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Tick-borne encephalitis joins the diseases under surveillance in the European Union

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Climate and environmental changes are suspected as major determinants that alter the distribution and transmission patterns of certain communicable diseases, especially those transmitted by arthropods, such as ticks (e.g. tick-borne encephalitis (TBE) and Lyme disease), mosquitoes, (e.g. Chikungunya and Dengue fever), or sandflies (e.g. visceral leishmaniasis). Apart from the effect on the natural conditions and favouring a wider distribution of vectors which may carry diseases, they can also influence occupational and recreational human behaviour and lead to an increased exposure to the risk of infectious diseases e.g. through increased time spent outdoors and harvesting food in woodlands with high concentrations of ticks [1-3].

In the European Union (EU), climate and environmental changes are believed to be a cause for the recent resurgence of 'old suspects' such as malaria, as well as the geographic expansion of diseases like West Nile fever or TBE [4].

On 5 September 2012, TBE was included in the list of notifiable diseases in the EU. The main European Commission Decisions on communicable diseases were amended to include TBE in the list of diseases for EU notification, along with it's own new case definition [5-7].

In 2011, TBE was already mandatorily notifiable in 15 European Union (EU) and European Economic Area (EEA) countries [8]. However, a reliable estimate of the incidence of TBE is not available due to differences in diagnosis, case definition and reporting in different endemic countries. Thus, the overall epidemiology and burden of tick-borne encephalitis in Europe remains unclear [8].

The aim of the new, common case definition is to provide high validity and good comparability of TBE data from the EU Member States to be able to better study this disease. It is hoped that reliable surveillance data will help in better mapping the disease risk. Such information available at the EU level should also facilitate development of more efficient prevention and control programmes at both national and international levels.

Tick-borne diseases are the most common vector-borne diseases in Europe with their infection rate and geographic distribution in Europe increasing since the 1980's. TBE is a viral tick-borne communicable disease that occurs in endemic areas across large regions of Europe and also in Asia. Most human cases occur following a bite by an infected tick. Consumption of raw milk and derived products is another mode of transmission of the disease [9]. The vectors of TBE virus in Europe are Ixodidae hard ticks, mainly *Ixodes ricinus* in central, northern and eastern regions and *Ixodes persulcatus* in parts of the Baltic States, Finland, and in Russia. The cycle of transmission of the virus includes reservoir hosts which are mainly small rodents.

TBE infection is described as a febrile influenza-like illness usually lasting 2 to 4 days followed by a symptom-free interval lasting a few days. For an estimated 20-30% of the patients it evolves in a neuroinvasive illness (e.g. meningitis, meningoencephalitis, meningoencephalomyelitis or meningo-radiculitis) which appears suddenly [9]. Every year, the TBE virus causes thousands of cases of neuroinvasive illness in humans across Europe and Asia and is becoming a growing public health concern despite that the disease is preventable by vaccination [10]. The true burden of the disease at EU level still has to be established even though it is known that TBE demands high costs for healthcare systems with intensive care in hospitals, and it's possible long-lasting sequelae [8].

Enhanced surveillance is needed to prevent and control TBE

The distribution of TBE cases in Europe indicates areas with different levels of endemicity. A harmonised approach for case reporting will allow for endemic foci mapping within the EU to support recommendations regarding identified risk groups of population, vaccination programmes, and recommendations for travellers [11]. In a majority of cases the location of infection by tick bites would not be precisely recorded from the patient but cross-linking information should increase

the mapping accuracy and the detection of changes in pattern distribution. In addition, various surveillance strategies, including screening of vector ticks and testing of animal hosts, should be better harmonised and be done more systematically in Europe to better understand the changing patterns of TBE.

Large amounts of environmental and epidemiological data are already collected in databases in the EU, which are mostly publicly available. However, these data are not brought together for analysis. ECDC is developing a European Environment and Epidemiology (E3) Network with an aim to better integrate environmental and disease data to increase our understanding of their complex relationships and to drive public health action. In the context of its mandate, ECDC is looking at possibilities to improve monitoring systems, that have the capability to connect epidemic intelligence and infectious disease surveillance data that are collated and hosted by ECDC, with meteorological variables, water quality records, air quality measures, remote sensing information, agricultural practices, etc.

At European level, ECDC is also pursuing how best to expand networks working in vector surveillance to monitor the distribution of vectors, for example tick species such as *Ixodes ricinus* vector of TBE and *Lyme borreliosis* or *Hyalomma marginatum*, a main vector of Crimean-Congo hemorrhagic fever. Enhancing global and regional surveillance and control of disease vectors has started in Europe in the VBORNET project since 2010 [4].

The new case definition and notifications of TBE together with a range of other surveillance activities are an important step to continue to improve the level of evidence on TBE in Europe to better help guide policies and measures to lower the burden of this vaccine-preventable disease.

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Incubation period as part of the case definition of severe respiratory illness caused by a novel coronavirus

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Non-specific symptoms of acute respiratory viral infections make it difficult for many countries without ongoing transmission of a novel coronavirus to rule out other possibilities including influenza before isolating imported febrile individuals with a possible exposure history. The incubation period helps differential diagnosis, and up to two days is suggestive of influenza. It is worth including the incubation period in the case definition of novel coronavirus infection.

Introduction

Two cases of severe respiratory infection have been confirmed as caused by a novel coronavirus [1]. The case definition has been issued by the World Health Organization (WHO), and is mainly based on acute respiratory illness, pneumonia (or suspicion of pulmonary parenchymal disease) and travel history [2]. To describe the clinical characteristics of the novel coronavirus infection, the incubation period has played a key role in suspecting Saudi Arabia and Qatar as geographic locations of exposure for the two cases mentioned above [1,3]. The presumed length of the incubation period was compared with known incubation periods of human coronavirus infections including that of severe acute respiratory syndrome (SARS) [3,4]. The present study intends to point out that the incubation period can be useful for all countries without ongoing transmission to distinguish the novel coronavirus infection from other viral respiratory infections, most notably influenza.

