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Query fever: an opportunity to understand the disease better

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This week's issue of *Eurosurveillance* presents two articles on Q fever. A surveillance report about a Q fever outbreak in Cheltenham, United Kingdom (UK), describes the traditional pattern of Q fever epidemiology involving clusters of cases reported around farms with infected animals (sheep, goats) [1]. The second article provides an update on a long-lasting and ongoing Q fever outbreak with a considerable increase in cases observed over the past three years, indicating an entrenchment of Q fever in certain areas of the country [2].

Q fever is a mandatorily notifiable disease in the European Union (EU). Until recently, a few hundred cases were reported annually, often in the context of circumscribed outbreaks [3]. The great majority of reported cases in the EU were adults with a male to female ratio of 1.8 and a seasonal pattern with more cases reported during summer months. However, given its non-specific clinical picture and mild course in the majority of cases, Q fever is known to be under-diagnosed and therefore under-reported [3]. Seroepidemiological studies conducted in some regions of EU Member States have indicated a seroprevalence ranging from 1% to 60% [4-7].

Intensive animal husbandry has long been associated with large epizootics. Europe still sees large outbreaks of e.g. swine fever and outbreaks recently occurred in Spain, Germany and Luxembourg and were seen in the UK in 2000 and in the Netherlands in 1997 [8]. The Netherlands also saw a 2003 influenza A(H7N7) virus outbreak in poultry. All the above outbreaks led to the culling of a large number of animals and the influenza A(H7N7) outbreak affected several hundreds of humans [9]. Intensive animal husbandry is now associated with the emergence of a large Q fever epidemic, affecting human health significantly and raising questions about the intensive animal husbandry in the proximity of densely populated areas as is the case in the Netherlands. It seems unlikely that the disease will spread geographically to areas with less intensive animal husbandry and at the pace noted in the Netherlands. However, it cannot be excluded that spores may spread through wind, as described in the article by Wallensten *et al*. (UK), and cases could also occur beyond the Netherlands, when farms with infected animals are located closely to borders.

Van der Hoek *et al*. (NL) report that around 20% of the Q fever cases reported in the Netherlands were admitted to hospital in 2008 and 2009. An earlier publication by Raoult *et al*. describes that 2 to 5% of cases were hospitalised in past outbreak settings [10]. Wallensten *et al*. are using these reference hospital admission percentages to estimate that possibly 500 people may have been infected in the Cheltenham outbreak. Applying the same range of hospital admission percentages to the outbreak in the Netherlands would result in 10,000 to 20,000 cases having occurred there in 2009.

Coxiella burnetii DNA was detected in some products for blood donation from affected areas in the Netherlands, and the subsequent precautionary screening of blood in areas with a high incidence of Q fever raises the question whether blood donors returning from affected areas and giving blood while potentially experiencing asymptomatic bacteraemia should potentially defer from doing so. In their paper, van der Hoek *et al*. express concerns that in the first few weeks of 2010 an important increase in cases was noted, earlier than compared with previous years. They conclude that Q fever is expected to remain a significant problem over the coming years while it is hoped that the number of human cases in 2010 will stabilise. Therefore, this rapid communication is very timely in alerting about the foreseeable persistence of the Q fever epidemic in the Netherlands in 2010. This epidemic brings a unique opportunity to learn more about a disease for which many questions still remain. It stresses again the need to complete and communicate preliminary results of ongoing studies in similar outbreak situations which are necessary for the rapid implementation of public health measures regarding risk groups, chronic disease, pregnant women and blood donation.

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Q fever in the Netherlands: an update on the epidemiology and control measures

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Since the steady rise in human cases which started in 2007, Q fever has become a major public health problem in the Netherlands with 2,357 human cases notified in the year 2009. Ongoing research confirms that abortion waves on dairy goat farms are the primary source of infection for humans, primarily affecting people living close (under 5 km) to such a dairy goat farm. To reverse the trend of the last three years, drastic measures have been implemented, including the large-scale culling of pregnant goats on infected farms.

Extent of the problem

The Netherlands is facing a Q fever problem that is still increasing in size since the last report in this journal [1]. In 2009, a total of 2,357 new Q fever patients were registered in the national infectious disease notification database. These patients fulfilled the case notification criteria of fever, pneumonia, or hepatitis, combined with a positive laboratory result. Q fever infection is asymptomatic in 60% of cases [2] and if symptomatic often presents as influenza-like illness. Increasing awareness among patients and doctors will likely result in detection of more relatively mild cases. However, the proportion of notified patients that had to be admitted to a hospital seems to have stabilised around 20%, after a decline from 2007 to 2008 (Table).

The high percentage of 50% in 2007 was largely influenced by active case finding in a retrospective survey among hospitalised cases. The 19.7% of 2009 are still much higher than the 2-5% hospitalisation that are reported in the literature [2].

In the first 10 weeks of 2010 a considerable number of cases has already been notified, which, based on experiences of preceding years and taking into account the drastic measures taken, was not expected at this time of year (Figure 1).

The intensified media attention in late 2009 and early 2010 might have caused an increase in the number of consultations. Improved laboratory capacity will also have influenced the number of notified cases and quality of the notified data. As can be seen in the epidemiological curve of 2007 there is a more or less scattered pattern due to delayed notifications. From 2009 onwards, routine PCR is included in the diagnostic workup of acute Q fever, which can accelerate diagnosis. However, PCR is only positive in early Q fever. The high background of notified cases in the winter of 2009-10 may be a reflection of high seroprevalence among the affected population, due to persisting antibodies, both IgG and IgM phase II, used to diagnose acute Q-fever. This, combined with non-specific clinical

Table

Hospital admissions for Q fever by year of notification, the Netherlands 2007-2009

Year of notification	Notified cases	Admitted to hospital			Percentage admitted (95% CI)	
		Yes	No	Information missing		
2009	2,357	459	1,869	29	19.7%	(18.1-21.3)
2008	1,000	207	785	8	20.9%	(18.4-23.5)
2007	168	83	83	2	50.0%	(42.4-57.6)

CI: confidence interval.

symptoms of Q fever, makes it difficult to differentiate between acute and past Q fever infections, and thus makes notifications less accurate.

In 2009, six deaths were reported, all in patients with other underlying medical conditions. The median age of the patients was 49 (interquartile range (IQR): 38-59), and 61% were male. In 2008, the median age was 50 years (IQR: 41-59), with 64%, male cases. Geographically, the epidemic affected an area that was larger than in the preceding years. A large new cluster was observed in Limburg, the southernmost province of the Netherlands, near a Q fever-affected dairy goat farm functioning as a healthcare farm (daily activities).

There is consensus among public health and veterinary professionals that most of the human Q fever cases are linked to abortion waves on large dairy goat farms, and to a much lesser extent on dairy sheep farms. Consequently, interventions have focused on these types of farms. However, there are indications that direct contact with non-dairy sheep has also caused a limited number of human cases: at least 28 among patients and staff of a mental health institution [3] and possibly up to 46 among 12,000 people who visited a sheep farm during the lambing season in February and March 2009.

