Vol. 12 · Issues 3–6 · Apr–Jun 2007

Eurosurveillance

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EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Vol. 12 · Issues 3–6 · Apr–Jun 2007

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Peer-reviewed European information on communicable disease surveillance and control

Eurosurveillance

Editorial Team
Based at the European Centre for Disease Prevention and Control (ECDC), 171 83 Stockholm | Sweden

Telephone Number:
+46 (0) 8 586 01138 or +46 (0) 8 586 01136

Fax number:
+46 (0) 8 586 01001

E-mail:
Eurosurveillance@ecdc.eu.int

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The Eurosurveillance print edition is a compilation of weekly and monthly electronic releases published on the Eurosurveillance website. Only a representative selection of Eurosurveillance's weekly release articles from each three month period are printed here, and the full listing of all Eurosurveillance articles can be found in the Archives section of the website.

Editorial

New eyes: improving Europe's infectious disease surveillance

Darina O'Flanagan (Darina.OFlanagan@mailx.hse.ie), Health Protection Surveillance Centre (HPSC), Dublin, Ireland

"The real voyage of discovery consists not in seeing new landscapes, but in having new eyes." Marcel Proust

This edition of Eurosurveillance contains reports of infectious disease surveillance systems from all corners of Europe. In some instances, routinely collected notifiable data coupled with microbiological data can provide sufficient information to allow appropriate public health intervention. In other instances, as described below in the pertussis paper, a period of active case finding is required to provide the basis of a comprehensive assessment of the changing epidemiology of an infectious disease [1]. For rapid assessment of incidence, sentinel systems from a sample of general practices can provide timely information, particularly in those diseases where most cases are not routinely tested microbiologically (e.g. influenza). As the papers here indicate, we need to continually evaluate our systems and ensure they are fit for purpose.

The report from Cyprus on a pertussis outbreak in 2003 demonstrates the effectiveness of an active reporting surveillance system. All paediatricians were recruited to report on a weekly basis on all suspected pertussis cases of any age. If no report (including zero reports) were received, the paediatricians were reminded by telephone. This active surveillance system resulted in the detection of an outbreak of 128 cases, 24 of which were laboratory-confirmed by the detection of positive *Bordetella pertussis*-specific IgA. Two thirds of the confirmed cases were aged between 10 and 20 years. While 13 of the confirmed cases (54%) were correctly vaccinated with five doses as in the Cypriot schedule, 23 of the 24 confirmed cases had received their last immunisation over four years previously. The outbreak was controlled within one month by a combination of Erythromycin chemoprophylaxis for close contacts and vaccination boosters for close contacts who were considered not to be fully immunised.

"The real voyage of discovery consists not in seeing new landscapes, but in having new eyes"

In most European countries, pertussis is a notifiable disease. However, the consensus is that the under-reporting of the routine surveillance system identified in Cyprus is a common problem worldwide [2]. A prolonged cough may be the only feature in teenagers and adults. Primary care physicians may be unaware of this atypical presentation and neither diagnose nor report. In addition, the variation in the use of diagnostic tests for pertussis in Europe may influence the sensitivity of testing, e.g. routine services for serological testing are frequently not available and while PCR tests are more sensitive than culture these methods are not universally applied [3]. Waning immunity in fully immunised individuals coupled with incomplete immunisation in some individuals, as in this study, is considered responsible for the shift in age distribution to older age groups. This has prompted the United States and some European countries to introduce an additional pertussis booster in adolescence. Interestingly, after this period of intensive active surveillance by paediatricians, the Cypriots have now moved to syndromic surveillance of pertussis by general practitioners. It will be interesting to see if, having sensitised the general practitioners to the changing epidemiology of the disease, this system is as efficient in detecting pertussis outbreaks promptly.

Two papers in this month's edition examine the surveillance of influenza. The paper from the Spanish Influenza Surveillance System ascertains to what extent the system meets guidelines currently being drafted by the European Influenza Surveillance Scheme. Sentinel physicians sent an impressive number of swabs on 11.5% of cases meeting the case definition for influenza-like illness. This figure exceeded the draft target set by EISS for 10% of cases swabbed. However, further discussion of the rationale for such a target would be welcome from EISS. Younger patients, males and vaccinated patients were more likely to be swabbed in the Spanish system. It is clear that an increasing number of regions in Spain are contributing to the system and, as in many other European countries, continuing audit bodes well for improvements in the surveillance of influenza.

The paper, from the United Kingdom (UK) looks at outbreaks of influenza and influenza-like-illness in schools in England and Wales in 2005/06. Despite relatively low influenza activity overall, the Centre for Infections (CfI) of the Health Protection Agency (HPA) in the UK started to receive reports in January 2006 of outbreaks of respiratory illness in school children. In response, CfI requested weekly reporting of outbreaks in schools through HPA health protection units. Six hundred and eighty-eight school outbreaks were identified and in 70 Influenza B was confirmed. The HPA is now exploring the feasibility of collecting absence data from schools on a regular basis to supplement the general practitioner influenza surveillance system and the data collected in the nurse led telephone advice system NHS Direct.

This report demonstrates the considerable morbidity associated with Influenza B epidemics causing major disruption to the educational system. The separate reporting of three associated deaths in the UK demonstrate that Influenza B infection is not as benign as often portrayed.

The incidence of Beijing genotype of *Mycobacterium tuberculosis* is studied in a 13-year look back at 332 isolates in the Elche region of Spain. A recent review has highlighted the importance of this emerging pathogen in several areas and its association in some areas with drug resistance [4]. In Estonia, the Beijing strain is reported in 29% of cases, where it is strongly associated with resistance to all tested drugs. In Western Europe, Beijing

genotype is more common among immigrant TB patients than among indigenous patients. In the Spanish Elche study reported here, only one isolate of the Beijing strain, with no resistance was identified, in a patient originally from Senegal. None of his close contacts who were placed on chemoprophylaxis developed tuberculosis during follow-up. While the data presented here is reassuring, population movements in Europe warrant continued vigilance in relation to the further emergence of this pathogen.

Trends in meningococcal disease in Poland and improvements to the surveillance system are described in a paper by Olga Gryniewicz et al. While there is a relatively low incidence by European standards, a recent increase in the proportion of cases caused by serogroup C has caused concern. Monitoring of all types of invasive meningococcal disease started in 2005 using a slightly modified case definition from the European Centre for Disease Prevention and Control (ECDC). At present, data from the National Reference Laboratory is not merged with the epidemiological notification data. The authors recognise the need to obtain more complete serogroup data. Diagnosis by molecular methods has only recently been applied to meningococcal disease and it can be expected that this will contribute to improved case ascertainment in the future.

