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

Vol. 16 | Weekly issue 39 | 29 September 2011

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Do European doctors support measles, mumps, rubella vaccination programmes enough?

P L Lopalco (Pierluigi.lopalco@ecdc.europa.eu)[1], M Sprenger[1]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden

Citation style for this article:
Lopalco PL, Sprenger M. Do European doctors support measles, mumps, rubella vaccination programmes enough?. Euro Surveill. 2011;16(39):pii=19979. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19979

Article published on 29 September 2011

Eliminating measles and rubella is a goal that all European countries are committed to meet by 2015 [1]. However, the latest epidemiological trend in the European Union (EU) is unfortunately not reassuring in this respect. In 2011 alone, up to August, more than 28,000 cases were reported already. About one third of them required hospitalisation and in the first six months of the year, measles was responsible for eight deaths and 22 cases of acute encephalitis [2].

Sub-optimal immunisation levels prevented meeting the elimination goal in the World Health Organization European Region in 2010 and are still a cause for concern. Notwithstanding that measles, mumps, rubella (MMR) vaccination is accepted by the vast majority of European parents, there is still a relevant proportion of children that miss the opportunity of being protected with MMR. Even if this proportion is on average lower than 10% of the target population, it hinders reaching the elimination goal [3]. There are many reasons for sub-optimal vaccination uptake, but one of the main obstacles is the false perception of parents that believe MMR vaccination to be more dangerous than the disease itself.

The article by Delaporte et al. in this issue of *Eurosurveillance* adds new evidence to the need for extraordinary efforts that should be put in place also in those settings where vaccination coverage levels may look satisfactory [4]. Concerted, coordinated and politically supported actions are needed in such situations and healthcare workers should be among the main actors.

Paediatricians, family doctors and health visitors/ nurses are the backbone of all national immunisation programmes in the EU. According to a recent survey carried out in the 27 EU countries, vaccinations are administered at the paediatrician's office in six, in local healthcare centres in nine, and in multiple settings in 12 countries [5]. Whether directly involved or not in implementing the programme, family doctors are considered by parents as primary and trustworthy sources of information on childhood vaccination [6-8]. This finding is supported by a recent international poll showing that academics and experts are considered highly credible sources of information in many areas [9]. In the specific case of family doctors, the bond of trust with parents of young children is particularly strong. A systematic review carried out in 2010 by Brown et al. shows that parents are more likely to trust their general practitioner, health visitor or practice nurse than the government: this relationship was observed in all five studies on the topic and was statistically significant in three of these [10]. In fact, information by the government may be perceived as biased by some alleged conflict of interest.

Correct and coherent information of parents plays a key role in the decision making process for vaccinating or not vaccinating children. Consequently, doctors' knowledge and positive attitudes towards MMR vaccination are crucial to meet the elimination goal. Therefore, it is important that information by healthcare providers to parents is balanced and based on evidence. Results of a study by Hilton et al. demonstrated that doctors too resolute about the safety of MMR were questioned by parents about their motives and knowledge; conversely when healthcare providers sounded vague, some parents interpreted this as concern that MMR is unsafe [11]. Also a national survey conducted in Italy in 2003, showed that lack of appropriate information accounted for 22% of the missed or delayed MMR vaccinations [12].

A survey published in 2001 by the French Committee for Health Education among 2,000 general physicians showed that 56% were in favour of MMR vaccination, but vaccinated depending on the situation and did not follow the vaccination calendar systematically [13]. Much worse, 6% were not at all or not in favour of MMR vaccination. Only 41% were strongly in favour of MMR vaccination and vaccinated systematically following the vaccination calendar. Similar evidence has been collected for healthcare workers in other European countries [14-16]. In Germany, for example, a survey

carried out in 2008 among 549 midwives showed that around 25% of them objected to measles vaccination [17].

To reach the elimination goal, the hurdle of at least 95% coverage with two doses of MMR vaccine has to be overcome. Many EU countries are close to reaching the goal, but additional commitment has to be put in place and should involve all stakeholders. National and international public health bodies need to support the elimination programme; doctors and other frontline healthcare workers are in direct contact with parents and children and thus play a paramount role. Often parents of young children are either poorly informed or, confused by an overwhelming amount of information coming from different sources. Evidence from the literature shows that paediatricians and family doctors are in a good position to empower parents to take an informed decision about MMR vaccination for their children. The Council of the EU has recently encouraged the Members States to increase health professionals' awareness of the benefits of vaccines and strengthen their support for immunisation programmes [18]. Public health officers and policy makers should thus actively involve doctors in the elimination effort and call upon them to take an active stand to convince parents of the benefits of MMR vaccination.

References

1. World Health Organization (WHO). Resolution. Renewed commitment to elimination of measles and rubella and prevention of congenital rubella syndrome by 2010 and Sustained support for polio-free status in the WHO European Region. Moscow: WHO; 2010. Available from: http://www.euro.who.int/__data/assets/pdf_file/0016/122236/RC60_eRes12.pdf.
2. European Centre for Disease Prevention and Control (ECDC). European monthly measles monitoring (EMMO). August 2011. Stockholm: ECDC; 2011. Available from: http://ecdc.europa.eu/en/publications/Publications/1109_European_monthly_measles_monitoring_August_2011.pdf
3. World Health Organization (WHO). Centralized information system for infectious diseases (CISID). [Internet]. Available from: http://data.euro.who.int/cisid/?TabID=260504
4. Delaporte E, Jeannot E, Sudre P, Wyler Lazarevic CA, Richard JL, Chastonay P. Measles in Geneva between 2003 and 2010: persistence of measles outbreaks despite high immunisation coverage . Euro Surveill. 2011;16(39):pii=19980. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19980
5. van Esso D, del Torso S, Hadjipanais A, Biver A, Jaeger-Roman E, Wettergren B et al. Paediatric primary care in Europe: variation between countries. Arch Dis Child. 2010;95(10):791-5.
6. Mc Murray R, Cheater FM, Weighall A, Nelson C, Schweiger M, Mukherjee S. Managing controversy through consultation: a qualitative study of communication and trust around MMR vaccination decisions. Br J Gen Pract. 2004;54(504):520-5
7. Pareek M, Pattison HM. The two-dose measles, mumps, and rubella (MMR) immunisation schedule: factors affecting maternal intention to vaccinate. British Journal of General Practice, 2000;50(461):969-71
8. Heininger U. An internet-based survey on parental attitudes towards immunization. Vaccine. 2006;24(37-39):6351-5
9. Edelman. Edelman Trust Barometer survey, 2011. Available from: http://www.edelman.com/trust/2011/uploads/Edelman%20Trust%20Barometer%20Global%20Deck.pdf
10. Brown KF, Kroll BS, Hudson MJ, Ramsay M, Greene J, Long SJ, et al. Factors underlying parental decisions about combination childhood vaccinations. Vaccine. 2010;28(26): 4235–48
11. Hilton S, Petticrew M, Hunt K. Parents' champions vs. vested interests: Who do parents believe about MMR? A qualitative study. BMC Public Health 2007; 7:42
12. Ciofi degli Atti ML, Rota MC, Bella A, Salmaso S; ICONA Study Group. Do changes in policy affect vaccine coverage levels? Results of a national study to evaluate childhood vaccination coverage and reasons for missed vaccination in Italy. Vaccine. 2004 ;22(31-32) : 4351–57
13. Institut national de prévention et d'éducation pour la santé (INPES). Committee français d'éducation pour la sante. Vaccination rougeole, oreillons, rubéole. Des inégalités persistantes. Dossier de presse, septembre 2001. French. Available from: http://www.inpes.sante.fr/70000/dp/01/dp010907.pdf
14. Posfay-Barbe KM, Heininger U, Aebi C, Desgrandchamps D, Vaudaux B, Siegrist CA. How Do Physicians Immunize Their Own Children? Differences Among Pediatricians and Non pediatricians. Pediatrics. 2005;116(5);e623-33
15. Cotter S, Ryan F, Hegarty H, McCabe TJ, Keane E. Immunisation: the views of parents and health professionals in Ireland. Euro Surveill. 2003;8(6):pii=416. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?
16. Hak E, Schonbeck Y , De Melker H , Van Essen GA , Sanders EA . Negative attitude of highly educated parents and health care workers towards future vaccinations in the Dutch childhood vaccination program. Vaccine. 2005; 23(24) :3103–7.
17. Robert Koch Institut Epidemiologisches Bulletin. 2008;21: 164-9.. German Available from: http://www.rki.de/cln_116/nn_199624/DE/Content/Infekt/EpidBull/Archiv/2008/21__08,templateId=raw,property=publicationFile.pdf/21_08.pdf
18. Council of the European Union. Council conclusions on Childhood immunisation: successes and challenges of European childhood immunisation and the way forward. Luxembourg 6 June 2011. Available from: http://www.consilium.europa.eu/uedocs/cms_Data/docs/pressdata/en/lsa/122391.pdf

Tick-borne encephalitis increasing in Sweden, 2011

A Lundkvist (ake.lundkvist@smi.se)[1,2,3], A Wallensten[1,3], S Vene[1], M Hjertqvist[1]
1. Swedish Institute for Communicable Disease Control, Solna, Sweden
2. Karolinska Institutet, Stockholm, Sweden
3. Uppsala University, Uppsala, Sweden

Citation style for this article:
Lundkvist A, Wallensten A, Vene S, Hjertqvist M. Tick-borne encephalitis increasing in Sweden, 2011.
Euro Surveill. 2011;16(39):pii=19981. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19981

Article published on 29 September 2011

Until August, 161 cases of tick-borne encephalitis (TBE) were recorded in Sweden for 2011, leading to an incidence of 1.7 per 100,000 population. Fifty to 59 year-olds (24%) were most affected, 55% of the cases were males. An increase in TBE in Sweden has occurred in the last decade and might be explained by enlarged tick populations, more contact between TBE virus infected ticks and man, and also by growing awareness of the disease. Climatic conditions may have contributed to the increase.

Until 25 September 2011, two hundred and four patients have been diagnosed as tick-borne encephalitis (TBE) cases, indicating that 2011 may be a record year for the number of TBE cases in Sweden.

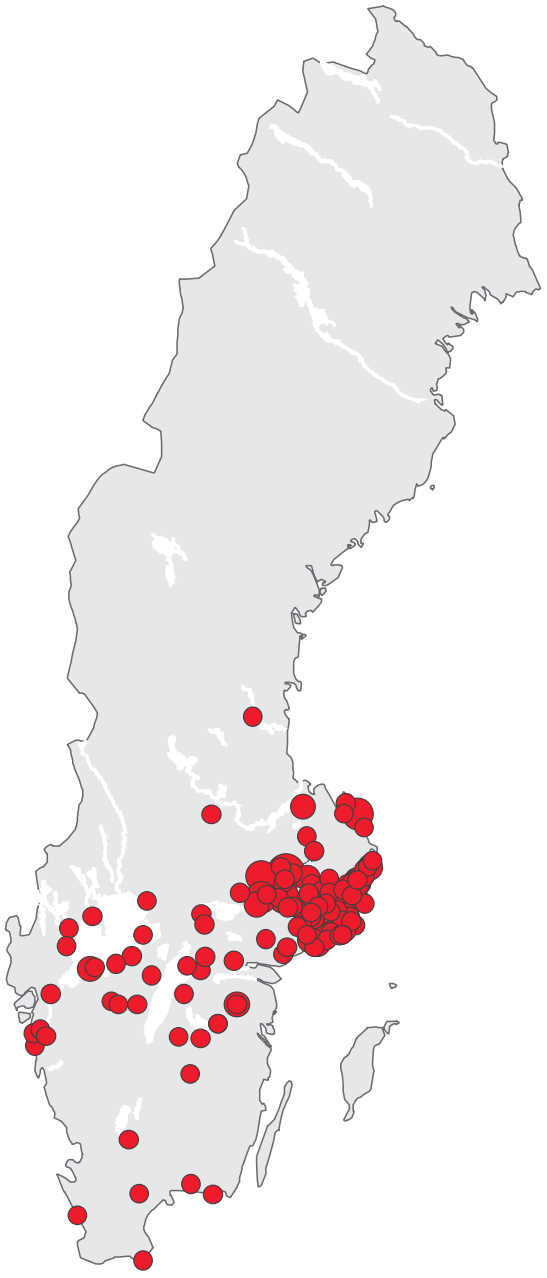
Background

Tick-borne encephalitis virus (TBEV) belongs to the *Flavivirus* family, which includes a number of other important human pathogens such as yellow fever, Japanese encephalitis, West Nile and dengue viruses. TBEV is transmitted to man by ticks (*Ixodes ricinus and I. persulcatus*) and is found in three subtypes; the European, the Siberian and the Far Eastern subtypes. The European subtype is present in Sweden, and the first clinical TBE case was recorded in 1954 and the virus was isolated in 1959 [1,2]. In Sweden, as well as in other countries around the Baltic sea, TBE is endemic in the coastal regions, but cases also occur around lakes in southern Sweden and on the Swedish west coast (Figure 1). In Norway and Denmark, TBEV was first described as late as in 2006 [3].

Human infection with TBEV may cause a potentially serious neurological disease. The vast majority of those who are infected will have mild or no symptoms, while in patients with more marked clinical illness, high fever and encephalitis may occur [4]. About 46 per cent of diagnosed patients suffer permanent neurological sequelae. The case fatality rate in Europe is less than two per cent [5].

Reliable laboratory diagnostics have been available since the mid 1950s and the disease has been notifiable

Figure 1
Location of tick-borne encephalitis cases in Sweden, 2010



The red dots show probable geographical location of infection for the cases.

by reporting to the Swedish Institute for Communicable Disease Control (SMI) since 1969. TBE is reported on the basis of clinical neurological symptoms and compulsory laboratory confirmation. The number of cases was quite stable during the 1960s and 1970s, but has increased from the mid-1980s (Figure 2).