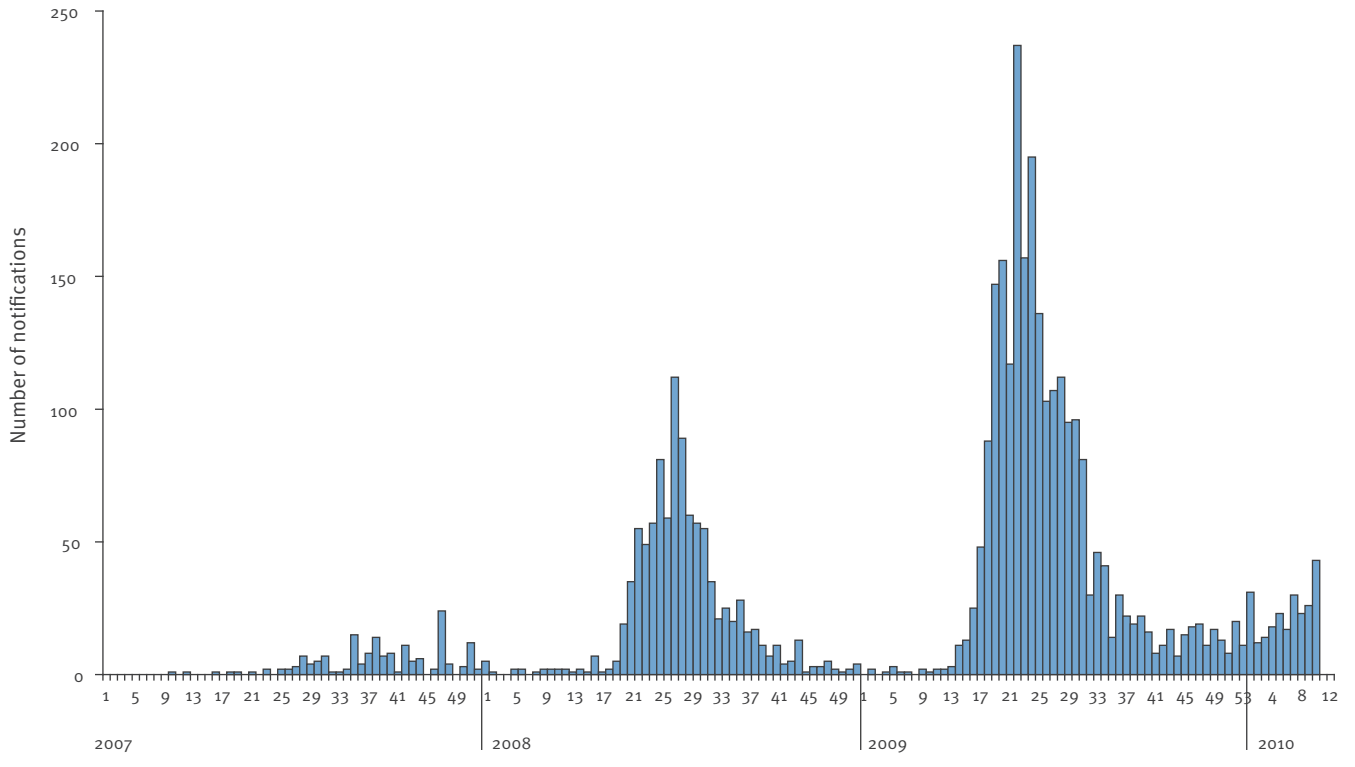
Control measures

In February 2009, a nationwide hygiene protocol became mandatory for professional dairy goat and dairy sheep farms. Between April and November 2009, approximately 250,000 small ruminants were mandatorily vaccinated, including those on farms in the high-incidence area in the south of the country (Figure 2), farms with a recent history of Q fever, and farms offering recreational activities. Veterinarians, physicians and the public were informed through targeted mailings, publications and the media. On 1 October 2009, bulk milk monitoring became mandatory on farms with more than 50 dairy goats or dairy sheep, and PCR-positive bulk milk has since been used as an additional criterion for veterinary notification of Q fever. The initial frequency of testing each farm every other month has been increased to once every two weeks as of 14 December 2009. By 18 February 2010, 74 dairy goat farms and two dairy sheep farms, out of the total of 360 dairy goat farms and 40 dairy sheep farms with more than 50 animals in the Netherlands, had been declared Q fever-infected based on PCR-positive bulk milk testing (Figure 2). The number of positive farms is expected to increase further towards the peak of the lambing season (March-April).

In retrospect, a large human cluster in an urban area in 2008 could clearly be linked to a dairy goat farm (with over 400 animals) with a Q fever related abortion wave a few weeks before the first human cases presented

Figure 1

Q fever notifications by year and week



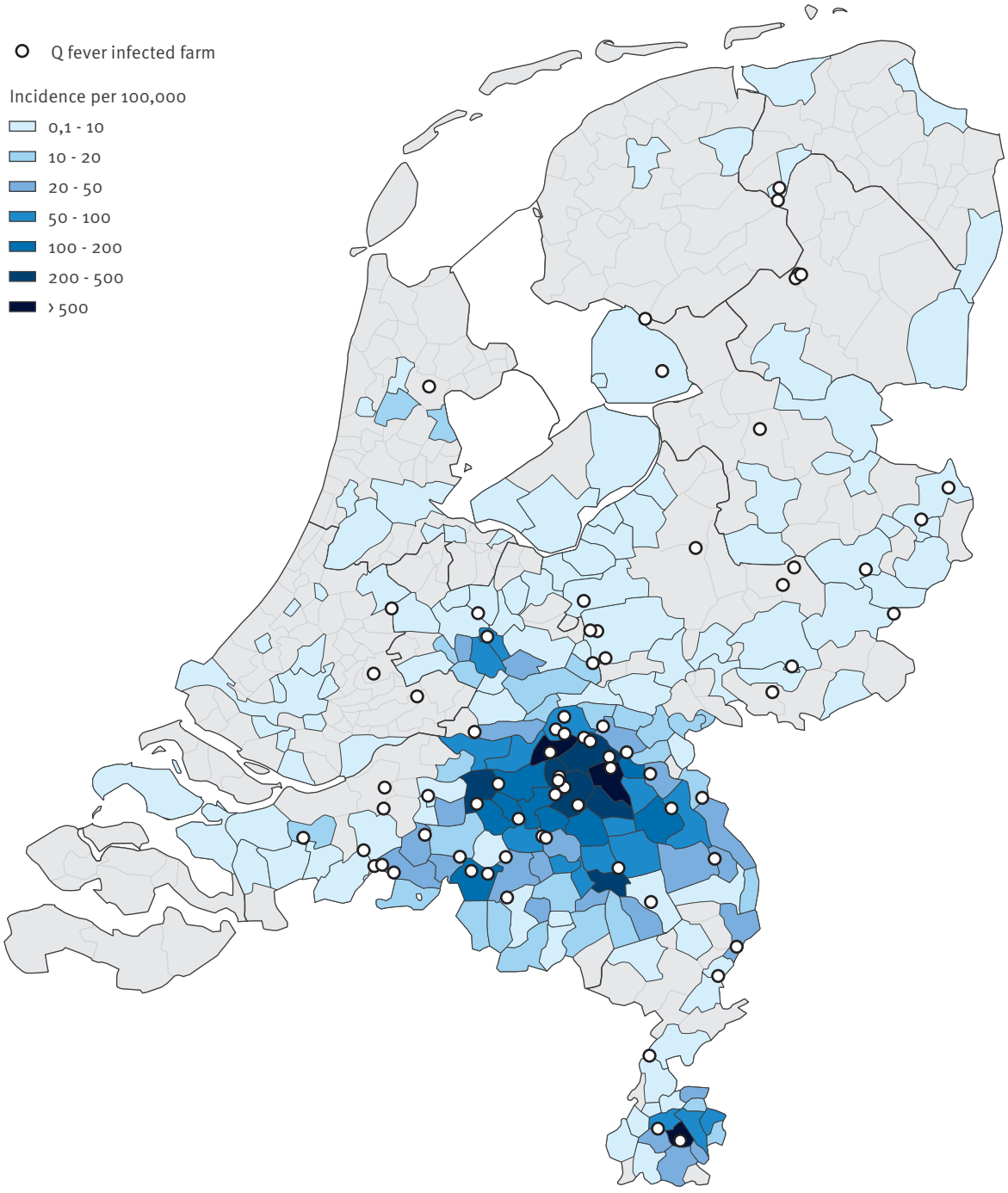
The epidemic curve (by week of onset of illness) is updated weekly and is publicly accessible at http://www.rivm.nl/cib/themas/Q-koorts/

[4]. People living within 2 km of the farm had a much higher risk for Q fever than those living more than 5 km away (relative risk 31.1; 95% confidence interval (CI): 16.4-59.1). Based on this study, a public information campaign has been targeted to zones of increased risk around affected farms. When a dairy goat or dairy sheep farm tests positive for *Coxiella burnetii* in a bulk milk sample for the first time, all inhabitants living within a radius of 5 km of the farm receive a letter informing them on the presence of a Q fever-positive farm in their proximity. The letter gives no specific advice, but allows people with known risk factors to avoid the farm. The list of positive farms is updated daily and is available to the public on the website of the Food and Consumer Product Safety Authority (www.vwa.nl, in Dutch).

In 2009, 59% of the notified human Q fever cases lived within a radius of 5 km of an infected dairy goat or dairy sheep farm, while only 12% of the Dutch population live within these zones. The incidence of Q fever

Figure 2

Incidence of human Q fever by municipality (n=2,357) and locations of Q fever infected dairy goat and dairy sheep farms, the Netherlands, 2009



Map compiled by Ben Bom, Expertise Centre for Methodology and Information Services, RIVM.

in 2009 was 69 per 100,000 population within, and six per 100,000 outside the 5 km-areas.

Screening of pregnant women

International literature suggests that a Q fever infection during pregnancy may lead to adverse pregnancy outcome in a large percentage of cases [5]. However, in a recently completed retrospective study in the high incidence area in the Netherlands, the presence of antibodies against *C. burnetii* in early pregnancy was not significantly associated with preterm delivery, low birth weight, or perinatal mortality (van der Hoek *et al.*, unpublished data). A large-scale prospective screening and treatment study coordinated by the University Medical Centre Groningen, was started in March 2010, aimed at providing more conclusive data on the need to screen pregnant women in high incidence areas.

Screening of blood donors

There is a theoretical risk for transmission of *C. burnetii* through blood transfusion. Preliminary results indicate that in 2009, *C. burnetii* DNA was detected in a small minority of blood donations in the affected area. The risk of infection is probably negligible, but as a precautionary measure, Sanquin Blood Supply Foundation, the organisation responsible for all blood products in the Netherlands, started screening donated blood for *C. burnetii* in the high-incidence area of the country on 15 March 2010.

Expectations for 2010

The veterinary interventions, especially vaccination, animal movement restrictions, culling and hygiene measures, are expected to have an impact in 2010 and 2011. However, the resilience of *C. burnetii* in the environment and the possible role of animal species other than small ruminants make a prediction difficult but could potentially lead to incidence levels not much lower or even higher than those observed in 2009. If spores persist in stables even after removing all animals or if environmental contamination and different animal reservoirs turn out to become relatively more important for transmission to humans, the striking seasonal pattern of the years 2007-2009 may be altered, possibly resulting in a more erratic transmission pattern over time. So far, there are no signs that the Q fever problem is spreading to neighbouring countries. It could be that factors such as lower population density, lower animal density, and different animal production methods in Belgium and Germany, compared to the Netherlands, play a role.

Research agenda

To fill the many knowledge gaps regarding Q fever, there is a large interdisciplinary research agenda in the Netherlands focusing on human and veterinary public health and individual patient care. Further elucidating the source and transmission routes will to a large extent depend on advances in molecular biology. Conclusive matching of the bacteria that are found in animals with human and environmental samples has not yet been successful. Obtaining *C. burnetii* DNA is difficult, except from placenta material of infected goats and sheep. Typing by multiple-locus variable-number tandem repeat analysis (MLVA) has been used on a limited scale in human and veterinary samples and indicated similarity in strains isolated from a small sheep herd with strains from the human cluster in the mental health institution in May 2008 [6]. However, while various different MLVA types were identified, research by the Central Veterinary Institute in Lelystad shows that one MLVA type prevails on many dairy goat farms in the high risk area in the southern part of the Netherlands, possibly indicating clonal spread in this area [7]. This hampers tracing the source of human Q fever in the high-risk area to a specific farm. In a newly started project, whole genome sequencing will be used to be able to distinguish between *Coxiella* bacteria from different sources.