Methods

Motivating case study

A preschool child from Saudi Arabia was admitted to a Hong Kong hospital equipped with an isolation ward in early October 2012, suspected of novel coronavirus infection. It had fever, cough and vomiting, but did not have pneumonia. One close contact had had a fever two days earlier, but had recovered before the day of admission [5]. Assuming that the contact was the source of infection, the serial interval was two days, which is typically longer than the incubation period [6,7], and thus, the incubation period is likely to have been two days or shorter. On the day following admission, the child tested negative for the novel coronavirus, but positive for influenza A(H1N1)pdm09 [5].

A similar event, but involving two cases of severe pneumonia, occurred in Denmark: A cluster of febrile patients, some of whom had a travel history to Qatar and Saudi Arabia, was suspected of infection with the novel coronavirus. However, later laboratory testing revealed that the respiratory illnesses were caused by infection with an influenza B virus [8].

We believe that the distinction between coronavirus and influenza virus infections in these settings could have been facilitated by considering the length of the incubation period.

Bayesian model

Let $f_i(t|\theta_i)$ be the probability density function of the incubation period t of virus i governed by parameter θ_i. The incubation period distributions for a variety of acute upper respiratory viral infections have been fitted to log-normal distributions elsewhere [4,9] and are assumed known hereafter. The median incubation periods of SARS, non-SARS human coronavirus infection, and influenza A and influenza B virus infections have been estimated at 4.0, 3.2, 1.4 and 0.6 days, respectively [4]. It should be noted that the median incubation periods of influenza A and B have been estimated as shorter than those of coronaviruses. The incubation period f_i is assumed to be independent across different viruses i. Due to shortage of information, we ignore the time-dependence and geographic heterogeneity in the risk of infection for all viruses. The posterior probability of novel coronavirus infection (which is labelled as i=1) given an incubation period t, Pr(novel coronavirus|t) is then obtained by using a Bayesian approach:

$$\Pr(novel\ coronavirus|t) = \frac{q_1 f_1(t|\theta_1)}{\sum_i q_i f_i(t|\theta_i)} \quad (1)$$

where q_i denotes the prior probability of virus i (e.g. q_1=Pr(novel coronavirus); the probability that the novel coronavirus is responsible for acute respiratory viral infection with unknown aetiology among all such infections), which can be equated to the relative frequency of virus i infection during a viral aetiological study (e.g. using the relative incidence by aetiological agent) [10,11]. Since the observed data are recorded on a daily basis, the incubation period in (1) is discretised as,

$$f_{i,t} \Rightarrow \int_0^t f_i(s|\theta_1)ds - \int_0^{t-1} f_i(z|\theta_1)dz \qquad (2)$$

for t>0.

Since the prior probability q_i is unknown for imported cases with acute respiratory illness, two conservative approaches, which would not lead to an underestimation of the probability of novel coronavirus infection, should be taken. Such approaches include (i) allocating an equal probability as the prior probability for all possible viruses (e.g. for a differential diagnosis of two viral diseases, we allocate 0.5 for each) or (ii) using results from published viral aetiological studies among people with an acute respiratory disease (e.g. using virus detection results among influenza-like illness (ILI) patients). As an example for the latter approach, the observed numbers of coronavirus infections and influenza A and B virus infections among 177 ILI cases in children with known viral aetiology have been 12, 40 and 5 cases, respectively, in Madagascar [12]. Here we focus on this particular dataset among children only, because the case in Hong Kong, whom we want to use to exemplify our theoretical idea, was of preschool age. Moreover, we used the data from Madagascar, because this study appeared informative as it closely investigated the frequency of different types of human coronaviruses among ILI cases in children [12]. It should be noted that n=12 in Madagascar does not represent the frequency of novel coronavirus infections, but the frequency of infections caused by other human coronaviruses, while the estimation of the posterior probability of novel coronavirus infection using equation (1) requires the prior probability of the novel coronavirus. Here we use this figure for the novel coronavirus, for the purposes of presenting of our theory.

Results

The Figure (panel A) shows the conditional probability of coronavirus infection given the incubation period (based on equation (1)), in a setting where one has to differentiate coronavirus infection from influenza virus infection, assuming an equal probability of 0.5 for either virus. Assuming that the observed incubation period of the child in Hong Kong was two days, the probability of non-SARS human coronavirus infection is smaller than 0.1%. When using the incubation period of SARS as a reference to represent the incubation period of novel coronavirus, the probability of the coronavirus infection with a two-day incubation period is 15.7%. In other words, the probability of influenza A given a two-day incubation period is as high as 99.9% and 84.3%, respectively, when comparing between influenza A and either non-SARS or SARS coronaviruses. Various control measures, including case isolation, contact tracing and laboratory testing can make use of this probability (e.g. contact tracing may assume that new generations of cases would arise on average every three days, consistent with influenza transmission). A calculation for influenza B virus yielded qualitatively similar results (Figure, panel A).

It should be noted that the actual relative frequency of novel coronavirus is much smaller than that discussed here, due to the absence of substantial human-to-human transmission events [3], while influenza A virus has already circulated in the human population. Thus, the posterior probability of novel coronavirus in reality would be much smaller than that illustrated in the Figure.

