratory results of all the cases reported in 2012 by using standardised reporting forms. We telephoned treating physicians of all reported cases for data validation and follow up of the patients' clinical status. Moreover, in-depth telephone interviews with all cases or their close relatives (as proxy respondents, when cases had severe disease and/or cognitive problems) using a semi-structured questionnaire were conducted to obtain a detailed travel history during the incubation period (2–14 days before symptom onset) and identify the suspected place of exposure.

Cases reported as having encephalitis (including meningoencephalitis), meningitis or acute flaccid paralysis were classified as having WNND. WNND classification was based on the treating physicians' clinical assessment and laboratory data (detection of WNV nucleic acid and/or WNV-specific antibody response in cerebrospinal fluid (CSF) and/or imaging findings), when available. Deaths in persons with WNV infection were recorded during hospitalisation.

Municipalities (the lowest administrative unit) with at least one human laboratory- diagnosed case of WNV infection during the 2012 transmission period were classed as affected areas.

We assigned week numbers using the International Organization for Standardization (ISO) 8601 standard [29].

Blood safety measures

Measures for the protection of blood donations against WNV infection were implemented in the affected areas. These included blood donor deferral, blood screening for WNV RNA and haemovigilance (a set of organised surveillance procedures related to serious adverse or unexpected events or reactions in donors or recipients and the epidemiological follow-up of donors, according to the eligibility criteria of donors of whole blood and blood components as referred to in article 4 and annex III of the Commission Directive 2004/33/EC [30]).

Laboratory methods

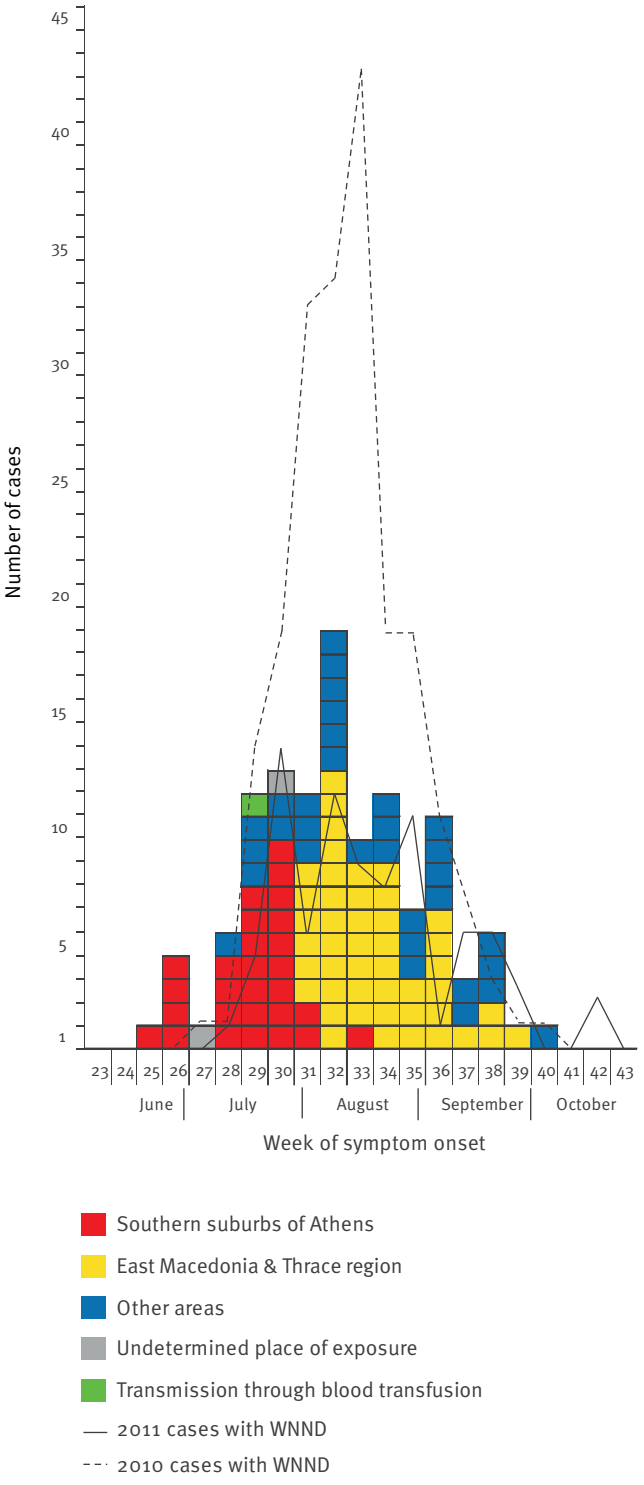
We obtained laboratory data from the four laboratories in which all the suspected WNV infection cases from all over Greece were tested: (i) National Reference Laboratory for Arboviruses, School of Medicine, Aristotle University of Thessaloniki; (ii) Department of Microbiology, School of Medicine, University of Athens; (iii) Department of Microbiology, Infectious Disease Hospital of Thessaloniki; and (iv) Department of Diagnostic Services, Hellenic Pasteur Institute.

Serum and CSF specimens were tested for IgM and IgG against WNV by ELISA (WNV IgM capture DxSelect and WNV IgG DxSelect, respectively, Focus Diagnostics Inc, Cypress, CA, United States). A real-time reverse-transcription (RT)-PCR [31] and an RT-nested PCR [32] were used.

After the diagnosis of the first human case, screening of donated blood for WNV RNA with targeted individual donation (ID) nucleic acid amplification testing (NAT) using the Procleix WNV Assay [33] or minipool

Figure 1

Laboratory-diagnosed (confirmed and probable) cases of West Nile neuroinvasive disease by week[a] of symptom onset, Greece, 2010 (n=197), 2011 (n=75), 2012 (n=109)[b]



WNND: West Nile neuroinvasive disease.

[a] Week number is according to the International Organization for Standardization (ISO) 8601 standard.

[b] Each box represents one laboratory-diagnosed case of WNND reported in 2012.

(MP) NAT of equal aliquots of six individual donations using the Gobas TaqScreen West Nile Virus Test [34] was implemented in the affected areas, from 11 July to 10 November. The screening was carried out in five Blood Centres (three in Athens, one in Thessaloniki and another in Alexandroupoli).

Data analysis

Descriptive analysis of the surveillance data was conducted, including the geographical and temporal distribution of WNND cases, age, sex, clinical manifestations, underlying diseases and clinical outcome.

We calculated risk ratios (RRs) to compare the incidence of WNND in different populations. Urban and rural areas were defined according to the Hellenic Statistical Authority data [35]: townships with more than 2,000 residents were classified as urban.

To identify predictive factors of developing WNND versus WNF, we calculated odds ratios (ORs), as WNF reported cases represented a small fraction of all WNF infections in the population [16]. An association was considered statistically significant when the p value was ≤0.05.

We constructed multiple logistic regression models to identify factors independently associated with disease severity. Initials models included all variables for which the p value was ‹0.1 or the OR was ›1.10 or ‹0.90. We removed variables one at a time, depending on the significance testing (p‹0.05) by the likelihood ratio test. We estimated adjusted RRs from binomial regression analysis including all variables that remained significant in the final logistic regression model. Imported cases and asymptomatic infections detected through haemovigilance were not included in the analysis.

The analysis was carried out using STATA version 12 software (Stata Corporation LP, Texas, United States).

Results

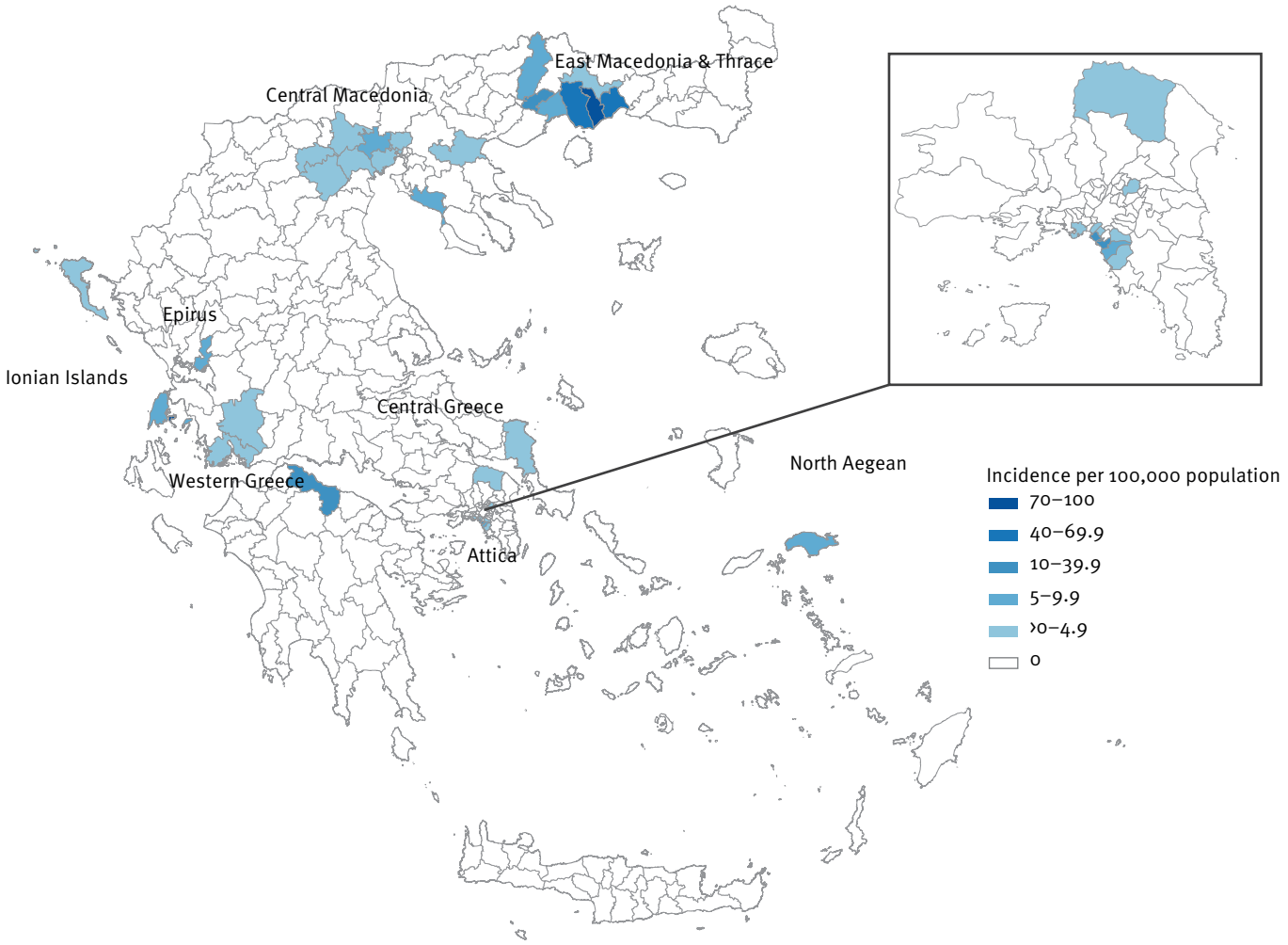
Descriptive analysis

In 2012, 163 cases of WNV infection were recorded. Two of the cases were classified as imported from the United States. Of the 161 locally acquired cases, 109 (47 confirmed and 62 probable) were classified as WNND and 52 (one confirmed and 51 probable) as WNF. The overall WNND incidence was one case per 100,000 population. One of the WNND reported cases was a Greek traveller whose infection was diagnosed in Germany [36]. Close relatives of 83% (n=91) of the 109 WNND cases, with severe disease and/or cognitive problems, were interviewed.