A paper from Semenza and Nichols looks at the incidence of cryptosporidiosis as reported by 16 European countries in 2005. Ireland and the United Kingdom have the highest reported incidence rates. However, the authors advise that the extent to which routine diagnostic laboratories screen for cryptosporidiosis is unclear and it is likely that there are substantial differences in ascertainment between countries. Evidence from the North- West of England is reported to show substantial reductions in the number of cases following improvements in drinking water treatment. The report demonstrates the power of good surveillance data in targeting resources to achieve control of this potentially severe disease in the young the elderly and the immunocompromised.

Finally, an evaluation of two surveillance systems for sexually transmitted infections (STI) in the South-West region of England rings true for many of us involved in national surveillance of sexually transmitted diseases. Aggregate data from the genito-urinary medicine clinics was neither timely nor representative of all diseases diagnosed in the community. While the laboratory data was timelier, the information was inadequate to assess risk factors that could enable targeted interventions. The authors describe developments in Scotland, where a web-based surveillance system allows real time secure data collection and validation. Ideally, the merging of laboratory and clinical data provides the best surveillance data, but concerns around data confidentiality have traditionally hampered progress in this regard with STI data. However, as the authors say, varying access limitation can overcome issues of confidentially. As described in this paper, many European countries have seen dramatic increases in the number of cases of STIs in recent years. The scale of the problem merits better surveillance and this paper points the way forward.

Europe is undergoing a period of unprecedented change, with more of us travelling further, faster and more often than ever before. New and emerging diseases present a real and current challenge to all of us charged with health protection. However, with developments in the pipeline from ECDC (such as TESSy – The European Surveillance System) and information technology allowing web-based real time collection and feedback of analysed data, we will be in a better position to meet these challenges and enable the more effective targeting of resources and prioritisation of interventions.

"Good surveillance does not necessarily ensure the making of the right decisions, but it reduces the chances of wrong ones." Alexander Langmuir 1963.

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Citation style for this article: O'Flanagan D, . New eyes: improving Europe's infectious disease surveillance. Euro Surveill 2007;12(5)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n05/1205-221.asp

Outbreaks of influenza and influenza-like illness in schools in England and Wales, 2005/06

H Zhao (hongxin.zhao@hpa.org.uk)[1], C Joseph[1], N Phin[2]

1. Respiratory Diseases Department, Health Protection Agency Centre for Infections, London, United Kingdom
2. Cheshire and Merseyside Health Protection Unit, Chester, Cheshire, United Kingdom

In England and Wales, clinical reports from primary care showed that influenza activity for the season 2005/06 only rose above the base line for four weeks during February 2006. However, outbreaks of influenza-like illness and/or gastrointestinal infection in schools began to be reported to the Health Protection Agency, Centre for Infections in early January 2006. To quantify the type, size and the spread of these outbreaks a reporting form was distributed to local Health Protection Units in England and to Wales for retrospective and prospective weekly completion. Between weeks 48/05 and 11/06, a total of 688 school outbreaks were reported, including 658 outbreaks of influenza-like illness with or without other symptoms. The remaining 30 outbreaks listed as gastrointestinal only were excluded from the present analysis. Influenza B was confirmed in 70 outbreaks where testing took place. 61% of the outbreaks were reported from primary schools for children aged 4-11 years. This large scale outbreak in school children with flu-like illness across England and Wales was not picked up by most of the routine surveillance schemes, therefore, we believe that a school absentee monitoring and reporting system may be needed to give an early warning of increased influenza activity, especially for the mild form of the disease caused by influenza B virus.

Introduction

An analysis of the hospital- and community-based data on influenza activity in England and Wales during 2005/2006 showed a season of relatively low activity. However, from week 03/06 the Centre for Infections (CfI) of the Health Protection Agency (HPA) started to receive reports of respiratory outbreaks involving large numbers of school children. The magnitude and number of school outbreak reports were not reflected in the weekly data from the routine influenza surveillance systems, nor were these reports collected on a routine basis. In order to assess the type, size and extent of these school outbreaks, the CfI influenza surveillance team requested that national weekly reporting of outbreaks through HPA Health Protection Units be carried out.

Methods

A weekly reporting form was distributed through regional epidemiologists to all local Health Protection Units (HPUs) so that data could be systematically collected and collated centrally. The form was sent out during week 6 (week commencing 06/02/2006) and the data collection activity finished in week 12 (week commencing 20/03/2006). The HPUs were requested to use this data collection form to report all respiratory outbreaks that occurred in any type of school in England and Wales, including infant schools or nurseries (children aged younger than 5 years), primary schools (aged 4-11 years), secondary schools (aged 11-18 years), boarding schools (aged 2 -18 years) and special education needs (SEN) schools (aged 2 - 19 years). The completed forms were to be returned to the CfI influenza surveillance team every Monday, with data covering the previous week. In addition, retrospective data was requested, as were updates of outbreaks previously reported. The reporting form included the name and address of the school where the outbreak occurred, the number and age range of the enrolled and affected children, the date of onset of the first case in the outbreak, the range of symptoms reported, the average duration of illness and the results of laboratory analysis of any respiratory

Table 1

Geographic distribution of respiratory outbreaks in schools in England and Wales during the 2005/06 influenza season (N=658)

HPA region	Number of Outbreaks (%)	Number of Students at Risk in Schools Reporting Outbreaks (%)	Number of Cases (%)	Overall Attack Rate (%)
West Midlands	221 (33.6)	83228 (37.5)	19189 (36.0)	23.1
South West	128 (19.5)	41339 (18.6)	7251 (13.6)	17.5
South East	122 (18.5)	33300 (15.0)	13819 (25.9)	41.5
North East	70 (10.6)	24396 (11.0)	4436 (8.3)	18.2
London	45 (6.8)	6142 (2.8)	956 (1.8)	15.6
Yorkshire and Humberside	41 (6.2)	21430 (9.7)	3124 (5.9)	14.6
East of England	12 (1.8)	5651 (2.5)	2329 (4.4)	41.2
East Midlands	8 (1.2)	1980 (0.9)	440 (0.8)	22.2
North West	7 (1.1)	2762 (1.2)	1239 (2.3)	44.9
Wales	4 (0.6)	1590 (0.7)	567 (1.1)	35.7
Total	**658 (100)**	**221818 (100)**	**53350 (100)**	**24.1**

or other samples taken during the outbreak. Data were received as an excel file and analysed weekly by region of report. Results were included in the HPA weekly flu bulletin and were made available on the HPA website for health professionals and the general public.

