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Editorial

PERTUSSIS: AN OLD DISEASE IN NEW CLOTHES

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In this issue of Eurosurveillance, two articles report data about pertussis. In other issues of this journal in 2007 (May and January), two other papers also covered epidemiologic data on pertussis.

These four articles come from the United Kingdom (UK), Spain (both this issue), Cyprus (May) and France (January). The epidemiological methods applied were quite different. The article from the UK by Weerasinghe et al. [1] is an outbreak investigation into adult pertussis with a 20-year-old student as an index case. In this study, the index case infected her sister, who infected her three weeks old infant. The article from Spain by Vera et al. [2] looks at pertussis epidemiology in the Madrid region between 1982 and 2005 by hospital discharge data and by surveillance; the surveillance system was changed in the late 1990s. The paper from Cyprus by Theodoridou et al. [3] in the May issue reported an outbreak that could be detected only when an active surveillance scheme was initiated. The article from France by Bonmarin et al. [4] in the January issue described the results of hospital-based surveillance in that country over a 10-year period.

Irrespective of their different methodologies and geographical backgrounds, all four articles shed light on the current epidemiology of pertussis, which is probably similar throughout Europe but differs from our previous understanding of whooping cough as a typical childhood disease.

Infant immunisation against pertussis has dramatically reduced the incidence of the disease in older infants, toddlers and children. Although the coverage of primary immunisation against pertussis varies from country to country, as has been documented by the data from EUVAC.NET [5], the number of reported pertussis cases in toddlers and children is rather low in most European countries. In the last decade, however, an increase in reported cases has been seen in many European Union (EU) countries and elsewhere, such as in the United States and Australia [6]. This increase was more or less intense, and it was found irrespective of how the reporting system was organised. There can be many reasons for the increase in reported cases: it may be a real increase of cases; it may be due to an increased awareness of pertussis by the medical community; it may be due to better diagnostic tools; or it may be a combination of all these factors, which is perhaps most likely.

It is now clear that neither infection nor immunisation against pertussis by whole-cell or acellular vaccines confer lifelong protection against re-infection, and thus *Bordetella pertussis* continues to circulate in all countries. Symptoms of re-infection vary widely, from trivial respiratory symptoms to full-blown pertussis with typical signs such as whooping and choking. Pertussis also shows typical epidemiological waves, as was demonstrated in the French hospital surveillance study [4]. These waves occur with regular frequency every three to four years.

In EU countries with high infant vaccine coverage, pertussis now occurs mainly in older children, in adolescents and adults, and in very young unimmunised infants. The latter group is of special concern, because most hospital admissions and almost all pertussis deaths are found here [6]. In contrast to the prevaccination era, adolescents and adults are now the main reservoir for the bacteria. Various studies have explored the incidence rate in adolescents and adult, and it was found to vary between 170 – 550 cases per 100,000 population per year in various studies irrespective of different study methodologies and different countries with different vaccination backgrounds [7,8].

Similarities have also been found when the sources of infection for newborns and very young infants were studied. Irrespective of whether this was done in retrospect or prospectively, and whether it was done in France [9], the UK [10], or other countries such as Germany, Spain, the US and Taiwan [11,12], it was observed that approximately 30-60% of sources could not be identified. Among the identifiable sources, >50% were parents, mostly mothers, but also fathers, grandparents and immunised siblings.

In this epidemiological setting, diagnosing pertussis is not trivial. Clinical symptoms in newborns and young infants can be atypical, and in some cases apnoea is the only clinical sign. Pertussis in older children, adolescents and adults is mainly characterised by prolonged coughing with or without whoops. The specificity of the clinical definition of pertussis with prolonged coughing is between 80 and 90% [13,14] and general practitioners and internists should include pertussis in their differential diagnosis of prolonged coughing, as the authors from the UK article again suggest [1].

The laboratory diagnosis of pertussis is also problematic [6]. In young infants and newborns, *Bordetella* PCR or culture offer a high specificity and a sufficient sensitivity, as exemplified by the young infant in the outbreak investigation in the UK [1], who was diagnosed by culture.

With regards to the laboratory methods used for case ascertainment, the French hospital-based surveillance relied on culture, PCR and serology [4]. In Cyprus [3], the diagnosis was made by detecting IgA-antibodies to *Bordetella* antigens. In the study from Spain [2], approximately 30% of cases were serologically confirmed, and 7% were confirmed by culture.

Laboratory methods for diagnosing *B. pertussis* infection suffer from various drawbacks: culture lacks sensitivity in older children, adolescents and adults, and is slow. PCR is a faster method, but lacks standardisation and also has low sensitivity (~10-20%) in adolescents and adults [15]. It is also expensive, and not paid by health systems in many EU countries. Serology is not at all standardised, and a World Health Organization reference preparation...
will not be available before 2008 or 2009. Additionally, the age-specific cut-off values distinguishing between recent infection and previous contact are not well defined. Furthermore, the antigens used for serology are also components of the acellular pertussis vaccines, so that diagnostic serology cannot be safely interpreted for long time following vaccination.

Given all these caveats, what solution could be offered? We can safely say that all current vaccination programmes are unable to eradicate \textit{B. pertussis}, so the bacteria will continue to circulate in all populations. Therefore, the primary goal is to achieve and maintain high (>95\%) coverage rates for primary vaccination in infants. In order to shorten the vulnerable phase of young infants, the first dose should be given as early as possible, which may protect infants from hospitalisation and death \cite{16}. Apart from a pre-school booster, additional vaccine strategies for adolescents and adults should be devised and implemented, depending on the local epidemiological situation and the logistics for implementation \cite{6}. Apart from reducing the burden of disease in the vaccinated population, all strategies should also take into account the effect on newborns and young infants. If novel vaccination strategies could reduce the overall circulation of \textit{B. pertussis} among all age groups, including the effects of herd immunity, we would hopefully no longer see clusters of cases as described in one of this issue’s articles \cite{1}.

\textbf{References}


Passive immunity against measles in infants: is there a need for policy changes in the European vaccination schedules?

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The elimination of measles by 2010 is part of the strategic plan for measles and congenital rubella infection in the European Region of the World Health Organization (WHO Euro). Many European Union (EU) countries are on the right track to reach this goal, but some problems still need to be solved; according to the data reported to EUVAC.NET, there are still several thousand measles cases reported in the EU annually [1]. Public health experts are well aware that the hardest efforts towards elimination of a disease usually have to be performed in the end phase of elimination programmes, when new and often unexpected issues arise and need to be faced in a short time.

A two-dose schedule of the combined measles, mumps and rubella vaccine (MMR1 + MMR2) is nowadays included in all EU immunisation programmes. In nine Member States, catch-up campaigns are also carried out [1]. However, several European countries only recently implemented the second dose of MMR and the vaccination coverage in a number of EU countries is well below the >95% needed for achieving herd immunity.

To avoid interference with maternal antibodies passively transmitted to the infant it is common knowledge that the MMR1 should not be administered too early in life. On the other hand there is a window of susceptibility to measles infection between the decay of passively acquired maternal antibodies and the start of the immune response elicited by vaccination. The right timing for administration of the MMR1 is determined by balancing the need to minimise the length of this window period to the development of an optimal immune response to the vaccine.

So far, providing the first MMR dose to children aged >=12 months has been the golden standard. In EU countries, MMR1 is offered between 12 - 18 months of age. In certain situations, as in France an early start is recommended for children attending day-care (MMR1 at 9 months of age followed by MMR2 at 12-15 months) or as in most countries before travelling to countries with wild-type measles circulating (MMR1 provided from 9 months of age). The MMR2 is usually offered after the 3rd year of life, with the exception of Austria and Germany where the MMR2 recently was recommended before the age of two.

In this issue, Cilla and colleagues compare the levels of measles-specific antibodies in two groups of parturient women in Spain who gave birth in 1990 (end of the epidemic period) and in 2006 (after eight years without virus circulation), respectively. The results from this survey are in line with similar studies recently carried out in Europe [2-4]: in the post-vaccination era the antibody levels in young adults are lower than those in the same age groups when the wild-type measles virus was widely circulating.

The issue of waning immunity after measles vaccination has been largely debated [5-8], especially in relation to the possibility of increasing number of measles cases in young adults. According to observations in settings where measles has almost been eliminated, such as in Scandinavia and the Americas, high vaccination coverage and active outbreak control may limit the effect of imported measles cases.

In the present situation, with wild virus still circulating in Europe and observed waning immunity, a discussion on a possible policy change with the first MMR dose provided at an earlier age may be warranted [9]. Scientific evidence could support such a change, including the research reported by Cilla and colleagues.

However, several issues have to be taken into account in the EU actual scenario. Anticipating the MMR1 before 12 months of age can definitively lead to the risk of development of a lower immune response to the vaccine in many children (especially those who received sufficient passive immunity from their mother). In such a situation the introduction of a policy change could add more interferences than real benefits. Changing the MMR vaccination schedule should be a public health decision taken after a thorough analysis not only of the available scientific evidence but also of many practicalities. At present, a general agreement on offering the MMR1 at 12 months of age in all EU countries would be a good compromise.

In addition, other health care measurements, besides those already implemented, may prove useful. Many of the recently measles infected individuals in Europe including in those countries close to elimination were in the age groups 25-50 years, too old to be offered measles vaccination, too young to be infected by natural measles and catch-up campaigns were never performed. To reach elimination for a disease like measles in our modern mobile societies close to all susceptible individuals need to be immunised. To obtain this goal and reach all the age groups that are susceptible, several alternative strategies could be tried such as; continue high vaccination coverage of all children with the two-dose schedule, offer measles vaccination to all age groups without a history of natural disease, offer all age groups who received one dose of measles a second dose to avoid breakthrough infections, offer measles vaccine to travellers to countries with endemic measles, offer measles vaccine to women planning to become pregnant with no history of natural measles or vaccination and include measles...
in the antenatal screening of pregnant women with no history of measles infection and vaccinate after delivery against measles.

Moreover, we actually do not know very well which level of protection is obtained long-term following the two doses of MMR vaccine, including the role of cellular immunity [10]. Many children are born to mothers in their third or fourth decade of life, and the long-term immunological memory after the varying vaccination schedules now in use within the EU ought to be evaluated. A third dose of MMR later in life may prove to be necessary in the future, especially in those countries with a well implemented measles immunization program and with steadily high coverage levels.

At present, however, the priority should be to strengthen existing measles elimination programmes and assure high vaccination coverage for two doses of MMR: it is important to keep in mind that most of the problems linked to waning immunity could be solved once the elimination goal has been reached.

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Knowledge of primary antimicrobial resistance of \textit{Helicobacter pylori} is important for the clinical management of infection-related gastroduodenal diseases. The first successful antimicrobial treatment of patients suffering from \textit{H. pylori}-associated peptic ulcer was carried out and studied in Perth, Australia in 1982, and initiated the global breakthrough in diagnosis and clinical management of the most prevalent gastroduodenal diseases [1]. This important medical development was recognized in 2005 by the attribution of the Nobel Prize to Barry Marshall and Robin Warren [2]. Their findings were essential for the understanding of the clinical impact of a gastric bacterial infection, which has already been described as associated with duodenal ulcer disease in the early 1920s [3] and was repeatedly mentioned during the following decades, but without clinical consequences [4]. This lack of clinical consequences was most probably due to the unavailability of antimicrobial agents at that time. So, earlier investigators did not have the opportunity for causal treatment, which could have proven evidence for the causative role of the observed infective organism.

The first cultivation of \textit{H. pylori} by the Australian researchers on solid culture medium under microaerobic conditions, which built on the pioneering studies of Jean-Paul Butzler and Martin Skirrow [5] in the campylobacter field, also undoubtedly paved the way to unravelling the pathogenicity factors and survival strategies of \textit{H. pylori}, and to that end essentially contributed to the unexpected carrier of this organism. Furthermore, cultivation and sensitivity testing of the bacteria are prerequisites for detecting its antimicrobial sensitivity spectrum, allowing specific antimicrobial treatment of the infection. Today, it is generally accepted that \textit{H. pylori} is the causative agent of a chronic gastritis, which in a proportion of cases is complicated by peptic ulcer disease, and during the lifelong infection paves the way for gastric mucosal atrophy and a cascade of pathogenetic events eventually ending in gastric malignancy [6]. About half of the world’s population currently harbours \textit{H. pylori} in their stomachs, with prevalence ranging from about 30% in industrialized countries to 80% or more in developing areas. Infection of only part of them will be detected during their individual life spans due to the fact that the majority of infected individuals will not suffer from any \textit{H. pylori}-related complaints.

Cases where antimicrobial eradication treatment is indicated are patients with gastric and duodenal ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, atrophic gastritis, after gastric cancer resection, and in first degree relatives of gastric cancer patients [7]. Especially in peptic ulcer disease and in MALT the early stages of lymphoma, antimicrobial eradication treatment is curative with relapse rates of less than 5% [8].

The current standard treatment of \textit{H. pylori} infections in Europe is based on Maastricht Consensus 2005, which recommends first-line antimicrobial schemes, including clarithromycin, combined with amoxicillin or metronidazole and standard doses of a proton pump inhibitor (PPI). Following the failure of first-line attempts, quadruple therapy or an alternative triple therapy is recommended [7]. Quadruple therapy, consisting of PPI, bismuth subcitrate, tetracycline and metronidazole, which is also in use as first-line treatment in some non-European countries, is equally or more effective as triple therapy but not often used due to problems with compliance. After the second treatment failure, culture of the organism and resistance-guided antimicrobial treatment is recommended.

Empirical first-line triple antimicrobial treatment in Germany is currently successful in 80% or more cases [9]. This highly satisfying success rate of triple therapy in patients who have not been treated before is explained by the favourable resistance rates currently observed in Germany, where primary resistance rates to metronidazole and clarithromycin are below 30% or 6% respectively, and double resistances are rare, as has been shown in an ongoing prospective German multicentre study [Kist M. manuscript in preparation].

Nevertheless, antimicrobial eradication treatment success of \textit{H. pylori} infections is jeopardized or favoured by a couple of interfering factors, such as patients’ compliance, the clinical course \textit{H. pylori}-related diseases or microbial virulence factors involved in the degree of inflammation and, last but not least, by host characteristics like gastric pH, diabetes or smoking [10, 11].

Resistance to antimicrobials in use is generally accepted as the most important jeopardizing factor; as a result, the recent Maastricht Consensus does not recommend the use of clarithromycin as a first-line drug in areas with more than 15-20% resistance, unless susceptibility has been tested before. The same is true for metronidazole, which is not recommended as a first-line drug in areas with primary resistance rates of more than 40% [7]. It should be noted that there is a danger that resistance will increase unless treatment guidelines are strictly adhered to.

In this context, the studies reported in this issue of Eurosurveillance by Chisholm et al. are important for guiding the most promising first-line treatment strategies. The authors investigated two geographically and demographically different areas in England and Wales, and report primary resistance rates, which varied between areas between 29% and 36% for metronidazole and between 8% and 13% for clarithromycin. Such resistance rates are substantially lower than those observed in France and in southern Europe, and are comparable to the German situation [12]. According to the Maastricht Consensus 2005, the findings described by the English group would mean that both clarithromycin as well as metronidazole can be chosen as first-line
components of triple therapies in patients who have not been pre-treated residing in the areas under study. The study presented is a non prospective, observational surveillance study, based on routine samples of gastric biopsies sent to two regional microbiological laboratories. Nevertheless, their findings are of relevance for the appropriate design of first-line drug regimes, at least in the areas studied.

Surveillance studies based on routine material and prospectively designed investigations can face several methodological drawbacks. First, there is a lack of standardisation of the techniques used for sensitivity testing in different laboratories. The agar dilution method that is generally accepted as gold standard of susceptibility testing in slow growing and fastidious microorganisms is too time-consuming and prone to technical errors due to the production of home-made culture media as well as the instability of some antimicrobials. In the light of practicability and reproducibility, the E-test might be the testing method of choice, especially if it can be read no later than 48 hours afterwards. A further problem of studies including metronidazole resistance testing is its high degree of dependence on the redox potential of culture media and of oxygen tension in the incubation atmosphere. On the other hand, reproducibility of low or high grade resistance to metronidazole clearly does not seem very prone to technical variability [12]. Studies that have shown only a weak correlation between metronidazole resistance and treatment success have, to my knowledge, never taken into account the degree of resistance of the isolates involved. It seems reliable that a high grade resistance of more than 256 mg/L should exhibit an impact on treatment success that is different from those of a minimal inhibition concentration of 32 mg/L.

A further drawback of susceptibility testing in H. pylori is the fact that the real clinical impact of given breakpoints cannot be generally delineated from in vitro test results, but due to the particular gastric environment must always be verified by clinical treatment trials. A further prerequisite of creating reliable study results is taking a study sample, which should be as representative as possible. The study of Chisholm et al. may be biased in relation to this by a selected population presenting at the gastroenterologists involved, as well as by the missing information of previous treatment attempts. In addition, only one antral biopsy was investigated from each patient as a rule. In our experience in Germany, isolates grown from samples taken from different gastric regions can exhibit diverse resistance patterns, possibly influencing the outcome of such a study.

A couple of questions remain unanswered in the paper presented, which demands further studies: the generally higher resistance rates in females, especially in the younger age group, must remain unexplained. A different ethnic background between both study areas may have different levels of access to medical care. Furthermore, the possibility that females may be pre-treated more frequently, which might result in higher resistance rates, is not known. More detailed data-mining and a multivariate analysis of data regarding such aspects could be helpful in future studies. Such studies might also provide better insight in the risk factors involved in the development of resistance, particularly in H. pylori.

Indeed, the development of resistance in H. pylori seems to be particular: nearly all relevant antimicrobial resistance mechanisms in H. pylori are due to point mutations in respective target structures [13, 14, 15, 16]; in this aspect the organism is comparable to campylobacter, which is in contrast to resistance development in campylobacter, which is a multifactor process depending on prevalence of resistant strains in the environment, in food of animal origin, as well as on development of resistance under treatment, the development of resistance in H. pylori is strictly an individual process, and, if not transmitted from mother to child, depends exclusively on the management of the individual patient [17]. This particular characteristic of H. pylori antimicrobial resistance, in contrast to other organisms, should allow the identification of risk factors for resistance development in H. pylori much more easily than in more complex situations given with rather ubiquitously distributed pathogens, and should also better allow the control of resistance development by individual patient-adapted clinical and therapeutical management strategies.

Also missing from the English study are data concerning the development of resistance after unsuccessful treatment attempts. Our own data from the ongoing German ResiNet surveillance study clearly show that after the first treatment failure resistance rates already exceed 50%, reaching dramatically high resistance rates of over 80% after repeated empirical eradication trials. These results underline the hypothesis that the development of resistance in H. pylori in contrast to other pathogens is nearly exclusively dependent on treatment strategies in the individual patient. Further, our ResiNet data clearly demonstrate that culture and susceptibility testing of H. pylori from gastric biopsies should already be mandatory after the first treatment failure. The latter should be recognized in future guidelines.

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The objective of this study was to describe the incidence (1982-2005) and epidemiologic characteristics of pertussis cases (1998-2005) in the Autonomous Region of Madrid using data drawn from the epidemiologic surveillance network and computerised hospital discharge data. In the 1990s, the trend in the pertussis incidence in the Autonomous Region of Madrid was clearly falling. The typical seasonal pattern of pertussis remained. A peak in incidence was observed in 2000, and another peak, 2.5 times higher, in 2003. They affected all age groups, but children under one year of age were the most frequent cases, followed by the five to nine year-olds. The greatest increase was seen in the age groups from 10 to 14 and from five to nine. Since 2002, the proportion of cases diagnosed serologically has increased. The incidence of hospital discharges among small children exceeded that of reported cases. More than half of the cases with known vaccination status had received at least three doses of vaccine. The upward trend observed since 2002 could be due to improved case detection, availability of serologic techniques, and a rise in the susceptible population aged five to 14 years. The fact that epidemic peaks continue to occur and that there is a seasonality to the disease seems to indicate that despite the vaccination programme the circulation of the bacteria has not been interrupted. The introduction of the acellular vaccine in 2000 does not appear to have played a significant role in the increase in disease incidence.

Introduction

Thanks to the introduction of pertussis vaccination in the first half of the 20th century, the incidence of pertussis has declined sharply in industrialised countries. In the pre-immunisation era, between 150 and 200 cases per 100,000 population were registered in developed countries [1]. By 2003, those figures had dropped to an incidence of 4 per 100,000 in the United States (US) and between 0.1 and 37 in the different European Union (EU) countries [2,3]. One of the World Health Organization’s goals for 2010 is to reducing the incidence of the disease to below one case per 100,000 population [4]. However, the number of pertussis infections — particularly among adolescents and young adults — has been increasing since the early 1990s in Canada, the US, Australia and some EU countries [5-8]. In Spain, the trend in pertussis incidence has clearly been falling during this period, dropping from between 80 and 160 cases per 100,000 population in the 1980s to 0.76 cases per 100,000 in 2005 [9]. However, a number of authors warn that the incidence of this disease is underestimated [10,11].

Pertussis has been a mandatory notifiable disease in Spain since 1982. Case-definition-based reporting with basic epidemiologic data began in 1996, when the national epidemiologic surveillance network was set up. Immunisation using whole-cell diphtheria-tetanus-pertussis vaccine (cDTP; three doses at the age of three, five, and seven months before 2006, and at the age of two, four and six months since 2006) was introduced in Spain in 1965 [9]. Since July 1994, the childhood vaccination schedule in the Autonomous Region of Madrid (ARM) recommends the administration of a fourth dose of cDTP at the age of 18 months, but until very recently the coverage was very low. A fifth dose of acellular pertussis vaccine (DTaP) at the age of four years is recommended only since November 2000 [12]. Therefore, the immunity level of the childhood population may be deficient, and most adolescents and young adults are probably susceptible to the infection due to the limited duration of vaccine immunity. Offering acellular vaccines to adolescents and adults could help to control the disease, but first the epidemiologic characteristics of pertussis in the ARM need to be ascertained.

The aim of this study was to describe the trend in pertussis incidence among the population of the ARM over the period from 1982 to 2005, and its epidemiologic pattern since basic epidemiologic data became available (1998-2005).

Methods

Data were obtained from the statutary disease reporting system (SDRS) and the epidemic alert and outbreak reporting system (EAORS) of the ARM epidemiologic surveillance network, from the vaccination information system (VIS) and from the computerised hospital discharge data (CHDD; person-based numbers) of ARM. The EAORS collects data on disease outbreaks detected by the healthcare system and other institutions. The VIS monitors vaccine coverage using data on distributed and administrated doses reported by healthcare units. Incidence rates were calculated on the basis of demographic data published by the ARM statistics institute.

We applied the case definition established by the ARM epidemiologic surveillance network. A laboratory-confirmed case was defined by isolation of Bordetella pertussis by culture from a clinical specimen [13]. For this study, a presumptive case was defined by IgG seroconversion or elevated IgG serum titres [11]. A case was defined as ‘confirmed’ if it was laboratory-confirmed or epidemiologically linked to a confirmed case. ‘Probable’ cases were either presumptive or epidemiologically linked to any presumptive case. A ‘suspected’ case was defined as having catarrhal disease with cough for two weeks, and at least one of the following symptoms: paroxysmal coughing, inspiratory and convulsive “whoop” or post-tussive vomiting, in the absence of other apparent causes and neither laboratory-confirmed nor epidemiologically linked to a confirmed case. All notified pertussis cases – suspected, probable, and confirmed – were included to estimate the pertussis incidence. We selected entries from the CHDD that displayed at principal or secondary diagnosis the following codes of the international classification of diseases (ICD-9CM) related to whooping cough: 033.0 (B. pertussis), 033.1 (B. parapertussis), 033.8 (B. bronchiseptica) and 033.9 (unspecified organism). Re-admissions were excluded.
We considered the following variables recorded by the SDRS and the EAORS: age, sex, area of residence, type of diagnosis, classification of case, association with another case, vaccination status; number of vaccine doses received, and time elapsed between administration of the last dose and symptom onset. We also collected data on age, sex, reporting year, ICD-9CM code, and case progression from the CHDD. Lastly, vaccination coverage by year, age, and number of doses administered were obtained from the VIS. A descriptive study was performed, using the SPSS 12.0 statistics package.

Results

Incidence and vaccination coverage 1982-2005

A total of 39,580 cases of pertussis were reported to the SDRS in the period from 1982 to 2005. The mean annual incidence was 68.4 cases per 100,000 population from 1982 to 1992, and 5.4 from 1993 to 2005, a 92% decline. Epidemic peaks occurred every three years. Prime vaccination coverage exceeded 85% from 1993 onwards, and 90% from 2001 (Figure 1).

Incidence 1998-2005

From 1998 onwards, the annual incidence was considerably lower than in the previous years, coinciding with the inclusion of basic epidemiologic data in the SDRS reporting. The mean annual incidence in this period was 3.12 cases per 100,000 population (Table 1).

The typical seasonal pattern of pertussis remained, with the frequency of pertussis being far higher in late spring and in summer (Figure 2). A peak in incidence occurred in 2000, and another in 2003. The mean annual incidence between 2002 and 2005 (3,21 cases per 100,000) was 2.6 times higher than that between 1998 and 2001 (1,25 cases per 100,000). The EAORS- and CHDD-based incidence estimates also reflected these incidence peaks (Table 1). One pertussis-related death in a two-month-old child was registered in 2005.

Distribution by age and sex, 1998-2005

The age range of cases reported to the SDRS from 1998 to 2005 was between zero and 63 years (median: four years; interquartile range: 0-23).

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>SDRS</th>
<th>EAORS</th>
<th>CHDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>19</td>
<td>0.37</td>
<td>0.00</td>
</tr>
<tr>
<td>1999</td>
<td>60</td>
<td>1.17</td>
<td>31</td>
</tr>
<tr>
<td>2000</td>
<td>119</td>
<td>2.29</td>
<td>35</td>
</tr>
<tr>
<td>2001</td>
<td>63</td>
<td>1.17</td>
<td>0</td>
</tr>
<tr>
<td>2002</td>
<td>163</td>
<td>2.05</td>
<td>71</td>
</tr>
<tr>
<td>2003</td>
<td>304</td>
<td>5.32</td>
<td>136</td>
</tr>
<tr>
<td>2004</td>
<td>182</td>
<td>3.34</td>
<td>29</td>
</tr>
<tr>
<td>2005</td>
<td>90</td>
<td>1.51</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>3.12</td>
<td>28</td>
</tr>
</tbody>
</table>

N: number; AI: annual incidence; * mean annual incidence. SDRS: statutory disease reporting system; EAORS: epidemic alert and outbreak reporting system; CHDD: computerised hospital discharge data.
range (IQR): 0-9 years). There was a slight predominance of female cases in all age groups (female to male ratio: 1.25). Cases aged under one year of age were the most frequent (37%), followed by those aged between five and nine years (28%) and those between one aged four years (13%) (Table 2). Among the children aged under one year, 91% of cases involved infants under the age of six months. Only 20% of cases were over 10 years old. Mean annual incidence was 79.3 cases per 100,000 population among the under one year-olds, and below 14 per 100,000 in the remaining age groups. The CHDD data also reflected a predominance of cases under one year of age; they accounted for 94% of hospital discharges. The rise in the incidence of cases notified to SDRS in the second peak affected all age groups.

When the incidence for the period from 2002 to 2005 was compared to that from 1998 to 2001 (Table 3), the greatest increase was seen in the 10 to 14 year-olds (relative risk (RR): 4.2) and five to nine year-olds (RR: 3.3), and the smallest increase in the age group between zero and one year (RR: 1.97). According to the CHDD, the mean annual incidence of hospitalised cases under one year of age was similar in both time periods.

Of the cases reported between 1998 and 2005, 28% were associated with another case. Only 10% of the cases under one year of age were epidemiologically associated with any other case; in the remaining age groups it was 25%.

**Diagnostic confirmation**

Of the cases reported in the period from 1998 to 2005, 7% were confirmed microbiologically (68 cases) and 29% serologically (287 cases). The number of microbiological case confirmations remained relatively stable, but serological case confirmation has become considerably more frequent in recent years.

**Vaccination status**

The vaccination status was known for 60% of notified cases under 15 years of age. Prime vaccination had been completed by 53%, and 39% had received more than three doses.

**Discussion**

The trend in pertussis incidence in the ARM was clearly falling in the 1990s, a finding that is in line with the situation observed for Spain as a whole, and also for the majority of other industrialised countries [1,9]. This could be explained by the fact that the vaccination coverage in this region has remained on a high level since the mid-1980s. The additional sharp decline in the number of pertussis cases in 1998 is probably due to underreporting as well as the more stringent case definition linked to the implementation of the new reporting system. Since 2002, the pertussis incidence in the ARM has been increasing again; this is consistent with the trend observed in several other developed countries in recent years [5-8]. The fact that epidemic peaks and the seasonality of the disease remained unchanged would seem to indicate that the circulation of B. pertussis has not been interrupted. It suggests that vaccination is more effective with regard to preventing the disease than to preventing B. pertussis infections [14].

Across the whole period from 1982 to 2005, the highest incidence of pertussis was among children under one year of age. The rising trend in disease incidence since 2002 was evident for all age groups and can be explained by the following factors:

- Improved case detection and reporting, thanks to advances in disease surveillance and diagnosis [8,9].
- Increased number of susceptible individuals due to the decline in natural immune boosters and vaccine immunity with time. In our region, children aged between five and 14 years registered the greatest rise in incidence since 2002. This susceptible population could constitute an important source of contagion for young infants [5,8,9].
- Decreased efficacy of immunisation programmes due to the introduction of the acellular vaccine in 2000. However, since the strongest increase in pertussis incidence was not observed among the age group most affected by the introduction of the new acellular vaccine, children between one and four years of age, this factor does not appear to contribute significantly to the general rise in incidence that we observed [5].
- Emergence of vaccine-resistant strains of B. pertussis; the significance of this factor is still unclear [15].

The proportion of cases associated with another case was very low among children under one year of age, which seems to reflect the difficulty in detecting the source of infection in young infants.

### Table 2

Number and percentage of cases and mean annual incidence by age group, Autonomous Region of Madrid, 1998-2005

<table>
<thead>
<tr>
<th>Age group</th>
<th>SDRS</th>
<th>CHDD</th>
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</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>362</td>
<td>544</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>317</td>
<td>119.2</td>
</tr>
<tr>
<td>6-12m</td>
<td>30</td>
<td>8.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>15</td>
<td>--</td>
</tr>
<tr>
<td>1-4 years</td>
<td>145</td>
<td>14.7</td>
</tr>
<tr>
<td>5-9 years</td>
<td>280</td>
<td>8.4</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>131</td>
<td>13.3</td>
</tr>
<tr>
<td>&gt;14 years</td>
<td>16</td>
<td>6.8</td>
</tr>
<tr>
<td>Total</td>
<td>1000</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 3

Number and mean annual incidence by age group, Autonomous Region of Madrid, 1998-2001 and 2002-2005

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>51.26</td>
<td>260</td>
<td>101.04</td>
</tr>
<tr>
<td>1-4 years</td>
<td>53</td>
<td>7.08</td>
<td>92</td>
</tr>
<tr>
<td>5-9 years</td>
<td>62</td>
<td>6.34</td>
<td>218</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>25</td>
<td>2.30</td>
<td>106</td>
</tr>
<tr>
<td>&gt;14 years</td>
<td>16</td>
<td>0.09</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td>258</td>
<td>1.24</td>
<td>727</td>
</tr>
</tbody>
</table>

RR: relative risk
Source: Statutory Disease Reporting System (SDRS)
Indeed, different authors have highlighted the high frequency of *B. pertussis* infection with atypical manifestations among adolescents and adults and how frequently they are the source of infection for young infants [16,17].

Lately, the diagnosis of pertussis has increasingly come to rely on new diagnostic techniques. The EU, CDC, and WHO have revised the laboratory criteria and included diagnostic techniques such as serology and PCR in the case definition of the disease [18-20]. In the ARM, the current case definition, only isolation of *B. pertussis* in a clinical specimen is accepted as a laboratory diagnostic criterion [13].

According to CHDD data, most hospital discharges in the period between 1998 and 2005 were infants under one year of age. The incidence of hospital discharges with a diagnosis of pertussoid syndrome in this age group was far higher than the number of under one year-old cases reported to the SDRS, highlighting the fact that this disease is highly underreported.

In contrast to the situation reported in other European countries, the ARM recorded only one pertussis-related death from 1998 to 2005 [3]. Routine introduction of laboratory tests for *B. pertussis* in hospitals for the differential diagnosis of respiratory disease compatible with pertussis in children, as well as conducting studies of the causes of death in the first months of life among patients with respiratory disease, could both advance the knowledge about the real burden of pertussis in terms of mortality.

In conclusion, the incidence data reported in this paper can only estimate the magnitude of the problem in the ARM. To further the epidemiological knowledge about pertussis on a local level, the current surveillance systems in our region must be reinforced and specific studies undertaken in order to ascertain the real burden of pertussis in terms of morbidity and mortality, the role played by older children, adolescents and adults in transmitting the disease to infants, and the efficacy and duration of the protection conferred by the vaccines that are currently used.