All cases occurred within a 16-week interval from 20 June (week 25) to 7 October 7 (week 41) 2012 and the outbreak peaked in the second week of August (Figure 1). The median period from symptom onset to diagnosis

Figure 2

Incidence (per 100,000 population) of West Nile neuroinvasive disease by suspected municipality of exposure, Greece, June–October 2012 (n=106)[a]



[a] The place of exposure could not be determined for two cases. One patient acquired the infection through blood transfusion and is also not included in the map.

for the WNND cases was 7 days (range: 2–53) and the mean was 9.29 (SD: 6.98) days.

Haemovigilance procedures demonstrated that one WNND case acquired the infection through blood transfusion: this patient was admitted to the intensive care unit and recovered. Another person transfused with a blood component derived from the same unit of blood from the implicated donor was also infected but did not develop symptoms. It is important to emphasise that blood collection from the implicated donor and both transfusions took place before diagnosis of the first case of WNV infection in Greece in 2012, which triggered the implementation of blood safety measures against WNV infection. Details of these haemovigilance findings and data on surveillance in the blood donor population will be presented elsewhere.

For two WNND cases, the probable place of exposure could not be determined, due to their complicated travel history during the incubation period. The remaining 106 WNND cases were infected in 19 of the 74 regional units of the country, in eight regions (Figure 2); 55% (58/106) of the cases occurred in eight regional units that had not been previously affected.

During the 2012 transmission period, two main outbreak epicentres were identified. From 20 June (week 25) to 16 August (week 33), 26% (n=28) of the 106 WNND cases occurred in the southern suburbs of Athens in Attica (incidence: 3.6 per 100,000 population): this had not been previously considered an established area for WNV. Six weeks after the beginning of the outbreak, and as the number of new cases was substantially decreasing in Attica, a second epicentre was detected in a newly affected rural wetland area in the

Table 1

Characteristics of cases with West Nile neuroinvasive disease, Greece, June–October 2012 (n=109)

Characteristic	Number of cases (%)[a]	Incidence (per 100,000 population)[b]	Risk ratio (95% CI)
Age group in years			
<20	2 (2)	0.09	Reference
20–29	3 (3)	0.23	2.5 (0.42–15)
30–39	3 (3)	0.17	1.9 (0.32–11)
40–49	4 (4)	0.23	2.6 (0.47–14)
50–59	12 (11)	0.80	8.7 (1.9–39)
60–69	29 (27)	2.34	26 (6.1–107)
70–79	31 (28)	2.94	32 (7.7–134)
≥80	25 (23)	4.22	46 (11–194)
Sex			
Female	38 (35)	0.67	Reference
Male	71 (65)	1.27	1.9 (1.3–2.8)
Place of exposure[c]			
Urban	55 (52)	0.67	Reference
Rural	51 (48)	1.87	2.8 (1.9–4.1)

[a] Percentages do not sum to 100% as a result of rounding.

[b] Population data from Hellenic Statistical Authority (EL. STAT.) [56].

[c] Three cases are not included (two cases with undetermined place of exposure and one case infected through blood transfusion).

Source: Hellenic Center for Disease Control & Prevention.

region of East Macedonia & Thrace, with 43% (46/106) of the WNND cases (incidence: 17.6 per 100,000 population), from 30 July (week 31) to 27 September (week 39) (Figure 1). Among these cases, 41 were recorded in the regional units of Xanthi and Kavala. The remaining cases mainly occurred in the regions of Central Macedonia (n=15) and Western Greece (n=7).

Among the WNND cases, 52% (55/106) were residents of urban areas, while the incidence of WNND in rural settings was almost three times higher than that in urban areas (Table 1). All 28 WNND cases in the southern suburbs of Athens and 11/46 of the cases in the region of East Macedonia & Thrace were from urban areas. In rural areas, the incidence of WNND was significantly higher among people who were male (RR: 2.3; 95% CI: 1.2–4.2, p=0.005), whereas in urban areas, the difference between the sexes was not statistically significant (RR: 1.6; 95% CI: 0.91–2.7, p=0.10).

The median age of WNND cases was 70 years (range: 11–95) and 65% (71/109) were male. The incidence of WNND cases increased from 0.17 per 100,000 in the 30–39 year-olds to 4.22 per 100,000 in those who were ≥80 years-old (Table 1). The median age and sex distribution of patients with WNND in the two epicentres did not significantly differ (p=0.93 and p=0.87, respectively).

Encephalitis/meningoencephalitis (83%; 90/109) was the most prominent clinical syndrome, followed by meningitis (16%; 17/109) and acute flaccid paralysis (5%; 5/109). In two patients, acute flaccid paralysis was the only symptom.

Fever was the most commonly reported symptom among WNND cases (99%; 106/107), followed by fatigue (84%; 83/99), confusion (79%; 82/104), weakness (74%; 73/98), headache (69%; 69/100), myalgia (62%; 56/91), arthralgia (56%; 48/85), chills (55%; 52/94), gastrointestinal symptoms (48%; 52/109), extrapyramidal signs/tremor (29%; 29/100), rash (16%; 16/101) and limb paresis (15%; 15/100).

Of the 109 WNND cases, 83 (76%) had at least one underlying chronic disease, with 54/109 (50%) cases having two or more coexisting conditions. The most commonly reported underlying conditions among the 109 WNND cases were hypertension (45%; n=49), diabetes mellitus (35%; n=38), heart disease (21%; n=23), cancer (11%; n=12), chronic neuropsychiatric disease (10%; n=11), stroke (9%; n=10), chronic renal failure (6%; n=7) and chronic respiratory disease (6%; n=6). Chronic neuropsychiatric disease included dementia, epilepsy, Parkinson disease and psychosis.

Of 80 WNND cases with the relevant information, 56 reported having agricultural/gardening activities and/or other outdoor activities in the countryside, while 21 of 94 cases reported having outdoor activities at night.

All 109 WNND identified cases were hospitalised and 18 (17%) were admitted to an intensive care unit (ICU).

Predictive factors of disease severity

Predictive factors of WNND versus WNF

The median age of WNND cases (70 years; range: 11–95) was significantly higher (p=0.001) than that of the diagnosed WNF cases (63 years; range: 14–92).

In the univariable analysis, the odds of WNND among all reported cases of WNV infection increased significantly (OR: 1.03; 95% CI: 1.01–1.05) with increasing age and was significantly higher among cases who were male (OR: 2.8; 95% CI: 1.3–5.8) (Table 2).

Patients with WNND were twice as likely to have at least one underlying condition than patients with WNF and almost three times more likely to have more than one underlying condition (Table 2).

Age (≥75 years) and male sex were the only factors associated with the presence of WNND in the final logistic regression model (Table 2).

Table 2

Demographic characteristics and underlying conditions of reported cases with West Nile neuroinvasive disease (n=109) and West Nile fever (n=52), Greece, June–October 2012

Characteristic	WNND Number (%)	WNF Number (%)	Crude odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
Age group in years				
<75	67 (61)	43 (83)	Reference	Reference
≥75	42 (39)	9 (17)	3.0 (1.3-7.7)	3.5 (1.5-8.1)
Sex				
Female	38 (35)	31 (60)	Reference	Reference
Male	71 (65)	21 (40)	2.8 (1.3–5.8)	3.1 (1.5–6.4)
Co-morbidity				
No underlying conditions	26 (24)	21 (40)	Reference	NA
One underlying condition	29 (27)	16 (31)	1.5 (0.63–3.4)	
≥2 underlying conditions	54 (50)	15 (29)	2.9 (1.3–6.5)	
≥1 underlying conditions	83 (76)	31 (60)	2.2 (1.0–4.6)	
Underlying conditions				
Hypertension	49 (45)	19 (37)	1.4 (0.68–3.0)	NA
Heart disease	23 (21)	9 (17)	1.3 (0.51–3.4)	
Diabetes	38 (35)	13 (25)	1.6 (0.73–3.7)	
Cancer	12 (11)	3 (6)	2.0 (0.51–12)	
Chronic neuropsychiatric disease	11 (10)	3 (6)	1.8 (0.45–11)	
Stroke	10 (9)	1 (2)	5.2 (0.69–228)	
Chronic renal failure	7 (6)	1 (2)	3.5 (0.43–161)	
Chronic respiratory disease	6 (6)	1 (2)	3.0 (0.34–139)	

NA: not applicable; WNF: West Nile fever; WNND: West Nile neuroinvasive disease.

[a] Adjusted for age and sex.

Source: Hellenic Center for Disease Control & Prevention.

Predictive factors of encephalitis/meningoencephalitis versus meningitis

The median age (72 years; range: 19–95) of cases with encephalitis/meningoencephalitis was significantly higher (p<0.001) than that of cases with meningitis (57 years; range: 11–80). The risk of developing encephalitis increased by 4% for each yearly increase in age (OR for trend: 1.04; 95% CI: 1.0–1.1).

Patients with at least one underlying condition (OR adjusted for age: 4.2; 95% CI: 1.0–17) were more likely to develop encephalitis/meningoencephalitis than meningitis.

Predictive factors of fatal outcome

A total of 18 WNND cases died, indicating an overall case fatality rate of 17%. The case fatality rate in the two main epicentres (southern suburbs of Athens, East Macedonia & Thrace) was lower, 7% (2/28) and 9% (4/46), respectively, than the rate recorded outside the main epicentres (34%; 12/35).

The median age of the fatal cases was 79 years (range: 72–95), with the age-specific case fatality rate in patients aged ≥75 years reaching 36% (15/42) (Table 3).

The case fatality rate did not differ significantly between sexes (p=0.69). Eight of the 18 WNND fatalities were hospitalised in an ICU. The median interval from WNV symptom onset to death was 16 days (range: 4–108).

Of the 18 patients with a fatal outcome, 16 had encephalitis/meningoencephalitis (one of whom also had acute flaccid paralysis) and two had meningitis. The risk of fatal outcome among WNND cases did not significantly differ (p=0.54) between cases with encephalitis/meningoencephalitis and cases with meningitis.

All patients who died had at least one underlying condition. Co-morbidity was a significant (p=0.009) risk factor for death, with the case fatality rate being almost six times higher among patients with chronic renal failure. Age (≥75 years) and chronic renal failure remained independent predictive factors of death in the multivariable analysis (Table 3).

