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

Vol. 17 | Weekly issue 12 | 22 March 2012

Editorials

Rapid communications

Letters

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Can the economic crisis have an impact on tuberculosis in the EU/EEA?

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Citation style for this article:
van der Werf MJ, Giesecke J, Sprenger M. Can the economic crisis have an impact on tuberculosis in the EU/EEA?.
Euro Surveill. 2012;17(12):pii=20122. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20122

Article published on 22 March 2012

Each year, 24 March marks World Tuberculosis Day in an attempt to raise public awareness about the epidemic. The European Parliament Committee on the Environment, Public Health and Food Safety will exchange their views on tuberculosis (TB) in Europe in a debate on 21 March 2012. In preparation of this debate concerns were raised about the effect of the current economic crisis on TB.

Many countries in the European Union (EU) and the European Economic Area (EEA) are in an economic recession. It is acknowledged that a recession or economic crisis can have an effect on the population's health, especially with respect to infectious diseases [1]. There are two main mechanisms through which an economic crisis can have an effect on infectious diseases. Firstly, if due to a decrease in country and individual income, less money is spent on healthcare and social welfare. And secondly, if due to an increase in poverty and stress, the number of people belonging to risk groups for infectious diseases increases.

There is evidence that budgets for healthcare are cut in times of economic hardship [2]. Experts from EU/EEA countries predict that there will be an impact of the current global crisis on the financial and human resources available for the control of communicable diseases [3]. Decreased spending on healthcare may result in a reduction of healthcare workers and even of the number and quality of available healthcare facilities, which will have an impact on access to healthcare. Low access to healthcare is associated with longer delays in the diagnosis of TB [4]. This would increase the pool of individuals with infectious TB, as would treatment that is delayed or of insufficient quality.

A financial crisis can increase the size of groups with a high risk for TB. For example, it is generally believed that rising unemployment favours criminal behaviour, and that this leads to a larger prison population [5]. On a population level it has been shown that the size of the prison population is associated with TB incidence [6]. Also, unemployment and job insecurity appear to lead to behaviour that increases the risk for TB, e.g. increased alcohol consumption [7,8]. A study of the impact of the New York City's fiscal crisis in 1975 found that the number of homeless people increased by 300% [9]. Homeless people are a well known risk group for TB [10,11].

Thus there is evidence that an economic crisis can impact on access to care and quality of care and on the number of individuals that are exposed to risk factors for TB. However, is there evidence that an economic crisis can influence tuberculosis incidence or mortality? A recently published systematic review assessing the impact of economic crises on communicable disease transmission and control included eight studies that report the effect of a crisis on TB [1]. Seven of the eight studies were conducted in non-EU countries and showed that a crisis indeed led to increased incidence, prevalence or mortality of TB. The eighth study, conducted in EU countries, did not show any significant effects. In that study, data for social protections, i.e. availability of social welfare programmes, and for job insecurity was missing for many countries, which makes the detection of immediate changes in mortality difficult. All eight studies were conducted before the current economic crisis started and do therefore not provide direct information about the effect of the current situation on tuberculosis.

On 19 March 2012, the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization Regional Office for Europe published the report Tuberculosis Surveillance and Monitoring in Europe 2012 [12]. The report will for the first time present monitoring indicators that assess the implementation of the Framework Action Plan [13,14]. A rapid communication published in this issue of *Eurosurveillance* presents an overview of these indicators [15]. One indicator is the trend in the TB case notification rate. Over the last five reporting years, the EU/EEA has experienced a sustained annual decline of 4.4% in TB notification rates, from 17.5 per 100,000 population in 2006 to 14.6 in 2010 [12]. Thus, the European data do not at this moment show an effect of the current economic crisis on TB. Since TB is a slow disease with a minimum

incubation period of eight weeks it may take time to see a significant increase in the number of cases. It is even possible that we will initially see a further decrease in the number of TB cases because the healthcare system may experience difficulties in diagnosing and notifying TB. However, it has been shown that in Europe, TB notifications are higher where national incomes are lower and/or income inequalities are higher [16]. If the current financial crisis affects these two variables, then TB rates may well rise.

National experts of EU/EEA countries who participated in a scoping study that assessed the effects of the current global crisis on communicable diseases expect that there will be budget cuts especially in prevention services and in services targeted at vulnerable and hard-to-reach population groups [3]. In Romania, the expiration of a grant from the Global Fund for AIDS, tuberculosis and malaria in June 2010 resulted in reduced provision of prevention services for intravenous drug users. This was followed by a rise in the combined use of opioids and amphetamine-type stimulants resulting in increased injecting frequency. It is likely that this has contributed to increased HIV transmission [17]. As a result of a financial crisis, the Department of Health of the City of New York cut the budget by 20% between 1974 and 1977 and lost 1,700 staff members; seven of 20 district health centres and six of 14 chest clinics were closed [2]. TB rates began to rise, and New York City experienced a subepidemic of multidrug-resistant TB (MDR-TB). A cost-of-illness study assessing the excess medical expenditures showed that about 10,000 excess TB cases (of a total of 47,000) occurred between 1979 and 1999 [2]. The excess medical expenditures were estimated at USD 0.5 billion. Thus, countries cutting budgets for TB control can expect challenges in controlling TB and increased costs for controlling TB in the future.

Given the likely influence of an economic crisis on the functioning of healthcare systems and on factors that affect the epidemiology of TB, it is expected that the current economic crisis will have an effect on the TB situation in EU/EEA countries. This will be especially true in countries that were already experiencing problems with TB control before [18]. Also, control of MDR- and extensively drug-resistant (XDR-)TB requires a well-established and functioning healthcare system that is able to diagnose cases and provide them with expensive treatment and long-term care. In the light of the predicted budget cuts, ECDC will monitor the effect of the economic crisis on TB in EU/EEA countries by collecting and analysing the TB notification data, and advocate to sustain or even enlarge the budget for TB control.

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Epidemiology of tuberculosis in the EU/EEA in 2010 – monitoring the progress towards tuberculosis elimination

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Citation style for this article:
Sandgren A, Hollo V, Huitric E, Ködmön C. Epidemiology of tuberculosis in the EU/EEA in 2010 – monitoring the progress towards tuberculosis elimination. Euro Surveill. 2012;17(12):pii=20124. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20124

Article published on 22 March 2012

The 2012 combined tuberculosis (TB) surveillance and monitoring report for the European Union and European Economic Area identifies a mean annual decline in TB notification rate by 4.4% from 2006 to 2010. Culture confirmation for new pulmonary cases and drug susceptibility testing have increased to 65.6% and 70.8%, but remain under their targets of 80% and 100%, respectively. Reporting of treatment outcome and co-infection with human immunodeficiency virus also remain suboptimal. Strengthened control practices are needed to allow progress towards TB elimination.

Monitoring progress towards tuberculosis elimination through surveillance

Surveillance is an essential element in monitoring the effectiveness of interventions aimed at controlling and eliminating tuberculosis (TB). It is one of the eight strategic areas of the Framework Action Plan to Fight TB in the European Union (EU) which was launched in 2008 by the European Centre for Disease Prevention and Control (ECDC) [1]. Since 1 January 2008, the ECDC and the World Health Organization (WHO) Regional Office for Europe have been jointly coordinating the TB surveillance activities in Europe and publishing a joint annual TB surveillance report [2]. In 2010, ECDC launched the follow-up to the Framework Action Plan: an epidemiological and strategic monitoring framework that allows progress towards TB elimination in the EU to be assessed [3]. The follow-up monitoring framework entails four epidemiological indicators calculated from individual case data and eight core operational indicators (Table 1). The monitoring is focused on giving an overview of the progress made towards elimination, by presenting the status and trends of the specific indicators for the EU and European Union and European Economic Area (EEA) as a whole and for the individual countries. The epidemiological trends are expressed as mean annual percentage changes, which are calculated over a period of either five or 10 years, to avoid the effect of random variation over time [3]. Starting this year, 2012, these epidemiological and core operational indicators are being monitored and are presented in the TB surveillance and monitoring report for Europe [4]. The 2012 report covers data for the TB cases notified in the 53 countries of the WHO European Region in 2010. This rapid communication presents an overview of the monitoring aspects of the report for the 27 EU Member States, Iceland and Norway (Table 2).