Vaccination

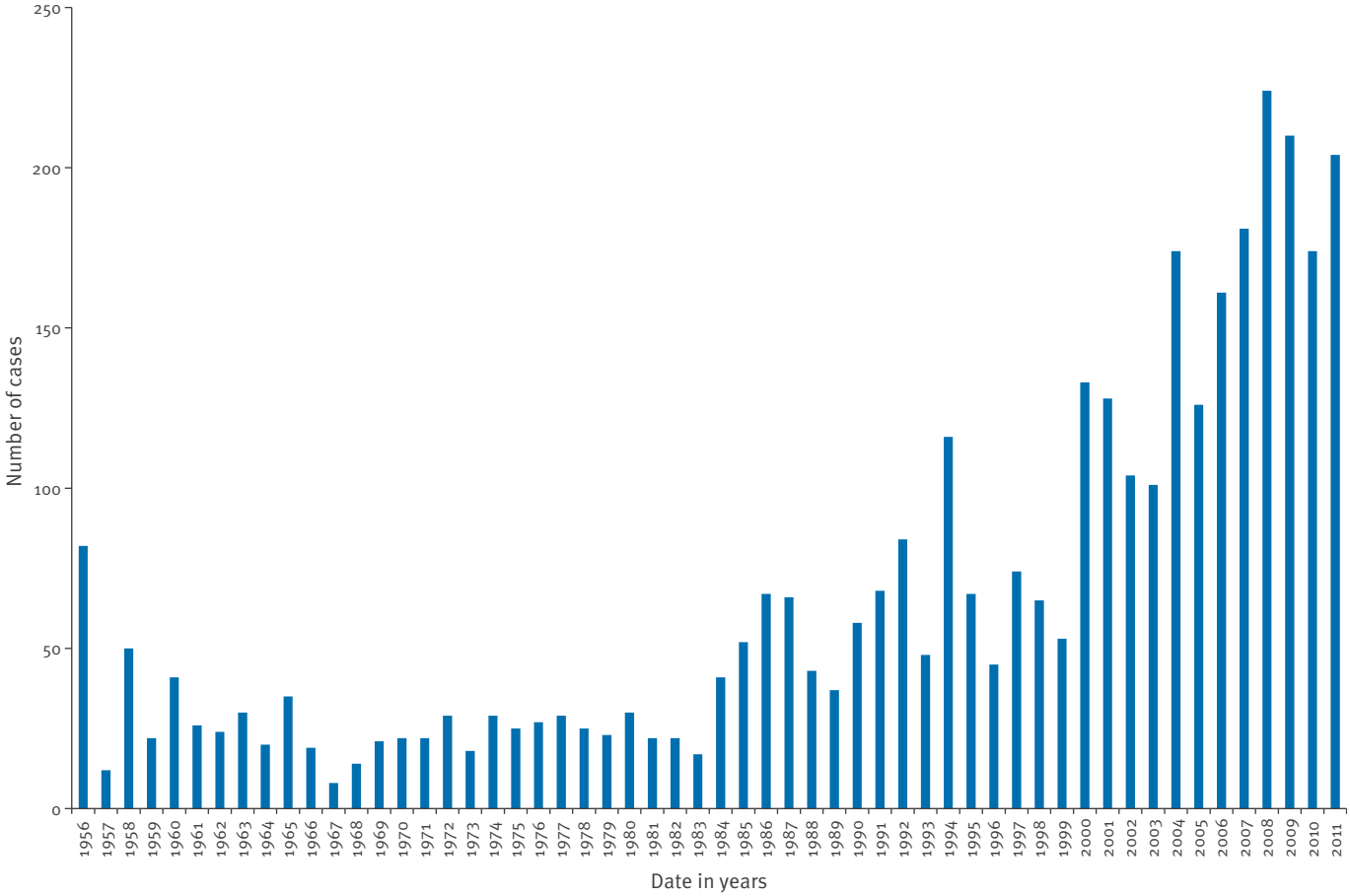
Vaccination was introduced in Sweden in 1988. Three doses are needed for protection [6]. Vaccination is not subsidised and is only recommended for people living or spending time in "high risk areas" (mainly the coastal areas of the counties of Uppsala and Södermanland, the Stockholm archipelago, around the Mälaren lake, and some local foci around the Vänern and Vättern lakes). TBE vaccination is not registered in Sweden, but the yearly number of sold doses (approximately 500,000) indicates that the vaccine coverage is still low. Only a few investigations on vaccine coverage have been performed, suggesting a maximum of 30% vaccinees in Stockholm county.

Increase in Swedish tick-borne encephalitis cases

Between 1956 and 1984, the yearly number of TBE cases in Sweden ranged from less than 10 to a maximum of 50. During the period from 1985 to 1999, the average number of yearly cases was 63. The number of individuals infected by TBEV has increased during the last 11 years (Figure 2). Until August 2011, 161 cases of TBE have been recorded in Sweden for 2011, leading to an incidence of 1.7 per 100,000 population for the whole country. Since TBE is restricted to some parts of the country, the incidences for the Södermanland, Uppsala and Stockholm counties are much higher, 9.29, 6.55 and 3.71, respectively. In August only, 83 cases were reported, which is more than during any other month during the past four years. Up to 25 September 2011, a total of 204 cases of TBE has already been reported for 2011, compared to a total of 174 for the whole of 2010 (2009:210, 2008: 224). The age group comprising 50 to 59 year-olds was the most affected (24%) and 55% of the cases were males. The age and sex-ratios were similar to previous years (Figure 3).

Figure 2

Number of yearly tick-borne encephalitis cases in Sweden, January 1956– September 2011[a] (n=3,648)



As the notification system has varied over the years (notifiable since 1969), the number of cases is not completely comparable over the whole time period.

[a] Data up to 25 September 2011.

Discussion and conclusions

In 2011, Sweden has seen an increase in notification of TBE cases up to 25 September that amounts to numbers amongst the highest recorded. Normally, additional cases are also reported in October, indicating that 2011 may be a record year concerning TBE in Sweden.

In our opinion, a potential explanation for the increase of TBE cases in Sweden during the last years is a general increase of the tick population (T Jaenson, personal communication, 26 September 2011), although human behaviour and contact with wildlife could also have contributed.

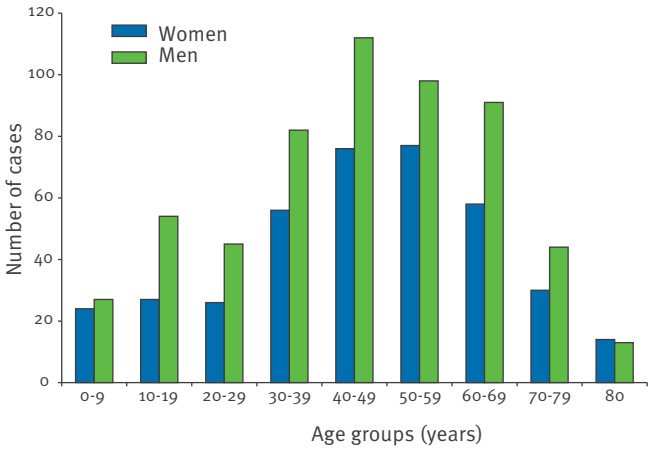
Factors that help tick populations thrive are among others, non-extreme temperatures, high humidity and the presence of snow cover during the winter, which acts as insulation. The last decades' increased mean annual temperature [7] may have provided more favourable conditions for ticks. In particular, the last years' ample snow cover, early springs with rapidly increasing temperatures as well as the not too hot or dry summers may have been important positive factors for tick survival and reproduction success [8,9]. However, climatic factors alone may not be sufficient to contribute to an increase of the tick-population. The density of the most important blood sources, e.g. rodents, deer or hares, is also important.

Factors concerning human exposure to ticks may be favourable weather and abundance of mushrooms or berries which stimulates outdoor activities. In recent years, springs have been warmer than before [10], the summers and autumns have been relatively warm, all of which are likely to have increased human exposure to ticks.

In conclusion, we believe that weather is likely to have stimulated both tick populations and human exposure resulting in an increase in human cases in 2011 in Sweden.

Figure 3

Age and sex distribution of tick-borne encephalitis cases, Sweden, 2006–2010 (n=954)



Acknowledgments

Prof. L. Lindquist, Stockholm, and Prof. T Jaenson, Uppsala, are greatly acknowledged for most valuable information and discussions.

References

1. Holmgren B, Lindahl J, von Zeipel G, Svedmyr A. Tick-borne meningoencephalomyelitis in Sweden. Acta Med Scand. 1959;164:507-22.
2. von Zeipel G. Isolation of viruses of the Russian Spring-Summer Encephalitis-Louping Ill group from Swedish ticks from a human case of meningoencephalitis. Arch Gesamte Virusforsch. 1959;9:460-9.
3. Skarpaas T, Golovljova I, Vene S, Ljostad U, Sjursen H, Plyusnin A, et al. Tickborne encephalitis virus, Norway and Denmark. Emerg Infect Dis. 2006;12(7):1136-8.
4. Ruzek D, Dobler G, Donoso Mantke O. Tick-borne encephalitis: pathogenesis and clinical implications. Travel Med Infect Dis. 2010;8(4):223-32.
5. Haglund M, Gunther G. Tick-borne encephalitis--pathogenesis, clinical course and long-term follow-up. Vaccine. 2003;21 Suppl 1:S11-8.
6. Vaccines against tick-borne encephalitis: WHO position paper - Recommendations. Who Publication. Vaccine. Forthcoming 2011 Jul.
7. Swedish Meteorological and Hydrological Institute (SMHI). Stockholms temperaturserie [Stockholm's temperature series]. Swedish. [Accessed 26 Sep 2011]. Available from: http://www.smhi.se/klimatdata/meteorologi/temperatur/stockholms-temperaturserie-1.2847
8. Burri C, Bastic V, Maeder G, Patalas E, Gern L. Microclimate and the zoonotic cycle of tick-borne encephalitis virus in Switzerland. J Med Entomol. 2011 May;48(3):615-27.
9. Jaenson T. Antalet fästingar ökar i Sverige [Increased tick abundance in Sweden]. Epi-Aktuellt. 2011; 10(28): 2-3. Swedish. Available from: http://www.smi.se/publikationer/smis-nyhetsbrev/epi-aktuellt/epi-aktuellt-2011/epi-aktuellt-vol-10-nr-28-14-juli-2011-/#p19589
10. Swedish Meteorological and Hydrological Institute (SMHI). Klimatindikator – temperatur [Climate indicator – Temperature]. Swedish. . [Accessed 26 Sep 2011]. Available from: http://www.smhi.se/klimatdata/meteorologi/temperatur/1.2430

Tick-borne encephalitis in Europe, 2007 to 2009

O Donoso Mantke (donosoo@rki.de)[1], C Escadafal[1,2], M Niedrig[1], M Pfeffer[3], on behalf of the Working group for Tick-borne encephalitis virus[4]

1. National Consultant Laboratory for Tick-borne encephalitis and further flaviviruses, Robert Koch-Institut (ZBS 1), Berlin, Germany
2. European Public Health Microbiology Training Programme (EUPHEM), European Centre for Disease Prevention and Control, Stockholm, Sweden
3. Institute of Animal Hygiene and Veterinary Public Health, University of Leipzig, Leipzig, Germany
4. European Network for the Diagnostics of 'Imported' Viral Diseases-Collaborative Labora-tory Response Network (ENIVD-CLRN), www.enivd.org

Citation style for this article:
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. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19976

Article published on 29 September 2011

As a follow-up of a retrospective survey on tick borne-encephalitis (TBE) in 2008, the European Network for Diagnostics of "Imported" Viral Diseases launched a new survey in 2010, to collect broader information on TBE prevalence between 2007 and 2009 and to observe possible changes compared to the previous data. A two-part questionnaire was mailed to contact points in all European Union (EU) Member States and four non-EU countries (Bosnia and Herzegovina, Norway, Russia, and Switzerland). The first part was identical to the 2008 survey, requesting information on case definition, diagnostic methods, investigations regarding tick-transmitted diseases, endemic foci mapping, vaccination programmes, and recommendations for travellers. The second newly added part, inquired about geographic and seasonal distribution of TBE cases, imported cases, TBE subtypes, animal cases, and prevalence in ticks and wildlife hosts. Of 28 partic-ipat-ing countries, 16 had TBE as a notifiable disease, as in the first survey. In the 2007–2009 period, the total number of notified cases (17,818) was lower than in 2004–2006 (21,339 cases), also when subtracting Russian cases (8,207 vs 9,073 cases respectively). The highest reported incidence was 18.5 per 100,000 population in Lithuania in 2009. The 2010 study showed that increased numbers of countries used PCR and nucleotide sequencing for particular investigations. Most countries, however, relied on specific antibody detection by enzyme linked immunosorbent assay for TBE laboratory diagnosis. Disparities nevertheless remained across countries regarding case definitions, and surveillance and prevention activities. To understand changing patterns in TBE transmission, surveillance strategies including screening of vector ticks and testing of animal hosts should be harmonised and done more systematically in Europe. Collected data will support rec-ommendations concerning diagnostic and mapping methods, case reporting, vaccination programmes and information campaigns.

Introduction

Tick-borne encephalitis (TBE) is due to a zoonotic arbovirus infection of the central nervous system (CNS) and affects humans. With an average of about 9,000 reported cases of TBE per year in Europe and Russia between 1990 and 2007, it is the most important tick-borne viral disease in Eurasia [1-7]. TBE is caused by TBE virus, a virus species of the genus *Flavivirus* within the Flaviviridae family, with three subtypes: the European subtype, the Siberian sub-type and the Far Eastern subtype [8,9], which are associated with varying degrees of disease severity [1-3,10-12]. More detailed information on the clinical picture, case definition and other issues of interest are available in a TBE fact sheet on the European Network for Diagnostics of "Imported" Viral Diseases (ENIVD) website [http://www.enivd.org] or in the 2010 spotlight for tick-borne diseases on the European Centre for Disease Prevention and Control (ECDC) website [http://ecdc.europa.eu].

In nature, TBE virus is propagated in a cycle involving permanently infected ticks and small mammals, especially rodents. Virus transmission occurs horizontally between tick vectors and vertebrate hosts, particularly between spring and autumn. In addition, co-feeding of infected and non-infected ticks on the same host as well as trans-stadial and trans-ovarial transmission of the virus, play a major role in virus transmission [13]. While most TBE virus infections of humans occur following the bite of an infected tick, alimentary routes of TBE virus transmis-sion by raw milk consumption have also been described [14-19].

The principal vector of the European TBE virus subtype is *Ixodes ricinus*, and for the two other subtypes I. persulcatus [3,20,21]. Although the virus has been isolated from several other tick species [1], only the two mentioned ixodid tick species appear to play an important role in virus maintenance [13]. Therefore, the epidemiology of TBE is strongly influenced by the ecology

and biology of ixodid ticks [2,3,20,21]. Unlike other tick-borne diseases, such as Lyme borreliosis, TBE is distributed in an endemic pattern of so-called natural foci over a wide geographical area covering northern Asia, Russia and central Europe. The distribution of TBE subtypes is closely related to the presence of the respective tick vectors in a certain geo-graphical area [2,6,20,21]. Co-circulation of two or all three subtypes was demonstrated in the Baltic states and Finland [22,23].

Countries with high-risk areas, i.e. with an incidence of over 10 per 100,000 population, are the Czech Republic, Estonia, Latvia, Lithuania, Russia and Slovenia. TBE is also an important issue in Germany, Poland, Switzerland, Sweden, Finland, Slovakia and Hungary [24,25]. Although TBE has a lower public health impact in Denmark, France, Greece, Italy, Norway and Turkey, new TBE foci or possible occurrence of TBE virus are reported in these countries [25-27]. Austria is the only country with progressively decreasing incidence rates since 1981 due to its vaccination campaign, but the occurrence of TBE may be relevant to unvaccinated tour-ists [24,25,28].

TBE is a growing concern in Europe, as an increase of TBE incidence has been observed in some risk areas and new foci have appeared in the last decade [29]. But the surveillance and notification schemes are not uniform, not always mandatory, and may affect the prevalence estimates for the disease in certain regions. Main problems are the lack of a Europe-wide standard case definition, varying diagnostic procedures and wide differences in the intensity and quality of national surveillance of TBE cases [25,28]. Thus, surveillance data from different countries are difficult to compare. Furthermore, little is known about the true TBE virus prevalence in tick populations or about the circulation of new subtypes in Europe.

A first survey was conducted by the ENIVD in 2008 on surveillance, prevention and labora-tory activities concerning TBE, with 22 participating countries [25]. Although the 2008 study covered a period from 2004 to 2007, the data recovered in 2007, when the respective national programs were ending their annual surveillance, were minimal compared to the three consecu-tive previous years. Here, we describe the results of a second more extended survey launched in 2010 aimed at collecting broader information on TBE prevalence between 2007 and 2009, and also allowing the comparison of two three-year intervals, between 2004 and 2009, to detect possible changes in TBE assessment and prevalence.

Methods

To request information on TBE diagnostics, surveillance and prevention activities in national surveillance systems, a two-part questionnaire was mailed to contact points in all Member States of the European Union (EU) and four non-EU countries (Bosnia and Herzegovina, Norway, Russia, and Switzerland) based on an ENIVD database of expert microbiologists and epidemiologists. The first part of the questionnaire was identical to the previous ENIVD-survey in 2008 [25] asking whether TBE was notifiable, and requesting information on annual case numbers, case definition, type of diagnostic methods, investigations regarding tick-transmitted diseases, mapping of endemic foci, vaccination programmes, and recommendations for travellers. The second part of the questionnaire was designed to collect more information about the recent situation for TBE on a more detailed scale with new questions as follows:

- Did you observe a change in the known geographic distribution of TBE in your country? If yes, is the range expanding or decreasing?
- Did you register human cases during winter?
- Which TBE subtypes are involved in general?
- Did you register imported cases?
- Do you have reports of clusters of cases?
- Do you have reports of cases in livestock or companion animals (pets)?
- Do you have information regarding prevalence in ticks/wildlife hosts? If yes, for which region? If not, do there exist plans to monitor ticks/wildlife hosts in the near future?