The case fatality rate, adjusted for age and chronic renal failure, did not differ significantly in the two epicentres (p=0.667); however, it was significantly higher in Western Greece (RR: 4.9; 95% CI: 1.4–17) and Central

Table 3

Factors predicting death for cases with West Nile neuroinvasive disease, Greece, June–October 2012 (n=109)

Characteristic	Number of deaths (n=18)	Case fatality rate (%)[a]	Crude risk ratio (95% CI)	Adjusted risk ratio[b] (95% CI)
Age group in years				
<75	3[c]	4.48	Reference	Reference
≥75	15	35.71	8.0 (2.5–26)	7.0 (2.2–22)
Sex				
Female	7	18.42	Reference	NA
Male	11	15.49	0.84 (0.36–2.0)	
Clinical manifestation				
Meningitis	2	11.76	Reference	NA
Encephalitis/meningoencephalitis	16	17.78	1.5 (0.38–6.0)	
Co-morbidity				
1 underlying condition	5	17.24	Reference	NA
2 underlying conditions	7	20.00	1.16 (0.41–3.3)	
≥3 underlying conditions	6	31.58	1.83 (0.65–5.2)	
Underlying conditions				
Hypertension				
No	9	15.00	Reference	NA
Yes	9	18.37	1.22 (0.53–2.9)	
Heart disease				
No	12	13.95	Reference	NA
Yes	6	26.09	1.9 (0.79–4.4)	
Diabetes				
No	9	12.68	Reference	NA
Yes	9	23.68	1.9 (0.81–4.3)	
Chronic neuropsychiatric disease				
No	14	14.29	Reference	NA
Yes	4	36.36	2.5 (1.0–6.4)	
Cancer				
No	15	15.46	Reference	NA
Yes	3	25.00	1.6 (0.55–4.8)	
Stroke				
No	15	15.15	Reference	NA
Yes	3	30.00	2.0 (0.69–5.7)	
Chronic renal failure				
No	13	12.75	Reference	Reference
Yes	5	71.43	5.6 (2.8–11)	4.5 (2.7–7.5)
Chronic respiratory disease				
No	16	15.53	Reference	NA
Yes	2	33.33	2.1 (0.63–7.3)	

NA: not applicable.

[a] Case fatality rate refers to the percentage of fatalities among cases within a specific characteristic category.
[b] Includes variables that remained significant in the final binomial regression model.
[c] Belonged to the 70–74 year age group.

Source: Hellenic Center for Disease Control & Prevention.

Macedonia (RR: 4.1; 95% CI: 1.2–15), compared with that of cases in the southern suburbs of Athens.

Laboratory results

Of the 161 locally acquired cases, 45 had a WNV-specific IgM antibody response in CSF (confirmed cases), 113 had WNV-specific IgM antibody response in serum (probable cases, CSF sample was not available) and in three (confirmed) cases (one from the south suburbs of Athens and two from East Macedonia), WNV nucleic acid was detected in blood or urine. In these three cases, sequencing revealed WNV lineage 2, with sequences with 100% genetic similarity (in the amplified fragment of the NS3 gene) with the Nea Santa-Greece-2010 strain (GenBank Accession number HQ537483) [23]). The whole genome sequence was obtained from a urine sample from a patient with WNND in the regional unit of Kavala, East Macedonia (strain Greece/2012/Kavala, GenBank accession number KF179639; the strain presented 99.7% sequence identity with the Nea Santa-Greece-2010 strain) [37].

As in previous years, there was no cross-reactivity with tick-borne encephalitis virus, while cross-reactivity was seen with Dengue virus (DENV); however, when a positive result was obtained for DENV, the titres were lower than those against WNV [38]. None of the patients had been previously vaccinated against yellow fever or Japanese encephalitis.

Of the 36,911 blood units tested by NAT (76.4% (n=28,205) ID-NAT and 23.6% (n=8,706) MP-NAT), four (1:9,228) were positive, including the one found through haemovigilance procedures.

Discussion

Human WNV infections were notified in Greece in 2012 for the third consecutive year in the context of an enhanced surveillance system in place since 2010. A new geographical pattern of WNV circulation was observed, with a more dispersed distribution of cases and two outbreak epicentres (one in a rural and one in an urban area) with different temporal patterns. The reason for this distinct temporal distribution is not clear. It might reflect different microclimatic conditions (such as temperature), vector distribution or bird migration patterns between the two areas. In addition, more than half of the reported cases occurred in areas that had not been affected in previous years, outlining the difficulty in predicting WNV circulation and defining areas at risk for following years. In 2013, cases continued to occur in previously affected areas, but also in one new regional unit [39].

This outbreak was the largest recorded in the European Union (EU) in 2012 and the second largest among the EU countries reporting to the European Centre for Disease Prevention and Control (ECDC) and information compiled by ECDC (the largest being in Russia, with 447 cases, and then followed by Israel with 83 cases, Serbia with 69, and Italy with 50) [40]. The 2012 incidence of WNND cases in Greece was 50% higher than in 2011, but remained lower than that in 2010. The first human cases occurred earlier than in previous years (26 and 16 days earlier than the first case of 2011 and 2010, respectively), probably due to the higher temperatures recorded in June 2012, especially in central and southern Greece. In the southern suburbs of Athens, the mean temperature in June 2012 was 28.6 °C, whereas in June 2011 and 2010 it was 25.4 °C and 26.1 °C, respectively [41]*. However, the effects of climatic conditions e.g. temperature and humidity, on local vector populations need further study.

All three obtained sequences from the PCR-positive samples belonged to WNV lineage 2, with 100% genetic similarity with the strain detected in 2010, suggesting that this strain has become established in Greece. In addition, WNV lineage 2 sequences were also obtained from Culex spp. mosquitoes collected in the regional unit of Xanthi, in the municipality with the highest incidence in Greece in 2012; as in the strain circulating in the two previous transmission periods, the strain contained the $H_{249}P$ substitution in the NS3 protein (GenBank accession number JX860675) [42], which might be associated with increased virulence of the strain [23].

One WNND case acquired the infection through blood transfusion before the implementation of blood safety measures, including screening of donor blood for WNV RNA by NAT in the affected areas in 2012. It should be noted that the blood donor involved gave blood eight days before the first confirmed human case was diagnosed and reported to the Hellenic Center for Disease Control & Prevention.

The higher incidence of WNND among male patients is consistent with findings from other countries [43], probably reflecting behavioural factors leading to increased exposure to mosquitoes, especially in rural areas. The majority of the WNND cases reported outdoor activities, which has also been identified as a risk factor for developing the disease [44]. Older age (≥75 years) was also found to be significantly associated with a higher risk of severe neurological disease. The association between age and severe disease has been well established [14,43, 45-52].

The overall case fatality rate (17%) among patients with WNND was higher than that in other countries [14,43, 45-48,53] and similar to that recorded in the 2010 outbreak in Greece (17%)* and the 2008–11 outbreak in Italy (16%) [54]. The high case fatality rate in regions with fewer reported cases might reflect a diagnostic bias: in areas where physicians were not sensitised to test all suspected cases for WNV infection, only the most severe cases were likely to be diagnosed, including those with a fatal outcome. More research is required to investigate the reasons for the regional difference in case fatality rate.

In our study, advanced age was found to independently predict WNND-related death, a finding compatible with many previous studies [14,43,45,46,48-50,52]. The literature is inconsistent regarding whether pre-existing medical conditions are predictive of WNND or death [49-52,55]. In our study, co-morbidity was not found to predict WNND; however, chronic renal failure was significantly associated with a fatal outcome. Specific underlying conditions (such as diabetes, immunosuppression, history of stroke) have been identified as risk factors for fatal outcome [48,50-52,55], while some other studies showed an association between chronic renal disease and severe WNV infection [55] or death [51], as in our study.

Limitations should be taken into account when interpreting our findings. The cases detected by the enhanced surveillance system represent the severe cases of WNV infection. Moreover, diagnosed WNF cases are considered to represent a small fraction of all WNF cases (probably the more serious in the spectrum of mild illness), as mild WNF cases are less likely to be diagnosed and reported. Moreover, central nervous system involvement was not always validated by laboratory or imaging results. Finally, the ORs and case fatality rates should be interpreted with caution, as small numbers are involved for some risk factors and outcome categories.

In conclusion, the occurrence of human cases of WNV infection in three consecutive years and the spread of the virus in newly affected areas suggest that WNV, and specifically WNV lineage 2, is established in Greece and transmission is expected to continue in the future. WNV circulation continued in 2013, with 86 diagnosed cases (51 of whom had WNND) [39].The established enhanced surveillance of WNV infection among humans and animals, comprehensive vector control and the implementation of the recommended blood safety and haemovigilance measures during the transmission period constitute the cornerstones of successful management of this seasonal public health threat.

Ongoing health education campaigns, including seminars and dissemination of information material, targeting specifically susceptible populations (i.e. the elderly and those with co-morbidities, including chronic renal failure) and physicians throughout the country may lead to more effective disease prevention and decreased numbers of fatalities.

* Authors' correction

The following corrections were made at the request of the authors on 4 April 2014: the 2011 and 2010 mean temperatures in the southern suburbs of Athens were corrected. In addition, some details of references 20, 21, 35 and 56 were amended. On 5 April 2014, the case fatality rate in the 2010 outbreak in Greece was amended.

Acknowledgments

We would like to thank all hospital physicians, laboratory personnel and local public health authorities who contributed to the surveillance of WNV infections in Greece, and especially the Xanthi's and Kavala's Directorates of Public Health and Social Welfare; the Microbiological Department of the Infectious Disease Hospital of Thessaloniki and the Hellenic Pasteur Institute for their contribution to the laboratory surveillance; all partners of the project 'Integrated surveillance and control programme for West Nile virus and malaria in Greece' (MALWEST) funded by the National Strategic Reference Framework 2007–13; and A Liona and A Ntakou, for their administrative support in surveillance activities.

Conflict of interest

None declared.

Authors' contributions

Danai Pervanidou, Kostas Danis, Marios Detsis, Theano Georgakopoulou, Sotirios Tsiodras, Agoritsa Baka, Jenny Kremastinou and Christos Hadjichristodoulou contributed to the surveillance and outbreak response.
Danai Pervanidou conducted the analysis and wrote the first draft of this manuscript. Kostas Danis and Kassiani Mellou contributed to the data analysis and the writing of the first draft. Christos Hadjichristodoulou supervised the surveillance activities.

Evaggelia Papanikolaou, Irene Terzaki, Lambrini Veneti, Anna Vakali and Georgios Dougas provided the surveillance data from the case investigations.
Anna Papa and Athanasios Tsakris provided the laboratory data of the human cases.

Constantina Politis and Kostas Stamoulis provided the haemovigilance findings and data on surveillance in the blood donor population.

All authors were members of the WNV outbreak response team. All authors read and critically revised the first as well as the subsequent drafts of this manuscript and approved the final version.

References*

1. World Health Organization (WHO). West Nile virus. Fact sheet N°354, July 2011. Geneva: WHO; 2011. Available from: http://www.who.int/mediacentre/factsheets/fs354/en/
2. Calistri P, Giovannini A, Hubalek Z, Ionescu A, Monaco F, Savini G, et al. Epidemiology of West Nile in Europe and in the Mediterranean basin. Open Virol J. 2010;4:29-37.
3. European Centre for Disease Prevention and Control (ECDC). Review of the epidemiological situation of West Nile Virus infection in the European Union. Update 19 September 2011. Rapid Risk Assessment: Stockholm: EDC; 2011. Available from: http://www.ecdc.europa.eu/en/publications/Publications/110920_TER_Rapid%20risk%20assessment_WNF.pdf
4. Marka A, Diamantidis A, Papa A, Valiakos G, Chaintoutis SC, Doukas D, et al. West Nile virus state of the art report of MALWEST Project. Int J Environ Res Public Health. 2013;10(12):6534-6610. http://dx.doi.org/10.3390/ijerph10126534
5. Centers for Disease Control and Prevention (CDC). Clinical evaluation & disease. West Nile virus. Atlanta, GA: CDC. [Accessed 6 Jan 2014]. Available from: http://www.cdc.gov/westnile/healthCareProviders/healthCareProviders-ClinLabEval.html
6. Danis K, Papa A, Papanikolaou E, Dougas G, Terzaki I, Baka A, et al. Ongoing outbreak of West Nile virus infection in humans, Greece, July to August 2011. Euro Surveill. 2011;16(34):pii=19951.