Discussion

Q fever is now considered a major public health problem in the Netherlands and has recently led to drastic measures, including the large-scale culling of pregnant goats and sheep. Despite the strictest veterinary measures possible, Q fever is expected to remain a significant problem over the coming years. The control measures are aimed at stabilising the number of human cases in 2010, while the sustained compulsory vaccination campaign in small ruminants which is implemented in 2010 nationwide for target farms, is expected to eventually cause a drop in human cases in 2011 and subsequent years.

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Norovirus outbreaks linked to oyster consumption in the United Kingdom, Norway, France, Sweden and Denmark, 2010

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This paper reports on several simultaneous outbreaks of norovirus infection linked to the consumption of raw oysters. Since January 2010, 334 cases in 65 clusters were reported from five European countries: the United Kingdom, Norway, France, Sweden and Denmark. The article describes the available epidemiological and microbiological evidence of these outbreaks.

Background

Norovirus in oysters

Oysters are grown in coastal waters of several countries and are considered a delicacy in most parts of the world. Like all bivalve molluscs, they feed by filtering large amounts of water through their gills. *In situ* studies with bioaccumulation of a virus indicator in oysters have shown that oysters can concentrate viruses up to 99 times compared to the surrounding water [1]. In water contaminated with norovirus, this leads to the accumulation of the virus within the flesh and gut of the oyster. Norovirus has been detected in 5 to 55% of oysters from Europe and the United States (US) by random sampling at market places and oyster farms [2-4]. The detection of norovirus in oysters follows the same seasonal trend as the norovirus epidemiology in the general population, i.e. norovirus in oysters is generally detected between October and February [1, 12]. Seventy-eight percent of shellfish-related illness from noroviruses in the US between 1991 and 1998 were associated with the consumption of oysters harvested between the months of November and January [1]. Contamination of oyster beds with noroviruses can occur after heavy rains cause flooding, which results in combined sewer overflow or hydraulic overload in sewage treatment plants [5, 13]. There are also examples of oyster harvesters disposing sewage into oyster-bed waters causing multi-state outbreaks of norovirus in the US [6]. Noroviruses are difficult to remove from oysters through cleansing and also stay infectious even if cleaned[7]. Oysters are often eaten raw, creating the potential for foodborne enteric virus infections.

Outbreaks previously reported in the European Union

Several norovirus outbreaks linked to the consumption of oysters have been reported in Europe in recent years [5, 8-10]. In a review by Baert *et al.* (2009), bivalve shellfish accounted for 17.5% (7/40) of internationally reported foodborne norovirus outbreaks in 2000-2007 [11]. A search of the Rapid Alert System for Food and Feed (RASFF) database (https://webgate.ec.europa.eu/rasff-window/portal/) revealed 19 alert notifications on norovirus findings in oysters and/or norovirus food poisoning associated with the consumption of oysters between March 2006 and March 2010. All of these alerts concerned oysters grown and sold within the European Union (EU) and 17 were reported between the months of January and April, reflecting the season when oysters are considered to be of the best quality.

Current situation (January to March 2010)

From January to March 2010, the European Centre for Disease Prevention and Control (ECDC) was informed through its Food- and Waterborne Diseases and Zoonoses (FWD) surveillance network about norovirus outbreaks linked to consumption of oysters in five EU/EEA countries: the United Kingdom (UK), Norway, France, Sweden and Denmark. In total 65 small clusters involving 334 cases were reported. Most cases had eaten oysters in restaurants. For the purpose of this article we defined a verified cluster as one where

(i) evidence was available that cases had consumed oysters within the incubation period (descriptive epidemiology) and (ii) norovirus was identified with reverse transcription RT- PCR (RT-PCR) in oysters from the same batch or from the same harvesting area as the oysters which were consumed by the cases (microbiological evidence). Following these criteria, 27 of the clusters were verified (Table).

Outbreak description

United Kingdom

In January 2010, local authorities in the UK notified 22 possible foodborne clusters of gastroenteritis associated with consumption of oysters in restaurants, affecting over 120 people to the Health Protection Agency (HPA). Investigations identified norovirus genogroup I (GGI) and genogroup II (GGII) in stool samples taken from cases in nine of the 22 clusters and in oysters in three of these clusters.

Oysters produced in England, Scotland and Ireland were implicated in the clusters. However, most were sourced from one producer in Ireland. Ireland issued a RASFF alert on 17 February after having detected norovirus in Irish oysters. Control measures taken in Ireland included closure of identified fishing areas and withdrawal of shellfish coming from these areas.

Norway

In Norway, eight clusters of gastroenteritis involving 39 cases were notified between 22 January and 6 February 2010. Cases became ill after having eaten oysters from one importer distributed to six different restaurants in Oslo. No stool samples were collected. The local food authorities traced back the oysters to one producer from Brittany in France. Two of three incriminated batches were analysed at the Norwegian School of Veterinary Science, and both tested positive for norovirus genogroup I (GGI) and genogroup II (GGII) by RT-PCR. A RASFF alert was issued on 11 February.

France

Six foodborne clusters of gastroenteritis were notified linking the consumption of oysters originating from the same area in Brittany (1) as the area incriminated in the Norwegian clusters. The French clusters occurred in weeks two to nine 2010, and involved 22 cases. The cases had consumed oysters mainly in restaurants but also in their homes. No stool specimen was available for analysis. Oysters coming from this area were sampled and norovirus was detected. Four additional clusters of gastroenteritis linked to consumption of oysters from a different area of Brittany (2) occurred in weeks four to seven, involving 45 cases. Cases and oysters from the area were tested and norovirus was confirmed. Norovirus GGI and GGII were detected in the stool samples of cases whereas the results confirming the genogroup of the norovirus positive oysters are still pending. The identified harvesting areas were closed and shellfish from these areas was recalled from the market. The measures were implemented from week seven to nine.

Sweden

Fourty-eight persons in 15 clusters developed acute gastroenteritis after having eaten oysters at a restaurant in Stockholm. Two additional persons ate oysters at another restaurant in Stockholm and also developed acute gastroenteritis. Oysters were consumed between December 2009 and early March 2010. The first restaurant served both Dutch and French oysters. No stool samples were taken from the 50 cases.

Denmark

Twenty-seven norovirus cases in six clusters who had consumed oysters at three different restaurants were reported from January to March 2010. Norovirus GG I and II were detected in stool samples from two of the cases. Norovirus GG II was detected in the stool sample of a third case. Oysters served at the restaurants originated from four coastal locations in France. Oysters from all four batches tested positive for norovirus GG I and II and were recalled from the Danish market. Three RASFF alerts were issued on 12 March and a fourth alert was recently submitted. Three additional clusters, bringing the number to nine, are currently being investigated.

Table

Norovirus clusters linked to consumption of oysters, United Kingdom, Norway, France, Sweden and Denmark, January to March, 2010 (n=65)

Country	Clusters	Verified	Total number of cases	NoV detection (genogroup)		Origin of oysters
				Cases	Oysters	
United Kingdom (England and Wales)	22	3	120	+ (I, II)	+ (I, II)	England, Scotland and Ireland
Norway	8	8	39	NA	+ (I, II)	Brittany, France
France (1)	6	6	22	NA	+	Brittany, France
France (2)	4	4	45	+ (I, II)	+	Brittany, France
Sweden	16	0	50	NA	NA	The Netherlands and France
Denmark	9	6	58	+ (I, II)	+ (I, II)	Different locations in France

NA; Not available

Discussion

This paper describes several outbreaks of gastroenteritis caused by norovirus occurring simultaneously in several European countries. Norovirus of both GG I and II were detected in oysters and in stool samples collected from cases in the outbreaks. This is a common finding in oyster-related outbreaks and reflects an environmental source of contamination [5, 14-16]. Bon *et al*. (2005) found up to seven different strains of norovirus in some outbreaks. This contrasts with person-to-person transmission occurring in settings such as hospitals or nursing homes, which most often involve a single genotype.

It is likely that current reports underestimate the true burden of norovirus infection in the community following consumption of oysters as restaurant-associated outbreaks are more commonly reported to public health authorities than outbreaks occurring in a household setting.

Even though norovirus contamination in oysters is a known source of gastrointestinal outbreaks, the number of such events in the first three months of 2010 is considered unusual in several of the involved countries and is above what is normally observed at EU level. This increase may be due to several factors. Firstly, it could partly be a surveillance artefact as the sharing of information regarding norovirus outbreaks through the FWD network is relatively recent and may have contributed to the reporting of these events. There is currently no evidence to suggest that the increase in reported outbreaks is due to increased transmission in the EU population. Norovirus activity in the current season appears to be higher than in recent years in Norway and the UK whereas France and Sweden did not observe a similar pattern. Secondly, as the contamination of the oyster harvesting areas is not restricted to a single location, it would indicate a broader environmental issue and not a localised contamination problem. It is possible that the unusually cold winter experienced in northern Europe during the first three months of 2010 favoured the contamination of the oysters as virus survival increases in cold water temperatures and reduced exposure to ultraviolet light [17].

In conclusion, an increased number of norovirus outbreaks related to the consumption of oysters have been observed at EU level in the last three months. The reason for this needs to be further investigated. With the expected decline both in the seasonal activity of norovirus and the seasonal consumption of oysters in Europe over the next coming month(s) it is likely that reports about outbreaks such as the ones described here will also decrease. However, consuming raw oysters involves potential exposure to norovirus and is particularly hazardous for immunocompromised or chronically ill persons. Therefore, countries might consider informing the public about the risks linked with consuming raw oysters. Furthermore, it is important that countries continue to notify these events through the RASFF in order for producers to be informed in a timely manner about contamination, enabling them to implement control measures.