References


**Robustness of Measles Immunity in Parturient Women in Gipuzkoa, Basque Country, Spain, in the Post-Vaccination Era**

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The infants of mothers with vaccine-induced immunity lose passive acquired measles antibodies earlier than infants of naturally infected mothers. This study included two cohorts of parturient women: one composed of women who gave birth in 1990 (end of the epidemic period), and another comprising women who gave birth in 2006 (after eight years without virus circulation). Immunoglobulin G (IgG) antibodies against measles (IgG-AM) were investigated by enzyme immunoassay in stored serum samples (-40°C). Measles-IgG titres of >400 mIU/mL were found in all 185 parturient women who gave birth in 1990, all with natural immunity. Of 185 women who gave birth in 2006, most of whom had vaccine-induced protection, measles-IgG were undetectable in 4.9% (<150mIU/mL), values were borderline in 7% (150-299 mIU/mL), and the geometric mean titre was lower (p<0.001), being 3.4 to 3.8 times lower in women aged <28 years. The changing levels of maternal measles antibodies suggest that in Spain, the window of susceptibility to measles in infants is increasing. To protect susceptible infants against measles in countries with long-established vaccination programs where measles immunity in parturient women was artificially acquired, it is essential to ensure that both doses of the routine measles vaccine achieve a coverage of >95%, and that infants receive the first vaccination dose before 15 months of age (e.g. at 12 months).

**Methods**

**Vaccination strategy against measles and vaccination coverage**

This study was performed in Gipuzkoa, a province in Basque country, northern Spain. In 1978, measles vaccination was introduced in our region in nine-month-old infants. In 1981, measles vaccination at this age was substituted by the measles, mumps and rubella (MMR1) vaccine in children aged 12-15 months (12 months since 1987). From the academic year 1991-92, a second dose of this vaccine (MMR2) was introduced in children aged four to 11 years. The coverage of MMR1 was >80% from 1984 and >90% from 1987, except for 1992 (87%). The mean annual coverage of MMR2 between 1993 and 2002 was 91%. The previous figures were minimum vaccine coverage, since the coverage obtained from two official surveys in Gipuzkoa for children born in 1977 and 1985 was 50% and 93%, respectively. The last year of epidemic measles virus circulation in Gipuzkoa was 1986 (an incidence of 480 cases per 100,000 inhabitants). Subsequently, after several years in which measles outbreaks occurred, virus circulation was interrupted in the second half of the 1990s and no cases of indigenous measles have been reported since 1998 [11].

**Study participants**

This study included two cohorts of parturient women: one composed of women who gave birth in 1990 (end of the epidemic period), and another comprising women who gave birth in 2006 (after eight years without virus circulation). In both cohorts, women were selected in an identical way: the first 10 women of each year of age between 20 and 39 years were selected from those that gave birth in the first trimester of 1990 or 2006, respectively. Since the aim was to determine the changing patterns of humoral immunity in the autochthonous population, women born outside Spain were excluded, due to the different vaccination programs and endemic situations in their countries of origin. A blood sample had previously been taken from all women in the context of prevention programs independent of the present study. Serum samples were stored at -40°C until processing. The study was approved by the Clinical Research Ethics Committee of Donostia Hospital.

**Laboratory methods**

The detection of immunoglobulin G (IgG) antibodies against measles (IgG-AM) was performed by using a commercial enzyme immunoassay (Enzygnost® Anti-Measles virus IgG, Dade-Behring, Marburg GmbH, Germany) following the manufacturer’s instructions. IgG-AM values were obtained in mIU/mL based on the International Standard for Anti-Measles Serum (first International standard preparation) of the WHO, included as reference sera by the manufacturer. Samples with less than 150 mIU/mL of IgG-AM were considered negative, those with between 150 and 299 mIU/mL were considered borderline and those with >=300 mIU/mL were...
considered positive. The samples and controls were dispensed on test plates, and the process was automated in a Behring Processor III. The samples were analysed in pairs; each pair was composed of samples from women of the same age but in a different study cohort (1990 or 2006). The pairs were analyzed in parallel in adjacent wells in the same run. All negative samples were reanalysed before being definitively classified as negative. The study was performed with a single batch of reagents.

**Statistical analysis**
The Chi-square test and Fisher’s exact test (two-tailed) were used to compare proportions. Women in each of the study periods were divided into groups of age. After excluding IgG-AM–negative samples, IgG-AM titres were logarithmically transformed and the geometric mean titre (GMT) and 95% confidence interval (CI) were calculated for the age groups of each of the study periods (data presented in the original scale). The Kruskal-Wallis test was used to study differences in the distribution of IgG-AM titres. Values of p<0.05 were considered significant. The statistical analysis was performed with the SPSS program, version 13.0.1 for Windows (Chicago, USA, 2003).

**Results**
A total of 370 women were investigated: 185 in 1990 and 185 in 2006. In the 1990 cohort, all women had IgG-AM titres of >300 mIU/mL (minimum titre 440 mIU/mL); the median was 4300 mIU/mL and the GMT was 3948 mIU/mL (95% confidence interval 3516-4434 mIU/mL) (Table 1). In the 2006 cohort, 22 women had titres of <300 mIU/mL (11.9%) (Chi square=23.4, p<0.001), while antibodies were undetectable (<150 mIU/mL) in nine women (4.9%) (Fisher’s exact test p=0.004), seven of them younger than 28 years old. In this cohort, the median was 1800 mIU/mL and the GMT was 1845 mIU/mL (95% confidence interval 1547-2200 mIU/mL).

The GMT and the 95% confidence intervals of the IgG-AM titres obtained in the five age groups in which the two samples were divided are shown in Table 1. The lower the age group considered, the greater the ratio between the titres obtained in the 1990 and 2006 cohorts. This finding is a result of two main factors: firstly, the women in the 1990 cohort belonged to cohorts with natural immunity while the younger women studied in 2006 belonged to cohorts with mainly vaccine immunity. Other authors have found lower antibody levels in vaccinated populations than in those with naturally acquired immunity [10,12]. Secondly, women in the 1990 cohort had lived most of their lives in an environment in which measles was endemic. In contrast, women in the 2006 cohort had lived the previous two decades among a population with low virus circulation (and with no measles virus circulation since 1998) and therefore had no contact with the virus, which might have boosted pre-existing immunity. Declining immunity to measles in vaccinated populations in the absence of wild-type virus circulation is a well-known phenomenon [12,13,14]. However, a notable finding of this study was that the decrease also affected women older than 30 years, belonging to cohorts with natural immunity. This finding supports recent data reported by Kremer JR et al., who observed that the maintenance of measles antibody levels in persons who had experienced natural infection was at least partially dependent on recurrent exposure to circulating wild-type virus [15].

| Table 1 | IgG against measles (IgG-AM; geometric mean titre [GMT] and 95% confidence intervals [95% CI]) in two groups of parturient women from whom a serum sample was obtained in 1990 or 2006. Women with IgG-AM <150 mIU/mL were not included (n=9 in 2006). Titres are expressed in mIU/mL |
|---|---|---|---|---|---|---|---|---|
| | 1990 | | | 2006 | | | |
| Age in years | N* investigated | GMT(a) | 95% CI | N* investigated | GMT(b) | 95% CI | P(c) |
| 20-23 | 29 | 3832 | 2876-5105 | 27 | 1011 | 601-1701 | <0.001 |
| 24-27 | 40 | 3988 | 3162-5029 | 35 | 1169 | 788-1735 | <0.001 |
| 28-31 | 40 | 4569 | 3562-5861 | 39 | 2357 | 1623-3422 | 0.011 |
| 32-35 | 40 | 4333 | 3338-5625 | 39 | 2681 | 1949-3689 | 0.035 |
| 36-39 | 36 | 3060 | 2237-4184 | 36 | 2303 | 1581-3354 | 0.316 |
| Total | 185 | 3948 | 3516-4434 | 176 | 1845 | 1547-2200 | <0.001 |

*| 1990: no significant differences were found when the five age groups considered were compared |
| 2006: Comparison between 20-23 years versus 28-31 years (p=0.010), 32-35 years (p=0.002) and 36-39 years (p=0.012); comparison between the remaining age groups were not significant |
| Kruskal-Wallis test |

**Discussion**
The present study shows a marked decrease in the robustness of immunity against measles in parturient women in 2006 compared with that in 1990, revealed by both the distinct percentages of immune women and by the antibody titres obtained. In the 1990 cohort, all the women studied had measles antibodies; in the 2006 cohort, the seroprevalence was still high (95%), but was significantly lower than that observed in the 1990 cohort, especially in women younger than 28 years old (seroprevalence of 89.9%). These women belonged to the first cohorts included in the measles vaccination program. In these cohorts, vaccine coverage was inadequate and, moreover, these women were unlikely to become infected with the wild-type virus, as most of them had lived most of their lives in an environment in which the incidence of measles was low [11].

In the 2006 cohort, the IgG-AM titres obtained from parturient women were clearly lower than those obtained from women in the 1990 cohort; 7% of women had borderline titres (150-299 mIU/mL) compared with none in the 1990 cohort. In addition, the lower the age of the women studied, the greater the ratio between the titres obtained in the 1990 and 2006 cohorts. This finding is a result of two main factors: firstly, the women in the 1990 cohort belonged to cohorts with natural immunity while the younger women studied in 2006 belonged to cohorts with mainly vaccine immunity. Other authors have found lower antibody levels in vaccinated populations than in those with naturally acquired immunity [10,12]. Secondly, women in the 1990 cohort had lived most of their lives in an environment in which measles was endemic. In contrast, women in the 2006 cohort had lived the previous two decades among a population with low virus circulation (and with no measles virus circulation since 1998) and therefore had no contact with the virus, which might have boosted pre-existing immunity. Declining immunity to measles in vaccinated populations in the absence of wild-type virus circulation is a well-known phenomenon [12,13,14]. However, a notable finding of this study was that the decrease also affected women older than 30 years, belonging to cohorts with natural immunity. This finding supports recent data reported by Kremer JR et al., who observed that the maintenance of measles antibody levels in persons who had experienced natural infection was at least partially dependent on recurrent exposure to circulating wild-type virus [15].
The lower robustness of measles immunity as a result of vaccination is not highly significant for individual protection against this illness, nor is it a threat for measles elimination programs [16,17,18]. However, the lower robustness of measles immunity could be highly important for immunity in infants, given that its duration depends mainly on maternal antibody levels [19]. In fact, the infants of mothers with vaccine-induced immunity lose measles antibodies earlier than those of mothers naturally infected [20]. In the large measles outbreaks in Ireland in 2000 and 2004, in England between December 2001 and May 2002, and in Romania from 2004-05, the highest attack rate occurred in children younger than 12 months [2-5]. In Spain, between 2002 and 2004, 24% of cases occurred in children younger than 16 months [6] and this age group was the most affected in an outbreak in 2006 in La Rioja, Spain [7]. Probably, the window of susceptibility to measles in infants is increasing and the role of susceptible infants below the age of vaccination may well be underestimated. In the next few years, the percentage of parturient women with low measles antibody titres will continue to increase in Spain as new cohorts with vaccine immunity reach reproductive age.

The most effective primary prevention strategy for measles among infants younger than the age of the first dose is to ensure high levels of immunity among older siblings and caregivers [21]. We believe that in Spain, vaccination should be recommended to all non-pregnant women of childbearing age born after 1977 to prevent measles antibody titres will continue to increase in Spain as new cohorts with vaccine immunity reach reproductive age.

References


Influenza activity in Europe during the winter 2005-2006 started late January - early February 2006 and first occurred in the Netherlands, France, Greece and England. Subsequently, countries were affected in a random pattern across Europe and the period of influenza activity lasted till the end of April. In contrast to the winter seasons in the period 2001-2005, no west-east pattern was detected. In 12 out of 23 countries, the consultation rates for influenza-like illness or acute respiratory infection in the winter 2005-2006 were similar or higher than in the winter 2004-2005, despite a dominance of influenza B viruses that normally cause milder disease than influenza A viruses. In the remaining 11 countries the consultation rates were lower to much lower than in the winter 2004-2005. The highest consultation rates were usually observed among children aged 0-14. The circulating influenza virus types and subtypes were distributed heterogeneously across Europe. Although the figures for total virus detections in Europe indicated a predominance of influenza B virus (58% of all virus detections), in many countries influenza B virus was predominant only early in the winter, whilst later there was a marked increase in influenza A virus detections. Among the countries where influenza A viruses were co-dominant with B viruses (9/29) or were predominant (4/29), the dominant influenza A subtype was H3 in seven countries and H1 in four countries. The vast majority of characterised influenza B viruses (90%) were similar to the B/Victoria/2/87 lineage of influenza B viruses that re-emerged in Europe in the winter 2004-2005 but were not included in the vaccine for the influenza season 2005-2006. This might help to explain the dominance of influenza B viruses in many countries in Europe during the winter season 2005-2006. The influenza A(H3) and A(H1) viruses were similar to the reference strains included in the 2005-2006 vaccine, A/California/7/2004 (H3N2) and A/New Caledonia/20/99 (H1N1), respectively. In conclusion, the 2005-2006 influenza epidemic in Europe was characterised by moderate clinical activity, a heterogeneous spread pattern across Europe, and a variable virus dominance by country, although an overall dominance of influenza B viruses that did not match the virus strain included in the vaccine was observed.

Introduction

Influenza has a considerable public health impact in Europe each winter. Although it is moderately contagious, it spreads rapidly by coughs and sneezes from people who are infected [1]. Influenza affects approximately 5-15% of the world's population with upper respiratory tract infections during seasonal epidemics every year [2]. Seasonal epidemics are associated with substantial demands on healthcare resources and considerable costs due to increases in general practice consultation rates, clinical complications, hospitalisations, drug treatment and absence from work [3,4]. Although difficult to assess, it is estimated that between 250,000 and 500,000 people die from severe illness as a result of influenza virus infection every year [2].

The European Influenza Surveillance Scheme (EISS, http://www.eiss.org) is a collaborative network of primary care physicians, epidemiologists and virologists that aims to contribute to a reduction in morbidity and mortality in Europe by active clinical and virological surveillance of influenza [5,6]. The participating national reference laboratories have functioned within EISS as the Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) since 2003. They report virus detection and identification data to EISS and work on improving the virological surveillance [7,8]. EISS aims to cover all member states of the European Union (EU), as required by EU Decision 2119/98/EC on the establishment of dedicated surveillance networks for communicable diseases [9]. During the winter 2005-2006, the EISS network included all 25 EU countries, as well as Norway, Romania and Switzerland. A total of 38 national influenza reference laboratories participated in EISS.

The identification of circulating viruses and the recognition of virological changes are major tasks for EISS in order to fulfil its early warning function [7]. There is a particular need to detect and monitor the emergence or re-emergence of viruses with pandemic potential and viruses that show a ‘mismatch’ with the vaccine strain components, and to monitor their clinical impact. During the winter period (from week 40 to week 20 of the following year) a Weekly Electronic Bulletin is published each Friday on the EISS website (http://www.EISS.org) and in the ECDC weekly Influenza News (http://www.ecdc.europa.eu/Health_topics/influenza/news_archive.html). This allows the network members, public health authorities and the general public to view influenza activity in all participating countries.

This paper presents an analysis and interpretation of influenza surveillance data collected by European countries that were members of EISS during the winter 2005-2006. In addition, the article presents an analysis of the relative and temporal distribution of influenza A and B viruses in the winter season on the basis of data from the past 10 years, as the high percentage and early appearance of influenza B viruses during the winter 2005-2006 were considered unusual.
### Methods

#### Population

All 28 countries that were members of EISS during the winter 2005-2006 actively monitored influenza activity from about week 40 of 2005 to about week 20 of 2006 (Table 1 below). In this paper, England, Northern Ireland, Scotland and Wales are referred to as separate countries because they have their own surveillance systems. EISS is therefore considered to include 31 countries. The characteristics of the sentinel networks are summarised in Table 1 of the article supplement (see: http://www.eiss.org/documents/eurosurveillance/eurosurveillance_supplement_2005_2006_winter.pdf). The median weekly population under clinical surveillance by the sentinel networks during the winter 2005-2006 varied from 0.4% to 100% of the total population of a country, representing a median number of 24.8 million inhabitants of Europe. In total, about 21,000 general practitioners (GPs), paediatricians and other physicians participated in the sentinel surveillance during the winter 2005-2006. However, the weekly number of physicians that actually reported was often lower. In general, the age distribution of the population under surveillance was representative for the age distribution of the total population in a country. However, in some countries the population under surveillance was skewed towards the lower age groups (partly due to a high proportion of paediatricians) and/or higher age groups. Further information on the representativeness of the population under surveillance in EISS can be found for most countries in Aguilera et al [10].

### Table 1

Overview of influenza activity during the 2005-2006 winter

<table>
<thead>
<tr>
<th>Country (N=31)</th>
<th>Week of peak clinical activity</th>
<th>Most affected age groups</th>
<th>Intensity (peak level)</th>
<th>Week(s) of peak virus detections</th>
<th>Dominant virus type/subtype</th>
<th>Geographical spread (peak level)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Influenza-like illness:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>No peak</td>
<td>0-4</td>
<td>Medium</td>
<td>13</td>
<td>A(H3N2)</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Belgium</td>
<td>9</td>
<td>5-14, 0-4</td>
<td>Medium</td>
<td>7</td>
<td>A(H1N1) + B</td>
<td>Widespread</td>
</tr>
<tr>
<td>Cyprus</td>
<td>4</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>13</td>
<td>0-4, 5-14</td>
<td>Low</td>
<td>8</td>
<td>B</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Denmark</td>
<td>12</td>
<td>0-4, 5-14</td>
<td>Medium</td>
<td>10</td>
<td>B</td>
<td>Widespread</td>
</tr>
<tr>
<td>England</td>
<td>7</td>
<td>5-14, 0-4</td>
<td>Medium</td>
<td>5</td>
<td>B</td>
<td>Regional</td>
</tr>
<tr>
<td>Estonia</td>
<td>11</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Finland</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Local</td>
</tr>
<tr>
<td>Greece</td>
<td>9</td>
<td>n.a.</td>
<td>Medium</td>
<td>5 + 8</td>
<td>B</td>
<td>Local</td>
</tr>
<tr>
<td>Hungary</td>
<td>12</td>
<td>n.a.</td>
<td>Low</td>
<td>13</td>
<td>B</td>
<td>Widespread</td>
</tr>
<tr>
<td>Ireland</td>
<td>10</td>
<td>5-14</td>
<td>Medium</td>
<td>9 + 10</td>
<td>A(H1N1)</td>
<td>Local</td>
</tr>
<tr>
<td>Italy</td>
<td>No peak</td>
<td>0-4, 5-14</td>
<td>Low</td>
<td>10</td>
<td>A(H1N1)</td>
<td>Local</td>
</tr>
<tr>
<td>Latvia</td>
<td>8</td>
<td>0-4, 5-14</td>
<td>Medium</td>
<td>8</td>
<td>B</td>
<td>Local</td>
</tr>
<tr>
<td>Lithuania</td>
<td>8</td>
<td>n.a.</td>
<td>High</td>
<td>10</td>
<td>B</td>
<td>Widespread</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>9</td>
<td>n.a.</td>
<td>Medium</td>
<td>8</td>
<td>B</td>
<td>Widespread</td>
</tr>
<tr>
<td>Malta</td>
<td>13</td>
<td>n.a.</td>
<td>Medium</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Netherlands</td>
<td>7</td>
<td>0-4, 5-14</td>
<td>Medium</td>
<td>9</td>
<td>A(H1) + B</td>
<td>Widespread</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>11</td>
<td>0-4, 5-14</td>
<td>Medium</td>
<td>10</td>
<td>A(H1) + B</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Norway</td>
<td>7</td>
<td>0-4, 5-14, 15-64</td>
<td>Medium</td>
<td>7</td>
<td>B</td>
<td>Widespread</td>
</tr>
<tr>
<td>Poland</td>
<td>12</td>
<td>0-4, 5-14</td>
<td>Medium</td>
<td>7</td>
<td>B</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Portugal</td>
<td>9</td>
<td>5-14</td>
<td>Low</td>
<td>8</td>
<td>A(H1) + B</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Romania</td>
<td>13</td>
<td>0-4</td>
<td>Medium</td>
<td>12 + 15</td>
<td>A(H3N2)</td>
<td>Local</td>
</tr>
<tr>
<td>Scotland</td>
<td>1</td>
<td>n.a.</td>
<td>Low</td>
<td>6</td>
<td>B</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Slovakia</td>
<td>13</td>
<td>5-14, 0-4</td>
<td>Low</td>
<td>12</td>
<td>B</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Slovenia</td>
<td>12</td>
<td>0-4</td>
<td>Medium</td>
<td>12</td>
<td>A(H3N2)</td>
<td>Widespread</td>
</tr>
<tr>
<td>Spain</td>
<td>11</td>
<td>5-14, 0-4</td>
<td>Medium</td>
<td>11</td>
<td>A(H1N1) + B</td>
<td>Regional</td>
</tr>
<tr>
<td>Sweden</td>
<td>8</td>
<td>n.a.</td>
<td>Low</td>
<td>n.a.</td>
<td>A + B</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Switzerland</td>
<td>12</td>
<td>0-4, 5-14</td>
<td>Medium</td>
<td>12</td>
<td>B</td>
<td>Widespread</td>
</tr>
<tr>
<td>Wales</td>
<td>6</td>
<td>0-4, 15-64</td>
<td>Low</td>
<td>6</td>
<td>B</td>
<td>Local</td>
</tr>
<tr>
<td><strong>Acute respiratory infections:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>5</td>
<td>0-4, 5-14</td>
<td>Medium</td>
<td>5</td>
<td>B</td>
<td>Widespread</td>
</tr>
<tr>
<td>Germany</td>
<td>10</td>
<td>0-4, 5-14</td>
<td>Medium</td>
<td>13</td>
<td>B</td>
<td>Regional</td>
</tr>
</tbody>
</table>

1. Sentinel data, except for dominant virus type/subtype for which sentinel and non-sentinel data were taken into account. For definitions of indicators see Box.
2. n.a. = not applicable as no data was available or insufficient data was available. No peak = activity was not above baseline or was flat during the whole winter. Finland did not report clinical data. Cyprus did not report virological data and Sweden did not report sentinel virological data.
3. Based on overall winter period consultation rates. If two or more age groups are shown the sequence is: most affected - less affected.
4. Estimated where possible taking into account the percentage of Influenza virus positive specimens and the absolute number of detections. If the percentage positive specimens was ambiguous only the absolute number of detections was used.
Clinical surveillance
In each of the countries, except Finland, one or several networks of sentinel physicians reported consultation rates due to influenza-like illness (ILI) and/or acute respiratory infection (ARI) on a weekly basis (for case definitions see: http://www.eiss.org/html/case_definitions.html). Twenty-six countries reported ILI consultations per 100,000 population; Malta and Cyprus reported ILI per 100 consultations and France and Germany reported ARI consultations per 100,000 population. In some countries the doctors have patients’ lists, which can provide an exact population denominator. In other countries people have a free choice of doctors, which means that the population denominator has to be estimated.

Virological surveillance
A proportion of the sentinel physicians, in most cases representative of the surveillance network in a country, also collects nose and/or throat swabs for virological surveillance using a swabbing protocol that guarantees representative swabbing during the winter period (see Table 1 in the article supplement) [10]. Combining clinical and virological data in the same population allows the evaluation of clinical reports made by the sentinel physicians and provides virological data for a clearly defined population - the general population that lives in the area served by the participating physician [11]. In addition to specimens obtained from physicians in the sentinel surveillance systems, the laboratories also collect and report results on samples obtained from other sources (e.g. from hospitals and non-sentinel physicians). These data are called ‘non-sentinel’ and are collected in order to have a second measurement of influenza activity (which contributes to early warning as the entire population is not covered by the sentinel system) and in order to assess the representativeness of the virological data obtained from the sentinel physicians [11]. Based on the collection of virological data, the total population under surveillance by EISS, during the winter 2005-2006, was almost equal to 495 million inhabitants living in the area covered by EISS [12].

The virological data includes mostly results from cell cultures followed by virus type and subtype identification and from rapid diagnostic enzyme-immunological or immunofluorescence tests identifying the virus type only. Many laboratories also use reverse transcription polymerase chain reaction (RT-PCR) routinely for detection, typing and subtyping. Almost 50% (15/31) of the countries reported antigenic characterisation data and almost 30% (9/31) of the countries reported genetic characterisation data of the virus isolates during the winter 2005-2006.

In addition to the circulation of the seasonal human influenza viruses, EISS laboratories monitored the possible transmission of the highly pathogenic avian influenza virus (H5N1) to humans in the countries covered by EISS.

The timing of the circulation of influenza A and B viruses and their relative distribution in the winter seasons was analysed using 10-year EISS data (1996-2006).

Indicators
During the winter period, the weekly clinical and virological data were collected and analysed by the national centres and then processed into the EISS database the following week via the internet [13]. The clinical consultation rates, the indicators of influenza activity (the intensity of clinical activity and the geographical spread of influenza), as well as the dominant virus type/subtype circulating in the population were established on a weekly basis by the national co-ordinators based on agreed definitions (see Box below) that were published previously [8,14]. The dominant type/subtype for the whole winter season was estimated per country (Table 1 above) using the algorithm published previously [14].

Spatial analysis
A spatial analysis of the timing of peak influenza activity across Europe was carried out using regression analysis of plots of the longitude and latitude of the centre of each country against the week of peak influenza activity of each country, as described previously [14].

Statistics
SPSS version 14.0 for Windows was used for statistical analyses. A P-value <0.05 was considered significant.

Box

Definitions of indicators

Baseline
Level of clinical influenza activity calculated nationally representing the level of clinical activity in the period that the virus is not epidemic (summer and most of the winter) based on historical data (5-10 influenza seasons).

Intensity
The intensity of clinical activity compares the weekly clinical morbidity rate with historical data:

- Low – no influenza activity or influenza activity at baseline level
- Medium – usual levels of Influenza activity
- High – higher than usual levels of Influenza activity
- Very high – particularly severe levels of Influenza activity (less than once every 10 years)

Geographic spread
The geographic spread is a WHO indicator that has the following levels:

- Sentinel and non-sentinel data (primary assessment sentinel data)
- A minimum number of 10 isolates
- If more than 10% of total A isolates are H-subtyped the H subtype is taken into consideration
- If more than 10% of total A isolates are N-subtyped the N subtype is also taken into consideration
- The limits for co-dominant virus types/subtypes are: 45%/55%

Results
The seasonal influenza epidemic started late in Europe, with consultation rates for ILI or ARI above levels seen outside the winter period first reported in the Netherlands (week 1/2006), France (week 4/2006), and England and Greece (week 5/2006) (Graphs 1 and 2 in article supplement). Only two countries reported a high intensity of clinical activity, Estonia in weeks 11-12/2006 and Lithuania in week 8/2006 (Table 1 above). Most countries (19 out of 30) reported at maximum a medium intensity. However, 11 countries reported low or very low levels of intensity and/or consultation rates for ILI or ARI: Austria, Germany, Hungary, Italy, Poland, Portugal, Romania, Scotland, Slovenia, Sweden and Wales. Overall, in 12 out of 23 countries, the consultation rates for ILI or ARI in the 2005-2006 winter were similar or higher when compared with the 2004-2005 winter, whereas in the remaining 11 countries the rates were lower to much lower (Graph 2 in article supplement).
The ILI and ARI consultation rates in Europe reached their peak as early as week 1/2006 in Scotland and as late as week 13/2006 in the Czech Republic, Malta, Romania and Slovakia, indicating that the influenza epidemic took at least 13 weeks to spread across Europe.

In individual countries, the week of peak ILI/ARI consultation rates coincided roughly with the week of peak sentinel influenza virus detections. In the 25 countries with paired data that could be evaluated the median week of peak ILI/ARI consultation rates was 10 (range week 1 – 13) and the median week of peak virus detections was 9 (range week 5 – 15) (Table 1 above). In eight (32%) of the 25 countries, the week of peak consultation rates coincided exactly with the week of peak virus detections. Including the countries with a difference of one week between the two peaks, the peak rates coincided in 15 (60%) of the 25 countries.

In countries reporting age specific data (N=21), the highest consultation rates during the influenza peak were observed among children in the 0-4 and 5-14 age groups, although consultation rates in Norway and Wales were also high in the 15-64 age group compared to those in the other age groups (Table 1 above).

In contrast to the previous four winters (2001-2005), the spatial analysis revealed no west-east pattern in the timing of peak influenza activity across Europe during the 2005-2006 winter ($R^2 = 0.032$; $P=0.491$ for west-east and $R^2 = 0.002$; $P=0.872$ for south-north).

For Europe as a whole, the largest number of influenza virus positive specimens was detected in week 8/2006 (Figure 1). About 80% of all influenza A(H1) virus detections were from Belgium, England, France, Italy, Portugal and Spain. In addition, the only influenza A virus H subtype detected in Luxembourg was H1. Twelve countries reported laboratory results for detection of the A(H5N1) virus but none of the 112 specimens from suspected and (possibly) exposed humans analysed were positive for the A(H5N1) virus. For a detailed breakdown of the virological data for Europe as a whole and by country, by week and source (sentinel or non-sentinel) see Figure 2 below, as well as Graph 2 and Tables 2 and 3 in the article supplement.

The distribution of virus types and subtypes by country and source (sentinel or non-sentinel) was analysed to evaluate the hypothesis that influenza B and A(H1N1) viruses are more often detected in sentinel specimens than in non-sentinel specimens (Tables 4 and 5 in the article supplement). By country (N=21), the proportion of type B viruses among viruses from sentinel specimens compared to viruses from non-sentinel specimens was significantly higher ($P<0.05$; Pearson Chi-Square) in ten countries, significantly lower ($P<0.05$) in two countries and not significantly different in the remaining nine countries. In contrast, by country (N=14), the proportion of A(H1) viruses among the type A viruses from sentinel...
specimens compared to non-sentinel specimens was significantly (P<0.05) lower in five countries, significantly higher in Spain only (89% vs 78%; P=0.032), whilst it was not significantly different in the remaining eight countries.

By dominant type and subtype, the circulating influenza viruses were distributed heterogeneously across Europe (Table 1 above). Although the figures for Europe as a whole indicated a predominance for influenza B virus (58% of all virus detections) (Figure 2), in many countries early in the winter influenza B virus was predominant whilst later in the winter there was a marked increase in influenza A virus detections (Graph 2 in the article supplement). Influenza B virus was the dominant virus in 16 countries. In the countries where influenza A viruses were co-dominant with B viruses (9/29) or were predominant (4/29), the dominant influenza A virus subtype was H3 in seven countries and H1 in four countries (Table 1 above).

The circulation of influenza B virus in the winter 2005-2006 was exceptional compared with data from the last decade (Figure 3). The winter 2005-2006 was the only one in Europe in ten years in which influenza B viruses were dominant. Influenza B virus circulation was suppressed (≤6% of all viruses) in the winters where there was a full-blown circulation of a new drift variant of the A(H3N2) virus, i.e. in the 1997-1998, 1999-2000 and 2003-2004 winters. In the other six winters the proportion of B viruses among all viruses did not exceed 36% (mean 27%; range 17-36%). In addition, the winter 2005-2006 was the only one in which, for Europe as a whole, influenza B viruses started to circulate and peaked earlier (3 weeks) than influenza A viruses. Of the previous nine winters, in four, the influenza B viruses started to circulate and peaked later than influenza A viruses (mean 5 weeks; range 3-7 weeks), in three, influenza A and B viruses started to circulate and peaked at the same time and in two, the timing could not be estimated as influenza B viruses were almost completely absent.

Of all 11,303 influenza virus detections, 3,128 have been antigenically and/or genetically characterised: 683 (28%) were A/New Caledonia/20/99 (H1N1)-like, 370 (12%) were A/California/7/2004 (H3N2)-like, 56 (2%) were A/Wisconsin/67/2005 (H3N2)-like (a drift variant of A/California/7/2004 included in the vaccine for the 2006-2007 winter), 1,816 (58%) were B/Yamagata/16/88-lineage and 203 (6%) were B/Jiangsu/10/2003-like (B/Jiangsu/10/2003 is a B/Shanghai/361/2002-like virus from the B/Yamagata/16/88-lineage that was included in the vaccine for the 2005-2006 influenza season).

**Discussion**

In the winter 2005-2006, influenza activity in Europe started late in January 2006, whereas in the previous winter it began in late December 2004 [14]. The 2005-2006 winter was the first one since 1996 in which, for Europe as a whole, the number of influenza B virus detections was higher than the number of influenza A virus detections (Figure 2). However, on a country level, virus type and even H-subtype dominance were very heterogeneous across Europe (Table 1 above). Most of the circulating influenza B viruses (90%) were similar to the B/Victoria/2/87 lineage of influenza B viruses that re-emerged in Europe in the winter 2004-2005 [14], but were not included in the vaccine for the influenza season 2005-2006. Remarkably, in a number of countries, a high number of influenza A(H1) viruses were detected compared to A(H3) viruses. Despite the predominant circulation of the B and A(H1) viruses, generally known to cause milder illness than A(H3) viruses [15], the peak of clinical influenza activity was similar or even higher in about half (12/23) of the countries, compared to the previous winter when A(H3) viruses were dominant [14] (Graph 2 in the article supplement).

Previously, we reported that a pattern could be seen in the timing of peak influenza activity in countries across Europe, mainly being a west-east movement, sometimes accompanied by a south-north movement later on in the winter [14]. However, the winter 2005-2006 did not fit into this pattern, as influenza activity started to peak in countries located in different parts of Europe and, subsequently, spread randomly across the whole region (Graph 1 in the article supplement). Viboud et al. showed that in the USA severe influenza epidemics, dominated by A(H3N2), are more synchronous (i.e. spread more quickly from state to state) than the milder epidemics, generally caused by A(H1N1) and B viruses [16]. In addition, they showed that population size and strong long-range human movement connections between states seem to be important for synchrony and spatio-temporal spread of influenza. As the 2005-2006 winter in Europe was heterogeneous with regard to circulating virus types and subtypes by country and with regard to the location of countries were influenza activity initially started to increase, the observations of Viboud et al. might explain the absence of a pattern in the timing of peak influenza activity for countries across Europe in the 2005-2006 winter.