When we use the empirically observed frequency of human coronaviruses based on the viral aetiological study data among ILI cases in children (Figure, panel B), the probabilities of coronavirus and influenza A and B virus are estimated at <0.1%, 65.7% and 1.4%, respectively. It is remarkable that an ILI with the incubation period of two days is most likely to be caused by influenza A virus. However, novel coronavirus may be suspected if the incubation period is in the order of three to five days.

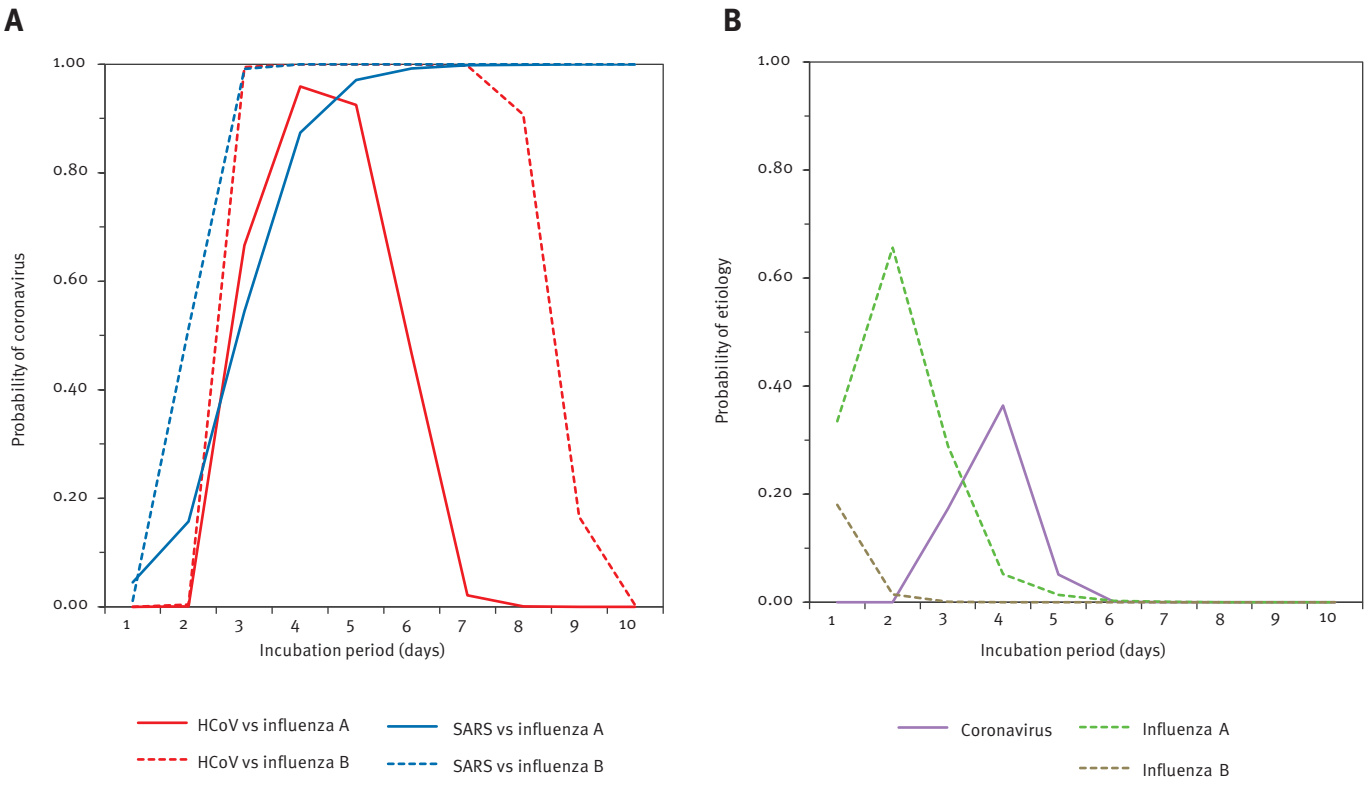
Discussion

As demonstrated in this report, the probability of infection with novel coronavirus can be inferred from the incubation period of each single case with suspected infection, which we believe is useful for deciding on a public health alert level and the extent of movement restriction and contact tracing among imported cases of acute respiratory viral infection, especially with mild and non-specific symptoms. We have shown that an incubation period of two days or shorter is strongly suggestive of influenza, while an incubation period from three to five days could potentially be consistent with the incubation period of human coronaviruses. Of course, the implementation of isolation measures, contact tracing and other interventions would also depend on other factors including the perceived importance and cost of the interventions, but we have shown at least that the incubation period would yield supplementary information for differential diagnosis and decision making. We believe that it is worth considering incorporating the incubation period into the case definition as soon as sufficient data on the incubation period have been collected.

In practice, the proposed approach suits case investigations (or outbreak investigations) in which precise information of contacts is collected, because estimates of the incubation period are often available. However,

Figure

Probability of coronavirus infection given the incubation period of a case



A. The probability of coronavirus infection given the incubation period, when comparing between coronavirus infection and influenza virus infection as possible diagnoses. We use 50% probability for each of the two viruses (i.e. coronavirus versus influenza virus) for a conservative argument to avoid an underestimation of the risk of novel coronavirus. Since known coronaviruses are classified into severe acute respiratory syndrome (SARS)-associated virus and non-SARS viruses, and because influenza viruses are crudely classified as type A and B viruses, there are four possible combinations for comparison. HCoV stands for human coronavirus infection other than severe acute respiratory syndrome (SARS).

