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Q fever outbreak in the village of Noćaj, Srem county, Vojvodina province, Serbia, January to February 2012

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From 27 January to 10 February 2012, a total of 43 cases of Q fever were notified in the village of Noćaj, Srem county, Autonomous Province of Vojvodina, Republic of Serbia. Q fever was laboratory confirmed in 37 notified cases. Alhough, the outbreak is considered over, the outbreak investigation is still ongoing in order to identify aetiologic factors relevant for this outbreak.

On 27 January 2012 after 10 patients were hospitalised with atypical pneumonia, an outbreak of Q fever was discovered in Srem county, Vojvodina province, Serbia. Laboratory testing of some of the first patients for pathogens such as *Coxiella burnetii, Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, influenza A and B, parainfluenza, and respiratory syncytial virus had all resulted negative, except for *C. burnetii*.

Between 27 January and 10 February, 2012, 43 cases of Q fever were reported. The majority of patients (n=41) were residents of Noćaj, a village with 2,120 inhabitants located in the vicinity of the city of Sremska Mitovica (Srem county) near the border between Serbia and Bosnia and Herzegovina. The attack rate in this period was 2%.

Hereby we describe the preliminary results of the ongoing outbreak investigations started on 30 January 2012, by the Center for Disease Control and Prevention of the Institute of Public Health, Sremska Mitrovica. The investigation was assisted by the World Health Organization (WHO), Regional Office for Europe.

Epidemiological investigation

Specific notification criteria and case definitions adapted to the current situation were applied. A probable case of Q fever, according to the European Union criteria, which are used in Serbia [1], was not relevant in this investigation because the source of the current outbreak was not yet identified, and no epidemiological link could be established.

A 'clinical case' was defined as having acute fever and one or more of the following: rigors, severe retrobulbar headache, acute hepatitis, pneumonia, or elevated liver enzymes' levels with onset of illness between 20 January and 10 February, and no other likely cause for illness in a patient who either lived or visited Noćaj in the period from 1 to 20 January, 2012. The risk period for exposure was estimated considering an average incubation period of 20 days [2] and time distribution of cases.

A 'clinical case' who had not been serologically tested was defined as a possible case of Q fever.

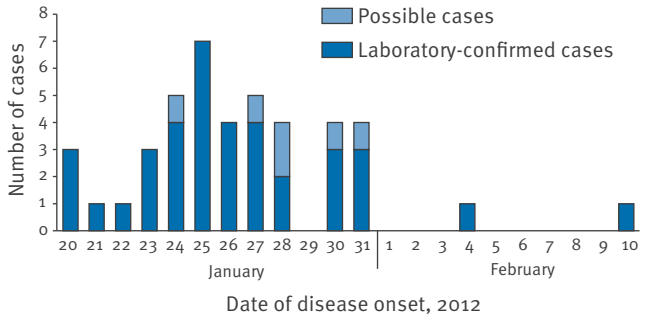
A laboratory-confirmed case of acute Q fever was defined as a 'clinical case' with serologic evidence of a positive IgM and/or IgG antibody result to phase II antigen *C. burnetii*, by enzyme-linked immunosorbent assay (ELISA). The results were interpreted in line with the manufacturer's guidance as follows: ‹9, negative; 9–11, equivocal; ›11, positive (ELISA, NovaLisa). Paired sera samples tested at least two weeks appart were taken for four patients for whom the result of the first sera tests were equivocal or negative (two sera samples were positive after the second test).

All sera samples were tested in the Reference Laboratory for Q fever, Institute of Public Health, Zrenjanin, Serbia. Of 43 notified cases, 37 were laboratory confirmed and the rest were classified as possible cases. All laboratory-confirmed cases were classified as acute Q fever cases. All cases of acute Q fever with known preconditions for chronic disease were reffered for laboratory follow-up in periods of three, six and twelve months after onset of illness, in order to detect

the development of chronic Q fever [3]. The majority of cases (n=41) reported illness onset between 20 January and 1 February 2012 (Figure).

Figure

Cases of Q fever by date of symptom onset, Noćaj, Sremska Mitrovica, Serbia, 20 January–10 February 2012 (n=43)



The male to female ratio of cases was 3.6:1. The mean age ± standard deviation was 35.65±14.3 years with the age distribution of cases ranging from 14 to 75 years. Data about the age and sex of cases rates are shown in Table 1.

Thirty-six of 43 registered cases were diagnosed with atypical pneumonia by chest X-ray. Sixteen of them were hospitalised. All patients had good outcomes without sequelae. The clinical features of Q fever in this outbreak are presented in Table 2.

During the epidemiological investigation in the village households, all present family members were interviewed about symptoms of Q fever and possible preconditions for chronic Q fever. Efforts were made to conduct laboratory testing, in order to detect recent Q fever infection in asymptomatic people, with known preconditions for chronic Q fever or at risk for complications, like pregnant women (n=10) and newborns (n=2), people with heart valvular diseases (n=1) or immunosupression (n=2). Also exposed healthcare workers (n=9) were tested. The testing was done by ELISA in order to detect a *C. burnetii* specific antibody response (IgG or IgM phase II), as previously described. By 26 March, eight additional cases of asymptomatic Q fever were discovered including three pregnant women, four exposed healthcare workers and one child with undefined symptoms. They were all refered to infectious disease specialists for review.

In exploratory interviews taken between 30 January and 16 February, 28 of 43 patients denied direct contact with livestock, although most of them own livestock in their households. In Serbia, reporting on aborted pregnancy in domestic animals is mandatory and requires a standard number of tests including tests for *C. burnetii*. However in the previous few months, local farmers and veterinary services in Noćaj had not observed such cases.

Only two patients in the current outbreak were not residents of Noćaj. They visited their relatives in Noćaj for a few hours each on different days (8 and 16 January). The time of the visits to Noćaj is compatibile with the incubation period and onset of disease in these particular patients. Overall 30 of 43 patients mentioned that they had visited a football tournament in the village school sport hall, from 4 to 7 January, 2012.

Environmental investigation and results

As the large number of cases in a small area was suggestive of a point source, smear samples were taken from heating ventilators, seats and the floor of the sport hall. DNA extraction from swabs was performed using QIAamp DNA Mini Kit (Qiagen, Germany) in the Veterinary Specialized Institute Kraljevo, Serbia. Two polymerase chain reaction (PCR) protocols were used for molecular detection of *C. burnetii*: The Real-Time PCR protocol published by Klee et al. [4] and the PCR protocol published by Berri et al. [5] The PCR assays for *C. burnetii* were all negative.

The Veterinary Scientific Institute, Novi Sad, conducted an epizootiologic investigation in the households of patients and their neighbours by order of the Republic Veterinary Inspectorate. Of 207 tested sheeps, goats and cattle, only one seropositive sheep in the village was found. Although seropositive, the vaginal swab sample of this seropositive sheep analysed by PCR was negative. Interestingly, this seropositive sheep was detected in a particular household in which two of seven human cases were registered during an outbreak of Q fever in Noćaj in 2009.

Epidemiological situation in Serbia

Q fever, a zoonosis distributed worldwide, was recognised as a specific disease in 1937 [6], and is caused by

Table 1

Cases of Q fever, by age group and sex, Noćaj, Sremska Mitovica, Serbia, 20 January–10 February 2012 (n=43)

Cases	Age groups in years							Total number of cases
	‹15	15–24	25–34	35–44	45–54	55–64	›65	
Number of male cases	1	7	12	5	7	2	0	34
Number of female cases	0	1	4	1	1	0	2	9
Total number of cases	**1**	**8**	**16**	**6**	**8**	**2**	**2**	**43**

C. burnetii. A wide range of animals serves as a natural reservoir for the pathogen [7]. Inhaling aerosols that are contaminated by *C. burnetii* is the most frequent route of transmission in large human outbreaks [8,9]. Q fever outbreaks are regulary reported thoughout Europe as well as in other parts of the world [10].

In Serbia, Q fever is a notifiable disease since 1966. Notification of Q fever is made on the basis of clinical diagnosis, epidemiological link and laboratory confirmation. During the last 14 years notification is based on European Union case-definition criteria in the absence of criteria adopted at the national level [1].

The Autonomous Province of Vojvodina, (Northern Province of Serbia) including Srem county is considered as an endemic region for Q fever. The latest seroepidemiological investigation of Q fever, which was conducted in 1985 and included 5,599 persons (representing 0.5% of the adult population of Vojvodina aged between 19 and 59 years), revealed a seroprevalence of *C. burnetii* antibodies of 9.3% [11]. In the period from 2002 to 2011, the incidence rate of Q fever in Vojvodina varied between 0.1–2.3 per 100,000 population. The incidence rate in Srem county varied between 0 and 2.1 per 100,000 population, with two outbreaks reported in 2009 [12] and 2011 (unpublished data). In the 2009 outbreak, seven human cases were notified in the village of Noćaj. Considering the high rate of mild cases and non-specific symptoms of Q fever [10], it is estimated that the actual incidences might be higher than presented above.

Table 2

Clinical features in cases of Q fever, Noćaj, Sremska Mitovica, Serbia, 20 January–10 February 2012 (n=43)

Clinical features	Number of cases
Fever (≥38°C)	35
Headache	27
Chills, shivers	22
Pneumonia	20
Muscle ache	19
Cough	13
Discomfort	4

Outbreak control measures

The Center for Disease Control and Prevention of the Institute of Public Health Sremska Mitrovica proposed to the management of the Noćaj elementary school to improve hygiene and proceed to a desinfection of the sport hall, and these measures were applied by order of the Provincial Sanitary Inspectorate.

General practitioners in the area and the nearest healthcare centre in Bosnia and Herzegovina were informed about the outbreak in order to make sure that any new arising cases of Q fever would be notified. All authorised institutions were informed, including the WHO, Regional Office for Europe following obligations included in the International Health Regulations (IHR) [13].

Efficient data sharing with the veterinary services was ensured in order to identify potential source(s) of the outbreak and to conduct veterinary control measures. Livestock trading, slaughter and use of unpasteurised milk and products from unpasteurised milk were temporarely prohibited in the investigated households until the serology results of tested animals were obtained.

Exclusion of blood donors (rather than screening) from the affected region was done. Health promotion campaigns to educate citizens on how to prevent possible Q fever infection took place in the village in the form of interviews, lectures and the delivering of information leaflets. Appropriate hygiene practices when dealing with livestock by-products of birth and manure and safe procedures for clothing and footwear were the key messages in the health education campaign for farmers. People at high risk for severe Q fever infection or complications were advised not to visit or stay in the livestock holding areas or barns.

In order to investigate potential factors for airborne spread of the bacteria, official meteorological data were analysed. Epidemiological reports were updated and published on the website of the Institute of Public Health of Sremska Mitrovica providing authoritative and accurate informations regarding the outbreak and reducing fear and panic in the village and area.

In order to prevent hospital acquired *C. burnetii* infections among healthcare workers and patients, the commission for the prevention of hospital infections in the general hospital Sremska Mitrovica proposed implementation of enhanced standard precautionary measures, such as monitoring compliance with hand hygiene, the use of gloves for contact with blood or body fluids, excretions and secretions, as well as anticipating the need for use of personal protective equipment (gowns, masks) according to the patient condition and type of procedure.

Discussion and conclusions

Considering the unusual high rate of hospitalisations and atypical pneumonia in this outbreak, we can assume that the number of cases is far higher than reported. The predominance of male sex among patients is not surprising, because the infection may be asymptomatic in 60% of Q fever infections, especially among women and children aged 15 years and younger [14-16].

Although a single animal source can cause many human Q fever cases [17], compared to 2009, the larger geographic area in which cases occurred in 2012 may indicate a multiple sources or possible airborne spread of *C. burnetii*. The low annual number of cases

of Q fever in Noćaj registered during past few decades was due to direct contact with animal placenta and/or birth products. The sudden and unusual acute presentation of the large outbreak in the current situation, required the consideration of other routes of Q fever infection. Although many cases in the village of Noćaj had attended the same football tournament in a school sport hall, the environmental investigation yielded negative results. Moreover, there were no registered cases of Q fever among residents of other villages who attended the tournament, nor among school children/staff where the tournament took place, which argues against the school sporthall as being the source of the outbreak. Until now, no common exposure has been identified among patients who did not attend the football tournament.

The data obtained from the epidemiological investigation were not indicative of a foodborne route of infection. The presumable route of infection in this outbreak is airborne by inhalation of contaminated dust and aerosol in the period around the orthodox Christmas. During January the weather in Noćaj was unusually dry and windy so the conditions to transmit *C. burnetii* were present. The heavy snowfall during February possibly reduced the further spread of this outbreak and limited its duration. We cannot rule out other possible causes via direct contact with livestock or by other possible exposures. Epidemiological investigation of infection sources and routes of transmission is ongoing. With this report, we would like to inform of this outbreak and raise awareness in neighbouring countries.

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Early estimates of seasonal influenza vaccine effectiveness in Europe among target groups for vaccination: results from the I-MOVE multicentre case–control study, 2011/12

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To provide an early estimate of 2011/12 influenza vaccine effectiveness (VE), we conducted a multicentre case–control study based on seven sentinel surveillance networks. We included influenza-like illness cases up to week 7/2012 from the vaccination target groups, swabbed less than eight days after symptom onset. Laboratory-confirmed influenza A(H3) cases were compared to negative controls. Adjusted VE was 43% (95% confidence interval: -0.4 to 67.7), suggesting low to moderate VE against influenza A(H3) in the early 2011/12 season.

Introduction

In the context of the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) Network we estimated the effectiveness of the 2011/12 trivalent vaccine against medically attended influenza-like illness (ILI) that was laboratory-confirmed as influenza. We undertook a multicentre case–control study based on the European Influenza Sentinel Practitioner Surveillance Networks (EISN) [1] from eight study sites (France, Hungary, Ireland, Italy, Poland, Portugal, Romania and Spain).

Data were collected from week 48/2011 to week 7/2012. During these 12 weeks of data collection, 867 (92.7%) of 935 laboratory-confirmed influenza cases recruited in the study were identified as influenza A(H3). This finding was consistent with data from the Community Network of Reference Laboratories (CNRL) for Human Influenza in Europe: of the 11,159 viruses detected from week 40/2011 to week 7/2012, 95.9% were influenza type A, and of 6,238 influenza A viruses subtyped, 97.5% were influenza A(H3) [2].

We provide early season estimates of the effectiveness of the 2011/12 vaccine against influenza A(H3) virus among those subpopulations identified as target groups for vaccination in the respective countries (Table 1) [3-10].

Methods

The study population consisted of non-institutionalised patients of all ages (over the age of 17 years in Hungary) consulting a participating practitioner for ILI and having a naso-pharyngeal swab taken less than eight days after symptom onset. Recruitment of ILI patients was based on exhaustive (Romania), systematic (Hungary, Ireland, Italy, Poland, Portugal, Spain) or quota sampling (France) [11]. The European Union case definition for ILI was used: sudden onset of symptoms, 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) [12]. A case of confirmed influenza A(H3) was an ILI patient who was swabbed and tested positive for influenza A(H3) virus using RT- PCR or culture. Controls were ILI patients who tested negative for any influenza virus.

Individuals were considered vaccinated if they had received a dose of the 2011/12 seasonal vaccine more than 14 days before the date of onset of ILI symptoms, and unvaccinated if they had received no vaccine or the vaccine was given less than 15 days before the onset of ILI symptoms. The variables collected during this season were the same as in 2010/11 [13], except for pandemic vaccination (not collected in 2011/12) and smoking (not collected in France). In each country we included ILI patients who presented to the practitioner up to the end of week 7/2012 who belonged to a target group for vaccination, with onset of symptoms more than 14 days after the start of national or regional influenza vaccination campaigns. For each study site, we excluded controls with symptom onset in the weeks before symptom onset of the first influenza A(H3) case, as well as cases infected with any non-A(H3) influenza virus.