In 10 out of 21 countries, the proportion of influenza B viruses was significantly higher among viruses detected in sentinel specimens compared to non-sentinel specimens. It can be explained by the fact that influenza B virus infections are mostly mild [15] and patients usually do not need hospital care. Although this assumption of the link between mild infection and low hospitalisation rate could be applied also in case of A(H1N1) infections, in only one out of 14 countries the proportion of A(H1) viruses was higher among type A viruses from sentinel specimens compared to non-sentinel specimens, whereas in 5 out of 14 countries, the proportion of A(H1) viruses was significantly lower among influenza A viruses detected in sentinel specimens compared to non-sentinel specimens. Hence, the severity of disease caused by the influenza B and A(H1N1) viruses is probably not the only factor that explains the differences between viruses detected in sentinel and non-sentinel specimens. Possibly, differences in the age distribution between and within the population under surveillance in the sentinel systems (Table 1 above in the article supplement) and patients consulting a physician in the non-sentinel systems, in combination with the patients’ vaccination and infection histories, might provide further explanations. More systematic analysis of available data and of the various surveillance systems is needed to draw more definitive conclusions.

The currently circulating influenza B viruses are antigenically and genetically divided into two distinct lineages represented by B/Yamagata/16/88 and B/Victoria/2/87 viruses, which have evolved to an extent that antibodies raised to viruses of one lineage offer reduced cross-reactive protection against viruses of the other lineage [17,18]. The trivalent influenza vaccine contains, however, only one B virus component. Because most B viruses isolated in the world by February 2005 were of the B/Yamagata/16/88 lineage type, the WHO recommended the inclusion of the B/Shanghai/361/2002-like virus (B/Yamagata/16/88 lineage) in the vaccine for the Northern Hemisphere 2005-2006 influenza season, similarly to the vaccine for the previous
The patterns observed when comparing the proportion of circulating influenza B viruses and the timing of onset of circulation and peaking of influenza B viruses with influenza A viruses for Europe as a whole (Figure 3) are not necessarily the same for individual countries. This is because the data for Europe as a whole is cumulated per week and not compensated for the time it takes the epidemic to spread across Europe (at least 13 weeks for the winter 2005-2006). The analysis of the timing pattern of circulation of influenza A and B viruses on a country level (not shown in this paper) demonstrates that in each winter there are exceptions to the pattern observed for Europe as a whole, as has also been observed for the 2005-2006 winter (compare Figure 1 for Europe as a whole with Graph 2 in the article supplement for individual countries). The patterns observed for Europe as a whole should therefore not be overinterpreted, and for a thorough analysis of distribution patterns of virus types and subtypes across Europe a finer analysis (e.g. on the country level) is currently being carried out.

During the winter 2005-2006, the A(H5N1) influenza virus which in Asia had caused epizootics and cases of transmission to humans with fatalities [22] appeared in Europe causing outbreaks in poultry and wild birds [23]. EISS received laboratory reports of A(H5N1) testing of human specimens, especially from EISS countries experiencing outbreaks among poultry and wild birds; all were negative. In Europe, human cases were only detected in Turkey [24]. However, this “near miss” situation in the area covered by EISS stressed the importance
of pandemic preparedness activities, including laboratory capacity. Therefore, the EISS network made available to all participating laboratories up-to-date RT-PCR detection protocols, recent sequence information and A(H5) controls for RT-PCR detection [7, 8]. Most laboratories participating in EISS now have the possibility to rapidly detect the A(H5) virus by molecular techniques. A recent EISS external quality assessment (EQA), carried out in collaboration with Quality Control for Molecular Diagnostics (http://www.qcmd.org), aimed at evaluating the detection, typing and subtyping of influenza viruses including the H5 virus, showed that about 65% (21/32) of the responding EISS laboratories were indeed capable of detecting the H5 virus. However, the study indicated also need for improvement, especially with regard to the sensitivity of the tests being used. Real-time RT-PCR tests outperformed block RT-PCR tests and the commercially available RT-PCR kits of which some failed to detect the A(H5) virus completely.

In conclusion, the 2005-2006 influenza epidemic in Europe was characterised by a late onset of influenza activity and a heterogeneous spread pattern across Europe. In addition, an uncommon overall dominance of influenza B viruses of the B/Victoria/2/87 lineage was observed, as well as an earlier onset of circulation and peaking of influenza B virus compared to influenza A virus, and a relatively high proportion of influenza A(H1) viruses in a number of countries.

Contributors
The members of EISS contributed by weekly submission of influenza surveillance data to EISS during the winter 2005-2006. TJ Meheroff, A Meijer, LE Meuwissen and WJ Paget carried out weekly analysis of the data and published the Weekly Electronic Bulletins during the winter 2005-2006. TJ Meheroff extracted the clinical and virological data from the EISS databases for the paper and drafted the graphs for the supplement. A Meijer carried out the overall analysis of the data and prepared the body of the manuscript. J van der Velden, as chair person of EISS, contributed by supporting the daily operation of EISS during the winter 2005-2006.

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Article supplement

The article supplement contains:
- Animations of the timing of the change of the clinical intensity and geographic spread indicators by country in Europe,
- Graphs of the weekly consultation rates and virus detections by country, and
- Tables with a detailed breakdown by country of the virological data from sentinel and non-sentinel sources.

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**Surveillance report**

**SURVEILLANCE OF PRIMARY ANTIBIOTIC RESISTANCE OF HELICOBACTER PYLORI AT CENTRES IN ENGLAND AND WALES OVER A SIX-YEAR PERIOD (2000-2005)**

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Antibiotic resistance is a key factor in the failure of Helicobacter pylori eradication therapy, yet few sentinel schemes exist to monitor trends in resistance at local, national or international levels. This study aimed, over a six-year period, to monitor resistance levels of H. pylori in England and Wales to the four antibiotics used in its treatment. A total of 1,310 isolates from Gwynedd in north Wales and from mid-Essex in south-east England were collected from 2000 to 2005 and tested for susceptibilities to metronidazole, clarithromycin, amoxicillin and tetracycline. Overall, metronidazole and clarithromycin resistance rates were 28.6% and 8.3% in Gwynedd and significantly higher (36.3%, p=0.0031, and 12.7%, p=0.0112) in mid-Essex. Rates of resistance to metronidazole and clarithromycin increased in both areas over this six-year period. Resistance rates were higher in female compared with male patients (38.1% vs 26.6% for metronidazole, p=0.0001, and 12.9% vs 7.5% for clarithromycin, p=0.0024), and were higher in patients <45 years compared with those ≥45 years (44.0% vs 29.0% for metronidazole, p=0.0002, and 15.0% vs 9.4% for clarithromycin, p=0.0233). This study highlights the importance of antibiotic resistance surveillance in H. pylori for providing information on local resistance rates for test and treat strategies.

**Introduction**

Helicobacter pylori infects an estimated 50% of the world’s population and is associated with the development of peptic ulcer disease, MALT (mucosa-–associated lymphatic tissue) lymphoma and gastric carcinoma. Treatment of infection can resolve ulcer disease in over 90% of patients and can result in complete remission of MALT lymphomas in approximately 75% of cases [1]. While rates of infection are somewhat lower at approximately 30% in developed countries, H. pylori presents a significant public health problem – in England and Wales alone an estimated 7.5 million people have active H. pylori infections [2].

Current therapeutic guidelines recommend a first-line treatment comprising a proton pump inhibitor, plus clarithromycin and amoxicillin, or metronidazole for penicillin-hypersensitive patients [3]. Resistance to either clarithromycin or metronidazole is increasingly recognised as a major contributory factor in eradication failure. Meta-analyses demonstrate an overall risk of treatment failure of 25 - 37% [4-5] and 55% [5] for, respectively, metronidazole- and clarithromycin-resistant strains. This highlights the importance of surveillance of antibiotic resistance in H. pylori, to influence local and national prescribing policies.

Surveillance of H. pylori antibiotic resistance in the pre-treatment population is difficult as few centres offer gastroendoscopy and culture as a primary diagnostic test, particularly with the advent of non-invasive “test and treat” strategies for patient management. Furthermore, a lack of standardised methods for susceptibility testing hinders comparison between studies, a problem that has been partially addressed elsewhere in Europe by development of national [6;7] or international [8;9] multi-centre surveillance schemes.

We have conducted the first large prospective two-centre surveillance study of antibiotic resistance in south-east England (mid-Essex) and in north Wales (Gwynedd), to provide information on antibiotic susceptibility that may influence local or national prescribing policies.

**Methods**

Geographical source of bacterial isolates and patient characteristics

Over a six-year period (2000-2005), a total of 1,310 isolates of H. pylori were cultured locally from single antral biopsies of 1,310 patients routinely attending an open access endoscopy clinic at the Ysbyty Gwynedd Hospital, Bangor (Gwynedd, north Wales, 664 patients) and at the Broomfield Hospital, Chelmsford (Mid-Essex, south-east England 646 patients). Both clinics offer gastroendoscopy and culture as a primary diagnostic test and so the patients in the study were predominantly sampled pre-treatment. Information on both patient age and sex was available for 1,203 isolates. Information on sex only was known for an additional 18 patients, and age only was known for a further 29 patients. Of the 1,221 patients for whom sex was known, 48.6% (n=593) were male, with a mean age of 58.6 years (range 19 – 95 years) and 51.4% (n=628) were female, mean age = 59.7 years (range 8 – 92 years). Of 1,232 patients for whom age was recorded, 1,007 (81.7%) were ≥45 years, 218 (17.7%) were >21 and <45 years and seven (0.6%) were <21 years of age. Only the patients of both known age and sex (n=1,203) were included in subsequent analysis of these patient characteristics in relation to antibiotic susceptibility. As information on the disease status of the patient was provided infrequently, this was not examined further in this study.

**Antibiotic susceptibility testing**

Susceptibility to metronidazole, clarithromycin, amoxicillin and tetracycline was assessed for all 1,310 isolates as described [10]. Isolates were classified as resistant by disk diffusion methods if growth inhibition zones were <30mm for either amoxicillin (2µg disc) or tetracycline (10µg disc). Metronidazole and clarithromycin Minimum Inhibitory Concentrations (MICs) were determined by E-test strips, which contain a predefined and continuous concentration gradient of each antibiotic. Isolates were classified as metronidazole-resistant (≥8mg/L), intermediate susceptibility (≥2mg/L, <8mg/L)
In contrast, resistance rates were significantly higher in female patients with a rate of metronidazole and clarithromycin resistance of, respectively, 26.6% (n=155) and 7.5% (n=44). (n=583) demonstrated rates of metronidazole and clarithromycin resistance. – 32.0 mg/L. None of the isolates included in this study were observed in seven isolates (0.5%) with MICs ranging from 1.0 mg/L. Reduced susceptibility to tetracycline was recorded in Gwynedd (n=9, 1.4%) and in mid-Essex (n=7, 1.1%). Reduced susceptibility to tetracycline was observed in seven isolates (0.5%) with MICs ranging from 1.0 – 32.0 mg/L. None of the isolates included in this study were amoxicillin-resistant.

**Antibiotic resistance in relation to patient age and sex**

Examination of pooled data in the male patients of known age (n=583) demonstrated rates of metronidazole and clarithromycin resistance of, respectively, 26.6% (n=155) and 7.5% (n=44). In contrast, resistance rates were significantly higher in female patients (n=620) for metronidazole (38.1%, n=236, p <0.0001) and for clarithromycin (12.9%, n=80, p=0.0024).

For patients aged <45 years (n=213), 43.2% of isolates (n=92) were metronidazole-resistant and 14.6% (n=31) were clarithromycin-resistant. In the >=45 years age group (n=990), resistance rates were significantly lower for metronidazole (29.0%, n=299, p = 0.0002) and to a lesser extent clarithromycin (9.4%, n=93, p = 0.0233), compared with the younger adult age group. Metronidazole resistance rates were higher in female patients in both the <45 age group (57.1% vs 28%, p<0.0001) and in the >=45 years age group (33.8% vs 26.3%, p=0.0105) (Table 2). In contrast it was only in the >=45 years group that clarithromycin resistance was significantly higher in females (12.0% vs 6.6%, p =0.0044) (Table 2).

**Results**

**Antibiotic resistance rates in relation to geographical location**

Overall, 28.6% (n=190) and 8.3% (n=55) of isolates from Gwynedd were resistant to metronidazole and clarithromycin, respectively (Table 1). Dual resistance to both metronidazole and clarithromycin was observed in 29 isolates (4.4%). In mid-Essex, 36.4% of isolates (n=235) were metronidazole-resistant, 12.7% (n=82) were clarithromycin-resistant and 8.4% (n=54) were dually resistant (Table 1). Rates of resistance to metronidazole (p = 0.0031, Fisher’s exact test) and to clarithromycin (p = 0.0112) were higher in mid-Essex compared with Gwynedd. The number of isolates referred annually for each centre varied considerably (Table 1), preventing detailed statistical analyses to identify temporal trends in antibiotic resistance. Both metronidazole and clarithromycin resistance fluctuated annually, but an overall upwards trend in rates of resistance to both agents (dual resistance) was observed throughout the study period in Gwynedd and in mid-Essex (Table 1).

A range of MICs were observed within the resistant phenotypes, with high-level resistance (>256 mg/L) accounting for, respectively, 83.8% and 73.7% of metronidazole- and clarithromycin-resistant isolates. While clarithromycin-susceptible isolates generally exhibited low MICs of <0.016, a wider MIC range was observed for metronidazole-susceptible isolates. Intermediate metronidazole susceptibility was recorded in Gwynedd (n=9, 1.4%) and in mid-Essex (n=7, 1.1%). Reduced susceptibility to tetracycline was observed in seven isolates (0.5%) with MICs ranging from 1.0 – 32.0 mg/L. None of the isolates included in this study were amoxicillin-resistant.

**Statistical analyses**

Potential associations between antibiotic resistance levels and location, age and sex of patients was assessed by Fisher’s exact test using GraphPad InStat, version 3.05 (GraphPad, San Diego, US). A p value of <0.05 indicated significant differences.

**Discussion**

The current study showed overall rates of resistance to metronidazole and to clarithromycin of 32.4% and 10.4%, respectively. In spite of being assessed by different methods in most earlier single-centre studies in the United Kingdom (UK) [9-11], metronidazole resistance rates were similar (ranging from 24% - 32%). However, rates were higher in ethnically diverse areas.
such as London [12,13]. Similar resistance rates (25%-34%) have been reported elsewhere in Europe also, including Germany [14], Bulgaria [15], France, Ireland, Denmark and the Netherlands [9]. Clarithromycin resistance in the current study was higher than reported in earlier studies elsewhere in the UK [9,11;16]. This may be due to geographical variations in resistance rates or indicate a rise in clarithromycin resistance since the earlier sampling periods. Rates of clarithromycin resistance in this study were comparable to those reported in Bulgaria [15], Poland [7] and Greece [9]. Higher rates of clarithromycin resistance (>25%) were reported in other European countries, including France, Portugal, Belgium and Italy [9], where macrolide use is high. In contrast, the rates of clarithromycin resistance in the current study are consistent with the lower use of macrolides in the UK, which is comparable with Scandinavian and other northern European countries [17].

This study demonstrated a higher incidence of metronidazole resistance in mid-Essex, compared with Gwynedd. According to data from a national census in 2001, 98.8% of the population in Chelmsford are white, 1.9% were born in another European Union (EU) country and 3.4% were born outside of the EU. The largest ethnic minority group is Indian [18]. The population in the Gwynedd region is 98.8% white, with 1.2% born in another EU country and 1.6% born outside the EU. The largest ethnic minority group is Chinese [19]. We have shown previously that metronidazole resistance is higher in certain ethnic groups, particularly in individuals born outside the UK [12]. Metronidazole is a key therapeutic agent for parasitic infections and this is the most likely explanation for the higher rates of resistance observed in some ethnic groups. The higher proportion of individuals not born in the UK in Chelmsford may therefore contribute to the higher rates of metronidazole resistance observed. Interestingly, clarithromycin rates were also marginally higher in mid-Essex.

It is not known if this is also due to differences in ethnicity. The use of prior macrolides is clearly associated with an increased risk of clarithromycin resistance in H. pylori in individual patients [20]. While the higher clarithromycin-resistant rates in mid-Essex may indicate greater consumption of macrolide antibiotics in this region, the reasons for this are unclear.

Our observation that metronidazole resistance was higher in female patients has been documented previously [11,14,16,21]. and is most likely to be due to the use of metronidazole to treat gynaecological infections such as bacterial vaginosis and trichomoniasis, a sexually transmitted infection. Treatment of trichomoniasis in particular could account for our observation that the highest rate of metronidazole resistance was in younger females (<45 years). Interestingly, the incidence of clarithromycin resistance was higher in females compared with male patients aged >45 years, whereas there was no significant sex bias in the younger patient group. Higher clarithromycin resistance in females was also documented in a multi-centre study in the United States [22]. Mutations (A2142G and A2143G) in the 23S rRNA gene associated with clarithromycin resistance in H. pylori confer cross-resistance to other agents in the macrolide, lincosamide, streptogramin B antibiotic group, including clindamycin [23]. The higher clarithromycin resistance rates in females may again be due to treatment of gynaecological infections, as clindamycin is used as an alternative to metronidazole in the treatment of bacterial vaginosis. Previously, older age has been reported to be associated with clarithromycin resistance, presumably due to use of macrolides to treat respiratory infections [22]. This association was not observed in our study, with slightly higher clarithromycin resistance rates apparent in the younger age group.

While resistance to metronidazole, clarithromycin and to both agents fluctuated annually, dual resistance in particular appeared to increase in both Gwynedd and mid-Essex. An earlier study (1995-1998) in Chelmsford showed metronidazole resistance rates ranging from 33.2% to 38.6% and clarithromycin resistance ranging from 2.3 to 5.7% [24]. While metronidazole resistance rates were similar in both studies, in the current study the clarithromycin resistance in Chelmsford was higher (ranging from 7.1%-11.2% between 2002 and 2005) than in the earlier study. This is of concern as resistance to clarithromycin in particular has a clear association with treatment failure [5]. Increasing rates of resistance to clarithromycin in particular are reported in Bulgaria [15], Spain [25] and Brazil [21], but in some cases few isolates were examined at each time point [21,25]. While some larger studies also have demonstrated increasing trends in clarithromycin resistance in Europe [15] and in the US [22], others showed no such increase [14]. Continued monitoring of resistance rates in larger study populations over a longer period would be essential in order to identify potential trends.

The limitations of existing therapies has led to the development of alternative “rescue therapies” involving agents not used in first or second-line therapies, such as the rifamycin derivative rifabutin and fluoroquinolones [26]. Resistance to these agents has not been examined here as, at the time this prospective study was initiated, few validation studies to determine appropriate cut-offs for resistance had been conducted. An extension of our approach to examine these alternative agents in future studies would provide invaluable information on the potential efficacy of “rescue therapies”.

Our study highlights the importance of antibiotic resistance surveillance to guide test and treat policies, although the findings do not indicate any immediate need to review current treatment regimens. Metronidazole and clarithromycin resistance rates were both higher in H. pylori from south-east England than northern Wales. The further development of long-term, multi-centre antibiotic susceptibility surveillance schemes to monitor temporal trends in resistance in H. pylori will be essential to ensure the efficacy of recommended eradication regimes.

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References


Gripenet has been monitoring the activity of influenza-like-illness (ILI) with the aid of volunteers via the internet in the Netherlands and Belgium since 2003 and in Portugal since 2005. In contrast with the traditional system of sentinel networks of mainly primary care physicians coordinated by the European Influenza Surveillance Scheme (EISS), Gripenet obtains its data directly from the population. Any resident of the three countries can participate in Gripenet by completing an application form on the appropriate websites (http://www.griepmeting.nl for the Netherlands and Belgium, http://www.gripenet.pt for Portugal), which contains various medical, geographic and behavioural questions. Participants report weekly on the website any symptoms they have experienced since their last visit. ILI incidence is determined on the basis of a uniform case definition. In the 2006/2007 season, 19,623 persons participated in Gripenet in the Netherlands, 7,025 in Belgium and 3,118 in Portugal. The rise, peak and decline of ILI activity occurred at similar times according to Gripenet and EISS. However, ILI attack rates in the Netherlands (6.6%), Belgium (6.1%) and Portugal (5.6%) were remarkably more similar in Gripenet than in EISS (0.8%, 3.9%, and 0.6% respectively). Monitoring ILI activity with the direct participation of volunteers provides similar incidence curves compared to the traditional system coordinated by EISS. Whereas EISS provides an established system whose data is validated by virology tests, Gripenet is a fast and flexible monitoring system whose uniformity allows for direct comparison of ILI rates between countries. A current objective of Gripenet is to engage more European countries.

Introduction

During the winter 2003/2004 season, the Netherlands and Belgium launched a system to monitor the activity of influenza-like-illness (ILI) with the help of volunteers via the Internet [1]. The success of this initiative, which attracted over 30,000 participants in the first year, inspired the establishment of a similar system in Portugal in 2005/2006 [2]. Throughout this paper, the system is referred to as “Gripenet”.

Traditionally, influenza surveillance in Europe is monitored by the European Influenza Surveillance Scheme (EISS), a collaborative programme of mainly primary care physicians, epidemiologists and virologists who actively collect clinical and virological data on influenza [3]. In this paper, we argue that the Gripenet monitoring system in which the data is gathered directly from the population offers some advantages over the established surveillance system based on the network of general practitioners (GPs). It has previously been shown that the participants of Gripenet in 2003/2004 in the Netherlands were representative for the Dutch population [4]. Here, we compare Gripenet results in the three countries with the EISS results from the same countries during the 2006/2007 season.

Methods

Gripenet

Gripenet is a fully internet-based system, currently hosted on two websites: http://www.griepmeting.nl for the Netherlands and Belgium (Flanders), and http://www.gripenet.pt for Portugal. Any resident of these countries can register for Gripenet by completing an online application form containing various medical, geographic, and behavioural questions (Table 1). Participants are mainly recruited via mass-media, which present information on the system and give regular updates of the latest results. Participation is further stimulated by email newsletters, online educational materials, competitions and presentations, and other activities. Once registered, participants receive a weekly email newsletter reminding them to complete their symptoms questionnaire. In this questionnaire participants are asked to select from a list of symptoms the ones they have experienced since their previous visit to the Gripenet website (Table 2). If symptoms are reported, participants are asked to provide the date of onset, and whether these led to change of behaviour and/or a GP consultation, and if so, the outcome of the consultation.

Table 1

Intake questions. List of questions the participants are requested to answer each year upon registration for Gripenet

- Postal code
- Month and year of birth
- Sex
- Daily occupation (school / work / home / other)
- Means of transportation (car / public / bike / foot)
- Number of common colds per year (<2, 2-5, >5)
- Vaccinated against flu this season (yes / no)
- Any of the following diseases (asthma / diabetes / none)
- How often do you smoke? (never / sometimes / daily)
- Do you eat 2 pieces of fruit and 200g of vegetables per day? (no / sometimes / always)
- Do you use supplements like vitamins? (no / sometimes / daily)
- How many hours of exercise per week (<1, 1-4, >4)
- Household situation (alone / only adults / with adults and children)
- Where do the children go? (nursery / school / stay at home)
- Do you have pets? (no / cat(s) / dog(s) / bird(s) / other)
The incidence of ILI is determined based on the symptoms reported, using a uniform case definition. ILI is defined as acute onset of fever of >=38°C, plus muscle pain, plus one of the following: cough, sore throat, and/or chest pain. The day of fever onset determines the onset of ILI. A participant is considered to be active between the day of registration and the day of the last completed symptoms questionnaire. Only participants who have completed at least three symptoms’ questionnaires are included in the analyses. The daily incidence is determined by the number of participants with an onset of ILI on a given day, divided by the number of active participants on that day. The weekly incidence for each day is determined by the total number of participants with an onset of ILI in the previous seven days, divided by the average number of active participants during those seven days. The ILI attack rate for both Gripenet and EISS is defined as the cumulative incidence rate over the total surveillance period, i.e. the fraction of the population under observation that had a reported onset of ILI.

**EISS**

During the 2005/2006 influenza season, 39 countries were members of EISS, and the sentinel surveillance was carried out by 21,162 GPs, paediatricians and other physicians. The population under clinical surveillance by the sentinel networks represents at least a median number of 24.8 million inhabitants of Europe. The population under surveillance in the Netherlands accounts for 0.7% of the total population, in Belgium 0.4%, and in Portugal 0.7%. Although there are differences in the general characteristics of the sentinel systems in each of the countries, the majority collect weekly incidences of ILI cases per 100,000 inhabitants, as is the case in the Netherlands, Belgium and Portugal [5]. The different case definitions used in these countries are shown in Table 3. Using historical data, several countries within EISS introduced an influenza activity baseline. The intensity of influenza activity is determined by measuring the influenza activity against the baseline and its geographical spread.

The ILI attack rate is defined as the average number of active participants during those seven days. The weekly incidence is determined by the number of participants with an onset of ILI on a given day, divided by the number of active participants on that day. The ILI attack rate in the Netherlands is calculated using the cumulative incidence rate over the total surveillance period, i.e. the fraction of the population under observation that had a reported onset of ILI.

## Results

We compared the Gripenet and EISS data from 15 December 2006 to 1 May 2007. Gripenet data showed that in the Netherlands, 17,056 out of 19,623 participants (87%) completed at least three symptoms questionnaires, in Belgium 6,062 out of 7,025 (86%) and in Portugal 2,167 out of 3,118 (69%). The national participation rate was 0.1% in the Netherlands (total population - 16.3 million, 0.1% in Flanders (6.2 million), and 0.02% in Portugal (10.5 million). In all three countries, the younger and older age groups are underrepresented (Figure 1). The geographical distribution of participants follows the patterns of population density, with higher concentration in the larger cities.

In the Netherlands, 25% participants matching the ILI case definition visited a GP (225 out of 907), in Belgium 67% (215 out of 322) and in Portugal 45% (45 out of 99). Influenza activity in Europe was, in 2006/2007, mainly due to influenza A (H3N2) [7]. In all three countries, the incidence curves provided by Gripenet show the same trends as the incidence curves of EISS (Figure 2). For each country the shapes of the curves are similar, with peak incidence occurring in the same week and approximately equal onset and decline of ILI activity. However, incidences calculated from Gripenet data are higher than those reported by EISS. According to Gripenet data, the ILI attack rate in the Netherlands was 6.6%, in Belgium 6.1%, and in Portugal 5.6%, while according to EISS data, it was 0.8%, 3.9%, and 0.6% respectively.

## Discussion

Although there is an approximately simultaneous rise, peak and decline of ILI activity in the Gripenet and EISS epidemic curves, quantitatively the incidences obtained by Gripenet are much higher than those provided by EISS. This could be partially explained by the use of different denominators in the incidence calculations. Gripenet participants are requested to fill in the questionnaire each week irrespective of whether they have experienced any symptoms, and the incidence of ILI is determined, considering only those participants who have filled in their symptoms’ questionnaire.
Gripenet is therefore independent of the rate at which people seek advice from a health professional. In contrast, the incidence determined by EISS depends on the GP visiting rates which differ across countries (as can be seen also in the Gripenet data), reflecting differences in the health care systems.

Other population-based surveillance systems for ILI have been tested [4], but they often depend on the proportion of the people which seeks advice from a health professional when experiencing ILI symptoms. An interesting real-time monitoring system used data on symptoms reported through the NHS Direct service in the UK, a nurse-led telephone helpline for medical advice [8,9]. Although such systems may perform very well within one country, applying them in other countries can bring very different results. Social and cultural differences between countries may affect the tendency for people to seek advice when experiencing ILI symptoms, leading to differences in reported incidence rates.

The ILI attack rates measured by Gripenet in winter 2006/2007 were very similar in the three countries (5.6% - 6.6%), while according to EISS, the ILI attack rate in Belgium (3.9%) was five times higher than in the Netherlands (0.8%) and seven times higher than in Portugal (0.6%). This is reflected in Figure 3 by comparing the incidence curves of the three countries according to Gripenet and EISS. The reasons for this discrepancy could be the different case definitions used by Dutch, Belgian and Portuguese sentinel GPs (Table 3), the different GP visiting rates per country and the extent to which the population under observation is representative for the general population. EISS is in the process of standardizing the case definitions for ILI used by the GPs in the different countries [10]. The GP visiting rates, however, are not realistically controllable.

More data and analysis are needed to establish a baseline for Gripenet. According to the Gripenet data collected in 2006/2007 (Figure 2), the ILI incidence outside the epidemic peak in the Netherlands (~200 per 100,000) is different from the rates in Portugal and Belgium (~50-100 per 100,000). However, outside the influenza seasons, virology tests only rarely confirm influenza cases, rendering a system based on symptoms to low specificity. Hence the reported differences are not necessarily related to differences in influenza attack rates.

Although Gripenet aims to attract a representative sample of the population, people who do not experience any ILI symptoms may not consider themselves suitable for participation. To remove the selection bias related to the new participants who have already been experiencing ILI symptoms at the moment of registration, participants are only active from the day of registration onwards, and the first symptoms questionnaire concerning the week before registration is not included in the analyses.

The non-representative nature of the Internet-using population results in a selection bias that is generally a major concern in web-based surveys [4]. Based on the data supplied by all participants upon application, the representativeness of the Gripenet sample can be determined. Marquet et al. showed that the demographic and health characteristics of the Gripenet participants in 2003/2004 in the Netherlands were remarkably similar to those in the general Dutch population. Similar studies for the Portuguese and the Belgian populations have not been performed yet. There is evidence, however, that the younger and older age groups are similarly underrepresented in all three countries (Figure 1).
**Figure 2 A, B, C.**
Comparison of incidence curves between Gripenet and EISS: (a) The Netherlands (b) Belgium; (c) Portugal

Note to Figure 2 a,b,c. The three plots represent weekly ILI incidences. EISS provides for each week (Monday - Sunday) the number of patients diagnosed with ILI per 100,000 of the population under observation by the sentinel network. Gripenet provides for each day the number of ILI onsets per 100,000 active participants (those who filled in their symptoms questionnaire for that period) in the preceding 7 days. The data points in the incidence curve of Gripenet which monitor the same time period (Monday – Sunday) as EISS are marked with squares. Note that Gripenet only monitors the Northern Dutch-speaking part of Belgium (Flanders), whereas EISS monitors the whole of Belgium.

**Figure 3 A, B.**
Comparison of incidence curves between the Netherlands, Belgium and Portugal: (a) Gripenet; (b) EISS

Note to Figure 3 a,b. Both plots represent weekly ILI incidences. The peak of the ILI activity was first reached in Portugal, closely followed by Belgium and then in the Netherlands. According to Gripenet data the height of the peak in ILI incidence in the Netherlands is lower than in Belgium and Portugal, but the activity lasted longer. Therefore, ILI attack rates in the three countries are similar according to Gripenet data (a). However, according to EISS data there is great variation (b).
Gripenet seeks to monitor the representativeness of the participants in all three countries, and direct recruitment aims at targeting the underrepresented sections of the population. The number of participants is critical for Gripenet’s success. A survey performed among 4,500 Dutch participants of Gripenet at the end of the first season showed that most of them were recruited via radio or television (47%), via newspaper (21%) and via internet sites (16%).

Since the Gripenet data are collected and analysed in one place, results can be published in real time, whereas EISS reporting each Thursday the ILI incidence for the previous Monday – Sunday period is four days behind. Gripenet also has the capability to publish a daily incidence rate, although it has been noted that participants with ILI tend to fill in their symptoms questionnaire earlier than participants without symptoms. This leads to an overestimation of ILI incidence rates for the most recent days, but the continuous updating ensures that they become increasingly more reliable as time passes. The advantage of Gripenet, however, lies not only in its potential for an earlier assessment of weekly ILI incidences, but also in the possibility of observing the daily fluctuations in real time, thus allowing to detect early warning signals. These time advantages could be reproduced by EISS as well, if all GPs reported electronically in real time, as has been demonstrated by pilot projects in France and Germany [11, 12].

The Gripenet system gathers a variety of valuable data on ILI activity, however, only a fraction of these have been analysed so far. For example, Gripenet has the potential of monitoring the geographical spread of ILI, using the postal codes of the participants. Demographic data can also be used to monitor ILI activity in different subgroups of the population. Comparing participants with different behaviours could give indications on risk factors. Detecting an earlier rise of ILI activity in certain subgroups could make Gripenet an even faster early-warning system.

The uniformity of this monitoring system makes it possible to compare ILI activity between countries without further data standardization. This has important practical implications for studies concerning the global spread of ILI activity. Current efforts are directed at recruiting more European countries to join the Gripenet. The strength of Gripenet lies in the unique central control of every element of the monitoring system: the recruitment of participants, the questionnaires, the case definitions, the analyses of the data and the presentation of results. This makes the system not only efficient but also very flexible. If desired, any specific component can be altered without disturbing the overall system functionality. For example, the case definition can at any moment, even retrospectively, be adapted to include demographical variables. Further advantages and disadvantages of Gripenet and EISS are listed in Table 4. The two systems can complement each other to provide a better understanding of ILI activity in Europe.

### Conclusion

Based solely on voluntary online reports from participants in the Netherlands, Belgium and Portugal, Gripenet detected an approximately simultaneous rise, peak and decline of the ILI activity as compared to EISS during the 2006/2007 influenza season. In contrast to EISS, however, Gripenet uses a uniform monitoring system, allowing the direct comparison of ILI activity between countries, potentially offering a platform to monitor the geographical spread of ILI throughout Europe. We believe that the established system of EISS, which is validated by laboratory results, could be complemented by the fast and flexible system of Gripenet. Furthermore, Gripenet could provide an important channel for influenza awareness and education in Europe. Our current strategy is to extend Gripenet to include more European countries, thus increasing the value of its results and its impact. Those interested in implementing Gripenet are encouraged to contact the corresponding author.