Tuberculosis situation in the EU/EEA in 2010

In 2010, 73,996 TB cases were reported by the 27 EU Member States, Iceland and Norway. The overall notification rate in 2010 was 14.6 per 100,000 population, with a mean annual decline in the case notification rate of 4.4% during the period 2006 to 2010. The target of reaching a mean decline over five years was met by the EU/EEA overall and by 22 of the 29 Member States. For the first time, all EU/EEA Member States had notification rates below 100 per 100,000 population and one additional country, Poland, joined the 22 countries already in the elimination phase defined as below 20 cases per 100,000 [5].

Resistant tuberculosis

Resistance to at least the first-line anti-TB drugs isoniazid and rifampicin was reported for, respectively, 1,374 (7.8%) and 529 (3.0%) of 17,559 new pulmonary TB cases tested for drug susceptibility in the EU/EEA. Three countries did not report, four countries did not have any isoniazid-resistant cases and six countries did not have any rifampicin-resistant cases. Drug susceptibility test results were known for 70.8% of the 24,785 new pulmonary culture-positive cases. All countries reported and four countries did not have any cases. The proportion of multi-drug resistant TB (MDR-TB, defined as resistance to at least isoniazid and rifampicin) among all culture-positive TB cases was 4.6% in the 29 reporting countries. This proportion corresponded to a mean five-year decline of 3.4% for the period 2006 to 2010, with seven of 22 countries reaching the set target of a declining trend. In 2010, 108 (13.2%) of the 819 MDR-TB cases tested for second-line drug resistance were reported to be extensively

Table 1

Indicators for monitoring progress of the Framework Action Plan to Fight TB in the European Union

Epidemiological indicators
1. Trends in case notification rate,
2. Trends in multidrug-resistant case notification rate,
3. Trends in ratio of notification rates in children versus adults,
4. Trends in mean age of TB cases.
Operational indicators
1. Availability of a national TB control plan,
2. Availability of guidelines for implementing the national TB control plan,
3. Percentage of European TB reference laboratory network members achieving adequate performance in the external quality assurance scheme,
4. Availability of a strategy for introducing and implementing new tools for TB control,
5. Percentage of new pulmonary TB cases confirmed by culture and percentage of cases tested for susceptibility to first-line drugs,
6. Percentage of EU Member States reporting treatment success rate,
7. Treatment success rate,
8. Percentage of TB patients for whom HIV status is known.

EU: European Union; HIV: human immunodeficiency virus; TB: tuberculosis.
Source: This Table has been adapted from [3].

Table 2

Monitoring of the follow-up to the Framework Action Plan to fight TB in the EU, 2010

Indicator	Target	EU/EEA status	Number of Member States reaching the target	Number of Member States reporting
Epidemiological indicators				
Trend in TB case notification rate	Mean five-year decline	-4.4%[a]	22	29
Trend in MDR-TB case notification rate	Mean five-year decline	-3.4%[a]	7	22
Trend in ratio of notification rate in children versus adults	Mean 10-year decline	-0.3%[a]	7	25
Trend in mean age of TB cases[b]	Increasing trend over 10 years	0.0%[a]	10	24
Core indicators				
Availability of a National TB Plan[c]	TB Plan available for all countries	50.0%	14	28
Availability of TB Guidelines	TB Guidelines available	Not collected	Not done	Not done
Laboratory EQA performance[d]	100% reference TB laboratories achieving 80% performance (smear, culture, DST)	79.0%	NA[e]	23
Availability of a new tool strategy	Strategy available	Not collected	Not done	Not done
Culture confirmation	80% culture confirmation in new pulmonary cases.	65.6%[a]	12	29
DST results of new pulmonary cases	100% DST results to first-line drugs among new pulmonary culture-positive cases	70.8%[a]	8	26
Proportion of Member States reporting treatment outcome	100%	82.8%	NA[e]	24
Treatment success rate	85% in new pulmonary culture-positive cases	78.8%[a]	4	24
Treatment success for MDR-TB	70% in new pulmonary MDR-TB	49.3%[a]	4	16
Proportion with known HIV status	HIV status known for 100% of TB cases	23.9%[a]	1	15

DST: drug susceptibility testing; EEA: European Union and European Economic Area; EQA: external quality assessment; HIV: human immunodeficiency virus; MDR-TB: multidrug-resistant tuberculosis; NA: not applicable; TB: tuberculosis.

[a] Data originating from individual case data.

[b] Crude mean age used for calculations.

[c] Results obtained from 2009 survey.

[d] Information is available only for DST to isoniazid and rifampicin, data currently obtained from International EQA scheme. In the future, these data will be obtained from the European Reference Laboratory Network for TB (ERLN-TB).

[e] EU level indicator, no trend involved.

Source: This Table has been adapted from [4].

drug-resistant (XDR-TB, defined as resistance to isoniazid, rifampicin, any fluoroquinolone and at least one of the injectable second-line drugs capreomycin, kanamycin or amikacin).

Childhood tuberculosis

In 2010, 3,035 TB cases were reported in children (under the age of 15 years), accounting for 4.1% of all notified cases. The trend in childhood TB gives an indirect measure of the level of transmission in the community [6]. The trend in mean age of TB cases is another estimate of how effective the TB control is in interrupting transmission in the community [3]. Overall, the ratio of notification rates in children versus adults declined by 0.3% over the period 2001 to 2010, and the mean age did not change at all in the same period with 45.0 years for 2001 and 45.1 years for 2010. There was, however, variation across countries, in that seven of 25 reporting countries met the target of a declining trend in the ratio of cases in children versus adults and 10 of 24 reporting countries met the target of an increasing trend in mean age.

Operational strategies, policies and practices

A national TB control plan was available in 14 of the 28 countries that had responded to a survey ECDC conducted for this purpose in 2009 [4]. No information has been collected yet about the availability of guidelines for implementing the national TB control plan or the availability of strategies for introducing and implementing new tools for TB control. The European Reference Laboratory Network for TB [7] is currently conducting external quality assurance (EQA) in laboratory proficiency for smear microscopy, culture and drug susceptibility testing (DST) for first- and second- line anti-TB drugs, thus the results are not yet available and not presented in this year's report. Twenty-three national reference laboratories reported on performance in DST for first-line anti-TB drugs following the international EQA schemes of the WHO Supra-National Reference Laboratory Network. All 23 laboratories reported full agreement of results, demonstrating high-quality DST.

Bacteriological confirmation of cases

Overall, 65.6% of new pulmonary TB cases were culture-confirmed. At country level, only 12 of 29 countries achieved the 80% culture-confirmation target among new pulmonary TB cases. Likewise, only eight of 26 countries achieved the target of testing 100% of new pulmonary culture-positive cases for susceptibility to first-line drugs. For the EU/EEA as a whole, 70.8% of culture-positive new pulmonary TB cases had DST results for first-line drugs available.

Treatment outcome

In the 2009 treatment cohort, 24 of the 29 countries reported on treatment outcome, falling short of the target of having all EU/EEA Member States reporting treatment outcome data. Seven countries reported treatment outcome for all cases. The treatment success rate was 78.8% for new pulmonary culture-positive cases, with only four of 24 countries reaching the target of more than 85% treatment success. Treatment success of new pulmonary culture-positive MDR-TB cases in the 2008 cohort was 49.3%, with only four of 16 reporting countries reaching the target (taking into consideration only countries reporting at least one MDR-TB culture-positive pulmonary case).

Human immunodeficiency virus co-infection in tuberculosis cases

Most EU/EEA Member States have not incorporated human immunodeficiency virus (HIV) testing for TB patients in the national plans or do not report HIV status. The target is that HIV status should be known for 100% of the TB cases. Overall in the EU/EEA, only 23.9% of the TB patients have a known HIV status. Only one of 15 reporting countries reached the 100% target.

Conclusions

These data demonstrate that most EU/EEA Member States have continued to experience a steady decrease in the overall TB notification rate during 2010. Several challenges remain, however, that need to be addressed. The proportions of bacteriologically confirmed TB cases and cases for which drug-susceptibility testing has been performed are increasing, but remain suboptimal in the EU/EEA, thus laboratory practices need to be further strengthened. Efforts are also needed to improve the reporting of treatment outcomes and to ensure successful treatment of new culture-confirmed TB and MDR-TB cases; for example only four of 24 countries reached the 85% target of treatment success among new pulmonary culture-positive cases. Further, reporting of HIV co-infection is lacking in many countries, indicating that national TB programmes are lacking targeted, incorporated TB/HIV plans. Monitoring overall EU/EEA trends can mask patterns for some indicators, in particular for mean age of TB cases and the ratio of notification rates in children versus adults, therefore some indicators may be more relevant to monitor at Member State level. We therefore encourage similar analyses to be performed at country level when possible. For the monitoring of progress towards TB elimination to be a valid tool, a surveillance system that captures close to 100% of all TB cases is a prerequisite. Thus, the monitoring framework might also be a tool for further improving the quality and coverage of surveillance systems.