Results

A total of 688 school outbreaks of influenza-like illness (ILI) and/or diarrhoea and vomiting were reported across England and Wales between weeks 48/05 and 11/06, the majority of them occurring from mid-January 2006 onwards. Among the outbreaks, 201 (29%) were reported with respiratory symptoms only, 353 (52%) with respiratory symptoms and diarrhoea and/or vomiting, 30 (4%) with diarrhoea and/or vomiting only, and 104 (15%) as ILI outbreaks without listing the symptoms. The 30 outbreaks reported with symptoms of diarrhoea and/or vomiting only are excluded from the following analysis, leaving 658 outbreaks of ILI with or without other symptoms.

There was considerable variation in the number of ILI school outbreaks reported from the nine HPA regions in England, and the one in Wales, probably due to the voluntary nature of the reporting scheme. The West Midlands reported the highest number of outbreaks (244), whereas the smallest number was reported from Wales (4) (Table 1). The total number of cases associated with the outbreaks was 54,786 (from 440 in the East Midlands to 20,337 in the West Midlands; mean: 5,479, median: 2,726).

Outbreaks occurred in different types of schools but mainly in primary schools (61%, Figure 1). The most affected population was children under 11 years of age (69% of the outbreaks and 51% of the total number of cases). The mean attack rate for the outbreaks in which the number of cases and the school population size were both reported was 23% (n=553; median: 20%; range: 1% - 94%).

Taking into consideration the week of onset, it was found that the number of reports started to increase significantly from week 02/06 onwards, peaking in week 05/06 when 196 outbreaks were reported, and decreasing to 64 reports in week 06/06. In comparison, the overall consultation rates for influenza and ILI obtained from the Weekly Returns Service of the Royal College of General Practitioners (RCGP*) which is the main influenza surveillance scheme for England and Wales, for the same period, reached a peak in week 07/06 that is two weeks later than the number of school outbreak reports (Figure 2a).

The school outbreak reports peaked in week 05/06 in all regions, whereas the RCGP rates were highest in the northern region in week 03/06 (two weeks ahead), in the central region in week 06/06 (one week behind) and in the southern region in week 07/06 (two weeks behind).

The standard age groups used in UK flu surveillance are 0-4 years, 5-14 years, 15-44 years, etc. The national surveillance data for the age group 5-14 years, which are the closest match to the schools' data, were examined to check for additional evidence of the rise in influenza activity in schoolchildren. RCGP consultation rates in the age group 5-14 indeed peaked in week 06/06 and were higher than for any other age group overall in 2005/06. Data from the national health advice telephone line (NHS Direct) showed that although cold/flu calls in all age groups peaked in week 06/06, calls in the 5-14 years age group were highest compared with all other ages. Call rates for fever among 5-14 year olds peaked in

FIGURE 1

Respiratory outbreaks by type of school in England and Wales during the influenza season 2005/06(N=658)

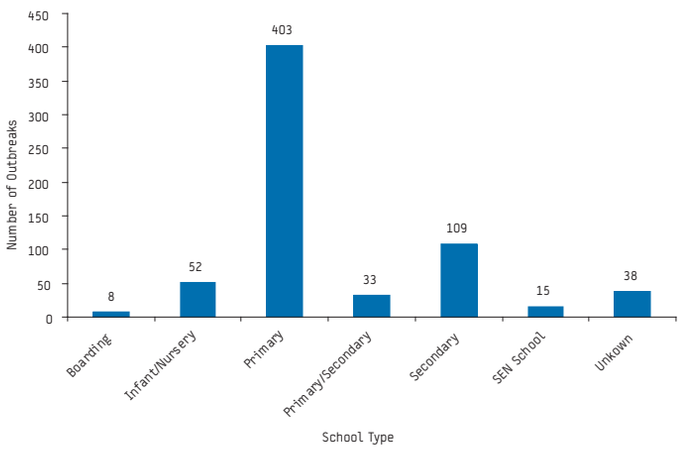


FIGURE 2A

Comparison of RCGP* rate with distribution of outbreaks in England and Wales influenza season 2005/06

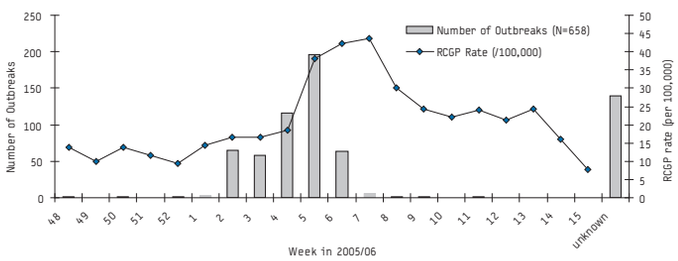
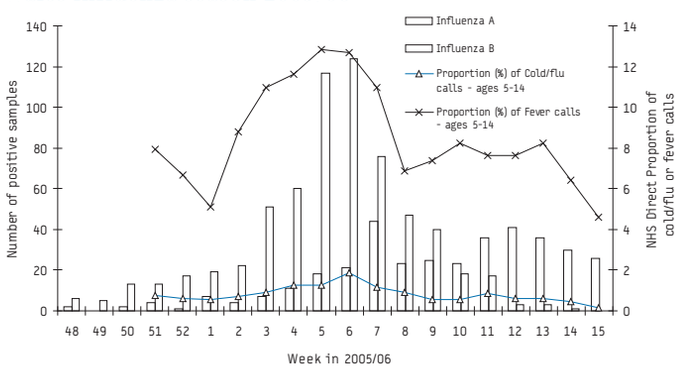


FIGURE 2B

NHS Direct call rate and virological date in England and Wales influenza season 2005/06



weeks 05/06 and 06/06 and showed the greatest symmetry with the school outbreak reports (Figure 2b).

Laboratory results

Influenza B was confirmed in all 70 outbreaks in which testing took place. Two outbreaks had both influenza A and influenza B confirmed. The predominant virus strain identified in samples from six of the outbreaks was influenza B/Hong Kong/330/2001-like virus [1] the same strain as that detected in other community settings during the 2005/06 season. The virological surveillance data [2] collected for the 2005/06 season identified influenza B as the dominant circulating influenza virus (395 out of 530 samples characterized - 74.5%). The detection of influenza B virus increased markedly from week 03/06, peaking in weeks

05/06 and 06/06 (Figure 2b). Of the influenza B viruses further characterized, 99% were antigenically similar to the influenza B/Hong Kong/330/2001-like virus. These data support the results obtained through school outbreak reporting, showing influenza B as the cause of many of the school outbreaks, and are compatible with the mild symptoms reported for the majority of children and the lack of a significant rise in overall RCGP consultation rates over the same time period. It is of note that the 2005/06 influenza B strain identified in England and Wales was also dominant in the influenza season of New Zealand between April–September 2005 [3,4] and was responsible for an influenza B epidemic in school age children in the North Island, New Zealand.