B. The probability of coronavirus infection given the incubation period, using empirically observed viral aetiology data as a prior information among influenza-like illness cases in Madagascar [12] with a total of n=177 samples for those aged younger than five years. The observed number of isolates, i.e. Influenza A (n=40), Influenza B (n=5), HCoV (n=12) and others (n=120), were used to calculate q_i in equation (1). n=12 for ordinary HCoV is here used as if it gave the frequency of a novel coronavirus, for the purpose pf presenting our theory. The incubation periods of viruses other than influenza viruses and human coronaviruses were assumed to be uniformly distributed from day 1 to day 10, for a conservative argument to avoid an underestimation of the probability of novel coronavirus.

three common technical issues should be discussed. Firstly, as an infection event cannot be directly observed, multiple contacts can limit straightforward information on an incubation period. For instance, we cannot technically rule out the possibility that the child case in Hong Kong was exposed to someone other than the close contact before travelling to Hong Kong. Secondly, the incubation period tends to be crude, especially for the first few cases, e.g. when the length of travel with an exposure is long for imported cases. Thirdly, one cannot guarantee that the incubation period of a novel pathogen is always similar to that of closely related pathogens. For instance, the incubation period of *Escherichia coli* O104:H4 infection has been shown to be longer than that of *E. coli* O157:H7 [13]. To address the second and third point, it is essential to collect multiple datasets of the incubation period with a brief exposure.

In addition to its value in differential diagnosis, considering the incubation period has important public health implications. Firstly, to help differential diagnosis during the course of an epidemic of any novel infectious disease, the distribution should be estimated as early as possible. For this reason, the detailed travel history of imported cases should be explored, as it can inform the distribution of incubation periods [9,14]. Moreover, outbreak reports, including case reports, should explicitly and routinely document the detailed history of exposure (e.g. the length and timing of exposure along with the illness onset date) of all cases. Secondly, the overall risk estimate (e.g. the relative

incidence) would be essential to validate the proposed Bayesian model (1), although in reality, the prior probability varies considerably with time and place. To understand the ongoing risk of infection with a novel virus explicitly, a population-wide serological survey, which allows to infer at least the cumulative incidence, would be a useful method to offer insights into the aetiology. Finally, while estimating the relative probability of alternative aetiologies can help with diagnosis, decisions on possible control measures (such as isolation of cases) could also be affected by other concerns including reduction in the risk of larger outbreaks.

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Listeriosis outbreak caused by Latin-style fresh cheese, Bizkaia, Spain, August 2012

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Two cases of laboratory-confirmed listeriosis were detected in Bizkaia, Spain, at the end of August. The epidemiological investigation indicated that these two cases were associated with the consumption of Latin-style fresh cheese made from pasteurised milk in Portugal. Different batches of the same cheese were analysed and confirmed as contaminated with *Listeria monocytogenes*. The product was withdrawn from the market and the population was advised not to consume this kind of cheese.

Two cases of pregnancy-related listeriosis were detected in Bizkaia, Spain, between 28 and 30 August 2012: a pregnant woman and a newborn. The epidemiological investigation indicated that the pregnant woman and the mother of the newborn had consumed the same type of fresh cheese during the two months before symptom onset.

Listeriosis is a bacterial food-borne illness that can also be transmitted from the mother to the foetus during pregnancy or at birth. Possible symptoms of the illness in newborns and adults are meningoencephalitis, septicaemia, or both; it can also lead to abortion during pregnancy [1]. Listeriosis is an uncommon illness but quite severe. Therefore, it is important to be extremely careful with the food consumption behaviours of certain risk groups [2].

In Bizkaia (a territory of the Basque Country, in the north of Spain, with a population of nearly 1,150,000 inhabitants), the incidence rate of listeriosis in the last ten years has been variable, between 0.88 and 2.11 per 100,000 inhabitants, with a mean of 15 cases per year (range: 7–23 cases) [3].

During 2012, as of 30 September, 10 cases of listeriosis have been notified in Bizkaia. Of these, meningoencephalitis has been identified in three cases, septicaemia in another three and mother-foetal transmission in the other four cases. The mortality rate recorded in 2012 has been of 30%.
Of the ten cases of listeriosis investigated in 2012 in Bizkaia, the first eight were sporadic cases whereas the routine epidemiological investigation of the last two cases who occurred in August revealed the consumption of a particular kind of cheese (Latin-style fresh cheese) as mentioned above.

Epidemiological investigation

After the detection of the two cases in August, epidemiological questionnaires were carried out. The two cases were interviewed about their food consumption during the incubation period (two months before onset of the symptoms). For this outbreak, a listeriosis case was defined as an individual with clinically-compatible illness, from whom *Listeria monocytogenes* was isolated from a normally sterile site and who had consumed a Latin-style fresh cheese two months before symptom onset. This soft cheese, made from pasteurised milk in Portugal was mostly commercialised in shops selling Latin specialities, which are present almost in all the Spanish autonomous communities as well as in Italy and Portugal.

On 12 September, all listeriosis cases who had been notified in 2012 (n=10) were contacted and asked specifically about the consumption of the Latin-style fresh cheese, the dates they had consumed it and the shop where they used to buy the cheese. There were no cheese leftovers in any of the patients' homes.

Results

The index case detected on 28 August 2012 was a 36 year-old woman with a 35-week twin pregnancy. She was hospitalised on 24 August with fever (39° C) that had lasted for three days. *L. monocytogenes* was isolated in blood culture and the strain was characterised as 1/2a serotype. The epidemiological investigation revealed the consumption of Latin-style fresh cheese

bought in shop A, two months before the onset of symptoms.

The second case was a hospitalised newborn baby who developed sepsis at birth. *Listeria* was isolated in the blood culture of the baby and in the placenta and the strain was characterised as 1/2a serotype. The epidemiological investigation revealed that his mother had consumed Latin-style fresh cheese acquired in shop B, one month and a half before giving birth.

The evolution of the two patients was favourable. The first case gave birth to two healthy babies and the second case left the hospital in good condition after three weeks in hospital.