Acknowledgments

The authors would like to thank all the nominated TB experts of the EU/EEA Member States for providing the surveillance data to TESSy. These are:
Ibrahim Abubakar, Peter Henrik Andersen, Delphine Antoine, Wouter Arrazola de Oñate, Thorsteinn Blondal, Paul Caruana, Nicoleta Cioran, Edita Davidaviciene, Francis Drobniewski, Connie Erkens, Jos Even, Lanfranco Fattorini, Maryse Fauville Dufaux, António Fonseca Antunes, Walter Haas, Chrystalla Hadjianastassiou, Sven Hoffner, Vincent Jarlier, Maria Soledad Jimenez Pajares, Jerker Jonsson, Jean - Paul Klein, Maria Korzeniewska - Kosela, Tiina Kummik, Daniel Lévy-Bruhl, Turid Mannsåker, Merja Marjamäki, Tanya Melillo

Fenech, Vladimir Milanov, Olga Moldovan, Joan O'Donnell, Vibeke Østergaard Thomsen, Analita Pace-Asciak, Despo Pieridou Bagatzouni, Erik Michael Rasmussen, Vija Riekstina, Elena Rodríguez Valín, Thomas Rogers, Karin Rønning, Sabine Rüsch-Gerdes, Petri Ruutu, Girts Škenders, Pavel Slezák, Ivan Solovic, Anaida Sosnovskaja, János Strausz, Petra Svetina - Sorli, Nora Szabó, Wim Van Der Hoek, Dick Van Soolingen, Piret Viiklepp, Jiri Wallenfels, Maryse Wanlin, John Watson, Ilona Zemanova, Manca Zolnir-Dovc, Zofia Zwolska.

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Early estimates of the effectiveness of the 2011/12 influenza vaccine in the population targeted for vaccination in Spain, 25 December 2011 to 19 February 2012

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Citation style for this article:
Jiménez-Jorge S, de Mateo S, Pozo F, Casas I, García Cenoz M, Castilla J, Gallardo V, Pérez E, Vega T, Rodriguez C, Quinones C, Martínez E, Giménez J, Vanrell JM, Castrillejo D, Serrano MC, Ramos JM, Larrauri A. Early estimates of the effectiveness of the 2011/12 influenza vaccine in the population targeted for vaccination in Spain, 25 December 2011 to 19 February 2012.
Euro Surveill. 2012;17(12):pii=20129. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20129

Article published on 22 March 2012

We present early estimates of influenza vaccine effectiveness (VE) in the population targeted for vaccination, during 25 December 2011 to 19 February 2012. The adjusted VE was 55% (95% CI: 3 to 79) against any type of influenza virus and 54% (95% CI: 1 to 79) against influenza A(H3N2) virus. This suggests a moderate protective effect of the vaccine in the targeted population in a late influenza epidemic with limited match between vaccine and circulating strains.

Background

The effectiveness of the trivalent seasonal and pandemic influenza vaccines has been estimated in Spain since the 2008/09 season using the observational test-negative case–control cycEVA study, the Spanish component of the European Centre of Disease Prevention and Control (ECDC)-funded project, I-MOVE (Monitoring Vaccine Effectiveness in Europe) [1].

The 2011/12 influenza seasonal trivalent vaccine composition recommended for the northern hemisphere included the same strains as in the previous season: the influenza A(H1N1)2009 pandemic strain A/California/07/2009, in addition to the A(H3N2) (A/Perth/16/2009-like) and B strains (B/Brisbane/60/2008-like) strains [2].

In Spain, the target groups for influenza vaccination this season were individuals over six months old with major chronic conditions or with risk factors such as pregnancy or morbid obesity, the elderly over 59 years old (over 64 years old in some regions), healthcare workers and caregivers [3].

The cycEVA study was able to provide intraseasonal influenza vaccine effectiveness (VE) estimates in the previous 2010/11 season [4]. Here we present early estimates of the effectiveness of the 2011/12 seasonal trivalent influenza vaccine in preventing medically attended laboratory-confirmed influenza infections in the population targeted for vaccination, during the time when the epidemic in Spain was increasing (25 December 2011 to 19 February 2012), eight weeks after its start.

Methods

In the current influenza season, seven regional networks belonging to the Spanish Influenza Sentinel Surveillance System, distributed throughout Spain, participated in the cycEVA study. We used similar methods to those carried out in the previous three seasons in the cycEVA study [4-7]. Briefly, the 231 participating sentinel general practitioners (GPs) and paediatricians systematically swabbed the first two patients each week aged under 65 years consulting for influenza-like

illness (ILI) and all patients aged 65 years and over consulting for ILI, from week 52 (25 December) 2011 to week 7 (19 February) 2012.

ILI patients were recruited according to a case definition based on that of the European Commission: sudden onset of symptoms and at least one of these four systemic symptoms (fever or feverishness, malaise, headache, myalgia), and at least one of these three respiratory symptoms (cough, sore throat, shortness of breath), in the absence of another possible differential clinical diagnosis [8]. Influenza cases were laboratory confirmed for the presence of influenza viruses by genome amplification methods reverse transcription-PCR and/or cell culture using a Madin-Darby canine kidney (MDCK) cell line. Controls were ILI patients who tested negative for any type of influenza virus.

We considered a patient vaccinated if they had received the 2011/12 influenza vaccine at least 14 days before the ILI symptom onset.

The variables assessed during this season were the same as in 2010/11 [7], except for pandemic vaccination status and functional status (the need for assistance in walking or bathing), which were not assessed this season.

The National Centre of Microbiology (World Health Organization National Influenza Centre-Madrid) selected a subset of influenza isolates in order to get a homogeneous distribution by age group, geographical origin and epidemiological week. The isolates were genetically characterised by sequencing the HA1 fragment of the viral haemagglutinin gene. Phylogenetic analysis of sequences was carried out in order to characterise the specific strains of influenza A and B viruses.

We estimated the influenza VE against any type of influenza virus and against A(H3N2) influenza virus (the predominant influenza subtype virus in Spain since the beginning of the 2011/12 season) in the target groups for vaccination, restricting the analysis to ILI patients swabbed less than eight days after onset of symptoms in order to reduce the chance of misclassification due to false-negative results over time.

We used a logistic regression model to calculate adjusted influenza VE, including in the model those variables that changed the crude odds ratio by more than 10% and met the two necessary criteria for confounding, i.e. to be a risk factor for the laboratory-confirmed influenza infection in non-vaccinated patients and to be associated with the influenza 2011/12 vaccination [9].

Results

ILI rate and influenza virus type in the 2011/12 influenza season

The ILI rate exceeded the epidemic threshold (53.43 ILI cases per 100,000 population) in week 52 (25–31 December) 2011 in Spain. The epidemic wave reached its peak in week 7 (13–19 February) 2012 at both the national level and in the seven regions participating in the cycEVA study [10]. The highest incidence was recorded in the age group 0–4 years, with a maximum weekly incidence of 656 ILI cases per 100,000 population.

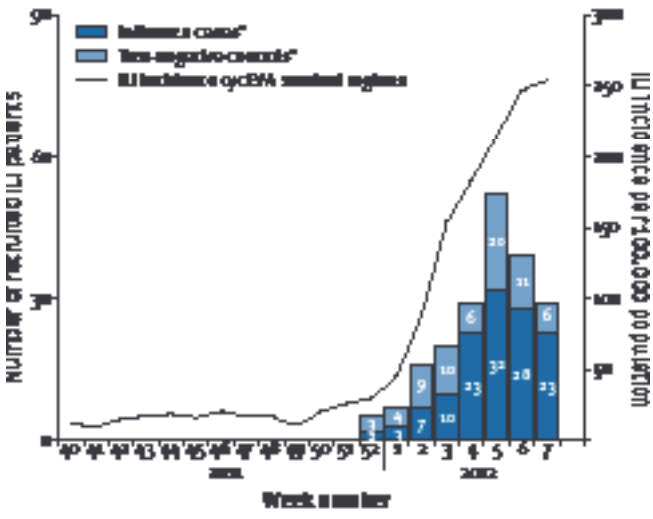
Since the beginning of the 2011/12 season, influenza A(H3N2) virus has been the predominant circulating subtype of influenza A virus in Spain: 90% of influenza A viruses were subtyped, 99% of those subtyped were influenza A(H3N2). The maximum percentage of influenza-positive samples was 69%, during the peak.