All contributors are listed in the acknowledgements section. The completed questionnaires were returned during the spring trimester of 2010. The TBE case numbers for 2009 were added afterwards, in summer 2010, in order to receive the complete notified data. Therefore, the results of this survey reflect national surveillance systems and case numbers for TBE up to these dates. Bosnia and Herzegovina and Romania did not contribute data to some of the re-sults presented in this study. As our goal was to obtain an overview on the assessment and situation of TBE in Europe, and Europe's eastern geographical frontier is delineated by the Ural Mountains in Russia, the TBE situation in Russia was surveyed. It is to be noted, however, that the Russian data presented here are for the whole country, including the non-European parts of Russia.

Results

Of 31 contacted countries, 28 (24 EU and four non-EU countries) participated in this survey, equivalent to a recovery rate of 90% (recovery rate from the first survey in 2008: 22 of 30 contacted countries, 73%) (Figure 1). Six additional countries participated compared to the first survey and included Bosnia and Herzegovina, Bulgaria, Denmark, Malta, Romania, and the United Kingdom.

Case reporting

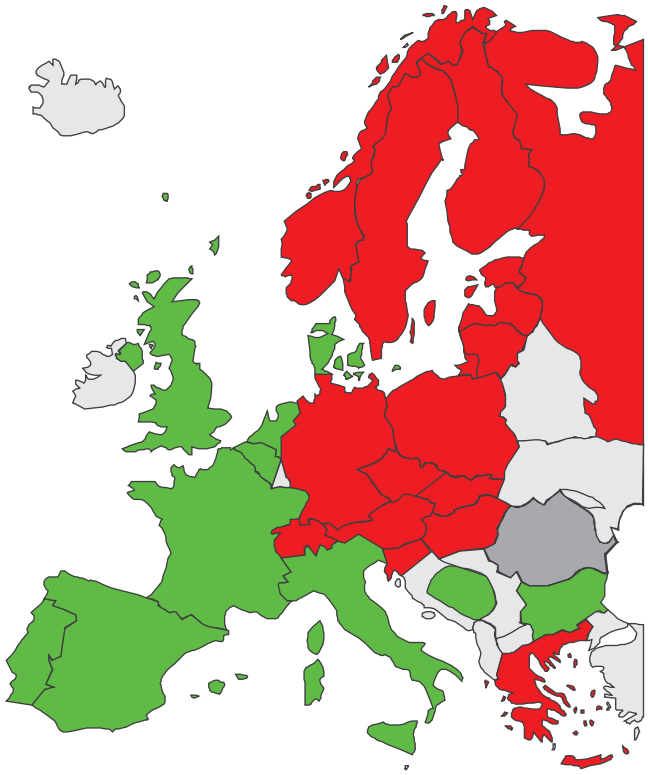
At the time of the survey, TBE cases were mandatorily notifiable in 16 of the 28 participating countries (57%). No information on this item was given by Romania (Figure 1). Of the 16 countries with TBE notification, five (Austria, Germany, Hungary, Norway, Slovenia) had a

case definition based on clinical criteria and laboratory confirmation, five (Czech Republic, Estonia, Finland, Greece, Poland) additionally included an epidemiological link (e.g. tick exposure or recent travel in TBE endemic area) in the case definition, and the remaining six countries had no official or clearly formulated case definition (Table 1). During the survey, Finland and Sweden reported that their case definitions were still under discussion by a Bal-tic/Nordic working group on tick-borne diseases since 2007. In comparison to the first survey in 2008, changes could be observed for Norway now having formulated a case definition; and for the Czech Republic, Greece and Poland where an epidemiological link has been included into their existing case definitions.

Although case definitions were provided by ten countries, differences still could be seen in the classification of relevant TBE cases according to clinical symptoms (e.g. classifications in Austria, Czech Republic, Hungary, Norway, or Slovenia), as well as in the application of laboratory tests for case confirmation (Table 1). Commonly, the routine laboratory diagnosis of TBE is based on the detection of specific antibodies by enzyme linked immunosorbent assay (ELISA) as done in 25 participating countries (96%; first survey in 2008: 91%). The application of reverse transcriptase-polymerase chain reaction (RT-PCR) and sequencing (SEQ) – which are included for particular investigations (e.g. tick/host infectivity studies or severe cases) – has dramatically increased in comparison to the first survey. The RT-PCR is applied by 17 countries (65%; 2008: 45%) and SEQ by 13 countries (50%; 2008: 1/22, i.e. 4.5%). Other methods included virus neutralisation test (six countries), immunofluorescence assay and virus isolation (five countries each), haemagglutination inhibition assay (four countries), and complement fixation test and Western blot (two countries each), respectively. No information on this item was given by Malta and the United Kingdom which are both non-endemic areas (Table 1).

Figure 1

Form of notification for tick-borne encephalitis in European countries and Russia participating in the survey, 2010 (n=28)



Surveillance activities

Information on further investigations regarding tick-transmitted diseases was provided by 21 countries (Table 1). Human survey studies on TBE (11 countries) and borreliosis (12 countries) were mainly conducted, followed by surveys on other less common tick-transmitted diseases/pathogens like rickettsiosis in seven countries; anaplasmosis/ehrlichiosis in four countries; Crimean-Congo haemorrhagic fever virus and other arboviruses in two countries. Surveys on prevalence of TBE virus in tick populations were also performed in 10 countries and on prevalence of borrelia in 11 countries; followed by tick surveys for anaplasma/ehrlichia in 11 countries; babesia in six countries; rickettsia in four countries; Crimean-Congo haemorrhagic fever- and louping ill virus each in one country; and only for tick density/activity in two countries. Finally, three countries reported to conduct TBE serosurveys in animals/livestock. Although most of these investigations are based on research funds and are hence not systematically done, a slight increase of those activities could be observed in general compared to the first survey.

A total of 17 countries provided information on what kind of data their TBE risk assessments are based on (Table 1). The mapping of risk areas is mainly based on the geographical inci-dence of autochthonous clinical cases (14 countries) and/or human seroprevalence data (four countries), while nine countries also included data on infected ticks in the risk assessment, and only two countries used data from natural animal reservoirs (e.g. rodents). In Belgium, Bulgaria, Denmark, Estonia, and Greece epidemiological assessment for mapping of TBE risk areas is in progress or planned.

Tick-borne encephalitis incidence and prevalence

As in the first survey, 16 countries reported to have TBE as a notifiable disease. The numbers and incidence rates of notified cases in these countries per year are shown in Figure 2 (except Greece with no reported TBE cases up to date). The overall number of notified cases during the currently observed three-year interval (17,818 cases from 2007 to 2009) decreased in comparison to

Table 1

Survey data on surveillance systems for tick-borne encephalitis in European countries and Russia, 2010 (n=28)

Country	Notifiable disease	Case definition	Diagnostic assays	Investigations regarding tick transmitted diseases	Mapping of endemic foci/ risk areas	Vaccination programme	Recommendations for travellers
Austria	Yes[a]	Serological proven hospitalised TBE cases	ELISA, VNT, PCR[b], SEQ[b]	TBE clinical case survey	For human TBE cases	Yes	Yes
Belgium	No	No	ELISA	Research on TBE, borreliosis, anaplasmosis, rickettsiosis, babesiosis	In progress for prevalences in humans and ticks	No (optional)	Yes
Bulgaria	No[c]	No	ELISA, CFT	Survey on borreliosis and rickettsiosis	Done for borrelia and rickettsia. Planned for TBE.	No (optional)	No
Czech Republic	Yes, since 1971	Positive anamnestic data, symptoms of aseptic meningitis or meningoencephalitis and laboratory confirmation - specific anti-TBE virus antibodies	Mostly ELISA, in NRL for arboviruses: ELISA, VNT, PCR[b], SEQ[b], VI[b]	Tick surveillance (TBE, Uukuniemi or Tribec viruses, borrelia and others), TBE virus serosurveys in wild animals and livestock	For human TBE cases and infected ticks	No, but recommended	Not known
Denmark	No	No	ELISA, PCR	No	Planned for TBE cases	No (optional)	Yes
Estonia	Yes, since 1970	Possible case: Typical clinical case history (biphasic course of infection), epidemiological links (e.g. tick attack) Confirmed case: with laboratory confirmation: not less than four-fold increase in antibody titre in pair-serums or IgM-antibodies in serum/CSF or positive PCR[d]	ELISA, PCR[b], SEQ[b]	Detection and genetic analysis of TBE virus, *Borrelia* spp., *Anaplasma phagocytophilum* and *Babesia* spp. in ticks	In progress for incidences/ prevalences in humans and ticks	No, just recommendations	Yes
Finland	Yes, since 1996	TBE virus-IgM positive, and compatible infection and anamnesis[e]	IgM micro-capture ELISA and HIA, VI[b], PCR[b], SEQ[b]	Interviews of all TBE patients. Tick field surveys (TBE virus, anaplasma, babesia and borrelia) not regular.	For human TBE cases, infected ticks and seroprevalences in animals	Yes but only for Åland islands, just recommendations for other regions	Yes
France	No	No	ELISA, PCR	No, only if there is a notion of clustered cases	Not available	No (optional)	Yes
Germany	Yes, since 2001	Clinical symptomatic case with positive PCR in blood/ CSF or IgM- and IgG-antibodies in blood/CSF or increase in IgG-antibody titre or intrathecal antibody production[f]	Mostly ELISA, in the Robert Koch Institute: ELISA, VNT, PCR, SEQ, VI, IFA	Research based on funds, not done systematically (prevalence studies in humans, animals and ticks for tick-borne diseases)	For human TBE cases	Yes	Yes
Greece	Yes[g]	Patients with fever, headache, and CNS involvement, especially if exposed to ticks or travelled recently in TBE endemic areas, and laboratory confirmation	ELISA, IFA, PCR, SEQ, VI	Surveys on apparently healthy population, patients and ticks for TBE, Crimean Congo haemorrhagic fever, rickettsia, anaplasma, ehrlichia and borrelia	In progress based on human serology and ticks infectivity in northern Greece, but no evidence for TBE virus found	No (optional)	Yes
Hungary	Yes, since 1977	Aseptic meningitis, encephalitis or meningoencephalomyelitis confirmed by laboratory tests	IFA, HIA, ELISA, VNT	Regular: suspected cases, serosurveys (TBE). Until 2008, EDEN project on collected ticks	For human TBE cases and natural foci	Yes, for occupationally endangered persons	No
Italy	No[h]	No	In regional laboratories: ELISA, in expert laboratory: HIA, ELISA, VNT PCR[b], SEQ[b]	No	Not known	Yes, for Veneto region	No
Latvia	Yes, since 1999	No	ELISA, PCR[b]	Survey in human specimens (TBE, borreliosis, anaplasmosis), survey in ticks (TBE, borrelia, anaplasma)	For human TBE cases and infected ticks	Yes, for children (since 2007). For adults only recommended	Yes
Lithuania	Yes, since 1969	No	ELISA	Seasonal ticks activity in observation sites	No	No (optional)	Yes
Malta	No[i]	No	Not available	Even if Mediterranean spotted fever is endemic locally, there are no ongoing specific investigations	No (limited information on local ticks)	No (optional)	No
Norway	Yes, since 1975	Clinical cases with encephalitis are notified based on laboratory confirmation, either by serological detection of specific IgM or significant increase of IgG or TBE virus detection in serum/CSF	ELISA, IFA[b], PCR[b], SEQ[b]	Tick field studies (TBE, borrelia, anaplasma, babesia), survey on human TBE and borreliosis cases, serosurvey on TBE in human and deer	For human TBE cases	No (optional)	Yes

Poland	Yes, since 1970	Possible: Clinically compatible case, and onset of illness during a period of increased tick activity (between April and November). Probable: Clinically compatible case, and increased probability of infection during previous six weeks (living in or visit to endemic area), and demonstration of specific IgM antibodies in serum, with no history of vaccination against any flaviviral disease during previous three months. Confirmed: Clinically compatible case, and demonstration of specific IgM and IgG antibodies in serum, or demonstration of intrathecal synthesis of specific IgM or IgG antibodies, or detection of specific anti-TBE virus antibodies by neutralisation test, or positive virus isolation from tissues, blood, or CSF.	ELISA, PCRb	Surveys on TBE, borreliosis, rickettsiosis	Based on reported TBE incidences. No official definition of endemic area, and maps are not officially published	No, but recommended for risk groups	Yes
Portugal	No[j]	No	IFA	Research and epidemiological studies on rickettsia, borrelia, arboviruses	No	No (optional)	Yes
Russia	Yes, since 1950	Case definition is not formalised	ELISA, PCR, SEQ, HIA	Research and epidemiological studies on TBE, borrelia and rickettsia in natural foci	Based on human TBE cases	Yes, in natural foci regions	No
Slovakia	Yes, since 1950	No official case definition	ELISA	In context of scientific projects (e.g. EDEN), not regular	No, not updated	No (optional)	Yes
Slovenia	Yes, since 1977	A case of TBE is considered to be confirmed by the following findings: fever, clinical signs/symptoms of meningitis or meningoencephalitis, an elevated CSF cell count (>5x100,000 cells/L), and serum IgM antibodies to TBE virus and/or IgG seroconversion	ELISA, PCR, SEQ[b]	Ongoing investigations on natural foci (TBE, borreliosis, rickettsiosis, anaplasmosis), routine laboratory surveillance activities on all tick-borne pathogens	For human TBE cases, ticks infectivity and reservoirs	Yes	Yes
Spain	No	No	ELISA, PCR, SEQ	Surveys on borreliosis, rickettsiosis and other bacterial tick-borne diseases	No	No (optional)	Yes
Sweden	Yes, since 2004[k]	No	ELISA, VNT, VIb, PCR[b], SEQ[b]	No, not any regular	Based on human TBE cases from 2009	No (optional)	Yes
Switzerland	Yes, since 2001	No, official standards are missing	ELISA, PCR[b], SEQ[b]	No	Mapping based on human TBE cases exists, mapping based on tick infectivity recently published [30]	Yes	Yes
The Netherlands	No	No	ELISA	Diagnostic services at Erasmus MC and National Institute for Public Health and the Environment (RIVM)	No, not planned	No (optional)	No
United Kingdom	No	No	Not available	Borreliosis laboratory diagnosis and epidemiology (by Health Protection Agency), research at a few universities on tick infectivity with borrelia, anaplasma, Louping ill virus	No, distribution of ticks is incompletly recorded	No (optional)	No

CNS: central nervous system; CFT: complement fixation test; CSF: cerebrospinal fluid; EDEN: Emerging diseases in a changing European environmnent; ELISA: enzyme linked immunosorbent assay; HIA: haemagglutination inhibition assay; IFA: immunofluorescence assay; NRL: National reference laboratory; PCR: polymerase chain reaction; SEQ: sequencing; TBE: tick-borne encephalitis; VI: virus isolation; VNT: virus neutralisation.

Data for this table are provided by listed contributors. Bosnia and Herzegovina and Romania contributed to the survey but only gave partial responses, so are not included in the table.

[a] Notified if meningoencephalitis. Start of notification not further specified.

[b] Methods not mainly used for diagnostic purposes, but for research in ticks/hosts studies and severe cases of patients.

[c] Reports on viral meningitis and encephalitis, not specifically tick-borne encephalitis.

[d] Case definiton used since 2004.

[e] A Baltic/Nordic working group on Tick-borne diseases since 2007 holds annual meetings, and the case definition is in the agenda (lead by G. Günther).

[f] Case definition of the Robert Koch Institute according to the Law for the Prevention of Infections (Infektionsschutzgesetz, IfSG), 2007.

[g] Notification as arboviral encephalitis since 2002 as part of the Commission decision 2002/253/EC.

[h] Notification is not mandatory. The disease is notifiable in some regions, but not at the national level and only on a voluntary basis.