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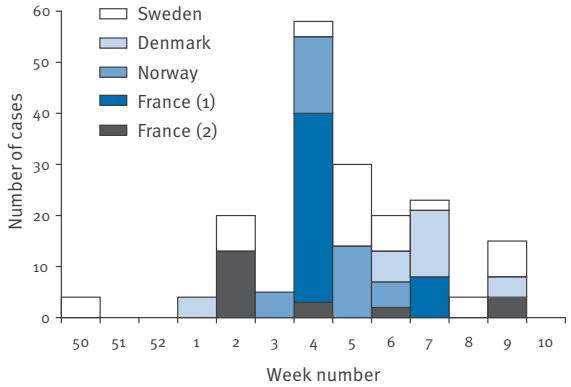
Swedish team: M Edlund, Environmental Health office, Stockholm.

Figure

Epidemic curve by week of onset of reported cases from Norway, France, Sweden and Denmark, December 2009 to March 2010 (n=183)



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Substantial increase in listeriosis, Denmark 2009

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In 2009, 97 cases of listeriosis were reported in Denmark (1.8 per 100,000), a significant rise over the previous year. The increase was seen both in cases of bacteraemia and meningitis and affected mainly people aged 70 years and older. A foodborne outbreak of eight cases was identified by pulsed-field gel electrophoresis typing. No explanation has so far been found for the marked increase in incidence. An increasing trend has been observed since 2003 and possible explanations are discussed.

Introduction

Invasive listeriosis is a serious foodborne infection caused by *Listeria monocytogenes*. The three major clinical presentations of listeriosis are sepsis, meningitis and materno-fetal infection. In a review of materno-fetal infections in Denmark 12 of 36 cases resulted in stillbirth and/or abortion [1]. In recent years the annual number of reported listeriosis cases has increased in several European countries including Denmark [2-4]. However, case definitions, diagnostic practices and surveillance systems differ across European countries, factors that must be taken into consideration when interpreting these data. In 2009, Denmark saw a further increase in the incidence of listeriosis, reaching 1.8 per 100,000 inhabitants. To our knowledge this is the highest incidence reported in a European country in recent years. In this paper, data from the Danish surveillance system are presented and discussed.

Materials and Methods

Culture-confirmed cases of listeriosis are notifiable by Danish diagnostic laboratories to Statens Serum Institut (SSI). Information on age, sex, isolation site, collection date of the specimen and hospital department from which the specimen is sent is compulsory. The laboratories also refer the isolated bacterium for typing. Data on the clinical presentation (septicaemia, meningitis or other), predisposing factors, antibiotic therapy, medicine and the general condition of the patient are reported on a voluntary basis. The case definition for listeriosis used in Denmark is according to the case definition by the European Commission [5]. Cases are divided into groups of sepsis, meningitis, materno-fetal infection or other, according to the site of isolation of *L. monocytogenes* and/or clinical presentation reported in the patients' charts. Hence a patient with a clinical diagnosis of meningitis may be counted as such even if *L. monocytogenes* was not isolated from cerebrospinal fluid but from another body fluid. Materno-fetal cases include pregnancy-associated cases and listeriosis in newborns in the first month of life. A materno-fetal infection counts as one case and is reported on the mother.

For the present report, mortality information was obtained from the Danish Civil Registry System (CPR-registret). To estimate the case fatality rate, death within 30 days of sample date was arbitrarily defined as death related to listeriosis. *L. monocytogenes* isolates from human cases are routinely typed by pulsed-field gel electroforesis (PFGE) to detect clusters as a means to survey for outbreaks. PFGE is performed according to the PulseNet method using the two enzymes *Asc*I and *Apa*I [6]. The number of cases in 2009 was compared to the number of cases in 2008. A *P* value was calculated using a likelihood ratio test, under the assumption that the annual number of cases follows a Poisson distribution.

Results

In 2009, 97 cases of listeriosis (1.8 per 100,000 population) were reported in Denmark, compared to 57 in 2008 (P=0.0014). Fifty cases were in females; three were materno-fetal infections. In the period from 1989 to 2008, the annual incidence varied between 0.4 and 1.1 per 100,000 (Figure 1).

The incidences in the age groups were 0.4, 3.7, 7.3, 12.1 and 22.0 per 100,000 for the age groups 0-59, 60-69, 70-79, 80-89 and 90+ years, respectively (Figure 2).

A review of the patients' clinical information did not reveal predisposing factors to listeriosis other than those already known (malignancies, diabetes mellitus, old age, pregnancy, immunosuppressing diseases and treatment) [7]. As not all clinical data from previous years are available as yet, a comparison with previous years was not possible for this analysis, however, the available data do not exclude that there may have been an increase in a single patient group. The distribution of clinical manifestations is depicted in Figure 3. The

sepsis to meningitis ratio remained at approximately five, largely unchanged compared with previous years. The incidence of materno-fetal infection was 4.8 per 100,000 live births. This was not higher than seen previously [1].

The case fatality rate was 28% in 2009, which was similar to previous years [7]. PFGE typing revealed 51 PFGE types among the 97 isolates from 2009. The most common type, type 42-40 (first profile in Figure 4) with 16 isolates scattered throughout the year, had also been commonly seen in previous years, representing 21% of the isolates in 2006 to 2009.

In the spring of 2009, a verified outbreak included eight cases [8]. The involved PFGE type (type 43-71; Figure 4) had not previously been seen in Denmark. In the autumn of 2009, a cluster of seven cases was identified by PFGE, but could not be confirmed as an outbreak. The PFGE type of this cluster (type 23-03; Figure 4) is a fairly common type represented by between two and five cases per year in previous years.

Figure 1

Annual incidence of listeriosis per 100,000 inhabitants, Denmark, 1989-2009

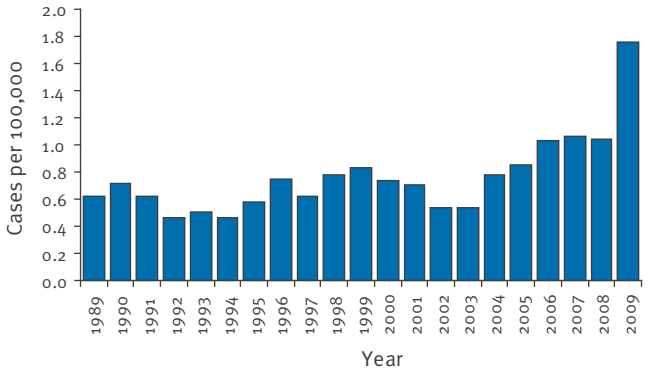


Figure 2

Annual incidence of listeriosis per 100,000 inhabitants by age group, Denmark, 2003-2009

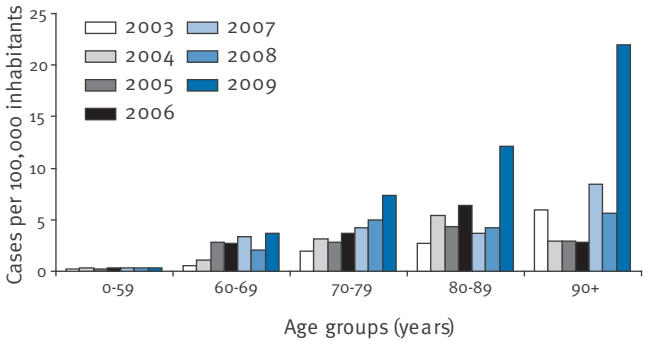
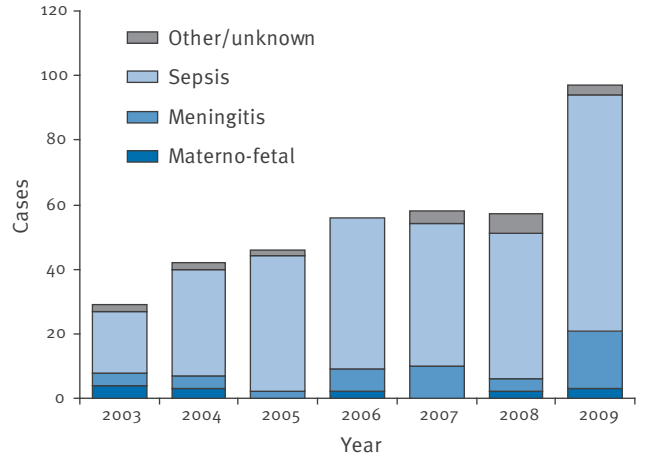


Figure 3

Distribution of clinical manifestations in reported listeriosis cases, Denmark, 2003-2009



Discussion

There has been a general increasing trend in the number of listeriosis cases in Denmark since 2003 and an additional marked increase from 2008 to 2009. The increase in listeriosis incidence in 2009 was seen particularly in the group of patients over 70 years of age. There is no single explanation for this dramatic increase. PFGE typing showed a high diversity of isolates in 2009 as well as in previous years, and the rise cannot be explained by a higher number of cases with any specific *L. monocytogenes* type. Even disregarding the 15 patients from the two clusters, the incidence is still very high (1.5 per 100,000). It is difficult to explain the steep increase from 2008 to 2009. However, several possible explanations for the general increase are conceivable; examples of such are listed in the Table.

There are indications that the consumption of ready-to-eat (RTE) products has increased. Consumer surveys from Statistics Denmark, comparing the period from 2005 to 2007 with the period from 2003 to 2005 indicates that expenditures for RTE products have increased by 87% for RTE meat products and by 34% for RTE fish products among individuals older than 60 years and living alone [9]. It will be valuable to obtain data on the frequency of contamination of RTE products with *L. monocytogenes* from the survey recently launched by the European Food Safety Authority [10], which should aid in assessing whether consumption of these products could represent a risk factor for acquiring listeriosis.