Public health technicians of Bilbao council inspected the two shops indicated by the patients (shops A and B). On 30 August samples of the cheese were collected from shop B for laboratory investigations. After the first results which indicated the presence of *Listeria*, new triplicate samples were collected on 7 September according to the Spanish legislation.

Listeria was found in all the six samples collected of the cheese; five of those samples were fairly beyond the food safety criteria (<100 cfu/g) [4,5] and one of them reached a value of $3.2x10^4$ cfu/g. All the strains isolated from the cheese in shop B were characterised as 1/2a serotype. In shop A, where the first case used to buy this kind of cheese, no sample of the Latin-style fresh cheese was available during the inspection but it was proved that it had been commercialised there since April 2012.

The strains isolated both from the pregnant woman and the newborn and those isolated from cheese were sent to the National Reference Laboratory from the Institute of Health Carlos III, Madrid, for characterisation. These strains were analysed by PFGE, by digesting the DNA with *ApaI* and following standardised protocols [6]. All the strains showed an indistinguishable pattern profile among them.

Control measures

After confirmation that the cheese was contaminated, an alert was issued via the Rapid Alert System for Food and Feed (RASFF) in Europe and the Public Health Department of the Basque Government ordered the withdrawal of the cheese from the market.

The great difference between the number of cheese packs distributed and those withdrawn from the market, and the long period until this cheese already sold reaches the expiry date (September or November), suggests that this product may still remain in several homes until November. Therefore, the Basque population was advised via mass media not to consume this type of cheese.

Health professionals in the Basque Country were informed about the situation and were recommended to strongly consider the diagnosis of listeriosis in high-risk individuals (pregnant or immunocompromised) with symptoms compatible with listeriosis and indicating having consumed Latin-style fresh cheese.

Conclusion

This report gives an indication that these two cases are not part of a longer ongoing outbreak and highlights that the investigation of every case of listeriosis is important even in a context of low incidence. Our report shows that a thorough epidemiological investigation allows a quick implementation of control measures that can prevent secondary cases.

Both cases described here were linked to the consumption of the same kind of cheese bought in stores selling Latin American specialities whose customers are mainly of Latin American origin. Outbreaks of listeriosis affecting pregnant Latin American women have been described before; in fact this group is described as a high-risk group because their consumption of fresh cheese is higher than that of people of other population groups [7,8]. The PFGE results and the results of the epidemiological investigation confirm the association between the listeriosis cases and the consumption of that particular type of cheese.

Taking into account the long incubation period of this illness, the widespread distribution of the cheese and its long period until reaching the expiry date, further cases may still occur although the cheese has been withdrawn from the market. So far, there have been no more cases in Bizkaia and we are not aware of any further cases having occurred in Spain or elsewhere.

Acknowledgments

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Measles outbreak in Andalusia, Spain, January to August 2011

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On 7 January 2011, a six year-old child living in a Roma community near Seville, southern Spain, was hospitalised with measles. Contact tracing identified a probable index case with onset of symptoms on 20 December 2011 and several unreported cases among children under the age of 15 years in the same town. The outbreak initially spread in districts in the city of Seville with a high proportion of Roma residents, and later to other cities and towns in Andalusia. While some towns experienced wide spread of the disease with significant clusters of cases, most of the affected locations saw non-clustered cases or very few secondary cases. The outbreak resulted in 1,759 confirmed or probable cases of which 393 (19%) required hospitalisation. Measles virus of genotype D4 was diagnosed in more than half of the cases. Significant differences ($p<0.0001$) by age group were found between clustered and non-clustered cases. The highest proportion of clustered cases occurred in the age group of 5-14 year-olds, while the highest proportion of non-clustered cases was seen in those older than 29 years. The last confirmed case related to this outbreak was reported on 20 August 2011.

Introduction

Measles is a highly infectious viral disease capable of causing large outbreaks. Because humans are the only reservoir of measles virus and there is an effective vaccine which induces lasting immunity in 98-99% of vaccinated children, it is theoretically possible to eradicate the disease. The countries in the European region of the World Health Organization (WHO) have committed to eliminating measles by 2015. Previous elimination targets in 2007 and 2010 were not met and the resurgence of measles in 2010 and 2011 put the 2015 target at stake [1,2].

The measles elimination plans for Spain and for Andalusia were launched in 2001 [3,4] in response to the 2015 WHO target for stopping indigenous measles transmission. The two strategic goals of the Andalusian plan were to improve the surveillance system for early case detection and control of the transmission and to increase vaccination coverage in children in order to improve population immunity.

A monovalent vaccine against measles had been in use in Spain since 1978, when the measles-mumps-rubella (MMR) vaccine was introduced in 1981 for children aged 15 months. In 1995, a second dose for children aged 11 years was included in the calendar. The age of administration of the second dose was changed to six years in 1999 and later to three years in 2004 [5].

The last major outbreak in Andalusia happened in 1986, with an incidence rate of 1,007 cases of measles per 100,000 population. Thereafter, the annual rate decreased to 39 cases per 100,000 population in 1995, the last epidemic year. The rate decreased further to 14 per 100,000 in 1996, and from 1997 to 2008, incidence rates were very low (<1 case per 100,000), except for two isolated outbreaks in 2003 in Almeria (2.51 cases per 100,000 population) and Algeciras in 2008 (3.0 cases per 100,000 population) [6]. Both outbreaks affected mostly unvaccinated young adults, but also spread to unvaccinated children under 15 months of age. Between 2002 and 2007, the number of cases reported annually ranged from 0 to 4.