### Acknowledgements

This research was funded by the Gulbenkian Foundation (FCG), the Portuguese Research Council (FCT) and the European Commission (grant MEXT-CT-2004-14338). We thank the European Influenza Surveillance Scheme, the Portuguese Gripenet team and the Grote Griepe monitoring team for providing us with the ILI Incidence data.

### References

1. de Grote Griepmeting. Available from: http://www.grotegriepmeting.nl


### Table 4

<table>
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<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td><strong>EISS</strong></td>
<td>Established system</td>
<td>Participating countries using different case definitions</td>
</tr>
<tr>
<td></td>
<td>Combine clinical and virological data in the same population</td>
<td>Dependent on the GP visiting rate</td>
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<tr>
<td><strong>Gripenet</strong></td>
<td>Uniform method, allows for direct comparison of ILI rates across countries.</td>
<td>Self-selection bias of participants</td>
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<td>Flexible</td>
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<tr>
<td></td>
<td>Real-time monitoring</td>
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<tr>
<td></td>
<td>Channel to participants for influenza-related information</td>
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EUROSURVEILLANCE Vol. 12 · Issues 7–9 · Jul–Sep 2007 · www.eurosurveillance.org 233
Hospital admissions for pneumonia, one of the most frequent complications of influenza, are more common in children and the elderly and in individuals with chronic disease. Portugal’s Northern Health Region is one of the country’s five health regions, and its 3.3 million inhabitants represent approximately one third of the country’s population. We conducted a retrospective study to characterise the trend and the geographical distribution of hospitalisations due to pneumonia and influenza in public hospitals in northern Portugal. The distribution of the hospitalisations was investigated using exploratory techniques of spatial analysis based on data for pneumonia and influenza cases discharged from hospital between 2000 and 2005. There were 53,314 hospitalisations due to pneumonia and influenza during that period, representing an annual average hospitalisation rate of 274 per 100,000 inhabitants. The exploratory spatial analysis showed a moderate space dependence in the region (Moran’s Index=0.51, p<0.05). The local indicator of space association for each area allowed the detection of a cluster of 11 municipalities in two north-eastern districts that had higher rates of hospitalisation than the remaining regions. The results showed that the spatial distribution of hospital admissions for pneumonia and influenza is not homogeneous in northern Portugal, indicating that it is not coincidental. The significant spatial dependence highlights the need to perform further studies to examine the underlying causes of such distribution.

Methods

Portugal, a country of approximately 10 million inhabitants, is divided into five health regions and two autonomous regions. The northern health region, with 3.3 million inhabitants, represents about one third of the country’s population, and is divided into five districts and 68 municipalities. In northern Portugal, geographical access to hospitals of the National Health Service is heterogeneous, so that people living in north-eastern districts have greater difficulty reaching a hospital than those living near the coast [9].

This study was based on data on patients discharged from the National Health Service Hospitals in northern Portugal, classified according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). We analysed all hospital discharges for pneumonia and influenza (ICD-9-CM 480-487; first-listed diagnoses) in the six-year period from January 2000 until December 2005. We chose to analyse hospitalisations due to pneumonia or influenza considering that these hospitalisations can be used as an indicator of influenza activity and severity. We began to work with these diseases in order to prepare the region for influenza pandemic. Data under analysis included, for each case, birth date, hospital admission date, sex, length of stay, residence, diagnosis and outcome (survival to hospital discharge or death).

We only studied the hospitalisations for patients living in northern Portugal, whose residence was identified at least at municipality level. After validation and analysis of data consistency, 97% of those cases were included in the study.

Descriptive summary statistics for all variables were calculated at region, district and municipality levels. The average rates of hospitalisation were calculated per 100,000 population for the region, district (five districts) and municipality, according to sex and age group. We calculated average rates considering the annual population estimates provided by the National Institute of Statistics. The seriousness of disease was evaluated on the basis of the average length of hospitalisation, the proportion of patients staying in intensive care units, and the case fatality rate. Crude average hospitalisation rates in each district and the remaining region were compared using chi-square test. In order to eliminate the effect of age distribution, we also compared age-standardised average rates using the direct method (IARC, Lyon 1976). Pearson’s correlation coefficient was used to study the relation between time and the number of hospitalisations, the number of deaths, and case fatality rates.

Currently, studying the geographical distribution of diseases is a powerful tool. Exploratory techniques are useful for describing data and should initiate any statistical analysis. Spatial analysis is no exception [10]. We conducted an Exploratory Spatial Data Analysis to assess spatial patterns in hospitalisations for pneumonia and influenza in northern Portugal. Disease mapping is considered
an exploratory technique. The maps are used for several purposes, such as the identification of areas with a suspected elevated risk of disease [10,12]. The construction of maps must be done using different class ranges in order to develop several approaches. We used different methods to form classes and to map out geographical distribution for the annual average rate of hospitalisation. The Jenks method minimises the squared deviations of the class means [13]. With quantile's method, which is suited for linearly distributed data, an equal number of observations fall into each class [11]. The standard deviation method assumes a normal Gauss distribution of data, and defines classes according to the distance from the mean, using the standard deviation as a unit [11]. In this kind of analysis, ‘small numbers’ can be a problem: rates calculated with small populations may not be reliable, eventually reflecting random variation [11]. Bayesian methods have been developed to remove the random effect [13]. We used Spatial Empirical Bayes Smoothing developed by Bailey and Gatrell [10]. This technique considers as a basic principle for spatial analysis that neighbouring areas are more likely to be similar than distant ones. To estimate the local risk, the model is based on the neighbours’ average rates adjusting each crude rate according to the size of the population and the variance. In our analysis, we considered first degree neighbours using the rook criterion [15]. To measure the correlation between observations of the same variable in different areas, we performed a spatial autocorrelation analysis, calculating global and local indicators. Global indicators are useful for characterising the whole region, while local indicators are useful when the range of values is wide [11]. Moran’s Index was used as a global test for spatial autocorrelation. Moran’s Index values vary between -1 and +1: if the index is >0, there is a spatial dependence showing similar neighbourhood areas; if the value is negative, the neighbourhood areas are discordant; if the index has a value near zero, there is no spatial dependence. As we are dealing with a considerable number of areas, different spatial associations may occur. Therefore, we used local indicators of spatial autocorrelation to provide a specific value for each area: local Moran Index, known as Local Indicator of Spatial Association (LISA) [10-12]. LISA maps were used to assess the hypothesis of spatial randomness and to identify local ‘hot spots’.

Data analysis was performed with the software packages SPSS 14, Microsoft Excel 2003, ESRI ArcMap 8.3 and GeoDa 095i, and statistical tests were performed considering exact 95% confidence intervals.

Table

<table>
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Figure 1

Monthly number of hospital discharges with main diagnosis of pneumonia or influenza in the Northern Health Region of Portugal (2005-2005)

Results

Between 2000 and 2005, a total of 53,314 hospital discharges for pneumonia and influenza were reported in northern Portugal. The table shows descriptive statistics according to sex, age group, and geographical level.

The annual average number of pneumonia and influenza hospitalisations in the area was 8,886, with a minimum of 7,293 observed in 2001 and a maximum of 10,595 in 2005. This number accounted for between 2.3% (2001) and 3.1% (2005) of the total number of hospitalisations. During the period under study, the number of pneumonia and influenza hospitalisations showed a tendency to increase (Pearson’s Coefficient: r=0.87).

The number of hospitalisations per month presents a pattern of seasonal variation (Figure 1). The highest values for hospital admissions occurred between December and March with a peak in January (except for 2003 and 2004).

The annual average rate of pneumonia and influenza hospitalisations in the region was 274 per 100,000. The rates in the north-eastern districts of Bragança and Vila Real were significantly higher than in the rest of the region, whereas the rates in the districts of Braga, Porto and Viana do Castelo were significantly lower than in the rest of the region (Figure 2). The regional rates were higher among extreme age groups: 1,132 per 100,000 for the elderly (>= 65 years) and 286 per 100,000 for children under 15 years of age. After age-adjustment, the annual average hospitalisation rate remained significantly increased in the district of Vila Real and significantly reduced in the districts of Porto and Viana do Castelo.
Male patients represented 56% of the hospitalisations in the region. The average duration of hospitalisation was 10 days, the proportion of patients treated in intensive care units was 3% and the case fatality rate was 14%. The fatality rate showed an increasing tendency during the period under analysis (Pearson’s Coefficient: \( r = 0.90 \)). We also observed an increasing tendency in the total number of deaths (Pearson’s Coefficient: \( r = 0.97 \)). The percent variation of the number of hospitalisations and of the number of deaths between 2000 and 2005 was +33% and +70%, respectively.

Figure 3 shows the spatial distribution for average rates of hospitalisation due to pneumonia and influenza according to the municipality of the patients’ residence, in the period between 2000 and 2005 in northern Portugal. Different methods for generating classes were used, namely Jenks, quantile, and standard deviation. The patterns obtained with the different methods are visually identical; all accentuate the higher rates in the north-eastern districts.

The value of the Moran’s Index was 0.51, indicating a moderate positive global autocorrelation and a spatial dependency. To identify local ‘hot spots’, the local Moran Index (Local Indicator of Spatial Association; LiSA) was calculated. Figure 4 shows a map based on LiSA results. It identified a cluster composed of 11 municipalities with high rates that bordered municipalities with equally high levels. Among the seven municipalities with low rates of hospital admission whose neighbours also had low values, one cluster of five was detected.

Discussion
Considering that a certain proportion of patients diagnosed with pneumonia are treated at home, others are hospitalised in the private sector, and that the access to health services influences hospitalisation [4,5,16], the hospitalisation rate found in this study represents an underestimation of the true incidence of pneumonia and influenza in the community [17]. Our results are similar to those reported in other studies, so we assume that the rate of hospitalisation for pneumonia and influenza is a reasonable estimate of the risk of hospitalisation for these diseases [1,18].
We observed an increasing tendency in the number of hospitalisations for pneumonia and influenza during the study period. Since this trend can certainly influence the specific allocation of health resources, the need to monitor this phenomenon must be carefully considered [19,20].

It is possible that the differences in the annual average hospitalisation rates that were observed between districts were due, in some districts, to differences in the age distribution of the population or to different hospital admission criteria as suggested in some studies [4,16]. It is also possible that they reflect differences in climatic, environmental, and other factors [4,8,21–23].

According to our analysis, an uneven age distribution does not explain the differences in the rates. However, factors related to health care services could in part explain the results: access, referral criteria to hospitals, admission criteria, etc. The distance to health care services, both primary health care centres and hospitals, is generally greater for people who live in the districts of Bragança and Vila Real than in urban districts like Porto or Braga. This fact could influence the timeliness of care and, ultimately, increase the severity of disease and the need for hospitalisation. Further analytical studies could contribute to identifying risk factors for pneumonia and influenza hospitalisations.

As in other studies, marked differences were observed in the rates of hospitalisation with respect to age. The rates were higher in those under 15 years and those over 65 years [1,4,5,8]. As in other studies, hospitalisations were more frequent in men [1,4,5]. The results obtained for the duration of hospitalisation, for the proportion of patients treated in intensive care units and for the fatality rates were similar to those found in other studies in Portugal [3,18]. However, the case fatality rates we identified in the Northern Health Region of Portugal were higher than those observed in some studies in Spain [5,6]. These findings could be explained by differences in admission criteria and access to hospital, although other factors of biological, cultural, social and economical nature are certainly also important.

The percent variation observed in the annual number of hospital deaths was greater than that observed in the number of hospitalisations. As the six-year period investigated here was rather short, we can assume that those differences are not exclusively due to ageing of the population. Further investigation is needed to establish whether the quality of clinical care plays a role or whether other factors are responsible for those findings.

The spatial distribution of hospital admissions for pneumonia and influenza in northern Portugal between 2000 and 2005 was not a result of chance. The moderate global spatial autocorrelation, identified by Moran’s Index, and the existence of statistically significant clusters, confirm a pattern of high rates in the north-east of the region and low rates in the west. Although we did not explore in detail other factors that could explain this imbalance, our results can help to formulate hypotheses for future studies. The next step should be the confirmation of these results applying other statistical methods to the data. This study can also contribute to the development or reinforcement of public health programmes aiming to reduce both morbidity and mortality associated with pneumonia and influenza. Vaccinations against seasonal influenza and pneumococcal infections are examples of preventive interventions with great impact on the incidence of those diseases [24-26].

Furthermore, the present study shows the need to accomplish further research in order to explain the causes associated with the demonstrated geographical pattern of pneumonia and influenza hospitalisations.

References


Outbreak Report

Pertussis: A Cluster of Linked Cases in the United Kingdom, 2006

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Pertussis is a vaccine-preventable disease with a high rate of complications, especially in young children. It often presents in an atypical fashion in adults and adolescents, making diagnosis difficult. This report describes a cluster of linked cases of three adults and one infant in a family, spread across the United Kingdom (UK). The initial follow-up was of a 20-year-old student with clinical symptoms of pertussis. This diagnosis led to the discovery of two other unvaccinated adult family members with symptoms that fit the case definition for pertussis and a laboratory-confirmed tertiary case in an unvaccinated infant who had to be hospitalised. This report aims to act as a reminder for including pertussis as a differential diagnosis in patients with a long duration of respiratory symptoms and highlights the importance of rapidly identifying and managing close contacts of cases. This is key in protecting the most vulnerable – namely, infants – from infection.

Introduction

Pertussis (whooping cough) is a commonly overlooked diagnosis in adults with respiratory symptoms, accounting for infection in 20% of adults presenting with prolonged cough in settings with high immunisation coverage [1]. The bacterial infection caused by Bordetella pertussis is characterised by a prolonged cough (lasting more than two weeks) with paroxysms, inspiratory whoop and post-tussive vomiting. The incubation period varies between six and 20 days and cases are infectious from six days after exposure and may last up to three weeks after the onset of typical paroxysms [2]. Complications of pertussis such as pneumonia and otitis following bacterial superinfection occur usually in childhood; with the highest number occurring in the first six months of life [3]. In adults and adolescents, it often presents atypically, making diagnosis difficult. Adults and school-age children are a known source of infection for younger family members who are too young to be immunised [2].

Pertussis is a vaccine-preventable disease with routine immunisation in the UK given to children at two, three and four months and a subsequent pre-school booster. The vaccine currently in use in the UK is an acellular vaccine that was first introduced in 2001 as a pre-school booster. The Health Protection Agency figures for England and Wales show statutory notifications of pertussis averaging 665 per year over the period 2000-2005, while during 2002-2004 on average 292 of these cases were laboratory confirmed diagnoses (serology, PCR or culture) per year . Increased notification as well as ascertainment has occurred among adults during this time [4].

The following outbreak report describes a cluster of infections affecting mostly adult members of a family and the subsequent infection of an infant. The Oxfordshire Health Protection Team was notified of a case of pertussis in a 20-year-old student in West Yorkshire on 27 October 2006. Contact tracing revealed that she had been in contact with several members of her family over the August Bank Holiday weekend. This article describes the identification and management of the cluster and seeks to highlight the importance of clinical awareness of pertussis in adolescents and adults and the performing of thorough contact tracing.

Methods and results

Outbreak investigation

Index case

The index case was in a 20-year-old university student in West Yorkshire. She developed a cough with post-tussive vomiting on 21 August 2006, which persisted for eight weeks. She had not been immunised against pertussis as a child and was never known to have suffered from pertussis. She had returned from a two-month trip to East Africa two weeks prior to the onset of her symptoms and had no recollection of any contact persons with similar symptoms whilst on the trip. During the three weeks following onset of symptoms, her ‘close household contacts’ (Figure 1) were her boyfriend, who lived in the same flat with her, and seven members of her family, who shared the same accommodation with her for three days over the Bank Holiday weekend at the end of August.

Secondary cases

Sister 1 developed a chronic cough with a whoop two weeks after contact with the index case (Figure 1). She was eight months pregnant at the time of contact and symptoms persisted until the week after delivery. However, she did not seek medical attention for her symptoms at any point in time. The investigation revealed that she was not immunised against pertussis during childhood.

Figure 1

Diagram of affected family members and their immunisation status. Cluster of cases of pertussis, United Kingdom, 2006
Sister 2 also developed symptoms that fit the case definition for pertussis [3], two weeks after the contact with the index case (Figure 1). She presented to her General Practitioner (GP) with symptoms of a non-specific cough at the time and tested negative for *B. pertussis*. The index case presented to her GP with information that her three-week-old niece had been diagnosed with whooping cough. A blood sample was sent for pertussis PCR and she was commenced on a 10-day course of oral Erythromycin. However, the result of the blood test did not confirm the diagnosis. The negative result could have been due to the delay of over two months between the onset of symptoms and testing. Paired serology would have been a better choice of test given the duration of symptoms [3].

All the other family contacts and the boyfriend remained asymptomatic and did not meet the requirements for prophylaxis as they had all received childhood immunisation.

**Discussion**

Professional and public loss of confidence in the pertussis vaccine due to a belief that there was a link to a group of children with brain damage published in a paper in 1974 [2] led to a drop in immunisation coverage of the whole cell pertussis containing DPT vaccine to 30% in 1975 in the UK (Figure 2). Many of those unvaccinated during the late 1970s and 1980s would have been infected with pertussis at this time and the drop in vaccination cover corresponds to the rise in pertussis notifications as shown in Figure 2.

This outbreak report seeks to highlight the importance of suspecting and recognising symptoms of pertussis in the adult population, especially in those who should but may not have been immunised during the pertussis vaccine ‘scare’ in the late 1970s. A causal relationship has already been noted with the decrease in vaccination coverage and a following rise in pertussis notifications [5]. We could be seeing a second impact now, 30 years on, with those born in the 1970s and not having been immunised presenting now with pertussis as adults but being diagnosed wrongly with other respiratory illnesses like asthma.

Pertussis is a statutorily notifiable disease, so immunisation history and contact tracing for close contacts in the preceding three weeks of the onset of symptoms in the patient are vital. In the case reported above, this would have led to antibiotic prophylaxis being prescribed to the pregnant sister and possibly the prevention of transmission to the newborn child. Close contacts of pertussis cases who are either unvaccinated, partially vaccinated or under five years of age should be given erythromycin treatment or prophylaxis [6]. The low rates of laboratory confirmation seen nationally compared to the notification rates is probably due to reluctance of physicians to subject patients to a nasopharyngeal swab [8] or the fact that culture diagnosis loses sensitivity with prolonged duration of symptoms [5].

Children and adults might be infected with pertussis even if they were vaccinated in the past because both immunity following vaccination and natural infection wane over time [2]. In the UK, where vaccination coverage by two years of age is currently around 94% [9], pertussis is often overlooked as a differential diagnosis. This is particularly so in adults, as noted above. It is possible that current notification rates that are based on clinical suspicion do not reflect the true incidence of pertussis, especially in the adult population.

**Conclusion**

This report highlights two major issues with regards to pertussis. Firstly, that a diagnosis of pertussis should form part of the differential diagnosis in any adult with prolonged cough. The sensitivity of this case definition is as high as 84-92% [10].

Secondly, due to the high secondary attack rate associated with unimmunised household contacts, a good family history and prompt notification and testing while providing prophylaxis is crucial in avoiding infection in the most vulnerable population – unimmunised infants.
References


Outbreak Report

Tuberculosis in a Yorkshire Prison: Case Report

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2. East Riding Primary Care Trust, East Yorkshire, United Kingdom

In 2005 there were 8.8 million new cases of tuberculosis (TB) globally and 1.6 million deaths. Incidence rates in Western Europe ranged between 4 and 10 per 100,000 in 2001, but TB is still a significant challenge in this region, especially due to delayed diagnosis and management. Prisons are a potential “breeding ground” for TB with a mean notification rate of 232 cases per 100,000 prisoners in Europe in 2002. This report describes the measures taken in response to a TB case in a British prison. Following diagnosis, the “stone in the pond” method was used to identify potential contacts. Selection criteria were agreed and screening tools included the Quantiferon test. These methods, combined with an effective integrated community and hospital TB service, resulted in the successful management of the incident.

Introduction

According to the latest figures published by the World Health Organization (WHO), 8.8 million new cases of tuberculosis (TB) were reported globally in 2005, and 1.6 million deaths. Of the new cases, 7.4 million were in Asia and sub-Saharan Africa [1]. The global re-emergence of TB in the early 1990s has been somewhat reversed over the last few years, although the decline is still slow in Africa and Eastern Europe, with the countries of the former Soviet Union still shouldering a considerable burden of the disease (80% of the estimated 444,777 cases in Europe in 2004, and the highest treatment failure rate (7%) in the world) [2].

In March 2005, a 28-year-old male of Pakistani origin who was admitted to the local acute hospital with epigastric pain, weight loss and localised crackles and wheeze in the left upper zone. The prison environment is a recognised “breeding ground” for infectious diseases, including TB [6]. A survey carried out in 2002 in several European countries found a mean notification rate of 232 new cases for 100,000 prisoners (range 0-17,808) with the highest rates in the custodial establishments of countries of the former Soviet Union [7]. In England, Wales and Northern Ireland, prison was the third most common setting for reported TB cases, after healthcare and educational establishments, and it accounted for 32 of a total of 337 TB cases reported in 2005 [5]. Prisons have also been linked to a major outbreak of isoniazid-resistant TB in North London, which started in 2001 [8,3]. This outbreak exposed the many challenges to TB control that the particular environment of prisons can display.

One of the key points of the WHO “Status Paper on Prisons and Tuberculosis” [2] is the desirability of the integration of prison health within ministries of health. However, even when prison healthcare is run by the same organisation as the rest of the country’s healthcare, as is the case in the UK, TB in prisons remains challenging when it comes to practicalities such as prompt diagnosis of cases, identification of contacts, screening, compliance with prophylaxis and treatment.

There are several factors that can hamper and/or make TB control more difficult in prison. Firstly, there are the security priorities. These often translate into a high transfer rate of prisoners across the country. Coupled with a lack of an efficient and rapid transfer of medical records, this can make the diagnosis and treatment of TB cases and its public health management difficult. Secondly, the relative rarity of TB means that many clinicians have no first-hand experience of TB and may have difficulties in recognising a disease that is similar to many other more common conditions, such as lung cancer and asthma. Thirdly, the limited provision of occupational health services for prison staff may generate a considerable amount of anxiety among those who have not undergone the recommended TB screening and vaccination [9] as part of their pre-employment procedures and have found themselves exposed to TB as result of their work. Fourthly, there may be anxiety among fellow prisoners and the behaviour of prisoners may differ from that of people in the wide community.

The available guidelines (of the British Thoracic Society (BTS) [10], now replaced by those of the National Institute for Health and Clinical Excellence (NICE) [11]) provide more of a general guide than specific solutions. Given all these factors, it is useful to share experience from the public health management of individual situation – hence the reason for this article, which describes some of these challenges and how they can be overcome.

Case report

In March 2005, a 28-year-old male of Pakistani origin who was a prisoner at Yorkshire training prison (a training prison hosts sentenced prisoners), gave a history of flu-like symptoms of three weeks duration from 11 March 2005 with expectoration of green sputum from 18 of March 2005. He had been a prisoner in another Yorkshire prison from 25 October 2004 before being transferred to the training prison on 7 February 2005. On 31 March 2005, he was admitted to the local acute hospital with epigastric pain, weight loss, cough and a referral diagnosis of “epigastric bleed”.

Relevant physical findings

He was pyrexial on admission at 38.3 degrees centigrade. The available guidelines (of the British Thoracic Society (BTS) [10], now replaced by those of the National Institute for Health and Clinical Excellence (NICE) [11]) provide more of a general guide than specific solutions. Given all these factors, it is useful to share experience from the public health management of individual situation – hence the reason for this article, which describes some of these challenges and how they can be overcome.

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Relevant physical findings

He was pyrexial on admission at 38.3 degrees centigrade. He had localised crackles and wheeze in the left upper zone.
**Clinical and laboratory investigations**

A chest X-ray showed consolidation of the upper lobe of lung, with loss of volume. He was found to be sputum-smear positive on 1 April 2005 (on microscopy numerous acid fast bacilli were seen). Sputum culture confirmed growth of *Mycobacterium tuberculosis*.

A diagnosis of pulmonary tuberculosis was established and the patient was started on multi-drug treatment (rifampicin, isoniazid, and pyrazinamide plus ethambutol - quadruple therapy). He returned to prison on 19 April 2005, and received a complete six-month course of treatment through the prison health centre.

Genetic fingerprinting of patient isolate carried out at the Health Protection Agency (HPA) Regional Centre for Mycobacteriology reference laboratory in Newcastle showed a MIRU-VNTR profile (226 425 173 423) and ETR profile (522) different from those identified in isolates of other two TB cases diagnosed in another Yorkshire prison in 2004-2005, i.e. prior to the transfer of the case described in this paper to the Yorkshire training prison (MIRU-VNTR profile 224 315 153 321 and 224 226 153 321 respectively, and ETR profile 424 and 224 respectively) [this information was obtained with the kind help of a Consultant in Communicable Disease Control in Leeds and the Reference Laboratory in Newcastle].

The case described here was notified on 5 April 2005 to the local Consultant in Communicable Disease Control (CCDC) to trigger contact tracing procedures, to detect any outbreaks and plan appropriate and effective interventions. A multidisciplinary TB incident control group was established, which was chaired by the CCDC and which comprised the Director Public Health of the relevant PCT, a lead TB nurse, a consultant microbiologist, an infectious disease consultant, the Deputy Governor of the prison and the Health Care Manager of the prison.

**Methods**

**Contact Tracing**

**Family contacts**

All the family contacts of the index case (a total of five) lived outside the area and the relevant CCDCs were contacted regarding their follow up. The screening of these contacts revealed no evidence of secondary transmission.

**Hospital contacts**

The index case stayed in the Accident and Emergency department at the local acute hospital for approximately four hours and in the Acute Assessment Unit (AAU) for 13 hours. Contacts there were managed by the lead TB physician in liaison with the Hospital Infection Control Doctor, who is one of the consultant microbiologists. Sixteen contacts were screened and no secondary cases were detected.

**Prison contacts**

Screening principles

The prison housed at that time approximately 600 prisoners, who were already sentenced, the majority of who did not share cells. The principle of the “stone in the pond” was followed, whereby screening starts with a restricted number of contacts, to be extended further if there is evidence of active transmission of disease. In this situation there were no cell mates and thus no obvious close contacts, so the prisoner’s daily activities were studied to establish potential contacts suitable for screening. The prisoner had attended three different training courses over the five weeks prior to his transfer to hospital. All courses were held in fairly small rooms holding no more than 10 students with limited or poor ventilation.

Studies suggest that significant exposure in these circumstances is a cumulative total exceeding eight hours within the same room as the infectious case [10,11]. Using this definition for contacts would have meant screening a fairly large number of prisoners (48), teachers (12) and prison officers (12), which would have gone against the principle of the “stone in the pond” (Table 1).

**Agreed screening criteria**

Therefore, first only those prisoners and teachers who had been attending classes with the case every week for all of the five weeks were considered. The minimum cumulative time spent with the case by any of these teachers or prisoners was 30 hours. Hence 30 hours contact time with the case was taken as the cut-off point for the screening process. In light of their close contact with the case, prison officers who had spent at least one 12-hour shift chained to the case while he was in hospital as part of the bed watch were also included in the screening process (Table 1).

**Tables**

**Table 1** Contacts selected for screening. Tuberculosis case in Yorkshire prison, 2005.

<table>
<thead>
<tr>
<th>Courses contacts</th>
<th>Close friends</th>
<th>Prison officers</th>
<th>Teachers</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>1</td>
<td>12</td>
<td>2</td>
<td>34</td>
</tr>
</tbody>
</table>

<p>| Contacts actually selected using the cumulative 30 hours cut-off point or bed watch |</p>
<table>
<thead>
<tr>
<th>Courses contacts</th>
<th>Close friends</th>
<th>Prison officers</th>
<th>Teachers</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>1</td>
<td>12</td>
<td>10</td>
<td>93</td>
</tr>
</tbody>
</table>

**Contacts selected for screening**

Through the use of this cut-off point, the first group of contacts (19 prisoners) was identified.

A second group of close friends was identified with whom the case had spent several hours on a regular basis. The use of the 30 hour cut-off point identified only one prisoner. It was also established that this prisoner had been sharing the cell with the index case in the previous prison, prior to their both being transferred to the current prison. Two teachers were identified through the 30 hours cut-off point and 12 prison officers were included as result of bed watch duties.

**Screening**

BTS Guidelines [10] recommended offering a Heaf test (a skin test, used in UK until 2005) to contacts without BCG scars and chest X-rays for those with BCG scars. However, due to the fact that most of the contacts had a BCG scar and that Quantiferon (QuantiFERON - TB GOLD) blood test was going to be available on this occasion, it was decided to offer a Heaf test to all contacts, irrespective of their BCG scar, in order to standardize and compare Quantiferon with the Heaf test.

Chest X-ray was then performed on those contacts that were Quantiferon and/or Heaf test positive.
The TB community nurses performed Heaf test and its reading a week later on prisoners inside the prison; blood samples for Quantiferon test were obtained through the health prison staff and then couriered to the reference HPA TB laboratory in Newcastle for testing; as no X-ray facilities were available within the prison, chest-X-ray of prisoners was carried out in prison by the X-ray department of the local hospital using a mobile unit. Prison officers and teachers, were offered appointments at the local hospital TB clinic for their screening. Prisoners, who were released prior to the screening taking place in the prison, were offered TB clinic appointments in their district of residence.

Results

First group (19 prisoners)

One prisoner out of this group refused to be screened; subsequently, prison health staff were instructed on risk assessment checking for TB symptoms and the prisoner himself was also made aware of symptoms of TB and the need to seek medical attention in case of developing any of these.

Four prisoners were released prior to screening. Following notification from the local TB nurse community service, these ex-prisoners were offered TB clinic appointments in their district of residence. Two of the four are known to have not attended their appointment, while no information on attendance is available regarding the other two.

Of the remaining 14 prisoners, one was positive on Quantiferon test, had grade 3 Heaf test reaction and no BCG scar; the chest X-ray was negative. This prisoner was put on prophylaxis for two months [rifampicin and isoniazid]. Two prisoners had grade 3 and 4 Heaf test reaction (had BCG scar) respectively but negative Quantiferon and negative chest X-ray. Taking into consideration these different results, the two prisoners were not offered prophylaxis.

Three prisoners had no reaction to the Heaf test (and no BCG scars) and no symptoms; they were offered BCG vaccination.

Second group (1 prisoner)

This prisoner (a close friend of the case) had a Quantiferon positive reaction and a grade 4 Heaf test result; had a BCG scar, no symptoms, and a negative chest X-ray. The chest physician preferred to offer prophylaxis (rifampicin and isoniazid for 3 months) to this officer, notwithstanding the patient’s age of over 35 years when prophylaxis is usually not offered [10,12], as this was deemed to be the safest option. This officer had a history of TB within the family.

The remaining 11 officers were all Quantiferon negative, had 0-1 or 2 Heaf test reaction and no symptoms; all but three had a BCG scar. None were put under prophylaxis but the eight officers without scar were offered BCG vaccination.

Fourth group (2 prison teachers)

Of the two teachers, one declined the Heaf test, but accepted a blood test, which was negative. This teacher also had a negative chest X-ray, no symptoms and had a BCG scar. The second teacher had the Heaf test grade 0, a negative chest X-ray and blood test, no symptoms and no BCG scar. This teacher was offered BCG vaccination.

This initial round of screening uncovered only one case and two people requiring prophylaxis. As the proportion of people potentially infected was below 10% of the screened population [10], the decision was taken that no further screening was indicated.

Discussion

This case report demonstrates both the challenges of dealing with TB in a prison and also some ways in which those challenges can be successfully addressed. The challenges include the movement of prisoners from one prison to another, the ways in which prisoners may act (for example tampering with the tests, see below), the concerns and attitudes of prison staff and the relatively low prevalence of TB that may lead to delayed diagnosis. These challenges are present even in places where prison and community healthcare is managed in a co-coordinated way. Guidelines are

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of people</th>
<th>Heaf positive (grade 3 or more)</th>
<th>Quantiferon positive</th>
<th>Chest X-ray abnormal</th>
<th>BCG scar</th>
<th>Outcome</th>
<th>BCG vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>19</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>10</td>
<td>1 refused</td>
<td>4 released</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 given prophylaxis</td>
<td>3</td>
</tr>
<tr>
<td>Second</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Considered case, put under treatment</td>
<td>0</td>
</tr>
<tr>
<td>Third</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>1 given prophylaxis</td>
<td>3</td>
</tr>
<tr>
<td>Fourth</td>
<td>2</td>
<td>0*</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

* One teacher declined Heaf test

*Table 2 Results of screening. Tuberculosis case in Yorkshire prison, 2005.*

Broncho-lavage sample. Because of the symptoms, highly positive tests, abnormal chest X-ray and close contact with the case, it was felt that the safest option was to consider him a case and he was put on treatment for TB for six months (quadruple therapy for two months followed by rifampicin and isoniazid for four months).

Third group (12 prison officers)

One of the 12 prison officers identified for screening had a Quantiferon positive result and Heaf test grade 4 result; had a BCG scar, no symptoms, and a negative chest X-ray. The chest physician preferred to offer prophylaxis (rifampicin and isoniazid for 3 months) to this officer, notwithstanding the patient’s age of over 35 years when prophylaxis is usually not offered [10,12], as this was deemed to be the safest option. This officer had a history of TB within the family.

The remaining 11 officers were all Quantiferon negative, had 0-1 or 2 Heaf test reaction and no symptoms; all but three had a BCG scar. None were put under prophylaxis but the eight officers without scar were offered BCG vaccination.
available for the management of TB in the community, for example in England and Wales from BTS [10] and now NICE [12], but these may not be entirely suitable for managing TB in a special setting such as a prison, where additional pragmatic measures may be necessary.