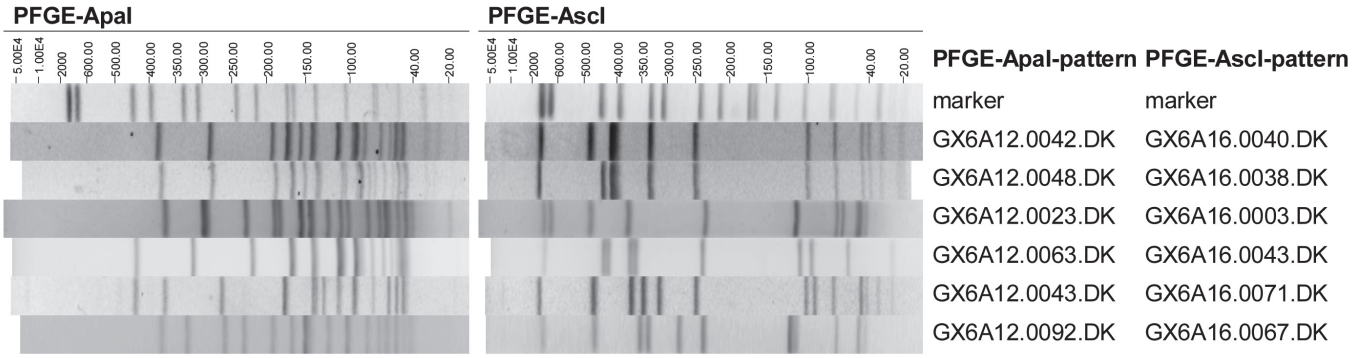
Susceptibility in the population may increase if the group of persons with predisposing factors, including immunosuppressive conditions and high age, grows [11], for instance due to better medical treatment and survival of seriously ill people such as cancer patients. As seen in Figure 2, the incidence has risen substantially within the group of over 70-year-olds, so demographic changes alone do not explain the increase. Because an increase is seen in sepsis and in meningitis cases (Figure 3), it seems unlikely that it can be explained by improved routines in taking blood cultures. Nor have, to our knowledge, healthcare practices and reporting procedures changed in recent years.

Another hypothesis to explain the increase in incidence would be that changes in empirical antibiotic therapy of patients presenting with sepsis could contribute to higher detection rates. While Danish recommendations formerly advised a combination of a penicillin and an aminoglycoside for the treatment of sepsis, the practice has now changed in many places in favour of cephalosporines as first-choice antibiotics. Cephalosporines, to which *L. monocytogenes* is resistant, are now the most used group of antibiotics in hospitals [12]. If samples for culture are taken after initiation of systemic antibiotic treatment, this could result in fewer false-negative samples. However, the change in treatment has come over several years and while it could have contributed to the gradual increase seen over several years, it seems unlikely that this alone would explain an increase from one year to another.

Unexplained year-to-year fluctuations in the incidence of listeriosis have been reported from several countries [2-4], and could be due to random variations in incidence. In 2010, seven cases of listeriosis have been reported in Denmark as of 1 March. Over the last 17 years, the number of cases in the two first months of the year has varied between two and 13, and it is still too early to predict a trend for 2010. The human, food and environmental sectors involved in listeriosis surveillance in Denmark are currently working together to gather all relevant information about the situation in order to find possible explanations and strategies for future intervention and prevention. Further investigation into typing of isolates and into consumption and handling of foods in the at-risk groups are among the possibilities being considered. Hopefully the results of these investigations will give indications as to possible public health interventions. Communications from other European countries on the situation and suggestions to explain the rise in cases seen in several countries will be of high value.

Figure 4

Representatives of the most common PFGE profiles in listeria isolates in Denmark in 2006-2009 (listed according to prevalence)



PFGE: pulsed-field gel electrophoresis.
The clusters in spring and autumn had the types 43-71 and 92-67, respectively. PulseNet nomenclature for type 43-71 is *Apa*I-pattern GXBA12.0043.DK, *Asc*I-pattern GXBA16.0071.DK.

Table

Potential explanations for the observed increase in the number of *Listeria monocytogenes* infections in Denmark

Overall explanation	Examples
Increased exposure	Increased consumption of ready-to-eat products
	Higher levels of contamination in specific products
	Suboptimal food storage conditions by the consumers
Demographic changes	More elderly in the population
	More persons alive with illness predisposing to listeriosis
	More people taking medicine predisposing to listeriosis
Outbreaks	People infected with specific bacterial strains from the same food source
Changes in strains	Increased virulence of *L. monocytogenes* isolates from patients
Surveillance artefacts	Increased number of blood cultures taken
	Increased reporting
	Better diagnostic methods
	Changes in the empirical use of antibiotics in the hospital systems

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Q fever outbreak in Cheltenham, United Kingdom, in 2007 and the use of dispersion modelling to investigate the possibility of airborne spread

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We describe the investigation of an outbreak of Q fever in the town of Cheltenham, England. The outbreak was detected in June 2007, and prospective and retrospective case finding identified 30 confirmed or probable human cases. The investigation identified windborne spread of *Coxiella burnetii* from nearby sheep farms as the most likely source of infection. A telephone survey was conducted to identify risk practices at local farms. Subsequently the atmospheric dispersion model NAME was used to identify whether air from the identified farms with high risk practices had been carried into Cheltenham town centre during the risk period. Three high risk farms were identified and the modelling showed that air from all of these farms was carried over Cheltenham in the estimated risk period. The investigation resulted in an information campaign to farmers and production of improved advice for livestock farmers on reducing the risks of transmitting Q fever to humans.

Introduction

Q fever is caused by the bacterium *Coxiella burnetii*, which has major zoonotic potential and is found worldwide in many different animal species, including wildlife [1]. It is not a notifiable disease in animals or humans in the United Kingdom (UK). Infection in animals is mainly subclinical and inapparent, although it can occasionally cause abortion. However, specific laboratory examinations for *C. burnetii* are not undertaken routinely in animals in the UK, and the infection is only likely to be detected as part of in-depth investigations into major abortion outbreaks in domesticated ruminant species. Furthermore, the veterinary diagnostic tests that are currently available are of limited value. Hence accurate surveillance data on prevalence is lacking, although it is considered endemic in domestic animal populations [2-3]. Large numbers of bacteria are present in the placenta and birth products of infected animals and are released during delivery [1]. The bacterium persists in the environment in a resistant spore-like form which may become airborne and transported long distances by the wind [4-7].

Humans may contract disease by inhalation or, more rarely, by drinking unpasteurised milk or through tick bites. The incubation period varies from 10 to 14 days but may be as long as 39 days depending on the infectious dose [8]. Disease in humans ranges from asymptomatic to severe and can be fatal. It often presents with fever or influenza-like illness, but may cause pneumonia, hepatitis, meningoencephalitis or perimyocarditis. Rarely the disease becomes chronic and leads to endocarditis [9]. Infection, particularly early in pregnancy, may result in abortion, or later in pregnancy to premature labour [10]. Several human outbreaks of Q fever have occurred in the UK, some of which have been associated with windborne spread of contaminated material from infected animals and contaminated farmland [5,11-12].

On 29 June 2007, the Gloucestershire Health Protection Team was notified of five cases of Q fever in patients living in the town of Cheltenham, England with onset of illness between 1 May and 14 June. No cases had been reported in this area in the previous three years. An outbreak investigation team was summoned to investigate the outbreak, consisting of members of the Health Protection Agency South West (HPA SW), Gloucestershire Hospitals National Health System (NHS) Foundation Trust, Cheltenham Borough Council,

HPA Centre for Infections (CFI), Veterinary Laboratories Agency (VLA) and Defra. It was considered that airborne infection from infected animals was the most likely source of the outbreak and the investigations described here were subsequently initiated to pursue this hypothesis further.

Methods

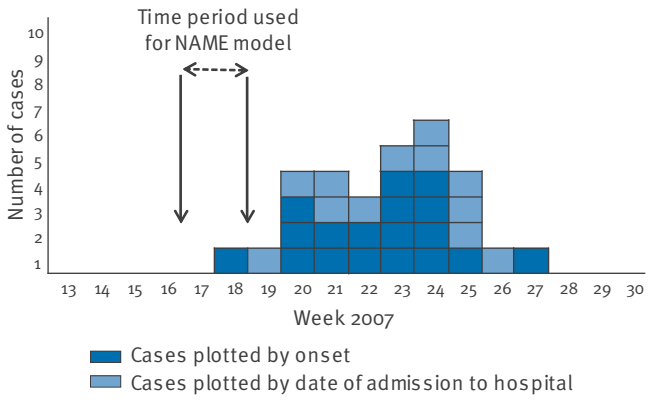
Epidemiological and laboratory investigations

Suspected cases were interviewed by telephone by staff of the HPA SW using a standard questionnaire for Q fever with additional questions relevant to the local area. The questionnaire included questions on: animal exposure, food history (including consumption of unpasteurised milk), risk activities, work details, tick exposure, distance of home to farmland and places visited. After a 6th case was reported, it was decided that active case finding should be undertaken. All General Practitioners (GPs) in the Cheltenham area were informed of the outbreak and encouraged to consider the diagnosis of Q fever in patients with relevant symptoms. Retrospective case finding was attempted by investigating hospital admission records for diagnoses of unspecified pneumonia. The purpose was to identify additional patients whose exposure history may have helped to identify a source of infection. No attempt was made to identify all possibly infected patients in the county as it was felt that self-limiting illnesses did not need to be identified. The most common presenting clinical feature that could be distinguished by clinical coding of admissions was searched for. Patients discharged with a diagnosis of unspecified pneumonia were contacted and asked to leave a blood sample for Q fever serology.