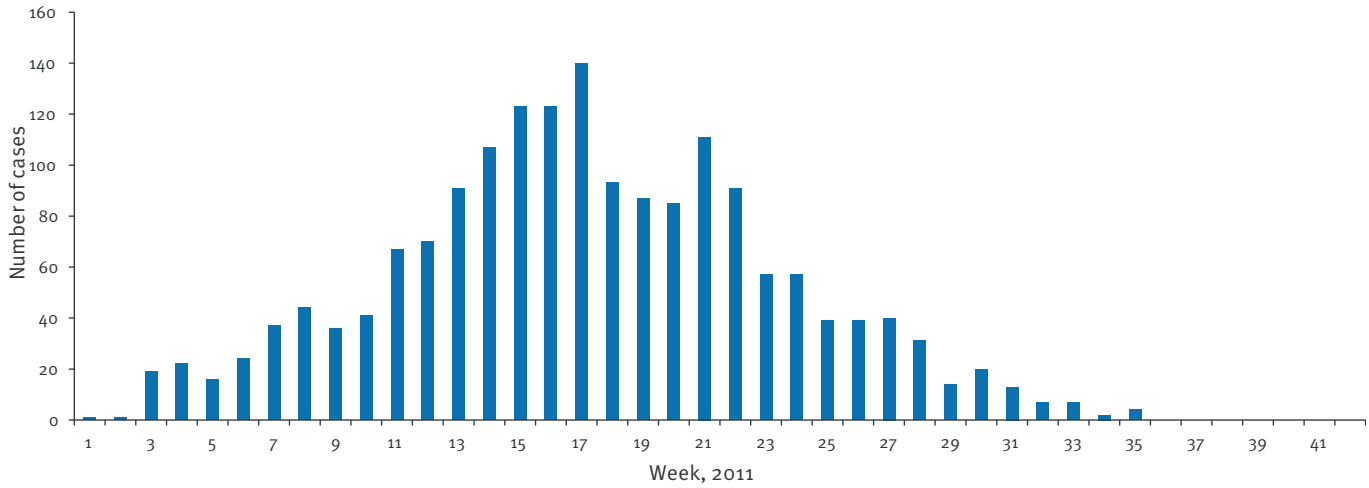
In 2010 this trend was broken by the appearance of a more widespread outbreak of measles that began in the city of Granada [7] in a group of adolescents who were not vaccinated on ideological grounds. It lasted for 10 months and spread to various municipalities in the eastern provinces of Andalusia. It was followed by the outbreak described in this paper, which reached a large number of municipalities in Andalusia in 2011. Both the 2010 and 2011 outbreaks were notified in the context of a widespread epidemic wave that has been affecting different European countries since 2008 [8,15].

Methods

The case definition in this outbreak investigation follows essentially the clinical, laboratory and epidemiological criteria established by the Europe the Centre

Figure 1

Number of measles cases by week, Andalusia, January to August 2011 (n=1,759)



for Disease Prevention and Control (ECDC) [16,17]. Confirmed cases were defined on the basis of clinical and laboratory criteria, while probable cases of measles were defined on the grounds of clinical criteria and an epidemiological link to a confirmed case between 7 and 18 days before onset of symptoms.

Laboratory diagnosis was achieved by demonstration of specific IgM antibodies, and/or virus detection by real-time RT-PCR targeting a fragment of the conserved F gene, and/or viral culture in a B95a cell line. The measles genotype was determined in positive samples or viral isolates by PCR and subsequent sequencing of the 450 nucleotides encoding the C-terminus of the nucleoprotein, as recommended by the WHO. Laboratory diagnosis was carried out at the regional virus reference laboratory of the Andalusian epidemiological surveillance system (Sistema de Vigilancia Epidemiológica de Andalucía, SVEA) at the University Hospital Virgen de las Nieves in Granada. Genetic characterisation in patient samples and viral isolates was performed at the national reference laboratories, the National Centre of Microbiology at Instituto de Salud Carlos III in Madrid and the Hospital Ramón y Cajal in Madrid.

The reporting of notifiable diseases, including measles, to the SVEA is done in an automated manner. Cases are recorded in digital health records ('Diraya') by physicians in all primary health centres in Andalusia. The clinical and epidemiological information recorded in Diraya is sent daily to the SVEA computer application, where epidemiological and laboratory information of every reported case is completed when available.

We compared characteristics of cases in municipalities having non-clustered cases or incidence rates below 100 cases per 100,000 population, with those occurred in municipalities with major clusters or higher incidence rates. In the city of Seville (703,021 inhabitants) we distinguished similarly between districts with more than 100 cases per 100,000 and those with fewer.

Outbreak description

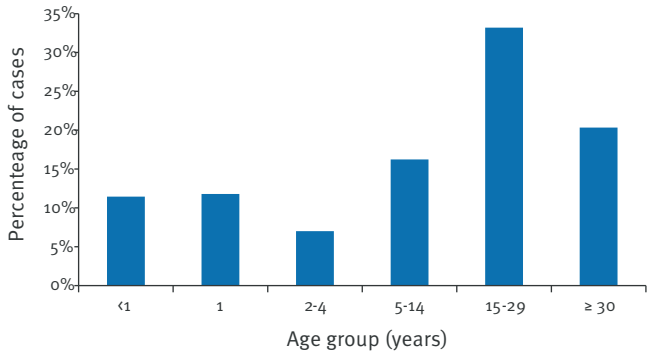
The first measles case in this outbreak was reported on 7 January 2011 in a six year-old Roma child with no history of vaccination. After admission to hospital, the diagnosis was confirmed by PCR. Contact tracing identified a likely primary case with onset of symptoms on 20 December 2010, along with other unvaccinated cases who attended the same school. All these cases were resident in the same district, placed in a municipality of 21,025 inhabitants near Seville. Vaccination coverage with two doses of measles-containing vaccine among school and preschool children between 3 and 11 years of age enrolled at this school was 56.0%.