The “stone in the pond” principle for screening was the basis for the approach in this case and ensured that there was adequate coverage of the potentially infected population while containing the amount of screening activity. There needed to be flexibility in the approach to the population selected for screening based on the particular environment of the prison, both for prisoners and for prison staff. The management of cases in other prisons would need to allow for similar flexibility, depending on the characteristics of the prison, for example sharing of cells and time spent in work, education or recreation.

The use of the selective immunological (interferon-gamma) test, commercially available as QuantIFERON – TB Gold, was particularly useful. It was performed on all the contacts in addition to the Heaf Test. This is a more specific test that removes false positive results due to previous BCG vaccination or opportunistic environmental mycobacteria and is better correlated with latent infection or dormant organisms [12]. There was a good matching between Quantiferon and Heaf test results in this screening exercise and the Quantiferon helped to avoid putting at least two people on prophylaxis. The two prisoners who had grade 3 and 4 Heaf test reaction respectively (and BCG scar) but negative Quantiferon and negative chest X-ray were suspected of tampering with the Heaf test, and therefore not offered prophylaxis. This is an example of where some departure from national guidelines may be beneficial and helpful in addressing issues such as potential tampering with Heaf tests.

The movement of prisoners and delayed diagnosis remain challenges. It would be helpful if prison regulations allowed for the restriction on the movement of prisoners during the investigation of a case or outbreak of a communicable disease. Two of the prisoners in this episode did not attend clinic appointments on release and the Quantiferon helped to avoid putting at least two people on prophylaxis. The two prisoners who had grade 3 and 4 Heaf test reaction respectively (and BCG scar) but negative Quantiferon and negative chest X-ray were suspected of tampering with the Heaf test, and therefore not offered prophylaxis.

This incident has highlighted the importance of raising awareness of symptoms of TB among prisoners, prison officers and health care workers working in prisons, as recommended in the recently published NICE guidelines on TB [12]. This will help to avoid delays in identifying active cases. In this incident, there were still challenges despite the integrated nature of healthcare provision. However effective and efficient management of the incident was only possible because of the presence of expert services in communicable disease control, clinical management of TB and community management of TB, which are the product of an integrated health system.

References


Outbreak Report

Outbreak of Salmonella Enteritidis Phage Type 13a: Case-Control Investigation in Hertsmere, United Kingdom

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1. Humber Health Protection Unit, East Yorkshire, United Kingdom
2. East Riding Primary Care Trust, East Yorkshire, United Kingdom

Cases of illness were reported to Hertsmere Borough Council among attendees of a children’s charity event in June 2006. Initial laboratory investigation identified Salmonella Enteritidis PT13a as a possible cause of the outbreak. We carried out an unmatched case-control investigation. The population at risk included all individuals who attended the event. Self-completion questionnaires were sent to 53 presumptive cases and 212 randomly selected potential controls. Information was available for 49 cases and 128 controls (overall response rate=75%). We calculated odds ratios from single and multivariable analysis and tested for all two-way interactions. Risk factors for diarrhoea were eating egg mayonnaise bagels (OR=34.1, 95%CI 10.5 – 111.3) and drinking apple juice (OR=16.1, 95% CI 3.5 – 74.2). There was weak statistical evidence to suggest that the risk of diarrhoea after eating egg mayonnaise bagels was greater in the afternoon. No food samples were available to confirm which food item might have caused this outbreak. Eggs from Spain were used by the caterer. The ecology of salmonella, experience from previous outbreaks and epidemiological findings from this case-control investigation suggest that the most likely cause of the outbreak was contaminated eggs.

Introduction

On Sunday 18 June 2006, a children’s charity event was held in Hertsmere, United Kingdom. The event was attended by children, parents of children, and staff (committee members and volunteers). The event was staged in two halves: the morning was for children aged 11 to 14 years and the afternoon for children aged eight to 10 years. On Monday 26 June 2006, Environmental Health Officers at Hertsmere Borough Council received a report from a general practitioner that several children had been ill, one with laboratory confirmation of salmonella infection. An Outbreak Control Team was established by Hertsmere Borough Council. Stool samples from individuals who had salmonella were sent for typing to the Laboratory of Enteric Pathogens at the Health Protection Agency, Centre for Infections. Salmonella Enteritidis phage type (PT)13a was identified. Salmonella Enteritidis PT13a is uncommon in England, with an average of 54 (range 23 to 77) isolates reported annually between 2001 and 2005 (Figure 1) [1]. Only about 13% of S. Enteritidis PT13a cases are known to be travel-related [1].

Methods

Epidemiological investigation

The investigation used an unmatched case-control design. Fifty-three presumptive cases, defined as individuals who attended the event and who subsequently developed diarrhoea, were identified either by the event organiser or by Hertsmere Borough Council. We identified the population at risk as participants, spectators, parents, volunteers or committee members who attended the event on Sunday 18 June 2006.

We used the following case definitions:

Confirmed case:

- belonged to the population at risk
- experienced diarrhoea (three or more loose stools in a 24-hour period) between 18 and 22 June 2006;
- presented a stool sample with a laboratory confirmed isolate of Salmonella non-typhi, with or without further characterisation as Salmonella Enteritidis or Salmonella Enteritidis PT 13a;
- had no history of travel abroad in the seven days preceding onset of illness;
- had no contact with other individuals in the household with a gastrointestinal illness in the seven days prior to onset of illness.

Probable case: Same criteria as for a confirmed case, except the laboratory confirmation of Salmonella infection.

Possible case: Same criteria as for a confirmed case, but with no information on one or more of the following: date of onset of illness, travel abroad or household contact with a case of diarrhoea in the seven days before illness.

![Figure 1: Number of cases of Salmonella Enteritidis phage type 13a by quarter, England 2001 to 2005](image-url)
Control group: belonged to the population at risk;
  ▸ did not experienced diarrhoea (three or more loose stools in a 24-hour period) between 18 and 22 June 2006;
  ▸ had no history of travel abroad in the seven days preceding onset of illness;
  ▸ had no contact with other individuals in the household with a gastrointestinal illness in the seven days prior to onset of illness.

Exclusions: Individuals who reported diarrhoea (three or more loose stools in a 24-hour period) either before or after the period between 18 and 22 June were excluded from the investigation.

Sampling was designed to select at least two controls per case. The organiser provided a list of 518 people who attended the event on 18 June 2006. A sampling frame for potential controls was made by removing all presumptive cases from the list. Of 465 potential controls, 415 (89%) had complete addresses. From this list, four potential controls per case were randomly selected to allow for non-response of potential controls and replacement of controls subsequently identified as cases. Random selection was done by reading the list of potential controls into STATA statistical software and using the “sample” command without replacement to randomly draw 212 individuals.

Data collection
We posted a self-completion questionnaire with a pre-paid return envelope to all individuals selected for this investigation. The questions regarded demographic details, attendance at the event, travel history, gastrointestinal illness among household contacts, health symptoms, healthcare utilisation, and consumption of food and drink supplied at the event. We piloted the questionnaire on two known cases to check for clarity. Parents or guardians were asked to complete the questionnaire on behalf of children under 16 years old. After one week, we sent non-responders a reminder letter and another copy of the questionnaire. Respondents who indicated that they had had diarrhoea but did not provide date of onset were contacted by telephone and asked to supply this information. For respondents whose telephone numbers were not available, we posted a copy of their partially completed questionnaires back to them and asked them to complete the missing sections.

Laboratory investigations
Local environmental health departments, HPA units, general practitioners (GPs) and medical microbiologists were asked to inform the investigation team of positive microbiological results relating to the event’s attendees. Isolates from presumptive cases were sent to the Laboratory of Enteric Pathogens at the Centre for Infection and were phage typed by the method of Ward et al. [2]. The event organiser provided a list of all food and drink items supplied at the event. We piloted the questionnaire on 25 respondents and 22 June were excluded from the analysis. A further five respondents were also excluded; three because their onset date of diarrhoea was after 22 June 2006 (all had positive isolates for S. Enteritidis PT13a), one of whom also had a history of travel abroad; one case because the onset of diarrhoea was before 18 June 2006; and one because of an incomplete questionnaire. Another seven respondents who reported having diarrhoea were classified as possible cases, and hence not included in the analysis, because their date of onset was not known.

In the end, there were 49 cases (25 confirmed plus 24 probable cases) and 128 controls (27 controls per case) included in the outbreak investigation. The response rate was similar for cases (77%) and controls (74%). Fourteen cases (two confirmed and 12 probable) were originally included in the study as potential controls. Of the 25 confirmed cases, laboratory isolates were characterised as S. Enteritidis PT13a for 19 outbreak-associated cases. Individuals who met the case definition for a possible case and the excluded respondents were not included in the calculation of odds ratios or multivariable models. We further excluded individuals who, when contacted, stated that they had not attended the event and therefore were not considered to belong to the population at risk. We used the following age groups: <8, 8-10, 11-14 and >=15 years old. Where questionnaire respondents ticked ‘Yes’ against foods they had consumed, but left the other food items blank, we assumed that they had not consumed them and we recorded these missing values as ‘No’ for the analysis.

We compared characteristics of cases and controls using a Chi-square test or Fisher’s Exact Test if the expected number in any cell was less than five. We calculated odds ratios, 95% confidence intervals and p-values, for each food item. We used a multivariable logistic regression model to estimate the odds ratio for each risk factor, adjusted for all the variables in the model. In an initial multivariable model we included variables for all food items with odds ratios in the single variable analysis greater than 1 and p=<0.2, a variable indicating morning or afternoon attendance, age group and sex. A backwards stepwise procedure was adopted wherein at each step the least significant variable was removed and a model with the remaining variables was fitted until all variables had p-values of about 0.1 or less, resulting in a final model.

We retained age group and sex in the model regardless of their statistical significance, as well as variables which were substantial confounders (i.e. that changed the odds ratios of one or more of the remaining variables by 10% or more). We also examined all two-way interactions between the remaining variables in the final model. We removed interactions that were not statistically significant (p>=0.01) from the model, least significant first. We repeated this until the remaining interactions were significant or there were no interactions. We conducted a sensitivity analysis to assess the effect of including respondents who had attended both morning and afternoon sessions. The odds ratios for the variables remaining in the model were attenuated and so we excluded these respondents from the final analysis. We used EpiData (v.3.1) for double data entry and validation [3]. Single variable analysis was done using EpiData Analysis (v.1.1) [3] and multivariable logistic regression using STATA v.8.2 [4].

Results
Population at risk
Of 265 questionnaires sent (to 53 presumptive cases and 212 controls), 199 (75%) were returned. Ten respondents had not attended the event and therefore were excluded from the analysis. A further five respondents were also excluded; three because their onset date of diarrhoea was after 22 June 2006 (all had positive isolates for S. Enteritidis PT13a), one of whom also had a history of travel abroad; one case because the onset of diarrhoea was before 18 June 2006; and one because of an incomplete questionnaire. Another seven respondents who reported having diarrhoea were classified as possible cases, and hence not included in the analysis, because their date of onset was not known.

In the end, there were 49 cases (25 confirmed plus 24 probable cases) and 128 controls (27 controls per case) included in the outbreak investigation. The response rate was similar for cases (77%) and controls (74%). Fourteen cases (two confirmed and 12 probable) were originally included in the study as potential controls. Of the 25 confirmed cases, laboratory isolates were characterised as S. Enteritidis PT13a for 19
cases, *Salmonella* non-typhi for four cases and *S. Enteritidis* for two cases. Characteristics of cases and controls are shown in Table 1. The proportion of males and females was similar for cases and controls. However, controls were more likely to have been a participant at the event and to be in the 11-14 year age group, and hence to have attended the morning session. Seventy-eight respondents attended the morning session, 86 the afternoon session and 11 attended both sessions. Two individuals did not indicate which session they attended.

All cases reported diarrhoea and abdominal pain, almost three quarters reported fever and nausea, one third reported vomiting and about a tenth reported blood in the stool (Table 2). Twenty-eight cases reported the duration of diarrhoea; the median was seven days (range of 1 to 16 days). Sixty-nine percent (n=34) of cases went to their GP and one adult was admitted to hospital for two days.

### Table 1

<table>
<thead>
<tr>
<th>Description of cases and controls. Outbreak of <em>Salmonella Enteritidis</em> PT13a, United Kingdom, June 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Age group (years)</strong></td>
</tr>
<tr>
<td>&lt; 8</td>
</tr>
<tr>
<td>8-10</td>
</tr>
<tr>
<td>11-14</td>
</tr>
<tr>
<td>15+</td>
</tr>
<tr>
<td>Not known</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Role during the event</strong></td>
</tr>
<tr>
<td>Participant</td>
</tr>
<tr>
<td>Spectator</td>
</tr>
<tr>
<td>Volunteer</td>
</tr>
<tr>
<td>Not specified</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Travel abroad during seven days before event</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Session attended</strong></td>
</tr>
<tr>
<td>Morning</td>
</tr>
<tr>
<td>Afternoon</td>
</tr>
<tr>
<td>Both</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

† Chi-Square test  
‡ Fisher’s Exact Test  
* Percentages do not add to 100 due to rounding off

### Table 2

<table>
<thead>
<tr>
<th>Symptoms reported by cases. Outbreak of <em>Salmonella Enteritidis</em> PT13a, United Kingdom, June 2006 (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of cases</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Blood in stool</td>
</tr>
</tbody>
</table>

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Table 3
Odds ratios for consumption of food items, outbreak of *Salmonella Enteritidis* PT13a, United Kingdom, June 2006 (n=177)

<table>
<thead>
<tr>
<th>No.</th>
<th>Food Item</th>
<th>Eaten</th>
<th>Case</th>
<th>Control</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Egg mayonnaise bagel</td>
<td>Yes</td>
<td>32</td>
<td>11</td>
<td>19.5</td>
<td>7.9 - 51.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>17</td>
<td>117</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Tuna mayonnaise bagel</td>
<td>Yes</td>
<td>17</td>
<td>46</td>
<td>0.9</td>
<td>0.4 - 2.0</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>32</td>
<td>81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cheddar cheese bagel</td>
<td>Yes</td>
<td>4</td>
<td>9</td>
<td>1.2</td>
<td>0.3 - 4.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>45</td>
<td>119</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Salmon bagel</td>
<td>Yes</td>
<td>2</td>
<td>14</td>
<td>0.3</td>
<td>0.0 - 1.6</td>
<td>0.1</td>
</tr>
<tr>
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</table>
Figure 2 shows the number of cases by date of onset of illness. There were four cases who fell ill on 18 July and 22 on 19 July; their number subsequently declined rapidly between 20 and 22 June. There was no discernable difference in the pattern of date of onset of illness between cases who attended the morning or the afternoon sessions.

Table 3 shows odds ratios comparing cases and controls for all 27 food items provided at the event. Odds ratios were statistically significantly raised for egg mayonnaise bagel (Item 1) and apple juice (Item 16) only.

Table 4 shows results from the multivariable logistic regression model. Sex and age group were not risk factors for illness. Attending the afternoon session, drinking apple juice and eating egg mayonnaise bagels remained risk factors for diarrhoea.

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95%CI</th>
<th>P-value for inclusion in the model</th>
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<td>0.0 - 1.6</td>
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<td>15+</td>
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<td>0.0 - 3.4</td>
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<tr>
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</table>

Note: The multivariable model excluded one case and 10 controls who attended both morning and afternoon session, one case and one control for whom information about session attended was not known, and five controls with information about age missing. The final model is based on 159 individuals (47 cases and 112 controls) with complete information on all variables.

It is unclear why drinking apple juice was also statistically associated with developing illness, even after taking into account the consumption of egg mayonnaise bagels. Apple juice was provided in cartons for individual use so it is implausible that the apple juice was independently contaminated with the same type of salmonella or that there was some cross contamination between egg bagels and apple juice. No other risk factors were associated with salmonella infection.

There were two individuals not included in the case-control investigation who nevertheless were of interest. One of the questionnaire respondents reported that she had not eaten at the event and had not become unwell. However, her brother, who had not attended the event, developed diarrhoea on 20 June 2006 after eating an egg mayonnaise bagel brought home from the event. There were no other cases of diarrhoea in the household. No stool specimen was taken. Also, one of the entertainers employed at the event took an egg mayonnaise bagel home and ate it four days later. He subsequently developed diarrhoea and S. Enteritidis PT13a was isolated from his stool sample. Although these two individuals were appropriately excluded from the analysis, they do provide additional epidemiological evidence that eating egg mayonnaise bagels was the likely cause of the outbreak.

### Discussion

#### Interpretation

This case-control investigation implicated eating egg mayonnaise bagels as the most likely risk factor for illness. Attending the afternoon session was also associated with developing illness. A statistical interaction between these risk factors suggested that the risk of illness from eating an egg mayonnaise bagel was higher in the afternoon than the morning session.

Before it was decided to undertake a case-control investigation, all presumptive cases were contacted by Environmental Health
Officers (EHOs) as part of their routine investigation of food borne illness. The EHOs asked about foods eaten at the event. In addition to experiencing illness, this may have encouraged cases to recall what they ate more vividly than controls, leading to recall bias and an overestimate of the risk factors. Also before the case-control investigation, Hertsmere Borough Council sent a letter to all individuals not suspected to be cases, informing them that an investigation was underway. Therefore, to test whether this might have biased their response, we included a question in the questionnaire asking whether respondents had received a letter. It turned out that controls who had received a letter were no more likely to report eating egg mayonnaise bagels (Chi-square=0.313, p=0.58) or drinking apple juice (Chi-square=0.658, p=0.41), suggesting that sending the letter did not bias their response.

Most attendees were children, and therefore parents or guardians were asked to complete the questionnaires on their behalf. This may have influenced the accuracy of the responses, possibly due to parents’ greater awareness of the outbreak as mentioned above. We have no evidence to support or refute that this would have introduced any systematic differences in the response from cases and controls.

A particular problem with using postal questionnaires compared to telephone interviews is that the questionnaires may not be completed fully. This occurred in this investigation and was especially common for the food item list, to which many respondents only ticked ‘Yes’, leaving the ‘No’ or ‘Don’t Know’ boxes blank. We assumed that missing responses indicated that the food item was not consumed. The proportion of missing responses (about 40% for each item) was similar for all food items and between cases and controls, making it unlikely that our assumption has introduced an important bias into the results. To check this, we conducted a sensitivity analysis by not recoding missing values to ‘No’. This produced similar results, with only egg mayonnaise bagels and apple juice having statistically significantly raised odds ratios in a single variable analysis.

Microbiological findings
After the event, no food samples were available for microbiological investigation. It was therefore not possible to confirm that egg mayonnaise bagels or apple juice caused the outbreak. The mayonnaise was pasteurised and was also used in the tuna mayonnaise bagels. The eggs were known to have been imported from Spain and outbreaks of S. Enteritidis phage type 13a have previously been associated with eggs imported from other European countries [6].

Conclusion and recommendations
In our case-control investigation we achieved a suitable response rate (75%) with sufficient cases and controls to conduct a statistically robust analysis. The ecology of salmonella, experience from previous outbreaks and epidemiological evidence from this case-control investigation suggest that the most likely cause of the outbreak was due to contaminated eggs. Guidance for the use of raw eggs by the catering industry highlights the importance of good hygiene practice [7]. Using eggs from flocks vaccinated against S. Enteritidis is also likely to further reduce the risk of salmonella infection among consumers.

Acknowledgements
We would like to thank all the individuals who completed and returned the postal questionnaire. We are grateful to Mark Reacher from the Health Protection Agency Regional Epidemiology Unit who provided valuable comments on successive drafts of the protocol, questionnaire and letters to parents. Caroline Black and Michelle Hardy diligently and efficiently entered the data and Marianne Quinn provided vital administrative support to prepare and send all questionnaire materials. Data about the number of cases of S. Enteritidis phage type 13a in England was provided by Iain Gillespie at the Health Protection Agency Centre for Infections.

References
4. StataCorp, Stata Statistical Software: Release 8.2. 2005, College Station, TX: StataCorp LP.

An outbreak of gastrointestinal disease (nausea, vomiting or diarrhoea) occurred among a party of wedding guests, staff and other guests in a hotel in the west of Ireland, in October 2006. Upon notification, a multi-disciplinary outbreak control team was convened to investigate and control the outbreak. In all, 98 people were ascertained ill. The median duration of illness was 48 hours. The attack rate ranged between 48 and 85%. The hotel voluntarily notified health authorities and co-operated fully with investigation and control measures. Strict prevention and control measures were instituted promptly, including air ventilation, enhanced hand hygiene, isolation of cases, temporary “cooked food only”, temporary alternative accommodation and specialised cleaning. Three cases of norovirus infection were laboratory-confirmed. There was no evidence of food- or water-borne transmission. Clinical and epidemiological findings indicated person-to-person transmission of norovirus. This report highlights the potential for large social gatherings to facilitate the spread of viral gastroenteritis by person-to-person transmission and via contaminated environment. Effective community management of this outbreak appears to have prevented its having an impact on local acute hospital services. The authors conclude that in addition to the existing national guidelines on the management of outbreaks of norovirus in healthcare settings, agreed guidelines for the management of norovirus outbreaks in the hotel and tourism industry are needed in Ireland.

Introduction

A wedding reception attended by 126 guests was held in a hotel in the west of Ireland on Friday 6 October 2006. Prior to serving the evening banquet, a guest had episodes of projectile vomiting at the dinner table and in close proximity to other tables in the function room. The guest had a further episode of vomiting in the toilet adjacent to the function room and then retired to a bedroom until departure on Sunday morning. Between 9.00 am on Saturday 7 October and 11.30 pm on Tuesday 10 October, 97 other people (including wedding guests, other hotel guests and hotel staff) developed gastrointestinal symptoms (nausea, vomiting or diarrhoea).

Out-of-hours public health and environmental health services are not in place in Ireland. As the outbreak occurred over a weekend, public health doctors and environmental health officers only visited the hotel on Monday morning, two and a half hours after being made aware of the outbreak and 66 hours after the index case had fallen ill. They met with the hotel management and interviewed the reception, cleaning, and kitchen staff. Inspections of the function hall, kitchen, reception area, toilets, bedrooms and leisure facilities were undertaken. No environmental samples were taken in these settings.

The symptoms of the index case and of the other cases, the probable exposure and the likely incubation period all led to the hypothesis of norovirus as cause of the outbreak.

Prevention and control measures

The following infection control measures were advised:
- isolation of cases,
- enhanced hand hygiene (even well after illness),
- hotel staff, especially food handlers, to report illness and, if symptomatic, be excluded from work until asymptomatic for 48 hours,
- adequate ventilation of the premises,
- deep cleaning with chlorine based agents according to guidelines [1],
- steam cleaning of soft furnishings,
- thermal washing of linen and towels at 60°C at least [1],
- removal of flowers and foliage,
- temporary closure of the leisure facilities,
- disinfection of ice buckets,
- hot food provision only / discontinuation of buffet service,
- accommodation of incoming guests temporarily in neighbouring hotels.

Methods

In accordance with regional guidelines, the Medical Officer of Health convened a multi-disciplinary Outbreak Control Team (including environmental health, microbiology and public health professionals) to take any necessary measures to investigate and control the outbreak. Relevant food menus were provided by hotel management and used to prepare a standardised questionnaire. Where contact numbers were provided by the hotel or wedding party, questionnaires were administered by telephone. In a small proportion of cases, questionnaires were posted and returned self-completed. Hotel guests and staff (or a proxy, mainly spouse or parent) interviewed were asked whether they were ill, and if so, to provide the date and time of onset of illness, type and severity of symptoms, association with other cases, travel history and food history. They were also asked about any recent history of gastrointestinal symptoms prior to the first episode of illness at the wedding, in order to determine whether illness may have affected anyone within 48 hours before the event.

A case was defined as a person who was either a guest or staff member of the hotel, and who had onset of nausea, vomiting or diarrhoea between 4 and 11 October.

After the initial ascertainment of cases through a telephone interview, nine cases agreed to provide stool specimens upon receipt of sterile universal containers with an accompanying completed laboratory specimen request form. Written instructions for the collection of the samples were also provided. Cases were asked to submit specimens to the Microbiology Laboratory of Mid-Western Regional Hospital, Limerick. Routine microbiological culture and sensitivity, as well as norovirus antigen testing, were requested, but no environmental samples were taken in these settings.
analysis for ova, cysts and parasites was not. Bacteriological culture for Campylobacter, Salmonella, Shigella, and enterohaemorrhagic \textit{Escherichia coli} was performed. The RIDASCREEN® (R-Biopharm, Darmstadt, Germany) Enzyme-linked Immunosorbent Assay (ELISA) technique was used to detect norovirus in faecal samples. Genotyping of the norovirus was not available. Environmental Health Services examined the premises for sanitation, food handling and preparation. Food and water samples were taken for bacteriological analysis and the results were interpreted in accordance with the relevant legislation and guidelines [2,3].

**Results**

In total, 98 cases of gastrointestinal illness were identified in the outbreak (11 hotel staff and 87 guests, of whom 61 were wedding guests and 26 were other hotel guests). All cases except four were adults. The age range of cases was 10 months to 88 years, with a median age of 35 years.

Of the 98 identified cases, the date and time of onset of symptoms was ascertained for 87 cases (76 were interviewed in person while for 11 cases information was supplied by proxy). The outbreak of gastroenteritis peaked 24 hours after the initial episode of vomiting in the index case, suggesting a point source. The epidemic curve (Figure) shows a peak of illness among hotel guests followed by a smaller peak among hotel staff. Hotel staff did not consume food prepared for the wedding party. Guests in the hotel not attending the wedding were ill despite having a different food source. Food histories obtained did not indicate a common source for gastrointestinal illness.

The commonest symptoms were vomiting and diarrhoea (Table). More men than women reported diarrhoea. The duration of illness ranged from three hours to five days, with a median duration of 48 hours. Nobody was reported to have been admitted to hospital as a result of illness.

Among 126 guests attending the wedding, 61 were known to be ill and eight to be well, whereas the status of 57 could not be ascertained. Thus the minimum attack rate can be estimated to be 48%. Taking into account only the 55 interviewed wedding guests, out of whom 47 were ill, the maximum attack rate was 85%. However, bias is probably present here, limiting the analysis of the situation, because the 55 respondent wedding guests were not picked randomly. They were the ones who could be contacted and who responded to requests to complete questionnaires/interviews. We were made aware of 14 other guests who reported being ill but who were not interviewed.

Since a definite attack rate in this outbreak was difficult to establish because of incomplete follow-up, we would suggest that it is more appropriate to present it as a range: 48-85%, because we did not know the illness status of 57 out of 126 wedding guests.

Attack rates on other groups could not be established because the numbers at risk were not discernable.

Nine stool samples were submitted from 10 October onwards and initial norovirus results were available already on 11 October. Specimens from six cases were received 48 hours after onset of illness and two of them yielded positive results. Two samples were received 72 hours after onset of illness and both were negative. One sample was received six days after onset, and tested positive. Hence, norovirus was detected in samples from three cases (both guests and staff). All stool samples were negative for bacteriological pathogens.

A total of 28 food samples were submitted for microbiological analysis, of which 14 were obtained from dishes served at the wedding. Three samples of tap water and two of bottled water were also submitted for analysis. Based on the analysis of food and water, there was no evidence to suggest that the outbreak was due to microbiological contamination. However, food samples were not analysed for norovirus. The laboratory analysis of food and water samples found no results in the potentially hazardous category [2,3]. There was no evidence to indicate that the outbreak was food- or water-related.

**Discussion**

Norovirus is a common cause of viral gastroenteritis with a low infectious dose. It can precipitate symptoms 24-48 hours after ingestion. Human vomitus is a common mode of transmission for norovirus. Vomiting may result in widespread aerosol dissemination of virus particles and their ingestion by other people. Outbreaks have been reported from person-to-person spread in hospitals [4], schools [5], hotels [6,7], concert halls [8], tour buses [9] and ships [10], as well as by contaminated food or water [11]. The difficulty of controlling person-to-person spread has been documented, especially...
if symptoms include vomiting [5]. Frequent hand-washing, disinfecting contaminated surfaces and washing fabrics reduces the likelihood of spread [12,13]. School closure [5] and taking a cruise ship out of service [10] have been effective in limiting spread. An expert group on norovirus set up by the European Centre for Disease Prevention and Control (ECDC) discussed the need for guidance to coordinate European actions to prevent and control norovirus outbreaks on cruise ships in 2006 [14].

Since January 2004, cases and outbreaks of norovirus infection in Ireland have been subject to statutory reporting [15]. Norovirus is now regularly implicated in large outbreaks of vomiting and diarrhoea in hotels [16] and in healthcare facilities such as hospitals and nursing homes [17], which pose particular infection control problems. National guidelines on the management of outbreaks of norovirus in healthcare settings in Ireland were published in 2003 [18]. Irish guidelines for the management of norovirus outbreaks in the hotel and tourism industry have not been agreed on, despite the presence of such guidelines in other jurisdictions (Scotland and England) [1,19].

In the event described in this paper, the hotel voluntarily notified health authorities about the outbreak of gastroenteritis and cooperated fully in the investigation and control measures recommended. However, an out-of-hours public health and environmental health service response may have facilitated better sample collection, case ascertainment and earlier hygiene assessment and intervention.

Initial control measures, including superficial cleaning of affected areas, linen disposal and isolating the index case proved insufficient, as further cases occurred after the index case. However, prompt multiple infection control measures, advised by the Outbreak Control Team and implemented by hotel management, effectively limited further transmission within the hotel setting.

This report highlights the potential for large social gatherings to facilitate the transmission of viral gastroenteritis by person-to-person spread and via contaminated environments. A precise attack rate in this outbreak was difficult to establish because of incomplete follow-up and uncertain denominator data for some exposed groups. An attack rate for the wedding guests could be determined as at least 48% with a possible range to maximum 85%. Similar results have been described in studies examining norovirus attack rates in like settings [20,21].

No one was admitted to hospital and effective community management of this outbreak appears to have prevented its having an impact on local acute hospital services. The authors conclude that in addition to the existing national guidelines on the management of outbreaks of norovirus in healthcare settings, agreed guidelines for the management of norovirus outbreaks in the hotel and tourism industry are needed in Ireland.

Acknowledgements

We wish to thank the staff of Limerick Environmental Health Services, Departments of Serology, Medical Microbiology and Official Food Safety Laboratory, Mid-Western Regional Hospital. A special thank you to all who contributed to the data collection.

References

Policy and guidance

Preparing for an influenza pandemic in Italy: resources and procedures in paediatric hospital units

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The World Health Organization (WHO) has stated that preparedness for effectively facing a major influenza epidemic should involve the training of physicians in the management of contagious diseases and upgrading hospital resources and procedures [1]. Children would be particularly vulnerable during an influenza pandemic and specific measures are needed to face the threat to them effectively. We performed a national survey to obtain information about the preparedness in facing a major influenza outbreak in Italian paediatric units. In Italy, paediatrics clinics are found in both paediatric wards and paediatric departments. Departments are more complex structures, containing several units with different specialisations and facilities. For this study, we interviewed heads of both departments and units. A structured questionnaire, including 30 items, was submitted to the heads of 150 paediatric hospital departments across the country. Responses were obtained from 123 units; 10% of these had rooms dedicated to infectious diseases, and 4% had experts in infectious diseases available and routinely applied procedures for preventing the spreading of acute infectious diseases. Only 8% of departments have paediatric intensive care facilities. Few paediatric units, usually located in large children’s hospitals or in academic paediatric departments, have a sufficient degree of preparedness to face severe influenza pandemics. A structural improvement of the paediatric units and the use specific procedures are essential for effectively care for children hospitalised because of contagious diseases.

Introduction

Preparedness for an influenza pandemic has become a major public health issue [1-3]. Global alert and response plans are in place to face the threat posed by the H5N1 influenza virus, and preparedness plans have been developed at national and European levels [4,5]. However, it was recently observed that, despite the planning and preparing for a possible pandemic, European countries are not yet ready to effectively face major epidemics of severe influenza [6,7].

The WHO has recommended that preparedness plans should include the identification of physicians and nurses specifically trained in the management of contagious diseases as well as recommendations to activate hospital resources and procedures in case of an influenza pandemic [1].

Children are at high risk of influenza and influenza-like illness [8,9], and they have specific age-related problems that require a management distinct from adults. Paediatric hospitals are therefore a major target for interventions to improve preparedness.

We carried out a national survey to obtain information on Italian paediatric hospital units and their preparedness for a major influenza outbreak. Specifically, we focused on the facilities and professional resources available and the procedures used in paediatric wards when a child with a severe, potentially contagious, disease is admitted.

Methods

A structured questionnaire was sent to the heads of paediatric hospital units in Italy. It was made up of 30 items, grouped in three sections. The first section included information on the general features of the hospital and the unit, i.e. logistical structures, including private rooms, toilets, and rooms equipped with negative pressure systems. The second section addressed the knowledge of healthcare workers and the presence of key personnel, namely physicians and nurses specifically trained in the management of contagious diseases. The third section included questions on the routine use of specific protocols and preventive procedures for infectious diseases that were applied. Each section of the questionnaire was separately analysed and evaluated for completeness. Key informants were invited to select “available”, “available in part” or “not available” to answer each question.

The questionnaire was submitted to the heads of 150 paediatric hospital units, chosen among the members of the Paediatric Italian Society, in 102 Italian cities, equally distributed in the North, Centre and South of Italy, between September and October 2005. Responses were obtained from 123 units, evenly distributed throughout the country. Of these, 97 were general paediatric units, five were referral paediatric infectious disease units, and 21 were specialised units in fields other than infectious diseases.

Results

Fifty-seven percent of the hospitals performed a paediatric triage based on the evaluation of contagiousness of diseases and 25% also had a specific emergency service for the management of infectious diseases. Fifty-two percent of the units had also a first-aid post for paediatric patients.