Participants' characteristics

Among the 231 GPs and paediatricians who agreed to participate in the study, 179 (77%) recruited at least one ILI patient. Of the 935 ILI patients recruited, 204 (22%) were in the vaccination target groups. After excluding four patients with unknown laboratory results and three swabbed more than eight days after symptom onset, 197 ILI patients were included in the study. These comprised 128 influenza cases (121 with influenza A(H3N2) virus, one with influenza A(H1N1) pdm09 virus, three in whom the influenza A virus was not subtyped and three with influenza B virus) and 69

Figure

Recruited influenza cases (n=128) and test-negative controls (n=69) targeted for vaccination and ILI incidence in sentinel regions, cycEVA study, Spain, week 40 (2–8 October) 2011–week 7 (13–19 February) 2012



ILI: influenza-like illness.

[a] Cases and controls recruited during week 52 (25–31 December) 2011 to week 7 (13–19 February) 2012 and with an interval between ILI symptom onset and swabbing of less than eight days.

test-negative controls. The weekly distribution of the recruited ILI patients followed the ILI incidence in the seven participating networks (Figure) as well as at the national level [10].

The characteristics of the recruited influenza cases did not differ from the test-negative controls in any of the variables assessed (Table 1). Although cases were older than controls (a median age of 60 years versus 49 years), this difference was not statistically significant (p=0.150). The median number of visits per patient to a GP or and paediatrician in the previous year was five in the cases and four in the controls (p=0.487). The percentage vaccinated was similar in the 2011/12 and the 2010/11 seasons in the cases (26% and 20%, respectively) and in the controls (33% and 32%, respectively).

Table 1

Characteristics of recruited influenza cases (n=128) and test-negative controls (n=69) targeted for vaccination, cycEVA study, Spain, week 52 (25–31 December) 2011–week 7 (13–19 February) 2012

Variable	Influenza cases[a]	Test-negative controls[a]	P value
Median age in years (range)	60.5 (3–82)	49 (3–86)	0.150[b]
Age group in years – number/total number (%)			
0–4	3/128 (2)	3/69 (4)	0.488[c]
5–14	11/128 (9)	4/69 (6)	
15–64	67/128 (52)	42/69 (61)	
≥65	47/128 (37)	20/69 (29)	
Sex: male – number/total number (%)	59/128 (46)	32/69 (46)	0.970[c]
Any chronic condition reported	69/127 (54)	44/69 (64)	0.202[c]
Pregnancy	5/128 (4)	1/69 (1)	0.338[c]
Morbid obesity[d]	7/127 (6)	5/69 (7)	0.629[c]
Any hospitalisation for chronic conditions in previous year	4/127 (3)	0/69 (0)	0.136[c]
Visits to a GP or paediatrician in previous year			
Median number of visits per patient (range)	5 (0–20)	4 (0–32)	0.487[b]
Number that did not visit	15/127 (12)	7/68 (10)	0.750[c]
Number that visited at least once	112/127 (88)	61/68 (90)	
Smoker	20/125 (16)	16/68 (23)	0.200[c]
Interval between symptom onset and swabbing less 4 days	123/128 (96)	66/69 (96)	0.881[c]
Vaccination status– number/total number (%)			
Received seasonal 2011/12 vaccine[e]	33/128 (26)	23/69 (33)	0.262[c]
Received seasonal 2010/11 vaccine	26/127 (20)	22/69 (32)	0.076[c]

GP: general practitioner; ILI: influenza-like illness.

[a] Cases and controls recruited during the specified time period (week 52 (25–31 December) 2011 to week 7 (13–19 February) 2012) and with an interval between ILI symptom onset and swabbing of less than eight days.

[b] Non-parametric test of the median.

[c] Chi-square test or Fisher's exact test, when appropriate.

[d] Defined as body mass index greater than 40 kg/m^2.

[e] Vaccination at least 14 days before the onset of ILI symptoms.

Table 2

Effectiveness of trivalent 2011/12 influenza vaccine against any type of influenza virus and influenza A(H3N2) virus in recruited influenza cases (n=128) and test-negative controls (n=69) targeted for vaccination, cycEVA study, Spain, week 52 (25–31 December) 2011–week 7 (13–19 February) 2012

Type/subtype of influenza virus	Number of influenza cases[a]	Number of test-negative controls[a]	Number of vaccinated influenza cases[a]	Number of vaccinated test-negative controls[a]	Vaccine effectiveness % (95%CI)	
Any type of influenza virus	128	69	33	23	Crude	31 (–39 to 65)
					Adjusted[b]	55 (3 to 79)
Influenza A(H3N2) virus	121	69	32	23	Crude	28 (–45 to 64)
					Adjusted[b]	54 (1 to 79)

ILI: influenza-like illness.

[a] Cases and controls recruited during the specified time period (week 52 (25–31 December) 2011 to week 7 (13–19 February) 2012 and with an interval between ILI symptom onset and swabbing of less than eight days.

[b] Model adjusted for age groups, smoking history and week of swabbing.

During the study period, 33 vaccine failures were notified: 32 were in cases with laboratory-confirmed influenza A(H3N2) virus and one was in a case with laboratory-confirmed influenza B virus. Of all the vaccine failures, 11 were cases who were older than 64 years and had at least one chronic condition.

Vaccine effectiveness estimates

The crude influenza VE against any type of influenza virus was 31% (95% CI: −39 to 65). The adjusted VE, adjusted for age groups, smoking history and week of swabbing, was 55% (95% CI: 3 to 79) (Table 2). Similar estimates were obtained when effectiveness of the vaccine against influenza A(H3N2) virus was assessed, with adjusted VE estimates of 54% (95% CI: 1 to 79).

Although the number of visits to GPs or paediatricians and hospitalisation for chronic conditions in the previous year were not identified as confounding variables, adding these variables to the model did not affect the adjusted estimates (Wald test p value of 0.6981 for GP or paediatrician visits and likelihood ratio chi-square (4 degrees of freedom): 3.1; p=0.54 for hospitalisation for chronic conditions).

Table 2. Effectiveness of trivalent 2011/12 influenza vaccine against any type of influenza virus and influenza A(H3N2) virus in recruited influenza cases (n=128) and test-negative controls (n=69) targeted for vaccination, cycEVA study, Spain, week 52 (25–31 December) 2011–week 7 (13–19 February) 2012

Genetic analysis of selected isolates

Sequence analysis of the amplified HA1 genome fragment showed that out of 48 influenza A virus strains studied, 31 clustered into the group represented by A/Stockholm/18/2011 defined by the V223I amino acid mutation (compared with the vaccine strain A/Perth/16/2009). The remaining influenza A viruses clustered into the group represented by A/Iowa/19/2010. Regarding influenza B virus, sequence analysis showed that the only virus analysed genetically in the study clustered into the Yamagata lineage, B/Bangladesh/3333/2007 genetic clade, which was not included in the seasonal vaccine.

Discussion

There are some noteworthy aspects of the current influenza season in Spain. Firstly, the epidemic peak was not reached until February 2012 [10]. Such a late epidemic peak was seen in only other two previous influenza seasons since 1996: in 2005/06 and 2006/07 [11,12]. Secondly, there has been a minimal contribution of the influenza A(H1N1)pdm09 virus, which has been the predominant virus since the 2009 pandemic [13,14].

Our influenza VE estimates in people in target groups for vaccination suggest a moderate effectiveness of the 2011/12 influenza vaccine against medically attended laboratory-confirmed influenza. The estimates were similar, whether against any type of influenza virus or A(H3N2) virus. However, these are preliminary results that should be interpreted with caution, taking into consideration the small sample size.

Several factors might have contributed to the moderate protective effect of the vaccine. Firstly, there has been a limited match between the circulating A(H3N2) strains compared with the vaccine strain in the northern hemisphere [15]. The majority of circulating A(H3N2) viruses in Spain were clustered into the group represented by A/Stockholm/18/2011, which was reported to be antigenically and genetically distinct from the vaccine virus A/Perth/16/2009 [16,17]. However, our VE estimates are consistent with those in studies carried out in previous years with a predominant circulation of seasonal influenza A(H3N2) virus. In these studies, influenza VE ranged from 10% to 68%, depending on the degree of antigenic match [18-22]. It is important to note that although the effectiveness of the influenza vaccine is often less pronounced during seasons with antigenic mismatch between vaccine and circulation strains [23], in some influenza seasons antigenic changes occurred without resulting in any apparent loss of vaccine effectiveness [24].