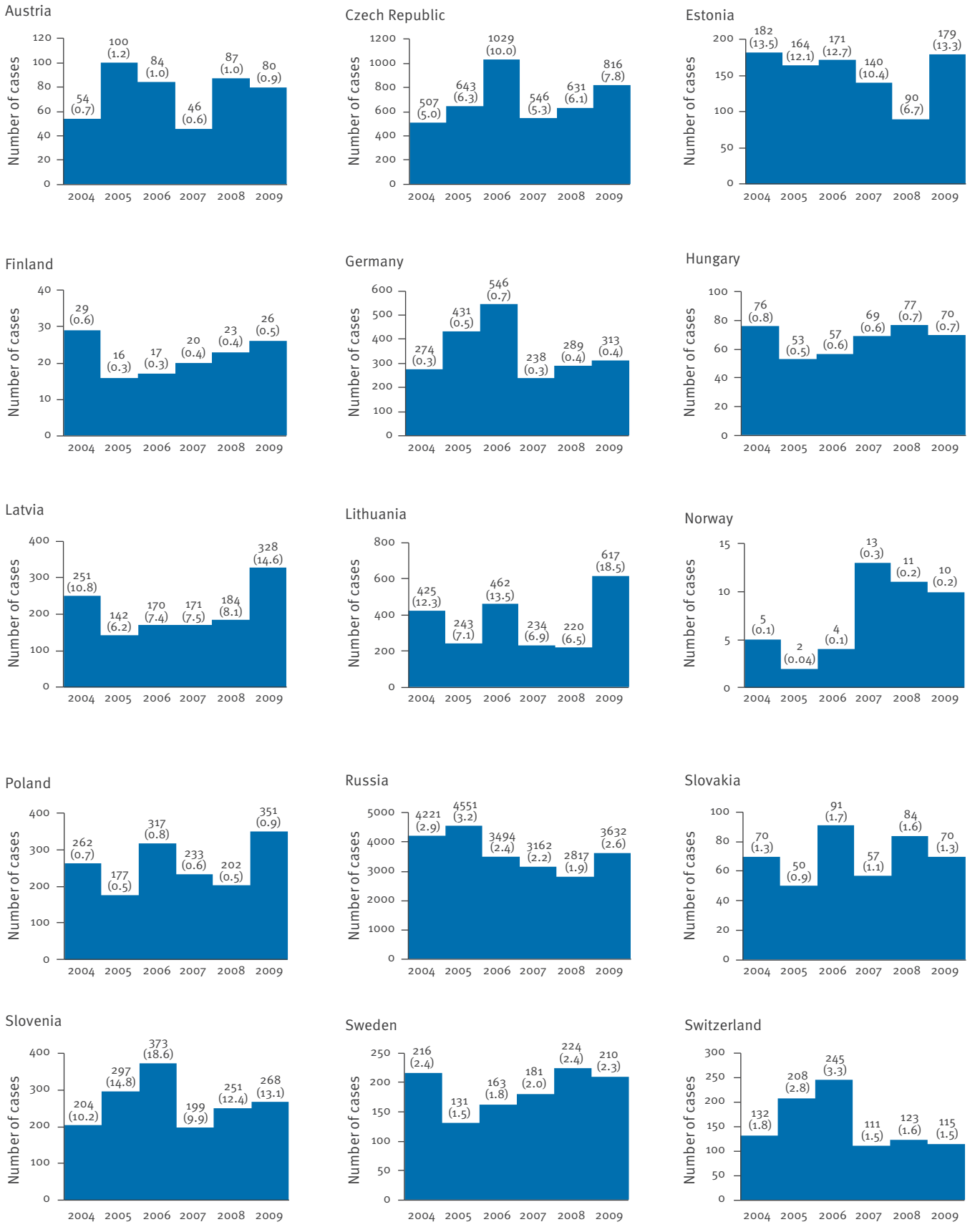
[i] Not specifically tick-borne encephalitis, though acute encephalitis is notifiable.

[j] Diagnostic since 1993, tick-borne encephalitis is included in the arbovirus serology panel.

[k] Notifiable along with other viral meningoencephalitic infections since 1 July 2004.

Figure 2

Annual case numbers and incidence rates per 100,000 population of tick-borne encephalitis, by country where tick-borne encephalitis is mandatorily notifiable, 2010 (n=16)



Greece not included due to no reported tick-borne encephalitis cases up to date.
Numbers in parentheses are the incidence rates per 100,000 population.
The scale for the y-axis differs between each graph.

the last interval (21,339 cases from 2004 to 2006), also when subtracting Rus-sian cases (8,207 vs 9,073 cases respectively). Looking at incidence values we cannot observe any clear trend as overall incidence rates have fluctuated from year to year. These fluctuations may well reflect that changes in TBE incidence are due to a complex interrelation of several factors, such as social (e.g. socio-political changes, human leisure activities), ecological (e.g. effect of climate change on vectors distribution) and/or technological factors (e.g. advanced diagnostics and medical awareness). Incidence rates were particularly high (over 10.0 per 100,000 population), fluctuating with peaks, in four countries: Estonia, Latvia, Lithuania and Slovenia. On the other hand, incidence rates have been rather low (under 1.0 per 100,000 population) all throughout the six years of the studies in Finland, Germany, Hungary, Norway and Poland. The epidemiological and laboratory sources of information for the TBE surveillance data are listed in Table 2.

None of the previously participating non-endemic countries, i.e. Belgium, Greece, Portugal, Spain, and the Netherlands became endemic during the period between the first and this survey. Also, Bosnia and Herzegovina, Malta and the United Kingdom, as new participants, did not report any indigenous occurrence of TBE. Bulgaria reported one case in 2009, but had none in 2007 and 2008 (data not shown). Since Bulgaria participated for the first time in our survey, we cannot determine whether this indicates a new endemic country. Belgium, Bosnia and Herzegovina, Bulgaria, Greece, Hungary, Malta, Norway, Poland, Portugal, Romania, Slovakia, Spain, the Netherlands, and the United Kingdom reported no change or no information about a change in geographical distribution. The remaining 14 countries declared that TBE is expanding within their borders (Table 3). The European situation with these new endemic areas is roughly depicted in Figure 3.
Summarised, there is an overall expansion in the geographical range of TBE towards each direction, as well as filling in not yet endemic areas within countries.

Together with the particular surveillance activities described above, 13 of the participating countries were able to trace and report imported TBE cases (Table 3). Although in most coun-tries this was a rare event with one or only a few cases, this underlines the importance of travel recommendations. It also reflects an enhanced awareness for imported diseases in general and the capability to diagnose an imported TBE case in particular.

Clusters of cases were reported from 13 of 21 countries responding to this particular question in the survey. TBE cases during the winter were reported from nine countries, while 13 coun-tries did not observe cases during the winter. No information was available from the remaining six countries (Table 3). Subtypes differing from the predominant European subtype (as registered in 13 countries) were additionally reported from Finland and Estonia (Siberian sub-type), and from Russia and Latvia (Siberian and Far Eastern subtypes). For Lithuania the information for the subtypes was not available, unfortunately, because of the geographic location it would have been interesting to learn whether only Siberian or both other subtypes are present. For the other countries, which did not provide data concerning the subtype involved, we can assume with certainty that it is predominantly the European subtype (Table 3).

Animal cases

Cases in animals were reported from Austria, Czech Republic, Sweden, and Switzerland but no specifics about the clinical presentation or the animal species are provided except for do-mestic pigs in Austria [17] and dogs in Sweden (Table 3). Finland and Italy reported only antibodies in animals with no correlating disease. In contrast to these few reports, almost all participating countries were investigating TBE in ticks or in wild animals or are planning to do so in near future. However, as shown in Table 3, many of these investigations seem to have more local character and are not planned for the entire area of the respective country. Only Denmark, Estonia, Italy, and Spain are not investigating ticks and wildlife animals and are not planning this, while Belgium, Finland, Slovenia, and Switzerland are monitoring the entire country. The remaining countries are investigating particular regions of interest but these studies only provide a patchwork of information, not a systematic overview.

Vaccination policy

Besides Austria, Finland, Germany, Hungary, Latvia, Russia, Slovenia, and Switzerland, since the last survey also Italy recently included TBE vaccination in an official governmental vaccination programme under certain country-specific conditions. In the remaining 17 countries, it is available as an optional vaccination, partly recommended, but not reimbursed by national health systems. No information on this item was given by Bosnia and Herzegovina and Romania (Table 1).

Travel recommendations

A total of 18 countries stated that they had more or less official recommendations regarding TBE vaccination for people travelling to endemic areas, while the other participating countries did not provide information on this issue (Table 1). Although the responses to this part of the questionnaire suggested that not all contact points had interpreted the question in the same way, it can be deduced that information for travellers is given for following purposes (updated since the last survey):

(i) Recommendation included in national vaccination programme for citizens visiting en-demic regions (stated by Austria, Germany and Poland);
(ii) Information on the endemic status of a country for citizens and visitors, including pre-vention measures (limited information in the Baltic states, Denmark,

Table 2

Official references for annual numbers of tick-borne encephalitis cases reported and expert/reference laboratories, in European countries and Russia participating in the survey, 2010 (n=28)

Country	Reference	Expert or reference laboratory[a]
Austria	www.virologie.meduniwien.ac.at/home/virus-epidemiologie/virusepidemiologische-information/lang_1-content.html (Clinical Institute of Virology, Medical University of Vienna)	F. X. Heinz, Clinical Institute of Virology, Medical University of Vienna
Belgium	www.iph.fgov.be/epidemio/epien/indexoooo.htm (Scientific Institute of Public Health, Brussels)	P. Heyman, Research Laboratory for Vector-Borne Diseases, Queen Astrid Military Hospital, Brussels
Bulgaria	www.mh.government.bg (Ministry of Health, Sofia)	I. Christova, NRL on Tick-borne infections, National Center of Infectious and Parasitic Diseases, Sofia
Czech Republic	www.szu.cz/publikace/data/infekce-v-cr (National Institute of Public Health, Prague)	J. Januška and H. Zelena, NRL for Arboviruses, Institute of Public Health, Ostrava
Denmark	Not available	A. Fomsgaard, Department of Virology, Statens Serum Institut, Copenhagen
Estonia	www.tervisekaitse.ee/ (Health Protection Inspectorate, Tallinn)	I. Golovljova, Laboratory of Virology, Institute for Health Development, Tallinn
Finland	www3.ktl.fi (National Institute for Health and Welfare, Helsinki)	O. Vapalahti, Department of Virology, Haartman Institute, University of Helsinki
France	Not available, because TBE is not a notifiable disease	C. Renaudat, NRC for Arboviruses, Institut Pasteur, Paris
Germany	www.rki.de/DE/Content/Infekt/EpidBull/epid__bull__node.html (Robert Koch-Institute, Berlin)	M. Niedrig and O. Donoso Mantke, Consultant Laboratory for TBE, Robert Koch-Institut, Berlin (Public Health) J. Süss, NRL on Tick-borne pathogens, Friedrich-Löffler-Institute, Jena (Animal Health)
Greece	The National Centre for Haemorrhagic fevers and Arboviral diseases in Thessaloniki is the only laboratory in Greece where laboratory diagnosis for TBE is being performed. If any positive case is detected the Ministry of Health is notified.	A. Papa, A' Department of Microbiology, Medical School, Aristotle University of Thessaloniki, Thessaloniki
Hungary	Yearbook of Health Statistics (National Center for Epidemiology, Budapest)	E. Ferenczi, NRL for Viral Zoonoses, National Center for Epidemiology, Budapest
Italy	At the moment no official reference reporting centre exists	L. Nicoletti, Department of Infectious, Parasitic and Immunomediated Diseases, Istituto Superiore di Sanitá, Rome
Latvia	www.lic.gov.lv/?p=1327&pp=10756&lang=258 (Infectiology Center of Latvia, Riga)	T. Kolupajeva, Infectology Center of Latvia, Riga
Lithuania	www.ulac.lt (Center for Communicable Diseases and Acquired Immune Deficiency Syndrome, Vilnius)	A. Griskevicius, Center for Communicable Diseases and Acquired Immune Deficiency Syndrome, Vilnius
Malta	Not available	Not available
Norway	www.msis.no (Norwegian Institute of Public Health, Oslo)	S. Gjeruldsen Dudman, Department of Virology, Norwegian Institute of Public Health, Oslo
Poland	www.pzh.gov.pl/oldpage/epimeld/index_a.html (National Institute of Public Health, Warsaw)	Officially not available
Portugal	Not available	M.J. Alves, Center for Vectors and Infectious Diseases Research, National Institute of Health, Águas de Moura
Russia	www.rospotrebnadzor.ru (Federal Service for Supervision of Consumer Rights Protection and Human Welfare, Moscow)	Laboratory of Arboviral Infection, Rickettsiosis and HIV- infection, L.A.Tarassevich State Institute for Standartization and Control of Medical Biological Preparations, Moscow
Slovakia	www.uvzsr.sk/index.php?option=com_content&view=article&id=431:vyskyt-klieovej-encefalitidy-na-slovensku-v-rokoch-1985-2008&catid=68:epidemiologia&Itemid=76 (Public Health Authority of the Slovak Republic, Bratislava)	NRC for Arboviruses and Hemorrhagic fever, Public Health Authority of the Slovak Republic, Bratislava (Reference laboratory) Institute of Virology, Department of Virus Ecology, Slovak Academy of Science, Bratislava (Expert laboratory)
Slovenia	www.ivz.si (Institute of Public Health Republic of Slovenia, Ljubljana)	T. Avšič-Županc. Institute of Microbiology and Immunology, University of Ljubljana
Spain	www.isciii.es/jsps/centros/epidemiologia/procedimientos.jsp (National Centre of Epidemiology, Institute of Health Carlos III, Madrid)	A. Tenorio, National Centre of Microbiology, Institute of Health Carlos III, Majadahonda
Sweden	www.smittskyddsinstitutet.se/publikationer/arsrapporter-och-verksamhetsberattelser/smis-epidemiologiska-arsrapporter/ (Swedish Institute for Infectious Disease Control, Solna)	Swedish Institute for Infectious Disease Control, Solna
Switzerland	www.bag.admin.ch/k_m_meldesystem/00733/00804/index.html?lang=de (Federal Office of Public Health, Bern)	O. Péter, Department of Microbiology, Institut Central des Hôpitaux Valaisans, Sion
The Netherlands	No official reference	Department of Virology, Unit Diagnostics, Erasmus MC, Rotterdam Laboratory of Virology, National Institute for Public Health and the Environment (RIVM), Bilthoven
United Kingdom	Not available	Not available

NRL: National Reference Laboratory; NRC: National Reference Centre; TBE: Tick-borne encephalitis.
Data for this table is provided by listed contributors except Bosnia and Herzegovina and Romania.
[a] Further contact information can be provided on request.