7. Bakonyi T, Ivanics E, Erdélyi K, Ursu K, Ferenczi E, Weissenböck H, et al. Lineage 1 and 2 strains of encephalitic West Nile virus, central Europe. Emerg Infect Dis. 2006;12(4):618-23. http://dx.doi.org/10.3201/eid1204.051379
8. Bakonyi T, Ferenczi E, Erdélyi K, Kutasi O, Csörgö T, Seidel B, et al. Explosive spread of a neuroinvasive lineage 2 West Nile virus in Central Europe, 2008/2009. Vet Microbiol. 2013 26;165(1-2):61-70.
9. Platonov AE, Fedorova MV, Karan LS, Shopenskaya TA, Platonova OV, Zhuravlev VI. Epidemiology of West Nile infection in Volgograd, Russia, in relation to climate change and mosquito (Diptera: Culicidae) bionomics. Parasitol Res. 2008;103 Suppl 1:S45-53. http://dx.doi.org/10.1007/s00436-008-1050-0
10. Wodak E, Richter S, Bagó Z, Revilla-Fernández S, Weissenböck H, Nowotny N, et al. Detection and molecular analysis of West Nile virus infections in birds of prey in the eastern part of Austria in 2008 and 2009. Vet Microbiol. 2011;149(3-4):358-66. http://dx.doi.org/10.1016/j.vetmic.2010.12.012
11. Pavlatos M, Smith CE. Antibodies to arthropod-borne viruses in Greece. Trans R Soc Trop Med Hyg. 1964;58:422–4. http://dx.doi.org/10.1016/0035-9203(64)90089-6
12. Antoniadis A, Alexiou-Daniel S, Malissiovas N, Doutsos J, Polyzoni T, Leduc JW, et al. Seroepidemiological survey for antibodies to arboviruses in Greece. Arch Virol. 1990;Suppl 1:277-85.
13. Papa A, Perperidou P, Tzouli A, Castiletti C. West Nile virus--neutralizing antibodies in humans in Greece. Vector Borne Zoonotic Dis. 2010;10(7):655-8. http://dx.doi.org/10.1089/vbz.2010.0042
14. Tsai TF, Popovici F, Cernescu C, Campbell GL, Nedelcu NI. West Nile encephalitis epidemic in southeastern Romania. Lancet.1998;352(9130):767-71. http://dx.doi.org/10.1016/S0140-6736(98)03538-7
15. Danis K, Papa A, Theocharopoulos G, Dougas G, Athanasiou M, Detsis M, et al. Outbreak of West Nile virus infection in Greece, 2010. Emerg Infect Dis. 2011;17(10):1868-72. http://dx.doi.org/10.3201/eid1710.110525
16. Ladbury GA, Gavana M, Danis K, Papa A, Papamichail D, Mourelatos S, et al. Population seroprevalence study after a West Nile virus lineage 2 epidemic, Greece, 2010. PLoS One. 2013;8(11):e80432. http://dx.doi.org/10.1371/journal.pone.0080432
17. Papa A, Danis K, Baka A, Bakas A, Dougas G, Lytras T, et al. Ongoing outbreak of West Nile virus infections in humans in Greece, July–August 2010. Euro Surveill. 2010;15(34):pii=19644.
18. Biggerstaff BJ, Petersen LR. Estimated risk of transmission of the West Nile virus through blood transfusion in the US, 2002. Transfusion. 2003;43(8):1007-17. http://dx.doi.org/10.1046/j.1537-2995.2003.00480.x
19. European Commission (EC). West Nile virus and blood safety. Introduction to a preparedness plan in Europe. Based on the EU Satellite Meeting of the Working Group on Blood Safety and WNV, Thessaloniki, 25-26 January 2011 And on the teleconference, 18 January 2012. Final working document 2012 v.2.1. Prepared by: Greece, Italy, Romania and France. Brussels: EC: 2012. Available from: http://ec.europa.eu/health/blood_tissues_organs/docs/wnv_preparedness_plan_2012.pdf
20. Politis C, Tsoukala A, Hatzitaki M, Pappa A, Englezou A, Zafeiriou C, et al. West Nile Virus (WNV) outbreak in Greece and blood safety measures. Vox. Sang. 2011;101(Suppl.1):42 (3D-S12-03).
21. Politis C, Pappa A, Hassapopoulou H, Pantelidou D, Perifanis V, Teli A, et al Transfusion transmitted West Nile Virus (WNV) infection in thalassaemic patients in Greece.Vox Sang. 2011;101 (Suppl.1):236 (P-390).
22. Papa A, Xanthopoulou K, Gewehr S, Mourelatos S. Detection of West Nile virus lineage 2 in mosquitoes during a human outbreak in Greece. Clin Microbiol Infect. 2011;17(8):1176-80. http://dx.doi.org/10.1111/j.1469-0691.2010.03438.x
23. Papa A, Bakonyi T, Xanthopoulou K, Vásquez A, Tenorio A, Nowotny N. Genetic characterization of a neuroinvasive lineage 2 West Nile virus, Greece, 2010. Emerg Infect Dis. 2011;17(5):920-2. http://dx.doi.org/10.3201/eid1705.101759
24. Valiakos G, Touloudi A, Iacovakis C, Athanasiou L, Birtsas P, Spyrou V, et al. Molecular detection and phylogenetic analysis of West Nile virus lineage 2 in sedentary wild birds (Eurasian magpie), Greece, 2010. Euro Surveill. 2011;16(18):pii=19862.
25. Papa A, Politis C, Tsoukala A, Eglezou A, Bakaloudi V, Hatzitaki M, et al. West Nile virus lineage 2 from blood donor, Greece. Emerg Infect Dis. 2012;18(4):688-9. Availablefrom: http://dx.doi.org/10.3201/eid1804.110771 http://dx.doi.org/10.3201/eid1804.110771
26. Papa A, Xanthopoulou K, Tsioka A, Kalaitzopoulou S, Mourelatos S. West Nile virus in mosquitoes in Greece. Parasitol Res. 2013;112(4):1551-5. http://dx.doi.org/10.1007/s00436-013-3302-x
27. Chaskopoulou A, Dovas CI, Chaintoutis SC, Bouzalas I, Ara G, Papanastassopoulou M. Evidence of enzootic circulation of West Nile virus (Nea Santa-Greece-2010, lineage 2), Greece, May to July 2011. Euro Surveill. 2011;16(31):pii=19933.
28. European Commission. Commission Decision of 28/IV/2008 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council. Official Journal of the European Union. Luxembourg: Publications Office of the European Union. 18.06.2008:L 159. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008D0426&from=EN
29. International Organization for Standardization (ISO). Date and time format - ISO 8601. Geneva: ISO. [Accessed 15 Jan 2013]. Available from: http://www.iso.org/iso/home/standards/iso8601.htm
30. Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. Official Journal of the European Union Luxembourg: Publications Office of the European Union. 30.3.2004:L91. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004L0033&from=EN
31. Linke S, Ellerbrok H, Niedrig M, Nitsche A, Pauli G. Detection of West Nile virus lineages 1 and 2 by real-time PCR. J Virol Methods. 2007;146(1-2):355-8. http://dx.doi.org/10.1016/j.jviromet.2007.05.021
32. Sánchez-Seco MP, Rosario D, Domingo C, Hernández L, Valdés K, Guzmán MG, et al. Generic RT-nested-PCR for detection of flaviviruses using degenerated primers and internal control followed by sequencing for specific identification. J Virol Methods. 2005;126(1-2):101-9. http://dx.doi.org/10.1016/j.jviromet.2005.01.025
33. Kacian DL, Fultz TJ. Nucleic acid sequence amplification methods. United States patent US 5,399,491. 1995.
34. Saldanha J, Shead S, Heath A, Drebot M; West Nile Virus Collaborative Study Group. Collaborative study to evaluate a working reagent for West Nile virus RNA detection by nucleic acid testing. Transfusion. 2005;45:97-102. http://dx.doi.org/10.1111/j.1537-2995.2005.04151.x
35. Hellenic Statistical Authority (EL.STAT.). Resident population, surface area and population density, by urban and rural areas, and by level, semi-mountainous and mountainous areas. Altitude mean weighted coefficient. a) Greece Total and Geographic Departments. 2001 Population Census. Piraeus: EL.STAT. [Accessed 13 January 2013]. Greek. Available from: http://www.statistics.gr/portal/page/portal/ESYE/BUCKET/A1602/Other/
36. Gabriel M, Emmerich P, Frank C, Fiedler M, Rashidi-Alavijeh J, Jochum C, et al. Increase in West Nile virus infections imported to Germany in 2012. J Clin Virol. 2013;58(3):587-9. http://dx.doi.org/10.1016/j.jcv.2013.08.027
37. Barzon L, Papa A, Pacenti M, Franchin E, Lavezzo E, Squarzon L, et al. Genome sequencing of West Nile Virus from human cases in Greece, 2012. Viruses. 2013;5(9):2311-9. http://dx.doi.org/10.3390/v5092311
38. Papa A, Karabaxoglou D, Kansouzidou A. Acute West Nile virus neuroinvasive infections: cross-reactivity with dengue virus and tick-borne encephalitis virus. J Med Virol. 2011;83(10):1861-5. http://dx.doi.org/10.1002/jmv.22180
39. Hellenic Center for Disease Control & Prevention. Weekly epidemiological report for the West Nile virus disease, Greece, 2013 - 06 November 2013. Athens: HCDCP; 2013. Available from: http://www.keelpno.gr/Portals/0/Files/English%20files/WNV%20reports%202012/Weekly_Reports_2013/WNV_weekly%20report_2013_11_06.pdf
40. European Centre for Disease Prevention and Control (ECDC). Table on cases - 2012. West Nile fever maps. Stockholm: ECDC. [Accessed 18 Jul 2013]. Available from: http://www.ecdc.europa.eu/en/healthtopics/west_nile_fever/West-Nile-fever-maps/Pages/2012-table.aspx
41. Hellenic National Meteorological Service. Climatic bulletins of June 2010, June 2011, June 2012. Hellinikon: Hellenic National Meteorological Service. [Accessed 22 Jun 2013]. Available from: http://www.hnms.gr/hnms/english/climatology/climatology_month_html?dr_month=06
42. Papa A, Papadopoulou E, Gavana E, Kalaitzopoulou S, Mourelatos S. Detection of West Nile virus lineage 2 in Culex mosquitoes, Greece, 2012. Vector Borne Zoonotic Dis. 2013;13(9):682-4. http://dx.doi.org/10.1089/vbz.2012.1212