We conducted a complete case analysis excluding individuals with missing values. We estimated the pooled

Table 1

Target groups for influenza vaccination in eight European Union countries, influenza season 2011/12

Country	Target groups for vaccination
France	• People aged 65 years and older • >6 months with chronic conditions (chronic respiratory disease, chronic respiratory failure, bronchopulmonary dysplasia, cystic fibrosis, chronic cardiac failure, cardiovascular disease, diabetes type 1 and type 2, severe neurological and muscular disease, chronic renal disease, body mass index >30) • Pregnant women in second and third trimester • Residents of long-term care facilities • Healthcare workers • Carers in direct contact with at-risk patients • Household contacts of at-risk children under the age of 6 months • Personnel working on cruise ships or planes, and tour guides
Hungary	• People aged 65 years and older • >6 months with chronic conditions (respiratory illness, body mass index ≥35, neuromuscular disease, cardiovascular disease except well treated hypertension, congenital or acquired immundeficiency including HIV infection and cancer,chronic hepatic or renal disease, chronic metabolic disease including diabetes) • Pregnant women or women planning to be pregnant during the influenza season • Healthcare and social workers
Ireland	• People aged 65 years and older • >6 months with chronic conditions (chronic respiratory disease, chronic heart disease, neurological disease, diabetes mellitus, liver disease, neurological disease including sclerosis, hereditary and degenerative disorders of the central nervous system, body mass index ≥40, immunosuppression due to disease or treatment including those with missing or non-functioning spleen) • Pregnant women (any stage and up to 6 weeks post partum) • Children with any condition that can compromise respiratory function, especially those attending special schools/day centres • Children and teenagers on long-term aspirin therapy (risk of Reyes syndrome) • Residents of nursing homes and other long-stay institutions • Carers in direct contact with at-risk patients • People in close, regular contact with pigs, poultry or water fowl • Healthcare workers
Italy	• People aged 65 years and older • >6 months with chronic conditions (chronic respiratory disease, chronic cardiovascular disease, neurological disease, diabetes mellitus and metabolic diseases including obesity with body mass index >30, liver disease, renal disease, immunosuppression and HIV infection, chronic inflammatory diseases, tumours, pathologies of the hematopoyetic organs, pathologies for which an important chirurgical intervention is planned, pathologies producing an increased risk of respiratory aspirations • Pregnant women in second and third pregnancy trimester • People working in essential public services • People working with animals that could be infected with influenza • Residents of nursing homes and long-term care facilities • Household contacts of at-risk persons • Healthcare workers • Children with long-term salicylate therapy
Poland	• People aged 55 years and older • > 6 months with chronic condition (asthma, diabetes, cardiovascular or respiratory disease, renal failure, hepatic disease, neurological disease, congenital or acquired immundeficiency, organ transplantion, body mass index ≥40) • Healthcare, school, trade and transport workers and other staff exposed to large numbers of people • Healthy children between 6 months and 18 years of age
Portugal	• People aged 65 years and older (but also recommended to those over the age of 60 years) • >6 months with chronic conditions (chronic respiratory disease, cardiovascular disease, metabolic disorders, renal or hepatic disease, congenital or acquired immunodeficiency, chronic neurological or neuromuscular disorders, any other condition impairing immunity or respiratory function, body mass index ≥ 30) • Pregnant women in second trimester • Household contacts and carers of children under the age of 6 months with high risk of developing complications • Health professionals, care givers in nursing homes and domiciliary service
Romania	• People aged 65 years and older • >6 months with chronic conditions (respiratory, cardiovascular, renal or hepatic diseases, diabetes, metabolic disorders, HIV infection, obesity • Pregnant women • Persons institutionalised for social care • Healthcare workers
Spain	• People aged 59 years and older or 64 years and older, depending on the region • >6 months with chronic conditions (diabetes, cardiovascular, lung, kidney or hepatic diseases, immunodeficiency, body mass index ≥40) • Pregnant women • Children <15 years under salicylate therapy • Healthcare workers, people in contact with high-risk groups, essential civil servants, people in contact with birds

HIV: human immunodeficiency virus.

seasonal influenza vaccine effectiveness (VE) as 1 minus the odds ratio (OR) expressed as a percentage, using a one-stage method with the study site as fixed effect in the model.

To estimate adjusted VE, we used logistic regression models including the following potential confounding factors: age groups (10-year age bands), sex, week of symptom onset, chronic disease (at least one), hospitalisations associated with a chronic disease in the last 12 months, and number of visits to a general practitioner or paediatrician in the last 12 months.

Results

Among the 1,056 practitioners who agreed to participate, 528 (50%) recruited at least one ILI case (Table 2).

Of the 2,090 ILI cases recruited, 575 belonged to a target group for vaccination. After excluding the weeks before symptom onset of the first influenza A(H3) case at each of the study sites and 10 cases positive for other influenza viruses, we included 208 influenza A(H3) cases and 330 influenza-negative controls (Figure). Poland is not included in this preliminary analysis as no influenza A(H3) case was detected.

The first study site to recruit an influenza A(H3) case in the target group for vaccination was Italy (week 48/2011), and the last sites were France, Romania and Spain (week 52/2011) (Table 2). The median number of weeks during which patients were recruited for the preliminary analysis was nine, ranging from six in France to 12 in Italy (Table 2).

Differences in the characteristics of influenza A(H3) cases and controls are presented in Table 3.

Among 533 individuals for whom vaccination status was available, 179 (33.5%) were vaccinated. The median time since vaccination was 105 and 74 days for cases and controls, respectively (p=0.031).

The complete case analysis was done for 530 individuals after excluding those with missing information on 2011/12 seasonal vaccination (n=5), on hospitalisations for chronic disease in the previous year (n=2) and on practitioners' visits in the previous year (n=1). The crude VE against influenza A(H3) was 42.9 (95% confidence interval (CI): 10.3 to 63.6) and the adjusted 43% (95% CI: -0.4 to 67.7) (Table 4).

Discussion

Our pooled early estimates suggest that the point estimate of the of the 2011/12 influenza vaccine against influenza A(H3) in the target group for vaccination was below 50%. These results are consistent with the VE against influenza A(H3) estimated in Australia for the season 2011 (58%, 95% CI: -53 to 89) [14] and with the Spanish early estimates of the 2011/12 VE against influenza A(H3) among target group for vaccination (54%, 95% CI: 1 to 79) [15].

Table 2

Participating practitioners and recruited influenza-like illness patients, by A(H3) influenza case-control status, vaccination status and study site, multicentre case-control study, study sites in eight European Union countries, week 48/2011–week 7/2012

Study site	Number of practitioners participating in the study	Number of practitioners recruiting at least one ILI patient[a]	Number of ILI patientsa recruited by practitioners	Inclusion period for the preliminary analysis (ISO weeks)[b]	Number of included ILI patients positive for influenza A(H3) and with known vaccination status[c]		Number of included ILI patients negative for any influenza and with known vaccination status[c]	
					Total	Vaccinated	**Total**	Vaccinated
France	499	169	325	Week 52/2011–week 6/2012	**4**	1	**24**	12
Hungary	94	63	354	Week 49/2011–week 7/2012	**2**	0	**112**	41
Ireland	28	11	60	Week 50/2011–week 7/ 2012	**5**	4	**3**	3
Italy	10	10	143	Week 48/2011–week 7/2012	**18**	6	**33**	15
Poland	35	15	45	Not included in preliminary analysis (no influenza A(H3) cases)	**0**			
Portugal	59	30	149	Week 51/2011–week 7/2012	**23**	5	**47**	24
Romania	100	56	128	Week 52/2011–week 7/2012	**18**	1	**31**	6
Spain	231	174	886	Week 52/2011–week 7/2012	**136**	37	**77**	24
Total	**1,056**	**528**	**2,090**		**206**	**54**	**327**	**125**

ILI: influenza-like illness; ISO: International Organization for Standardization.

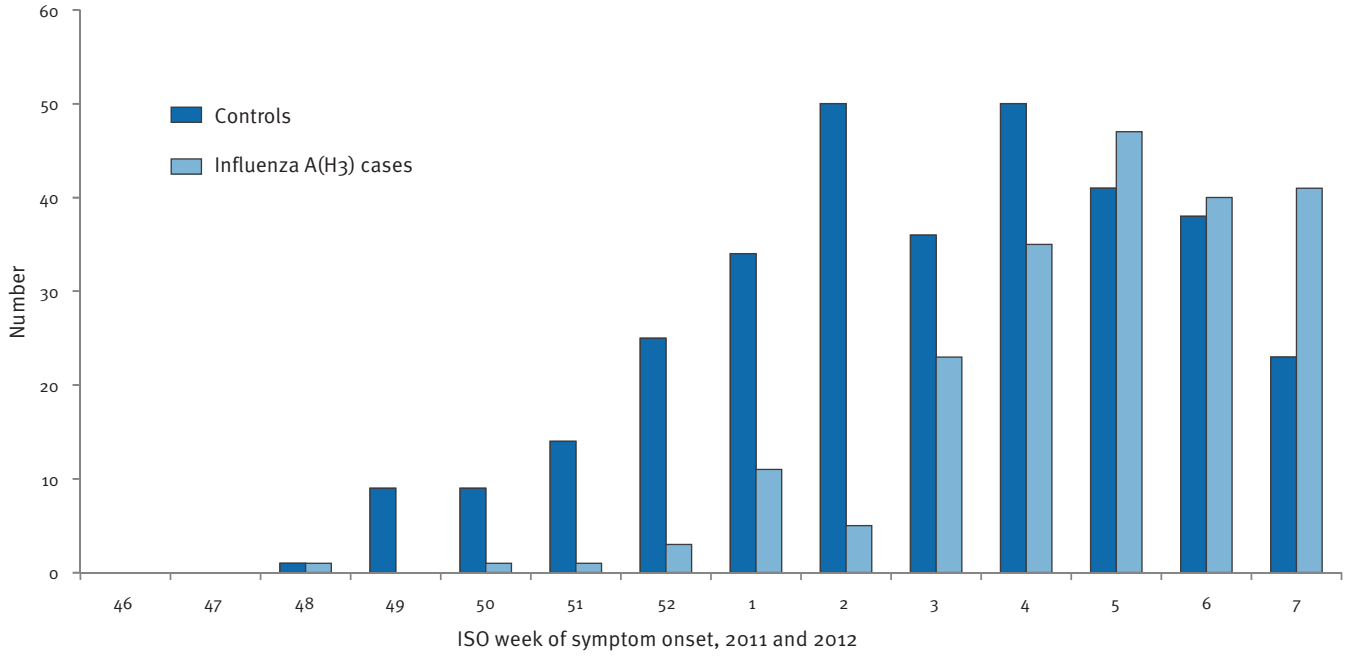
[a] ILI patients meeting the European Union case definition, swabbed less than eight days after onset of symptoms within the study period.

[b] From 15 days after the start of the vaccination campaign to week 7/2012; we excluded controls with an onset of symptoms in the weeks before the first influenza A(H3) case in the study site.

[c] ILI patients in a vaccination target group included in the study, after excluding those with missing information on laboratory results, vaccination status or date of vaccination.

Figure

Influenza A(H3) cases (n=208) and influenza-negative controls (n=330) in vaccination target groups recruited at study sites in seven European Union countries, by week of symptom onset, week 48/2011–week 7/2012



International Organization for Standardization (ISO) definition of a week.

The late start of the 2011/12 season in Europe [2] and the low influenza incidence in some of the eight countries participating in the multicentre case–control season limited the sample size for this preliminary analysis. By week 7/2012, four of the eight countries participating in the study had not reached the peak of the influenza season.

We included ILI patients swabbed less than eight days after symptom onset. Due to the small sample size we did not assess potential misclassification (false influenza A(H3)-negatives because of late swabbing) by restricting the analysis to those swabbed less than four days after ILI onset. However, only 12% of the ILI patients included in this preliminary analysis were swabbed more than three days after onset of ILI symptoms (Table 2). This will be addressed in the final analysis.

There were important differences between target groups for vaccination and non-target groups (data not shown). The vaccine coverage was 2.8% in the non-target groups compared to 33.8% in the target groups and the median age was 26 years and 56 years respectively. In this preliminary analysis our results are restricted to the population for which the vaccine is recommended. We collected information on the main potential confounding factors described in the literature [16]. The crude and adjusted VE were similar, suggesting that within this subpopulation and using a specific laboratory-confirmed outcome, the presence of known confounding was minimised.

The low to moderate VE we observed may be explained by a limited match identified between the circulating influenza A(H3) virus strains and the vaccine strain [2]. In February 2012, the vaccine strain selection committee at the World Health Organization (WHO) concluded that there was evidence of increasing antigenic and genetic drift in circulating influenza A(H3N2) and consequently recommended to include a different influenza A(H3) vaccine strain in the 2012/13 seasonal vaccine [17].

In the 2011/12 season, the time lag between the beginning of the vaccination campaigns and the start of the influenza season was longer than in previous seasons. In our preliminary analysis, the delay from vaccination to onset of symptoms was longer in cases than in controls. This may suggest that waning immunity has contributed to the moderate VE observed. However, with the sample available for this preliminary analysis, we could not verify this hypothesis.

Our preliminary estimates suggest that, among the target groups for vaccination, the effectiveness of the 2011/12 influenza vaccine is low to moderate against medically-attended ILI confirmed as influenza A(H3). At the end of the season, a larger sample size per study site may allow us to estimate also the VE against other influenza viruses, by age group, and to further explore hypotheses on the reasons for the low VE observed early in the season.

Table 3

Characteristics of A(H3) influenza cases (n=208) and test-negative controls (n=330) in vaccination target groups included from study sites in seven European Union countries, week 48/2011–week 7/2012

Characteristic	Number of influenza cases/ total n (%)[a]	Number of test-negative controls/total n (%)[a]	P value
Median age	56.0	56.0	1.000[b]
Age group (years)			
0-4 5-14 15-64 ≥65	6/208 (2.9) 17/208 (8.2) 115/208 (55.3) 70/208 (33.7)	13/330 (4.0) 10/330 (3.2) 201/330 (61.0) 106/330 (32.1)	0.050[c]
Females	117/208 (56.3)	208/330 (53.6)	0.124[c]
Symptoms			
Fever Malaise Headache Myalgia	198/206 (96.1) 194/202 (96.0) 179/207 (86.5) 185/207 (89.4)	293/320 (89.1.7) 277/304 (91.1) 243/327 (74.3) 258/327 (78.9)	0.003[c] 0.033[c] 0.001[c] 0.002[c]
Days between onset of symptoms and swabbing			
0 1 2 3 ≥4	8/208 (3.9) 74/208 (35.6) 63/208 (30.3) 44/208 (21.2) 19/208 (9.1)	21/330 (6.4) 113/330 (34.2) 100/330 (30.3) 48/330 (14.6) 48/330 (14.6)	0.101[c]
Seasonal influenza vaccination[d], 2011/12	54/206 (26.2)	125/327 (38.2)	0.005[c]
Seasonal influenza vaccination, 2010/11	50/206 (24.3)	126/323 (39.0)	<0.001[c]
Obese	21/207 (10.1)	57/330 (17.3)	0.024[c]
Heart diseases	36/208 (17.3)	107/330 (32.4)	<0.001[c]
At least one chronic disease	121/208 (58.2)	254/330 (77.0)	<0.001[c]
Smoker			
Current Former Never	30/202 (14.9) 22/202 (10.9) 150/202 (74.3)	49/302(16.2) 53/302(17.5) 200/302(66.2)	0.087[c]
Median number of practitioners' visits in the previous 12 months	4	5	0.031[b]
Any hospitalisation in the previous 12 months for chronic diseases	9/208 (4.3)	23/327 (7.0)	0.262[c]
Median number of days from vaccination[d] to onset of ILI symptoms	105	74	<0.001[b]

ILI: influenza-like illness.

[a] Unless otherwise indicated.

[b] Non-parametric test of the median.

[c] Two-sided Fisher's exact test.

[d] Vaccination more than 14 days before onset of ILI symptoms.

Table 4

Pooled crude (n=530) and adjusted (n=521) 2011/12 seasonal influenza vaccine effectiveness against laboratory-confirmed A(H3) influenza in target groups for vaccination at study sites in seven European Union countries, week 48/2011–week 7/2012

Crude versus adjusted	Cases/controls	Vaccinated cases/controls	Vaccine effectiveness (%)	95% confidence intervals
Crude[a]	206/324	54/123	42.9	10.3 to 63.6
Adjusted model [b, c]			43.0	-0.4 to 67.7

[a] Study site included in the model as fixed effect.

[b] Model adjusted for presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, age group, practitioners' visits in the previous 12 months (0-1, 2-4 and ≥5 visits) and week of symptom onset.