Table 3

Data to identify trends for tick-borne encephalitis in surveyed European countries and Russia, 2010 (n=28)

Country	Change in distribution	Cases during winter	Tick-borne encephalitis virus subtypes	Imported cases	Clusters of cases	Cases in animals	Prevalences in ticks and wildlife hosts
Austria	Expanding in western Austrian states, e.g. Tirol and Vorarlberg	No	European	No	Milk-borne TBE cases in Vorarlberg in 2008	Yes	No plans to monitor ticks but occasionally investigated
Belgium	No	No	European	Yes	No	No	Monitoring in progress
Bulgaria	No information	No	No information	No	No	No	Planned investigations in ticks, reservoirs and suspected patients
Czech Republic	Yes, expanding	Yes	European	Rarely	Yes	Yes	Information for the northeast part of the country
Denmark	Yes, first TBE cases outside of Bornholm, in northern Zealand	No	European	Yes	Yes	No	No
Estonia	Expanding on Saaremaa and Hiiuma islands	No	Only European subtype was sequenced from patients, but Siberian subtype also circulates in ticks	No	Yes	Not available	No
Finland	Yes, known range is increasing (more north)	No	European and Siberian	Occasional imports from Russia and Switzerland	Few	Only seroprevalences	Yes, for all Finnish foci
France	Classical endemic regions Alsace and Vosges. Detection of one single case for the first time in Gironde in 2006, and for the second time in Rhône-Alpes in 2007.	No information	Not provided	One case from Poland in 2008	One cluster in 2005	No	No, a study will start in coming months
Germany	Slowly expanding inside the known risk areas	Sporadically	European	Yes (e.g. 11 cases in 2009)	Yes, in southern Germany	No	Yes, for several regions
Greece	No	No	Not available	Up to now, no	No	No	Low prevalence of Greek Goat Encephalitis Virus in ticks was found for Vergina, Vavdos and Kastoria
Italy	Expanding in Friuli and Trentino regions in the last five years	Yes	European	Yes, from Slovenia	Yes, in Friuli region	Only antibodies found in sheep	No
Latvia	Extended distribution of cases in the central and also western parts of the country	Rare, in mild winters	All three TBE virus subtypes	Yes, but rarely	Rarely, in case of alimentary infection with goat milk	No information	Yes, long-term monitoring sites were located in the central and eastern part of the country
Lithuania	Yes, expanding	Yes	Not available	Yes	Yes	No information	Yes, planned to be expanded from five to 10 regions
Malta	No information	No	No information	No	No information	No information	Not available
Norway	Due to very few cases a trend towards spread of the virus is not possible to be concluded	No	European	Yes, few cases from Austria, Hungary, Germany and Latvia	No	No	Yes, for the region of Aust-Agder
Poland	No information	No	European	No	No information	No	Incomplete data from different regions available for goats and ticks
Russia	Yes, expanding	No	All TBE subtypes	No	In some regions, more than just clusters	No information	Incomplete data on regional level. Ticks are monitored, animals not.
Slovakia	No	one to three cases per winter	European	Not distinguished	Not recently	No	Yes, from scientific studies but only from few selected localities
Slovenia	Yes, expanding	Yes, rarely	European	No	No	No	Yes, for the whole country from ticks and hosts
Spain	No	No cases	None	Yes	No	No	No
Sweden	Yes, the range is expanding especially to the north. TBE is also becoming more prevalent on the west coast of Sweden	Single cases at the end of March and beginning of December	European	Yes	Yes	Previously, occasional diagnoses in dogs	No data with reasonable coverage at present. Further sampling is planned
Switzerland	Yes, TBE virus circulates in tick populations in new areas (e.g. Valais)	Yes, few	European	No	Yes (four to five cases in the same area and year)	Yes	Yes
The Netherlands	No	No	No information	Yes	No	No	No information
United Kingdom	Not available	Not available	Not available	Not available	Not available	Not available	Not available

TBE: Tick-borne encephalitis.

Data for this table is provided by listed contributors except Bosnia and Herzegovina, Hungary, Portugal and Romania.

Slovakia and Slovenia; and comprehensive information in Finland, Sweden and Switzerland);
(iii) Information on the endemic status of foreign countries for citizens travelling abroad, including prevention measures (stated by Belgium, France, Greece, Norway, Portugal and Spain).

Discussion

Since our first survey in 2008 [25], six additional countries (Bosnia and Herzegovina, Bul-garia, Denmark, Malta, Romania, and the United Kingdom) provided data regarding their TBE epidemiological situation, which gave a more comprehensive picture for Europe. Bosnia and Herzegovina reported that TBE is not of public health importance and that the country is only registering imported cases every year. From Romania we know that a regional surveillance of TBE neuroinvasive infections has been started in June 2008 by the Public Health Institute in Cluj, including patients with an epidemiological link (residents of previously confirmed endemic areas, tick bite, occupational exposure, or consumption of raw milk/milk-products from infected animals), but further details were not available. So, unfortunately, the TBE epidemiological situation for Romania and other eastern European countries, which did not participate in this survey, still remains unclear.

Knowledge about endemic foci is currently almost exclusively based on reported human cases. As in the first survey, 16 of the 28 participating countries reported to have TBE as a notifiable disease. A variety of (laboratory) case definitions exists mostly aiming at taking the particular level of endemicity into account. While about one third of those countries with TBE notification use a combination of clinical picture and laboratory testing, a further third adds epidemiological aspects, while in the remaining third no officially approved case definition exists.

For the latter, it is questionable how valid the number of officially recorded TBE cases is. Among these countries are those with high incidence rates suggesting that TBE is a disease "easily" diagnosed by any physician. We doubt that this procedure is helpful in order to precisely estimate cases and consequently to assess infection risks in these particular countries. Likewise, it would be important to know, who is reporting TBE cases in countries where this disease is a rare event and on what ground. It is hard to judge if the reported numbers reflect the reality. We conclude that having a clear standardised case definition for surveillance purposes is a must in reporting numbers of a notifiable disease such as TBE regardless whether it is highly prevalent or not. For an appropriate collection of epidemiological data, minimum criteria for a standardised TBE case definition should be to include all relevant types of CNS symptomatic (aseptic meningitis, meningoencephalitis and/or meningoencephalomyelitis), at least laboratory-confirmed by detection of specific antibodies in serum or cerebrospinal fluid, in order to avoid under-ascertainment of cases.

In comparison to the last survey, the number of countries using molecular diagnostics has increased markedly with more than half of the countries using PCR techniques and nucleotide sequencing. RT-PCR methods can be of great diagnostic value in the early diagnosis of TBE and in the discrimination among virus subtypes, but only if the patient is hospitalised during the febrile first (viremic) phase of infection [35]. However, as outlined in Table 1 molecular diagnostic methods are mainly used for research purposes and not for clinical diagnostics. A former external quality assurance (EQA) showed that RT-PCRs used in laboratories do not discriminate between TBE virus subtypes [36]. Co-circulation of Siberian and European TBE virus subtypes were reported from Finland and Estonia, and co-circulation of all three subtypes is known to occur in Russia and Latvia. This has to be taken into account in these countries.

Some recent reports from single countries provide good data and strong evidence for a change (expansion) in geographical distribution of TBE [25-27] but in most European countries similar assumptions are just

Figure 3

Areas of known occurrence of tick-borne encephalitis in Europe, 2010

Data of each country surveyed were transferred to the geographical map of Europe with red showing known TBE virus-endemic areas.

Data from the Crimea peninsula [31,32] and from Albania [33,34] were taken from older maps and the literature, and are not based on our survey data.

a guess, so the rationale for the second part of our questionnaire was to get solid, first hand data from European countries that may relate to travel, climate change and similar. Many participating countries provided detailed description of new endemic areas which will be a great basis for a TBE atlas we intend to create in the near future.

From an epidemiological point of view, clusters are more reported cases than average and expected by chance, in a given time period (although this is not defined) in a certain area. As such, they are an indicator of unusual transmission patterns or other reasons leading to more cases than "normal". Since we have not defined the term cluster in our questionnaire, we assume that contact points have interpreted this differently. Alimentary infection is well known leading to such clusters and three countries reported such events during the observation period [17-19]. The other clusters may also relate to an undiscovered alimentary source or may relate to a natural focus with high prevalence of TBE virus in ticks and a high local transmission (e.g. an attractive and highly frequented recreational area).

Inactivated vaccines are available to prevent TBE in humans and many studies have demon-strated their safety and efficacy [37]. Consequently, the vaccine coverage has a major influence on disease occurrence. Calculation of vaccination rates is based on sold vaccine doses per year and country, but the true protection rate depends on the correct basic immunisation scheme which includes three injections for each individual. Thus, the number of sold vaccine doses does not reflect directly the percentage of correctly vaccinated and thus protected persons. So, caution is necessary when, for 11 of the participating countries, the percentage of vaccine coverage is compared with incidence (personal communication, Peter Gerold, Baxter, 17 August 2010) [29]. In fact, such comparison would only be useful in a situation of similar incidence rates but different percentages of vaccine coverage or vice versa. Nevertheless, the well known example of Austria with a high prevalence of TBE virus has by far the highest vaccine coverage (88% of the total population have a history of TBE vaccination) and an incidence below 1 per 100,000 population. Using the neighbouring Czech Republic (16% vac-cine coverage, incidence 7.8 per 100,000 population) and Slovenia (12%, 13.1 per 100,000 population) provides strong evidence for the negative correlation of vaccination and incidence. However, Slovakia (1%, 1.3 per 100,000 population) would argue against it, clearly showing that a comparison is not useful without knowing the prevalence in each country. In light of the increasing frequency of reported imported and travel associated cases of TBE, more emphasis has to be put on educating the population in endemic areas as well as providing travel recommendation that certainly include vaccination [29,38].

The participating countries mainly applied the surveillance data from clinical cases as an indicator for predicting endemic foci and for recommending preventive measures. Due to the fact that we observed TBE cases in winter, recognised imported cases all over Europe, and wit-nessed a geographical expansion within known endemic areas, as well as new spread outside the known foci, epidemiology of TBE seems to become more complex than previously thought. In order to understand the changing patterns in TBE transmission we strongly recommend putting more emphasis in developing new surveillance strategies. These should include screening of vector ticks by RT-PCR in suspected foci but more importantly the serological testing of animals (wildlife, livestock and companion) for prevalence studies of TBE virus (and other important tick-borne diseases). Some of the participating countries started such programmes, but these should be harmonised and done more systematically on the European level.

The international awareness for TBE is on the rise, and at EU level, TBE is considered of high relevance and a series of activities have been launched with the goal of improving awareness of this tick-transmissible disease [7]. Our survey contributes to this end by providing detailed information concerning TBE epidemiology for most European countries. The results of our study will help to develop further recommendations for the standardisation and quality control in TBE diagnostics, surveillance and prevention activities

Acknowledgments

The ENIVD is part of the ECDC "Outbreak Assistance Laboratory Network" and received funding as the ENIVD Collaborative Laboratory Response Network (ENIVD-CLRN) under the contract no. ECDC/2008/011. We are indebted for information regarding the national surveillance system on TBE to: Stephan Aberle, Medical University of Vienna, Austria; Christel Cochez and Paul Heyman, RLVBD Queen Astrid Military Hospital, Brussels, Belgium; Mirsada Hukić, Clinical Centre University of Sarajevo, Bosnia and Herzegovina; Iva Christova, National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria; Hana Zelená, Institute of Public Health Ostrava, Czech Republic; Anders Fomsgaard, Statens Serum Institut, Copenhagen, Denmark; Irina Golovljova, National Institute for Health Development, Tallinn, Estonia; Kuulo Kutsar, Health Protection Inspectorate, Tallinn, Estonia; Olli Vapalahti, Haartman Institute, Helsinki, Finland; Charlotte Renaudat, Institut Pasteur, Paris, France; Gerhard Dobler, Bundeswehr Institute of Microbiology, Munich, Germany; Anna Papa, Aristotle University of Thessaloniki, Greece; Ildikó Visontai and Emöke Ferenczi, National Center for Epidemiology, Budapest, Hungary; Maria Grazia Ciufolini and Loredana Nicoletti, Istituto Superiore di Sanità, Rome, Italy; Antonino Di Caro, Istituto Nazionale per le Malattie Infettive "Lazzaro Spallanzani", Rome, Italy; Tatjana Kolupajeva and Antra Bormane, Infectiology Center of Lat-via, Riga, Latvia; Algirdas Griskevicius, Center for Communicable Diseases and AIDS, Vilnius, Lithuania; Gianfranco Spiteri, Infectious Disease Prevention and Control Unit, Malta; Susanne Dudman and Gabriel Anestad, Norwegian Institute of Public Health, Oslo, Norway; Wladzimierz Gut and Pawel Stefanoff, National Institute of Public Health, Warsaw, Poland; Maria J.

Alves, CEVDI National Institute of Health, Àguas de Moura, Portugal; Cornelia Ceianu, INCDMI Cantacuzino, Bucharest, Romania; Maya S. Vorobyeva and Vladimir I. Zlobin, L.A. Tarassevich State Institute for Standardization and Control of Medical Biological Preparations, Moscow, Russia; Alexander Platonov, Central Research Institute of Epidemiology, Moscow, Russia; Boris Klempa, Slovak Academy of Sciences, Bratislava, Slovakia; Hana Blaskovicova, Public Health Authority of the Slovak Republic, Bratislava, Slovakia; Tatjana Avšič-Županc and Nataša Knap, University of Ljubljana, Slovenia; Antonio Tenorio and Odorina Tello, Instituto de Salud Carlos III, Majadahonda-Madrid, Spain; Sirkka Vene and Marika Hjertqvist, Swedish Institute for Infectious Disease Control, Solna, Sweden; Christian Beuret, Spiez Laboratory, Switzerland; Marion Koopmans and Gert-Jan Godeke, Rijksinstituut vor Volksgezondheid, Bilthoven, The Netherlands; Sarah Randolph, University of Oxford, United Kingdom.
We are indebted to Dirk Meisel (Storck Druckerei GmbH, Bruchsal, Germany) for the graphic design of Figure 3.