43. O'Leary DR, Marfin AA, Montgomery SP, Kipp AM, Lehman JA, Biggerstaff BJ, et al. The epidemic of West Nile virus in the United States, 2002. Vector Borne Zoonotic Dis. 2004;4(1):61-70. http://dx.doi.org/10.1089/153036604773083004
44. Han LL, Popovici F, Alexander JP Jr, Laurentia V, Tengelsen LA, Cernescu C, et al. Risk factors for West Nile virus infection and meningoencephalitis, Romania, 1996. J Infect Dis. 1999;179(1):230-3. http://dx.doi.org/10.1086/314566
45. Lindsey NP, Staples JE, Lehman JA, Fischer M; Centers for Disease Control and Prevention (CDC). Surveillance for human West Nile virus disease—United States, 1999-2008. MMWR Surveill Summ. 2010;59(2):1-17.
46. Weinberger M, Pitlik SD, Gandacu D, Lang R, Nassar F, Ben David D, et al. West Nile fever outbreak, Israel, 2000: epidemiologic aspects. Emerg Infect Dis. 2001;7(4):686-91. http://dx.doi.org/10.3201/eid0704.017416
47. Weiss D, Carr D, Kellachan J, Tan C, Phillips M, Bresnitz E, et al. Clinical findings of West Nile virus infection in hospitalized patients, New York and New Jersey, 2000. Emerg Infect Dis. 2001;7(4):654-8. http://dx.doi.org/10.3201/eid0704.017409
48. Nash D, Mostashari F, Fine A, Miller J, O'Leary D, Murray K, et al. The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med. 2001;344(24):1807-14. http://dx.doi.org/10.1056/NEJM200106143442401
49. Chowers MY, Lang R, Nassar F, Ben-David D, Giladi M, Rubinshtein E, et al. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. Emerg Infect Dis. 2001;7(4):675-8. http://dx.doi.org/10.3201/eid0704.017414
50. Bode AV, Sejvar JJ, Pape WJ, Campbell GL, Marfin AA. West Nile virus disease: a descriptive study of 228 patients hospitalised in a 4-county region of Colorado in 2003.Clin Infect Dis. 2006;42(9):1234-40. http://dx.doi.org/10.1086/503038
51. Murray K, Baraniuk S, Resnick M, Arafat R, Kilborn C, Cain K, et al. Risk factors for encephalitis and death from West Nile virus infection. Epidemiol Infect. 2006;134(6):1325-32. http://dx.doi.org/10.1017/S0950268806006339
52. Patnaik JL, Harmon H, Vogt RL. Follow-up of 2003 human West Nile virus infections, Denver, Colorado. Emerg Infect Dis. 2006;12(7):1129-31. http://dx.doi.org/10.3201/eid1207.051399
53. Sirbu A, Ceianu CS, Panculescu-Gatej RI, Vazquez A, Tenorio A, Rebreanu R, et al. Outbreak of West Nile virus infection in humans, Romania, July to October 2010. Euro Surveill. 2011;16(2):pii=19762.
54. Rizzo C, Salcuni P, Nicoletti L, Ciufolini MG, Russo F, Masala R, et al. Epidemiological surveillance of West Nile neuroinvasive diseases in Italy, 2008 to 2011. Euro Surveill. 2012;17(20):pii=20172.
55. Lindsey NP, Staples JE, Lehman JA, Fischer M. Medical risk factors for severe West Nile Virus disease, United States, 2008-2010. Am J Trop Med Hyg. 2012;87(1):179-84. http://dx.doi.org/10.4269/ajtmh.2012.12-0113
56. Hellenic Statistical Authority (EL. STAT.). Estimated population by sex and 5year age groups on 1st January (Years 1991 - 2012). Piraeus: EL. STAT. [Accessed 15 Jan 2013]. Available from: http://www.statistics.gr/portal/page/portal/ESYE/PAGE-themes?p_param=A1605&r_param=SPO18&y_param=2012_00&mytabs=0

Epidemiology of tick-borne encephalitis in Switzerland, 2005 to 2011

M Schuler[1], H Zimmermann[2], E Altpeter[2], U Heininger (Ulrich.Heininger@ukbb.ch)[1]
1. Division of Infectious Diseases and Vaccines, University Children's Hospital (UKBB), Switzerland
2. Division of Transmissible Diseases, Federal Office of Public Health (FOPH), Berne, Switzerland

Citation style for this article:
Schuler M, Zimmermann H, Altpeter E, Heininger U. Epidemiology of tick-borne encephalitis in Switzerland, 2005 to 2011. Euro Surveill. 2014;19(13):pii=20756. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20756

Article submitted on 13 May 2013 / published on 3 April 2014

We provide an update on the epidemiology and disease characteristics of tick-borne encephalitis (TBE) in Switzerland. Data were collected through the mandatory notification system of the Federal Office of Public Health. Between 2005 and 2011, a total of 1,055 TBE cases were reported, with a peak of 244 cases in 2006. The average yearly incidence was 2.0/100,000 inhabitants nationwide, with the highest regional value (7.8/100,000) in eastern Switzerland. Incidence by age peaked in 60–69 year-old patients, males predominated in all age groups. Most patients suffered from meningoencephalitis (n=567) or meningitis (n=246), seven of 1,055 patients (0.7%) died. Of 617 patients who were 40 years and older, 442 (72%) suffered from a severe course of illness, compared to 196 (51%) of 384 patients younger than 40 years. Most patients were not immunised against TBE, and in 33 of 1,055 patients (3%), vaccine failure was found possible. Ongoing surveillance of TBE and intensified efforts in promoting TBE vaccination for the population at risk will be needed in light of its considerable morbidity.

Introduction

Tick-borne encephalitis (TBE) is an acute infection involving the central nervous system (CNS) with potentially serious outcome. It is caused by the TBE virus (TBEV), which belongs to the Flavivirus family. Transmission of TBEV to humans occurs by bites of infected ticks, in Europe mainly *Ixodes ricinus*. After an incubation period of four to 28 days (usually seven to 14 days), the clinical presentation of TBE usually starts with one to seven days of influenza-like illness (ILI), followed by an afebrile and mostly asymptomatic interval [1]. A few days later, CNS manifestations such as meningitis, meningoencephalitis or encephalomyelitis may occur in approximately one third of patients [2]. The case fatality rate is less than 2%, whereas permanent sequelae such as cognitive or neuropsychiatric complaints, balance disorders, headaches, dysphasia, hearing defects, and spinal paralysis are reported in up to 46% of patients [3].

In Switzerland, TBE occurs in specified endemic areas and is a notifiable disease. The average national incidence of TBE in Switzerland between 1984 and 2004 was 1.4/100,000/year, with values reaching up to 7.9 in endemic cantons (highest values: Thurgau 7.9, Schaffhausen 4.3, Zurich 2.7, and Aargau 2.2) [4]. Age distribution of patients revealed two peaks, i.e. in six to 14 year-old children and in 60 to 69 year-old adults. Children younger than six years were rarely affected [4].

Effective vaccines are available to prevent TBE, but no curative treatment exists [2,5]. In Switzerland, TBE vaccination coverage with at least one dose in 2007 was 17% for the whole country, with no difference between males and females [6]. The highest coverage was 25% in the 13 to 19 year-olds; In endemic regions, coverage varied between 28 and 47% [personal communication A Zacharias, 14 March 2014]. In the period 2010 to 2012, vaccination coverage in 16 year-old adolescents in endemic regions ranged from 42 to 71% for one and 39 to 64% for three doses [7]. While coverage with the first dose of TBE vaccine indicates the population with an initiated immunisation series, optimal protection requires a complete primary series with three vaccine doses, followed by regular booster doses.

The aim of this study was to provide an update on the epidemiology and disease characteristics of TBE in Switzerland for the years 2005 to 2011 in light of a notable increase in reported cases in recent years [8].

Methods

Data source and collection

TBE has been a notifiable disease in Switzerland since 1984. Laboratories have to report to the Federal Office of Public Health (FOPH) and the cantonal medical officer (CMO) one or more of the following test results: i) positive test for anti-TBEV IgM serum antibodies, ii) anti-TBEV IgG serum antibody seroconversion, iii) a ≥4-fold rise in anti-TBEV IgG serum antibodies in paired serum specimens, and iv) successful TBEV genome

Table 1

Classification of reported tick-borne encephalitis cases, Switzerland, 2005–2011

Case classification	Laboratory criteria		Clinical criteria
Not a case	Positive IgM serology		No ILI and no neurological symptoms
Possible case	a)	Positive IgM serology	ILI or non-specific neurological signs and symptoms
	b)	Positive IgM + positive IgG serology[a]	Any
Probable case	a)	Positive IgM serology	Meningitis, meningoencepalitis, encephalomyelitis or pareses
	b)	Positive IgM + positive IgG serology[a]	ILI or non-specific neurological signs and symptoms
Confirmed case	a)	Positive IgM + positive IgG serology[a]	Meningitis, meningoencepalitis, encephalomyelitis or pareses
	b)	TBE-RNA detection by PCR	Meningitis, meningoencepalitis, encephalomyelitis or pareses

ILI: influenza-like illness; TBE: tick-borne encephalitis.

[a] or anti-TBE IgG serum antibody seroconversion or ≥4-fold rise in anti-TBE IgG serum antibodies.

amplification. The CMO is then obliged to ask for additional information from the patient's physician, such as clinical presentation, disease progression, TBE vaccination history and tick bite within four weeks before onset of illness, in a standardised reporting form and submit this to the FOPH [9]. All data for this study have been provided by the FOPH in compliance with Swiss data protection laws.

Data inclusion and surveillance definitions

Patients were excluded from further analysis if they were classified as 'not a case' on the basis of laboratory results and documented clinical characteristics, whereas possible, probable and confirmed cases were included for further analysis (Table 1). The reason to include possible, probable and confirmed cases into the analysis was to monitor TBE infection rather than only the disease, and to compare time trends with the past data from 1984–2004 [4]. Patients resident in the neighbouring Principality of Liechtenstein (FL) were excluded.

Analysis

The data set for analysis comprises possible, probable and confirmed cases according to the definitions given in Table 1. All analysis of data was done using Microsoft Excel 2008 and SPSS (version 20.0, SPSS, Inc., Chicago, United States) software. Analysis included cross tables and incidence estimations. No statistical inference was done because surveillance data are not a random sample.