Secondly, preliminary analysis in the cycEVA study would suggest a decrease of the influenza VE estimates with time since vaccination (data not shown). The median delay between the date of vaccination until the date of onset of symptoms was 106 days in cases versus 88 days in controls (p<0.004).

Taking into account several hypotheses that could explain this finding, we cannot exclude the possibility that this preliminary result could be related either to increasing circulation of the drifted strain in the epidemic peak or to potentially waning immunity in the months following vaccination. However, a bigger sample size is needed to investigate more fully the influenza VE during this atypical season. In addition, serological studies could help by investigating the seroprotection level in the studied population.

It is important to note that the population targeted for vaccination includes individuals vaccinated in successive influenza seasons, resulting in a more homogenous group in terms of potential confounding factors. In fact, in our study we found no differences in health-seeking behaviour or hospitalisation for chronic conditions in the previous year among cases and controls.

One limitation of our study was that the influenza vaccination coverage in the test-negative controls aged more than 64 years was higher than that in people of this age group in the GP and paediatricians' catchment area (70% vs 56%). That is why we cannot extrapolate our VE estimates based on a population attended by GPs to all elderly people [5]. Another limitation is related to possible selection bias since swabbing was

recommended for all older than 64 years old ILI patients and not for those targeted for vaccination.

This is the second season in which the cycEVA study has allowed early estimates of influenza VE in Spain to be obtained. In 2010/11, intraseasonal and end-season estimates were similar [4,25], supporting the feasibility of generating and disseminating preliminary influenza VE estimates while virus circulation is still ongoing. The results presented here provide important information that will help to guide national authorities and policymakers in their recommendations for influenza vaccination. It would be helpful to remind clinicians of the importance of antiviral treatment for patients with severe influenza, while more evidence is gathered to support reconsideration of the timing of the influenza vaccination campaign every season.

In conclusion, these preliminary results suggest a moderate protective effect of the seasonal 2011/12 vaccine in preventing medically attended laboratory-confirmed influenza in the target groups for vaccination, during a season characterised by a late epidemic and a limited match between vaccine and circulating influenza strains. However, finding a protective value of the vaccine among those targeted for vaccination reinforces the importance of official recommendations for annual influenza vaccination.

Acknowledgements

We are grateful to sentinel GPs, paediatricians and virologists participating in the cycEVA study, as well as to all professionals participating in the Spanish Influenza Surveillance System. We thank Isabel Pachón y Aurora Limia (Coordinating Centre for Health Alerts and Emergencies within the Spanish Ministry of Health and Social Policy) for the information provided on influenza vaccination. We also thank the EpiConcept team for their fruitful discussions and comments on the cycEVA study. This work was supported by the ECDC through the I-MOVE project and by the Carlos III Institute of Health (Influenza A(H1N1)pdm09 Programme (GR09/0017)).

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Fatal case of imported human rabies in Amadora, Portugal, August 2011

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Citation style for this article:
Santos A, Calé E, Dacheux L, Bourhy H, Gouveia J, Vasconcelos P. Fatal case of imported human rabies in Amadora, Portugal, August 2011. Euro Surveill. 2012;17(12):pii=20130. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20130

Article published on 22 March 2012

We report on a case of imported human rabies in Portugal, in July 2011 in a woman who presented initially complaining of back pain, without relating exposure to animal bites. She had travelled from Portugal to Bissau, Guinea-Bissau, in April where she had been bitten by a dog on 1 May. She was diagnosed with rabies on 26 July and died two weeks later in spite of being treated following the Milwaukee protocol.

Case report

On 19 July 2011, a 41-year-old woman, born in Guinea-Bissau and a resident of Amadora, Portugal, consulted the emergency department of the local hospital with lower back pain radiating to the left leg. She did not relate having been exposed to animal bites and was not asked about animal exposure or travel history. She was discharged with symptomatic therapy. As the hypothesis of rabies was not initially suspected she was not vaccinated. Five days later, on 24 July, she returned to the emergency department presenting new symptoms: anorexia, hydrophobia, aggressiveness and agitation. She was neurologically evaluated and diagnosed with an encephalitic syndrome and peripheral polyneuropathy, with the working diagnosis of rabies encephalitis. The same day, she was transferred to the intensive care unit (ICU) of the hospital Pulido Valente, Lisbon.

On 25 July, biological samples were taken (a skin biopsy, a cerebrospinal fluid (CSF) sample and three saliva samples) and sent to the World Health Organization (WHO) Collaborating Centre for Reference and Research on Rabies, Institut Pasteur, France, for diagnosis. Based on clinical symptoms, treatment following the Milwaukee protocol was initiated [1]. This protocol was applied for the first time in 2004, when a teenager survived clinical rabies caused by the bite of a bat, following supportive intensive care and the use of an anti-excitatory strategy that included general anaesthesia, antiviral drugs and neuroprotection, with amantadine, ketamine, midazolam and ribavirin [1]. An amended version of the protocol (V3.1) [2] was used to treat the patient described (amantadine, ketamine, midazolam, nimodipine and valproic acid).

One day later, on 26 July, the rabies diagnosis was confirmed by reverse transcription polymerase chain reaction, RT–PCR, [3] on the three saliva samples. The CSF and the skin biopsy remained negative. On 29 July, the typing results indicated that the causal virus was a lyssavirus of the rabies virus species belonging to lineage Africa 2 group B, which usually circulates in Senegal, Guinea-Bissau and Sierra Leone [4]. Despite treatment with an adapted version of the updated Milwaukee protocol including invasive mechanical ventilation and heavy sedation, the patient's condition progressively worsened and finally died 15 days after diagnosis.

Case history obtained through relatives, revealed that the patient had travelled to Bissau, capital of Guinea-Bissau on 22 April. In Bissau on 1 May, she was bitten by a dog in the lower left limb and the dog was shot on the same day, a common measure in a country where animal rabies is enzootic. No tests were carried out on the dog to confirm rabies. The patient went to the local health authorities of Bissau to report having been bitten by a dog and as vaccine was not available in the country she was not vaccinated. She returned to Portugal on 28 May without any symptoms and had not initiated any vaccination schedule. While in Portugal, she developed the first symptoms.

Public health measures

On 26 July, the local public health department in Amadora received information of the suspicion of a case of human rabies from the Hospital Pulido Valente in Lisbon. The health authority in Amadora notified the Directorate-General of Health in Lisbon and on the same day, interviewed the patient's family. It was possible to identify her contacts among relatives and health professionals. Risk assessments were carried out for those who might have been in contact with the case. Human infection usually occurs following

a transdermal bite or scratch by an infected animal. Transmission may also occur when infectious material, usually saliva, comes into direct contact with the victim's mucosa or with fresh skin wounds.

Six individuals were identified for treatment with post-exposure prophylaxis (PEP) which consisted of four intramuscular doses of rabies vaccine, 1 ml, with two doses on day 0, followed by one dose each on day seven and 21. Although scientific evidence for human-to-human transmission is limited to few cases worldwide [5,6], it was decided to also give PEP to the husband, considering the sexual intercourse during the communicability period. Furthermore, five health professionals from the Lisbon central hospital, who performed or helped with invasive procedures, were vaccinated following specific indications from the Directorate-General of Health. Fast identification of all the persons who had been in contact with the patient was done through efficient cooperation between the hospitals, local public health authorities and the Directorate-General of Health. All parties communicated with each other and supported the epidemiological investigation in a coordinated way in order to allow for rapid application of public health measures. The case was reported through the European Union Early Warning and Response System (EWRS) and the focal point of the World Health Organization International Health Regulations (IHR) in Guinea-Bissau was contacted.

New guidelines for epidemiological inquiries as well as for vaccination and prophylaxis were developed by the Portuguese Directorate-General of Health following the event.

Epidemiological background

Rabies is a viral zoonosis largely distributed worldwide. The natural reservoirs are mainly dogs (canine rabies represents 99% of the source of infection for humans [7]), foxes, raccoon dogs, skunks and bats. However, a large number of other mammals can be infected and can act as vectors. In Europe, the main epidemiologic cycle of rabies in sylvatic terrestrial non-flying animals is maintained by the red fox (*Vulpes vulpes*) and the raccoon dog (*Nyctereutes procyonoides*). Large vaccination campaigns of foxes were implemented in numerous western and central European countries. However, fox rabies is still present in the eastern and in some southern parts of Europe, such as Croatia, Serbia and Slovenia [8,9]. Bat rabies has also been diagnosed in numerous European countries, with reports of transmission to humans. There have been three confirmed deaths since 1985 [10]. Spill-over infections from bat rabies to terrestrial mammals [10] is still a threat, thereby maintaining its potential to infect humans.