After the end of this outbreak in week 35 of 2011, 1,759 confirmed or probable cases (Figure 1) had been reported in Andalusia. The same measles virus genotype D4 was identified in more than 50% of cases. The overall incidence rate was 21 cases per 100,000. Cases related to this outbreak occurred in at least 120 municipalities of Andalusia, representing 16% of all Andalusian municipalities. Most of the cases were non-clustered or clustered with incidence rates below 100 cases per 100,000 population, although 88.1% occurred in towns in the province of Seville. A total of 827 cases (47%) occurred in 14 clusters, with incidence rates of over 100 cases per 100.000, in five districts of the city of Seville and nine in nearby municipalities, including the one where the outbreak began and in which incidence rates reached 489.9 cases per 100,000. In the city of Seville, which registered 39.9% of the reported cases, the incidence rate was 99.8 per 100,000.

The age of cases ranged from two weeks to 57 years with a mean of 16.5 years (median: 16 years). The mean

Figure 2

Measles, percentage of cases by age group, Andalusia, January to August 2011 (n=1,759)



age of cases increased over time and was 15 years during the first four weeks and 19 years during the final four weeks of the outbreak.

Of all cases, 23.2% were younger than two years, 23,2% were 2-14 years-old, 33.2% were 15-29 years-old and 20.3% were 29 years and older (Figure 2). Some 16,2% occurred in children younger than 15 months of age, who were not eligible for vaccination. However, the highest incidence rates were seen in those younger than two years: 266.4 cases per 100,000 in children younger than one year and 242.5 cases per 100,000 in one year-old children (Figure 3).

A significant difference (p<0.0001) was found between the mean age of clustered cases (14.4 years) and non-clustered cases (18.6 years), due to significant differences in the proportions of cases by age group, We found no significant differences in the incidence rate in children younger than 15 months (not vaccinated due to their age) when comparing the major clusters of this outbreak (rates over 100 cases per 100,000) with non-clustered cases or clusters with low incidence rate (Table). However, in major clusters, 23.2% of the cases occurred in the age group of 5-14 year-olds, compared with only 12.2% in non-clustered cases or clusters with low rate of incidence (p<0.0001). These percentages were reversed in older age-groups, with 11.7% and 27.6%, respectively, in cases older than 29 years (p<0.0001).

Among the 535 cases with information about history of vaccination, 68.2% had received no previous MMR dose. This situation was more frequent in clustered cases (71.9%) than in non-clustered cases (61.1%). These differences were larger in the age group of 2–14 year-olds (76.0% in clustered versus 54.0% in non-clustered cases).

A total of 393 cases (19.2%) were hospitalised. Although the majority of hospitalised cases were older than 15 years (74.8% of total hospitalised cases), hospitalisation rates were highest, more than 50 per 100,000 population, in children under the age of two years in Andalusia. The severity of the disease, calculated as hospital admissions per cases was also high in children under the age of two-years (215 admissions per 1,000 cases) and adults over the age of 29 years (262 per 1,000. The most frequent complication in hospitalised patients was pneumonia (31.0%), followed by digestive disorders (22.2%), respiratory insufficiency and dyspnoea (14.3%) and liver disorders (9.5%). No encephalitides or deaths were reported.

Among the cases in this outbreak were 41 healthcare professionals, all between 25 and 39 years of age. None of them were fully vaccinated. There have been no reported cases of transmission from healthcare workers to hospital inpatients in this outbreak.

Control measures

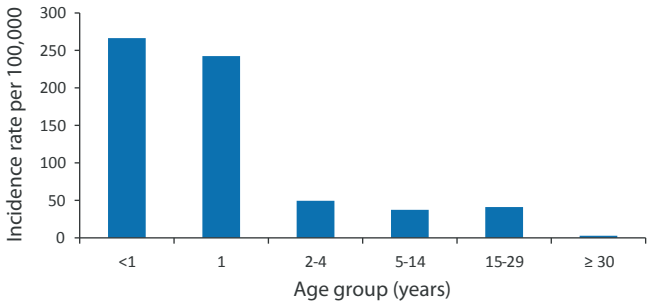
At the beginning of the outbreak, control measures were implemented in all schools, kindergartens and health centres in affected areas and in work centres with a reported case, in accordance with the Plan for Elimination of Measles in Spain [3] and the Protocol of Alerts from the Ministry of Health of Andalusia [17].

Vaccination status was reviewed for all children attending schools in towns or districts in cities with one or more cases of measles. A dose of MMR vaccine was offered to all children and adolescents who were not fully vaccinated.

Cases were excluded from school until at least four days after rash onset. Measles susceptibility was determined for all children attending nursery schools in affected areas and for staff under the age of 40 years with no history of the disease or documented evidence of vaccination, offering susceptible individuals a dose of MMR vaccine. Vaccination status was determined by age. Children under 15 months were considered susceptible for not having reached the age of vaccination. Those over 40 years were not considered due to the high proportion of acquired immunity.

Figure 3

Measles incidence rate by age group, Andalusia, January to August 2011 (n=1,759)



Table

Distribution of measles cases by age group: clustered with incidence rate ≥100 per 100,000 versus non-clustered or clustered with incidence rate <100 per 100,000, Andalusia, January to August 2011 (n=1,759)

Age group	Clustered with incidence rate ≥100 per 100,000			Non-clustered or clustered with incidence rate <100 per 100,000			p value
	N	%	Cumulative %	N	%	Cumulative %	
0–14 months	136	16,5	16,5	147	15,8	15,8	0,70
15 months–4 years	115	13,9	30,3	120	12,9	28,6	0,53
5–14 years	192	23,2	53,5	114	12,2	40,9	< 0.0001
15–29 years	287	34,7	88,2	294	31,5	72,4	0,16
≥30 years	97	11,7	100,0	257	27,6	100,0	< 0.0001
Total	**827**	**100,0**	-	**932**	**100,0**	-	-

The age groups in this Table differ from those in the Figures to accommodate for the fact that children under the age of 15 months are not eligible for vaccination.