Figure 1

Annual incidence of tick-norne encephalitis in Switzerland, 1984 to 2011 (n=2,421)

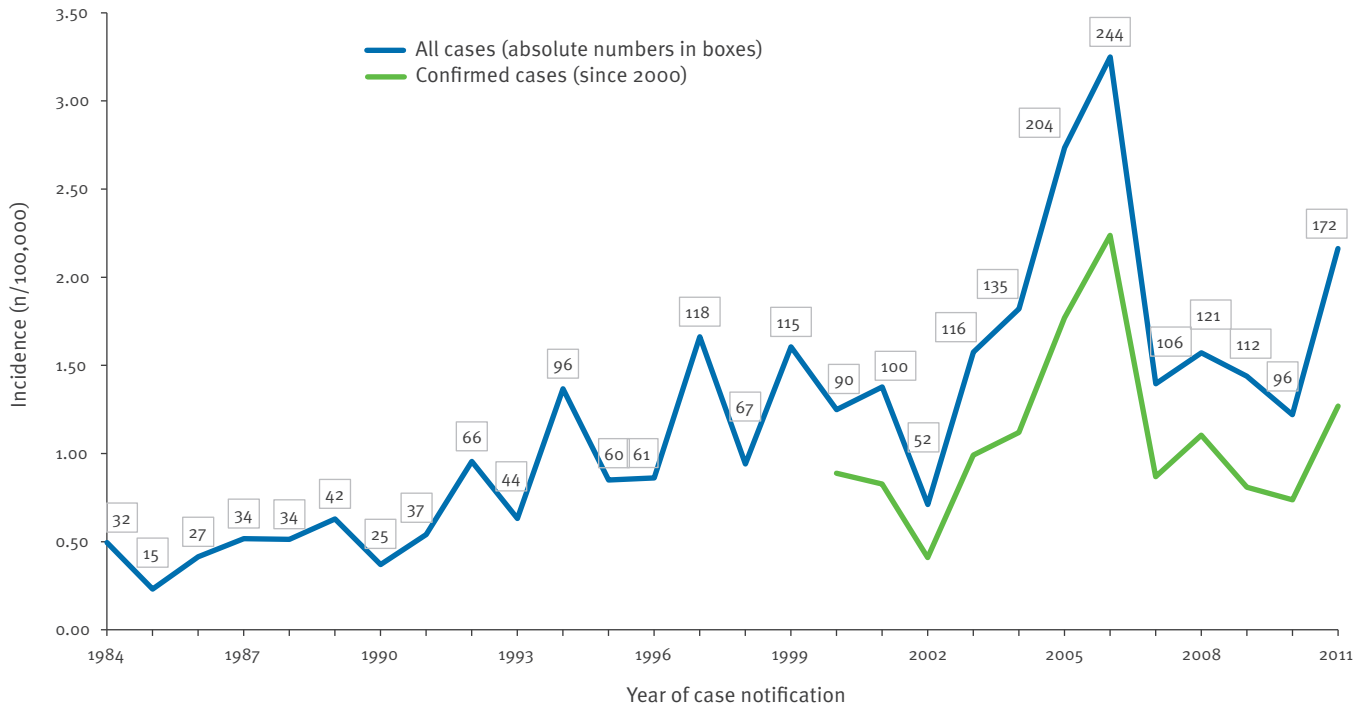


Table 2

Number and incidence per 100,000 inhabitants of tick-borne encephalitis cases by year and canton of residence, Switzerland, 2005 to 2011 (n=1,055)

Canton	Yearly incidence (total number)							
	2005	2006	2007	2008	2009	2010	2011	2005–2011
TG	9.8 (23)	9.3 (22)	8.0 (19)	3.7 (9)	10.2 (25)	6.4 (16)	**7.5 (19)**	7.8 (133)
NW	7.5 (3)	20.0 (8)	7.4 (3)	2.5 (1)	2.5 (1)	0.0 (0)	**12.1 (5)**	7.4 (21)
UR	2.9 (1)	11.4 (4)	8.6 (3)	8.5 (3)	0.0 (0)	2.8 (1)	**0.0 (0)**	4.9 (12)
AG	6.3 (36)	4.7 (27)	2.2 (13)	2.2 (13)	2.2 (13)	1.8 (11)	**3.7 (23)**	3.3 (136)
ZH	4.9 (62)	5.4 (69)	2.4 (32)	3.3 (44)	2.2 (30)	1.4 (19)	**3.1 (43)**	3.2 (299)
LU	5.3 (19)	5.3 (19)	1.7 (6)	1.6 (6)	1.6 (6)	2.4 (9)	**2.4 (9)**	2.9 (74)
AI	0.0 (0)	6.5 (1)	0.0 (0)	6.4 (1)	0.0 (0)	0.0 (0)	**6.4 (1)**	2.8 (3)
SH	5.4 (4)	4.1 (3)	0.0 (0)	2.7 (2)	2.6 (2)	2.6 (2)	**1.3 (1)**	2.7 (14)
BE	1.6 (15)	4.2 (40)	0.6 (6)	2.1 (20)	1.7 (17)	1.3 (13)	**2.2 (22)**	2.0 (133)
SG	2.6 (12)	1.1 (5)	1.5 (7)	1.7 (8)	1.5 (7)	1.7 (8)	**3.3 (16)**	1.9 (63)
OW	6.0 (2)	3.0 (1)	0.0 (0)	2.9 (1)	0.0 (0)	0.0 (0)	**0.0 (0)**	1.7 (4)
GR	3.2 (6)	2.7 (5)	1.6 (3)	1.1 (2)	1.6 (3)	0.5 (1)	**1.0 (2)**	1.7 (22)
AR	1.9 (1)	1.9 (1)	0.0 (0)	0.0 (0)	3.8 (2)	0.0 (0)	**3.8 (2)**	1.6 (6)
FR	1.2 (3)	3.9 (10)	1.1 (3)	0.4 (1)	1.1 (3)	1.4 (4)	**2.1 (6)**	1.6 (30)
GL	2.6 (1)	2.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	2.6 (1)	**0.0 (0)**	1.1 (3)
SO	2.0 (5)	2.4 (6)	0.4 (1)	0.0 (0)	0.0 (0)	0.4 (1)	**0.8 (2)**	0.9 (15)
SZ	0.7 (1)	0.0 (0)	1.4 (2)	0.0 (0)	0.0 (0)	1.4 (2)	**2.0 (3)**	0.8 (8)
VD	0.8 (5)	1.7 (11)	0.7 (5)	0.9 (6)	0.1 (1)	0.3 (2)	**1.1 (8)**	0.8 (38)
BS	0.5 (1)	2.2 (4)	0.0 (0)	0.5 (1)	0.0 (0)	0.5 (1)	1.1 (2)	**0.7 (9)**
JU	1.4 (1)	1.4 (1)	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (1)	**0.0 (0)**	0.6 (3)
BL	0.8 (2)	1.1 (3)	0.7 (2)	0.0 (0)	0.4 (1)	0.7 (2)	**0.4 (1)**	0.6 (11)
ZG	0.9 (1)	0.0 (0)	0.0 (0)	0.9 (1)	0.9 (1)	0.0 (0)	**0.9 (1)**	0.5 (4)
VS	0.0 (0)	0.3 (1)	0.0 (0)	0.3 (1)	0.0 (0)	0.6 (2)	**1.3 (4)**	0.4 (8)
NE	0.0 (0)	1.2 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	**0.6 (1)**	0.3 (3)
TI	0.0 (0)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	**0.3 (1)**	0.1 (2)
GE	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	**0.0 (0)**	0.1 (1)
CH	2.7 (204)	3.3 (244)	1.4 (106)	1.6 (121)	1.4 (112)	1.2 (96)	2.2 (172)	**2.0 (1,055)**

AG: Aargau; AI: Appenzell Innerrhoden; AR: Appenzell Ausserrhoden; BE: Bern; BL: Basel (county); BS: Basel (city); CH: Switzerland; FR: Fribourg; GE: Geneva; GL: Glarus; GR: Graubünden; JU: Jura; LU: Lucerne; NE: Neuchâtel; NW: Nidwalden; OW: Obwalden; SG: Saint Gallen; SH: Schaffhausen; SO: Solothurn; SZ: Schwyz; TG: Thurgau; TI: Ticino; UR: Uri; VD: Vaud; VS: Valais; ZG: Zug; ZH: Zurich.

TBE incidences were calculated based on data on the permanent resident population provided by the Federal Statistical Office [10]. Incidence rates by canton refer to the patient's place of residence, not to the presumed place of a tick bite.

Results

General characteristics

Between 2005 and 2011, 1,177 reports of TBE were notified to the FOPH. Of these, 114 (9.7%) were categorised as 'not a case' and excluded, as were the eight patients (0.7%) living in FL. Of the remaining 1,055 cases, laboratory reports were available for 1,004 (95%), and the physician reporting form with clinical and laboratory data was available for 1,008 (96%). For 47 cases, only the laboratory report was available. Complete data sets were available from 1,001 patients (95%). Of the 1,055 cases, 133 (13%) were classified as possible cases, 249 (24%) as probable cases and 673 (64%) as confirmed cases.

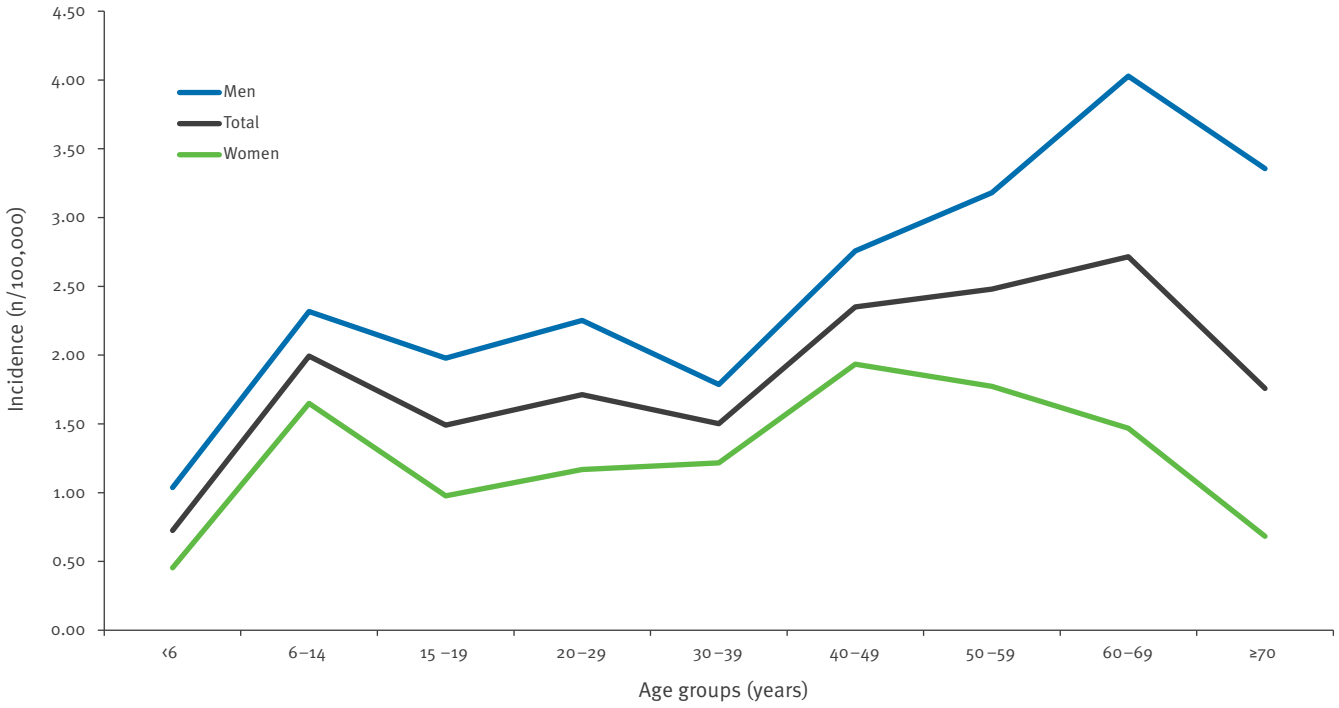
Epidemiological findings

There were two peaks of reported TBE cases (combining possible, probable and confirmed cases as defined in Table 1) during the study period: one during the years 2005 (n=204) and 2006 (n=244) and one in 2011 (n=172). From 2007 to 2010, the number of cases was relatively stable with an average of 109 cases per year.