The standard laboratory method in use in the clinical diagnostic laboratory for screening for Q fever was the phase I and II complement fixation test (CFT) which, if positive at a titre of 1:16 or greater, prompted referral of the serum to the HPA reference laboratory for analysis by enzyme-linked immunoassay (EIA).

Figure 1

Epidemic curve for the outbreak of Q fever in Cheltenham 1 May-8 July 2007 (n=30)



Cases were plotted with date of onset if this information was known, otherwise the date of hospital admission was used.

The following case definition was used in the investigation: A confirmed case was defined as a person who lived in or visited Cheltenham between 1 April and 31 June 2007 who presented with pneumonia or clinical symptoms consistent with Q fever acquired during this time period. A confirmed case subsequently also needed to exhibit IgM antibody titres displaying assay positivity in serial dilutions of more than 1:80 or a four-fold increase of phase II CFT titres against *C. burnetii* with paired sera taken at least seven days apart. A probable case was defined as a person that lived in or visited Cheltenham between 1 April and 31 June 2007 who presented with pneumonia or clinical symptoms consistent with Q fever acquired during this time period. A probable case subsequently also needed to exhibit IgG antibody titres displaying assay positivity in serial dilutions of more than 1:80 or a single test with four-fold raised CFT titre against *C. burnetii* compared to baseline. The risk period for exposure was at the time of the ongoing outbreak investigation estimated to have been 23 April–7 May 2007. This period was chosen to cover the time distribution of cases from the earliest disease onset date minus maximum incubation period until onset of disease in the last detected case minus minimum incubation time. More cases were identified retrospectively. Testing for Q fever was initiated by GPs or hospital physicians on request of the Health Protection Agency South West on the basis of respiratory symptoms or symptoms of a influenza-like illness (such as malaise, lethargy, myalgia, arthralgia and headache). Additionally, blood samples received for testing for any respiratory pathogens were automatically included by the laboratory.

Veterinary investigation

The location of livestock farms in the vicinity of Cheltenham and the numbers of animals present were mapped using data obtained from the Animal Health Agency. The VLA was consulted regarding recent reports of Q fever affecting farm animals in the area. In order to further investigate the possibility that nearby livestock farms may have been the source of the outbreak, a semi-structured telephone questionnaire survey was carried out to investigate any potentially relevant disease history (i.e. abortions/reproductive failures) and husbandry practises on local farms that may have contributed to the risk. The selection of farms was based on their geographical location in relation to the distribution of cases, using meteorological information regarding the predominant wind directions at the likely time period of exposure. The likelihood of a farm being the source of the outbreak was categorised empirically using a qualitative risk assessment approach, where three categories of risk factors were assessed. Firstly, the risk of infection: human illness, reproductive problems in livestock and presence of ticks that are potential vectors for *C. burnetii*. Secondly, the risk of release: lambing/calving dates and place, manure handling and movement of animals. Lastly the risk of human contact: distance from town centre, distribution of manure

to public, transport of animals and manure in densely populated areas and public access to animals. The qualitative risk assessment was based on the proportion of risk practices present in relation to all possible risk practices. Since little is known about the relative importance of different risk factors for transmission of *C. burnetii* in farm animals, the practices were not weighted. The farms were categorised as low, medium or high risk, based exclusively on the risk assessment, without establishing whether *C. burnetii* was present in the animals.

Environmental investigation

In addition to livestock farms, other premises with livestock such as abattoirs and livestock markets were considered as possible sources. Information on these was obtained via the Meat Hygiene Service and local Animal Health offices. Information on other events involving animals which had been held in the area and the location of allotments (potential manure risk) were also collected. Risk sites were visited and investigated.

Meteorological investigation

Meteorological observations of near surface (10 m above ground) wind speed and wind direction in the time period before the onset of disease in confirmed and probable cases were obtained from the Met Office's observation site in Pershore approximately 30 km north of Cheltenham to help identify the source of the outbreak. This information was used to assist the veterinary investigation to decide on which farms to interview as described above.

Later, Numerical Atmospheric-dispersion Modelling Environment (NAME) [13], an atmospheric dispersion model, was used to investigate potential airborne transport of the *C. burnetii* between a number of suspected sources (notably local farms identified by veterinary investigation) and the infected persons in Cheltenham. NAME has a wide range of applications including air quality forecasting, predicting the transport and spread of chemical, biological and nuclear material, producing volcanic ash forecasts, identifying source locations and strengths, investigating pollution episodes and airborne spread of diseases. The model can be run in forward mode, predicting the transport and spread of airborne material released from an identified source. Alternatively, it can be run in backward mode, predicting the transport backwards in time from an identified receptor point, thereby showing the air history of material arriving at the receptor point and identifying potential sources.

NAME was run for the estimated risk period 23 April to 7 May, both in forward mode to give the predicted area at risk from the suspected farms and in backward mode to give the air history for air arriving in Cheltenham. Input meteorological data used in this study to drive NAME was hourly three-dimensional meteorological data from the Met Office's numerical weather prediction model (the Unified Model [14]) with a horizontal spatial resolution of 12 km. The accuracy of the atmospheric dispersion modelling is directly related to the accuracy of the input meteorological data and, whilst the meteorological data is likely to represent the larger scale atmospheric motions, it is not expected to capture the small scale local flow within the urban conurbation of Cheltenham (e.g. channelling of the flow within street canyons).

Table

Patient demographics and presenting symptoms, Q fever in Cheltenham May-July 2007 (n=30)

Criteria	Number (%)
Age range	19-72 years
Male	21 (70%)
Female	9 (30%)
Hospital admission	24 (80%)
Identified retrospectively	15 (50%)
Smoker	11 current smokers (37%), 7 ex-smokers (23%)
Non-smoker	9 (30%)
Smoking status unknown	3 (10%)
Presenting symptoms:	
Fever	25 (83%)
Headache	17 (57%)
Myalgia/Arthralgia	18 (60%)
Chest pain	13 (43%)
Cough/Shortness of breath[1]	26 (87%), 13/15 non lookback (87%)
Nausea (N), vomiting (V), diarrhoea (D)	4 NVD, 3 NV, 2 N, 1 D
Other symptoms	2 Loin pain, 2 dizziness, 1 confusion, 1 skin rash

1 Because retrospective case finding was based on presentation with pneumonia, the proportion with cough that were not part of retrospective case finding is also shown.

Results

Descriptive epidemiology and laboratory findings

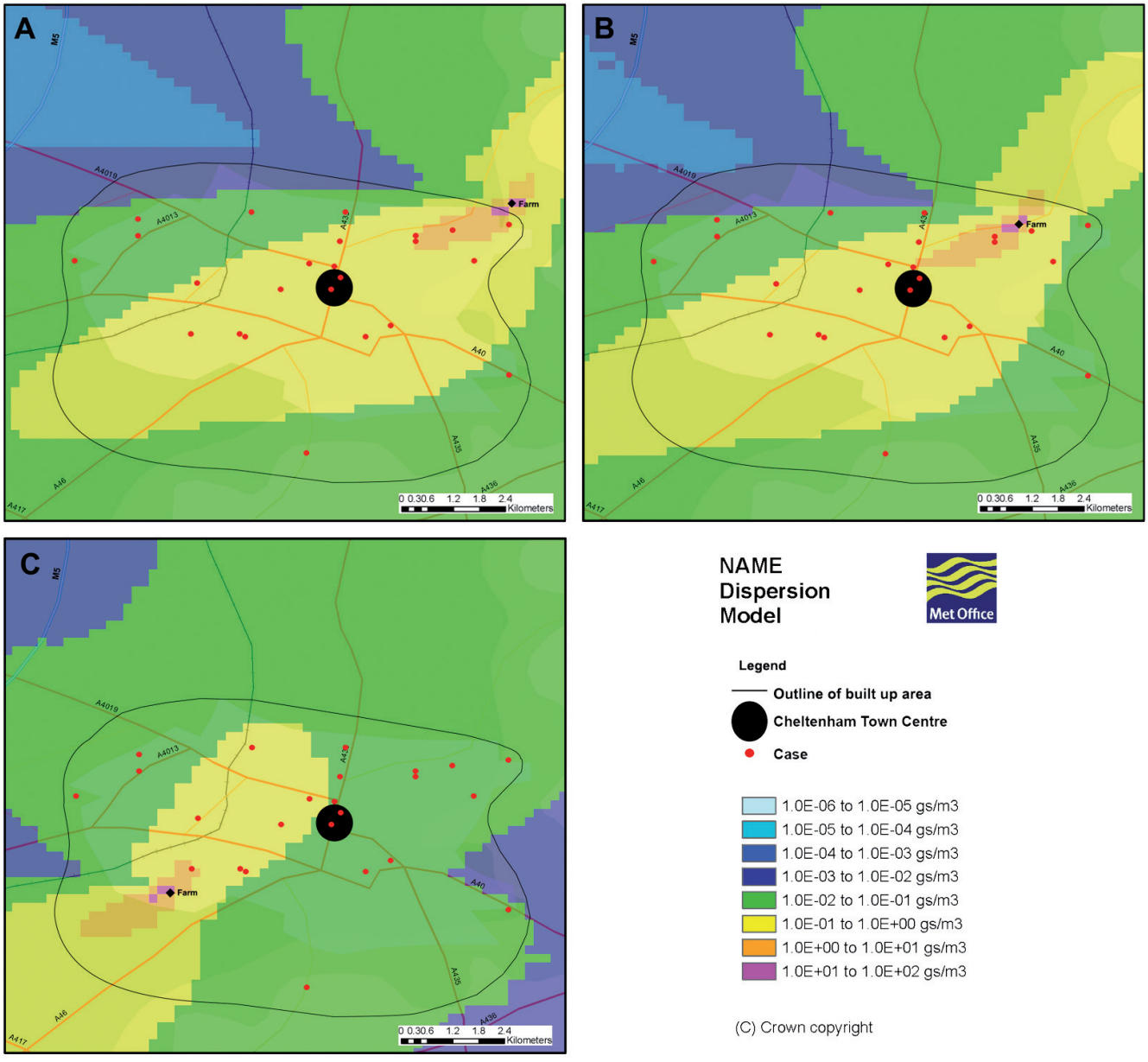
Interviews with suspected and confirmed cases did not reveal any common exposures other than living in or having visited Cheltenham town centre. The questionnaire did not identify any shared risk exposures or activities that could have resulted in transmission. The only factor the cases had in common was being a resident of or having visited central Cheltenham. A total of 30 cases all living in Gloucestershire were identified that met the case definition for a confirmed or probable case in the outbreak period. Fifteen had been identified through retrospective case finding among people hospitalised with pneumonia. Of the total of 30 cases, nine were female and 21 were male. The age range was 19-72 years and the median age was 48 years. The first onset of disease was on 1 May and the last on 8 July (Figure 1). Twenty-four cases were hospitalised. A summary of reported symptoms and demographics is given in the Table.