The results for the three sections of the questionnaire are summarised in the table. The number of wards or rooms dedicated to infectious diseases was quite low (36%). Rooms equipped with negative pressure systems were available in only 7% of units, and we estimated that approximately 10% of these rooms were available for contagious diseases on average. Despite the lack of effective measures to prevent the spreading of potentially contagious diseases, only 3% of interviewed hospitals declined the admission of children affected by infectious diseases.

<table>
<thead>
<tr>
<th>Facility/Procedure</th>
<th>Available</th>
<th>Available in Part</th>
<th>Not Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric Intensive Care</td>
<td>12%</td>
<td>10%</td>
<td>78%</td>
</tr>
<tr>
<td>Negative Pressure Systems</td>
<td>7%</td>
<td>-</td>
<td>93%</td>
</tr>
<tr>
<td>Specific Protocols</td>
<td>57%</td>
<td>-</td>
<td>43%</td>
</tr>
<tr>
<td>Emergency Service</td>
<td>25%</td>
<td>-</td>
<td>75%</td>
</tr>
</tbody>
</table>

The questionnaire was submitted to the heads of 150 paediatric hospital units, chosen among the members of the Paediatric Italian Society, in 102 Italian cities, equally distributed in the North, Centre and South of Italy, between September and October 2005. Responses were obtained from 123 units, evenly distributed throughout the country. Of these, 97 were general paediatric units, five were referral paediatric infectious disease units, and 21 were specialised units in fields other than infectious diseases.
The degree of preparedness in facing a severe contagious disease was indirectly investigated by the availability of intensive care units. According to key responders, paediatric intensive care units were available within the department of only 8% of the units included in this survey. Twenty percent of centres referred infected children in need of intensive care to adult wards, and 32% referred children to units that were external to their institution. In no case was a specific paediatric intensive care unit dedicated to contagious diseases available. This is a serious problem in cases of contagious children who need ventilation or intubation [10].

The level of training in infectious diseases also revealed causes for concern. Medical and nursing personnel specifically trained in infectious diseases were available in 11% of units (Table). Many units relied on consultants for infectious diseases from units admitting adults (32%). Only six units (5%) claimed they routinely applied the adequate isolation precautions (Table). Many units relied on consultants for infectious diseases from units admitting adults (32%). Only six units (5%) claimed they routinely applied the necessary isolation precautions (Table).

To evaluate the overall preparedness of paediatric units in facing highly contagious/highly severe infectious diseases, we examined whether multiple measures were simultaneously available in the same unit (Table). Several centres (71%) had a variable combination of logistical facilities, trained medical and nursing staff and applied appropriate procedures. However as well as many as 25% of responding units did not have either logistic or specific educational qualification, and were thus totally unprepared to manage severe infectious diseases. Overall, only 4% of units had dedicated rooms and staff for infectious diseases, and effective isolation precautions based on specific protocols and procedures. Only the latter units may be considered actually or potentially capable to care for children with highly contagious, severe infectious disease.

**Conclusion**

The survey revealed that the preparedness of paediatric Italian units to confront a potentially fast spreading, severe contagious disease is far from adequate. Only a few units, usually located in large children's hospitals or academic paediatric departments, seem to be capable of facing the problem effectively. Most responding centres have major deficiencies, ranging from the lack of applications of routine precautions to prevent the spreading of contagious diseases to the lack of more advanced and expensive equipment, such as negative pressure rooms. Although our survey cannot be considered a formal investigation of the situation in Italy, the distribution of units and their size could be considered representative of the organisation of hospital care for children in this country. Hospital care for children in Italy is characterised by a predominance of small units that are effective against mild diseases, but that are not prepared to face major clinical problems. A major issue in the context of a severe contagious illness is the lack of intensive care dedicated to contagious children. Medical and nursing personnel trained in infectious diseases, specific logistic facilities in the wards and more rooms dedicated to infectious diseases, particularly in intensive care, are strongly needed. These facilities should be available at least in large tertiary care centres.

**Table**

<table>
<thead>
<tr>
<th>Facilities, resources and specific operational procedures for the management of potentially contagious diseases in 123 Italian paediatric hospital units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>A- logistic facilities for contagious diseases</td>
</tr>
<tr>
<td>B- specifically trained physicians and nurses</td>
</tr>
<tr>
<td>C- application of specific protocols and procedures</td>
</tr>
<tr>
<td>A + B + C</td>
</tr>
</tbody>
</table>

1 Based on a qualitative evaluation of each section of the questionnaire, taking into account optimal standard needs

2 Expressed as absolute number (percentage of hospital units)

**Action proposed**

Preparedness for influenza pandemics would be improved by the implementation of specific paediatric guidelines and operational procedures at local level. A national pandemic preparedness plan was recently produced with the following goals, in case of a major influenza epidemic:

- to reduce the virus transmission,
- to recognize and manage the infections;
- to decrease the hospitalisations and
- to reduce the economic impact of a pandemic [5].

The plan includes seven key actions, ranging from the virologic surveillance, to the measures needed to ensure the administration of adequate care, including antibiotic and antiviral drugs in hospitals, even in extreme operational conditions such as those envisaged in the worst scenario of a major epidemic. In the light of the results of the present survey, there is a significant issue with preparedness regarding an influenza pandemic in children. The key points at this stage are twofold: first, to identify a paediatric coordinating centre at the local level, such as regional level, capable to provide information, and second, to improve general education, as it seems that there is little knowledge about the spreading of severe infections. A key action needed in the field of education is the production of guidelines; an important document was recently released that covers treatment in the community and in hospitals [11]. The recommendations were specific for adults and children further supporting the view that preparedness should be considered specifically for children.

In Italy, a net of paediatric centres was set up at the onset of HIV infection spreading. The network of referral centres for paediatric patients infected with HIV proved to be a very effective tool, as it provided indications for patient management, collected data and informed paediatricians about the epidemiology of the then new infection. Some of the largest centres in Italy gained major experience in facing complex and severe infectious diseases and developed the ability to rapidly respond to the challenges of new diseases, also using the opportunities offered by web communication. One could envisage a national paediatric network of referral centres for infectious diseases, bearing in mind that “the
spread of avian influenza is an example of the need to strengthen defences against all infectious disease” [12].

Acknowledgements
The authors are grateful to all Italian Paediatric Centres which participated to the study, to the Italian Society for Paediatric Infectious Diseases, and to Dr. A Franzetti (Luigi Sacco Hospital, Milan, Italy). We would also like to thank Jean Gilder for text editing.

References

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Interferon gamma release assays (IGRA) offer an alternative to tuberculin skin testing (TST or Mantoux) for the diagnosis of tuberculosis (TB) latent infection (LTBI) or as an additional diagnostic method for active TB (recently reviewed in 1-5).

Two detailed sets of guidelines, one from the Centers for Disease Control, United States (CDC) [6] and the other from the United Kingdom National Institute for Clinical Excellence, [7] have been generated on the appropriate use of novel IGRAs for the diagnosis of LTBI and active TB. In the formulation of these guidelines, two commercial systems were considered, the T Spot (Oxford Immunotec, UK) and Quantiferon Gold (Cellestis, Australia).

Public health specialists involved in TB control, mainly in European countries with low and intermediate incidence of TB, met in Vilnius, Lithuania, in September 2006, to consider the use of IGRA assays against the background of those two guidelines and the increasing demand for the use of these assays. The group did not feel that it was necessary to write their own guidelines but rather to emphasise the main points of agreement with the published guidelines.

This statement represents a consensus of the group. As the field is rapidly evolving, the group felt that this guidance should be kept under regular review as new data becomes available.

For the diagnosis of latent TB infection

There was consensus on the value of the use of these tests for the diagnosis of LTBI as described in the two guidelines [6,7] based on the following agreed points:

- Although there is no clear gold standard for LTBI, IGRA, in published contact tracing incidents, reflect the degree of exposure to infectious cases more accurately than does TST. This suggests that IGRAs are more specific than TST. Discordant results between IGRAs and TST, however, cannot be completely explained by the notion that IGRAs are more specific with regard to cross-reaction with non-tuberculous mycobacterial (NTM) infections or with the Bacille Calmette Guerin (BCG) vaccine.

- Both commercial systems probably perform well for LTBI detection in immunocompetent individuals.

- Studies of IGRA sensitivity suggest they are at least as sensitive as TST in TB patients but may be less sensitive than TST for detecting LTBI in immunocompetent individuals.

- Theoretically, a combination of TST (with its high sensitivity) followed by IGRAs (with their greatest specificity) should be an optimal approach for contact tracing in incidents where there is a known index or source case. Clearly this advantage is negated where the patient does not return for reading of the TST. In those cases, the single-visit IGRA would be more advantageous.

- Although it is reasonable to assume that a positive IGRA is as predictive of later active TB as a positive TST, there is no evidence so far to suggest a higher or lower degree of predictability (see future work).

- IGRAs are of value for diagnosing/excluding LTBI in children or HIV-positive (or other immunocompromised) individuals, including those about to receive anti-tumour necrosis factor or other immunomodulating therapy.

- IGRAs are of value in any situation requiring serial TST testing, e.g. occupational health-related screening/exposure.

Future work

The group felt that further work was needed in the following areas:

- In low and intermediate incidence environments, longitudinal studies are needed to establish the real probability of a positive IGRA predicting future active TB. This is challenging but this should not delay the use of these tests in general.

- It is not clear that IGRAs and TST are measuring the same pool of immunological effector cells and further analysis of the underlying immunology is required.

- Test reproducibility should be addressed in studies of serial examinations of infected individuals. Apparent reversion of positive infection is known to occur in a small number of individuals but the meaning of this reversion is unclear.

- Similarly, there is a need to define the comparative sensitivity of TST and IGRA assays in different populations.
Active TB

- IGRAs are of some value in diagnosing active TB but should NOT replace appropriate microbiological and molecular investigation. IGRAs have no benefit in known pulmonary TB cases with bacteriological/molecular confirmation.

- Studies have shown a variable but generally high sensitivity (75-97%) of IGRA. The sensitivity may be slightly reduced by active disease, as TST is reduced by anergy in severe disease.

- The specificity is very high (90-100%, where there is no evidence of previous active TB). IGRAs do not cross-react with BCG but cross-react with a small number of non-tuberculous mycobacteria.

- IGRAs would have the greatest potential benefit in the diagnosis of TB in cases that are difficult to diagnose, such as children, immunocompromised patients such as HIV-positive individuals, and in cases of extra-pulmonary TB (especially TB meningitis).

- There is evidence for the usefulness of IGRAs to diagnose active TB in children and HIV-positive individuals, but little for diagnosing extra-pulmonary TB at this time.

- Overall, both tests perform similarly but the T spot may be more sensitive in HIV-positive and severely immunocompromised individuals and has fewer indeterminate results. However, this may be due to the current cut-offs used for these tests (see future work). Conversely, the Quantiferon assay is easier to perform and is less time-sensitive.

Future work

The group felt that further work was needed in the following areas:

- More carefully designed head to head studies are needed in general, particularly for groups that are hard to diagnose (children, HIV-positive and other immunocompromised individuals, and those with extra-pulmonary TB, particularly TB meningitis).

- Analysis of cut-offs used in both assays and consideration of different cut-offs for different patient groups is needed.

- The reproducibility of the test should be addressed by a series of repeated or sequential examinations of patients and exposed persons.

There is a place for IGRAs in the diagnosis of both latent infection and active TB; their use should be carefully considered in relation to the likely value to the individual and to the public good.

References


Policy and guidance

Defining core competencies for epidemiologists working in communicable disease surveillance and response in the public health administrations of the European Union

C Varela (Carmen.Varela@ecdc.europa.eu), D Coulombier on behalf of the Preparedness and Response Unit, European Centre for Disease Prevention and Control, Stockholm, Sweden

Strengthening the capacity to combat infectious diseases in the European Union (EU) is a core function of the European Centre for Disease Prevention and Control (ECDC), clearly expressed in its mandate [1].

Two main elements are critical for building and strengthening epidemiological capacity:

- Infrastructure - resources in terms of budget, facilities, equipment, etc. of national public health administrations.
- Human resources - sufficient numbers of trained and/or experienced professionals.

To fill the gaps in professional performance, it is necessary to define the tasks and skills required of field epidemiologists. The development of such a list of core competencies was highlighted as a priority among the conclusions of the first ECDC consultation with EU Member States on training in field epidemiology, in December 2005 [2].

The ECDC, along with a group of experts, has developed a list of suggested core competencies for field epidemiologists working in public health institutions in the European Union, at all levels, from sub-national (provinces, districts, regions) to national and supranational (European and international). An agreed definition of the term “field epidemiologist” is not available, but the group of experts has proposed one for the purpose of this activity (Table 1) [3].

Core competencies

A competency is a combination of knowledge, skills and abilities that a professional must demonstrate and that are critical to perform work effectively.

Core competencies are defined first for middle-level professionals, as opposed to junior or senior epidemiologists. Despite the risk of creating artificial categories in the career development ladder, this approach has been taken to facilitate the process. At a later phase, the competencies can be developed for other career stages.

The term “core” indicates that the competencies should be a minimum pre-requisite for any field epidemiologist, regardless of

Table 1

<table>
<thead>
<tr>
<th>Field epidemiologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;An epidemiologist who applies the science of epidemiology to the prevention and control of public health problems and works in intervention and response activities&quot;</td>
</tr>
</tbody>
</table>

Competency

"The combination of knowledge, skills and abilities that a professional must demonstrate and that are critical to perform work effectively"

Any competency statement should consist of the following elements:

- action verb (observable or measurable performance of a worker)
- content (subject matter, type of performance, specific task)
- context (limitations or conditions of work environment)

Domain

Groups of competencies, organized according to a specific area of knowledge or skills involved

Skills

Ability, proficiency, facility, or dexterity that is acquired or developed through training or experience

Knowledge

Familiarity, awareness, or understanding gained through experience or study

Curriculum

Set of courses and their contents offered by an institution, such as a school or university as part of a training programme

Table 2

Use of the list of “workforce” core competencies

<table>
<thead>
<tr>
<th>Employers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Develop job descriptions</td>
</tr>
<tr>
<td>Plan career development cycle of the professionals in the organization</td>
</tr>
<tr>
<td>Assess the epidemiologic capacity of the organization in order to shape it according to needs</td>
</tr>
<tr>
<td>Evaluate individual performance</td>
</tr>
<tr>
<td>Plan training for employees</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epidemiologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-assessment</td>
</tr>
<tr>
<td>Plan career development</td>
</tr>
<tr>
<td>Plan learning activities according to individual needs</td>
</tr>
</tbody>
</table>
the level he/she occupies in the public health administration. They should be common to all professionals in this field.

Use of the list of core competencies
We believe that the list may have several users:
- Employers, such as public health institutes and administrative bodies at all levels in the EU, who may use the list to assess their epidemiological capacities and needs.
- Epidemiologists themselves who may use the list for planning and evaluating their own career development (Table 2).

In addition, teachers and facilitators can use the list to design strategies and programmes to train future generations of epidemiologists in order to meet the needs of public health agencies.

Among the competencies, one can distinguish “workforce” competencies, as opposed to “instructional” ones, depending on the perspective taken for their development: i.e. employers or trainers views, respectively.

According to the MACH model (the acronym is made up of the initials of the authors’ surnames [4]), both approaches are complementary and can be part of a more complex cycle, where the primary outcome is organizational performance. In this model, the contribution of employees is defined by the workforce competencies or tasks; from these, the instructional competencies are developed in order to conduct needs assessments and planning of relevant training. The training and the personal skills influence the individual performance, which in turn affect the organizational performance thus closing the cycle [4].

Furthermore, we hope that publishing and promoting this list of core competencies in the EU’s public health system can help to:

- agree on a definition of “field epidemiologist” and achieve the recognition of the profession;
- allow Member States to assess their resources and define their needs;
- set priorities by teachers and curriculum developers; and
- increase the comparability of field epidemiology training programmes, which could facilitate mobility in the EU through accreditation initiatives.

Further development
We want to encourage a discussion of this list of core competencies by experts in the field. We also plan to review and update the list at regular intervals, as public health practice and knowledge evolves.

In July 2007, an online survey was launched on the ECDC website (http://www.ecdc.europa.eu). It seeks to score a list of 85 competencies that belong to 26 domains in eight areas (Table 3), through a Likert scale (1 to 5). The aim is to see whether there is a general agreement as to the core competencies and to collect, comments about the domains and areas included. The survey is anonymous but the participation of epidemiologists from different public health administrations of all EU Member States is especially welcome. To take part, please visit: http://www.ecdc.europa.eu/online_survey.html. The survey is open until 31 August 2007.

Table 3
Suggested ECDC classification of areas and domains in public health epidemiology

<table>
<thead>
<tr>
<th>Category</th>
<th>Area</th>
<th>Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific for the profession</td>
<td>Applied epidemiology</td>
<td>1. Public health science</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Public health policy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Risk assessment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Public health surveillance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Outbreak Investigation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Epidemiological studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Laboratory issues</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8. Public health guidance</td>
</tr>
<tr>
<td>Common to other professions</td>
<td>Biostatistics</td>
<td>9. Probability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10. Inferential statistics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11. Sampling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12. Mathematical modelling</td>
</tr>
<tr>
<td></td>
<td>Applied informatics</td>
<td>13. Internet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14. Statistical and other data analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15. Editing and presentations</td>
</tr>
<tr>
<td></td>
<td>Communication</td>
<td>16. Risk communication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17. Written communication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18. Oral communication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19. Use of new technologies</td>
</tr>
<tr>
<td></td>
<td>Management</td>
<td>20. Planning and use of resources</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21. Team building and negotiation</td>
</tr>
<tr>
<td></td>
<td>Capacity development</td>
<td>22. Mentorship</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23. Training</td>
</tr>
<tr>
<td></td>
<td>Ethics</td>
<td>24. Protection of Individuals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25. Confidentiality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26. Conflicts of interests</td>
</tr>
</tbody>
</table>


Acknowledgements
Experts from Field Epidemiology Training Programmes (FETPs), the Association of Schools of Public Health in the European Region (ASPHER), the Training Programmes in Epidemiology and Public Health Intervention Network (TEPHINET), the Centers for Disease Prevention and Control (CDC) of the United States, the EPIET (European Programme for Intervention Epidemiology Training) coordinators and the EPIET Alumni Association (EAN) played a key role in the development of the list of core competencies, both in e-mail-based reviews through questionnaires and during the Expert Meeting on 31 January 2007 [3].

References

On 11 July 2007, the French Minister of Health launched the National Tuberculosis Control Program and a new policy on Bacille Calmette-Guérin (BCG) vaccination. The latter includes the suspension of universal mandatory BCG vaccination of children with a shift to selective vaccination. BCG vaccination is now strongly recommended for children with a high risk of contracting tuberculosis (TB). These children are defined as those born in a country with a high incidence of TB, or with at least one parent born in such a country, or any child planning to stay at least one month in such a country, or with a history of TB in his/her close family. Children living in the Ile-de-France (Paris and suburb) or French Guyana regions, and children considered by a physician as living in an environment with a high risk of exposure to TB are also targeted by the new BCG recommendation. This decision is the result of a debate initiated in 2000 by the Institut de Veille Sanitaire, Saint Maurice (National Institute for Public Health Surveillance, InVS), the Advisory Board on Immunisation and the Ministry of Health. This led, in 2002, to the discontinuation of all BCG revaccinations and all routine tuberculin testing (other than those performed as part of an investigation of a contagious TB case or those performed before vaccination).

Several factors have contributed to the change in BCG policy. France is considered to have a low incidence of TB, with 8.9 cases per 100,000 population in 2005. As in other western European countries, TB in France has declined over the last century and tends to be concentrated in areas and in certain population groups such as the homeless, immigrants coming from countries with a high prevalence of TB and the elderly. In 2005, France's TB incidence was below 10 per 100,000 in all regions, except in Ile de France and French Guyana (19.7 and 44.0 per 100,000 respectively). The notification rate was also higher in homeless persons (210/100,000), in persons born abroad (41.5/100,000), especially in those born in sub-Saharan Africa (160/100,000) and in persons aged 80 years and older (21.7/100,000) [1]. The incidence of sputum smear-positive cases of TB and the incidence of meningitis in children have decreased and in 2002-2004 were below the thresholds recommended by the International Union Against Tuberculosis and Lung Diseases (IUATLD) [2] for considering a possible discontinuation of BCG vaccination.

In 2005, the Advisory Board on Immunisation recommended the shift to a selective vaccination under the condition of reinforcing TB control in France. Following this recommendation, the debate was triggered by the withdrawal from the market in January 2006 of the BCG multi-puncture device, almost exclusively used for primary vaccination, and its replacement by the BCG SSI to be administered intradermally. The difficulty of using this technique in young infants for untrained medical staff as well as its less favourable safety profile compared to the multipuncture technique – in a context where the targeting of BCG to high-risk children was already under discussion have led to a decrease in BCG vaccination coverage of more than 50%, despite the vaccination still being mandatory.

The potential for discrimination linked to the criteria used to define the children for whom BCG vaccination would be recommended was addressed through consultations with the Comité Consultatif National d’Éthique (National Ethics Committee) and the Haute Autorité de Lutte contre les Discriminations et pour l’Égalité (Authority against Discrimination). In addition, the Ministry of Health called for a citizens’ conference. This was held by the French Society of Public Health (SFSP) in late 2006.

Following these consultations and the finalisation of a national TB control program, the Advisory Board on Immunisation issued new recommendations in March 2007 on which the new BCG policy is based. The new TB control programme should lead to an improved control of the disease, therefore decreasing the risk of exposure for unvaccinated children. The programme aims to maintain the decrease of TB incidence and to reduce inequalities. It is based on six major objectives:

1. To ensure an early diagnosis and an adequate treatment for all TB cases
2. To improve TB screening
3. To optimise the BCG policy
4. To maintain anti-TB resistance at a low level
5. To improve the epidemiological surveillance and the knowledge on the determinants of TB
6. To improve the piloting of TB control

These objectives will be reached through measures such as improving TB awareness and information about access to health care and social rights for population at higher risk of TB, the development of guidelines and training of health care workers and the strengthening of control measures for contagious cases. TB surveillance has already been adapted to enable monitoring of the impact of both the implementation of the plan and the modification of the BCG policy. The recent changes include the collection of new information on the notification of TB cases in order to more effectively identify the target population for BCG (place of birth of the child and his/her parents for children younger than 15 years, and history of TB in the closed family) as well as the implementation of treatment outcome monitoring. Specific coverage surveys will have to be regularly carried out in order to
monitor BCG coverage in the newly targeted population, before the routine vaccine coverage monitoring tools can be adapted to the BCG selective policy.

The challenge will be the rapid implementation or strengthening of TB control measures, other than BCG, included in the national TB control programme, and the capacity to maintain a high coverage in high risk children targeted by the new recommendations.

For further information
On the new tuberculosis control programme and the new BCG policy in France:
http://www.sante.gouv.fr/htm/dossiers/tuberculose/sommaire.htm

On the epidemiology of tuberculosis and the surveillance system in France:
http://www.invs.sante.fr/surveillance/tuberculose/default.htm

References


Two reports gathering scientific information and public health opinion regarding human H5N1 vaccines have been published today by the European Centre for Disease Prevention and Control (ECDC) [1,2]. Aware that such vaccines were being developed by the pharmaceutical industry and that the European Union countries would be facing decisions as to whether or not to invest in them, the ECDC’s Advisory Forum requested a scientific report on this matter. However, rather than making firm recommendations, which is hardly possible at this stage, the report gathers together relevant scientific information and public health opinion. They were written with input from two groups of European experts and using data from industry that is increasingly available in the public domain in the form of peer-reviewed papers [3]. While reviewing and describing the scientific evidence, the experts attempted to answer some of the most important questions regarding the possible use of such vaccines for mitigating the potential impact of an influenza pandemic [1,2].

What is the rationale for considering these vaccines? Although it is not possible to determine in advance what influenza virus will cause the next pandemic, the continuing reports of A/H5N1 outbreaks among birds and the high case-fatality rate observed among humans who have been occasionally infected raise concerns over the imminent risk of an A/H5N1 influenza pandemic [4]. This is supported by the fact that A/H5N1 outbreaks in birds continue to occur in several countries worldwide and the viruses seem to be well established in some bird populations, which makes their eradication particularly difficult. In addition, the virus has shown the capacity to undergo antigenic evolution, with at least three different clades currently circulating (clades 1, 2 and 3) [5]. Therefore, although transmission from birds to humans is relatively uncommon and human-to-human transmission very uncommon, there is some risk that a new virus, with the ability to effectively spread among humans, will evolve from the current A/H5N1 strains [4].

The impact of the next influenza pandemic will largely depend upon the virulence of the pandemic virus and the level of immunological susceptibility of the exposed population. Since much of the population is by definition immunologically naïve against a pandemic virus, the development, stockpiling and administration of an effective vaccine in advance of an H5 pandemic could in theory significantly reduce its impact. This has led to the vaccines being sometimes called “pre-pandemic”, although this term is not recommended by ECDC since it assumes that an H5 pandemic is inevitable, which is not the case [4]. Modelling studies have suggested that the strategy of having a stockpiled vaccine (and possibly deploying it in advance), even if incompletely matched to the pandemic virus, may prevent more infections and deaths than waiting for specific ‘true’ pandemic vaccines (6,7). It has also been suggested that these vaccines should play a role in the World Health Organization’s Early Containment Strategy [8].

There are currently substantial constraints to the development and production of such vaccines on a large scale. Global influenza vaccine production capacity is already limited [9] and this limitation is made worse by the large amount of haemagglutinin (HA) antigen often needed for these vaccines to confer adequate protection. To some extent, however, this is being overcome by better use of innovative adjuvants by the pharmaceutical industry [3]. In order to increase vaccine supply generally a global pandemic influenza action plan has been developed by the WHO [9].

The production of an H5N1 vaccine may be further limited by the availability of A/H5N1 virus isolates from human infections. Through the Global Influenza Surveillance Network, the WHO is continuously collecting and sharing viruses and information on the antigenic characteristics of all influenza viruses [10]. This includes the A/H5N1 viruses isolated from human cases and provides essential information on the characteristics of the viruses that should be used for vaccine development [5,11]. However, the willingness to share H5N1 samples from humans has lessened in Indonesia, the country that has experienced more human cases than any other to date in 2007. Reportedly this is because there is no agreement guaranteeing that when a vaccine becomes available it would preferentially receive it during a pandemic [12].

Since the pandemic virus might be a drifted strain of the currently circulating A/H5N1 viruses, in order for the vaccine to be effective it should offer a broad cross-protection towards different strains [11]. Researchers have embarked on studies aimed at developing human H5N1 influenza vaccines with such characteristics, and some promising results have been already published in peer-reviewed journals. For example, different degrees of cross-reactivity with different strains of A/H5N1 viruses have been achieved using different vaccine formulations and the use of new generation adjuvants allowed a remarkable reduction of the amount of haemagglutinin (HA) antigen needed to achieve the desired immunological response [3]. However, as the ECDC documents suggest, these results cannot be easily translated into recommendations for public health policy-makers. The vaccines are likely to be expensive and many fundamental questions remain open with a clear need to continue the research in these areas.

References


Citation style for this article: Influenza team (ECDC). Human influenza A/H5N1 ("pre-pandemic") vaccines: informing policy development in Europe. Euro Surveill 2007;12(9):E070920.3. Available from: http://www.eurosurveillance.org/ews/2007/070920.asp#3
Prevalence surveillance system of nosocomial infections in Norway

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In 1996, the Norwegian Ministry of Health issued regulations on the prevention of nosocomial infections (NI). The regulations were revised in 2005 [1]. As part of the infection control programme, hospitals and long-term care facilities (LTCFs) are obliged to have a surveillance system for NI in place and to report the results to the Norwegian Institute of Public Health (NIPH). NIPH coordinates the surveillance activities and publishes annual statistics.

NIPH received the first annual reports from two thirds of the hospitals in 1999. That year, surveillance reports from LTCFs were sent from only one of the 19 counties in Norway [2]. Separate surveillance protocols for either hospitals or LTCFs were developed in 2002, and at present all hospitals and around one third of the LTCFs participate every year.

Methods

The hospitals and LTCFs are invited to participate in two nationwide point-prevalence surveys each year. The system is compatible with the recommendations of the “Hospitals in Europe Link for Infection Control through Surveillance” (HELICS) cooperation project of the European Union.

NIPH collects information on the occurrence of the most common nosocomial infections [3]:

- Urinary tract infections
- Lower respiratory tract infections
- Superficial and deep surgical site infections
- Soft tissue skin infections (only in LTCFs)
- Septicaemias (only in hospitals)

The case definitions are simplified versions of the definitions recommended by the Centers for Disease Control and Prevention (CDC). Patients who underwent surgery 30 days prior to the infection (or one year in the case of implant surgery) are also reported.

A paper version of the surveillance protocol was posted to all institutions in 2002 and 2004. Since autumn 2005, NIPH sends out an invitation by e-mail before every survey. In addition the protocol is available on the NIPH homepage (http://www.fhi.no).

On the day of the prevalence survey each ward or unit registers infections according to the protocol. The infection control personnel coordinate the data collection and report to NIPH either directly into the web-based surveillance tool or by mail or e-mail. Almost all hospitals report electronically. An increasing part of the LTCFs participate, this year it was two thirds. The reports that are received are summary data and contain no patient identification. Since 2007 all institutions can see their own prevalence data presented online and compare their results with the regional and national results. In addition, two seasonal and one annual summary report are published on the NIPH web site.

Results

The development of the prevalence of NI at hospitals in Norway from 2002 to 2007 is shown in Figure 1. The NI prevalence has been stable in the last years, including the distribution of the different types of infection.

The development of the prevalence of NI in LTCFs in Norway from 2002 to 2007 is shown in Figure 2. The surveys show that also in LTCFs, the prevalence over the years has been relatively stable.

Discussion

The prevalence surveys cannot replace the surveillance of the incidence of NI. They give only snap-shot impressions of the infection status of the patients hospitalised on a certain day, and the results must be interpreted with caution, especially in small units. The results must be evaluated in connection with other available information and can then be useful to indicate the extent and distribution of NI by type of department, size of health care institution and geographic location, show the development over time and indicate problems that may require more extensive investigation.

The web-based surveillance tool simplifies and secures the data registration at the hospitals and LTCFs as well as at the NIPH. In addition, it gives the institutions faster and easier access to the results.

References


**Figure 1**

Prevalence of four types of nosocomial infections in Norwegian hospitals, 2002 - 2007

**Figure 2**

Prevalence of four types of nosocomial infections in Norwegian long-term care facilities, 2002 - 2007
Short report

AN OUTBREAK OF ESCHERICHIA COLI O157 PHAGE TYPE 2 INFECTION IN PAISLEY, SCOTLAND

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Scotland has higher rates of Escherichia coli O157 infection than other countries in the United Kingdom (UK) and Europe [1]. The National Health Service’s (NHS) Greater Glasgow and Clyde Public Health Protection Unit is currently investigating an outbreak of E. coli O157 infection in Paisley. Between 10 and 17 August 2007, nine confirmed cases of E. coli O157 infection were identified, of which six have been confirmed as Phage Type 2.

Investigation, management and control
On 10 August, laboratories reported to NHS Greater Glasgow and Clyde Public Protection Unit two cases of E. coli O157 in residents of a single postcode area of Paisley. Besides some unsurprising common factors, one case reported buying food from branch A of a supermarket chain, and the family of the second case (who was too ill to provide information) reported that he frequently shopped at branch B of the same chain. A problem assessment group on 10 August concluded, however, that there was insufficient evidence to suggest a common food source, and initiated further epidemiological, microbiological, and environmental investigation.

On 13 August, five further cases of E. coli O157 infection were reported. Of these, three were members of the first two cases’ families. In all, family group 1 consisted of three cases and family group 2 of two. The second member of family 2, a 66 year-old woman, died on 13 August. The remaining two new cases were apparently unrelated to each other and to the earlier cases, except for the same area of residence.

Both the apparently sporadic cases reported having bought and consumed cold sliced meats from the delicatessen at branch B of the supermarket chain within the likely incubation period of two to 10 days. At least one member of each family group and the two apparently sporadic cases had consumed various cold cooked sliced meats from the delicatessens of the branches at which they shopped. There was no link between the two branches and apart from the consumption of cooked meats from the same supermarket chain, these cases had no other common social or food history link.

Topside of beef was the cooked meat most frequently reported by cases. This meat was supplied by a subsidiary of the supermarket chain and distributed nationally exclusively to the chain.

The Outbreak Control Team (OCT) formulated several working hypotheses. Firstly, that the product linking most of the cases was nationally distributed. Alternatively, that there was an as yet undiscovered link between the two branches of the supermarket chain. Thirdly, but less plausibly, that similar faults had occurred independently in both branches of the supermarket chain.

All working hypotheses presupposed that the vehicles of infection were the cold cooked meats sliced on the branch premises and did not include other items sold from the delicatessens or pre-packed meats from any of the branches of the chain. The OCT concluded that, pending the results of further investigations, there was sufficient evidence to issue a press release instructing the public not to consume cold meats from the delicatessens of the two supermarket branches. In addition, general practitioners, NHS24, hospital departments and the Scottish Executive were alerted.

At subsequent meetings of the OCT, on August 14 and 15, phage type 2 was confirmed in four cases. The OCT noted that there had only been four other cases of this uncommon type in Scotland in 2007, all resident of Greater Glasgow and Clyde.

By 17 August, two further cases had been confirmed. Both had consumed cold meats from the delicatessen at branch B.