[c] Onset week 49 dropped due to no cases (nine records dropped).

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Health professions and risk of sporadic Creutzfeldt–Jakob disease, 1965 to 2010

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In 2009, a pathologist with sporadic Creutzfeldt–Jakob Disease (sCJD) was reported to the Spanish registry. This case prompted a request for information on health-related occupation in sCJD cases from countries participating in the European Creutzfeldt Jakob Disease Surveillance network (EuroCJD). Responses from registries in 21 countries revealed that of 8,321 registered cases, 65 physicians or dentists, two of whom were pathologists, and another 137 healthcare workers had been identified with sCJD. Five countries reported 15 physicians and 68 other health professionals among 2,968 controls or non-cases, suggesting no relative excess of sCJD among healthcare professionals. A literature review revealed: (i) 12 case or small case-series reports of 66 health professionals with sCJD, and (ii) five analytical studies on health-related occupation and sCJD, where statistically significant findings were solely observed for persons working at physicians' offices (odds ratio: 4.6 (95 CI: 1.2–17.6)). We conclude that a wide spectrum of medical specialities and health professions are represented in sCJD cases and that the data analysed do not support any overall increased occupational risk for health professionals. Nevertheless, there may be a specific risk in some professions associated with direct contact with high human-infectivity tissue.

Introduction

Creutzfeldt–Jakob disease (CJD) is a fatal neurodegenerative disease characterised by deposition of a pathological isoform of the normal cellular prion protein (PrP^C) [1]. The annual CJD incidence worldwide is 1–2 per million population [2]. CJD exists in various forms: genetic, caused by mutations in the *PRNP* gene encoding PrP^C, acquired (variant and iatrogenic) and sporadic. Most cases have sporadic CJD (sCJD) – the cause of which is unknown. Occupational risk related to sCJD has been assessed in several case–control studies as a secondary study objective, with inconsistent results [3-7] and there have been occasional reports of health professionals with sCJD [8-12].

Occupation has not been included as a variable in all CJD surveillance protocols [13]. Nonetheless, there is concern about potential occupational excess risk of sCJD among health professions, as shown by a recent study on guidelines in European Union (EU) Member States and Norway for the prevention of CJD transmission in medical settings. This study showed that 12 of the 17 contributing countries had specific recommendations targeted at minimising occupational exposure;

eight of the 12 had systems for reporting or registering work-related incidents at hospitals or laboratories [14].

In March 2009, a CJD case was reported to the Spanish CJD registry, who was classified as having sporadic CJD. As the patient was an experienced general pathologist and neuropathologist, it was speculated that the disease might have been a result of the person's professional activities. The event was commented on in medical, scientific and mass media in Spain and elsewhere, e.g. [15]. The patient died after a four-month disease course, characterised mainly by cognitive decline, ataxia and myoclonus. The disease prion protein subtype, i.e. strain, was confirmed histochemically and biochemically as MM1, the most common subtype [2]. Risk factors for developing CJD, including blood transfusion, iatrogenic exposure (e.g. to dura mater, cadaveric pituitary-derived growth hormone) and mutations in the *PRNP* gene, were not identified. Assessment of the patient's routine hospital work indicated that the patient had had a history of minor injuries during post-mortem examinations (personal communication, E. García-Albea, April 2009).

Box

Search terms used in first step of two literature searches on sporadic Creutzfeldt–Jakob disease (sCJD) in health professionals and analytical studies on occupational risk of sCJD for health professions and selection criteria used in a second step, reported 1 January 1989–1 October 2011

MEDLINE
The search strategy was based on the following medical subject headings (MeSH) terms:

- prion diseases/prions/Creutzfeldt-Jakob syndrome; and
- health occupations/allied health occupations/ occupational groups/occupations/occupational dentistry/case control studies.

Embase
The search strategy was based on the following Emtree thesaurus terms:

- prion/prion disease/prion protein/Creutzfeldt Jakob disease/ Creutzfeldt Jakob disease agent; and
- occupation/occupation and occupation-related phenomena/ medical profession/nursing as a profession/nursing career/paramedical profession/professional development/ occupational accident/occupation and occupation-related phenomena/occupational accident/occupational disease/ occupational exposure/occupational hazard/occupational health/occupational health nursing/occupational health service/occupational medicine/occupational physician/ occupational safety/occupational therapist.

Selection criteria

Inclusion
Either specific reference to the subject (Creutzfeldt–Jakob disease and health profession) or analytical study design (either case–control or cohort), regardless of the study's stated objective.

Exclusion
Identification of the document as a letter or review, news, comment, congress abstract, when reference to health professions was not explicitly made.

Following notification of this patient, the Spanish registry circulated a request for information to each national surveillance team participating in the European Creutzfeldt Jakob Disease Surveillance Network (EuroCJD), which dates back to 1993 and currently encompasses 25 collaborating centres in EU Member States and European Free Trade Association (EFTA) countries and a further eight in countries around the world, including Australia, Canada and Japan [16]. These centres provide data from national registries either through the EuroCJD website or, as with Japanese data, at regular network meetings. The request asked for the following: (i) information on the diagnosis (year of birth and death, sex and place of residence) of reported cases of sporadic CJD among active or retired pathologists from 1996 onwards; and (ii) comments based on personal experience of occupational risk and CJD among health professionals, including technicians working at pathology laboratories.

There has been limited systematic research targeted at identifying occupational risk factors for sCJD in healthcare settings. This paper reports on the data supplied to the Spanish CJD registry in response to the request, and on the results of two literature reviews of sCJD – one on case reports involving health professionals and the other on epidemiologically assessed healthcare-related occupational risk of sCJD.

Methods

Individualised occupational data from national CJD surveillance teams

The Spanish CJD registry obtained answers in English to at least one of the requests for information from 21 national surveillance teams. The amount of information provided varied: in general, only data that had already been registered was reported; with regard to occupational history in CJD – recorded by profession or activity branch – several countries provided information on people in whom CJD had been excluded or on controls.

The data received were divided into two groups, for further analysis – one describing health professionals who were sCJD cases and the other describing health professionals among controls or non-cases. We did not attempt a formal epidemiological assessment of healthcare-related occupational risk of sCJD based on this information, for instance using a case–control design.

Case reports of sCJD among health professionals

Countries with available registry data on cases' occupations sent individualised data on physicians with neuropathologically confirmed or probable sCJD or other types of CJD [17,18]. Some countries provided such data on other health professions. In the few instances in which occupation as a pathologist was identified, professional experience or job duration at a laboratory or department was specified. The results were tabulated, using the original definitions from the countries'

reports. No standard occupational classification was used for grouping response results and each case was assigned to one occupational category. Frequently, the occupational categories corresponded to a combination of professional profiles, e.g. specialities and work types (clinical, administrative, laboratory, etc.). In such cases, the category most likely to involve direct contact with human tissue or patients was selected.

Healthcare-related occupations among controls and non-cases

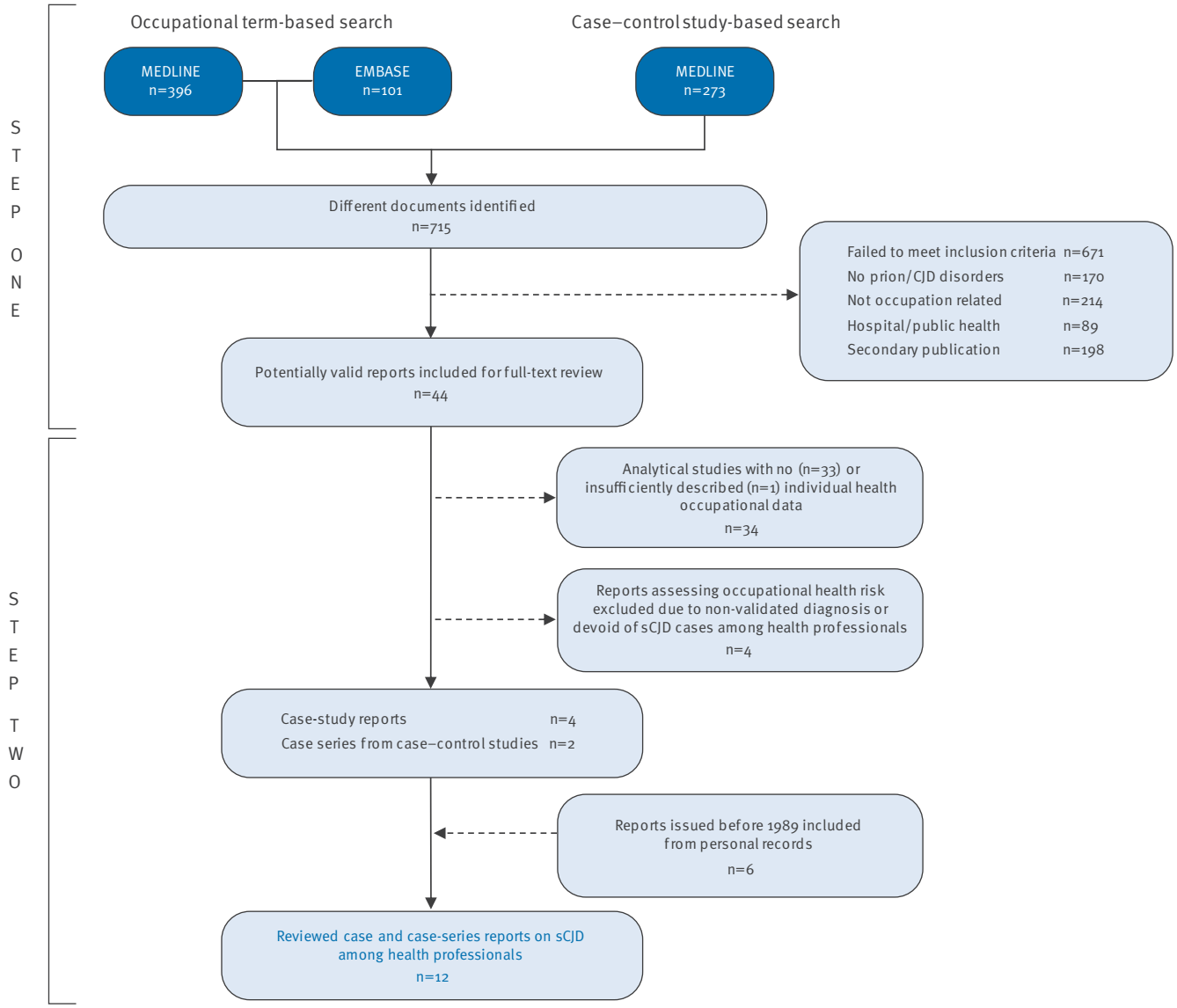
Some CJD surveillance teams with a sufficient sample size provided data on occupation of people with suspected sCJD who were finally classified as not having CJD (non-cases) and also of those in control groups. Five EuroCJD countries with large populations – Germany, Italy, Japan, Spain and the United Kingdom (UK) – provided this type of data, both published and unpublished. These countries supplied data on physicians who were controls Italy and Japan also provided information on other health professionals who were non-cases. Information on different categories of health professionals was available for British controls. Occupation was usually categorised on the basis of original records at registries. In a few instances, reporting physicians or relatives were consulted about the predominant activity, e.g. general practice vs radiology, of the non-cases.

Literature reviews

The first step in the literature reviews sought to identify reports of sCJD among health professionals, whether reported as case studies or drawn from analytical studies published during 1 January 1989 to 1 October 2011. We carried out several searches in MEDLINE and Embase using the medical subject headings (MeSH) and Emtree thesaurus terms listed in the Box, to identify case studies on CJD in health professionals and

Figure 1

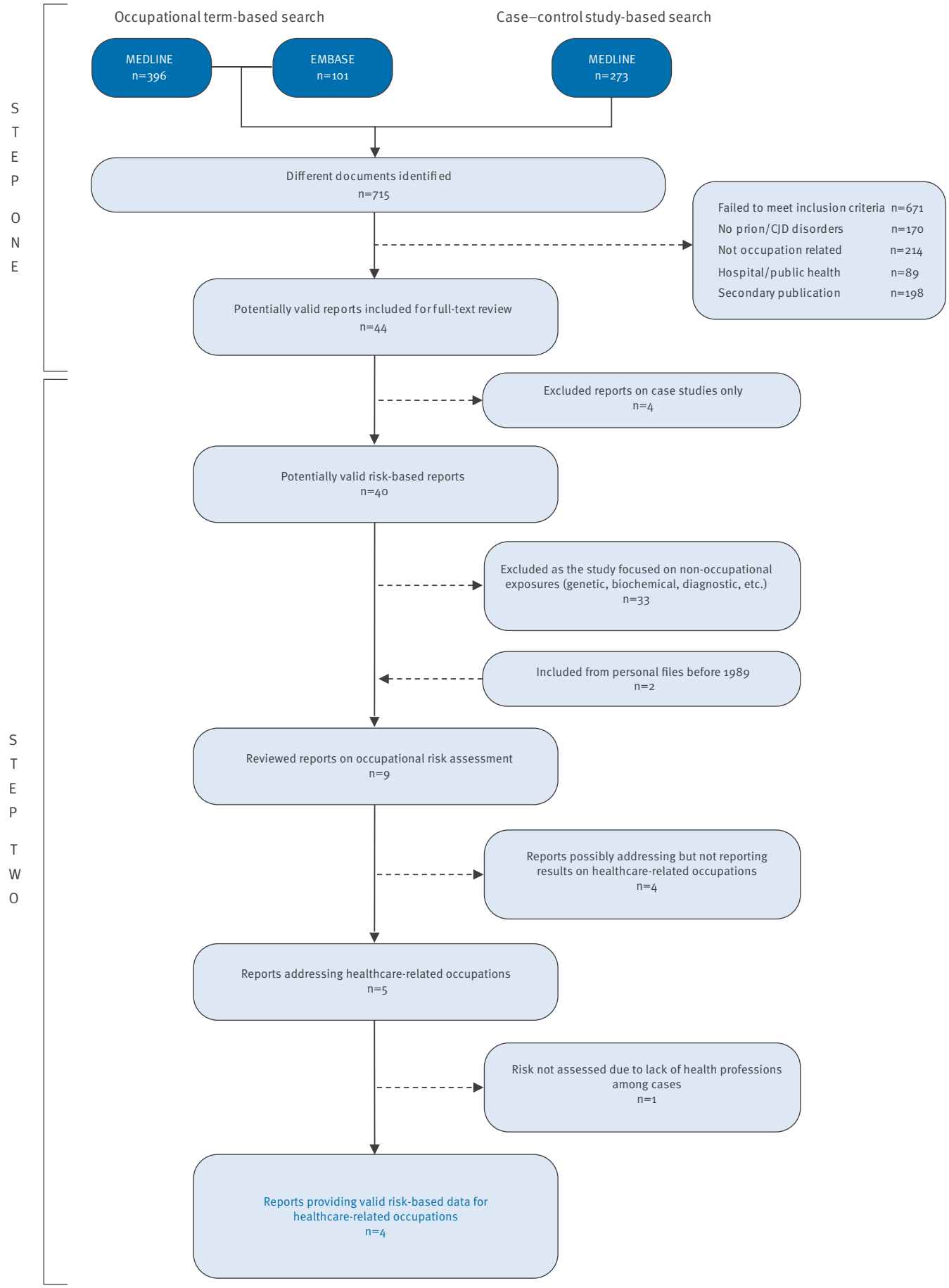
Literature review of case reports of sporadic Creutzfeldt–Jakob disease among health professionals, 1979–1 October 2011



sCJD: sporadic Creutzfeldt–Jakob disease.

Figure 2

Literature review of analytical studies on occupational risk of sporadic Creutzfeldt–Jakob disease for health professionals, 1982–1 October 2011



sCJD: sporadic Creutzfeldt–Jakob disease.

analytical studies on occupational risk of CJD for health professions. The initial searches yielded a total of 715 different documents.

In a second step, two independent assessors applied predefined sets of inclusion and exclusion criteria (Box) to the titles of the retrieved documents or, where available, to their abstracts.

Documents that met the inclusion criteria were processed further for full-text analysis in order to obtain the case description or to assess health-related occupational risk of sCJD.