Veterinary investigation

There had been no recent reports of Q fever affecting farm animals in the area. We identified sixteen

Figure 2

NAME air dosage maps obtained by modelling a continuous release from the high risk farms (A, B, and C) for the time period 23 April-7 May 2007



NAME: Numerical Atmospheric-dispersion Modelling Environment.
The areas of highest dosage (pink, orange and yellow) covers Cheltenham town centre. A black diamond marks the location of the farm. Red dots mark the addresses of cases resident in Cheltenham. A black line illustrates the outer limit of the built up areas in Cheltenham. The filled black circle marks the town centre which all cases, including those not resident in Cheltenham, had visited at some time during the risk period for exposure.

farms that stocked farm animals in proximity to the Cheltenham town centre that were located along a south-west to north-easterly line to accommodate for the predominant wind directions for the period from 23 April to 7 May. Eleven farms completed the telephone survey. The remaining five farms either did no longer have livestock or could not be contacted. The risk assessment classified five low-risk farms, three medium-risk farms and three high-risk farms. The high risk farms A, B, and C were located 4.4 km, 2.7 km and 4.2 km from the town centre. All three farms stocked sheep and two farms also stocked cattle. Farm A calved and lambed during the risk period, transported a large batch of animals through Cheltenham town centre and sold manure to nearby allotments. Farm B reported outdoor lambing during the risk period and burning the fresh straw bedding and birth products outside every few days. This is an unusual management practice. Usually, abortion and birth products would be incinerated and bedding stacked up in a heap for a long time to kill pathogens before disposal. Farm C reported outdoor lambing and a few stillbirths and had several sheep movements close to the town centre.

Environmental investigation

The environmental investigation did not reveal any places or events in the town of Cheltenham that could have posed a risk during the estimated risk period from 23 April to 7 May.

Meteorological investigation

According to the meteorological observations from the Pershore observation site the predominant wind direction in the Cheltenham area during the estimated risk period was from the north-east and to a lesser extent from the south-west, which is the prevailing wind direction in the UK. Wind speeds were unexceptional, ranging from light winds to breezy conditions. Dispersion modelling using NAME showed that air from each of the suspected farms may have exposed the town to the bacterium at some point over the study period assuming there had been a continuous release (Figure 2). Therefore, none of the suspected farms could be ruled out as potential sources.

Discussion

At least 30 people were infected with *C. burnetii* in this outbreak. Further cases were not sought from household contacts or those with other possible presenting symptoms as the aim of the retrospective case finding was to aid the epidemiological investigation to identify the source of the outbreak. Previous outbreaks indicated that 2%-5% of those infected may be hospitalised [15]. Extrapolating from the 15 cases we identified retrospectively through hospital admission suggests that possibly up to 500 people may have been infected. The population of Cheltenham town is approximately 110,000 people and there are approximately 560,000 people in Gloucestershire who may visit Cheltenham as well as possible visitors from outside the county. National guidelines do not recommend the identification of all patients with Q fever and the seroprevalence among farmers, veterinarians, and people living in rural communities suggest that undiagnosed infection is common [15-16]. It was therefore not deemed appropriate to attempt mass screening.

The age and sex distribution of identified cases was similar to that of other outbreaks [1]. The epidemic curve shows that cases fell ill over a period of at least seven weeks, suggesting either that the release of bacterium was continuous or intermittent over a similar number of weeks or that the incubation period varied greatly. The incubation period may be prolonged when the infectious dose is small, which is likely in long-distance windborne transmission. No common risk factor was identified between cases other than living in, or having visited, Cheltenham and therefore we hypothesised that windborne spread of *C. burnetii* from nearby farms was the probable source of infection. Conditions were at times breezy, and strong winds have played a role in other outbreaks [5]. The predominant wind direction during the two-week period studied was from the north-east rather than the prevailing wind direction from the south-west which was the second most common wind direction. The telephone survey to the selected group of nearby farms revealed some high risk practices that could potentially have resulted in windborne spread. These were discussed with the farmers concerned and the practices ceased. Advisory information for farmers on Q fever control was also circulated via veterinary practices in England and Wales and put on VLA, HPA and HSE websites. Transportation of animals through populated areas has caused outbreaks previously [17], as have outdoor lambings [7]. One farm burnt the fresh straw bedding and birth products outside on several occasions, and this practice may facilitate windborne spread of *C. burnetii* by releasing incompletely burnt contaminated material into the air. The number of farms contacted was fairly small because of limited resources, but it included all the main livestock farms in the area. However, the possibility that we missed other farms with risk practices cannot be ruled out.

Laboratory investigation of the animals on the high-risk farms for evidence of *C.burnetii* infection was considered by the outbreak control team but was decided against, because the potential value of any results was perceived to be limited. The long time interval from the exposure date to sampling of the animals would complicate interpretation because, for example, farms may have sold infected animals that had aborted. Furthermore, interpretation of positive results would be complicated by the fact that little is known about the seroprevalence of infection in livestock in the UK generally and it would not be possible to put the serological results into perspective. The only scientifically viable option would have been to design a prevalence study combined with collection of risk factor information on all farms in the area. That was considered beyond the scope of this outbreak investigation.

To further support the outbreak investigation hypothesis that windborne spread from a local farm caused the cases in Cheltenham we employed the use of an atmospheric dispersion model. We chose NAME as this model has previously been used successfully to investigate airborne spread of diseases such as foot and mouth [18], bluetongue [19] and Legionnaires' disease. The model was run for the period from 23 April to 7 May. This time period was chosen as it would have explained the cases that were known at the time of the outbreak investigation but cannot explain all cases that were identified later. The modelling showed that air from all the farms was transported to Cheltenham town centre at some point during the period studied. Each of them could therefore have been the potential source of infection and none of the high-risk farms could be excluded. As we do not know the exact dates of transmission, we cannot say that one farm was more likely than the other, as the wind directions may have varied day by day within the studied period.

The modelling could, however, have been refined to potentially give more conclusive evidence, if further detailed information regarding the outbreak had been obtained such as more specific information on the potential time of release of *C. burnetii*, release rates of the bacterium, concentrations required for infection and exact time of infection. These parameters were not available due to uncertainties in the epidemiological investigation. Firstly, we know that all the cases lived in or visited Cheltenham town centre, but we do not know whether their presence coincided in time with windborne transport of contaminated air to Cheltenham town centre from a high risk farm. Secondly, the area of risk of exposure calculated by the atmospheric dispersion model may be an overestimate, if the release of *C. burnetii* was not continuous over the two-week transmission period identified. The release may not have been continuous as the time period between disease onsets suggests that people were infected intermittently over an extended period. Thirdly, although *C. burnetii* infection is considered endemic in UK farm animals, precise information about the infectious status of the investigated farms was unavailable. A well structured serological survey to measure the extent of *C. burnetii* infection in farmed livestock in the UK would answer questions relating to prevalence and relative geographical risk to the human population and greatly assist any further similar outbreak investigations.

Conclusion

Despite limitations, we believe that atmospheric dispersion models can be a valuable tool in similar outbreak investigations and this is supported by other disease outbreak studies using NAME [18-19]. In the Cheltenham outbreak it added support to our hypothesis of windborne spread of *C. burnetii* from a high risk farm, when an analytical study was not feasible. Furthermore, this investigation identified likely risk practices on local farms and engaged concerned stakeholders in the consideration of preventive measures leading to improved advice for farmers [20]. Enhanced local surveillance in the area in the following year (2008) did not reveal any cases of Q fever which suggests that high risk practices may have ceased.

Finally this investigation showed the strength and benefits of different agencies and authorities working closely together. In this investigation the close collaboration and information exchange between veterinary, human health, and meteorological agencies and the local authorities was perceived as beneficial by all involved. We believe that sharing and applying different techniques and information between different fields of research is of paramount importance for successful outbreak investigations.

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Risk groups and other target groups – preliminary ECDC guidance for developing influenza vaccination recommendations for the season 2010-11

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Providing guidance on risk and target groups for seasonal influenza immunisation is difficult for the 2010-11 season since there is no experience with the new influenza A(H1N1) virus in its seasonal form. Arguments exist for offering immunisation to people with chronic illness and older people, and also for other risk and target groups including pregnant women. A more rigorous approach is being developed to produce annual evidence-based guidance on risk and target groups for influenza vaccination.

The 2009 influenza A(H1N1) pandemic has changed the landscape for seasonal influenza [1]. While more than one scenario is possible for the next influenza season (2010-11) the most likely prospect identified in a *Forward Look Risk Assessment* by the European Centre for Disease Prevention and Control (ECDC) is that the new influenza A(H1N1) virus will dominate [2]. Such a 'new' seasonal influenza will be different from the 'old' influenza and presumably have similarities to the autumn/winter pandemic wave of 2009 (Table 1), although there will presumably be less transmission because of immunity in the population following the 2009 transmission and immunisation programmes.