The total number of confirmed cases was now nine (Table). Despite a case of haemolytic uraemic syndrome from an adjacent NHS board in a youth who had reportedly consumed food from a different branch of the supermarket chain, and unconfirmed reports of a case from elsewhere in the UK who had shopped at the chain, the hypothesis of a nationally distributed foodstuff was becoming less plausible. The hypothesis of a similar fault having occurred at two branches of the same supermarket chain was also unlikely. The OCT decided to recheck the only case history which contradicted

<table>
<thead>
<tr>
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<th>Family</th>
<th>Age</th>
<th>Onset of symptoms</th>
<th>Phage type</th>
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<td>1</td>
<td>23</td>
<td>05/08/07</td>
<td>2</td>
</tr>
<tr>
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<td>2</td>
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<td>2</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>45</td>
<td>05/08/07</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>45</td>
<td>01/08/07</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>66</td>
<td>10/08/07</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>86</td>
<td>10/08/07</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>71</td>
<td>06/08/07</td>
<td>pending</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>81</td>
<td>11/08/07</td>
<td>pending</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>70</td>
<td>06/08/07</td>
<td>pending</td>
</tr>
</tbody>
</table>
the hypothesis that a fault might have occurred only in branch B. The index case in family group 1 subsequently confirmed having bought and consumed cold cooked meats exclusively from the delicatessen in branch B.

On 17 August, the OCT therefore concluded that the most likely cause of the outbreak was the cross-contamination of various cold cooked meats at the delicatessen of a single branch of a supermarket chain. However, epidemiological, microbiological and environmental investigations are still ongoing, and information is being gathered from approximately 20 other people who have reported symptoms following the consumption of meats from branches A and B of the supermarket chain.

References


Short report

Outbreak of Shigellosis in Denmark Associated with Imported Baby Corn, August 2007

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On 16 August 2007, the Danish regional food authority (Fødevareregion Øst) and the Statens Serum Institut (SSI) became aware of an outbreak of Shigella sonnei infections. The first cases to be reported were employees of two companies. They had eaten a variety of vegetables, including raw baby corn and sugar snaps in their workplace canteens. Preliminary interviews with further cases indicated that the probable source was imported baby corn or sugar snaps that had been distributed at the beginning of August. The suspected foods were distributed by one wholesaler to greengrocers, catering firms, restaurants and shops throughout the country. Due to the strong suspicion about these food vehicles, the Veterinary and Food Administration issued a recall of baby corn and sugar snaps on 17 August. Furthermore, the SSI undertook investigations to determine the extent of the outbreak and its source.

A cohort study was undertaken in one of the many workplaces to have been affected by the outbreak to test the primary hypothesis that infection was associated with eating baby corn in the work canteen. Of 103 web-based questionnaire responses returned by 21 August from people who had eaten in the canteen, 24 reported gastrointestinal symptoms consistent with Shigella infection. In the questionnaire, one set of questions focused on which days the employees had eaten in the canteen and the others on which food items had been eaten in the canteen on the 6 and 7 August, the two days when the suspected baby corn was known to have been served. There was a higher, although non-significant, relative risk of illness among people who had eaten in the canteen on 6, 7 or 8 August. The relative risk for gastrointestinal symptoms among people who had eaten baby corn was 4.6 (95% CI: 2.0 - 10.9) on 6 August and 4.0 (95% CI: 1.7 - 9.6) on 7 August. The attack rate in those employees who ate baby corn on 6 or 7 August was 64%.

Concurrent with the cohort study, notified cases from different parts of Denmark were interviewed and asked about food intake prior to onset of symptoms. The results of these interviews were consistent with baby corn being the source of infection. Moreover, a large number of workplaces were found to be affected by the outbreak and their canteens had served baby corn from the suspected imported batches in their salad bars. Taken together, the available epidemiological and food trace-back evidence strongly supported the finding that baby corn imported from Thailand was the source of the outbreak.

Between 6 and 24 August 2007, the SSI received notifications of 122 S. sonnei isolates. This is almost triple the number of isolates confirmed for the whole of 2006 (46 isolates). A case in this outbreak was defined as any case of S. sonnei infection acquired in Denmark after 1 August 2007 excluding those who had travelled to an endemic area in the three days before onset of symptoms or those that could be explained by an alternative exposure.

To date, 120 cases have met the agreed case definition (2 of the 122 notified ones were excluded as travel-related). Cases were reported through the laboratory surveillance system from the whole of Denmark, but most cases (97/120, 81%) were reported from Zealand. The median age was 38 years (range 1-92 years) and 90 cases (75%) were female. Information on symptom onset dates, which ranged from 6 August until 17 August, was available for 55 cases (Figure). A quarter of these cases (13/55) were known to have been admitted to hospital.

Antibiotic resistance typing on 11 samples taken from cases provided a list of the most effective antibiotics. S. sonnei isolates from this outbreak were resistant to tetracycline and ampicillin, but susceptible to nalidixic acid, ciprofloxacin, sulphonamides, chloramphenicol, and gentamicin. Typing of isolates by Pulse Field Gel Electrophoresis is ongoing. Microbiological examination of the suspected batches of baby corn from Thailand revealed that the isolates were resistant to tetracycline and ampicillin, but susceptible to nalidixic acid, ciprofloxacin, sulphonamides, chloramphenicol, and gentamicin. The results of these investigations were consistent with the hypothesis that the source of infection was imported baby corn.
of imported baby corn has detected high levels of *Escherichia coli*, indicating faecal contamination. Additionally *Salmonella* (serotypes as yet undetermined) have been found in two batches. *Shigella* have so far not been detected, but analyses are still ongoing.

An Early Warning Response System report was issued on 18 August. The available information suggests that the outbreak is confined to Denmark but we encourage other countries to be aware of potential clusters of *S. sonnei* cases. A small number of cases have been reported from Sweden but those contacted so far all appear to have been infected in Denmark. However, it is known that a small part of a batch of baby corn imported into Denmark was sold on to Sweden. This is currently undergoing microbiological examination to determine whether it was contaminated. Furthermore, among the cases in the outbreak there were individuals who acquired the infection on the ferry between Oslo and Copenhagen and it was found that baby corn from an incriminated batch was served on this ferry.

Due to the long shelf life of baby corn (three weeks), the interventions made to trace the source of infection and to recall the product are likely to have prevented additional cases of illness. Although *Shigella* infections do occur in Denmark and small outbreaks are occasionally seen, most cases are travel-related. The last large *S. sonnei* outbreak in Denmark was in 1998, also associated with eating raw baby corn imported from Thailand [1].

References


An outbreak of multi-resistant Shigella sonnei in Australia: possible link to the outbreak of shigellosis in Denmark associated with imported baby corn from Thailand

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An outbreak of shigellosis was recently reported in Denmark associated with the consumption of imported baby corn from Thailand [1]. We report a similar outbreak of shigellosis in Queensland, Australia that is possibly linked to the Danish outbreak through a common source in Thailand.

Queensland Health has investigated 11 laboratory-confirmed cases of Shigella sonnei (biotype g) with most cases having reported either consuming imported baby corn from Thailand or eating at a venue where imported baby corn was commonly served. These cases included two from another Australian State – Victoria – who had travelled to Queensland. Four cases were part of a larger outbreak among a film production crew where there were a further 43 probable cases (with symptoms including acute diarrhoea with or without vomiting, stomach cramps and fever between 9 and 14 August), although it was not possible to conduct a cohort study. Another two cases were infected while in hospital and a further two cases ate at a common holiday resort. All case isolates were resistant to augmentin, ampicillin, tetracycline, sulphonamides, trimethoprim, and streptomycin but susceptible to nalidixic acid, norfloxacin, ciprofloxacin, gentamicin, chloramphenicol, and ceftriaxone.

The dates of onset of illness among the 11 laboratory-confirmed cases were from 9 to 27 August, 2007. The median age of cases was 31 years (range 18-76 years) and seven cases were female.

Results of Pulsed Field Gel Electrophoresis (PFGE) testing of the human isolates from Queensland show a profile that is indistinguishable from that of human isolates from the outbreak in Denmark using the enzyme XbaI and the same running conditions as Denmark. We plan to run further gels on Australian S. sonnei isolates from the past three years to review the diversity of strains. We also plan to conduct further PFGE using a second enzyme BlnI (AvrII).

The traceback investigation to date shows that eight of the 11 cases may have eaten baby corn that was part of a very small consignment imported in late July by a single wholesaler in Queensland from an agent in Thailand. This Thai agent appears to be different from the Thai business that exported baby corn to Denmark, but the producer of the baby corn may still be the same, which remains to be investigated. Microbiological testing of baby corn from current batches is currently underway, although there was no leftover baby corn from the original consignment for testing.

Australia is attempting to trace the source of the baby corn with the assistance of Thai authorities. Onset date of illness for the last reported case was 27 August, and therefore no product recall has been initiated. Enhanced case surveillance has commenced to enable a more rapid response to the investigation of cases.

References


Short report

ONGOING MEASLES OUTBREAK IN SWITZERLAND: RESULTS FROM NOVEMBER 2006 TO JULY 2007

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Introduction

After some sporadic cases and small outbreaks (43 cases) during the first semester of 2006, and a four month period of low measles activity (three cases), an outbreak of measles was detected in the canton of Lucerne in November 2006. From then until 17 July 2007, 483 cases were reported by physicians or laboratories for the whole country. This is 10 times more than the average number of cases reported for the corresponding period over the past eight years (mandatory surveillance of measles was introduced in 1999). Of these, 279 cases (58%) occurred in the canton of Lucerne. The incidence for the whole country and all ages, calculated for the eight-month period from November 2006 to July 2007, was 6.5 cases per 100,000 inhabitants. For children under the age of 16 years living in the canton of Lucerne, it was 343 per 100,000.

Outbreak description

The first five known cases, who were eight to nine year-old children living in the town of Lucerne, fell ill almost simultaneously in mid-November. Four of them reported an exposure at school. The origin of the outbreak is unknown. Since then, the disease has spread to the neighbouring countryside; further outbreaks were reported in other cantons: Bern (especially in the area of Biel) in February (68 cases), Geneva in March and again in May (37 cases), and Zug in April (26 cases). These outbreaks are still ongoing. Of 26 cantons, 19 reported at least one measles case. No epidemiological links between the outbreaks have been confirmed, but 27 viral strains obtained from the saliva of cases from different parts of the country – including the first cases in Lucerne – belonged to the D5 genotype. The only exception was one B3 virus that was probably imported from Italy. Exactly the same D5 sequences were recently identified in a Japanese student visiting Canada, and D5 measles viruses were involved in a large outbreak in Japanese universities last spring, suggesting a possible importation of measles from Japan to Switzerland [1,2]. The monthly number of cases has been increasing steadily over this eight-month period, reaching a maximum of 108 cases in June (Figure 1).

Most cases (57%) have been confirmed, either by a positive IgM or PCR result (45% of the total cases), or by an epidemiological link with a laboratory confirmed case (12% of the total cases). Thirty-four percent of the cases fulfilled only the clinical case definition (fever and rash, as well as cough or rhinitis or conjunctivitis), whereas in 9% of the cases, clinical data were not yet available or did not completely fulfill the case definition.

Fifty-three percent of cases were males. Figure 2 shows the age distribution of the cases. Half of them were aged between five and 14 years. The median age was 10 years. Six percent of the 445 cases for whom a detailed questionnaire had been submitted were vaccinated against measles (18 with one dose and nine with two doses), 87% were unvaccinated, and the vaccination status of the remaining 7% was unknown. There were 43 cases (10%) requiring hospitalisation. Among 445 cases for whom information about complications was available, four cases were reported with encephalitis (1%), all among children, 29 cases with pneumonia (7%, median age 10 years), and 31 cases with otitis media (7%). No deaths were reported.

Control measures

Various measures were taken by the cantonal medical authorities to control this outbreak. They included targeted information, such as letters to the parents in the implicated schools and day-care

Figure 1

Epidemiologic curve of the measles outbreak in Switzerland as of 17 July 2007 (n=484, mandatory notifications)

<table>
<thead>
<tr>
<th>Month</th>
<th>Number of reported measles cases</th>
</tr>
</thead>
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<tr>
<td>2006</td>
<td>1</td>
</tr>
<tr>
<td>2007</td>
<td>0</td>
</tr>
<tr>
<td>Rash onset per month</td>
<td>Number of reported measles cases</td>
</tr>
</tbody>
</table>

Figure 2

Measles cases, by age, reported through the national mandatory notification system, Switzerland, November 2006–July 2007 (n=482)

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>3</td>
</tr>
<tr>
<td>1 - 4</td>
<td>16</td>
</tr>
<tr>
<td>5 - 9</td>
<td>26</td>
</tr>
<tr>
<td>10 - 14</td>
<td>23</td>
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<td>15 - 19</td>
<td>16</td>
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<tr>
<td>20 - 29</td>
<td>8</td>
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<tr>
<td>30 - 39</td>
<td>5</td>
</tr>
<tr>
<td>&gt;= 40</td>
<td>4</td>
</tr>
<tr>
<td>% of reported measles cases</td>
<td>Age groups (years)</td>
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EUROSURVEILLANCE Vol. 12 · Issues 7–9 · Jul-Sep 2007 · www.eurosurveillance.org 273
centres, letters to the doctors of the affected areas, as well as general information through the media and the Bulletin of the Federal Office of Public Health [3,4]. This information contained recommendations to check the vaccination status of children and young adults and to complete immunisation if necessary. In specific cases, contact tracing was carried out to prevent (vaccination or administration of immunoglobulin) and detect new cases. In at least two cantons, non-immune siblings of the index cases were asked to stay at home, in order to limit the transmission to schools.

Discussion

Measles is a highly contagious disease, with a secondary attack rate of over 90% among non-immune contacts. During this outbreak, a large variety of different settings for transmission were identified, such as families, schools, an anthroposophic boarding school, day-care centres, ski camps, sports clubs, a military accommodation facility, a cinema, planes, an airport, and ‘measles parties’ (voluntary exposure of children to an infected person).

The current ongoing outbreak clearly shows that measles is not only a childhood disease: 28% of the cases were 16 years-old or older. With one patient out of 10 hospitalised, sometimes with severe complications, it also shows that measles, even in children, cannot be considered a mild disease. Two groups were involved in particular: children and teenagers whose parents did not wish them to be vaccinated, and to a lesser extent, young adults who were not immunised because they were born before the introduction of a general measles vaccination programme and who had not been infected during childhood due to an already reduced circulation of the virus. The first recommendation for measles vaccination dates from 1976, but an active promotion campaign for measles, mumps, and rubella (MMR) vaccination was started only in 1987.

The best protection against measles and its complications remains the widespread vaccination of young children. In Switzerland, this vaccination is voluntary and reimbursed by mandatory private health insurance. It includes two doses of MMR vaccine, one at the age of 12 months and another at the age of 15 to 24 months [5]. A catch-up vaccination is recommended for anyone under the age of 40 who has no documented vaccination, or no reliable history of having had measles or specific antibodies. Despite a slight increase in recent years, the measles vaccination coverage in Switzerland remains significantly below the 95% necessary for measles elimination [6]. The coverage for one dose is about 86% at two years of age (78% in the canton of Lucerne), 89% at school entry and 95% at the age of 16 years. Overall it reaches only 70 to 75% for the second dose.

In addition to this insufficient vaccination coverage, the frequent lack of appropriate measures to control sporadic cases and beginning outbreaks (there is no national plan of action for measles elimination yet) still allows measles outbreaks to occur in Switzerland, sometimes with large numbers of patients: 6,400 estimated cases in 1997, 613 reported cases in 2003 [7], and 483 cases so far this year. Thus, under the current conditions, it is unlikely that the WHO’s goal to eliminate measles from Europe will be achieved by 2010.

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On 4 August, a 22-year-old male tourist from London presented at a hospital in Jerusalem, Israel, with general malaise, a high fever and a blotchy maculopapular rash over his face, trunk and limbs, including palms and soles. A junior health officer recommended hospitalisation, which the patient refused, partly as a result of there being no definitive diagnosis. Later the same day, the patient visited a private urgent care centre in Jerusalem. Although there was an absence of typical symptoms seen in the early stages of measles, such as Koplik’s spots, dry cough and conjunctivitis, the physician in the centre suspected measles. He had seen very few cases of measles previously, but as the staff of the clinic are kept informed of infectious disease outbreaks globally by the focused use of Google Health News installed on desktops at the clinic, he was aware of recent outbreaks of measles in parts of the United Kingdom (UK), including London, which had been reported in the British media [1,2]. This, coupled with the patient’s rash and his other symptoms, led to a suspicion of measles, which the man had not been vaccinated against due to adverse reaction in a sibling.

On 7 August, measles was laboratory-confirmed in the Central Virology Laboratory of the Ministry of Health at Tel Hashomer (Sheba Medical Center): serology was strongly positive for rubella (measles) antibodies (IgM). The virus genotype responsible for the outbreak was D4, the same genotype prevalent in the ongoing outbreak in the United Kingdom [3]. The test was organised by the Public Health Services of the Ministry of Health, to which the suspected case was referred – measles is a notifiable disease in Israel. The patient’s history revealed earlier oral lesions and conjunctivitis. He could not indicate the source of infection, but recalled having visited his General Practitioner in London several weeks earlier, where another patient in the waiting room may have had a rash.

Upon admission, our patient was isolated in a separate room and treated for malaise, fever, cervical lymphadenopathy and dehydration. Intravenous fluids were given daily over a four-day period. He recovered and was discharged two weeks after admission. His eight-month old son was given gamma globulin, while the rest of his household was contacted by the Jerusalem branch of the Ministry of Health and vaccinated where necessary.

On 1 August, the patient had attended a wedding in Jerusalem with an estimated 2,000 guests, almost all of whom were members of the Toldot Aharon (literally ‘generations of Aaron’), also known as the Satmar, an ultra-orthodox Jewish movement with sizeable communities in the United Kingdom (UK), the United States, Belgium, Switzerland, Argentina and Israel. Globally, there are thought to be around 20,000 members of this movement. Guests at the wedding came from Israel, Europe and the United States. Considering the incubation period of measles (10-12 days), these people may have been exposed.

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To date in 2007, there have been 187 cases of measles confirmed in London, United Kingdom (UK), reported up to the end of week 34 (24 August). Among these, 36 confirmed cases and 17 probable cases reported in London between March and June 2007 were associated with an outbreak in a travelling community gathering in the South East of the city [1].

Since May, an increase in confirmed and epidemiologically linked cases has been reported in North East and North Central London (105 confirmed cases). This is an area of London with a large orthodox Jewish community. In this area, 43% of cases were in the 1-4-year age group and 19% in the 5-9-year age group. A number of cases in older children and adults have also been reported. The predominant genotype has been D4.

In recent weeks, the outbreak has spread into the wider community, affecting susceptible individuals who are either unimmunised or partly immunised.

Nationally, uptake for measles, mumps and rubella (MMR) immunisation is measured at two and five years of age. Between January and March 2007, the uptake of MMR vaccine at five years of age was at 87% for the first dose and 73% for the second dose. In spite of a London-wide ‘Capital Catch-up Campaign’ in 2004-5, the uptake in London for MMR is measured at two and five years of age. Between January and March 2007, the uptake of MMR vaccine at five years in England was at 87% for the first dose and 73% for the second dose. In March to June 2007, 87% for the first dose and 73% for the second dose.

Our experience suggests that larger families are often not vaccinated and that families have little understanding of the need to vaccinate their children with two doses of MMR. This will be explored further in a detailed analysis following the outbreak.

A targeted, proactive approach to intervention has been taken by local front-line health care workers and the Health Protection Unit. This has included extending community-based immunisation clinics; engaging local community-specific media; and liaising with primary care teams and local hospitals, as well as the Learning Trust school nurses and health visiting teams. A national press release supported these efforts, and locally, efforts are being made to maintain this impetus. Overall, these interventions have received a positive response within the affected communities. The challenge will be to maintain this level of proactive support at the local level.

In the longer term, consideration should be given to tackling the gradual increase in susceptible school-age children in London with an immunisation programme delivered to a broader age range of children and young adults.

References

Short report

Outbreak of Q fever among a group of high school students in Slovenia, March-April 2007

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A group of 33 veterinary students and two teachers contracted a laboratory-confirmed Q fever infection during a training course on a sheep farm in Slovenia in March 2007. The disease is caused by Coxiella burnetii, an intracellular bacterium found worldwide in various species of farm and domestic animals.

Outbreak investigation

On 17 April 2007 the Communicable Disease Centre at the National Public Health Institute was informed about a case of Q fever in an 18 year-old student of a veterinary high school. The patient had developed high fever and a severe headache on 30 March 2007. Chest X-rays showed pneumonia. The student reported that her classmates in the same school year had been complaining about similar symptoms.

We suspected that the patient and her schoolmates might have been exposed to a common source of Q fever when attending a training course on a sheep farm (Farm A) located in the southwestern part of Slovenia in March 2007 [1]. An epidemiological investigation was launched involving all third grade students of the veterinary high school.

Epidemiological and clinical data

The patient’s high school year has 66 students. As part of their training, 45 of the students spent several hours between 5 and 23 March 2007 on Farm A, together with three teachers. They were trimming sheep’s feet, disinfecting wounds, and applying intramuscular vitamins and anti-helmintic injections as a preventive measure to healthy animals in a stable with approximately 500 sheep. Parturition time of the sheep on Farm A was from end of January to beginning of March this year.

We interviewed all individuals who had been at Farm A, and tested them for Q fever. In addition, 20 students who had not participated in the training course in March were included as a control group. One student from the control group had spent a short time on Farm A in autumn 2006. All interviewed individuals (68 altogether) had been in contact with different domestic animals at home and during school training courses at several locations.

Among 48 exposed individuals, there were 34 (71%) with high fever (38°C or more) with or without a headache. Four individuals (8%) had serious headaches only, and three individuals (6%) reported symptoms of a common cold. Seven individuals (15%) were asymptomatic. The first person to develop symptoms of high fever and headache started to feel ill on 20 March 2007.

Among the 20 control subjects (including the student who had spent a short time on the sheep farm in autumn 2006), three students reported having a prolonged cough, and one had symptoms of a common cold. Sixteen (80%) students were completely asymptomatic.

Laboratory investigation

Serum samples were collected from 63 individuals (93% of the 68 interviewees) and sent to the Institute of Microbiology and Immunology, Medical Faculty in Ljubljana. They were tested by indirect immunofluorescence (FOCUS diagnostics) for the presence of IgG and IgM antibodies to C. burnetii phase I and II antigens. A laboratory-confirmed case of acute Q fever was defined as an individual with IgM titres higher than 1:16 and/or IgG titres higher than 1:256.

Overall, the results confirmed acute Q fever in 36 individuals (57% of the 63 tested). Serum samples from 26 individuals (41%) were negative and the test result of one sample was inconclusive.

Laboratory-confirmed Q fever cases by onset of symptoms, Slovenia, March and April 2007 (n=32)*

<table>
<thead>
<tr>
<th>Date of onset of symptoms</th>
<th>Number of cases</th>
</tr>
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<tbody>
<tr>
<td>18/03</td>
<td>1</td>
</tr>
<tr>
<td>21/03</td>
<td>1</td>
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<tr>
<td>24/03</td>
<td>1</td>
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<td>27/03</td>
<td>2</td>
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<tr>
<td>20/04</td>
<td>1</td>
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</tbody>
</table>

* All cases shown had visited Farm A in March 2007. The date of onset of symptoms was known for only 32 of the 35 cases.

Of a total of 48 individuals who were exposed on Farm A in March 2007, 44 were tested and 35 of those (80%) were seropositive. They are shown in the Figure by date of onset of symptoms.

Eight exposed individuals (18% of 44 tested) were not infected, and one had an inconclusive result. In the control group, none was seropositive, except for one student who visited the sheep farm in autumn 2006. The serology results of exposed versus non-exposed individuals are summarised in the Table.
Among the 36 laboratory-confirmed cases (35 exposed in March 2007 and one exposed in autumn 2006), four were asymptomatic, while the other 32 (89%) suffered from high fever, headache, chills, muscle aches, sweating and nausea. Twenty-five patients (69%) consulted a physician, and three (8%) developed radiologically confirmed pneumonia. Although 13 cases (36%) were given antibiotic treatment, only six (16%) received adequate antibiotic therapy with doxycycline, quinolones or macrolide antibiotic. At the time the treatment was initiated, the laboratory results indicating Q fever infection were not known.

**Conclusion**

The data analysis showed a significant statistical correlation between a positive serological test for *C. burnetii* and attendance of the training course on the sheep farm in March 2007 (p value <0.001). There was no significant statistical correlation between a positive test and attendance of school training courses in other places or contact with domestic animals at the students’ homes. We concluded that the sheep farm was the source of the Q fever outbreak.

**Outbreak control measures**

The first Q fever outbreak among humans in Slovenia was mentioned in 1954. Two outbreaks were described in 1985. The source of one was contact with a sheep herd; the other occurred among workers at a tannery, who were probably exposed through contact with sheep hides [2]. Further outbreaks due to contact with infected sheep were reported in 1991 and 1992 [3,4]. Between 1996 and 2005, between zero and five Q fever cases were notified in Slovenia [5].

The Communicable Disease Centre at the National Public Health Institute was collaborating with regional epidemiologists from Ljubljana and Koper, and with the veterinary high school and faculty of Ljubljana on the outbreak investigation. Further collaboration with the Department for Infectious Diseases and the Health Inspectorate at the Ministry of Health, and the Veterinary Office at the Ministry of Agriculture resulted in a cascade of public health and veterinary measures.

**Public health measures**[1]

- suspension of all student training courses and visits to the sheep farm;
- ban on selling dairy products from the sheep farm;
- improvement of sanitary conditions on the sheep farm;
- serological testing of farm employees;
- workplace risk reassessment (farm employees, forestry workers in the vicinity), in process;
- serological testing of students who had been trained on the sheep farm in 2007, final results expected;
- clinical and serological follow up of seropositive human cases, in process.

**Veterinary measures**[6]

- serological testing of animals at the sheep farm (to date 60% seropositive animals);
- re-introduction of Q fever monitoring in small and large ruminants proposed by the Veterinary Chamber;
- vaccination of animals considered, vaccine procurement in process.

The regions endemic for Q fever have never been determined in Slovenia. A joint research project is planned by public health and veterinary scientists to investigate the burden of disease in animals and humans, to determine endemic areas of Q fever in order to develop a sufficient basis for workplace risk assessments, and to determine the risk for the general population.

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<table>
<thead>
<tr>
<th>Table: Laboratory-confirmed cases of Q fever in individuals exposed or not exposed on a sheep farm in Slovenia, March 2007</th>
</tr>
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<tbody>
<tr>
<td>Test Results</td>
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<tr>
<td>---------------</td>
</tr>
<tr>
<td>Seropositive</td>
</tr>
<tr>
<td>Seronegative</td>
</tr>
<tr>
<td>Inconclusive</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Not tested</td>
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<tr>
<td>Total</td>
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</table>

* 35 exposed in March 2007 and 1 exposed in autumn 2006.
We describe a fatal case of psittacosis in a pet shop worker in Slovakia, who probably contracted the disease from exotic birds. The patient showed first symptoms in December 2005 and died in January 2006 of irreversible shock and multi-organ failure.

Infections with avian chlamydia Chlamyphila psittaci (C. psittaci), formerly known as Chlamydia psittaci, are of special significance for human and veterinary medicine [1]. Infected psittacine birds do not always show signs of illness, meaning that humans can contract infection by inhaling contaminated dust or the nasal discharges of infected but apparently healthy birds [2].

Psittacosis in humans is mainly an occupational disease: employees in poultry-slaughtering and processing plants, veterinarians, pet shop employees and farmers are the main risk groups [3]. The clinical picture can require intensive antibiotic treatment and ranges from inapparent infection to sepsis with multi-organ failure. Infected humans typically develop headache, chills, dry cough, sore throat, malaise, and myalgia with or without respiratory involvement. In addition, a severe life-threatening pneumonia with high fever and multi-organ failure may occur [4]. With appropriate and timely antibiotic therapy, the mortality is less than 1% [5].

Psittacosis occurs worldwide and is a notifiable disease in many countries [6,7]. Its incidence in industrialised countries seems to be increasing due to the importation of exotic birds. In Slovakia, however, human cases are very rare [8]. According to the annual reports of the Regional Public Health Office, only 25 human cases of psittacosis were reported between 1990 and 2006.

Case description
The case described here affected a 42-year-old woman with no underlying disease, working with psittacine birds in a pet shop. In December 2005, she suddenly became ill with hyperpyrexia and shivers, but had no dyspnoea, cough, or other influenza-like symptoms. After a three-day treatment with cefuroxime axetil, she was short of breath, had backache, a dry cough and headache, and lost her appetite. Seven days later, she was transferred to an intensive care unit and treated with various antibiotics (piperacillin sodium 4.5 g, tazobactam sodium 400 mg and ciprofloxacin 400 mg), antimycotic drugs (voriconazole 400 mg) and intravenous fluids. In addition, she was mechanically ventilated. Radiographic examination of the chest showed a severe bronchopneumonia with 90% involvement of lungs and atelectasis. Despite 12 days of antibiotic treatment, she died due to irreversible shock and multi-organ failure in January 2006. The autopsy revealed an interstitial pneumonia.

Laboratory analyses showed a mildly increased white blood cell count and red blood cell sedimentation rate. Urinalysis showed a mild proteinuria. The C-reactive protein level was high (338 mg/l). Liver function test values were mildly increased. Urine, sputum, and blood cultures were negative in the microbiological examination. A suspected chlamydial infection, based on clinical and epidemiological findings, was confirmed by serological examination. In an acute serum sample, collected on day 10 of her treatment in the intensive care unit, antibodies to C. psittaci with titres of 1:1280 (both IgM and IgA) and 1:80 (IgG) were found by immunofluorescence test, indicating acute chlamydial infection. The titres of antibodies to C. pneumoniae were lower, ranging from 1:256 to 1:64 for IgA and IgG, respectively. The serum was found to be negative for antibodies to Coxiella burnetii and Mycoplasma pneumoniae but not for antibodies to influenza B virus (a titre of 1:160 in complement fixation test).

Figure Detection of Chlamydia psittaci by PCR, Slovakia, January 2006

PCR for C. psittaci ompA; M: 100 bp ladder; 1: positive control, 2: lung tissue, 3: yolk sac inoculated with lung tissue, 10 days post inoculation, 4: Vero cells inoculated with lung tissue, 5 days post inoculation, 5: L-929 cells inoculated with lung tissue, 5 days post inoculation.
Chlamydiae were isolated post mortem from lung tissue [9]. The presence of *C. psittaci* was confirmed by immunofluorescence and PCR of the *ompA* gene encoding the major outer membrane protein (Figure) [10]. A PCR for *C. pneumoniae* was negative.

A colleague working in the same pet shop had an elevated titre (1:320) of *C. pneumoniae* IgG antibodies, but only low titers (1:80) of IgG and IgA antibodies to *C. psittaci*. She suffered from a febrile illness, which disappeared after a week of antibiotic treatment (doxycyclin and cefuroxime).

Although the birds in the pet shop were asymptomatic, pooled sera of five of the birds showed low titres of antibodies to *C. psittaci*. Autopsy of lung and spleen tissues of the sacrificed birds was negative for chlamydia in immunofluorescence and PCR.

**Conclusions**

To our knowledge, this is the first documented lethal human case of psittacosis in Slovakia. Based on the results, we suggest that exotic birds in the patient’s care in the pet shop may have been the source of the chlamydial infection. Since the clinical signs of this disease resemble those caused by other bacteria and viruses, and present as febrile respiratory disorders and atypical pneumonia, differential diagnosis is necessary.

We conclude that public and animal health authorities in Slovakia should put greater emphasis on controlling the spread of *C. psittaci* among psittacine birds and humans as well as avoiding the introduction of exotic pet birds to the country. We also conclude that clinicians should take great care to obtain a solid anamnesis when treating respiratory illness.

**Acknowledgements**

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AN OUTBREAK OF CHIKUNGUNYA FEVER IN THE PROVINCE OF RAVENNA, ITALY

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Chikungunya fever is a viral disease transmitted by Aedes spp mosquitoes. The infection is endemic in parts of Africa, South-east Asia and on the Indian sub-continent. Since 2005, large outbreaks have been reported in several islands in the Indian Ocean and in India [1]. Travellers from areas affected by chikungunya have been diagnosed with chikungunya fever in several European countries, including Italy [2], but local transmission involving mosquitoes has not occurred so far.

During the month of August, local health authorities of the province of Ravenna, Region Emilia-Romagna, Italy, detected an unusually high number of cases of febrile illness in Castiglione di Cervia and Castiglione di Ravenna, two small villages divided by a river. At the end of the month, clinical and epidemiological investigations carried out by the local Health Units in collaboration with the Region and the Reference Laboratory of the Istituto Superiore di Sanità in Rome, suggested an arbovirus as the possible cause of the outbreak. Serological testing and PCR confirmed the diagnosis of chikungunya fever. In addition, the chikungunya virus was detected by PCR in Aedes albopictus, which is considered to be the most likely vector for this outbreak.

The case definition used includes high fever and joint pain and/or rash and/or asthenia, and, for cases with no apparent link with the two initially affected villages, or with areas affected by secondary clusters, laboratory confirmation.

Number of cases
To date (4 September 2007), a total of 197 cases have been reported. Of these, 166 fulfil the case-definition criteria: 147 are from the initial outbreak area of Castiglione di Cervia or Castiglione di Ravenna, whereas 19 are from secondary clusters in neighbouring suburbs of the towns of Cesena (13 cases) and Cervia (six cases). The remaining 31 suspected cases need further epidemiological investigation (i.e. affected areas visited in the last 14 days) and/or laboratory confirmation. These cases, with no apparent link with the main affected areas, are scattered throughout the Region; their blood samples have not been tested yet.

The index case is believed to be a foreigner coming from an affected area in the Indian subcontinent and not resident in Castiglione. He arrived in Italy on June 21 and developed symptoms two days later when he was in Castiglione di Cervia. The peak of the epidemic curve occurred during the third week of August. Other sporadic cases have been recently detected in neighbouring areas, but the epidemic curve shows a decreasing trend in Castiglione di Cervia and Castiglione di Ravenna.