The main risk of canine rabies resides in the translocation of unvaccinated animals originating from countries bordering the east and south of Europe [11,12]. From 2008 to 2011, at least three reports have described the importation of rabid dogs from Africa to Europe [13-15]. One of the reports concerned an infected dog imported from Morocco, identified in France, that travelled to Portugal and Spain and which may have infected susceptible dogs [14]. Between January 2000 and January 2009, there were 13 reports of cases of imported human rabies in Europe [9]. The 2010 European Centre for Disease Prevention and Control (ECDC) annual epidemiological report describes one case of human rabies in the European Union (EU), a woman in a rural area of Romania that had been bitten by a fox [16]. The annual average number of cases of human rabies in the EU has been limited to one in the last years. This single case would seem to confirm that trend [16].

Conclusion

Rabies is a zoonotic disease fatal in humans which can be prevented either through vaccination or if adequate measures are applied after exposure [17] Portugal is a country free of rabies since 1960 [18] and the probability of an autochthonous case is virtually inexistent. However, the possibility of imported cases, especially from the Portuguese-speaking African countries (mainly Angola and Guinea-Bissau where rabies is an epizootic) exists, mainly because of the influx of migrants to Portugal and to other parts of Europe [11,12]. This report, and a recent report about an imported rabid puppy [19], confirms the need for vigilance with regard to human and animal rabies.

The handling of the case described is an example of efficient coordination between the local public health authorities, the hospital, the Portuguese Directorate-General of Health and the collaboration with an international laboratory, the Institut Pasteur in Paris. There was constant and rapid exchange of information between these entities to confirm the case and to identify the exposed individuals. The case is another example of the failure of the Milwaukee protocol applied to rabid patients [20,21].

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Tick-borne encephalitis transmitted by unpasteurised cow milk in western Hungary, September to October 2011

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Citation style for this article:
Caini S, Szomor K, Ferenczi E, Székelyné Gáspár Á, Csohán Á, Krisztalovics K, Molnár Z, Horváth JK. Tick-borne encephalitis transmitted by unpasteurised cow milk in western Hungary, September to October 2011.
Euro Surveill. 2012;17(12):pii=20128. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20128

Article published on 22 March 2012

In October 2011, a cluster of four tick-borne encephalitis (TBE) cases was identified in Hungary. Initial investigations revealed a possible link with consumption of unpasteurised cow milk sold by a farmer without authorisation. We performed a cohort study including all regular customers of the farmer. Overall, eleven cases (seven confirmed and four suspected) were identified. Customers who had consumed the farmer's unpasteurised cow milk had more than a two-fold increased risk for being a TBE case, although not at statistically significant level.

Introduction

On 14 October 2011, the Department of Infectious Disease Epidemiology at the National Center of Epidemiology (NCE) in Budapest was alerted about a cluster of four hospitalised tick-borne encephalitis (TBE) cases that had occurred between 19 September and 1 October 2011, in the area surrounding K, a small town in western Hungary close to the Austrian border. All four patients had already been interviewed by local public health authorities when NCE was alerted: none of them could remember having recently been bitten by a tick, but all of them referred to having consumed unpasteurised cow milk during the incubation period, which had been purchased from a farmer who has ten dairy cows producing about 70 litres milk per day. The milk of this farmer was sold without being pasteurised and without authorisation, to regular customers from approximately 40 families residing in four villages in the countryside surrounding K. The farmer was forbidden to sell milk on 14 October 2011. On 18 October two epidemiologists from NCE went to K to help local public health staff with the epidemiological investigation.

The tick-borne encephalitis virus (TBEV) is an RNA virus belonging to the genus Flavivirus, family Flaviviridae. Three subtypes are described: European (the most common subtype in Europe), Siberian and Far Eastern. TBEV is transmitted by ticks, *Ixodes ricinus* being the most common vector in central Europe [1]. The virus can be transmitted by bites of infective ticks or, less frequently (but more successfully and with a shorter incubation period [2]), by consumption of unpasteurised milk from infected animals. Approximately two thirds of human TBE virus infections are asymptomatic. In clinical cases, TBE often has a biphasic course: after an incubation period of 7–14 days, infected people develop aspecific symptoms lasting approximately one week (first phase), followed, after a few days, by neurological symptoms (second phase) in approximately one third of those who experience first-phase symptoms [3]. The case fatality ratio is around 1–3% for the European and Siberian subtypes and 20% for the Far Eastern subtype [1]. Vaccine for the prevention of TBE is available. In Hungary, groups at risk such as forest workers, geologists and laboratory workers are advised to get vaccinated [4].

Two surveys were conducted in 2008 and 2011 respectively to collect information on incidence of TBE in the sixteen European countries where TBE is a notifiable disease [5,6]. Overall, 17,818 cases were reported from 2007 to 2009, 53% coming from Russia. The highest annual incidence rates (>10/100,000 population) were observed in Baltic countries and Slovenia. A few TBE outbreaks caused by consumption of non-pasteurised goat and sheep milk and goat cheese were previously reported from central and northern Europe, including Hungary [7-13].

In Hungary, TBE is notifiable by law since 1977. Overall, 686 cases of TBE were reported from 2001 to 2010. According to NCE data, annual incidence rates were between 0.5–0.8/100,000 inhabitants from 2001 to 2010. Males represented 70% of reported cases, and

the age group with the highest number of reported cases was the 40–49 year old for both sexes.

The highest TBE incidence rates were observed in the West Transdanubian region of the country (Figure), where the present outbreak took place. Usually, in-depth individual epidemiological investigations are performed only when a cluster of TBE cases in time and space is detected. In the last decade, two TBE outbreaks related to raw goat milk consumption were reported in 2007 and 2008, with respectively 25 and two individuals affected [7,14].

We aimed at investigating whether consumption of unpasteurised cow milk from the suspected farmer was associated with being a case.

Methods

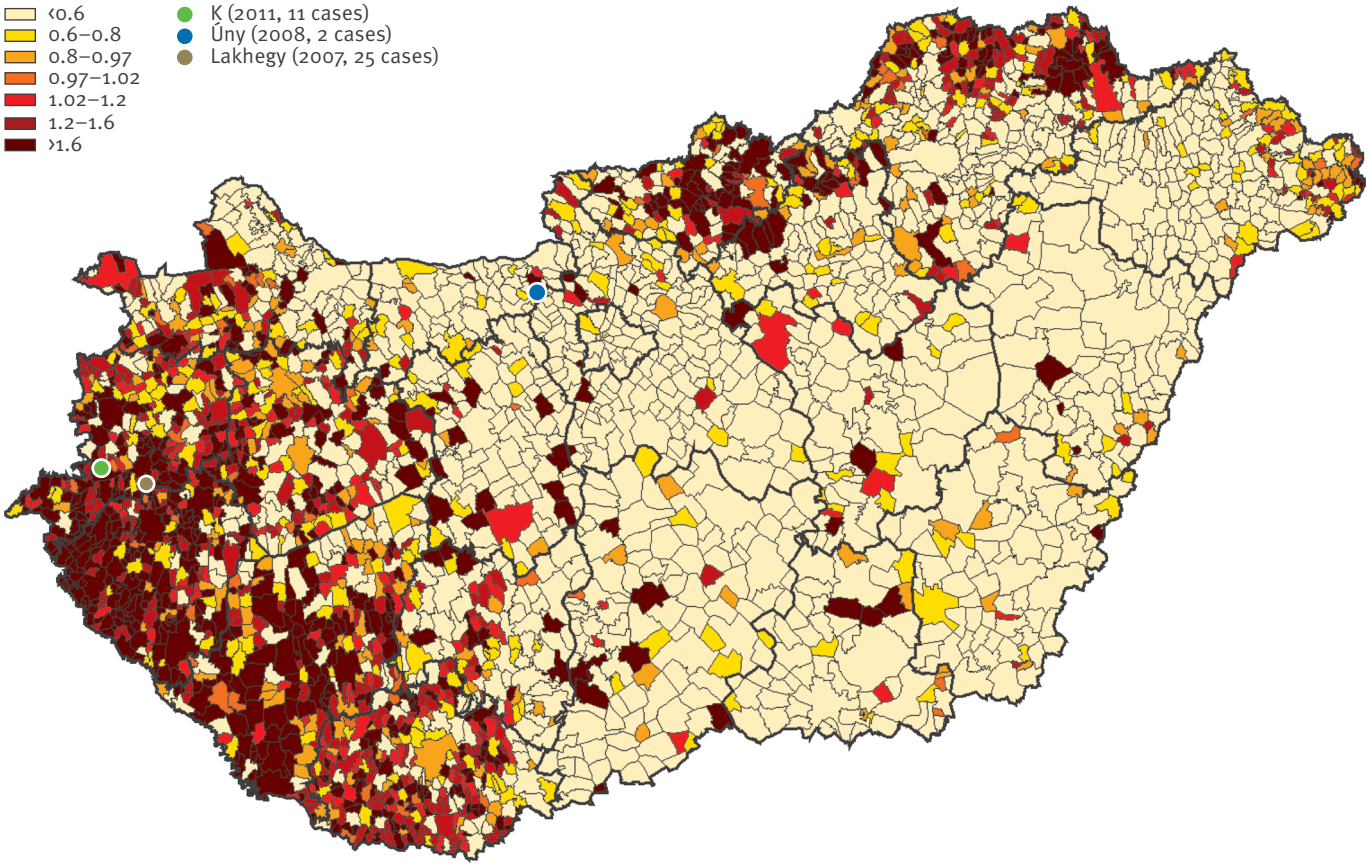
Considering that the first case was observed on 11 September 2011, that the selling of milk was discontinued on 14 October 2011, and that the incubation period of TBE is usually 7–14 days, the study period extended from 28 August to 28 October 2011. All the members of the families who bought milk from the suspected farmer during the study period were considered as a cohort.