After the selection criteria for had been independently, though not always unanimously, applied to the 715 documents by two reviewers, EAC and JPC, 671 were rejected and 44 selected for further analysis by both reviewers (Figures 1 and 2).

Case reports of sCJD among health professionals

Of the 44 documents selected for full-text review, 34 were excluded as the studies did not examine health-related occupations (Figure 1). Four studies that failed to include specific categories of health professionals with sCJD or in which the diagnosis of CJD was not validated were also excluded [3,6,7,19]. Six studies – four case reports [10-12,20] and two case–control studies, which provided information on health-related occupations in sCJD case series [5,21] – were selected for data extraction. Five case studies and one case-control study retrieved from personal records before 1989 were also included [4,8,9,17,22,23]. Thus, the final analysis of 12 reports included data on individual health professionals from case reports [8-12,17,20,22,23] and numbers of health professionals with sCJD from three reports on case–control studies [4,5,21]. These 12 reports included sCJD cases fulfilling diagnostic criteria for neuropathologically confirmed sCJD or for probable sCJD (people in the latter category were only included in case–control studies) [5,24]. Where health professions were listed in the case series of a large case–control study and numbers were not reported, only one individual, e.g. a dentist, was counted [5].

Epidemiologically assessed healthcare-related occupational risk of sCJD

Of the 44 documents selected for full-text review (the same 44 mentioned above), 40 fulfilled the inclusion criteria. After analysis of the texts, seven analytical studies on occupation and risk of sCJD remained for potential data extraction [3,5-7,19,21,25].Those excluded were multipurpose case–control investigations that made no mention of occupation in the results, occupation-unrelated meta-analyses, genetic case–control studies and public-health occupational profiles derived from empirical data. Four analytical studies reported before 1989 were reviewed: two were included [4,26] and two rejected [27,28]. Nine documents [3-7,19,21,25,26] provided data on occupational risk but only five of these addressed healthcare-related occupations [5-7,19,26]. Due to the low numbers (absence of exposed cases) in one study [26], risk-based data for health professions were only available from four case–control studies [5-7,19]. Reported associations for healthcare-related occupational risk obtained from these four epidemiological studies and raw negative findings from the above-mentioned study [26] were tabulated.

Results

Individualised occupational data from national CJD surveillance teams

Health professionals among registered sCJD cases

A total of 202 health professionals were listed among 8,321 cases of sCJD registered by 21 respondent countries participating in EuroCJD (Table 1). Of these, 65 (32%) were physicians and 137 were other healthcare workers. The highest numbers by medical speciality were general practitioners (n=9), surgeons (n=7), internists (n=7), dentists (n=4), ophthalmologists (n=3) and pathologists (n=2). The proportion of physicians or dentists among all registered sCJD cases was 65/8,321 (0.8%).

Health professionals among non-cases or controls

Table 2 shows individual data reported for health professions among non-cases or controls in five countries (Germany, Italy, Japan, Spain and the UK). Among 83 healthcare workers, 15 were physicians, six of whom had unknown specialisations, and three were surgeons. The percentage of physicians and dentists among CJD cases in Germany, Italy, Japan, Spain and the UK combined was 0.7% (34/4,949 (Table 1). This was similar to the proportion in the combined controls 0.5% (15/2,968).

Literature reviews

Reported sCJD in health professionals

Individual occupational profiles of reported health-related professionals with sCJD are outlined in Table 3. The data are derived from 12 studies, three of which were case–control studies. In these 12 studies, a total of 66 health workers with sCJD were reported, at least eight of whom were physicians [4,5,8-12,17,20-23]. One report described genetic CJD with phenotype resembling sCJD in three Slovakian health workers (two nurses and one dermatologist) with a mutation in codon 200 of the *PRNP* gene [11].

The following professions have been reported in sCJD cases: dentists (n=5), dental surgeon (n=1), neurosurgeons (n=2), pathologist (n=1), internist with training in pathology (n=1) and orthopaedic surgeon who had worked with sheep and human dura mater for industrial purposes (n=1) [12]. The majority of the remaining health professionals were nurses, two of whom had worked in neurosurgery and neurological care. Two other workers had been or were technicians at pathology laboratories.

Table 1

Occupational profile of sporadic Creutzfeldt–Jakob disease cases reported to the European Creutzfeldt Jakob Disease Surveillance Network (EuroCJD), 1965–2010 (n=8,321)

Occupation	Number of sCJD cases, by country[a], in the specified time period																					
	AR	AU	AT	BE	CA	CY	DK	FR	DE	HU	IL	IT	JP	NL	PT	SK	SL	ES	SE	CH	UK	Total
	1983–2009	1970–2008	1993–2008	1997–2009	1998–2009	1995–2009	1997–2009	1993–2008	1994–2007	1994–2009	1965–2007	1993–2008	1999–2009	1993–2008	1997–2009	1993–2010	1985–2009	1993–2009	1997–2007	1993–2009	1980–2009	
Physicians or dentists																						
Cardiovascular surgeon	0	0	0	-	-	-	-	-	0	0	0	0	1	0	0	0	0	0	-	0	0	**1**
Surgeon/urologist	1	0	0	-	-	-	-	-	1	0	0	0	0	0	0	0	0	0	-	0	0	**2**
Surgeon and neuropathologist	0	0	0	-	-	-	-	-	1	0	0	0	0	0	0	0	0	0	-	0	0	**1**
Traumatologist/surgeon	1	0	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	0	-	0	0	**1**
Ophthalmologist	0	0	0	-	-	-	-	-	0	1	0	1	0	0	0	0	0	1	-	0	0	**3**
Surgeon (not specified)	0	0	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	1	-	0	0	**1**
Pathologist	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	**1**
Neuropathologist's assistant	0	0	0	-	-	-	-	-	1	0	0	0	0	0	0	0	0	0	-	0	0	**1**
Forensic medicine	0	0	0	-	-	-	-	-	0	0	0	1	0	0	0	0	0	0	-	0	0	**1**
Dentist	1	0	1	-	-	-	-	-	0	0	2	0	0	0	0	0	0	0	-	0	0	**4**
Traumatologist	1	0	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	0	-	0	0	**1**
Plastic surgeon	0	0	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	1	-	0	0	**1**
Paediatrics/anatomy	0	0	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	0	-	0	1	**1**
Cardiologist	0	1	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	0	-	0	0	**1**
Internist	0	0	2	-	-	-	-	-	2	0	0	3	0	0	0	0	0	0	-	0	0	**7**
Clinical oncologist	1	0	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	0	-	0	0	**1**
Toxicologist	0	1	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	0	-	0	0	**1**
General practitioner	0	3	0	-	-	-	-	-	0	0	1	3	0	0	0	0	0	1	-	0	1	**9**
Psychiatrist	0	0	0	-	-	-	-	-	0	0	0	0	1	0	0	0	0	0	-	0	0	**1**
Paediatrician	1	0	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	0	-	0	0	**1**
Radiologist	0	0	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	0	-	0	1	**1**
Scientist	0	0	0	-	-	-	-	-	0	1	0	0	0	0	0	0	0	0	-	0	0	**1**
National service medical corps	0	0	0	-	-	-	-	-	0	0	0	0	0	0	0	0	0	0	-	0	1	**1**
Alternative medical practitioner	0	0	0	-	-	-	-	-	2	0	0	0	0	0	0	0	0	0	-	0	0	**2**
Epidemiologist	0	0	0	-	-	-	-	-	0	0	0	0	0	0	0	1	0	0	-	0	0	**1**
Geriatrician	0	0	0	-	-	-	-	-	0	0	1	0	0	0	0	0	0	0	-	0	0	**1**
Virologist	0	0	0	-	-	-	-	-	0	0	1	0	0	0	0	0	0	0	-	0	0	**1**
Other (specialisation not specified)	0	0	0	-	-	-	-	9	0	0	0	4	0	0	0	0	0	4	-	0	0	**17**
Number of sCJD cases among physicians or dentists	**6**	**5**	**3**	**-**	**-**	**-**	**-**	**9**	**7**	**2**	**5**	**12**	**2**	**0**	**0**	**1**	**0**	**9**	**-**	**0**	**4**	**65**
Other health professionals																						
Laboratory technician	0	-	0	-	-	-	-	-	-	0	0	1	1	1	-	0	0	-	-	-	2	**5**
Sterilisation department	0	-	0	-	-	-	-	-	-	0	0	0	0	1	-	0	0	-	-	-	0	**1**
Veterinarian	1	-	0	-	-	-	-	-	-	1[b]	0	1	0	0	-	0	0	-	-	-	0	**3**
Hospital employee	1	-	0	-	-	-	-	-	-	0	0	2	0	0	-	0	0	-	-	-	5	**8**
Other	0	-	0	-	-	-	-	-	-	1[b]	0	17	17	0	-	2	2	-	-	-	45	**84**
Number of sCJD cases among all other health professionals	**2**	**-**	**0**	**-**	**-**	**-**	**-**	**36**	**-**	**2**	**0**	**21**	**18**	**2**	**-**	**2**	**2**	**-**	**-**	**-**	**52**	**137**
Number of sCJD cases among all healthcare professionals	**8**	**5**	**3**	**-**	**-**	**-**	**-**	**45**	**7**	**4**	**5**	**33**	**20**	**2**	**-**	**3**	**2**	**9**	**-**	**-**	**56**	**202**
Total number of registered sCJD cases[c]	**206[d]**	**607**	**160[e]**	**184[f]**	**406[f]**	**9[f]**	**88[f]**	**1,462**	**1,576**	**145**	**133**	**778[d,g]**	**955**	**253[f]**	**93[f]**	**58[f]**	**38[h]**	**813[d]**	**163[f,h]**	**217[f]**	**827[g]**	**8,321[c]**

AR=Argentina, AU= Australia, AT=Austria, BE=Belgium, CA=Canada. CY=Cypus, DK=Denmark, FR=France, DE=Germany, HU=Hungary, IL=Israel, IT=Italy, JP= Japan, NL=Netherlands, PT=Portugal, SK=Slovakia,SL=Slovenia, ES=Spain, SE=Sweden, CH=Switzerland, UK=United Kingdom.

sCJD: sporadic Creutzfeldt–Jakob disease. The dashes represent years for which there are no data.

[a] There were no reports of sCJD among Polish pathologists, clinicians or medical technicians (personal communication, Dr J. Kulczycki, May 2009)./ [b] The two (non-medical) health workers were pathology assistants./ [c] Data for countries reporting presence versus absence of sCJD among pathologists (Belgium, Canada, Cyprus, Denmark and Sweden) are not included in the total number./ [d] Confirmed or probable cases./ [e] Austria reported 233 sCJD cases during 1969 to 2009 (one genetic transmissible spongiform encephalopathy excluded), including 84 cases of sCJD with occupational data (1993–2008). / [f] sCJD deaths obtained from the EuroCJD website [16].Otherwise different categories of registered sCJD on request./ [g] sCJD cases with occupational data only./ [h] Occupational data not registered.

Only one of three case–control studies [4,5,21] provided data on specialities but gave no indication of the numbers involved [5]. It is likely that most cases mentioned in the EuroCJD study by Van Duijn et al. [5] were included in country-specific occupational counts of the case set obtained from the extended EuroCJD consortium in response to the current request.

Health-related occupational risk of sCJD

The nine analytical papers on occupations and sCJD identified [3-7,19,21,25,26] tended to focus on healthcare and animal care-related occupations, with Cocco et al.'s study furnishing detailed data on other occupations [19]. This study used a large number of non-validated CJD diagnoses from death records in the United States and controls selected after exclusion of persons with neurological diseases reported as the cause of death [19]. The main findings for healthcare-related occupations from five papers are summarised in Table 4. While three of four studies on health professions did not demonstrate excess risk [5-7], statistically significant findings – for persons working at physicians' offices – were solely reported by Cocco et al. [19].

Discussion

Despite a number of case reports of sCJD in physicians and technicians, the findings of this EuroCJD survey do not suggest an increased risk of sCJD in health professionals, nor do analytical studies show a clear excess risk for health-related professions. Methodological limitations of analytical studies in which occupational data were frequently provided by informants who were probably aware of the sCJD diagnosis [3-7,26] argue in favour of a cautious interpretation of the positive association reported for persons working at physicians' offices [19]. Consequently, the main finding of this literature review and complementary EuroCJD observation is that health professionals, including medical staff, are not at greater risk of developing sCJD. However, this cannot exclude the possibility that there may be an occupational risk in specific circumstances, for example, for people in contact with high-risk central nervous system tissue, and appropriate precautions, as recommended by national authorities, should therefore be followed, particularly regarding laboratory work.

Although in some studies occupation was specifically analysed [19,25] and occupation may be the subject of specific inquiry in some surveillance systems, a limitation of some registries and scientific studies is that occupation may not have been systematically recorded. When occupation was recorded, it is unlikely that a framework for consistent occupational data collection was used, so that neither registries nor case–control studies have incorporated the classic epidemiological double approach. Recording of occupation may not identify specific chemical or biological exposures, which would require data for professions (job titles, medical specialisations) being cross-referenced with branches of activity (laboratory, administrative or clinical patient-contact work). The lack of registered surveillance data that combine profession with activity (e.g. contact with human tissue), when compared with the descriptions from previous case reports and the incident in Spain, illustrates the limits of the validity of available data for analytical purposes and precludes formal use of statistical testing. Although our study does not provide evidence of an excess risk of sCJD in health professionals, the fact that the data collected were mainly linked to medical speciality rather than actual activity might have concealed an excess risk of sCJD for some specific health professionals.

A case–control study seeking to examine the putative occupational risk posed by surgical injuries should have a biologically clear working hypothesis and a custom-tailored methodology. Matrices designed by linking medical speciality and surgical/forensic-anatomical/pathological activity, in which the health

Table 2

Occupational profile of non-cases or controls obtained through the European Creutzfeldt Jakob Disease Surveillance Network (EuroCJD), 1980–2009 (n=2,968)

Occupation	Number of professionals, by country, in the specified time period					
	DE	IT	JP	ES	UK	
	1994–2007	1993–2008	1999–2009	1993–2009	1980–2009	**Total**
Physicians						
Traumatologist/surgeon	0	1	0	0	0	**1**
Surgeon (not specified)	0	1	0	0	1	**2**
Internist	0	1	0	0	0	**1**
General practitioner	0	1	0	0	1	**2**
Psychiatrist	0	0	0	1	0	**1**
Paediatrician	1	0	0	0	0	**1**
Scientist	0	0	0	0	1	**1**
Other (specialisation not specified)	6	0	0	0	0	**6**
Number of physicians	**7**	**4**	**0**	**1**	**3**	**15**
Other health professionals						
Laboratory technician	-	2	-	-	5	**7**
Hospital employee	-	1	-	-	13	**14**
Other	-	10	-	-	34	**44**
Number of other health professionals	**-**	**13**	**3**	**-**	**52**	**68**
Number of healthcare professionals	**7**	**17**	**3**	**1**	**55**	**83**
Total number of non-cases or controls	**1,061[a]**	**656[b]**	**268**	**167**	**816[a,b]**	**2,968**

DE=Germany; IT=Italy ; JP=Japan; ES=Spain; UK=United Kingdom.
The dashes represent years for which there are no data.

[a] Controls from own case–control study.

[b] Only persons with occupational data.

professional can come into direct contact with high human-infectivity tissue by accident might not provide a sufficient background for analysis, without appropriate control being made for the influence of *PRNP* genotype, surgical or laboratory work history and long latency. Assuming that among non-cases or controls the proportion of medical specialities with potential exposure (surgeons, forensic surgeons and other surgical specialists, pathologists) may be low, i.e. approximately 1 per 1,000 (based on the figures of 3/2,968 in Table 2), the study size that would afford the necessary statistical power for a proper examination of the specific practices of health professions is higher than that provided by existing CJD registries in any one country. Since complementary analyses would be needed for professional and activity categories defined in terms of temporal references that have not been explored to date, such as 'ever employed' or 'currently employed', as well as duration of employment, requirements for study size and collaboration would be even higher.