The yearly national incidence rates (n cases/100,000 inhabitants) in Switzerland fluctuated within a range of 1.2 (2010) and 3.3 (2006), leading to an average yearly incidence of 2.0 for the whole study period, with the highest average value of 7.8 in the canton of Thurgau in eastern Switzerland (Figure 1, Table 2). When the incidence of reported TBE cases since initiation of surveillance in 1984 is considered (Figure 1), an increasing

Figure 2

Incidence of tick-born encephalitis by age and sex, Switzerland, 2005 to 2011 (n=1,053)



trend of yearly incidences can be seen. Each of the 26 Swiss cantons reported at least one patient with TBEV infection during the study period. Nonetheless, case numbers fluctuated considerably from year to year, with only nine cantons notifying at least one patient every year.

Incidence was consistently higher in men in all age groups (Figure 2). Further, incidence was low in children under the age of six years, constant at equal levels for age groups between six and 39 years, and reached highest values between 40 and 69 years of age.

Most cases of TBE with known date of manifestation (n=884) occurred between April and September, peaking in June (n=221; 25%) and July (n=228; 26%). From October to March, only few cases with TBE were reported: three (0.3% of total) in January, one (0.1%) in February, eight (0.9%) in March and 10 (1.1%) in December. Comparison of different age groups showed no substantial variability with regards to TBE seasonality (data not shown).

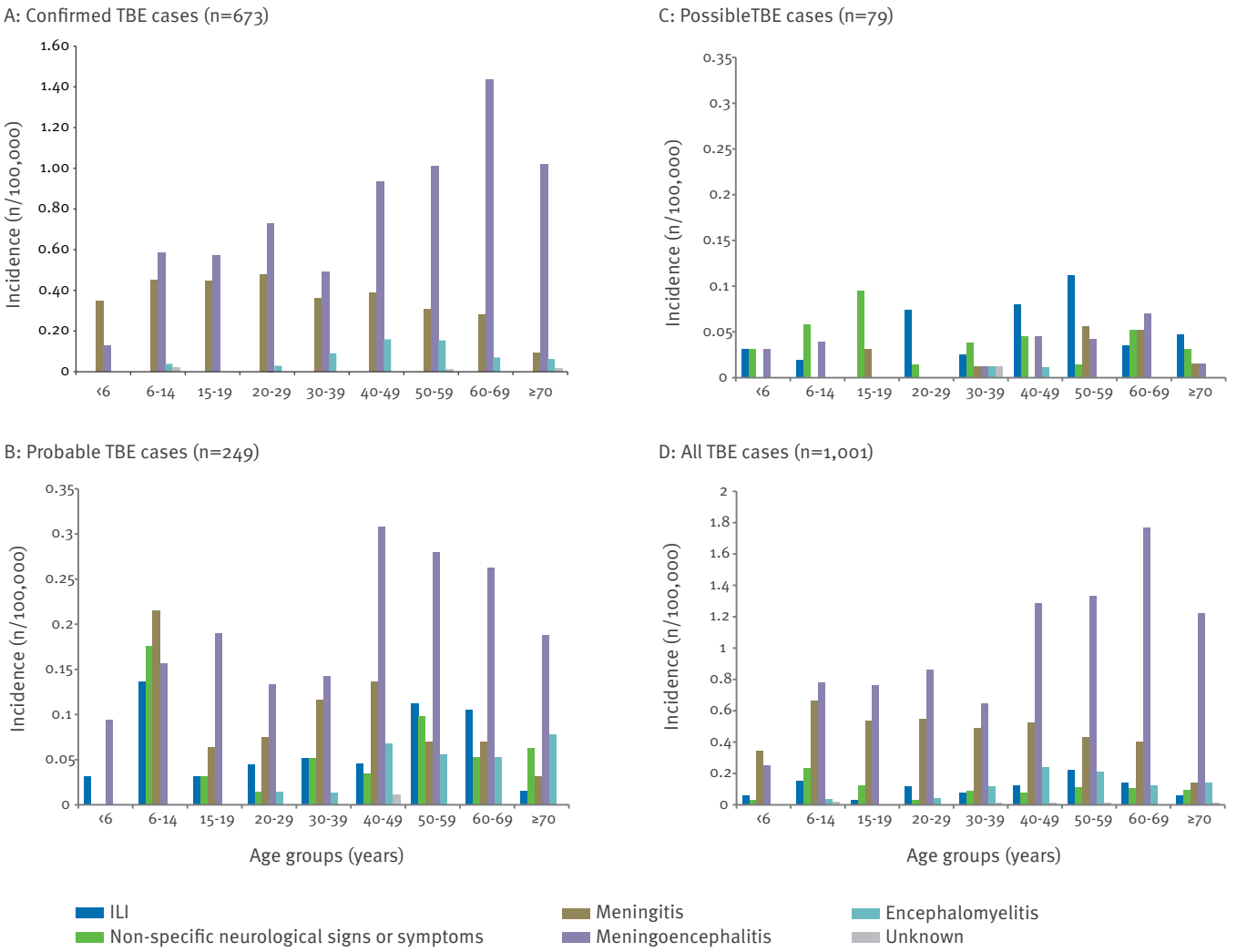
In 478 (45%) of 1,055 patients, a history of tick bite(s) within four weeks before onset of illness was reported, whereas 147 patients (14%) could not remember any tick bite. In 430 patients (41%) the history of tick bite was unknown. Sixty-seven (6.4%) patients experienced tick bites outside their cantons of residence, 50 (4.7%) in Switzerland and 17 (1.6%) in a foreign country. Almost half of the patients (n=502; 48%) were either bitten in the canton of their residence or had permanently stayed in the canton of their residence during the maximal incubation period, i.e. up to four weeks before onset of illness.

Clinical findings

Meningoencephalitis was the most frequent manifestation in probable and confirmed TBE cases and overall (Figure 3). A clinical diagnosis was available in 1,001 of 1,008 cases (99%) with physician report. The official TBE notification form requires reporting physicians to specify the patient's CNS manifestations as one of five clinical diagnoses: 'meningitis', 'meningoencephalitis', 'encephalomyelitis', 'radiculitis' and 'others' where free text can be entered [9]. Due to the difficulties in exact clinical differentiation and according to international literature [1,2,11], we combined encephalomyelitis and radiculitis in one category for the purposes of our analysis. Furthermore, patients presenting with headache, vertigo, paraesthesia, myoclonia and similar manifestations as reported under 'others' were categorised together as 'non-specific neurological signs and symptoms'. Five patients received the diagnosis 'paresis' without indication of other neurological symptoms (i.e. no meningitis, meningoencephalitis or radiculitis): three had a paresis of the facial nerve, one had an unspecified cranial nerve paresis and one had a paresis of unknown localisation. The total number of patients with paresis (combined with other neurological manifestations) is unknown. Of 617 patients of at least 40 years of age, 442 (72%) suffered from a severe course of illness, i.e. with meningoencephalitis, encephalomyelitis or pareses, compared with 196 (51%) of 384 patients under the age of 40 years (Figure

Figure 3

Incidence of clinical findings in cases of tick-born encephalitis, by age, Switzerland, 2005 to 2011 (n=1,001)*



ILI: influenza-like illness; TBE: tick-borne encephalitis

3). There was no year-by-year variability in proportions of diagnoses from 2005 to 2011 (data not shown).

Of the 1,055 patients with TBE, 789 (75%) were hospitalised, 193 (18%) were reportedly treated as outpatients, and for 73 (6.9%) patients, the respective information was missing. Precise dates of admission to and discharge from hospital were available for 666 (84%) of the 789 hospitalised patients. The mean duration of hospitalisation was 9.0 days (interquartile range (IQR): 5–11 days). Duration of hospitalisation increased with the age of the patient in a linear pattern, from a mean of 5.0 days (IQR: 3–7 days) in children up to the age of 14 years to a maximum mean of 14.6 days (IQR: 9–18 days) in those 70 years and older.

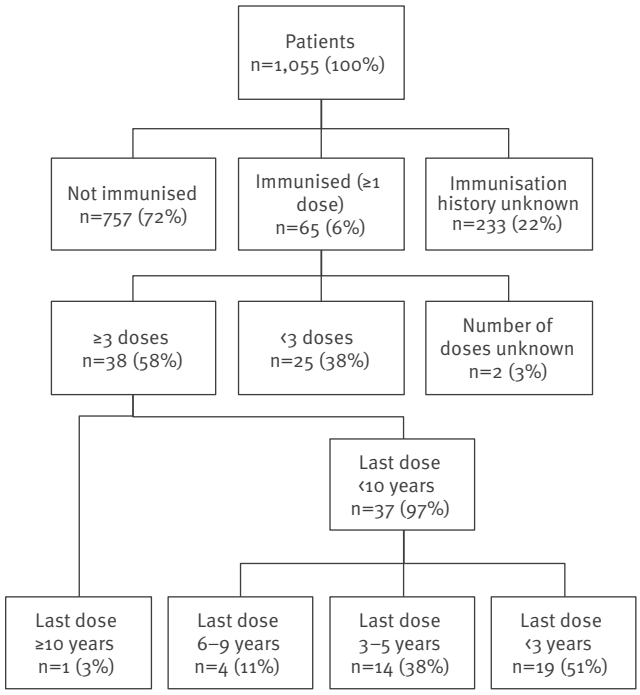
Nine (0.9%) of 1,055 patients died in timely association with TBE. For seven of them, the course of the TBE illness was fatal, whereas the remaining two deaths were most likely unrelated to TBE: one patient died after abdominal surgery and another after a bicycle accident. Of the seven patients with fatal TBE, five had a diagnosis of meningoencephalitis and two had a diagnosis of encephalomyelitis. The age range of these seven patients was 15 to 87 years (median: 81 years), three were female (age: 15–38 years), four were male (age: 81–87 years).

Tick-borne encephalitis immunisation history

Sixty-five (7.9%) of 822 patients with known immunisation status had a history of at least one dose of TBE vaccine administered at least four weeks before onset of disease, and 38 (4.6%) patients had received a complete primary vaccination series with at least three doses (Figure 4). In 19 of these 38 patients, the last dose was administered less than three years before disease onset. In five patients (three confirmed, one probable and one possible case), the last dose had

Figure 4

Vaccination history in patients with reported tick-borne encephalitis in Switzerland, 2005 to 2011 (n=1,055)



been administered more than five years before TBE disease; it is therefore possible that the disease in these five patients could have been prevented with a booster dose, as indicated in the package insert approved by Swissmedic [12,13]. As the coverage of vaccinated people in Switzerland is not known, it is not possible to calculate whether these rare cases are in the limits of expected vaccine failures. Of the remaining 33 patients (4.0%) with possible vaccine failure (i.e. who had received at least three doses of vaccine and the last dose within five years before disease onset), 19 patients (2.3% of 822) were classified as confirmed, three (0.4%) as probable and 11 (1.3%) as possible cases.