On 17 and 18 October face-to-face interviews were conducted at the houses of all families, using a standardised questionnaire. Information was obtained on demographics (age and sex), symptoms of TBE (first and second phase) during the study period, date of onset and duration of symptoms, outcome of the disease, tick bites during the study period, vaccination status against TBE, weekly quantity of milk bought during the study period, and type (raw, heat-treated or both) of cow milk consumed.

The anti-TBEV serology tests were performed by indirect immunofluorescence assay for TBE virus-specific

Figure

Empirical Bayesian smoothed indirect standardised incidence ratios of tick-borne encephalitis, by municipality, Hungary, for 1998–2008 and location of outbreaks related to the consumption of unpasteurised milk between 2007 and 2011*



TBE: Tick-borne encephalitis.

A green dot indicates the TBE outbreak area reported in this study, which is related to the consumption of unpasteurised cow milk. A brown and a blue dot indicate respective locations of previous TBE outbreaks, which were related to consumption of raw goat milk.

Reproduced with permission from Zöldi V, National Center for Epidemiology, Hungary. [Zöldi V, Juhász A, Nagy C, Szilágyi A, Páldy A. Tick-borne encephalitis and Lyme borreliosis in Hungary – The epidemiological situation between 1998 and 2008. ESCAIDE, Poster Session, Lisbon, 11-13 November 2010.]*

IgM and IgG. Paired blood samples and/or cerebrospinal fluid (CSF) of patients with TBE clinical criteria were tested. Paired samples were tested in parallel on the same antigen slide. Specific slides with the first Hungarian TBEV isolate strain "Kem I" [15,16] infected VERO cells were prepared in house. A twofold dilution series was made of each serum sample with phosphate buffered saline (PBS) starting at 1:10 and was titrated to determine the antibody titre end points. CSF samples were tested without dilution. The testing protocol was as described earlier [7].

Criteria for laboratory diagnosis of TBE were the presence of TBE virus-specific immunoglobulin M (IgM) in CSF or in blood. TBE clinical criteria were defined as subfebrility (37.0–38.0 °C)/fever (>38.0 °C) and malaise/headache/dizziness, or encephalitis. Clinical samples for serology at NCE were obtained from patients who met at least one of the TBE clinical criteria and gave consent.

A confirmed case was a cohort member with disease onset between 28 August and 28 October 2011 including at least one TBE clinical criterion and one of the laboratory criteria. A suspected case was a cohort member with disease onset between 28 August and 28 October 2011 including at least one TBE clinical criterion and for whom a clinical sample for laboratory analysis was not available.

Exposure was defined as consumption of milk (only raw, only heat-treated, both raw and heat-treated) purchased from the suspected farmer during the study period.

Risk ratios (RRs) and risk differences (RDs) and their respective 95% confidence intervals (95%CI) were calculated to compare attack rate among consumers and non-consumers of milk (any milk or raw milk only) so as to investigate the possible association between consumption of unpasteurised cow milk and being a case.

Blood samples were taken from each of the farmer's 10 lactating cows on 17 October but proved to be not suitable for analysis. Milk samples were therefore taken from all 10 cows on 2 November 2011 and tested by polymerase chain reaction (PCR) for the TBE virus.

Results

The farmer declared to provide 41 families (112 people) with milk. One person did not wish to participate in the investigation, two people could not be contacted, and one person stated not having bought milk from the farmer in question. We also excluded from the cohort five people who were partly or fully vaccinated against TBE. Finally, 103 people (52 females, median age 46 years, range 1–96) from 36 families were included in the cohort.

Overall, eleven cases (seven females, median age 44 years, range 1–85) of TBE were reported (seven confirmed, including the four cases initially reported, and four suspected). One of the suspected cases, who was included in the cohort, had been hospitalised with clinical symptoms on TBE prior to NCE being alerted of the TBE cluster. This person had eventually died without having been tested for TBE virus. Of all cases (n=11), only the four initially reported cases suffered from encephalitis. The seven confirmed (altogether 11) TBE cases clustered in six (altogether seven) of the 36 families in the cohort.

The table shows results of the analysis. No confirmed cases and only one suspected case were observed among those who did not drink any milk, the risk difference being significantly higher than the null value for confirmed cases. Those who reported any/raw milk consumption from the suspected farmer had more than twice the risk of developing the disease compared to those who reported not having drunk any/raw milk, although statistical significance was not reached.

Milk samples taken from the cows tested negative for the TBE virus.

Table

Attack rates among tick-borne encephalitis cases by exposure to unpasteurised cow milk, risk ratios and differences, Hungary, September–October 2011

Inclusion criteria for cases	Exposure type	Exposed			Unexposed			Risk ratio (95% Confidence Interval)	Risk difference (95% Confidence Interval)	Percentage of cases explained by exposure
		Cases	Non-cases[a]	Attack rate	Cases	Non-cases[a]	Attack rate			
Confirmed (N=7)	Any milk[b]	7	78	8%	0	18	0%	- (-)	8.2% (2.4 to 14.1)	100%
Confirmed and suspected (N=11)	Any milk[b]	10	75	12%	1	17	6%	2.12 (0.29 to 15.52)	6.2% (-6.3 to 18.8)	91%
Confirmed (N=7)	Raw milk	5	47	10%	2	49	4%	2.45 (0.49 to 12.07)	5.7% (-3.9 to 15.3)	71%
Confirmed and suspected (N=11)	Raw milk	8	44	15%	3	48	6%	2.62 (0.73 to 9.31)	9.5% (-2.2 to 21.2)	73%

[a] The number of non-cases is obtained by subtracting the number of cases (N), as defined in the column "inclusion criteria for cases" from the total number of people in the cohort (n=103) and then subsequently considering how many are in either exposed or unexposed categories. When only confirmed cases are considered as cases, the rest of the cohort, including suspected cases, constitutes non-cases.

[b] Any milk includes raw milk and raw milk that has been heat-treated but not pasteurised.

Discussion

To our knowledge, this is the first report of a TBE outbreak supposedly transmitted by unpasteurised cow milk in the European Union (EU). Other reports were published about TBE outbreaks in the EU transmitted by goat [7-11,13] and sheep [12] milk. A TBE outbreak transmitted by cow milk [17] was previously described in eastern Russia (close to the border with North Korea) where the Siberian and Far Eastern subtypes of TBE virus are more common than the European subtype.

Our investigation presents some methodological limitations. First, the statistical power of our investigation was rather low (less than 0.30), despite that all but three members of the cohort were interviewed. Second, only symptomatic cohort members were tested, while it is known that two thirds of people infected with TBE are completely asymptomatic: some misclassification of case-status is therefore very likely to have occurred. If we assumed that the number of infected cases would be three times the number of symptomatic cases, and re-calculated RRs according to this assumption, the point estimates would not change but RRs for consuming raw milk would reach statistical significance: RR:2.45 (1.03–5.82) for confirmed cases and RR:2.62 (1.35–5.07) for confirmed and suspected cases.