Table 3

Health-profession-related sporadic Creutzfeldt–Jakob disease case reports from literature review, 1979–1 October 2011

Number of cases and their professions	Source
3 dentists 1 neurosurgeon 1 dental surgeon 6 nurses 1 assistant nurse	[17]
1 neurosurgeon	[23]
3 nurses 2 assistant nurses	[22]
1 histopathology technician	[8]
1 histopathology technician	[9]
1 physician 1 dentist 3 career nurses 2 people with brief nursing experience	[4][a]
1 pathologist	[20]
1 internist, formally trained in pathology 30 years previously	[10]
1 orthopaedic surgeon handling sheep and human dura mater 20–25 years before symptom onset	[12]
32 cases that included a physician; neuropathologist; nurse; laboratory technician; dentist and ambulance worker	[5][a]
1 nurse, gastrointestinal section	[21][a]
1 nurse and 1 ambulance driver without E200 mutation 2 nurses, 1 physician (dermatologist) with sporadic-like forms, carriers of E200K mutation 1 nurse (not from Slovakia. where the cases were reported), genotyping not done	[11][b]

[a] Described in case–control studies and, in general, fulfilling criteria as probable or confirmed sporadic Creutzfeldt–Jakob disease (sCJD) [17, 24].

[b] Mention of clinical features, genetic study or country of origin is frequently made in Slovakian cases given the high incidence of genetic forms and the relevance of genotyping for correct classification of CJD.

In conclusion, a wide spectrum of medical specialities and health professions are represented in sCJD registries. Although selection due to higher ascertainment may lie behind the case reports of certain professions involved in clinical management or care of patients with sCJD, the biological significance of these observations remains uncertain and available data do not indicate an increased risk of sCJD in health professionals. However, the methodological issues mentioned above indicate the need for caution in drawing conclusions from the data and large-scale studies with specific causal hypotheses are needed in order for further research to be undertaken into the potential link between health professions and sCJD

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Table 4

Summary of methods and main results of analytical epidemiological research into healthcare-related occupations and sporadic Creutzfeldt–Jakob disease, literature review, 1982–1 October 2011

Methods						Main occupational findings	Source
Type of study Study purpose Occupational hypotheses tested	Study population	Study period	Number of cases (number of confirmed sCJD cases)	Type of controls and controls sampling design	Occupations studied and source of information on occupational exposure	Specific occupational groups reported Odds ratio (95% CI), if calculated	
Case–control Multiple occupations. Prior health-related hypotheses were pathologists, other health professionals, work at hospitals and work at other health facilities	>6 million deaths in 24 states of the USA	1984–1995	636 cases identified as CJD diagnosis in death certificates coded as per the Nineth International Classification of Diseases (ICD9) ICD9-046.1 >25 years at death	3,180 randomly selected controls corresponding to persons whose death certificate did not contain as cause of death CJD (ICD9-046.1) or some neurological diseases (ICD9- 290.0-319.9; 320.0-349.9; 430.0-438.9; 440.0; or 780.0-781.9)	Occupational (159) and industrial (147) categories reported in death certificate, coded as per the 1980 United States Bureau of Census Classification. Age, residence, marital status at death Database publicly available	Persons working at physicians' offices OR: 4.6 (1.2–17.6) Physicians OR: 4.6 (0.7–29.0) Nursing aides, orderlies and attendants OR: 0.5 (0.1–1.6) Hospital workersOR: 1.0 (0.6–1.7) Nurses and staff of care facilities OR: 0.8 (0.2–2.6) Other health service staff OR: 1.1 (0.3–3.8)	[19]
Case–control Genetic factors Lifetime: - medical and dental history - animal exposures - diet - occupation (categories not specified)	Six European countries	1993–1995	405 (194 confirmed)	Age (5 years)- and sex-matched 405 hospital controls	Cases: proxy interview; controls: proxy interview (where possible)	Health professionals Occupations included: physician, neuropathologist, nurse, laboratory technician, dentist and ambulance worker OR: 0.92 (0.69–1.32) None of the professions studied was significantly associated with increased risk of CJD in a pooled analysis	[5]
Case–control Lifetime medical history, drug use, diet and occupation	Swiss resident population	2001–2004 during high sCJD incidence period [30]	69 cases: 61 confirmed and 8 probable. Symptom onset in 2001–2004	224 controls 69 GP-based 2004–2005 (using exclusion criteria) matched by age, sex, district and GP list 155 random digit telephone dialling in 2005; matched by age, sex, residence and language	EuroCJD questionnaire. Proxy interviews, response rate 68%.	Medical profession OR: 1.49 (0.43–5.15) Pharmaceutical laboratory OR: 3.39 (0.21–55.20) ORs adjusted for age, sex and education	[7]
Meta-analysis case–control Multipurpose in three studies For occupation, data used from two UK- and USA-based, studies [4,27-29]	Selected populations in the UK and USA	UK (England and Wales): 1980–1984 USA (Pennsylvania and other mid-Atlantic states): 1970– 1981	118 cases: UK 92 (70 confirmed) diagnosed 1980–1984 in England and Wales USA 26 (13 confirmed) diagnosed in 1970–1981 in Pennsylvania and other mid-Atlantic states	213 age- and sex-matched controls UK 184 hospital patients (1 neurological and 1 medical set) USA 40 (18 relatives, 22 hospital patients)	Not reported UK cases: proxy interview; controls: proxy interview USA mail questionnaire before interview. Cases: proxy phone interview; controls: direct phone interview	Health professionals OR: 1.5 (0.5–4.1) adjusted for age, sex and study site	[6]
Case–control Multiple, mainly non-occupational exposures	Japan, national	1975–1977	60 (37 confirmed of 75 initially recruited cases)	Age (5 years)- and sex-matched controls (n=103): 56 neighbours and 47 spouses	Occupation life history at time of onset, and 5 years and 10 years before onset. Cases: proxy interview Controls: direct interview	Health professionals No health-related professions were observed among cases A few public health workers were included among controls OR not calculated	[26][a]

CJD: Creutzfeldt–Jakob disease; EuroCJD: European Creutzfeldt Jakob Disease Surveillance Network; GP: general practitioner; OR: odds ratio
UK: United Kingdom; USA: United States of America.

[a] The information on health-related occupations from this study was not included in the meta-analysis [6].

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Description and analysis of 12 years of surveillance for Creutzfeldt–Jakob disease in Denmark, 1997 to 2008

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Prospective surveillance of Creutzfeldt–Jakob disease (CJD) was initiated in Denmark in 1997, following the observation of variant CJD in the United Kingdom. Demographic, clinical and diagnostic information was collected for each patient with clinical suspicion of CJD. Here we describe the methods for surveillance and the observed outcomes between 1 January 1997 and 31 December 2008. A total of 83 patients were classified as sporadic CJD, 47 were definite diagnoses, 34 probable and two possible. This resulted in a mean incidence of 1.26 patients with probable and definite sporadic CJD per million inhabitants. Two sporadic CJD patients were found to have a genetic variant of unknown significance: Thr201Ser and Glu200Asp. One patient was diagnosed with Gerstmann-Sträussler-Scheinker syndrome. No patients were classified as having variant, iatrogenic or familial CJD. The Danish surveillance system, like those in other countries, has a multidisciplinary approach, which is labour-intensive and time-consuming but ensures the most complete set of information possible. With this approach we think that patients with variant CJD would have been detected had they occurred in Denmark. Certain aspects of CJD surveillance need further discussion at European level and beyond, in order to find a balance between efficiency of the systems and accuracy of surveillance data.

Introduction

Creutzfeldt–Jakob disease (CJD) is a rare, fatal disorder characterised by rapidly progressive dementia. CJD belongs to the group of transmissible spongiform encephalopathies (TSE) or prion diseases. Four different aetiological subtypes of CJD have been defined: sporadic CJD (sCJD), which is the most common, the familial subtype (fCJD), the iatrogenic subtype (iCJD) and variant CJD (vCJD) [1]. Other related prion diseases are: Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). A definite diagnosis of CJD and distinction between the sporadic and variant type can only be made through post-mortem brain autopsy or biopsy. When no autopsy has been performed, a combination of diagnostic criteria can lead to a probable or possible diagnosis.

In 1996, vCJD was first described in the United Kingdom (UK) [2]. This subtype of the disease was soon linked to bovine spongiform encephalopathy (BSE) [3] and developed into an epidemic, which peaked in the UK in 2000 [4]. Between 1995 and 2008, a total of 205 patients with vCJD were identified worldwide [5].

Mandatory notification of CJD was introduced in several European countries in 1997. Following this, prospective surveillance of TSE was introduced in Danish law the same year [6], making it mandatory for physicians to report patients with clinical suspicion of a TSE to Statens Serum Institut (SSI). In 1998 Denmark became part of the NEUROCJD network, which later merged with the EUROCJD network, a project of the European Union (EU) aimed at coordinating surveillance in Europe, harmonising data collection and providing information on the epidemiological characteristics of CJD.

The purpose of the Danish national surveillance for TSE is to detect and monitor vCJD, in order to be able to take appropriate public health measures. However, due to similarity in clinical features and the rarity of the disease, all subtypes of CJD, and even GSS and FFI, are under surveillance. This article describes the Danish national surveillance system for TSE and provides an epidemiological overview of the outcomes for the years 1997–2008.

Methods

During the 12-year period the Department of Epidemiology carried out the surveillance of infectious diseases in Denmark, including surveillance of TSE, on behalf of the National Board of Health. The Department of Epidemiology also regularly informed physicians about the incidence of notified diseases and new developments through the epidemiological bulletin, Epi-News.

Case finding

If a patient was clinically suspected to have a form of TSE, the Department of Epidemiology of SSI had to be notified. When notified, the Department of Epidemiology sent a supplementary questionnaire to the reporting physician. The questionnaire explored a set of variables on demography, clinical presentation at onset, interpretation of electroencephalography (EEG), magnetic resonance imaging (MRI) and laboratory results. Physicians were also invited to provide additional documentation, in the form of discharge letters, EEG and MRI reports and neuropathological findings following autopsy.

Since 2004, the 14-3-3 protein, which reflects non-specific neuronal damage in the brain when present in cerebrospinal fluid (CSF), has been used for active case-finding [7]. Analysis of CSF was only performed by the Department of Clinical Biochemistry and Immunology at SSI. Samples were identified by a unique patient identifier from the civil registry system [8], which was also used for the mandatory notification. If a patient had a positive 14-3-3 qualitative test and mandatory notification was missing, the Department of Epidemiology contacted the physician. If a TSE diagnosis was considered, the physician was asked to submit the mandatory notification form and questionnaire.

As part of a study on the risk of developing sCJD after surgery, the national hospital discharge and cause of death registers were used to identify patients with probable and definite diagnosis and onset of CJD between 1987 and 2003 [9]. This information was used for active case finding of individuals who were not notified between 1997 and 2003.

Three steps in classification

Diagnosis of sCJD was retrospectively classified as possible, probable or definite according to the 1998 Rotterdam criteria (Table 1, [10]) and vCJD according to the 2000 UK criteria [11]. For each patient a three-step process was followed for classification. The notifying physician was the first to classify the disease on the questionnaire. Subsequently, the diagnosis was evaluated by a medical epidemiologist at SSI, who may have re-classified on the basis of the available documentation. If necessary, the physician was contacted for further details. An expert panel, consisting of a neuropathologist, a clinical neurophysiologist, a clinical laboratory physician and medical epidemiologists, met yearly to evaluate the notifications and decide on a final classification.

Regular exchange of information between the epidemiologists and the other members of the expert panel during the year ensured an assessment of each notified patient before the annual meeting. However, the classification was subject to change until an agreement was reached by the expert panel during the annual meeting. Patients who were still alive at the time of the annual meeting were followed up until death and discussed in the meeting of the following year for final classification. The surveillance data were based on the year of death of the patient.

Table 1

World Health Organization criteria for diagnosis of sporadic Creutzfeldt–Jakob disease

Criteria		
I		Rapidly progressive dementia
II	A	Myoclonus
	B	Visual or cerebellar problems
	C	Pyramidal or extrapyramidal features
	D	Akinetic mutism
III		CJD-typical periodic sharpwave complexes in electroencephalography
Classification		
Definite sCJD		Requires neuropathological/immunocytochemical confirmation
Probable sCJD		I + two of II + III OR possible sCJD + positive 14-3-3 protein
Possible sCJD		I + two of II + duration <2 years

sCJD: sporadic Creutzfeldt-Jakob disease.
Source: Rotterdam 1998 criteria [10].

Diagnostic methods

Electroencephalography and magnetic resonance imagin

EEG and MRI were performed by the local hospitals for the clinical management of the patient. All EEGs were reviewed by specialists in clinical neurophysiology. A CJD-typical EEG implied that periodic sharpwave complexes (PSWC) had been identified in at least one EEG. For final classification by the expert panel, criteria from the World Health Organization (WHO) were used for EEG reviewing [10]. In the majority of cases the original recordings were reviewed by the expert panel. When this was technically impossible, due to incompatibility of electronic systems, the original reports were reviewed and the local clinical neurophysiologists were contacted when clarifications were needed. Since MRI scans were not part of the classification criteria until January 2010, they were not systematically reviewed by the expert panel, but reports of MRI scans which were available from the patient journals were recorded in the surveillance system for future reference.

Laboratory techniques

The standard set of tests performed at the clinical laboratory at SSI when CJD was suspected consisted of qualitative 14-3-3 protein detection, supplemented with measurement of neuron-specific enolase (NSE), both of which are markers of neuronal damage, which are released in CSF during the course of different diseases, such as CJD and acute encephalitis. The 14-3-3 protein was detected in CSF using Western blot analysis developed by SSI [7], using antibody raised against the N-terminus of the beta 14-3-3 (sc-629 from Santa Cruz Biotechnology). When the test showed weak bands the analysis was run again. If the band was present the second time the patient was classified as 14-3-3 positive, irrespective of the size of the band. NSE levels were determined using time-resolved amplified cryptate emission (TRACE) technology [7]. NSE levels were considered elevated for CJD diagnosis if they were above 35 ng/ml. In case of a discrepancy between the results of the 14-3-3 and NSE analyses the 14-3-3 result was the decisive marker.

In addition, physicians had the option to request sequence analysis of the prion protein gene (*PRNP*) on genomic DNA isolated from blood. The *PRNP* gene was sequenced to establish the genotype at known polymorphic loci, i.e. codon 129 and 219, which have been ascribed a role as disease modifiers [12], and to identify putative disease-causing mutations. Specific genetic variants are relatively prevalent in certain populations and the occurrence of such mutations was established as part of the surveillance in cases where DNA material from whole blood was available. Genetic analysis was performed according to previously described standard procedures [13].

Autopsy

Autopsy, necessary to confirm or exclude the diagnosis, could be performed when family consent was given. Autopsies were performed at local hospitals or at the National Reference Centre for Creutzfeldt–Jakob Disease and other Spongiform Encephalopathies, Neuropathology Laboratory, Rigshospitalet, Copenhagen. In most cases the neuropathological investigation was performed at the National Reference Centre. The brains were fixed in 10% formalin for six to eight weeks before cutting. Paraffin blocs from all cerebral lobes, striatum, thalamus, hippocampus, brain stem, pons, cerebellum and medulla were scrutinised using hematoxylin and eosin, luxol fast blue, Periodic acid-Schiff and other conventional stains. Immunohistochemistry included staining for beta-amyloid, tau, p-tau, alfa-synuclein, ubiquitin, GFAp, CD68, NF, and for prion proteins (PrP) with 3F4 and KG9 antibodies. Also, paraffin-embedded tissue blot was applied in some cases.

Data analyses

Surveillance data of CJD patients collected from 1 May 1997 to 31 December 2008 were used for these analyses. All notified patients classified as possible, probable and definite were included. Results for 14-3-3 protein and NSE levels were available from 1 January 1998 to 31 December 2008, and genetic analysis of *PRNP* from 1 January 2001 to 31 December 2008.