References

1. Gritsun TS, Lashkevich VA, Gould EA. Tick-borne encephalitis. Antiviral Res. 2003;57(1-2):129-46.
2. Charrel RN, Attoui H, Butenko AM, Clegg JC, Deubel V, Frolova TV, et al.Tick-borne virus diseases of human interest in Europe. Clin Microbiol Infect. 2004;10(12):1040-55.
3. Gunther G, Haglund M. Tick-borne encephalopathies: epidemiology, diagnosis, treatment and prevention. CNS Drugs. 2005;19(12):1009-32.
4. Lindquist L, Vapalahti O. Tick-borne encephalitis. Lancet. 2008;371(9627):1861-71.
5. Mansfield KL, Johnson N, Phipps LP, Stephenson JR, Fooks AR, Solomon T. Tick-borne encephalitis virus - a review of an emerging zoonosis. J Gen Virol. 2009;90(Pt 8):1781-94.
6. Heyman P, Cochez C, Hofhuis A, van der Giessen J, Sprong H, Porter SR, et al.A clear and present danger: tick-borne diseases in Europe. Expert Rev Anti Infect Ther. 2010;8(1):33-50.
7. Kunze U; ISW TBE. Tick-borne encephalitis: the impact of epidemiology, changing lifestyle, and environmental factors. Conference report of the 12th Annual Meeting of the International Scientific Working Group on Tick-Borne Encephalitis (ISW-TBE). Vaccine. 2011;29(7):1355-6.
8. Thiel HJ, Collett MS, Gould EA, Heinz FX, Houghton M, Meyers G. Flaviviridae. In: Fauquet CM, Mayo MA, Maniloff J, Desselberger U, Ball, LA, editors. Virus Taxonomy: Classification and Nomenclature, Eight Report of the International Committee on the Taxonomy of Viruses. London: Elsevier Academic Press; 2005:981-98.
9. Kovalev SY, Kokorev VS, Belyaeva IV. Distribution of Far-Eastern tick-borne encephalitis virus subtype strains in the former Soviet Union. J Gen Virol. 2010;91(Pt 12):2941-6.
10. Holzmann H. Diagnosis of tick-borne encephalitis. Vaccine. 2003;21 Suppl 1:S36-40.
11. Pogodina VV, Bochkova NG, Karan' LS, Frolova MP, Trukhina AG, Malenko GV, et al.Comparative analysis of virulence of the Siberian and Far-East subtypes of the tick-borne encephalitis virus. Vopr Virusol. 2004;49(6):24-30.
12. Poponnikova TV. Specific clinical and epidemiological features of tick-borne encephalitis in Western Siberia. Int J Med Microbiol. 2006;296 Suppl 40:59-62.
13. Labuda M, Randolph SE. Survival strategy of tick-borne encephalitis virus: cellular basis and environmental determinants. Zentralbl Bakteriol. 1999;289(5-7):513-24.
14. Gresikova M, Sekeyova M, Stupalova S, Necas S. Sheep milk-borne epidemic of tick-borne encephalitis in Slovakia. Intervirology. 1975;5(1-2):57-61.
15. Vereta LA, Skorobrekha VZ, Nikolaeva SP, Aleksandrov VI, Tolstonogova VI, Zak-harycheva TA, et al.The transmission of the tick-borne encephalitis virus via cow's milk. Med Parazitol (Mosk). 1991;(3):54-6.
16. Kerbo N, Donchenko I, Kutsar K, Vasilenko V. Tick-borne encephalitis outbreak in Estonia linked to raw goat milk, May-June 2005. Euro Surveill. 2005;10(25): pii=2730. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2730
17. Holzmann H, Aberle SW, Stiasny K, Werner P, Mischak A, Zainer B, et al.Tick-borne encephalitis from eating goat cheese in a mountain region of Austria. Emerg Infect Dis. 2009;15(10):1671-3.
18. Kriz B, Benes C, Daniel M. Alimentary transmission of tick-borne encephalitis in the Czech Republic (1997-2008). Epidemiol Mikrobiol Imunol. 2009;58(2):98-103.
19. Balogh Z, Ferenczi E, Szeles K, Stefanoff P, Gut W, Szomor KN, et al.Tick-borne encepha-litis outbreak in Hungary due to consumption of raw goat milk. J Virol Methods. 2010;163(2):481-5.
20. Suss J. Epidemiology and ecology of TBE relevant to the production of effective vaccines. Vaccine. 2003;21 Suppl 1:S19-35.
21. Randolph SE. Tick ecology: processes and patterns behind the epidemiological risk posed by ixodid ticks as vectors. Parasitology. 2004;129 Suppl:S37-65.
22. Golovljova I, Vene S, Sjölander KB, Vasilenko V, Plyusnin A, Lundkvist A. Characteriza-tion of tick-borne encephalitis virus from Estonia. J Med Virol. 2004;74(4):580-8.
23. Jaaskelainen AE, Sironen T, Murueva GB, Subbotina N, Alekseev AN, Castren J, et al.Tick-borne encephalitis virus in ticks in Finland, Russian Karelia, and Buryatia. J Gen Virol. 2010;91(Pt 11):2706-12.
24. Suss J. Tick-borne encephalitis in Europe and beyond--the epidemiological situation as of 2007. Euro Surveill. 2008;13(26). pii: 18916. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18916
25. Donoso Mantke O, Schadler R, Niedrig M. A survey on cases of tick-borne encephalitis in European countries. Euro Surveill. 2008;13(17). pii: 18848. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18848
26. Fomsgaard A, Christiansen C, Bodker R. First identification of tick-borne encephalitis in Denmark outside of Bornholm, August 2009. Euro Surveill. 2009;14(36). pii: 19325. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19325
27. Ergünay K, Saygan MB, Aydoğan S, Litzba N, Sener B, Lederer S, et al. Confirmed expo-sure to tick-borne encephalitis virus and probable human cases of tick-borne encephalitis in central/northern Anatolia, Turkey. Zoonoses Public Health. 2011;58(3):220-7.
28. Stefanoff P, Polkowska A, Giambi C, Levy-Bruhl D, O'Flanagan D, Dematte L, et al.Reliable surveillance of tick-borne encephalitis in European countries is necessary to improve the quality of vaccine recommendations. Vaccine. 2011;29(6):1283-8.
29. Petri E, Gniel D, Zent O. Tick-borne encephalitis (TBE) trends in epidemiology and current and future management. Travel Med Infect Dis. 2010;8(4):233-45.
30. Gaumann R, Muhlemann K, Strasser M, Beuret CM. High-throughput procedure for tick surveys of tick-borne encephalitis virus and its application in a national surveillance study in Switzerland. Appl Environ Microbiol. 2010;76(13):4241-9.
31. Panov AG.Tick-borne encephalitis. MEDGIZ. 1956:67. Russian.
32. Vynograd I, Biletska G, Lozynsky I, Plastunov V, Kozlovsky M. The problem of arboviral infections in the Ukraine. Poster session presented at: IJSTD X Meeting in Weimar: 2009 Mar 19-21. Weimar, Germany.
33. Eltari E. Epidemiology of tick-borne encephalitis in Albania. Ellipse. 1991:29: 449-450.
34. Eltari E, Gina A, Bitri T, Sharofi F. Some data on arboviruses, especially tick-borne en-cephalitis, in Albania. Giornale di Malattie Infettive Parassitarie. 1993:45:404-11.
35. Donoso Mantke O, Achazi K, Niedrig M. Serological versus PCR methods for the detection of tick-borne encephalitis virus infections in humans. Future Virol. 2007;2(6):565-72.
36. Donoso Mantke O, Aberle SW, Avsic-Zupanc T, Labuda M, Niedrig M. Quality control assessment for the PCR diagnosis of tick-borne encephalitis virus infections. J Clin Virol. 2007;38(1):73-7.
37. Rendi-Wagner P. Advances in vaccination against tick-borne encephalitis. Expert Rev Vaccines. 2008;7(5):589-96.
38. Wiedermann U. Tick borne encephalitis TBE--vaccination in non-endemic countries. Travel Med Infect Dis. 2010;8(4):251-6.

Measles in Geneva between 2003 and 2010: persistence of measles outbreaks despite high immunisation coverage

E Delaporte (Elisabeth.delaporte@etat.ge.ch)[1], E Jeannot[2,3], P Sudre[1], C A Wyler Lazarevic[2], J L Richard[4], P Chastonay[3]
1. Epidemiology and Communicable Diseases Section, Cantonal Health Service, General Directorate for Health, Department of Regional Affairs, Economy and Health, Geneva, Switzerland
2. Youth Health Service, Department of Education, Geneva, Switzerland
3. Institute of Social and Preventive Medicine, University of Geneva medical school, Geneva, Switzerland
4. Infectious Diseases Division, Federal Office of Public Health, Berne, Switzerland

Citation style for this article:
Delaporte E, Jeannot E, Sudre P, Wyler Lazarevic CA, Richard JL, Chastonay P. Measles in Geneva between 2003 and 2010: persistence of measles outbreaks despite high immunisation coverage.
Euro Surveill. 2011;16(39):pii=19980. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19980

Article published on 29 September 2011

Despite high immunisation coverage, several measles outbreaks occurred in the canton of Geneva between 2003 and 2010, with 161 reported cases (52 in 2003, 16 in 2005 and 93 in 2007–2010). It affected mainly 10–14 year-old children in 2003 (31%), and adults 20 years and older in 2005 (75%) and 2007–2010 (39%). Several cases were imported from neighbouring cantons and countries, as confirmed by the diversity of the genotypes identified (D8, D6, D5, D4 and G3). Infections were mainly transmitted via family (54%) and school (22%) in 2003, hospital (71%) and family (29%) in 2005, and family (55%) and school (26%) in 2007–2010. In 2003, 6% of infected patients were vaccinated, 27% in 2005 and 2% in 2007–2010, none of them with two doses of measles-containing vaccine. Between 2003 and 2008, measles vaccine coverage, particularly for the second dose, increased by 23 percentage points to 91.7% in the 28 month-olds, by 27 points to 92.3% in the 5–6 year-olds, and by 19 points to 86% in the 13–14 year-olds. In a cosmopolitan setting where immunisation coverage is high but not sufficient to eradicate measles, outbreaks can be limited by efficient surveillance and early control measures. Catch-up vaccination needs to be reinforced among teenagers and young adults.

Introduction

In Switzerland, measles immunisation with a single dose of monovalent vaccine has been recommended since from 1976. In 1985, this vaccine was replaced by one dose of the measles-mumps-rubella (MMR) vaccine, and in 1996, a second dose of the MMR vaccine was introduced. Currently, the first dose is recommended at the age of 12 months, and the second at 15–24 months. In the canton of Geneva, measles immunisation coverage in children aged 28 months was 89.7% for the two vaccine doses in 2007, after a continuous progression since its introduction [1]. This increase resulted, at least in part, from continuous efforts of physicians to vaccinate infants, health authorities providing regular individual information to parents, and media coverage of local measles-related events. However, several measles outbreaks have been recorded in this canton since 2003, with a total of 161 cases at the end of 2010. Following two outbreaks in 2003 and 2005, several outbreaks occurred in quick succession between 2007 and 2010 in the wider context of a national epidemic.

Measles eradication is a public health priority at both national [2] and European level. The World Health Organization (WHO) had set the goal of eliminating measles in Europe by the end of 2010 [3], but this has recently been postponed to 2015 [4]. In order to achieve this goal, an immunisation coverage of at least 95% with two doses is necessary [5]. The immunisation coverage in the Geneva canton approaches this threshold, but it appears still too low and too recent to provide herd immunity so as to stop the transmission of the measles virus [1]. Measles outbreaks regularly occur as a result of the progressive increase, during inter-epidemic periods, of non-immunised people and young adults vaccinated with only one dose, in addition to the regular importation of measles from neighbouring regions.

This article describes the measles outbreaks that occurred in the canton of Geneva between 2003 and 2010 and aims to assess whether an efficient alert system related to early and effective measures is able to control measles outbreaks in a canton where immunisation coverage is suboptimal to eliminate measles.

Methods

Surveillance of measles cases

In Switzerland, physicians have been required since 1999 to notify within 24 hours to the cantonal health authorities all cases presenting the symptom triad of fever, maculopapular rash, and one or more of the

following symptoms: cough, rhinitis or conjunctivitis. This initial notification is followed by another, more detailed notification. Similarly, since 1988, laboratories are obliged to notify all confirmed measles cases within 24 hours.

Our analysis was based on measles cases in the canton of Geneva that were notified by physicians and laboratories between 1 January 2003 and 31 December 2010. It also included cases in contacts, defined as cases who did not seek medical consultation and were thus not included in the mandatory notification but instead reported orally by physicians or patients and investigated by the cantonal health authority.

Notification data from suspected cases with a negative laboratory result or post-vaccination measles (one case) were excluded. The analysed cases were classified as clinical or confirmed cases. Clinical measles was defined as the occurrence of a generalised rash associated with fever and one or more of the following symptoms: cough, rhinitis or conjunctivitis. A case was considered confirmed if there was i) a positive laboratory test (measles-specific IgM, RT-PCR, virus isolation or IgG seroconversion/IgG titre increase) and at least one of the aforementioned clinical signs, or ii) clinical measles with an epidemiological link to a laboratory-confirmed case.

In selected cases, the viral genotype was identified in saliva samples by the Robert Koch Institute, Berlin, Germany, and, from 2007 onwards, by the Central Laboratory of Virology of the University Hospital of Geneva (HUG).

Imported measles referred to cases where the virological or epidemiological data confirmed that the exposure occurred outside the canton or country during the 7–21 days before onset of the rash [3]. A case linked to imported measles referred to a locally infected patient in the setting of a transmission chain that started with the imported case.

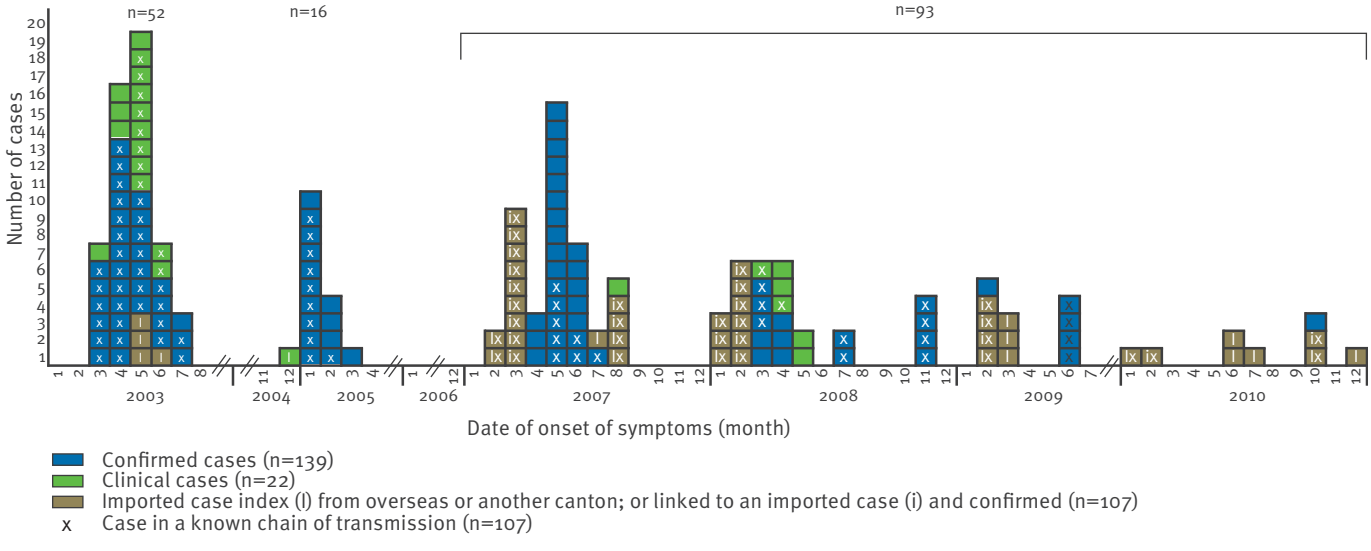
Surveillance of immunisation coverage

The method used to collect data has been described in detail previously [6,7]. The annual immunisation coverage involved children at the age of 28 months, 5–6 years, and 13–14 years in a given year between 2003 and 2008. After this date, the sampling method changed. The indicator used to analyse the immunisation coverage and its evolution was the proportion of children who received either one or two doses of the measles vaccine. We analysed only data from children whose vaccination records were available and interpretable.

Analysis of measles cases and immunisation coverage of children aged 28 months was conducted using SPSS software for Windows, version 18. For school-aged children, Stata software, version 10, was used. Comparisons between the groups were performed by means of the chi-squared test; a two-sided p value of

Figure 1

Epidemic curve of measles cases and transmission chains, Geneva canton, 2003–2010 (n=161)



0.05 was considered statistically significant. For the measure of immunisation coverage, 95% confidence intervals (CI) were employed.

Results

Census of the cases

Between 2003 and 2010, three large measles outbreaks followed one another in the canton of Geneva (453,000 inhabitants in 2009), with a total of 161 cases reported to the General Directorate of Health (Direction générale de la santé, DGS) (Figure 1). The duration and intensity of these outbreaks were variable. In 2003, 52 cases were reported over a period of five months (annual incidence rate of 12.0 per 100,000 inhabitants), while in 2005, 16 cases were reported over four months (annual incidence rate of 3.6 per 100,000 inhabitants). In contrast, the series of outbreaks between 2007 and 2010 was especially long, with 93 cases occurring over 47 months (annual incidence rate of 5.1 per 100,000 inhabitants). After an initial outbreak of 43 cases over five months in 2007 and another one of 23 cases over five months at the beginning of 2008, several outbreaks with very low case numbers and duration followed, with isolated cases also occurring.

In 2003, 37 confirmed cases were reported (19 laboratory-confirmed and 18 with an epidemiological link to a laboratory confirmation), 16 in 2005 (14 laboratory-confirmed and two with an epidemiological link), and 86 in 2007–2010 (62 laboratory-confirmed and 24 with an epidemiological link). In 2003, 43 of 52 cases were reported as part of the mandatory notification system, compared with all 16 cases in 2005 and 78 of 93 cases in 2007–2010. The other cases (nine in 2003 and 15 in 2007–2010) were identified by active case finding among patients, their contacts, and physicians' practices.

In 2003, the median duration between the onset of symptoms (medical consultation date is generally unknown) and receipt of the first written notification by the physician or laboratory was nine days. For the 16 cases occurring in 2005, this duration was 13 days for the first eight cases and 8.5 days for the final eight cases. Comparing the first 10 cases in 2007 with the nine cases in 2010, it decreased from 8 to 6.5 days.

Demographic characteristics and laboratory findings

In 2003, 32 men and boys and 20 women and girls contracted measles whereas 43 men and boys and 50 women and girls were reported in 2007–2010. In 2003, 16 children were aged between 10 and 14 years, whereas 12 adults were aged 20 years or older in 2005 and 36 in 2007–2010. Median age of the infected subjects was 12 years in 2003, 32.5 years in 2005, and 16 years in 2007–2010. In 2005, the majority of cases were adults and there was a slight increasing trend in the subjects' age, which was statistically non-significant (linear regression model).