Misclassification of exposure may also have occurred concerning heat-treatment of milk. If we assume that cases and non-cases were comparably unaware of correct procedures for boiling milk [18], the misclassification of exposure would be non-differential, and the RR reported would be biased towards one. If, however, the non-cases were more likely to report that they had boiled the milk when the boiling was not effective, this misclassification would be differential, and the RR calculated would be overestimated.

Milk samples taken from the cows tested negative for TBEV. This is not fully surprising considering that the milk samples were taken on 2 November, i.e. 15 days after the last (suspected) case was observed. Balogh et al [19] showed that experimentally infected goats can shed TBEV in milk for more than twenty days after infection, but no data exist about persistence of TBEV in milk of infected cows.

The potential for the spreading of infectious diseases by drinking unpasteurised cow milk is well known. Concerning TBE, the proportion of cases infected via unpasteurised milk has been estimated to be 0.9% in Czech Republic from 1997 to 2008 [9] and 9% in Slovakia [20]. Cisak et al found that more than 20% of goat and sheep milk samples and 11% of cow milk samples tested positive for TBEV in a survey in eastern Poland [21], an area with high incidence of TBE. Considering that cow milk is far more frequently consumed than goat and sheep milk, and that the habit of buying milk from small farmers (that may not fulfil all requirements for milk safety) is not rare, especially in the countryside, implication of consuming unpasteurised cow milk as cause of TBE outbreaks should not be overlooked.

TBE transmitted by unpasteurised milk could be effectively prevented by vaccinating people and/or dairy animals [19]; although it is not clear yet how long the immunity against TBEV persists in animals. However, many other infective agents (*Mycobacterium bovis*, *Brucella* spp., *Campylobacter* spp., *Streptococcus* spp., etc) may be transmitted by milk for which a vaccine is not available [1]. Therefore, public health services should primarily focus their efforts towards prohibiting the sale of milk by farmers without authorisation and informing the public about the risks associated with consumption of unpasteurised milk and the beneficial effects of boiling such milk before drinking or processing it.

Acknowledgments

Éva Stanitz, county chief medical officer, Vas County Government Office; Lászlo Szűcs, local chief medical officer, Vas County Government Office.

* Authors' correction

The title of the figure and the information regarding the source of the map were corrected on 31 July 2012 at the request of the authors.

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Letter to the editor: Rabid puppy-dog imported into the Netherlands from Morocco via Spain, February 2012

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Citation style for this article:
Santa-Olalla Peralta P, Mayoral Cortés JM, Sierra-Moros MJ. Letter to the editor: Rabid puppy-dog imported into the Netherlands from Morocco via Spain, February 2012.
Euro Surveill. 2012;17(12):pii=20123. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20123

Article published on 22 March 2012

To the editor: We read with interest the article by van Rijckevorsel et al. on a rabid puppy-dog imported into the Netherlands from Morocco via Spain, recently published in *Eurosurveillance* [1]. We would like to complete the information on this event with actions taken by the Spanish health authorities and lessons learnt.

On 16 February 2012, Thursday afternoon, the Coordinating Centre for Health Alerts and Emergencies at the Ministry of Health in Spain received a selective message via the Early Warning and Response System (EWRS) from the Dutch health authorities, communicating the laboratory confirmation of rabies in a puppy-dog from Morocco that had been imported into the Netherlands via Spain. The dog was transported by car from Morocco to Spain by a Dutch couple who stayed in Spain for a week before departure by plane to the Netherlands. Dutch authorities informed that a risk exposure had been identified in at least three persons living in Spain (Contacts 1, 2 and 3). These persons had already been informed by the Public Health Service Amsterdam with the advice to seek medical care for post-exposure prophylaxis.

Upon reception of this message, immediate public health action was initiated in Spain:

A request for more information such as the name of the hotels where the couple had stayed in Spain, dates, itinerary and contact details of the contacts living in Spain was made in order to complete contact tracing and start prophylaxis. Information on the couple's itinerary, hotels and restaurants visited, and on human and animal contacts of the dog was obtained from different sources the following day, after active request from the Spanish authorities.

Information available at that time was sent to the Spanish Alerts' Network (consisting of public health professionals at national and regional level and other sectors involved in detection and response) and an alert concerning this event was issued to the regional public health authorities who alerted their regional health services and started an active search for possible contacts at risk in hotels and places visited by the Dutch couple, once this information was available on the evening of 17 February. Health centres and veterinary services serving the area concerned were also contacted to make sure that no people seeking medical attention for dog bites or any incident with a dog had been reported. As a result of these actions, no further human or animal contacts were identified in addition to the first three human contacts identified by Dutch authorities.

Contact details of contacts living in Spain were at no time accessible for the Spanish authorities because of Dutch national laws which do not allow the disclosure of personal data. This delayed public health action in Spain and caused unnecessary difficulties. For instance, as instructed by phone by the Dutch authorities, Contacts 1 and 2 sought medical care on 16 February, before the Spanish authorities were informed of this event. This caused confusion in the healthcare centre as in mainland and insular Spain there has not been any rabies in terrestrial animals since 1975. Following current protocols, Contacts 1 and 2 were asked to provide a written proof of their exposure history, while adequate healthcare and follow-up were organised the same day. Post-exposure prophylaxis (first dose of vaccine) was given after they presented email documentation from the Dutch National Institute for Public Health and the Environment mentioning the laboratory confirmation of rabies in the puppy. Human rabies immunoglobulin was available on the morning of 17 February but both contacts failed to show and left the country that evening without informing Spanish health authorities.

Contact 3 could not be followed until they contacted Spanish health authorities several days later. Despite being informed of the exposure risk and offered

prophylaxis following current protocols, this contact refused to take it.

A summary of the control measures taken in Spain was posted on the EWRS site on 23 February 2012.

An internal evaluation of this event has shown the need to reinforce the appropriate control at customs and following of European Union (EU) legislation on non-commercial movement of pet animals [2]. We also think that the public should be made aware through travel advice of the risks and their responsibility when bringing back animals from abroad [1].

Lessons learnt also include difficulties in accessing personal information within the EU despite efforts made by the European commission and the EU Member States, as well as the need to respect official channels for communication with contacts living in another Member State. Public health activities to be carried out in a given country should be managed by the health authorities of that country who are responsible for risk management in their territory and know the current protocols and response mechanisms in place. The use of channels other that those established in each country can create dysfunction for all actors involved in the response, including a deficient attention to the exposed or affected population.

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Authors' reply: Rabid puppy-dog imported into the Netherlands from Morocco via Spain, February 2012

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Citation style for this article:
an Rijckevorsel GG. Authors' reply: Rabid puppy-dog imported into the Netherlands from Morocco via Spain, February 2012. Euro Surveill. 2012;17(12):pii=20125. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20125

Article published on 22 March 2012

To the editor: The additional information from the Spanish Health Authorities is much appreciated. In their letter the Spanish Health Authorities express their concerns about the informal channels used by the Amsterdam Public Health Service in tracing three persons living in Spain (Contacts 1, 2 and 3). In their opinion access to the personal details of these contacts was denied because of Dutch national laws prohibiting such disclosure of information. However, Dutch national laws do allow Public Health Services to reveal personal data to third parties, but only with the approval of the involved contact, or when contacts cannot otherwise be reached. Also, in case of direct health emergency this law can be overruled.

The Amsterdam Public Health Service regrets the confusion caused in this case by not using the official channels in the process of contact investigation. However, in this case the owners of the rabid dog had contacted their three personal friends before the official channels could be informed. Upon realising these friends were likely at risk (Category II and III exposure), the Amsterdam Public Health Service considered it right at that time to advise them persons to consult a doctor as soon as possible for post-exposure prophylaxis. Rabies is a devastating infectious disease which only can be prevented by timely post-exposure prophylaxis. Identifying contacts is therefore of utmost importance and needs immediate public health action. As described in the rapid communication, the Centre for Infectious Disease Control at the National Institute for Public Health and the Environment (CIb/RIVM) informed their Spanish counterparts at the earliest convenience with as much detailed information as was available at that time.

The lesson learnt from this case is that clear communication between all parties involved is needed for a successful response to public health threats which require instant actions.