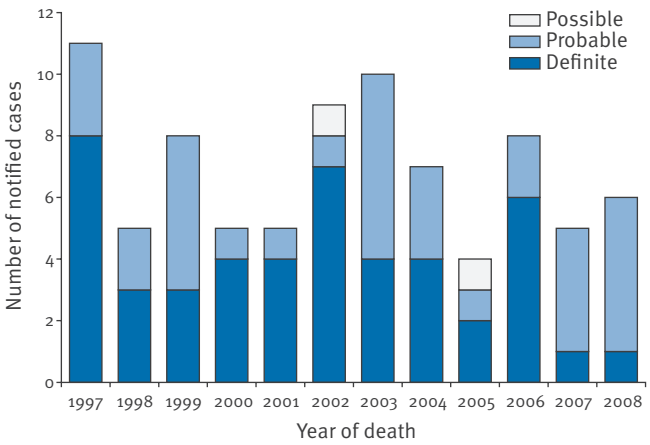
Incidence of probable and definite diagnoses was calculated using the population size of Denmark on 1 January of each year available from the Danish Office of National Statistics [14]. Only probable and definite diagnoses of CJD were included in the calculation of incidence, since that is the measure that was reported in the EUROCJD surveillance and allowed the comparison of our data with other countries. The incidence could also be compared to countries reporting annual mortality since CJD has a short duration of illness and always leads to death. Poisson regression with an interaction term was applied to compare the age-specific incidence between men and women. One-way analysis of variance (ANOVA) was used to analyse the duration of illness by age group and Mann–Whitney test to compare the duration of illness among men and women. The level of significance was set at 0.05.

Results

Of the patients notified between 1 May 1997 and 31 December 2008, 83 were classified as sCJD and one as GSS. No patients were classified as variant, iatrogenic or familial CJD or FFI. Clinical symptoms at onset and demographic characteristics were described for all 83 sCJD patients, EEG findings for 81 patients and MRI findings for 63 patients. Information related to CSF investigation was available for 52 patients concerning 14-3-3 protein and for 51 concerning the NSE. Polymorphism and genetic analyses were available for 43 and 39 patients, respectively.

Figure 1

Patients with sporadic Creutzfeldt–Jakob disease by year of death and final classification, Denmark, 1997–2008 (n=83)



Demographic description

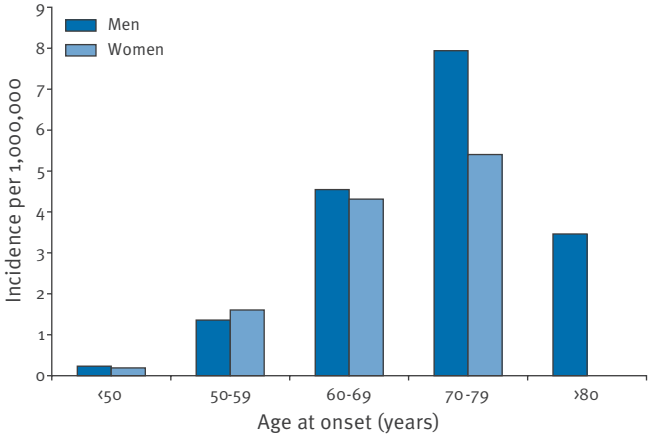
Among the 83 sCJD patients 47 (57%) were classified as definite, 34 (41%) as probable and two (2%) as possible. Forty-four sCJD patients were male (53%) and 39 female (47%). All patients were residents in Denmark. Figure 1 shows the number of patients by year of death and by final classification. The average number of possible, probable and definite sCJD patients per year was seven. The proportion of definite diagnoses in the total number of sCJD patients (definite, probable, possible) during the first 10 years of the surveillance varied between 38% in 1999 and 80% in 2000 and 2001, after which it declined to 20% in 2007 and 17% in 2008.

With a mean population size of 5.4 million inhabitants during the 12 year period, the mean incidence of probable and definite sCJD patients in Denmark over this period was 1.26 per million (95% confidence interval (CI): 1.01–1.56), and varied between 2.09 per million in 1997 and 0.55 per million in 2005. The median age at onset of disease for patients with probable and definite diagnosis was 66 years (range: 40–88 years). Figure 2 shows the incidence of the 81 patients with definite and probable diagnosis stratified by sex and age at onset. Incidence increased with age until it peaked at 70–79 years and dramatically dropped for persons older than 80 years. No women older than 80 years were reported with CJD. Although there was a higher incidence of sCJD among men than women in the age groups 70–79 years and ›80 years, the age-specific incidence was not significantly different between men and women (p=0.187).

The median duration of illness from onset until death for the 81 probable and definite sCJD patients was 3.8 months (range: 1.2–21.8 months). Older age was associated with shorter duration of illness (ANOVA, p=0.002). There was no association between duration of disease and sex (Mann–Whitney p=0.12).

Figure 2

Incidence of definite and probable sporadic Creutzfeldt–Jakob disease, by sex and age at onset, Denmark, 1997–2008 (n=81)



Diagnostic findings

Table 2 describes the different diagnostic findings among the definite, probable and possible sCJD patients. A majority of 67 patients (81%) presented with rapidly progressive dementia at onset, without other cognitive or physical symptoms present alone during the first two weeks of illness. Of the 14 patients with other presentations, nine were confirmed as sCJD with autopsy. For three patients with a probable diagnosis, the primary clinical presentation was classified as Heidenhain's syndrome, a visual impairment which leads to cortical blindness. No patients were seen with a pure psychiatric onset.

Of 82 patients for whom an EEG report was available 58 were reported to have an EEG typical for sCJD. Among the 46 patients with a definite diagnosis 31 had an EEG typical for sCJD; among the 34 with a probable diagnosis the proportion of patients with a typical EEG was higher with 27 patients.

For 63 patients an MRI report was also available and 43 of these patients showed abnormalities. Atrophy and unspecific abnormalities were most commonly reported, in 26 and 27 patients, respectively. Hyperintensity in the caudatus and putamen was less common with 17 patients, and hyperintensity in the thalamus was only reported in two patients.

For 52 patients 14-3-3 protein was tested and 41 had a positive result. Of the 20 definite cases seven had a negative 14-3-3 result. NSE levels were available for 51 patients; of these 37 had elevated levels above 35 ng/ml.

Polymorphisms in codons 129 and 219 were examined for 43 patients. The distribution of amino acids on codon 129 was methionine (Met) homozygocity for 24 patients, valine (Val) homozygocity for 11 patients and Met/Val heterozygocity for eight patients. Codon 219 showed homozygocity for glutamic acid (Glu) in all 43 patients. Table 3 shows the EEG results for 43 patients for whom the polymorphisms were tested. A majority of 21 of 24 patients with Met/Met at codon 129 had a typical EEG (Table 3). This proportion was smaller among patients with Met/Val (four of eight). Only one of 10 patients with Val/Val had a typical EEG.

In addition, 39 patients were tested for genetic variants (Table 2). No octarepeat variants were found among these patients. In two CJD patients we found a *PRNP* mutation. The first patient had a definite sCJD diagnosis and showed a new mutation in codon 201 from threonine (Thr) to serine (Ser), resulting in homozygosity for Ser. On codon 129 this patient had a Met/Met polymorphism. Microsatellites were tested on both sides of the gene, confirming that no deletion was present. The second patient had a probable sCJD diagnosis and showed a mutation from Glu to aspartic acid (Asp) in codon 200. This patient was heterozygous for Met/Val at codon 129. The patients were referred to local

Table 2

Diagnostic characteristics of patients with definite, probable and possible sporadic Creutzfeldt–Jakob disease, Denmark, 1997–2008 (n=83)

	Definite	Probable	Possible	Total	
	n	n	n	n	%
Clinical presentation at onset[a]	47	34	2	83	
(a) Rapidly progressive dementia	36	29	2	67	81 %
(b) Heidenhain's syndrome	0	3	0	3	4 %
(c) Pure psychiatric onset	0	0	0	0	0 %
(d) Slowly progressive dementia	1	0	0	1	1 %
(e) Pure cerebellar onset	4	1	0	5	6 %
(f) Extrapyramidal onset	2	1	0	3	4 %
(g) Stroke-like onset	1	0	0	1	1 %
(h) Sensory symptoms at onset	1	0	0	1	1 %
(i) Not possible to categorise	2	0	0	2	2 %
EEG[b]	46	34	2	82	
EEG typical for sCJD	31	27	0	58	71 %
MRI[b]	34	27	2	63	
Abnormal MRI	22	19	2	43	68 %
Hyperintense caudatus/putamen	8	7	2	17	27 %
Hyperintense thalamus	0	2	0	2	3 %
Atrophy	14	11	1	26	41 %
Unspecific abnormalities	15	10	2	27	43 %
14-3-3 protein in cerebro-spinal fluid[b]	27	24	1	52	
Positive for 14-3-3	20	21	0	41	79 %
Neuron-specific enolase in cerebro-spinal fluid[b]	26	24	1	51	
Neuron-specific enolase elevated (≥35 ng/ml)	18	19	0	37	73 %
Polymorphisms[b]	22	20	1	43	
Codon 129: Met/Met	12	12	0	24	58 %
Codon 129: Met/Val	2	5	1	8	19 %
Codon 129: Val/Val	8	3	0	11	26 %
Codon 219: Glu/Glu	22	20	1	43	100 %
Genetic variants[b]	19	19	1	39	
Octarepeat variants	0	0	0	0	0 %
PRNP mutation	1	1	0	2	5 %

EEG: electroencephalography; MRI: magnetic resonance imaging; PRNP: prion protein gene; sCJD: sporadic Creutzfeldt-Jakob disease.

[a] Description of the categories of symptoms at onset [10]:

(a) Encephalopathic illness with dementia and diverse other neurological features, progressing rapidly over weeks to a few months, with no individual cognitive or physical deficit being present alone for more than two weeks.

(b) Impairment of visual acuity and/or field, progressing to cortical blindness, without other significant clinical deficit for the first two weeks of illness.

(c) Psychiatric symptoms, without the presence of other features for at least four weeks.

(d) Dementia developing over months to years, without any other significant neurological features for the first six months.

(e) Progressive cerebellar syndrome without other significant features, for at least two weeks.

(f) An extrapyramidal syndrome involving Parkinsonian features with or without chorea, athetosis or dystonia, but without other significant features for at least two weeks.

(g) Onset is abrupt enough for a diagnosis of stroke in the initial stages.

(h) Somato-sensory symptoms alone for at least two weeks.

(i) These patients had a complicated medical history, which made it impossible to categorise.

[b] These diagnostic characteristics were not available for all 83 patients.

Table 3

Electroencephalography results and polymorphisms in codon 129 for patients with definite, probable and possible sporadic Creutzfeldt–Jakob disease (n=42)

	Met/Met		Met/Val		Val/Val	
	Typical EEG	Total	Typical EEG	Total	Typical EEG	Total
Definite	9	12	0	2	1	7
Probable	12	12	3	5	0	3
Possible	0	0	1	1	0	0
Total	**21**	**24**	**4**	**8**	**1**	**10**

clinical genetics departments for clinical assessment and to explore the family history.

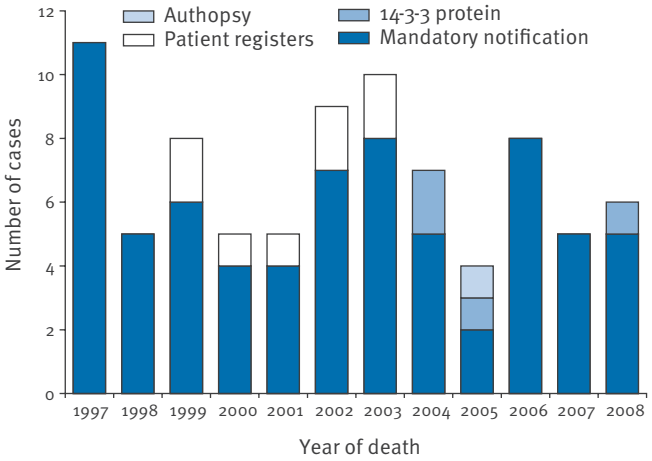
One patient was found to have GSS. At the age of 58 he developed what was considered a myelopathy. Over the following years the patient further developed gait disturbances, ataxia, dysarthria, double vision and difficulties swallowing. For a long time a form of spinocerebellar ataxia was suspected, but all genetic analyses for that as well as EEGs and computed tomography (CT) scans were normal. Eventually, the patient developed dementia. At autopsy characteristic spongiforme encephalopathy with proteinase K-resistant PrP-positive plaques was diagnosed and a P102L mutation was demonstrated in the *PRNP* gene.

Sources of notification

Between 1997 and 2008, 70 of the 83 patients with an sCJD diagnosis were reported through the standard mandatory notification system (Figure 3). One patient was notified by the neuropathologist of the expert panel. The study of the national hospital discharge and cause-of-death registers identified eight additional sCJD patients who died in the period between 1997 and 2003. Active case-finding with the 14-3-3 test, which started in 2004, identified 26 patients with a positive result (data not shown). After careful evaluation of each of these patients, only four were classified as having sCJD (Figure 3).

Figure 3

Initial source of surveillance referral of patients with possible, probable and definite sporadic Creutzfeldt–Jakob disease, Denmark, 1997–2008 (n=83), by year of death, 1997-2008, Denmark (n=83)



The time between onset of illness and notification differed between the sources of notification. For the mandatory notification system the median time was four months (range 0.8–32.9 months), whereas the median time between onset and notification by a physician after active case finding with a positive 14-3-3 test was 8.8 months (range 3.5–25.8 months). The one patient who was notified by the neuropathologist had onset of symptoms 14.1 months before the notification.

Discussion

The Danish national surveillance system for CJD integrates the expertise of different professionals and has a multidisciplinary approach. In this paper we describe 12 years of Danish CJD surveillance. We provide a demographic, diagnostic and clinical overview of notified patients and discuss the accuracy of the surveillance methods used.

Our assessment is subject to some limitations. The decision to ask for certain diagnostic tests and to notify a patient depends on the clinical presentation of the patient and the management of individual physicians. Therefore, the availability of diagnostic tests, especially the genetic analyses, might have been biased. Nevertheless, the Danish surveillance system was able to collect a rather complete set of information for each patient. The completeness of the dataset varied between 75% and 100% for variables related to demography, clinical symptoms, EEG and MRI.

Consistent with the fact that sCJD is the most common form of TSE, 83 of 84 notified patients in the Danish surveillance were diagnosed with sCJD and only one with GSS. The mean incidence of 1.26 definite and probable cases per million people per year is consistent with the observed overall annual mortality of 1.39 per million for sCJD in Europe, Australia and Canada [15]. As CJD has a short duration of illness always leading to death, the incidence and annual mortality can be compared. The incidence was highest among persons between 70 and 79 years of age and dropped dramatically among persons older than 80 years. This pattern is also described by other European countries as well as Canada, Australia, Taiwan and Japan [15-19]. Although the drop in sCJD incidence among women in the oldest age group was more pronounced in the Danish surveillance than described by other countries, the difference between women and men of that age was not statistically significant. This dramatic drop after the age of 80 could reflect the real disease epidemiology. Although clinical and neuro-biochemical features are similar among the age groups [20], another explanation could

be that the disease was misclassified in the older age groups, for example as Alzheimer's disease, for which the incidence steadily rises with age [21].

Rapidly progressive dementia is typically the first presentation in patients with CJD [22] and was also the most commonly reported as presentation at onset in our surveillance. The finding that 4% of the patients had Heidenhain's syndrome at onset is consistent with observations from a large group of British patients [23]. The typical PSWC in the EEG occur in about two thirds of patients with sCJD and iCJD, in 10% of patients with fCJD, but not in patients with vCJD [24]. The overall finding that 58 patients of 82 had a typical EEG is comparable to those data. Wieser et al. described that PSWC occur most often in patients with Met homozygosity at codon 129 of the *PRNP* gene and only occasionally in patients with Met/Val heterozygosity and Val homozygoty [24]. A similar distribution was seen in our surveillance data.

Zerr et al. found that the highest diagnostic accuracy of the MRI scan was obtained when either a combination of at least two cerebral cortical regions (temporal, occipital or parietal) show an increased signal or when a high signal increase is observed in both the caudate nucleus and the putamen [25]. These findings led to an adjustment in the classification criteria used within the EUROCJD network as of 1 January 2010, adding a high signal in caudate nucleus and/or putamen to the criteria on the same level as PSWC in the EEG. Interestingly, among the Danish patients only 17 of 63 patients showed a high signal in caudate nucleus and/or putamen. This may be due to the fact that reports were not systematically reviewed and shows the need to implement systematic review of MRI scans now that MRI scans have been added as a diagnostic criterion for CJD.