RNA from 41 saliva samples or throat swabs was analysed and 35 were successfully sequenced (Table). In 2003, the detected viruses belonged to genotypes D8 (n=3) and D5 (n=1). In 2005, the circulating viruses were genotypes D6 (n=3) and D8 (n=1). In 2007, genotype D5 predominated (n=13), but genotype B3 was also detected (n=1). Genotype D5 was identified in 2008 (n=3) and 2009 (n=3), and simultaneously with genotype D4 (n=2) in 2009. Finally, in 2010, three different virus genotypes, D4 (n=1), G3 (n=2), and D8 (n=1), were found. Moreover, one case of post-vaccination measles (genotype A) occurred 12 days after a post-partum MMR vaccination.

Among the 47 cases for whom the vaccination status was known in 2003, three had received one dose of the measles vaccine. In 2005, among the 11 cases with known vaccination status, three were vaccinated, whereas in 2007–2010, among the 82 cases with known vaccination status, only two were vaccinated. During these outbreaks, none of the infected subjects

Table

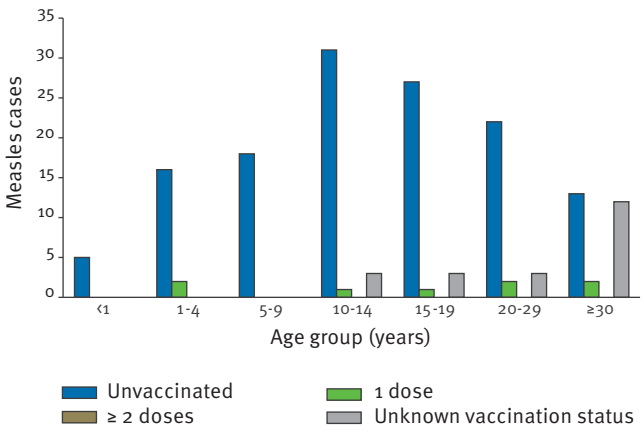
Distribution of measles virus genotypes, canton of Geneva, 2003-2010 (n=35)

Year	Number of samples tested	Measles virus genotype detected						
		B3	D8	D6	D5	D4	G3	A
2003	4	0	3	0	1	0	0	0
2004	0	0	0	0	0	0	0	0
2005	4	0	1	3	0	0	0	0
2006	0	0	0	0	0	0	0	0
2007	19	1	0	0	13	0	0	1
2008	5	0	0	0	3	0	0	0
2009	5	0	0	0	3	2	0	0
2010	4	0	1	0	0	1	2	0
Total	**41**[a]	**1**	**5**	**3**	**20**	**3**	**2**	**1**

[a] Six samples could not be successfully typed.

Figure 2

Cases of measles according to vaccination status, Geneva canton, 2003-2010 (n=161)



had received a full two-dose vaccination. None of the five under one year-old infants who contracted measles were vaccinated. The proportion of patients whose vaccination status was unknown increased with age (Figure 2).

Chains of transmission

In 2003, six chains of transmission were identified, comprising 42 of the cases reported in that year. They consisted of two large chains of transmission of six generations following the index case, involving 19 and nine cases, respectively, one chain of two generations (four cases), and three chains of a single generation with four, three, and three cases, respectively (Figure 1). In 2005, three chains of transmission were identified in 10 cases: two chains of a single generation involving five and two cases, respectively, and one chain of two generations with three cases. Finally, 15 chains of transmission (55 cases) were observed in 2007–2010: one large chain of four generations involving nine cases, three chains of two generations with eight, four, and three cases, respectively, and 11 chains of a single generation with two to four cases (Figure 1).

Several cases were imported from foreign countries and some of them were related to secondary cases: France in 2003 (one imported case and three secondary cases, unknown genotype), Ethiopia in 2007 (one imported, no secondary, genotype B3) and Germany in 2008 (one imported, eight secondary, genotype D5). Eight of the nine cases occurring in 2010 were imported or related to imported cases, originating from India (one imported, one secondary , genotype D8), London (one imported, one secondary, genotype G3), Italy (one imported, no secondary, unknown genotype) and France (three imported, no secondary, genotype D4 for one case). Several cases were also imported from other Swiss cantons or related to these importations: Zurich in 2005 (one imported, no secondary, unknown genotype), Berne in 2007 (one imported, seven secondary, genotype D5), Vaud (one imported, two secondary, unknown genotype) and Ticino (two imported, two secondary, genotype D5). In 2009, importations from the cantons of Vaud (three imported, four secondary, genotype D5 for two cases) and Berne (one imported, no secondary, unknown genotype) were identified. There were no cases imported from other cantons in 2010.

Measles infections were mainly transmitted via family (20 of 37) and school (eight of 37) in 2003, hospital (five of seven) [8] and family (two of seven) in 2005, and family (21 of 38) and school (10 of 38) in 2007–2010. Outbreaks had high transmission rates among unvaccinated siblings and in schools with a philosophy that attracted parents reluctant to vaccinate their children. Several cases of nosocomial transmission were also reported in medical practices attended by parents who refused to vaccinate their children. During the outbreak in 2005, cases of nosocomial transmission were identified among young non-vaccinated or insufficiently vaccinated healthcare professionals who did not receive catch-up vaccinations after the initiation of the two-dose vaccination schedule [8]. There were, however, no cases of transmission by a caregiver.

Complications

In 2003, seven of 52 patients developed at least one complication compared with three of 16 in 2005 and 11 of 93 in 2007–2010. Three patients were hospitalised in 2003, four in 2005, and 18 in 2007–2010. The most common complication was pneumonia, which was observed in five of the patients in 2003, one in 2005, and seven in 2007–2010. Two patients required admission to the intensive care unit. No encephalitides or deaths were reported.

The median age of patients with complications was 21 years, compared with 14 years for those without complications. The number of patients with complications or requiring hospitalisation increased significantly with age ($p<0.05$): no infants under one year of age, two children aged 1–4 years, three aged 5–9 years, five aged 10–14 years, six for the 15–17 years and 20 adults aged 20 years or more. The risk of hospitalisation increased even more significantly with age ($p<0.005$). No infants or children aged 1–4 years were hospitalised, two children aged 5–9 and two aged 10–14 years, four children aged 15–19 years, and 17 adults aged 20 years or more. The risk of pneumonia was largest for children aged 10–14 years ($n=5$). The most frequent reason for hospitalisation was poor general health (nine patients, with a median age of 24.5 years), followed by pneumonia (seven patients, median age of 14 years). None of the patients who developed a measles-related complication was vaccinated.

Preventative measures for subjects in contact with measles-infected patients

In 2003, the cantonal health authorities implemented the following measures for people who were in contact with measles-infected patients: i) communication and information of the patient's environment (school, crèche) along with vaccination recommendations, ii) rapid identification of measles-susceptible contacts, considered to be individuals without at least one dose of the measles vaccination, history of measles or serologically-confirmed immunity, and iii) post-exposure vaccination of contacts within 72 hours. Since 2007, an additional measure has been introduced in situations where no post-exposure vaccination was given within a suitable delay. In these situations, the exposed person should avoid contact with susceptible individuals for a period of 18 days following the last exposition to the case.

Since 2003, among the 14 non-immunised contacts who were identified and received post-exposure vaccination (13 siblings of cases and one friend), three did not develop measles. For two of them, the vaccine was administered within 72 hours after exposure, and for the third (who was exposed to an unconfirmed index case), the vaccine was administered on the fifth day.

Among the 11 contacts who did develop the disease, median duration between the onset of symptoms in the index case and the vaccination was five days (range: 3–6 days).

During the 2007–2010 outbreaks, school exclusion measures were taken for 15 non-immunised contact subjects with clear evidence of exposure, including siblings, a mother (teacher), and a friend. Among them, 13 developed measles during the exclusion period. No secondary cases resulted from 12 of these cases (the situation for the final case is uncertain).

Surveillance of measles immunisation coverage

Between 2003 and 2008, a total of 25,390 28-month-old children who were officially registered as residents in the canton of Geneva were eligible for the monitoring of their vaccination records. However, information was unavailable for 2,923 of them. Thus, the analysis was based on 22,467 28-month-olds, which corresponds to an overall response rate of 88.5%. For children aged 5–6 years and 13–14 years, a cross-sectional analysis was repeated in the school years 2003/04 and 2008/09 in these two age groups. All the pupils attending state schools in Geneva were included in this study, but the analysis was only based on those whose vaccination records were completed and interpretable, and had been sent to the Youth Health Department (Service de la santé de la jeunesse – SSJ), which represented 90% of the total.

Between 2003 and 2008, immunisation coverage of 28-month-olds with one vaccine dose increased from 94.8% (95% CI: 94.1%–95.4%) to 96.1% (95% CI: 95.5%–96.7%) (p=0.002) (Figure 3A). For two doses, it strongly increased from 68.9% (95% CI: 67.5%–70.3%) to 91.7% (95% CI: 90.9%–92.6%) (p<0.001) (Figure 3B). For the 5–6-year-olds, immunisation coverage for one vaccine dose increased from 92.7% (95% CI: 91.8%–93.5%) to 96.1% (95% CI: 95.3%–96.8%) (p<0.001). For two doses, coverage strongly increased from 65.4% (95% CI: 63.8%–67.0%) to 92.3% (95% CI: 91.3%–93.3%) (p<0.001). Finally, for the children aged 13–14 years, immunisation coverage for one dose increased from 89.7% (95% CI: 88.7%–90.6%) to 91.1% (95% CI: 90.2%–92.2%) (p=0.03). For two doses, it increased from 67.2% (95% CI: 65.7%–68.7%) to 86% (95% CI: 84.8%–87.2%) (p<0.001).

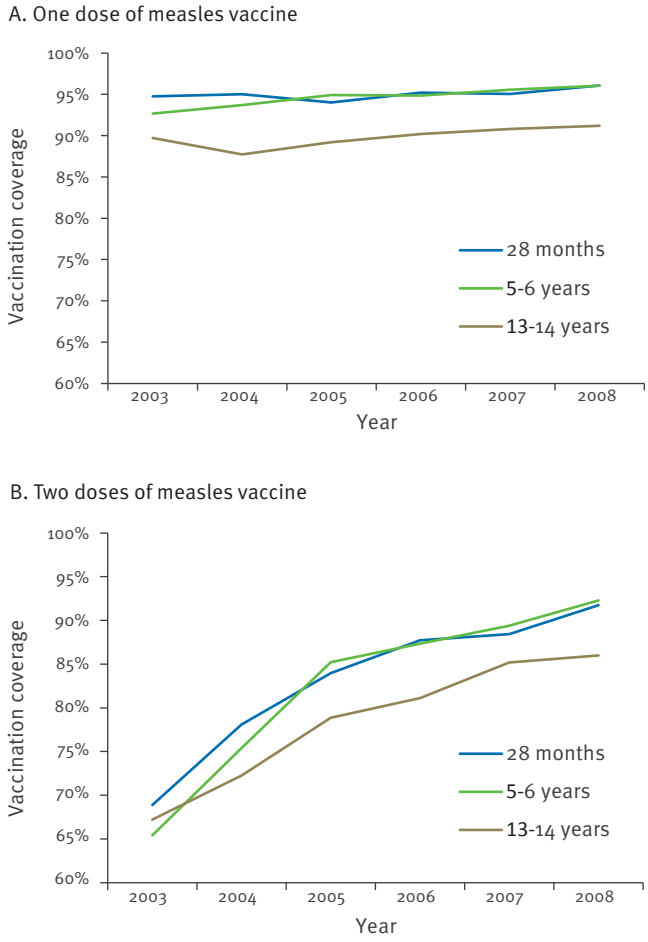
Discussion

Between 2003 and 2010, 161 measles cases were reported to the General Directorate of Health in Geneva, of whom 25 were detected by active case finding during contact tracing. The actual number of cases in the canton during these eight years is probably higher due to the fact that some infected subjects might not have sought medical attention; furthermore, clinical diagnosis may be difficult in the absence of a history of contagion, and some physicians may omit to notify cases.

The surveillance and alert system was reinforced during the period under analysis, with increasingly earlier notifications made by laboratories and physicians over the years. Moreover, there was a marked reduction in the notification delay between the beginning and end of each outbreak. This improvement of the reaction time, from 9–13 days to 8–6 days or less, is at least partially related to reducing the official notification time frame from one week to 24 hours in 2006, to the media coverage of successive measles outbreaks, and to increased awareness of healthcare professionals following information from the cantonal health authorities. However, there were some late notifications during every outbreak. The efficiency of the alert system was also illustrated by the early notification of several cases with suggestive symptoms, which turned out not to be measles. Thus, 15 suspect cases were investigated, 13 during the period from 2007 to 2010, but subsequently excluded due to negative serological results. In a recent publication, the WHO proposed that a the sensitivity of surveillance in countries with a measles elimination target is satisfactory when a minimum of two suspected measles cases per 100,000 inhabitants are identified as non-cases in subsequent (laboratory)

Figure 3

Evolution of measles immunisation coverage in children aged 28 months, 5–6 years, and 13-14 years between 2003 and 2008 in the canton of Geneva (n=63,189)



analyses and discarded [9]. In the canton of Geneva, for the period from 2007 to 2010, the rate was still clearly inferior to the WHO target, with an annual mean of 0.7 discarded cases per 100,000 inhabitants. However, the actual number of discarded cases is certainly higher, considering that the requests to diagnostic laboratory analysis are not currently subject to mandatory notification. Yet, it is not uncommon for physicians to wait for laboratory results and declare measles only if it is confirmed, which is contrary to the legal requirements for mandatory notification.

Control measures have progressively been reinforced since 2003. The identification of non-immunised contacts of measles cases and their vaccination within 72 hours after exposure has become more widespread. School exclusion measures, which did not apply in 2003, became the rule in 2007 for non-immunised siblings of cases. More recently, these measures were extended to all non-immunised contacts in schools and crèches. If rapidly applied, these home quarantine measures are particularly effective given the extreme contagiousness of the virus, and the paramount role played by non-immunised siblings and school transmission in the spread of measles [10]. However, the efficacy of such measures is better still when immunisation coverage is high. In Switzerland, such quarantine is permitted by the federal law on epidemics but not applied equally by the different local health authorities. In Geneva, parents were informed that this was a possibility in case of a school outbreak. Mandatory exclusion from school and nurseries was applied in collaboration with the institutions' directors and, in all instances, well accepted. Most excluded persons developed measles within a few days.

Whereas measles is often regarded as harmless by the general population, 14% of the patients in Geneva developed at least one complication, and 16% were hospitalised during the period from 2003 to 2010. During the 2005 outbreak, which affected mainly adults, the proportion of patients with complications or requiring hospitalisation reached 38%. The risk of complications and hospitalisation, or hospitalisation alone, significantly increases with patients' age. Indeed, in adults aged 20 years and older, these risks were 37% and 30%, respectively. Yet, an increase in the median age of measles cases was observed in the Geneva canton between 2003 and 2010, even though it was small and not statistically significant. At the national level, the proportion of cases aged 20 years and older doubled between the 2003 and 2006–2009 epidemics, increasing from 8% to 19% [11,12].

Given this rise in patients' median age, in parallel with the improved immunisation coverage in children and teenagers, the proportion of adult measles cases accompanied by complications and/or hospitalisation is likely to increase. However, regardless of their age, none of the Geneva patients with complicated measles were vaccinated, which indirectly, but reassuringly, confirms that the vaccine effective against measles and its complications. Consequently, catch-up vaccination with up to two doses of the MMR vaccine remains relevant for all measles-naïve subjects, especially adults born after 1963 [13].

Between 2003 and 2008, measles immunisation coverage continuously increased in the three age groups studied. This increase was particularly pronounced for the second dose: an increase by 23 percentage points to 91.7% for 28-month-olds, by 27 percentage points to 92.3% for 5–6-year-olds, and by 19 percentage points to 86% for 13–14-year-olds. Thus, in the canton of Geneva, immunisation coverage of young children is currently approaching the 95% threshold, thus allowing for measles elimination [14]. However, this evolution is rather recent and does not rule out the accumulation of a fairly large number of non-immunised people, particularly among young adults who are no longer exposed to the wild virus (nearly one of five cases was between 30 and 45 years-old in the canton of Geneva).