The median age of patients with completed vaccination series with at least three doses (n= 38) was 53 years (IQR: 37–65.5 years), that of unimmunised patients (n=757) was 46 years (IQR: 27–59 years). The frequency of hospitalisation in patients with at least three doses of TBE vaccine was lower (26 of 38, 68%) than that of unimmunised patients (592 of 757, 78%).

Discussion

Between 2005 and 2011, a total of 1,055 TBE cases fulfilling the case definition and living in Switzerland were reported to the FOPH, with a peak of 244 cases in 2006. When compared to the previous surveillance period, 1984 to 2004 [4], the average annual incidence increased from 1.4 to 2.0 in this current study. This could be due to an increase in endemic areas, in the tick population, or in human exposure through increased outdoor activities, or a combination of these factors. Similar trends have been observed in several other TBE-endemic countries in Europe [14]. Alternatively, increased awareness of TBE may have lead to increased reporting.

Still, the presented data on TBE in Switzerland are probably underestimates because of missed diagnoses and possible underreporting. If the physician does not suspect TBE, a laboratory test for TBE will not be ordered and therefore the diagnosis will be missed. This is particularly possible assuming that meningitis or ILI are the leading clinical features. In agreement with this assumption, fewer cases of TBE meningitis than cases of TBE meningoencephalitis are reported in Switzerland, which is in contrast to reports from other European countries with endemic TBE [1,11].

In comparison to other TBE-endemic countries in Europe, the incidence in Switzerland (range 1.2–3.3/100,000) is low. Especially in eastern Europe, much higher yearly incidences were reported for the period 2005 to 2009, such as those from the Czech Republic (range: 5.3–10.0/100,000), Estonia (range: 6.7–13.3/100,000), Latvia (range: 6.2–14.6/100,000) or Slovenia (range: 9.9–18.6/100,000) [14]. In contrast, the nationwide average incidence in Germany in 2005 to 2011 (range: 0.3–0.7/100,000) was lower than in Switzerland, but values in the endemic regions of southern Germany, e.g. Baden-Württemberg (range: 0.9–2.6/100,000) and Bavaria (range: 0.8–1.7/100,000) were comparable to those of neighbouring Switzerland [15]. Until the national mass vaccination campaign was started in 1981, Austria was the country with the highest recorded TBE morbidity in Europe, with incidences ranging from 3.9 to 9.0 per 100,000 in the period from 1972 to 1982 [16,17]. Not surprisingly, reported incidence rates in the non-immunised Austrian population are still in this range, whereas they dropped to about 1 per 100,000 (range for 2005–2011: 0.6–1.3) in the total population due to a vaccination coverage of at least 85% which was achieved during the past decade [17-19].

Epidemiological data from different countries should be compared with caution, as there are different reporting standards, varying case definitions and classifications as well as differences in vaccination coverage. In an effort to improve data comparability in the future, the European Commission proposed an institutional case definition for EU Member States in August 2012 [20]. In contrast to our current case classification, the new classification only differentiates between probable and confirmed cases, but does not define possible cases. Furthermore, only manifestations of CNS inflammation such as meningitis, meningoencephalitis, encephalomyelitis and encephaloradiculitis are accepted clinical TBE criteria, whereas ILI or non-specific neurological signs and symptoms do not qualify a case. Still, 81% (673 confirmed and 182 probable cases, Figure 3, panels A and B) of our 1,055 cases fulfilled the new EU case

definitions. It is of importance that not only disease is monitored, but also infection, because infection is a much more sensitive indicator than disease with respect to the epidemiology.

TBE is a disease that occurs in local endemic regions, therefore population-based incidence rates have to be interpreted cautiously [21]. Because history of tick bite was reported by less than half of the patients in this study, we decided to determine incidence rates based on the patients' cantons of residence. Local incidence rates can be much higher than the reported national average of 2 per 100,000 inhabitants; they can also be higher than incidences by canton because endemic foci do not match with political borders.

Despite convincing evidence of the vaccine's effectiveness and safety [22], TBE vaccination coverage in endemic regions of Switzerland is in the range of approximately 25–50% and therefore still low [7]. In our study population, most of the patients were not immunised against TBEV or their immunisation history was unknown (n=990; 94%). Assuming a 99% effectiveness of complete vaccination [5], TBE could have been prevented in 1,041 of the 1,055 patients. Nevertheless, 3.1% of the patients were completely immunised (at least three doses, last dose within five years before disease) and have to be regarded as cases of apparent vaccine failure. Considering that no curative treatment of TBE exists and that there is high long-term morbidity [1], more effort should be made to increase TBE vaccination coverage in risk groups.

In conclusion, ongoing surveillance of TBE and intensified efforts in promoting TBE vaccination for the population at risk will be needed in light of the increasing incidence and its considerable morbidity.

*Author's correction:

On request of the authors, subtitles in Figure 3 as well as the graph in Figure 3A were corrected on 7 April 2014.

Conflict of interest

None declared.

Authors' contributions

HpZ has collected the TBE data. MS, HpZ and UH have analysed the data. MS wrote the first draft of the manuscript. All other authors have contributed to further versions of the manuscript and approved the final version before submission.

References

1. Kaiser R. The clinical and epidemiological profile of tick-borne encephalitis in southern Germany 1994-98: a prospective study of 656 patients. Brain. 1999;122(Pt11):2067–78. http://dx.doi.org/10.1093/brain/122.11.2067
2. Dumpis U, Crook D, Oksi J. Tick-borne encephalitis. Clin Infect Dis. 1999;28(4):882–90. http://dx.doi.org/10.1086/515195
3. Haglund M, Günther G. Tick-borne encephalitis – pathogenesis, clinical course and long-term follow-up. Vaccine. 2003;21 Suppl 1:S11–8. http://dx.doi.org/10.1016/S0264-410X(02)00811-3
4. Zimmermann H, Koch D. [Epidemiology of tick-borne encephalitis (TBE) in Switzerland 1984 to 2004]. Ther Umsch. 2005;62(11):719–25. German. http://dx.doi.org/10.1024/0040-5930.62.11.719
5. Heinz FX, Holzmann H, Essl A, Kundi M. Field effectiveness of vaccination against tick-borne encephalitis. Vaccine. 2007;25(43):7559–67. http://dx.doi.org/10.1016/j.vaccine.2007.08.024
6. Kunze U. TBE - awareness and protection: the impact of epidemiology, changing lifestyle, and environmental factors. Wien Med Wochenschr. 2010;160(9-10):252–5. http://dx.doi.org/10.1007/s10354-010-0798-x
7. Tabelle mit vollständigen Resultaten zur Durchimpfung 1999-2012. [Table with complete results on Vaccination coverage 1999-2012]. Berne: Bundesamt für Gesundheit. [Accessed: 21 Mar 2013]. German. Available from: http://www.bag.admin.ch/themen/medizin/00682/00685/02133/index.html?lang=de
8. Bundesamt für Gesundheit. Zeckenenzephalitis (FSME): weitere Zunahme der gemeldeten Fälle im 2006. [Tick-borne encephalitis (TBE): further increases in reports cases in 2006]. Bulletin BAG. 2007;4:57–60. German.
9. Meldeformular Zeckenenzepahlitis. [Reporting form tick-borne encephalitis]. Berne: Bundesamt für Gesundheit. [Accessed: 31 Jan 2013]. German. Available from: http://www.bag.admin.ch/k_m_meldesystem/00733/00814/index.html?lang=de
10. Bevölkerungsstand und -struktur – Detaillierte Daten. [Population status and structure – detailed data]. Neuchâtel: Bundesamt für Statistik. [Accessed: 31 Jan 2013]. German. Available from: http://www.bfs.admin.ch/bfs/portal/de/index/themen/01/02/blank/data/01.html
11. Karelis G, Bormane A, Logina I, Lucenko I, Suna N, Krumina A, et al. Tick-borne encephalitis in Latvia 1973-2009: epidemiology, clinical features and sequelae. Eur J Neurol. 2012;19(1):62–8. http://dx.doi.org/10.1111/j.1468-1331.2011.03434.x
12. Baxter AG. FSME-Immun - Fachinformation des Arzneimittelkompendium Schweiz. [FSME-Immun – professional information of the drug compendium Switzerland]. Basel: Documed AG. [Accessed 18 Feb 2013]. German. Available from: http://compendium.ch/mpro/mnr/1932/html/de
13. Novartis Pharma. Encepur N - Fachinformation des Arzneimittelkompendium Schweiz. [Encepur N – professional information of the drug compendium Switzerland]. Basel: Documed AG. [Accessed 18 Feb 2013]. Available from: http://compendium.ch/mpro/mnr/9151/html/de
14. Donoso Mantke O, Escadafal C, Niedrig M, Pfeffer M, on behalf of the Working group for Tick-borne encephalitis virus. Tick-borne encephalitis in Europe, 2007 to 2009. Euro Surveill. 2011;16(39):pii=19976.
15. Robert Koch Institute (RKI). SurvStat. Berlin: RKI. [Accessed 20 Feb 2013]. German. Available from: http://www3.rki.de/SurvStat
16. Kunz C. TBE vaccination and the Austrian experience. Vaccine. 2003;21(Suppl 1):S50–5. http://dx.doi.org/10.1016/S0264-410X(02)00813-7
17. Heinz FX, Stiasny K, Holzmann H, Grgic-Vitek M, Kriz B, Essl A, et al. Vaccination and Tick-borne Encephalitis, Central Europe. Emerg Infect Dis. 2013;19(1):69–76. http://dx.doi.org/10.3201/eid1901.120458
18. Clinical Institute of Virology. Virusepidemiologische Information 2006-2012. [Virus epidemiological information 2006-2012]. Vienna: Medical University of Vienna. [Accessed: 21 Feb 2013]. German. Available from: http://www.virologie.meduniwien.ac.at/home/virus-epidemiologie/virusepidemiologische-information/lang_1-content.html
19. Statistik Austria. Bevölkerungsstand und Bevölkerungsveränderung. [Population status and population change]. Vienna: Bundesanstalt Statistik Österreich. [Accessed: 5 Mar 2013]. German. Available from: http://www.statistik.at/web_de/statistiken/bevoelkerung/bevoelkerungsstand_und_veraenderung/index.html
20. European Commission. Commission Implementing Decision of 8 August 2012 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council (2012/506/EU). Official Journal of the European Union. Luxembourg: Publications Office of the European Union; 27.9.2012:L262. Available from: http://eur-lex.europa.eu/JOHtml.do?uri=OJ:L:2012:262:SOM:EN:HTML
21. Zeckenenzephalitis – Verbreitung der Endemiegebiete. [Tick-borne encephalitis – distribution of endemic areas]. Berne: Bundesamt für Gesundheit. [Accessed: 31 Jan 2013]. German. Available from: http://map.geo.admin.ch/?X=190000.00&Y=660000.00&zoom=1&lang=en&topic=ech&bgLayer=ch.swisstopo.pixelkarte-farbe&layers=ch.bag.zecken-fsme-impfung&layers_opacity=0.75
22. Schumacher Z, Bourquin C, Heininger U. Surveillance for adverse events following immunization (AEFI) in Switzerland - 1991-2001. Vaccine. 2010;28(24):4059–64. http://dx.doi.org/10.1016/j.vaccine.2010.04.002