Polymorphisms at codon 129 have a strong modifying effect on disease susceptibility and phenotype [26]. Individuals homozygous for Met or Val at codon 129 are susceptible to developing sCJD [12]. The proportion of Danish sCJD patients homozygous for Met was indeed higher than the 35% in the healthy Danish population [27]. Lysine (Lys) at codon 219 has been suggested to be a protective factor against sCJD [28], and has only been shown in Asian and Pacific populations [29]. The finding that all sCJD patients who had a genetic analysis in our surveillance system were homozygous for Glu in codon 219, was therefore not surprising.

The homozygous Thr/Ser mutation in codon 201 was associated with Met/Met polymorphism in codon 129 and a deletion was excluded on microsatellite analysis. The Glu/Asp mutation in codon 200 was associated with Met/Val on codon 129. The Glu/Asp mutation occurred in the same codon as the mutation Glu/Lys which has been found in more than 70% of fCJD patients [30]. However, neither the Glu/Asp mutation nor the Thr/Ser mutation have been described before as associated with fCJD. It is therefore likely that these were novel mutations rather than mutations indicating fCJD, although the family history of these patients was not available to further assess this statement. The fact that the Thr/Ser mutation was homozygous suggest even more strongly that it was a novel one, as the chance of inheriting the same unknown mutation from both parents is extremely low. The clinical significance of novel mutations is difficult to establish as insignificant missense mutations do tend to occur in the *PRNP* gene. Considering this, we classified both patients as sCJD patients, with the addition that they had a genetic variant of unknown significance.

The patient with GSS had the classical morphology and proteinase K-resistant PrP-positive plaques previously described [1]. Also, the P102L mutation is the same as the one identified in the family from Vienna, which was first described to have GSS [31]. The Danish case is considered to represent the 34th known family in the world with the disease.

Surveillance systems for TSE have been described for Germany, France and Belgium [16,17,20]. In France the surveillance has identified 25 vCJD patients to date, while Germany and Belgium have not found any vCJD patients [5]. In Germany, suspected CJD patients were identified by referral from the treating physician, or after discussion of the 14-3-3 test result with a surveillance neurologist [16]. French patients suspected to have CJD were either notified by the physician or, more often, by a laboratory following a request for a 14-3-3 test [17]. In Belgium, all patients in the seven collaborating university hospitals clinically suspected of having probable CJD were reported. Patients with a clinical suspicion from other hospitals were identified through the 14-3-3 test [20]. Like the Danish system, the systems in Germany, France and Belgium are based on a multidisciplinary approach which operates on a central level and involves detailed traceback of patient files, laboratory results and diagnostic investigations such as EEG, MRI and neuropathology. These systems also use the 14-3-3 test, although they apply it in different ways. In Denmark, active case-finding with 14-3-3 has identified four additional patients over a five-year period, and 22 false positives. With such a low yield it is questionable whether the use of 14-3-3 test for active case finding is effective. Even more so, because the 14-3-3 test is often false negative in vCJD and the use of 14-3-3 protein therefore does not improve the sensitivity of the surveillance system for vCJD [32]. An advantage of using the 14-3-3 test for active case finding is that it reminds physicians of the mandatory notification and maintains awareness. If the 14-3-3 test was removed from the surveillance system as a source of notification, it would be of utmost importance to regularly remind physicians of the need to notify suspected cases, as the system would then fully rely on the mandatory notification. The multidisciplinary approach with traceback of files and additional case finding is a time-consuming and labour-intensive

method. It may, however, be the only way to identify as many CJD cases as possible, and it minimises variation in how the different variables in a complex classification process are interpreted. Algorithms and sensitivity analyses have been encouraged in order to enhance clinical diagnosis [7]. By supporting the physician's diagnosis, those algorithms could contribute to a more efficient surveillance.

With monitoring of vCJD as the main aim of the surveillance, it is important to examine whether not finding any vCJD in Denmark is a true indication that there really were no cases. Denmark is an agricultural country and only a small proportion of cattle and beef are imported. Since the surveillance of BSE in cattle started in 1990, 15 animals with BSE have been identified in Denmark, and an additional three in exported Danish cattle [33]. These are very low numbers compared to 184,600 cattle with BSE in the UK and 1,006 in France between 1988 and 2008 [34]. Respectively, 164 and 23 patients with vCJD were notified in these countries between 1995 and 2008 [5]. With the low number of cattle diagnosed with BSE in Denmark, despite thorough testing, it is unlikely that human cases of vCJD exist. In addition, it is unlikely that patients with vCJD have been misclassified as sCJD in our system, considering that the patients we report here were older than vCJD patients described in France and the UK (mean age 37 and 30 years, respectively) [35]. None of our patients was younger than 40 years at disease onset. Moreover, none of the Danish patients were reported to have psychiatric symptoms at onset, which is the most typical presentation of vCJD [11].

A median delay of four months was observed between onset of disease and notification. This could be caused by the complicated diagnostic process, but is also likely to involve a delay between clinical suspicion of diagnosis and notification. Active case finding through the 14-3-3 test did not shorten this delay.

The number of autopsies performed on patients with a probable and possible diagnosis declined, leading to a lower number of definite diagnoses and a larger uncertainty in the surveillance. An American study showed that reluctance of the family to give consent was one of the most important barriers to performing an autopsy [36]. This does not, however, explain why the number of autopsies decreased over those 12 years. Physicians might have been less likely to arrange for an autopsy in the more recent years, compared with the time shortly after the vCJD epidemic in the UK. The decline in autopsies increases the need for accurate clinical and laboratory data to assess the number of possible and probable diagnoses.

In conclusion, the Danish CJD surveillance registered an incidence of 1.26 probable and definite sCJD cases per million between 1997 and 2008. No patients with vCJD were found. The observed delay of four months between onset and notification could be of concern for public health measures should a patient with vCJD be detected. Awareness among physicians needs constant attention as it is important for timely notification as well as for the number of autopsies performed. In addition, it is important to further assess the cost effectiveness of the surveillance, with a view to the labour-intensive methods and the use of 14-3-3 protein for active case finding. We therefore recommend evaluating TSE surveillance in a broader context and generating discussion on a European level and beyond.

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A human metapneumovirus outbreak at a community hospital in England, July to September 2010

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We describe an outbreak of human metapneumovirus (hMPV) which occurred in July–September 2010 at a community hospital in the East of England. Based on the medical and nursing records, cases were retrospectively defined as suspected if they had had an influenza-like illness (ILI), and probable if they had had an ILI and an epidemiological link to a laboratory-confirmed case. Of a total of 17 symptomatic inpatients, five were classified as probable cases, five were laboratory confirmed and seven were suspected. The attack rate was 29.4% for confirmed and probable cases combined. The median age of symptomatic inpatients was 85 years-old (range 68–96) and the majority (16/17) of symptomatic inpatients had an underlying medical condition. Control measures introduced appeared to restrict further exposure of susceptible patients to infection although modelling suggested that up to four of 10 confirmed and probable cases (40%) could have been prevented through more timely diagnosis and recognition of an outbreak. These findings suggest that there should be increased awareness of hMPV infection within healthcare settings, particularly when the population at risk has a high prevalence of underlying co-morbidities.

Introduction

Human metapneumovirus (hMPV) is a paramyxovirus discovered in the Netherlands in 2001 [1]. It was first isolated from nasopharyngeal aspirates from children hospitalised with undiagnosed respiratory tract infection (RTI) although it has been identified retrospectively in samples from children with upper respiratory tract illness (URTI) from 1982 [2]. hMPV is part of the same family as parainfluenza, measles and mumps virus. Its genetic organisation is very similar to human respiratory syncytial virus (RSV). There are two main genotypes identified to date (A and B) with two subtypes within each. Circulation of subtypes appears to be temporal, with re-circulation occurring periodically [3,4]. In the United Kingdom (UK), hMPV and RSV co-circulate throughout the winter season both in hospitalised patients and in the community, with peak incidence found between December and March [5-7]. In two studies carried out in Scotland, of over 7,000 and over 9,000 community specimens, hMPV was the fifth and the sixth most frequently detected respiratory virus [3,8].

Studies have shown that, although clinical severity is not clearly associated with hMPV subtype, pathological signs on chest X-ray were observed more often in subtype B [9]. Clinical signs in healthy adults range from mild influenza-like illness (ILI) to severe RTI and are associated to both upper and lower RTI [10]. In adults with underlying conditions, it has been demonstrated that hMPV is a major causative agent of RTI and can be associated with fatal outcomes [11]. Recent studies have shown that hMPV infection may also be subclinical [12] or asymptomatic, especially in healthy and young individuals and sometimes among healthy elderly (≥65 years old) patients [13]. However, asymptomatic infection in frail elderly individuals and people with underlying disease are rare [14]. This has also been observed in animal models [15]. Amongst elderly individuals with confirmed hMPV infection, the most frequent diagnoses are ILI or an upper RTI followed by bronchitis and pneumonia [11]. Only limited studies of hMPV infection of elderly adults or institutionalised elderly adults are available [11,13,16]. In these studies the attack rate varies from 18% to 72% and the case fatality rate among elderly inpatients of a long-term care facility reached 50% of six laboratory-confirmed cases during one outbreak (9% of 96 reported possible cases in the same outbreak) [11]. Nosocomial transmission of hMPV within a healthcare setting has been documented [11,13,16,17]. Studies conducted in

paediatric wards in Korea and Hong Kong suggest that hMPV has an incubation period ranging from five to nine days for a symptomatic nosocomial case [17,18]. In the Netherlands, a seroprevalence study has shown almost 100% seropositivity by five years of age [1,7,19]; but, like RSV, primary infection with hMPV does not seem to induce lifelong immunity and re-infections occur in all age groups [14,19-22]. To date no vaccine or specific antiviral treatment is available which make non-pharmaceutical infection control interventions crucial in preventing the transmission of the virus.

On 3 August 2010, two inpatients from one ward of a community hospital (CH) in the East of England presented with respiratory symptoms. On 9 August 2010, by which time a total of eight inpatients had developed respiratory symptoms, this ward as well as a second ward of the hospital were closed to admissions, visits were restricted, and discharges to nursing homes and locations where there might be immunocompromised individuals were discontinued.

On 12 August 2010 an hMPV outbreak was declared in the two wards of the CH and an Outbreak Control Committee (OCC) convened on 13 August 2010. As recommended by the Health Protection Agency when managing an outbreak of respiratory illness in care homes, the following additional control measures were implemented [23]: patients were cohorted, physiotherapy sessions were suspended, respiratory infection control precautions were instituted including the use of surgical face masks and filtering facepiece (FFP3) masks, gloves and plastic aprons, attention to hand hygiene was intensified along with the use of alcohol hand rub; symptomatic staff were excluded until six days after onset or when well enough to work, whichever was the later; pregnant and immunocompromised staff were sent home until the outbreak was declared over; environmental cleaning using general-purpose detergent was augmented. The OCC defined a suspected case as any person with acute respiratory tract illness of abrupt onset, characterised by two or more of the following symptoms: fever (>38°C), cough, sore throat, runny nose and dyspnoea; and in the seven days prior to the onset of symptoms, who had been in close contact (less than one metre) with a suspect, probable or confirmed case of hMPV. A probable case was a person meeting the definition of a suspected case and with infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure (hypoxemia, severe tachypnoea). A confirmed case was a person meeting the definition of a suspected case and with a laboratory testing demonstrating one or more of the following: positive real-time reverse

Table 1

Characteristics of patients hospitalised during an outbreak of human metapneumovirus at a community hospital in the East of England, United Kingdom, July–September 2010 (n=34)

Characteristic		Inpatients n/N[a]	Cases		
			Confirmed cases (n=5) n/N[a]	Confirmed and probable (n=10) n/N[a]	All symptomatic (n=17) n/N[a]
Sex	Male	16/34	3/5	6/10	11/17
	Female	18/34	2/5	4/10	6/17
Residing	On his/her own and alone	13/30	2/4	3/9	6/16
	By his/herself with help	13/30	2/4	6/9	9/16
	With family	4/30	0/4	0/9	1/16
Underlying condition	Respiratory	15/33	2/4	4/9	9/16
	Cardiac	27/33	3/4	7/9	13/16
	Liver	0/33	0/4	0/9	0/16
	Kidney	11/33	1/4	2/9	5/16
	Diabetes	8/33	1/4	2/9	3/16
	Malignancy	7/33	0/4	0/9	2/16
	At least one of the above	30/33	3/4	8/9	13/14
Admitted from	Home	3/31	0/4	0/9	0/15
	General practioner referral	4/31	1/4	2/9	4/15
	Another hospital	24/31	3/4	7/9	11/15
Outcome	Still hospitalised at community hospital	9/33	0/5	1/10	3/17
	Discharged	15/33	4/5	7/10	8/17
	Transferred	2/33	1/5	1/10	2/17
	Dead	7/33	0/5	1/10	4/17

[a] N: Total number of persons of a category, for whom the information was available.

transcription-polymerase chain reaction (rRT-PCR) for hMPV or positive viral culture for hMPV.

On 8 September 2010 the OCC declared the end of the outbreak with no cases having occurred for more than 12 days.

The objectives of our study were: (i) to retrospectively describe the outbreak, (ii) to examine risk factors associated with clinical infection; (iii) to retrospectively determine the number of cases that could have been prevented through earlier implementation of control measures in order to (iv) inform public health guidance for future hMPV outbreaks.

Methods

Our investigation was a retrospective cohort study. The study population for our analytic study included all hospital inpatients who resided at the CH between 31 July 2010 and 9 September 2010. Data on demographics, medical history and admission history were collected from medical and nursing records. Healthcare workers (HCW) with reported ILI during the study period were interviewed by telephone for details of their illness (but were not included in the study population). The study was undertaken as part of a formal outbreak investigation, and in line with National Research Ethics Service guidance and formal ethical approval was not required. More sensitive case definitions were used for the retrospective study than those used by the OCC. Particularly, we removed the requirement of a suspected case to have been in known close contact with a previous case (<1 metre) and the clinical evidence of pneumonia or respiratory failure for a probable case.

Case definitions

A suspected case was defined as a patient presenting with ≥ 1 respiratory symptoms (rhinorrhoea, sore throat, or cough) or ≥1 constitutional symptoms (fever (≥38°C), loss of appetite, fatigue or myalgia) [23]. A probable case was a patient meeting the definition of a suspected case and with an epidemiological link (determined from the transmission model described below) to a symptomatic confirmed or probable case, and whose date of onset occurred within five to nine days prior, or after an exposure day. An exposure day was defined as shared time within a single day in the same room as a confirmed or a probable case. A confirmed case was a patient meeting the definition of a suspected case, with additional positive rRT-PCR for hMPV, on a throat swab.

Analysis

Cumulative incidence (attack rate) among patients was estimated including all confirmed and probable cases and the denominator of all patients admitted during the relevant timeframe. In order to avoid selection bias by counting potential non-hMPV cases, we performed the analysis with only confirmed cases and undertook a separate analysis with both probable and confirmed cases. We compared cases to non-cases, by age, sex and underlying medical conditions. The distribution of quantitative variables was compared using the t-test; associations with qualitative data were tested in a univariable analysis using the Chi-squared statistic. For both tests we used a significance level of 5%.

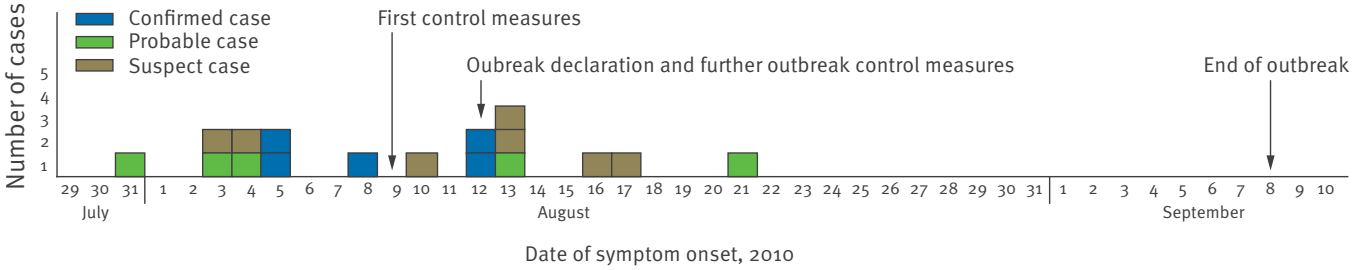
Estimation of possible transmission events among inpatients

Patient locations within the hospital during their infectious period were used to model potential transmission events. In the absence of relevant data from the literature on the infectious period in hMPV cases, the infectious period was defined for this study as the number of days (inclusive) from the date of onset to the end of symptoms. For the four cases where the date of end of symptoms was not known, the average duration of the symptomatic period of confirmed and probable cases in the study was used (eight days).