Clinical presentation
In the large majority of the patients, the disease was mild and self-limiting. Preliminary data from Castiglione show that fever lasted for a few days in most patients and a macular rash appeared in more than 50% of cases; however, arthralgia was intense and often persistent even after the abatement of fever. Only one death occurred, in an 83-year-old man with severe underlying conditions.

Control measures
An active surveillance system based on general practitioners and hospital emergency units was set up in the whole Region on 29 August. Implemented control measures include the use of insecticides (pyrethroids and antilarval products) in public as well as private sites within 100 metres around the residence of all confirmed and suspected cases, and communication to the public to inspire active involvement in vector control measures and general health education. A protocol on how to measure the efficacy of the control measures is being implemented.

A surveillance system for monitoring Aedes albopictus distribution has been active in the whole of the Emilia-Romagna Region since 2006. A surveillance for chikungunya infection in A. albopictus is being considered. Blood, organ and tissue donation has been suspended in the affected area, i.e. Ravenna municipality, Cervia, Cesena, Cesenatico.

References

CHIKUNGUNYA IN ITALY: ACTIONS IN AND IMPLICATIONS FOR THE EUROPEAN UNION

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The current outbreak of chikungunya fever in north-eastern Italy described above [1] marks the first recorded occasion that this virus has been transmitted by mosquitoes within Europe. Aedes albopictus (often referred to as the “tiger mosquito”) is thought to be the main vector for the current outbreak in Italy. Aedes albopictus is known to be present in areas of several European countries, including Albania, Italy, France, Belgium, Montenegro, Switzerland, Greece, Spain, Croatia, the Netherlands, Slovenia, and Bosnia and Herzegovina [2]. Although it seems likely that the vector is present in other countries as well, no surveillance data are available. Outside of Europe, cases of chikungunya fever continue to be reported from several areas in India.

The European Centre for Disease Prevention and Control (ECDC) is currently working with the health authorities in Italy, the European Commission and partners in all Member States to ensure an adequate response at EU level. Epidemiology and entomology experts were consulted in order to best estimate the risk for European citizens visiting areas where chikungunya virus is transmitted. On our website (and copied below), recommendations are given to persons visiting such areas, or for persons coming back from them and who develop symptoms (http://www.ecdc.europa.eu). A fact sheet on chikungunya, including information on the virus and the vector, and on where the disease currently occurs, is also available from the website [3].

Recommendations to visitors to areas with chikungunya transmission

As of 6 September, our main recommendation for visitors to areas where there is transmission of the chikungunya virus is to take the following measures to minimise the exposure to mosquito bites while there:

- Use of anti-mosquito devices and wearing long sleeves, especially during the hours of highest mosquito activity;
- Mosquito repellent based on a 30% DEET concentration is recommended; Before using repellents, pregnant women and children under the age of 12 years should consult a physician or pharmacist. For newborn children under three months, repellents are not recommended; instead, insecticide-treated bed nets and protective clothing should be used;
- Pregnant women, immuno-deprived people and people suffering from a severe chronic illness should consult their physicians prior to the travel in order to assess their risk and get recommendations on personal preventive measures.

Recommendations for those who return from the area

Persons who have visited any area where chikungunya virus transmission occurs, and who develop a high fever along with unexplained joint pain in the 12 days after their return are advised to seek medical attention. It is especially important for these persons to take preventive measures to reduce mosquito bites while symptomatic in order to avoid possible further mosquito transmission to others (see above).

Recommendations developed after the risk assessment carried out last year (following a large outbreak in the Indian Ocean), are still valid [4]. We therefore encourage all EU Member States:

- To raise awareness among health-care providers regarding the current outbreak of chikungunya in Italy, to stress the need to consider chikungunya fever as a differential diagnosis and to implement universal protective precautions when collecting or handling chikungunya fever suspected patient samples;
- To raise awareness of the public that on the importance of taking the above-described preventive measures to avoid mosquito bites when travelling to areas where chikungunya virus transmission occurs;
- To strengthen vector surveillance as well as vector control programmes during the mosquito season.

References


Short report

Outbreak of chikungunya in the French territories, 2006: lessons learned

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Description of the epidemic on Réunion Island

March-December 2005

On 17 March 2005, the Institut de Veille Sanitaire (InVS) launched an alert about the risk of chikungunya fever to the French territories in the Indian Ocean, based on information about an outbreak on the Comoros from the World Health Organization (WHO).

The first imported case was confirmed at the end of April, followed in early May by three autochthonous cases. These led to an intensification in monitoring through a surveillance system coordinated by the regional epidemiology unit. It relied on a combination of case reports and active and retrospective case-seeking around reported cases by the vector control team as part of their mosquito eradication activities.

The increasing burden

The first reports of atypical and serious cases and of mother-infant vertical transmission were received in late September. At the same time, mortality surveillance began, initially by an analysis of death certificates. The epidemic accelerated dramatically from 19 December 2005. At the end of December, the number of weekly cases jumped from less than 400 to more than 2,000. Strategies of surveillance and vector control had to be reviewed. The objective of surveillance then turned towards comprehensive monitoring of the epidemic and estimates of incidence. The change from one system to another entailed some communication problems, with laboratory-confirmed infection and symptoms other than fever being considered asymptomatic.

Monitoring the epidemic and estimating its impact (Réunion Island)

The epidemic peaked in early February 2006. Overall, between March 2005 and June 2006, the surveillance system estimated that almost 266,000 people (about 35% of the population) had a clinical form of chikungunya on Réunion Island [1]. In 2006, the regional health bureau processed 254 death certificates that mentioned chikungunya as a cause of death, compared with none in 2005.

At the same time, InVS epidemiologists conducted active case finding for hospitalised severe and atypical forms. An atypical form was defined as any clinical presentation requiring hospitalisation with laboratory-confirmed infection and symptoms other than fever and joint pain. A severe form was defined as a case requiring Intensive Care Unit (ICU) treatment. We identified 878 cases of atypical forms of chikungunya, including 44 maternal-neonatal, 224 paediatric and 610 adult cases. Digestive or cardiovascular disorders were the symptoms observed most frequently. Overall, 222 hospitalised adults required ICU treatment and support of at least one vital function and 11% (65) died [2].

Finally, mortality surveillance showed that the total number of deaths on the island increased with the epidemic peak. Observed mortality was significantly higher than expected for February (+33%) and March (+25%). This was no longer the case in April (+10%, not statistically significant) or May (+0%) and since June 2006, mortality has been lower than expected [3].

Situation in Mayotte

The first cases were reported in Mayotte in April 2005, and the initial epidemic phase ended in June 2005. During this period, the surveillance system set up by the health and social services (DASS) of Mayotte identified 73 suspected cases. A second epidemic wave started in January 2006 and peaked in mid-March. Over the entire epidemic period, physicians of Mayotte reported 7,290 suspected or confirmed cases. Because of the low rate at which patients sought medical care, the surveillance system allowed the follow-up of the course of the epidemic but did not reflect the real scale of the epidemic. It had to be completed by population-based studies with and without serologic antibody assays. Analysis of serum samples from pregnant women in October 2005 and in April 2006 showed that, during this period, the percentage of women who had been infected rose from 2.5 to 25%. A survey carried out in May 2006 by InVS, estimated that one quarter of the 170,000 inhabitants reported symptoms compatible with chikungunya. An InVS serosurvey at the end of 2006 showed that 38% had been infected by the virus and that, among them, one quarter reported that they did not have chikungunya, and could therefore be considered asymptomatic.

Situation in the West Indies

Both the exchanges between Réunion Island and the French districts in America and the presence of the Aedes mosquito in these areas made the introduction of the virus possible there. Measures implemented once the first imported case was reported in February 2006 were described in a plan [4] with four components:

- encouragement for all travellers returning from areas with a risk of transmission to report that they had visited such an area, even if they had no symptoms. Control measures were undertaken to take into account even the possible asymptomatic cases;
- early reporting by all healthcare professionals of suspected and confirmed cases;
- systematic intervention by mosquito eradication workers at the home of travellers and cases and reinforcement of mosquito eradication activities, associated to communication activities;
- prevention of transmission in health care settings.
Once the Indian Ocean epidemic began, nine imported chikungunya cases were identified in the French districts in America: three in Martinique, three in Guadeloupe, and three in Guayana. They remained isolated and did not lead to any secondary transmission.

**Situation in metropolitan France**

Neither the geography nor the climate of Europe is similar to those of the French overseas districts described above. Nonetheless, the main virus vector on Réunion Island, the *Aedes albopictus* mosquito, has been found in several metropolitan districts, especially along the Mediterranean coast and in Corsica. Given that nearly 300,000 tourists from metropolitan France visit Reunion Island each year, imported chikungunya cases must be quantified for assessment of the potential risk of autochthonous transmission in mainland France. Each month since the beginning of the epidemic in the Indian Ocean, InVS has extracted data from the database of four laboratories that diagnose chikungunya in metropolitan France.

Between 1 January 2006 and 31 December 2006, a total of 783 cases of chikungunya were identified [5]. The peak in February-March 2006 matched the epidemic peak in Réunion Island. Except for one case of infection associated with a healthcare procedure, no case of native chikungunya transmission has yet been reported in metropolitan France. The Minister of Health ordered that chikungunya be added to the mandatory reporting list in July 2006, with a reinforced reporting system in the in Alpes-Maritimes and Corsica as well as in the French West Indies and Guayana.

**Lessons learned from the outbreak and perspective**

**Extent of the risk associated with arboviruses in the overseas areas**

The chikungunya epidemic brutally reminded us that arboviruses are a developing health risk in overseas France because of their potential emergence or extension to new territories or the appearance of still more threatening forms.

**Need for a surveillance system appropriate for specific health risks**

The health risks associated with infectious diseases in the overseas territories of France have several particularities. Numerous vector-borne diseases are rampant there. They include malaria in Guayana and Mayotte, dengue in all the territories (with hemorrhagic forms emerging since the 1980s), Chagas disease in Guayana, West Nile disease in the West Indies, and so on. A reliable, representative sentinel network of General Practitioners is an essential basis for a reactive system for this specific health risks, but might also enrol every partner in the health care system. The chikungunya epidemic showed the importance of being able to follow in almost real time the changes in non-specific indicators related to mortality and to hospital activity, especially emergency department units. The investment of laboratories is also of primary importance to confirm emerging pathogens or the implication of well-known germs in new clinical presentations.

**Need to rely on all participants of the healthcare system in health crises**

The difficulties in the exchange of information during the epidemic highlighted the importance of collaborating with all the actors of the healthcare system, including physicians in private practice for daily surveillance and hospital staff physicians for reporting the serious and emerging disease forms, even excluding emergency situations.

**Important role of the media and the social mobilisation**

Social communication and mobilisation were absolutely necessary even for strengthening the surveillance system and for implementing control measures. The role of the media is essential, but this event underlined the difficulty of communicating with sufficient reactivity, transparency and quality in the scientific information required.

**Need for mobilising rapid expert assessment and reinforce the connection between epidemiological surveillance and research**

The chikungunya crisis illustrated the need for a broad capacity of expertise, at the local as well as the national levels. This expertise, if it is “pluralist” (that is, combines research, public health, and clinical medicine) and multidisciplinary (calling in particular on the social sciences), should allow pertinent and shared analyses of various answers to these questions. The creation in early 2007 of the Centre de Recherche et de Veille dans l’Océan Indien (Regional Centre for Indian Ocean Health Surveillance and Research, CRVOI) in Réunion Island, as a scientific interest group in which InVS participates can be considered as a regional response to this need. An international meeting on chikungunya and other arboviral emerging diseases, taking place in December 2007 in Réunion Island, should be a good opportunity to share epidemiological and scientific research points of view.

**Increasing importance of the international aspect of health surveillance**

Attention to health events occurring abroad that might affect the French population is especially important in the overseas districts, which are at the heart of regional environments whose epidemiologic risks they share and with whom they have many population exchanges. The chikungunya outbreak illustrated once again the importance of a reliable epidemic intelligence network. The Indian Ocean health crisis in 2006 led the countries of this region, including France for Réunion and Mayotte, to propose the reinforcement of the pre-existing regional network for epidemic alert and response. This project, supported by the WHO and the Indian Ocean Commission, should be operational by the end of 2007.

**References**


Chikungunya fever is an arboviral disease transmitted by *Aedes* mosquitoes. The disease was first described in 1953 in Tanzania and has since become endemic in parts of Africa, Southeast-Asia and on the Indian sub-continent [1-5]. Chikungunya virus (CHIKV) is an alphavirus belonging to the family Togaviridae which has a single-stranded RNA genome, a 60-70 nm diameter capsid and a phospholipid envelope. The Makonde name 'chikungunya' means 'that which bends up' and refers to the stooped posture many patients develop as a result of painful and invalidating polyarthralgia commonly associated with the disease [1]. While in the past chikungunya was not generally considered to be a life-threatening disease, recently a substantial number of deaths (254) have been attributed, directly or indirectly, to this virus [2]. Some patients with a confirmed CHIKV infection developed severe clinical signs (i.e. neurological signs or fulminant hepatitis) that justified hospitalisation in an intensive care unit. Cases of neonatal encephalopathy and major aligic syndrome associated with vertical transmission of the virus were also reported [3,4].

CHIKV has been imported to Europe (France, Germany, Switzerland, Italy and Norway) by infected travellers returning from tropical areas with high incidence rates, and *Aedes albopictus* has been introduced into several European countries (Albania, Belgium, Bosnia, Croatia, France, Greece, Italy, Montenegro, The Netherlands, Serbia, Slovenia, Spain and Switzerland)* [6-9]. So far, none of the imported cases has resulted in subsequent transmission of the virus. But, it has been suggested that if viraemic patients arrive in Southern Europe during the summer they could cause a European outbreak [8,10]. Currently, an outbreak in Northern Italy has attracted much attention as the first autochthonous CHIKV European outbreak [8,10]. Currently, an outbreak in Northern Italy has attracted much attention as the first autochthonous CHIKV European outbreak [11].

For disease control in the borderless European Union early recognition and efficient diagnostic methods are indispensable. Therefore, external quality assurance (EQA) studies of diagnostic methods are important to increase the awareness of emerging diseases and to establish and evaluate appropriate detection assays. In June 2007, the European Network for Diagnostics of Imported Viral Diseases (ENIVD) started an EQA analysis of both serological and molecular diagnostics used for CHIKV detection. Here we give preliminary results regarding the laboratory capacity and diagnostic quality for detection of CHIKV infections in Europe.

**Methods**

Since sensitivity and specificity of the often used in-house serological tests (immunofluorescence assay, plaque reduction neutralisation assay, hamaglutination inhibition assay, ELISA) and PCR (real-time PCR, nested-PCR) [1] are poorly evaluated, two proficiency panels with test samples were generated to assess the quality of CHIKV diagnostics. For the EQA of serological diagnostics, each participating laboratory received a panel of 12 coded lyophilised samples comprising samples positive for antibodies against CHIKV and negative controls. All used human sera were diluted before being freeze dried in aliquots of 100 µl as described previously [12]. For the EQA of molecular diagnostics, panels were generated by diluting inactivated virus stock solutions. The panels comprise samples with different CHIKV strains (from Réunion, India, Seychelles, Mauritius and East-Africa) including a dilution series for evaluation of the assay sensitivity, and negative control samples. Supernatants from chikungunya infected cell cultures were inactivated by heat and gamma irradiation before being aliquoted and freeze dried as described previously [13]. The participants in each of the EQA parts were asked to analyse the material provided using the procedures routinely used by them in suspected human cases. Assay details, such as the type of methods used, protocols, references and suppliers of commercial kits (if any), were requested. Rates of <70% correct classified results were considered as a bad performance.

This EQA analysis was advertised as a study on diagnostic proficiency run by the ENIVD, including publication of the results in a comparative and anonymous manner. Participation was open and free of charge to all laboratories performing CHIKV diagnostics. Selection of invitees was based on the register of ENIVD members, on a further announcement done by the World Health Organization (WHO) as well as on the contributions of the participants to the literature relevant to this topic.

**Preliminary results**

A total of 24 laboratories from 15 European countries – Austria (1), Belgium (1), Denmark (1), France (3), Germany (5), Greece (1), Ireland (1), Italy (2), Norway (1), Portugal (1), Slovenia (1), Spain (1), Sweden (1), Switzerland (2) and The Netherlands (2) – participated in at least one part of EQA (20 expert laboratories for PCR and 18 expert laboratories for serology) by sending back their results within 69 days after receiving the samples.

**PCR**

The analysis of the results revealed considerable variations in sensitivity and specificity for the PCR. While most laboratories showed sufficient sensitivity and specificity (16/20) some (4) had general problems with low sensitivity and specificity showing failures in detection of viral loads well above any known detection limit (>29,000 RNA copies per millilitre) and/or detection of different CHIKV strains. However, only one laboratory showed a false positive result in a negative sample indicating contamination during the PCR processing.

**Serology**

For serology we found even greater differences between the results of the various laboratories, probably partly due to the different assays used. Of 14 laboratories that performed analysis for IgM/IgG, eight showed a good result for both IgM and IgG.

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while others detected only sera with a high IgM titre. Of the four laboratories that did only serology for IgG three showed a rather good performance whereas one laboratory had a low sensitivity and specificity and showed <70% of correct results. Fortunately, none of the participating laboratories showed false-positive reactions from cross-reactivity with antibodies against viruses other than CHIKV.

**Conclusion**

Preliminary results of this first EQA analysis revealed considerable variations in both availability and performance of CHIKV diagnostics across Europe. Capacity for detection of CHIKV seems to be much lower in Eastern Europe compared to the West. Of the 10 Member States that joined the European Union in 2004, only one laboratory in Slovenia took part in the evaluation. In the rest of Europe, however, we found a wide distribution of laboratories performing CHIKV diagnostic, even though some did less well than others.

The great variation in the performance of the different laboratories presents a similar picture as found in EQA studies performed for other rare and/or exotic viruses like Hanta or Dengue [14-16]. This was the first EQA study for CHIKV. Several laboratories started to diagnose it with lack of experience and missing assay evaluation, which may explain the great diversity of the results. The final evaluation will show which of the PCR and serology assays used perform best with highest sensitivity and specificity. All laboratories with a bad performance were immediately informed and improvements suggested.

A possible solution to overcome the mentioned gaps is to share diagnostic capacity within Europe (i.e. send specimens to expert laboratories abroad), as it is done in the case of other rare diseases. The task of coordinating this belongs to ENIVD. Whether diagnostic capacity regarding CHIKV needs to be enlarged in the future will very much depend on the development of the epidemic situation. Growing risk of infection for people travelling to new and/or enlarged CHIKV endemic areas as well as the spread and establishment of *Aedes albopictus* in Europe may considerably increase the demand for efficient diagnostic of chikungunya fever in the coming years.

Information on ENIVD and CHIKV is available on the public website at: [http://www.enivd.org](http://www.enivd.org)

Users can also find there an overview on all diagnostic tests performed by the network, recommendations for laboratory procedures and fact sheets of important emerging and re-emerging viral diseases.

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* Authors correction

In the second paragraph, Portugal was erroneously listed among European countries where *Aedes albopictus* has been introduced. This was corrected on 27 September 2007.

**References**


Short report

Outbreak of trichinellosis in north-western Poland, June 2007

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An outbreak of trichinellosis is ongoing in Zachodniopomorskie voivodeship (West Pomerania), a province in north-western Poland bordering Germany, and has to date affected 201 people. The outbreak was first notified to the local public health department in Kamien Pomorski on 9 June 2007. Four patients were hospitalised with clinical symptoms suggestive of infection with *Trichinella* larvae – fever, joint pain, periorbital and facial oedema, vomiting, stomach-ache and headache. The first results of the epidemiological investigation showed a link between illness and consumption of raw pork meat and meat products that had been produced in one meat processing plant and were sold in shops.

The highest number of suspected cases was reported during the first week of the outbreak between 11 and 17 June – in total 122, including 43 hospitalised patients. By 2 July, the number had increased to 201 people, 73 of them were hospitalised. The initial diagnoses were based on clinical symptoms. Serological tests are now being conducted by the Department of Medical Parasitology at the National Institute of Hygiene, Warsaw. To date, 60 serum samples have been examined; of those, 28 were IgG anti-*Trichinella* positive and five had an equivocal (+/-) result. Leftover pork is being examined for *Trichinella* larvae by the National Veterinary Research Institute, Pulawy.

A single producer who delivered meat products to shops in different towns in Zachodniopomorskie voivodeship could be identified as the source of the outbreak. This meat processing plant was closed on 15 June, and all meat products produced there in May and June have been recalled from shops and storehouses. Consumers from the voivodeship territory were informed by the Voivodeship Sanitary Inspection about the necessity of returning or destroying the suspect products. Announcements were posted in shops, in which meat products from the implicated factory were sold. Moreover, the information was announced in the local media.

A message was sent through the Early Warning and Response System (EWRS) and the rapid alert system for food and feed (RASFF) in the middle of June to inform other European Union countries about the ongoing outbreak of trichinellosis in Poland. None of the meat products from this plant have been exported to other countries. During the investigation, the local epidemiologists were informed of linked cases in Ireland and Germany who had been visiting relatives in Poland.

**Outbreak of Trichinellosis in North-Western Poland – Update and Exported Cases, June–July 2007**

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**Cases in Poland**

Last week, we reported an outbreak of trichinellosis in West-Pomerania, Poland, that had involved 198 cases (excluding exported cases) as of 2 July [1].

From 2 to 17 July, 16 additional cases of trichinellosis were registered in Poland, bringing the total number of people infected in this outbreak in Poland to 214, as of 18 July. Due to serious clinical symptoms, 81 patients were hospitalised.

Serological examinations on 119 of the Polish patients were performed in the National Institute of Hygiene (NIH) in Warsaw, using an in-house ELISA test with excretory-secretory *Trichinella* antigen. The results for 73 samples were positive, and seven samples gave equivocal results. In one case *Trichinella* larvae were found in a muscle tissue sample.

Molecular examinations were performed to determine the species of *Trichinella*. The result of these examinations indicated *Trichinella spiralis* as the cause of the outbreak.

**Exported cases**

Several other cases linked to this outbreak of trichinellosis have occurred in other European countries.

Two cases were reported in Ireland in a couple that had visited their relatives in West-Pomerania in May. More information can be found in the accompanying article ‘Importation of Polish trichinellosis cases to Ireland, June 2007’ in this issue of Eurosurveillance [2]. Three further linked cases were found in a family in Germany who had travelled to Poland at the end of May, and are described in the accompanying article ‘Cluster of trichinellosis cases in Germany, imported from Poland, June 2007’ [3].

In addition to this family cluster, a fourth German case has been reported to the Public Health authorities in Hamburg, Germany. The patient had visited relatives in West-Pomerania for a week in mid May together with her family. During her stay, she consumed raw pork sausage bought in a local butchery, whereas her family members did not. From the end of May, she started to develop symptoms of fever, myalgia and periorbital oedema. About one month later, trichinellosis was diagnosed by proof of elevated antibody titres against *Trichinella* spp.

A fifth suspected case occurred in North Rhine-Westphalia, Germany. A man who had visited relatives in West-Pomerania for three days in mid May developed symptoms of trichinellosis 19 days after his return to Germany, such as facial and periorbital oedema, myalgia and conjunctivitis. He was admitted to hospital on 10 June. During his stay in Poland he had consumed raw pork sausage.

**References**


Importation of Polish Trichinellosis Cases to Ireland, June 2007

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A Polish national in his late 20s presented in June to the emergency department of a hospital in Dublin. He had suffered from fevers, periorbital swelling, conjunctival injection, myalgia and diarrhoea for the preceding ten days. The patient had been living in Ireland for the past year but returned to north-west Poland for holidays in April 2007. During his stay he purchased and consumed lightly-smoked pork sausages. He first consumed some of the sausages in the beginning of May and returned to Ireland a week later.

By the end of May he began to feel unwell and noticed that his eyes began to swell and he developed conjunctivitis. He attended an ophthalmologist who diagnosed a viral conjunctivitis. The following day he developed a high-grade fever, diarrhoea and pains in his legs. He also complained of a dry cough. His general practitioner treated him with chloromycetin eye drops and co-amoxiclav for three days with no resolution of symptoms. He was then referred to hospital for further investigation.

The patient indicated that the Polish radio had reported an outbreak of trichinellosis in the region of Poland that he had visited [1,2,3]. As a result of this, and based on his clinical presentation and characteristic blood investigations (eosinophilia, elevated muscle enzymes), a presumptive diagnosis of trichinellosis was made. Serum samples were sent for detection of anti-Trichinella antibodies, and treatment was commenced with mebendazole. The patient’s Polish fiancée who had travelled to Poland with him and consumed some of the sausages, was also ill with similar symptoms and following appropriate investigations was started on mebendazole. The serology results for both patients were obtained by the end of June and confirmed by an indirect fluorescent antibody test for *Trichinella* of >512 from the Hospital for Tropical Medicine in London.

Public health investigation

After the first case presentation appropriate contact was made with the relevant authorities within the Health Protection Surveillance Centre (HPSC) and the Department of Public Health in Dublin [4]. HPSC confirmed the outbreak of trichinellosis in north-west Poland with the Polish authorities. Preliminary investigations point towards sausages produced from uncooked pork meat as the source of the outbreak. The product is not for sale in Ireland. However, the index case brought some of the sausages with him on his return to Ireland.

In addition to the index case and his fiancée, there were two female members in the Irish household. However, neither had consumed the sausage and it was not eaten by anyone other than the index case and his fiancée. None of the sausage was available for testing.

All accident and emergency consultants, ophthalmologists and general practitioners in the Health Service Executive Eastern area were alerted to the possibility of similar cases occurring in individuals entering the country from Poland who may have consumed the contaminated product.

An alert was also sent to the Polish community in Ireland through Ireland’s Polish language weekly newspaper.

References


Citation style for this article: Lévy-Bruhl G, Paty M, Antoine D, Bessette D. Recent changes in tuberculosis control and BCG vaccination policy in France. Euro Surveill 2007;12(9):E070913.3. Available from: http://www.eurosurveillance.org/ew/2007/070913.asp#3
In this article we describe the clinical presentation of a cluster of trichinellosis cases in a German family.

Trichinellosis is caused by Trichinella spiralis and other closely related species and has a worldwide distribution. Humans, as well as other mammalian species, become infected when eating raw or undercooked contaminated meat [1]. Over the last years no reports of trichinellosis in domestic animals were documented in Germany, while cases have been reported from Lithuania and Poland until 2004 [2].

Treatment and clinical development

Two patients, father and daughter, presented to our infectious disease clinic at the end of June, complaining of severe muscle pain, abdominal pains, swelling of the face and low grade fever. They reported visiting the town of Bytow in Poland about four weeks earlier where they bought and consumed pork meat and sausage in a local butchery. On the way, they also bought sausage in the city of Nowogard in West-Pomerania.

Trichinellosis was suspected on the basis of the clinical presentation and history. A marked eosinophilia was detected in both patients and the father also showed highly elevated liver (ALAT/ASAT 259/348 U/L) and muscular (CK 6000 U/L) enzymes as a sign of hepatitis and rhabdomyolysis. Both patients were treated with albendazole. Due to the severity of symptoms the father was also given prednisolone.

The patient informed us that his wife had been admitted to a hospital with fever, diarrhoea, abdominal pain and myalgias and was treated with broad spectrum antibiotics. She was transferred to our hospital with signs of hepatitis and rhabdomyolysis, and eosinophilia (eosinophils 51%, 6300/µl). Her electrocardiogramme (ECG) on the day of admission was normal, but when albendazol and prednisolon treatment was started on the next day, the ECG showed irregularities. On the same evening, she collapsed, had a cardiac arrest and had to be resuscitated. She was transferred to the intensive care unit where she was monitored until the antiparasitic therapy had been completed.

The clinical diagnosis was confirmed by serological testing in all three patients on 28 June (two days after collection of samples). All patients showed elevated antibody titres against T. spiralis in enzyme-linked immunosorbent assay (ELISA) and immunoblot. The commercial ELISA (DRG Diagnostic) uses an excretory-secretory antigen obtained from T. spiralis larvae whereas the Western Blot contains crude larval extract antigen. These results may also support an infection with Trichinella spp. other than T. spiralis. Due to the clear clinical picture, together with the serological results, further diagnostic procedures were not initiated. The Trichinella species that caused the infection was therefore not identified. After completion of antiparasitic therapy all three patients fully recovered.

Discussion

The clinical picture of trichinellosis is directly related to the number of larvae ingested and has two clinical stages: the intestinal stage and the muscular stage. Larval migration into the muscles can cause facial oedema, subungal, conjunctival and retinal haemorrhages, muscle pain, weakness, and fever [3]. The tropism of T. spiralis for striated muscle can cause the myocardium to be affected in 21–75% of infected patients. Complications such as cardiac arrhythmias are considered the most common cause of death associated with trichinellosis [4]. T. spiralis-associated myocarditis is not caused by direct invasion and encystation of larvae in the myocardium but is probably induced by an inflammatory response resulting in eosinophilic myocarditis [5].

The clinical suspicion of trichinellosis is based on the epidemiology associated with the typical clinical presentation and the presence of eosinophilia. Confirmation is based on serology and, if those results are equivocal, on muscle biopsy. The treatment consists of the administration of albendazole or mebendazole in conjunction with steroids for severe cases.

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A 59-year-old Danish woman presented to her general practitioner (GP) at the end of June. A few weeks earlier, during a meal at home in Denmark, she had consumed a slice of pork sausage (‘teewurst’, German sausage) brought to her by three Polish visitors. Later she learned that one of her guests had fallen ill, and that two of them, including the one who had fallen ill, were shown to be seropositive for trichinellosis. When the woman contacted her GP and submitted a blood sample for serological analysis, she had no symptoms. The initial ELISA test was positive, and seropositivity for trichinellosis was confirmed by immunoblotting. The woman subsequently received treatment with a high dose of mebendazole.

A son of the woman and two other adults who are thought to have also consumed the sausage are currently being tested for trichinellosis; so far none of them have reported any symptoms.

This summer, an outbreak of trichinellosis in Poland affecting over 200 people has been described [1]. Cases in Ireland [2] and Germany [3] have also recently been reported. This is the first case in Denmark that could be related to the Polish outbreak.

A note on this case was published in the news section of the website of Statens Serum Institut (http://www.ssi.dk).

References


Short report

Salmonella Kottbus outbreak in infants in Gran Canaria (Spain), caused by bottled water, August-November 2006

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Introduction
Since October 2006, the Spanish National Reference Laboratory has reported a series of isolations of Salmonella Kottbus on the island of Gran Canaria [1]. The fact that most of the cases were in infants under one year of age and needed hospitalisation, caused significant concern among the general public. Information published in the media contributed to this alarm.

Outbreaks due to this Salmonella serotype are rare in the literature with only five outbreaks published since 1959 [2-6]. No cases of Salmonella Kottbus had been isolated and reported in Spain since 1996 [7,8]. We decided to conduct epidemiological and environmental studies to describe the characteristics of the cases and to determine the possible source of infection.

Methods
During October and November 2006, we actively searched for and collected information on cases. We designed a matched case-control (1:2) study that was conducted while cases were still occurring. A case was defined as an infant under one year of age with gastroenteritis and with laboratory confirmed Salmonella Kottbus. Controls were selected from among healthy children that had visited the same paediatrician as the cases for a regular consultation, and were matched by age, sex, date of consultation and address.

We interviewed parents on food and drinks consumption of the children using a trawling questionnaire including questions about breastfeeding and consumption of vegetables, dairy products, meat, fish, etc. To identify risk factors, bivariate analysis and conditional logistic regression were used to calculate crude odds ratios (OR) and Mantel-Haenszel odds ratios (MH-OR).

Results
Of 46 identified and confirmed cases, 41 were included in the study and the rest declined to participate or were not found. The average age was five months (95% CI 2.5-7.5), and 27 of those 41 cases (66%) were male. Nineteen cases (46%) had underlying diseases or were immunocompromised (e.g. previous infectious diseases, neurological pathologies, and newborn pathologies such as gastric reflex, lactose intolerance, low birth weight, premature birth, etc.). The geographical analysis showed that the cases were distributed along the island following one of the main highways (Figure 1).

Figure 1
Spatial distribution of Salmonella Kottbus cases, Gran Canaria, August to November 2006
All cases occurred in 2006 between weeks 34 and 45. The epidemic curve suggested a continuous common source (Figure 2).

The case-control analysis identified a statistically significant association with the consumption of locally produced bottled water (without gas) (OR=8.04; 95% CI 2.24-43.3) and natural fruits (OR=0.04; 95% CI 0.005–0.44). The conditional logistic regression showed an MH-OR of 36.3 (95% CI 3.18-414.4) for water consumption, adjusting for age, sex, date of consultation, address and fruit consumption.

A carrier pigeon loft was found near one water reservoir of the local factory and we could verify that pigeons frequented this reservoir. Microbiological and environmental analysis detected *Salmonella* Kottbus in bottles randomly selected from markets, and also in the local factory where the water was bottled. Moreover, *Salmonella* sp. was detected in the pigeons.

**Discussion and conclusion**

This is the first published outbreak of *Salmonella* Kottbus associated with commercial bottled water in Spain and Europe. A significant proportion of patients had concomitant diseases, which may explain why this group was affected so strongly.

The spring may have been contaminated by pigeons that used the water deposit as a watering place.

The implicated brand of water was for local distribution only and was sold in different supermarkets on Gran Canaria. As a consequence of the investigation, the factory was closed down, all supermarkets were informed and the bottled water was recalled. Public Health authorities inspected the markets over several days to verify the recall.

In future studies we suggest the inclusion of bottled water as a possible source of *Salmonella* infection, especially in certain risk groups, and to consider including detection of *Salmonella* in water controls.

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