Discussion

The large number of reported school outbreaks of respiratory infection was the most significant feature of the 2005/06 influenza season in England and Wales. This occurred despite the overall GP consultation rates for influenza and influenza-like illness rising above the baseline level of 30 per 100,000 population for four weeks only, from week 05/06 until week 08/06, and peaking at 43.7 per 100,000 during week 07/06 [2,5]. There were also anecdotal reports of schools in the north of England being affected by influenza already in early December 2005, well before the more widespread outbreaks in the rest of England and Wales were reported in January and February. Influenza B was the dominant virus in circulation during the 2005/06 season and this strain is known to disproportionately affect younger age groups but is clinically less severe than influenza A infection. The age specific consultation rates between weeks 04/06 and 08/06 were highest in 5-14 year-olds, reflecting the likelihood that many of the reported outbreaks were due to influenza B infection.

Many of the school outbreaks were reported to have been complicated by the simultaneous symptoms of diarrhoea and vomiting. Together these two conditions caused large scale school disruptions and in some cases, temporary school closures. Although influenza B is a mild illness, some hospitalisations of children were separately reported, as were three deaths. School outbreaks in the southern hemisphere earlier in 2005 also recorded some high morbidity among children in New Zealand [3,4].

The school outbreaks attracted media attention nationally and locally, particularly in the West Midlands where the number of outbreaks was highest, which led to increased ascertainment of data in some regions. In contrast, some other regions reported that information on local outbreaks was difficult to obtain and so could not comply with the weekly request for information. The fact that the routine national surveillance schemes using general practice consultation data failed to detect a rise in overall influenza activity during the period of the school outbreaks meant that a significant level of influenza activity remained unnoticed. This has implications for the effectiveness with which the current surveillance system is able to give early warning of an impending influenza season or even the first wave of a future pandemic. Syndromic surveillance, such as that practised by NHS Direct with data obtained through nurse led telephone calls, may now be of greater value as an early warning system than primary care surveillance in situations where people are mildly ill or no longer choose to seek medical care and advice directly from their general practitioner.

The HPA is currently exploring the feasibility of collecting and integrating data from schools on outbreaks and illness absenteeism with the Department for Education and Skills and local HPUs, with a view to establishing within each region an early warning system of increased flu activity at the local level. The detection of a large or sudden increase in non-authorised absenteeism levels in sentinel schools through a weekly reporting system could act as the trigger for investigations into whether influenza might be the cause. These investigations would provide information early in the season, and during the season, of circulating respiratory viruses, changes in viral type and their impact on school age children. Local health protection units would have the opportunity to follow up outbreaks in these schools in real-time, and thus gather useful data at the local level that would contribute to the overall surveillance picture at the national level. The data would be obtained from age specific cohorts rather than individual patients and should provide added value over and above the data provided by consultation rates or calls to NHS Direct, since it does not rely on children seeking medical care at the individual level.

There are many limitations to this report of outbreaks in schools. As mentioned earlier, data collection was voluntary, and underreporting was in evidence. Although all HPU's were asked to report to us the information defined in the data collection form, they frequently only responded once they received an outbreak report from a school, and did not actively contact schools in their area to see whether an ILI outbreak was occurring. However, despite the underreporting, we still received an exceptionally large number of reports of school ILI outbreaks. We believe this provided a good indication that a large scale influenza B infection occurred across the country when considered together with other syndromic and virological surveillance data.

A new school surveillance system is now being piloted in England to investigate whether non-authorised school absenteeism data can be used as a proxy for influenza activity within the school setting. If successful, the data will be used as an early warning detection system for seasonal influenza and will be incorporated into weekly national surveillance for further assessment of the impact and burden of influenza in the community at large.

Conclusion

► Large scale school outbreaks of flu-like illness, most likely attributable to influenza B, occurred during the 2005/06 influenza season in England and Wales;

► The most affected population associated with these reported outbreaks were school children aged 11 years or younger, consistent with peak rates in children aged 5-14 years from RCGP and NHS Direct data;

► This increased flu activity was not detected in time or magnitude by the established national routine flu surveillance systems operating in England and Wales;

► The incorporation of data from schools on rates of absenteeism and outbreak reporting may provide an early indication of the start of the influenza season in future.

Acknowledgements

HPA's Local and Regional Services (LaRS) Division, regional epidemiologists and all HPUs who submitted the outbreak data. Also Rekha Yadav and Joy Field for maintaining and updating the outbreak database.

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Citation style for this article: Zhao H, Joseph C, Phin N, . Outbreaks of influenza and influenza-like illness in schools in England and Wales, 2005/06. Euro Surveill 2007;12(5)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n05/1205-222.asp

Characterisation of swabbing for virological analysis in the Spanish Influenza Sentinel Surveillance System during four influenza seasons in the period 2002-2006

A Larrauri (alarrauri@isciii.es), S de Mateo, and the Spanish Influenza Sentinel Surveillance System*

Public Health Surveillance. National Centre for Epidemiology, Carlos III Institute of Public Health, Madrid, Spain

This study sought to characterise the swabbing pattern in the Spanish Influenza Sentinel Surveillance System (SISSS) and ascertain to what extent the system meets the guidelines currently being drafted by The European Influenza Surveillance Scheme (EISS). Data on seasons 2002/2003 to 2005/2006 were drawn from SISSS. The study analysed collection and dispatch of swab specimens for virological analysis by reference to variables relating to patient sex, age group, vaccination status, specimen collection period, period of influenza activity, time of swabbing and epidemiological season. SISSS adapts to EISS recommendations with respect to the specimen collection period and period of influenza activity, but there is a tendency to collect fewer specimens than recommended as the age of patients increases, and in the case of elderly patients (65 years and older), frequency of collection is clearly insufficient. Furthermore, sentinel physicians collect a higher percentage of specimens in cases where patients have received the influenza vaccine.

Introduction

SISSS forms part of EISS, which covers 30 European countries [1]. Influenza sentinel systems are based on sentinel physicians reporting clinical cases due to influenza-like illness (ILI) and/or acute respiratory infection (ARI), and integrate clinical and virological data collected in the same population.

Via the sentinel systems based in its member countries, EISS ensures the timely collection of epidemiological and virological data and the weekly dissemination of such data during influenza seasons. All physicians belonging to the respective sentinel networks report diagnosed cases of influenza as per a case definition, obtain nasal or nasopharyngeal swabs, or nasopharyngeal aspirates from patients, and then send these specimens to the national reference laboratories for confirmation of diagnosis and characterisation of the influenza viruses in circulation.

EISS is drafting recommendations, which are still under discussion (Tamara Meerhoff, personal communication), to standardise the sentinel swabbing routine used in the networks. The recommendations, which EU Member States would have to adapt, refer to the population in which specimens are to be obtained; the periods in which such specimens must be collected; and the manner of collection and dispatch. This study sought to:

- Characterise the swabbing pattern in SISSS;
- Ascertain to what extent the system meets the guidelines currently being drafted by the EISS; and
- Propose any necessary corrections, where applicable.