At the beginning of the outbreak, unvaccinated children attending these nursery schools aged between 12 and 15 months received a dose of MMR vaccine. In the context of the current outbreak, also those aged between 6 and 11 months received a dose of MMR vaccine and were summoned for a second dose at the age of 15 months according to the vaccination schedule.

Unvaccinated contacts of cases with no previous history of measles were immunised with the MMR vaccine within 72 hours after exposure, except for those who could not be vaccinated (children under the age of six months, pregnant women and immunocompromised persons), who were treated with human polyvalent immunoglobulin.

As a pre-exposure measure at population level, the age for administration of the first dose of MMR vaccine was lowered to include all children older than 11 months in municipalities which had one or more cases. A second dose of MMR vaccine will be administered to these children when they reach the age of three years, according to the current vaccination schedule.

A dose of MMR was also offered to all healthcare workers under 40 years at hospitals or ambulatory health centres in the outbreak area who had no history of measles infection or documented evidence of measles vaccination. They were asked to sign a waiver when they did not accept it.

In week 17 of the outbreak, the Andalusian Health authorities summoned the heads of all Health Districts in the region in order to implement a campaign for reviewing and updating the MMR vaccination coverage in children between 2 and 16 years of age, starting first in areas dominated by underserved populations.

Discussion

The measles outbreak began among a Roma population with low vaccine coverage and spread rapidly due to the high number of susceptible individuals and the high mobility of this population, which generated a high number of contacts. This facilitated the spread to surrounding communities with pockets of unvaccinated susceptible children in many municipalities in Andalusia. These areas with low vaccination coverage saw an accumulation of clustered case among unvaccinated children, while in the rest of the population, the outbreak spread more slowly, leading to significant geographical differences in the spread of the outbreak. Other municipalities only saw non-clustered cases or small numbers of cases, with a higher proportion of young adults who became ill.

This outbreak occurred in a context of a recent re-emergence of measles in Europe since 2008 [8-15], with some outbreaks affecting Roma populations [9-11]. Also in other parts of Spain, measles outbreaks have been reported, with the same genotype as the one in Andalusia in Madrid in 2010 [18] and a different genotype B3 in Granada in October 2010 [7].

Among the causes that may in recent years have contributed to the formation of pockets of susceptible children were the limited use of preventive services in certain population groups and the paradox that followed the success of childhood immunisation programmes. The high vaccination coverage made the disease disappear during the past decade and led to a low perception of risk regarding the severity of measles or its health and social costs. This situation may also have contributed to a further relaxation of health services in developing risk management strategies for vaccination of vulnerable populations. We understand that cultural or religious beliefs questioning vaccination or vaccine safety had no relevance for the origin and development of the outbreak described here.

In recent outbreaks reported in Europe [8] the largest proportion of cases occurred in childen aged between 5 and 14 years. In successive epidemic waves in

Switzerland and France [13-15,19], this has also been the most affected age group, and vaccination coverage for one dose of MMR vaccine was below 90%.

In our outbreak, the largest proportion of cases were adults aged 15 to 39 years. Although the vaccination coverage in Andalusia in general is appropriate to interrupt transmission of the disease in the population (over 95% during the last 12 years), a seroprevalence study conducted in 1996 in the population between 2 and 40 years of age showed that more than 5% of individuals in the cohort born between 1977 and 1986 (currently between 25 and 34 years-old) were susceptible [,20]. Updating the vaccination of these age groups has so far not been considered feasible, so more cases may occur in this age group in the future.

In addition, we saw a high incidence rate and a considerable number of hospital admissions among children younger than 15 months, who were not vaccinated because of their age. In particular the proportion of cases among children 12 to 15 months of age (5.3% of total) indicates a need to lower the age for the first dose of MMR in our childhood vaccination schedule.

The most frequent complications in hospitalised patients were pneumonia, digestive disorders, respiratory insufficiency and dyspnoea, which is in line with the complications described in scientific literature [21]. We would like to point out that liver disorder was detected in 12 cases, involving aminotransferase elevation (nine cases), hepatomegaly (two cases) and cholestasis (one case). Half of these cases were male, the age ranged from 24 to 39 years, and none of them had any underlying disease. Although this complication is infrequent, it has also been described in literature [22,23].

It is important to emphasise the importance of preventing measles transmission in healthcare through staff. The risk of disease in non-immune healthcare workers is much higher than in the general population and vaccination in this group must be strengthened [24,25]. About 20% of the cases in this outbreak were hospitalised, figures lower than reported in France (33.3%) [14,15] and higher than in Switzerland (15%) [13]. To prevent transmission in waiting rooms of health centres, emergency rooms and hospital wards, training sessions were organised for staff of health services in the outbreak area, and a written waiver was requested from staff declining the offered vaccine. However, 41 healthcare workers became ill, which constitutes a high risk of nosocomial transmission to non-immune or immunocompromised patients, as the essential respiratory isolation measures are not sufficient to prevent nosocomial transmission [25].

In our view, interventions to control the outbreak, particularly through early notification of cases to facilitate early post-exposure immunisation, vaccination in schools and preschools, and lowering the age for vaccination in affected education institutions have probably reduced the intensity and duration of the outbreak especially in children.

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