Based on the immunisation coverage data for dose and age and the notified measles cases, the Swiss Federal Office of Public Health estimated the number of susceptible subjects younger than 20 years to be 8,300 for the canton of Geneva alone, i.e. 8.6% of this age group [15] (unpublished results), while this proportion is much smaller in adults born after 1963. Subjects born before this date are considered to be immunised due to the widespread circulation of measles during their childhood. Overall, the proportion of immunised subjects in the Geneva population is probably approaching the threshold for herd immunity, at least in part thanks to the clear support and involvement of local physicians. New outbreaks, however, remain highly probable in the case of virus introduction, all the more so because non-immunised subjects largely belong to age groups with strong social interactions: teenagers and young adults.

The number, extent, and duration of measles outbreaks may largely be limited if the surveillance and alert system remains sufficiently effective, early and effective control measures are taken, and immunisation coverage remains at its current level and possibly increases among young adults. Thus, the extent of the transmission chains decreased between 2003 and 2007–2010: in 2003, two chains of transmission of six generations each comprising 19 and nine cases were identified (no exclusion measures were in place for non-immunised subjects), whereas in 2007–2010, chains were mainly limited to two or three cases of intrafamilial transmission owing to post-exposure vaccination and early home quarantine of non-immunised contacts. Moreover, due to one of the best immunisation coverage rates in Switzerland and a routine intervention for each case, the canton of Geneva was one of the least affected districts during the 2006–2009 measles epidemic in Switzerland, with a four-year cumulative incidence rate of 17 per 100,000 inhabitants versus

57 for the whole of Switzerland, the highest rate of 527 per 100,000 inhabitants being found in the Appenzell Innerrhoden canton [12].

Data relating to the exposure of infected patients together with the genotypic diversity suggest that the introduction of cases from other cantons and from abroad was responsible for some of the outbreaks in Geneva canton. In 2003, the viruses circulating in the Geneva and Schwyz cantons belonged to the genotype D8, but no epidemiological link could be found between these two distant cantons. The main circulating genotype in Switzerland during this period was the D5 genotype, which was identified in one Geneva case. Between 2007 and 2009, the D5 genotype (as well as B3 and D4 in 2009) predominantly circulating in Switzerland was identified in the Geneva canton. In 2010, eight of the nine notified cases were imported from abroad (India, France, Italy, and the United Kingdom) or were related to these importations, with only two very short chains of transmission and three distinct genotypes D8, D4, and G3). The G3 genotype [16], which had never previously been identified in Switzerland, was imported from London. Shortly thereafter, another case involving the same genotype with an identical genetic sequence occurred in Geneva, without any known exposure.

Since the summer of 2008, a change in measles epidemiology has been perceptible in the Geneva canton. Earlier, four outbreaks had occurred that were relatively large (52, 16, 43 and 23 cases) and temporally distant (separated by 16, 22 and four months). Since the summer of 2008 there have been mostly isolated cases and small outbreaks related to imported cases, in relation to a large variety of identified genotypes. The situation observed in 2010 in the canton of Geneva largely corresponds to what is expected after measles elimination, except that with a rate of 6.5 autochthonous cases per million population (i.e. three secondary cases per 463,919 inhabitants), the measles incidence in the canton still exceeds the elimination target of one per million.

These encouraging advances made towards measles elimination on a local level show that determined, politically supported action to promote vaccinations and fight outbreaks do bear fruit. The elimination of measles from Europe by 2015 requires such efforts on a broad scale.

Acknowledgments

The authors would like to thank Ms. Martine Girard, Brigitte Le Lin, Odile Lacour, Nicole Abbès, and Véra Serena (Epidemiology and communicable diseases section, Cantonal health service, General directorate for health, Department of regional affairs, economy and health, Geneva, Switzerland), Dr Stéphane Hugonnet and Anne Iten (Hospital Infection control Service, Cantonal University Hospital of Geneva, Switzerland) and Pr Claire-Anne Siegrist (Center for Vaccinology and Neonatal Immunology of the Faculty of medicine of the University of Geneva). We also acknowledge the help of the following laboratories and private practitioners: Drs A. Mankertz and S. Santibanez (WHO Regional Reference Laboratory for Measles and Rubella, Robert Koch Institute, Berlin) for genotyping numerous samples, and Drs L. Kaiser, P. Cherpillod, and et S. Cordey from the Central Laboratory of Virology of the University Hospital of Geneva for the RT-PCRs and genotyping of some of the samples. The authors would also like to thank Dr E. Masserey, deputy State Medical Officer of the canton of Vaud and Ms. M. Attinger from State Medical Office of Vaud, as well as the French health authorities from the Departments of Ain and Haute-Savoie for their help at the intercantonal and transborder levels.

References

1. Federal Office of Public Health. Couverture vaccinale en Suisse 2005-2007. [Vaccination coverage in Switzerland 2005-2007]. Bull OFSP. 2010;11:367-77. French. Available from: http://www.bag.admin.ch/themen/medizin/00682/00685/02133/index.html?lang=fr&download=NHzLpZeg7t,lnp6IoNTU042l2Z6ln1ae2IZn4Z2qZpnO2Yuq2Z6gpJCJdIJ7fWym162epYbg2c_JjKbNoKSn6A
2. Richard JL, Masserey V. Elimination de la rougeole: un objectif national réaliste. [Measles elimination: a realistic national goal]. Bulletin des medecins suisses. 2010;91: 522-4. French.
3. World Health Organization Regional Office for Europe (WHO Euro). Eliminating measles and rubella and preventing congenital rubella infection. WHO European Region strategic plan 2005-2010. Copenhagen: WHO Euro; 2005. Available from: http://www.euro.who.int/__data/assets/pdf_file/0008/79028/E87772.pdf
4. World Health Organization Regional Office for Europe (WHO Euro). Renewed commitment to elimination of measles and rubella and prevention of congenital rubella syndrome by 2015 and sustained support for polio-free status in the WHO European Region. Resolution EUR/RC60/R12. Copenhagen: WHO Euro; 16 Sept 2010. Available from: http://www.euro.who.int/__data/assets/pdf_file/0016/122236/RC60_eRes12.pdf
5. Anderson RM, May RM. Immunisation and herd immunity. Lancet. 1990;335(8690):641-5.
6. Jeannot E, Wyler Lazarevic CA, Duperrex O, Chastonay P. [Evolution of vaccine coverage from school year 2003-2004 to 2006-2007, for 5 to 6-year-old children in Geneva.] Med Mal Infect. 2010; 40(1): 27-30. French.
7. Jeannot E, Wyler Lazarevic CA, Duperrex O, Chastonay P. [Evolution of the immunization coverage of 13 to 14 year-old adolescents in Geneva between four years]. Santé Publique. 2009;21(6):605-11. French.
8. Hugonnet S, Pittet D, Siegrist C, Vermeulen B, Sudre P, Aramburu C, et al. Rougeole et plan stratégique institutionnel en cas d'épidémie. [Measles and strategic institutional plan in the case of an epidemic]. Swiss-NOSO bull. 2005;12(1):5-8.
9. Suivi des progrès accomplis en vue d'éliminer la rougeole. [Monitoring progress towards measles elimination]. Wkly Epidemiol Rec. 2010;85(49):490-4. French.
10. Delaporte E, Wyler- Lazarevic CA, Richard JL, Sudre P. Contributions des fratries non vaccines à une flambée de rougeole en Suisse. [Contribution of unvaccinated siblings to a measles outbreak in Switzerland]. Rev Epidemiol Sante Publique. 2004;52(6):493-501. French.
11. Richard JL, Zimmermann H. Recent increase in measles in children and teenagers in Switzerland. Euro Surveill. 2003;7(23):pii=2237. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2237
12. Richard JL, Masserey Spicher V. Large measles epidemic in Switzerland from 2006 to 2009: consequences for the elimination of measles in Europe. Euro Surveill. 2009;14(50):pii=19443. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19443
13. Office fédéral de la santé publique, Commission fédérale pour les vaccinations. Plan de vaccination suisse 2010. Directives et recommandations. Berne: Office fédéral de la santé publique; 2010. Available from: www.infovac.ch/doc.php?Item=1&id=640
14. Lang P, Zimmermann H, Piller U, Steffen R, Hatz C. The Swiss national vaccination coverage survey, 2005-2007. Public Health Rep. 2011;126 Suppl 2:97-108.
15. Federal Office of Public Health. Nouvelle vague de l'épidémie de rougeole en début d'année 2009: description et mesures. [New wave of the measles epidemic in early 2009: description and measures.]. Bull OFSP. 2009;27:484-91. Aailable from:html

?lang=fr&download=NHzLpZig7t,lnp6IoNTU042l2Z6ln1ae2IZn4Z2qZpnO2Yuq2Z6gpJCHe31_g2ym162dpYbUzd,Gpd6emK2Oz9aGodetmqaN19XI2IdvoaCUZ,s-

16. Brown KE, Mulders MN, Freymuth F, Santibanez S, Mosquera MM, Cordey S, et al. Appearance of a novel measles G3 strain in multiple European countries within a two month period, 2010. Euro Surveill. 2011;16(17):pii=19852. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19852

Highlights from the clinical symposium on Shiga toxin-producing *Escherichia coli* / haemolytic uremic syndrome, Berlin, September 2011

A Jansen (andreas.jansen@ecdc.europa.eu)[1]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

Citation style for this article:
Jansen A. Highlights from the clinical symposium on Shiga toxin-producing Escherichia coli / haemolytic uremic syndrome, Berlin, September 2011. Euro Surveill. 2011;16(39):pii=19977. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19977

Article published on 29 September 2011

On 9 September 2011, the Estrel Convention Center in Berlin was the venue for a first clinical symposium on Shiga toxin-producing *Escherichia coli* / haemolytic uremic syndrome (STEC/HUS) reflecting on the large STEC outbreak in Germany earlier this year. The German Society of Nephrology (DGfN) invited internationally renowned clinical experts and microbiologists to discuss the basic science and diagnostics of STEC infections and the different options for treating an EHEC-associated HUS, including plasmapheresis, antibody therapy with Eculizumab, and extracorporeal immune adsorption.

Opening the symposium, Helge Karch from Münster University Clinic gave a brief update on the microbiology and the diagnosis of STEC strains. He pointed out that a STEC O104:H4 strain was first isolated in Germany in 2001 from a child with HUS [1]. This strain (HUSEC041) was not identical with the 2011 outbreak strain, but showed similar molecular features (like the outbreak strain, this isolate was (*stx2*)-positive and (*eae*)-negative). A specific multiplex PCR for the 2011 outbreak strain has been developed within three days after the first isolate was available, and was made publicly accessible [2]. Interestingly, the microbiological features of the outbreak strain as known by today could not explain its pathogenicity as observed in the outbreak, leaving several open questions.

Gérard Krause from the Robert Koch-Institute, Berlin, presented the final outbreak report including the epidemiological investigations [3]. So far, there is no evidence that STEC O104:H4 has established as an endemic strain in Germany, but strict surveillance will be continued.
The discrepancy between the (severe) histopathological image of kidney specimens collected from 14 HUS patients and the (relatively positive) long-term disease outcome was highlighted by Udo Helmchen, Hamburg-Eppendorf University Clinic. Intermediate results from 14 HUS cases demonstrated that diffuse glomerular endotheliosis (14/14), and diffuse tubulointerstitial injury (14/14) were the primary histological features of HUS caused by the outbreak strain. Surprisingly, the outcome of these findings was much better than expected. Based on the preliminary results of the follow-up, probably none of the 14 patients will be dependent upon constant dialysis, thus indicating that the initial histopathological ratings were possibly misleading.

The use of Eculizumab, a monoclonal antibody directed against the complement protein C5, in patients with HUS was one of the specific therapeutic challenges of the outbreak. Rolf Stahl, from Hamburg-Eppendorf University Clinic, reflected on his rationale leading to the off-licence use of this treatment in patients not responding to more established treatment options, i.e. plasma exchange therapy. He did not present any results from the analysis of patients' data, though, leaving the question as to whether Eculizumab was effective or not, open.

This outbreak presented a new and surprising clinical picture with regard to the neurological signs of the patients – this was the main point of the presentation from Karin Weissenborn, Hannover Medical School. The neurologist described her experiences with 43 cases which were followed up during their hospital stay, and of which 42 developed HUS. Cognitive dysfunction, including dysphasia (n=22), apraxia (n=16), and agraphia (n=13) were detected among the patients. In addition, panic attacks (n=13) and hyperreflexia (n=24) were common. Seizures/myoclonia occurred in eight patients. The Minimal Mental Status test proved particularly valuable in assessing cognitive dysfunctions in HUS patients. In Magnetic Resonance Imaging (MRI), a bilateral diffusion disorder was observed in the thalamus area and the basal ganglia. However, there were also patients with no MRI findings although they showed severe neurological impairments. Most, but not all cases, showed a complete remission of neurological signs within weeks.

The use of immunoabsorbtion in severe HUS cases was presented by Sylvia Stracke, Greifswald University's

Medical Faculty. She pointed out that the patients worsened neurologically while on plasma exchange therapy. In addition, the evidence for plasma exchange therapy turned out to be rather weak, with most information derived from uncontrolled case series, and absence of prospective, randomised controlled studies. While searching for a therapeutic alternative (especially for the neurological signs), the characteristic time-span between onset of gastroenteritis and onset of the neurological complications (5–12 days) was the key clinical finding indicating that additional (auto)antibodies were probably involved in the pathogenesis of the severe neurological complications. The intravascular reduction of these (auto)antibodies by immunoabsorbtion was considered to be one possible reason for the success of this therapy with regard to the neurological complications of HUS patients.

With regard to the discussion about the use of antibiotics in EHEC infections, Winfried Kern, from the University of Freiburg, summarised that antibiotics still cannot be generally recommended for EHEC infections. He pointed out that available evidence for or against antibiotic treatment is still sparse. Randomised controlled trials are necessary in order to elucidate whether antibiotics are effective in reducing the morbidity and mortality of EHEC infections. Especially azithromycin and rifaximin should be subject to further clinical studies for the reduction of microbial load in EHEC patients.

Finally, Jan Kielstein, from Hannover Medical School, presented preliminary results from the German EHEC-HUS registry. So far, data from 589 patients have been included into the registry. Of all HUS patients, 93% underwent therapeutic plasma exchange, and 36% received Eculizumab therapy. The overall mortality rate was 4.4%.

To conclude, two major issues of future concern emerged during the symposium: firstly, the lack of evidence with respect to 'established' (or abandoned) therapeutic options in EHEC/HUS; secondly, the uncertainty of prognostic markers - especially with regard to histopathological features of kidney biopsies in HUS patients. The excellent cooperation between different clinicians, and between clinicians and microbiologists, proved to be a valuable resource during the outbreak. However, this outbreak was mainly restricted to Germany. To prepare for a similar event not restricted to a single European country, structures for timely exchange of clinical data and experiences at European level are urgently needed.

References

1. Mellmann A, Bielaszewska M, Köck R, Friedrich AW, Fruth A, Middendorf B, et al. Analysis of collection of hemolytic uremic syndrome-associated enterohemorrhagic Escherichia coli. Emerg Infect Dis. 2008;14(8):1287-90.
2. University of Münster. Institute for Hygiene. Konsiliarlabor für Hämolytisch– Urämisches Syndrom (HUS). [Consiliar Laboratory for haemolytic uremic syndrome (HUS)]. Münster: Institute for Hygiene. [Accessed 23 Sep 2011]. German. Available from: http://www.ehec.org/
3. Robert Koch Institute (RKI). Abschließende Darstellung und Bewertung der epidemiologischen Erkenntnisse im EHEC O104:H4 Ausbruch Deutschland 2011. [Final presentation and evaluation of the epidemiological evidence in the EHEC O104:H4 outbreak in Germany 2011]. RKI: 9 Sep 2011. German. Available from: http://www.rki.de/cln_160/nn_205760/DE/Content/InfAZ/E/EHEC/EHEC-Abschlussbericht,templateId=raw,property=publicationFile.pdf/EHEC-Abschlussbericht.pdf