Methods

Data on four seasons from 2002/2003 to 2005/2006 were drawn from SISSS. We included the number of influenza cases reported to this system each season by the sentinel networks that sent individualised data to the central unit (2002/2003: Aragon, Balearic Islands, Canary Islands, Castile & León, Valencian Region and the Basque Country; 2003/2004 and 2004/2005: the above-mentioned plus Castile-La Mancha, Extremadura, Navarre and La Rioja; 2005/2006: each above-mentioned Region plus Catalonia and Ceuta).

In Spain, 16 Autonomous Regions (AR) (Comunidades Autónomas) had influenza sentinel networks in place during the 2005/2006 season, accounting for approximately 90% of the population nationwide, with a total of 413 general practitioners (GPs), 125 paediatricians and 15 support laboratories. The population covered by the system in the 2005/2006 season numbered 771,133, giving an overall coverage of 1.78% of the total population of Spain's 16 AR. Similarly, all the networks complied with a series of requirements as to the minimum population covered (>1%) and representativeness in terms of age, sex and degree of urbanisation.

Clinical information was obtained from network sentinel GPs and paediatricians, who participated on a voluntary basis and submitted individualised reports of all medical visits attributable to influenza syndromes detected in their reference populations in accordance with a case definition as per the International Classification of Health Problems in Primary Care (ICHPPC-2-D) for "influenza-like illness" (context of influenza epidemic, plus four of the following criteria: onset within 12 hours of cough, fever, chills, prostration and weakness, myalgia or general pain, rhinitis, pharyngitis, contact with a case; or six of those criteria) within the surveillance periods identified as the winter seasons (usually, from week 40 of one year to week 20 of the next). For virological influenza surveillance, sentinel physicians obtained nasal or nasopharyngeal swabs or nasopharyngeal aspirates from a subset of patients, which were then sent to network-affiliated laboratories for determination of influenza virus.

The dossier collected on each case includes epidemiological and clinical data, with virological data incorporated later. These individualised data, together with the population coverage achieved, are available at the central unit within a period of 24 to 48 hours after the end of each week. This allows for swift dissemination of the information on the evolution of influenza activity in Spain,

through periodic reports that are systematically updated on the Internet (see http://vgripe.isciii.es/gripe/inicio.do).

The study analysed the collection and dispatch of swab specimens for virological analysis by reference to variables relating to: patient sex, age group and vaccination status; and specimen collection period, period of influenza activity, time of swabbing and epidemiological season. We defined the "influenza activity period" as corresponding to the epidemiological weeks of each season in which influenza incidence exceeded the baseline activity threshold, and the "influenza activity-free period" as the remaining weeks, which tend to coincide with the start and end of the surveillance seasons.

When it came to characterising the time of swabbing in the course of the epidemiological week, we defined "time of swabbing" as the difference between the date of dispatch of the specimen to the laboratory and the middle day of the relevant reporting week (Wednesday, as the epidemiological weeks runs from Sunday to Saturday), in the four seasons analysed.

Firstly, we described the relative frequency of swabbing vis-à-vis the remaining variables reported (calculation of percentages of dispatch of specimens and their variability, including test for trend and deviation from linearity). In a second step, a multivariate logistic regression model was used to estimate the adjusted effects (odds ratio, OR) of the same variables on the performance of a swab specimen. All data analyses were performed using the SPSS v14.0 and Stata v8.0 computer software programmes.

Results

Univariate analysis of the first part of this study showed that during the last four influenza seasons (2002-2006), sentinel network physicians obtained 4,005 swab specimens for dispatch to system-affiliated laboratories, which represented a swab percentage of 11.53% vis-à-vis cases reported with influenza syndrome. When the distribution of this percentage was analysed by reference to patient-related epidemiological variables, significant variations were observed in terms of sex, age and vaccination status (Table 1), with a higher relative frequency of specimens being dispatched for males versus females and for vaccinated versus unvaccinated patients. There was a gradual decline in swabbing with patients' age. Analysis of this showed a significant trend (X^2 (1 gl)=345.62; p<0.001), which did not deviate from linearity (X^2 (2gl)=2.57; p=0.277).

Figure 1 shows the percentage of specimens collected from vaccinated and unvaccinated patients according to patients' age. For each age group, there was a significantly higher (p<0.001) percentage of swab specimens collected and dispatched among vaccinated versus unvaccinated patients. Differences were more pronounced in patients aged under 15 years old, with triple or double the percentage of swabs collected and dispatched to laboratories for vaccinated versus unvaccinated patients among the 1-4 and 5-14 age groups respectively.

Table 1

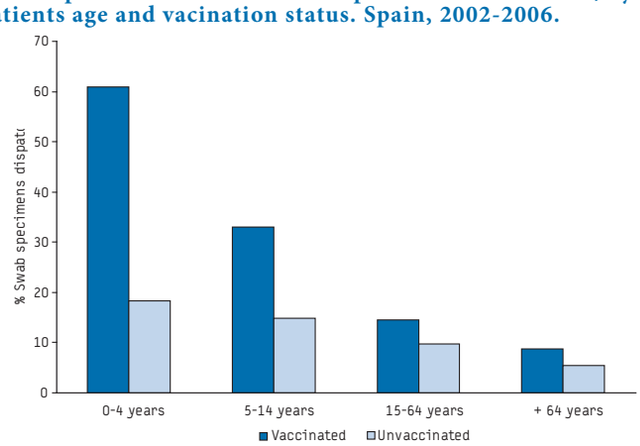
Swab specimens collected in the Spanish Influenza Sentinel Surveillance System, by sex, patient age and vaccination status, in the period 2002-2006

	No. of swab specimens dispatched	% Swab specimens dispatched*	P value**
Sex			
Male	2,152	12.2	0.02
Female	1,831	11.1	
Age group			
0-4 years	498	18.8	<0.001
5-14 years	1184	15.0	
15-64 years	2123	10.1	
65 years and older	199	6.5	
Vaccination status			
Vaccinated	383	13.2	<0.001
Unvaccinated	3,546	11.6	

*Percentage of collected and dispatched swab specimens with respect to number of cases reported with influenza syndrome.
**Chi-squared test was used.

Figure 1

Percentage of collected and dispatched swab specimens with respect to number of cases reported with influenza, by patients age and vacination status. Spain, 2002-2006.



When the characteristics of swabbing for virological analysis were studied in reference to epidemic period, we observed that, with respect to total reported cases, the percentage of specimens collected was lower in periods of influenza activity, though in absolute numbers, the number of specimens dispatched in such periods was logically higher (Table 2). Furthermore, there were also significant variations when the indicator was analysed by season, with a high percentage of swabbing in the last season, 2005/2006. Indeed, the swabbing percentage was almost double that of the previous seasons (Table 2).