The model determines possible exposure periods of recipient cases to symptomatic cases (donors) and was written in R [24]. We assumed a minimum incubation period of five days prior to the onset of symptoms and a maximum incubation period of nine days. The model scans all infectious donors for overlap with the assumed incubation period of recipients when both

Figure 1

Distribution of cases from an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010 (n=17)



donor and recipients beds were within the same room in the CH. The model does not produce any measure of the likelihood of individual transmission events and is wholly deterministic; all possible transmission events are reported based on the entire overlapping period between the assumed incubation period and infectious period. Symptomatic HCW were not included in modelling of possible transmission events as they had been working in all the patient rooms within the hospital during their shifts.

Laboratory analyses

Throat swabs and sputum from seven symptomatic patients were tested locally by multiplex rRT-PCR for swine influenza A(H1N1), RSV, enterovirus, parainfluenza virus 1, 2, 3 and 4, rhinovirus, influenza A virus, adenovirus, hMPV, and influenza B virus. Samples from confirmed hMPV cases were sent to the Health Protection Agency Reference Laboratory in Colindale for sequencing of the fusion protein (F) gene.

Table 2

Characteristics of cases during an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010 (n=17)

Case number	Duration of Illness[a] (days)	Time of specimen collection (days after symptom onset)	Laboratory confirmed	Case status[b]
1	12	Not collected	Not tested	Probable
2	4	Not collected	Not tested	Suspected
3	16	Not collected	Not tested	Probable
4	21	20	Not tested	Suspected
5	7	Not collected	Not tested	Probable
6	NA	7	Positive	Confirmed
7[c]	NA	7	Positive	Confirmed
8	18	4	Positive	Confirmed
9	10	Not collected	Not tested	Suspected
10	9	Same day	Positive	Confirmed
11	5	Same day	Positive	Confirmed
12	4	Not collected	Not tested	Probable
13	NA	Not collected	Not tested	Suspected
14	NA	Not collected	Not tested	Suspected
15	10	Not collected	Not tested	Suspected
16	2	Not collected	Not tested	Suspected
17	5	3	Negative	Probable

NA: Data not available in the medical records or medical records not available.

[a] The number of days between onset and last date of reported symptoms.

[b] Assessed retrospectively according to the investigation case definition.

[c] The medical records for this patients were not retrieved; however this patient was confirmed by the laboratory as having human metapneumovirus infection.

Table 3

Clinical symptoms of cases during an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010 (n=17)

Symptom	Probable and confirmed cases[a] (n=10)	Suspected cases[b] (n=7)
Cough	8	2
Cough and wheezing	4	3
Fever	5	2
Fatigue	2	2
Rhinorrhoea	1	1
Loss of appetite	2	1
Sore throat	1	0
Myalgia	0	0

[a] Clinical information was not available for one case.

[b] Excluding probable and confirmed cases.

Results

Patient characteristics

There were a total of 34 patients hospitalised in the CH during the study period. The demographic and medical characteristics of the patients hospitalised during the time of the outbreak are described in Table 1. There were as many men as women. The hospitalised patients had a median age of 79 years (range: 51–100). Almost all of the inpatients with available information (30 of 33) had at least one underlying condition. The majority (24 of 31) were admitted from an acute hospital. Two cases were admitted to the community hospital for respiratory disease (chronic obstructive pulmonary disease and persistent chest infection). One inpatient was admitted for palliative care. Among the 24 inpatients that were no longer in hospital on 9 September 2010, 15 had been discharged, two had been transferred to an acute hospital, and seven had died.

Human metapneumovirus infection in inpatients

Overall, there were five confirmed cases, five probable cases, and seven suspected cases among the inpatients (Table 2). The median age of the confirmed cases was 78 years (range: 71–94), that of the confirmed and probable 84 years (range: 68–96) and that of all cases 85 years (range: 68–96). Laboratory analyses revealed that all five confirmed cases had been infected, with hMPV genotype A, subtype 2 clade 4 [3]. The earliest case identified during the investigation was a probable case with onset of symptoms on 31 July 2010 (Figure 1). The first two confirmed cases both had onset of symptoms on 5 August 2010.

Specimens were taken from suspected cases for laboratory testing on 12 August 2010 (5 cases) and 24 August (2 cases). The calculated cumulative attack rate (number of confirmed and probable cases/total number of inpatients) during the 37 days study period

was 29.4% (95%CI: 13.3–45.5). Details of clinical symptoms and patient characteristics are shown in Tables 2 and 3.

The mean duration of illness was 7.6 days (range 1–18 days) for the 10 confirmed and probable cases where it could be calculated. Of these, one died, another was transferred to an acute hospital, and seven were discharged. The remaining case was still hospitalised at the time of data collection.

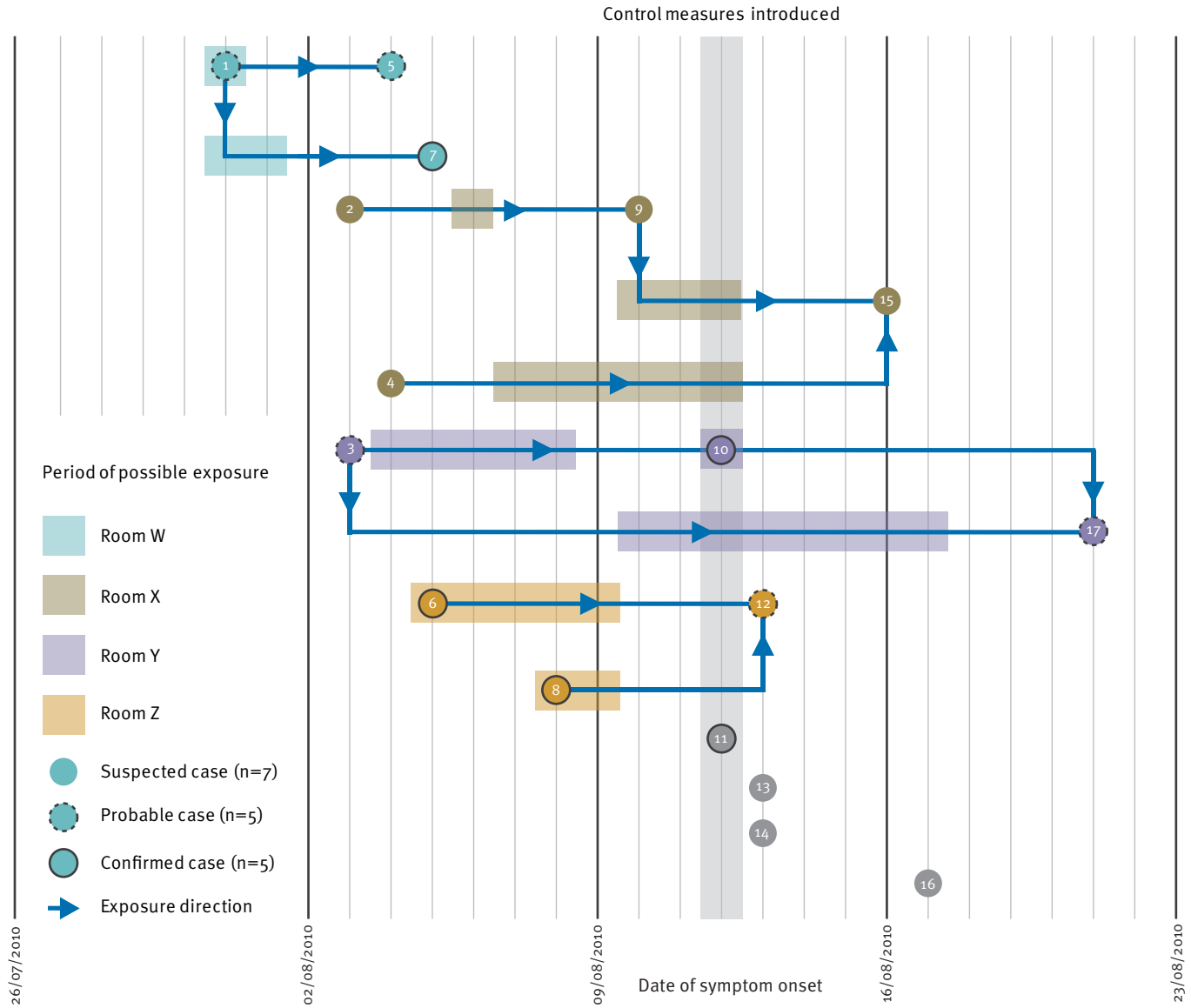
Seven inpatients died over the study period: Four of the 17 hMPV cases and three of the 17 other inpatients. The hMPV cases were not more likely to die than the other inpatients hospitalised during the same period (p=0.324). No common underlying condition, age group or sex was significantly associated with infection in either analyses (results not shown).

Symptomatic healthcare workers

We interviewed three of six HCW who were reported symptomatic during the study period. Of the two who were tested by throat swabs, both were negative for hMPV; however, specimens were taken 18 and 21 days after onset. Assuming an incubation period of five to nine days, the dates of onset of HCW are consistent with exposure on the ward during duty and occurred between 1 and 16 August 2010. Two of the three

Figure 2

Possible transmission networks predicted by a donor–recipient model, during an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010 (n=17)



The number within each circle is the study identification number of each patient. Horizontal coloured bars represent possible exposures (in the direction of the underlying arrow) of infectious donors to recipients at the colour-coded locations.

interviewed HCW had onset of symptoms on a day they worked. They were all on night shifts and took care of all inpatients. Symptoms lasted for seven, 10 and 21 days respectively and all recovered. None had a specific underlying condition or relevant travel history outside of the UK.

Modelling predictions of preventable cases among human metapneumovirus inpatient cases

Using dates of onset and end of the symptomatic period we plotted probable periods of exposure for each symptomatic case (Figure 2). Six early cases (identification (ID) number 1, 2, 3, 4, 6, and 8) have no discernable source of infection. According to our model of transmission, a maximum of 10 potential transmission events could have occurred as illustrated in Figure 2 (between cases 1-5, 1-7, 2-9, 9-15, 4-15, 3-10, 3-17, 10-17, 6-12, 8-12). Four later cases (ID number 11, 13, 14, and 16) are not linked to other cases within the proposed transmission networks (Figure 2).

From this schematic depiction of the outbreak we were able to infer the possible number of cases that may have been prevented, had full control measures been implemented earlier (Table 4). Following the control measures implemented on 12 August 2010, our exposure model suggests that only one potential exposure occurred (between case number 3 and 17), indicating that control measures might have been successful in restricting further transmission. The model shows that had control measures been implemented after the first three cases were recognised 40% (4/10) of the total number of probable and confirmed cases could have been prevented.

Table 4. Predicted total outbreak size given hypothetical dates of control measure implementation during an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010

Discussion

The outbreak described here is one of the few documented outbreaks of hMPV within a healthcare setting [10,11,16,17,25]. Although the case definitions used in this analytical study differ from those used during the course of the outbreak, incorporation of the modelling data has provided information which has been used to assess aspects of the dynamics of this outbreak which could not have been otherwise studied. We estimated an attack rate of 29.4% based on the retrospective study definition of confirmed and probable hMPV cases. This is within the range of values described in previous outbreak investigation in similar settings [11,13,16]. Our modelling of possible exposure periods together with the laboratory findings are consistent with a degree of nosocomial transmission of hMPV within the CH. The model used in this study was wholly deterministic and was used to detect all possible transmission events that could have occurred given the assumed range of incubation and infectious periods. Although such an approach is suitable for the analysis of this study, the further inclusion of a measure of uncertainty by a full sensitivity analysis would enable specific person-to-person transmission events to be assessed more fully but is beyond the scope of this paper.

Due to the non-specific nature of the symptoms of hMPV infection, and the lack of laboratory confirmed cases, we adopted a conservative approach to our analysis and excluded all symptomatic cases who had neither been laboratory confirmed nor had a possible transmission link with a confirmed case. We also excluded data from the HCW and limited the exposure link to contact with a symptomatic confirmed case within the same room. Of course, we cannot be certain that HCW were not involved in transmission networks of hMPV within the CH but given the available data it was impossible to include HCW in modelling with any level of precision. Nonetheless, inclusion of HCW in the model would only have generated more suggested

Table 4

Predicted total outbreak size given hypothetical dates of control measure implementation during an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010

Date of hypothetical control measure implementation	Number of suspected cases to given date	Number of confirmed or probable cases to given date[a]	Total number of probable and confirmed cases in the outbreak[b]	Number of cases prevented (% reduction)[c]
03/08/2010	3	2	6	4 (40)
04/08/2010	5	3	8	2 (20)
05/08/2010	7	5	9	1 (10)
08/08/2010	8	6	9	1 (10)
09/08/2010	8	6	9	1 (10)
10/08/2010	9	6	10	0
12/08/2010[d]	11	7	10	-

[a] Assessed retrospectively.
[b] Had all exposures prior to the proposed implementation date been prevented.
[c] The percent reduction is calculated using the combined confirmed and probable cases as denominator.
[d] Date control measures were implemented, date of positive result of human metapneumovirus confirmed cases.

transmission events which make the estimates of possible transmission reduction here a likely conservative underestimate.

Separate analyses using just confirmed cases (n=5) and confirmed/probable cases (n=10) found no risk factor to be significantly associated with infection when comparing cases to non-cases; nor did they show evidence of increased mortality associated with the infection. Of course, the power of detecting a statistically significant difference is limited due to the high frequency of co-morbidities in the population at risk. Asymptomatic cases of hMPV infection are not common among a population of frail elderly adults [14]. Therefore we feel confident that we accounted for all suspected cases of hMPV infection among the inpatients. However, asymptomatic cases might have occurred among the HCW.

We could not identify a possible exposure to hMPV infection for five confirmed and probable cases; this was likely related to the restricted definition of exposure used. It is very likely that virus transmission not only occurred when sharing the same room but also during daily activities (e.g. lunch) or healthcare activities (transmission from HCW to patient). Symptomatic HCW were tested long after the onset of symptoms making it problematic to comment on the role of HCW in the possible introduction of hMPV into the CH. Symptoms lasted up to three weeks for both inpatients and HCW. Data on the duration and magnitude of viral shedding following infection with hMPV are limited. In hospitalised children the duration of viral shedding has been documented as five days [26] but may be much longer for the elderly [27]. It may be important for further studies to address this issue in order to provide further insight into the probability of both transmission and laboratory diagnosis following the onset of symptoms.

Early recognition and laboratory confirmation of the causative agent are crucial to restricting the spread of a respiratory pathogen within a healthcare setting and adapting infection control strategies [14]. This is critical in situations where the incidence of respiratory illness in the population is high (as was the case for the outbreak described here) and early detection of an outbreak of respiratory virus infection may often be masked by the underlying level of chronic or sporadic respiratory syndrome. Furthermore, this outbreak occurred towards the end of summer when clinical surveillance may be less focused on respiratory syndromes. These elements may have contributed to making the start of the outbreak difficult to identify.

Admissions and discharges were suspended by the nursing staff after eight symptomatic cases had occurred. Further control measures within the ward were implemented four days later, after 11 patients had presented with ILI, including five who later tested positive for hMPV. The Health Protection Agency defines an Acute Respiratory Illness (ARI) outbreak as "two or more cases arising within the same 48 hour period or three or more cases arising within the same 72 hours period, which meet the same clinical case definition and where an epidemiological link can be established" [23]. Transmission modelling suggests that had control measures been implemented at the time of the occurrence of the third symptomatic case, 40% of the cases could have been prevented; however, any interpretation of this must take into account the difficulty in clinical case ascertainment in a care setting where the prevalence of non-specific hMPV symptoms is high. The occurrence of ARI cases in a vulnerable population should be detected at an early stage in order to implement control measures and prevent further cases, especially within healthcare settings, where the exposed population is particularly vulnerable to increased disease severity, such as the very young, the very old, or those with chronic medical conditions.

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