The presence of drifted influenza A(H3N2) viruses cannot be ruled out and influenza B viruses will be an inevitability [2]. Pandemic strains also always change, and another possibility is a drifted influenza A(H1N1) virus with somewhat different properties such as higher transmissibility or higher morbidity in older people. It is currently unknown if infection or vaccination in 2009 and early 2010 will result in immunity and protection in that situation, and the World Health Organization (WHO) and the European Medicines Agency (EMA) have recommended all three antigens for next season's vaccines (pandemic influenza A(H1N1), influenza A(H3N2) and influenza B) [7].

A more severe season than the autumn/winter wave of 2009-10 cannot entirely be excluded [2]. This happened in the second winter of the last ('Hong Kong') pandemic when the virus became more transmissible and killed more people in its second European season (1969-70) than in 1968-69 [2,8]. Under those circumstances the unused stocks of the adjuvanted pandemic vaccines with a very good safety profile would be invaluable, provided that the necessary stability for use next autumn is documented.

Particular uncertainty arises over the risk groups and target groups. This is important as in European countries the influenza vaccination strategy is based on protecting the vulnerable. ECDC has previously produced evidence-based guidance to help European Union (EU) Member States decide on these groups. This was done based on the evidence from interpandemic (seasonal) influenza from 1970 to 2007 [9]. ECDC is obliged to produce such guidance annually under a new Health Council Recommendation that foresees the following [10]:

The Member States are encouraged to adopt and implement national, regional or local action plans aimed at improving seasonal influenza vaccine coverage to a coverage rate of 75% for older age groups and if possible for other risk groups, preferably by the 2014-15 season;

- The Member States' action plans and policies are to take into account definitions of older age groups and risk groups as contained in guidance by ECDC as well as measurements of uptake in all risk groups and analyses of why some people do not wish to receive vaccination;
- The Member States are to foster education, training and information exchange on seasonal influenza and vaccination by organising information action for healthcare workers, information action for risk groups and their families, and organising effective information to remove obstacles to vaccination uptake;
- The Member States are invited to report on a voluntary basis to the Commission on the implementation of this recommendation, in particular vaccination coverage achieved among risk groups;

- The Commission is invited to report regularly to the Council on the implementation of this recommendation, on the basis of the data the Member States will make available.

With a new seasonal influenza based on a pandemic virus that behaved differently from the old seasonal influenza (Table 1), solid evidence-based guidance cannot be produced at present. However, a number of countries have to order vaccines for the coming season now, and the size of those orders depends on decisions on which groups to immunise. The objective of this paper is to satisfy its new obligation and to answer questions received from countries by discussing the issues that they should take into consideration when making such decisions.

There is one particularly important difference between the coming season and the pandemic period. When risk groups and other target groups for pandemic vaccines were identified in the summer of 2009 by the WHO Strategic Advisory of experts on Immunization (SAGE) [11] and the EU Health Security Committee, the initial vaccine supply was limited and had to be rigorously

Table 1

Differences between old seasonal influenza and 2009 pandemic influenza in Europe

	Seasonal influenza 1970-2008	2009 pandemic influenza
Circulating influenza viruses	Two influenza A viruses: A(H1N1), A(H3N2) and some influenza B viruses	Almost exclusively pandemic influenza A(H1N1), a few influenza A(H3N2) and some influenza B viruses
Antiviral resistance	Common and transmissible oseltamivir resistance in influenza A(H1N1) viruses (2008-9) and adamantane resistance in influenza A(H3N2) viruses	Rare and to date only transmitting under certain circumstances
Setting for transmission	Probably any setting where people come together	Schools are considered especially important, along with homes
Experiencing severe disease	Those in clinical risk groups and older people	Young children, pregnant women and those in clinical risk groups, but 20–30% of people experiencing severe disease were outside any risk group Many people born before the mid-1950s seem to be immune, but those who are not do experience severe disease, more so than any other age group.
Acute respiratory distress syndrome	Extremely rare	Uncommon but does occur, even in young fit adults.
Mortality	Few confirmed deaths reported each year in official statistics Estimates of up to 40,000 deaths in a more severe year in the European Union (EU) using statistical methods [3] based on European data [4,5]	Substantial numbers of confirmed deaths announced by the EU Member States (over 2,800 deaths as of March 2010) Not yet calculated for the EU, but estimated in the United States at over 11,000 deaths [6]

Table 2

Risk groups for seasonal influenza 2008-9 and pandemic influenza 2009

	Seasonal influenza up to 2008-9		Pandemic influenza 2009	
	Risk of severe disease and death	Vaccine effectiveness	Risk of severe disease and death	Comments
Potential risk groups				
Persons with chronic diseases	Increased, well documented	Limited documentation	Increased, well documented	Included people with morbid obesity and children with neurodevelopmental conditions
Older people	Increased, well documented	Reasonable documentation	Low incidence, but highest risk of complications of any age group if infected	
Pregnant women	Possibly increased, limited documentation	Unclear	Increased risk of complications	Limited data and documentation from Europe [9]
Children	High incidence, complication risk moderate	Good documentation	Increased risk of hospitalisations, less risk of severe disease	
Healthy adults	Low	Good documentation	Increased risk of severe disease and death	
Target groups for vaccination				
Healthcare workers	NA	Some documentation of reduced incidence in patients	NA	Unknown

NA: not applicable.

prioritised. That is no longer the case and vaccine can be produced in sufficient amounts for groups at both higher and lower risk. For lack of experience with the 'new' seasonal influenza except in its pandemic form, considerations will have to draw on the pandemic experience and public health judgement.

Persons with chronic underlying conditions

The previous risk group guidance for seasonal influenza highlighted persons with chronic diseases [9] (Table 2). In the 2009 influenza A(H1N1) pandemic those with chronic diseases were also a risk group, though with some differences as there were some new high risk groups like chronic neurological diseases and morbid obesity [12].

Older people

Older people were another recognised risk group for the 'old' seasonal influenza [9]. In the 2009 influenza A(H1N1) pandemic they had a low incidence of influenza probably due to pre-existing immunity. However, the risk of complications and death in older people who were infected was higher than in any other age group [12]. They will also be at risk from A(H3N2) and B influenzas. When there is no shortage of vaccine the existing limited evidence and public health considerations would therefore support efforts to vaccinate even healthy older people.

Pregnant women

The evidence for risk of complications from the 'old' seasonal influenza in otherwise healthy pregnant women was contradictory [14]. With the pandemic influenza, however, they were one of the risk groups, though European data are as yet scarce [12]. Whether they will still be at increased risk with the 'new' seasonal influenza is unclear [2]. In some countries, vaccination coverage with pandemic vaccine in pregnant women was high last autumn, but vaccination started too late to give clear indications of effectiveness. The safety record has been reassuring [13]. For this group the probable risk of complications from influenza infection will have to be weighed against a reluctance to vaccinate pregnant women in some countries and the limited knowledge about vaccine effectiveness. Questions about adjuvanted vaccines may not arise, because most manufacturers have stated they will not be using adjuvants for the seasonal vaccines.

Children

There has been a general recommendation in the US and also in a few European countries (Finland and some other) for vaccination of all children older than six months against seasonal influenza [15]. The documentation of the burden of disease presented by the 'old' seasonal influenza in Europe was considered too limited to produce general guidance [16]. However, the incidence of paediatric disease and complications during the pandemic waves was considerable [12].

There are practical difficulties in introducing general paediatric influenza immunisation. Immunisation of immunologically naïve young children may require two doses of vaccine. The more acceptable nasal live attenuated vaccines are not available in Europe, and scheduling injectable doses between the vaccines already recommended for infants in the childhood immunisation programmes is a problem. These difficulties must be weighed against the risk of severe influenza outcomes and the possibility of indirectly protecting other risk groups by vaccinating children [17].

Healthy young adults

One of the unusual features of the 2009 pandemic influenza A(H1N1) was the appearance of complications and deaths in young, healthy adults [12]. This is a phenomenon also seen in other pandemics, most clearly in the 'Spanish Flu' 1918-20. It is unknown whether an increase in the rates of complications in healthy young adults will occur during the next influenza season, but the US has included them in their targeted groups for immunisation to the effect that vaccination is recommended for everyone over the age of six months (although actual coverage for this group is well under 50%) [18]. This is one of the fields where more knowledge is most needed, and decisions are most difficult.

Healthcare workers

Information on policies, practices, and coverage for influenza vaccination in Europe is gathered through annual surveys by the Vaccine European New Integrated Collaboration Effort (VENICE) Project [15]. These surveys document that among the many potential target groups healthcare workers are the group most commonly identified for vaccination, and ECDC guidance has highlighted them because of their risk of transferring the infection to persons in the risk groups [12].

Conclusion

There will inevitably be epidemics of influenza during the winter of 2010-11, with the new influenza A(H1N1) probably dominating. However, the scientific information for evidence-based guidance for vaccination is presently insufficient for a more precise guidance. To fulfil its new obligations, ECDC will be undertaking annual reviews of the accumulating information that will first come from the southern hemisphere from July 2010 onwards and then every year in the European influenza seasons.

In the meantime the public health justification for vaccinating people from the age of six months with chronic diseases, older people and healthcare workers seems to be sufficient to identify them as target groups for vaccination. There are also some reasons to believe that pregnant women, young children and young healthy adults will be at risk from a seasonal influenza dominated by the new influenza A(H1N1) viruses. This must be weighed against the limited knowledge about vaccine effect, the costs and the practical difficulties related to vaccination when the recommendations for the coming season are decided.

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