When time of swabbing for virological analysis was characterised, we observed, firstly, that the date of specimen dispatch to the laboratory was reported in 3,581 cases, accounting for 90.3% of all swab specimens taken. In 98% of such cases, the patients' swab specimens were obtained by the physicians in the three days prior or subsequent to the middle day of the epidemiological week in which the case was reported, whereas specimens collected at longer time intervals accounted for 2% of the total volume of swabs performed (data not shown).

The multivariate analysis undertaken in the second part of this study assessed the independent effects exerted by each of the patient-related and time-of-swabbing variables on the collection and

TABLE 2

Table 2. Collection and dispatch of swab specimens, by epidemic period and study season, Spain, 2002-2006

	No. of swab specimens dispatched	% Swab specimens dispatched*	P value**
Epidemic period			
No influenza activity	1,245	19.7	<0.001
Influenza activity	2,760	12.1	
Influenza season			
2002-2003	611	11.2	<0.001
2003-2004	776	10.7	
2004-2005	1,231	8.5	
2005-2006	1,387	18.6	

*Percentage of collected and dispatched swab specimens with respect to number of cases reported with influenza syndrome.
**Chi-squared test was used.

dispatch of swab specimens. Table 3 shows the adjusted OR of the above variables along with their 95% confidence intervals, obtained with logistic regression analysis in a model that included collection and dispatch of swab specimens as the dependent variable, and the remaining variables analysed as the independent variable. All the relationships observed in the univariate analyses remained in evidence after the multivariate analysis. Independently, the collection of swab specimens was linked to age (proving significantly lower in the oldest age groups), sex (higher in males than females) and vaccination record (higher among patients who reported being previously vaccinated). Similarly, the percentage of collection of clinical specimens was lower in periods of peak influenza activity, and significantly higher in the last season, 2005/2006, than in the previous three.

Discussion

A recent EISS analysis on swab forms used by the 30 countries reporting to it reveals that 17 of them, including Spain, show appreciable improvement in terms of the information collected in the most recent season compared to the previous one, and meet the EISS requirements (Tamara Meerhoff, personal communication). Nevertheless, although there are clear recommendations about swab specimen collection procedures in the Spanish system, there are no strict rules as to the number of swab specimens and/or specific population groups in which such specimens are to be collected, in view of the fact that this largely depends on the capacity of the support laboratories and specimen-dispatch logistics.

The number of swab specimens collected and dispatched for virological confirmation in the first two seasons (2002/2003 and 2003/2004) was clearly lower than that in the last two seasons (2004/2005 and 2005/2006). We feel that this could be due to the fact that in the 2003/2004 season, SISSS was enlarged by the addition of four more regional networks that did not consolidate their operations until the 2004/2005 season, the first in which a substantial increase was observed in swab specimens collected by sentinel physicians. Furthermore, in the 2004/2005 season, Spain underwent influenza activity of greater intensity than it had in the preceding seven seasons, with elevated incidence rates across all age groups during the upward phase of the epidemic wave [2]. This situation may have influenced sentinel physicians' readiness to collect a greater number of swab specimens from patients seeking medical attention during the following season, something that may in turn account for the higher swabbing percentage observed in the last season, 2005/2006, compared to previous seasons.

EISS' draft guidelines, which are still under discussion, indicate that swabbing must be performed during all phases of the epidemic, although it should be boosted at the start and end of the season to ensure that the surveillance system fulfils an early alert function and enables detection of possible strains in circulation. In Spain, ISSS adapts to this recommendation inasmuch as physicians collect respiratory swab specimens from patients throughout the season, although the percentage of swabbing is relatively higher in periods of reduced influenza activity.

In addition, EISS' draft guidelines recommend that the percentage of the collection of specimens should be at least 10% across all age groups. In Spain, as in other European countries [3], a lower number of swab specimens is collected in the 0-4 and 65-and-over age groups. However, while the Spanish system falls short of the necessary percentage of the collection and dispatch of swab specimens in the group of patients aged 65 years and older (6.5%), it exceeds the recommended minimum in patients under the age of 15 years. Indeed, as can be seen from the results, though the percentage collection of swab specimens for all cases reported in the four seasons (11.4%) surpasses the EISS requirement, there is nevertheless a tendency to collect fewer specimens as the age of patients increases, and in the case of elderly patients frequency of collection is clearly insufficient. Accordingly, we would like to encourage specimen collection by GPs in patients aged 65 years and older; to meet EISS guidelines (which require collection of specimens to be at least 10% in all age groups), one third more specimens would have had to be collected among the 65 and older age group (up to 300 specimens in the four seasons studied).

Moreover, history of influenza vaccination in the current season has also been observed to influence swab specimen collection, in the sense that sentinel physicians collect a higher percentage of specimens in cases where patients have received the influenza vaccine. Our study reveals that the younger the patient, the greater the influence of vaccination status on the collection of swab specimens. This is particularly so in the under-15-year group, where the proportion of specimens collected by sentinel physicians among vaccinated children is double (5-14 years) or triple (0-4 years) that among unvaccinated children. This is a major selection bias that could interfere when it comes to assessing the effectiveness of the influenza vaccine. Spain has one of the highest influenza vaccination coverages in the world [4], which in the 2005/2006 season was 70% among the 65 years and older segment of the population [5]. General coverages in Spain decline sharply among persons aged 64 years or under and are estimated to be 6% among children [6]. These figures heighten the importance of the influence of vaccination status on the collection of swab specimens in SISSS, since it is in age groups with lower influenza vaccination coverages that physicians take a far higher proportion of specimens from vaccinated versus unvaccinated patients.

SISSS sentinel physicians have been shown to be representative of the population for age and geographic distribution, including rural and urban distribution [7]. However, the influence exerted by those factors mentioned above may translate as selection bias when it comes to swabbing the monitored population, the basis of virological information that is essential for surveillance. The system's capacity for reliable detection of influenza viruses circulating in the Spanish population could be limited if a certain

degree of representativeness in the collection of specimens and an adequate number of specimens cannot be ensured. The existence of other factors pertaining to the availability of means for collection and transport of specimens is doubtless also a determinant in the selection of cases for virological confirmation, but a lack of knowledge of such factors renders it impossible to judge the role that they play. As a result, the specimen collection protocol of the Spanish System stresses that respiratory specimens for viral isolation, or viral detection of nucleic acids or antigens, be collected in the first four days of the disease, as this is the period of maximum viral excretion and laboratory results depend on good timeliness of swabbing [8]. However, a lack of data on the date of symptom onset among cases (a variable registered by the system but not available in our analysis) prevented us from assessing its determinant role in the selection of specimens. The only fact established was that in 98% of cases specimens were dispatched for analysis in the week when they were collected.

The above problems of representativeness could be resolved by requiring systematic random procedures in the system for collecting swab specimens from patients. However, it is not clear how feasible such procedures would be for a population-based surveillance system with so many reporting physicians and so many limitations in terms of laboratory and preservation resources and dispatch of specimens. For the present, our criterion, akin to the guidelines proposed by EISS, is to continue to insist that a sufficient number of appropriate specimens be obtained at all ages during periods of least activity; likewise, it is essential that the importance of collecting swab specimens, regardless of patients' vaccination status and/or age, be recalled at the beginning of each influenza season. Both recommendations will contribute to ensure early detection of the circulation of influenza virus in the European continent, one of the fundamental goals of any influenza surveillance system.

* This group was formed by the Sentinel General Practitioner Networks of Andalusia, Aragon, Asturias, Balearic Isles, Canary Islands, Cantabria, Castile-La Mancha, Castile & León, Catalonia, Valencian Region, Extremadura, Madrid, Navarre, Basque Country, La Rioja and Ceuta, in collaboration with the following laboratories that participated in virological surveillance: Influenza Centre (WHO), National Microbiology Centre, Majadahonda-Madrid; Influenza Centre (WHO), Valladolid Faculty of Medicine; Influenza Centre (WHO), Barcelona Clinical Hospital; Virgen de las Nieves Hospital, Granada; Miguel Servet Hospital, Zaragoza; Nuestra Señora de Covadonga Hospital (Asturias Central Hospital), Oviedo; Son Dureta Hospital, Palma; Dr. Negrín Hospital, Las Palmas; Marqués de Valdecilla University Teaching Hospital, Santander; Valencian Microbiology Institute; Navarre University Teaching Hospital, Pamplona; Nuestra Señora de Aránzazu Hospital, San Sebastián; La Rioja Hospital, Logroño; INGESA Hospital, Ceuta; and the Vigo and Ourense Hospital Complexes.

Acknowledgements

All sentinel practitioners, contributing virus laboratories and epidemiologists at the regional sentinel networks for collecting and relaying the data needed to conduct this study.

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Citation style for this article: Larrauri A, De Mateo S, . Characterisation of swabbing for virological analysis in the Spanish Influenza Sentinel Surveillance System during four influenza seasons in the period 2002-2006. Euro Surveill 2007;12(5)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n05/1205-223.asp

Epidemiology of meningococcal meningitis and changes in the surveillance system in Poland, 1970-2006

O Gryniewicz, J Kolbusz, M Rosinska, A Zielinski, P Stefanoff (pstefanoff@pzh.gov.pl)

Department of Epidemiology, National Institute of Hygiene, Warsaw, Poland

The objective of this study was to describe the general features of meningococcal meningitis epidemiology in 1970-2006 in Poland, in the context of changes made in surveillance system methods. Because of limited availability of case-based data, a more detailed analysis was performed only for the period 1994-2006 with special focus on case-fatality and diagnostic certainty. The reported annual number of meningococcal meningitis cases reached its peak of 416 (incidence 1.2 per 100,000) in 1981, after which it decreased to 76 cases in 2003 (incidence 0.2), and then increased to 151 cases in 2006 (incidence 0.4 per 100,000). The observed decrease was consistent with the decline in the number of live births and the drop in mortality from meningococcal disease observed using an independent reporting of death certificates. In 1994-2006, 1,677 cases of meningococcal meningitis were registered, with annual incidence varying between 0.2 and 0.5 per 100,000 inhabitants. Median age of patients was 4 years and 73% of cases were under 18 years of age. The majority of cases were caused by group B meningococci, but a trend towards increasing proportion of serogroup C has been identified. Meningococcal meningitis only was reported in 79% of cases, and meningitis with concomitant septicaemia in 21%. The overall case fatality was 3.7% - 4.5% in cases of meningitis only, and 7.1% in cases of meningitis with septicaemia. Based on the case definition introduced in 2005, 88.1% of the cases would be classified as confirmed and 4.8% as probable, whereas 7.1% would not fulfil the criteria of the case definition. Although diagnostic certainty of reported cases has improved in recent years, it is still problematic. Further efforts are needed to increase the proportion of serogrouped cases and assess the burden of meningococcal disease in Poland.

Introduction

The most common manifestations of the invasive meningococcal disease in Europe include meningitis (50-55% of all cases), septicaemia (5-20%), and meningitis accompanied by septicaemia (20-30%) [1]. Meningococcal meningitis occurs particularly often among infants and young children. It may cause serious neurological defects and is often lethal, if treatment is delayed. Meningococcal disease can be confirmed by microbiological examination (Gram stain of samples from cerebrospinal liquid or blood culture). Meningococcal infection can be usually successfully treated, if antibiotics are administered early after the onset of illness [1-3]. Appropriate epidemiological investigation of meningococcal disease clusters is also important, including contact tracing and providing chemoprophylaxis for the household and other close contacts. When chemoprophylaxis is administered within 24 h from the contact it may decrease secondary case rates by almost 90% [3]. In recent years several countries in Europe introduced group C conjugate vaccine in their immunisation schedule [4,5].

Trends observed while monitoring only meningococcal meningitis correlate well with the total burden of meningococcal disease, and in some countries with clinician-based surveillance systems surveillance of meningococcal disease has been restricted to meningitis cases only [6]. In Poland the surveillance of meningococcal invasive disease, initiated in 1970, was limited to meningitis cases until 2005 [7].

Meningococcal vaccine is not included in the Polish mandatory and free-of-charge immunisation programme. However, since 2003, vaccination against group C meningococci is recommended for children above 2 years of age and for patients who have undergone splenectomy. The list of recommended vaccines is published by the Poland's Chief Medical Officer and is used to advise parents, but the full cost of the vaccine has to be covered by them alone. The official estimates indicate a very poor vaccine uptake, ranging from 834 persons vaccinated in 2003 to 1,851 vaccinated in 2005 (data for 2006 is not available yet).

The primary aim of this study was to describe the general features of meningococcal meningitis epidemiology in 1970-2006, in the context of changing surveillance system. The secondary aim was the description of clinical outcomes and diagnostic procedures used to confirm meningococcal meningitis in 1994-2006.

Methods

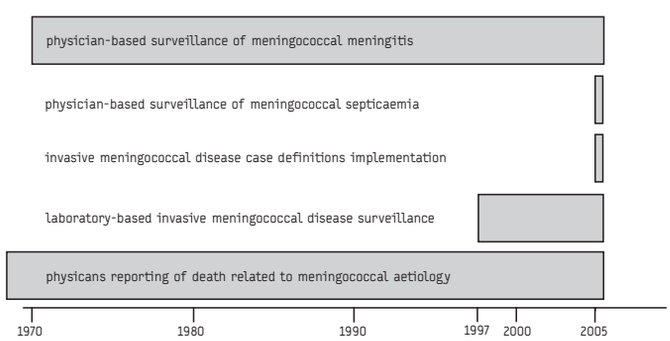
The Polish epidemiological surveillance system is still paper-based, but has been considerably modified in recent years. Physicians are obliged by law to report all newly diagnosed cases of meningococcal meningitis (since 2005 invasive meningococcal disease) to the local sanitary-epidemiological stations (SES). Typically, public health officers carry out epidemiological investigation of cases and their closest contacts and complete the standardized surveillance reports. Data on cases are collected at local SES and forwarded biweekly to the National Institute of Hygiene which publishes regular surveillance reports on its website (http://www.pzh.gov.pl/epimeld). Additionally, every three months completed surveillance reports containing demographic, clinical and laboratory data on each case are sent through regional SES to the National Institute of Hygiene. Annual reports on meningococcal disease are prepared at the Department of Epidemiology of the National Institute of Hygiene [7]. Independently of mandatory reporting of communicable diseases to SES, physicians are required to fill in death certificates, including the primary and secondary causes of death, and submit them to the Central Statistical Office. Data from death certificates, including information on meningococcal disease coded using the International Classification of Diseases, are available at least since 1968, when ICD-8 and ICD-9 classifications

were used (036 - Meningococcal infection), followed by ICD-10 used since 1999 (A39 – Meningococcal disease).

Changes in surveillance of meningococcal disease since the beginning of its reporting in 1970 are schematically presented on Figure 1. The case definition for meningococcal disease was implemented in 2005. Before 2005, cases were ascertained based on clinical diagnosis and potential laboratory confirmation. In 1997, the National Reference Laboratory (NRL) for Meningococci started a separate, sentinel-type laboratory system requiring hospitals to send strains isolated from meningococcal disease cases to the NRL for further analysis (Figure 1). Data from the two systems are not collated at the national level. Therefore, the information on laboratory tests performed and serogroup used in this study was obtained exclusively from epidemiological surveillance forms.

Figure 1

Surveillance of meningococcal disease in Poland, 1970-2006



The present study is based on aggregated data for 1970-1993 and case-based data for 1994-2006. Individual level information from the period 1970-1993 is not available. Surveillance forms for the period 1994-1998 did not include information on exposures and epidemiological links. Therefore, part of the analysis is limited to years 1999-2006.

In order to assess trends in diagnostic certainty of cases reported to the Polish surveillance system, data for 1994-2004 were retrospectively described using the case classification used currently in Poland, being a slightly modified translation of the case definition recommended by the European Centre for Disease Prevention and Control (ECDC). Because the case definition was not used before 2005, all cases of meningococcal meningitis have been included to calculate the incidence. Population data and data on disease-specific mortality were obtained from the Central Statistical Office (http://www.stat.gov.pl).

Case definition of meningococcal disease used in Poland since 2005

Clinical description:

Clinical picture compatible with meningococcal disease, e.g. meningitis and/or meningococcemia that may progress rapidly to purpura fulminans, shock and death. Other manifestations are possible.

Laboratory criteria for diagnosis:

► Isolation of *Neisseria meningitidis* from a normally sterile site (e.g. blood or cerebrospinal fluid (CSF) or, less commonly, joint, pleural or pericardial fluid)

► Detection of *N. meningitidis* nucleic acid from normally sterile site

► Demonstration of Gram-negative diplococci from normally sterile site by microscopy For probable case:

► Single high titre of meningococcal antibody in convalescent serum

Case classification

Possible: N.A.

Probable: A clinical picture compatible with invasive eningococcal disease without any laboratory confirmation, or with *N. meningitidis* identification from a non-sterile site, or with high levels of meningococcal antibody in convalescent serum.

Confirmed: A clinically compatible case that is laboratory-confirmed.

Note that asymptomatic carriers should not be reported

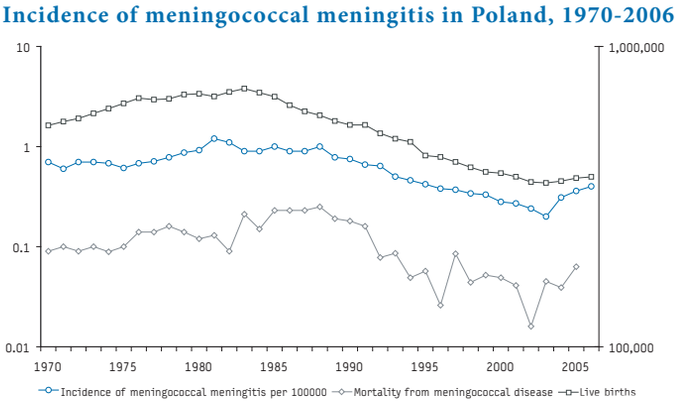
Results

Incidence of meningococcal meningitis

Incidence of meningococcal meningitis during 1970-2006 ranged between 0.2 and 1.2 per 100,000 (Figure 2). In this period, the reported number of meningococcal meningitis cases decreased from the maximum of 416 (incidence 1.2 per 100,000) in 1981 to the minimum of 76 cases in 2003 (incidence 0.2) and then increased to 151 cases in 2006 (incidence 0.4 per 100,000). The observed decrease in meningococcal meningitis incidence was consistent with the decline in number of live births in Poland. The decrease in mortality from meningococcal disease in the period 1985-2006, as shown by death certificate data, provides an independent confirmation of meningococcal disease burden decrease in Poland (Figure 2). The number of deaths attributed to meningococcal infection decreased from 96 in 1986 (mortality 0.25 per 100,000) to 6 in 2002 (mortality 0.02). Since 2003, an increase in meningococcal meningitis incidence has been observed, with parallel increase in meningococcal disease mortality.

Figure 2

Incidence of meningococcal meningitis in Poland, 1970-2006



Demographic data

During 1994-2006, 1,676 cases of meningococcal meningitis were registered, of which 966 (58%) were males (mean annual incidence 0.40), and 710 (42%) were females (mean annual incidence 0.28).

Mean age of patients was 14.4 years; median age was 4.0 years. Out of 1,677 reported cases 73% of patients were under 18 years of age. Age-group specific incidence of meningococcal meningitis during the years 1994-2006 is presented in Figure 3. A decreasing trend was observed in age group 0-4, ranging from 4.5 per 100,000 in 1994 to 1.8 in 2002. The highest incidence was seen in infants, ranging from 13.2 per 100,000 in 1994 to 5.4 in 2003. An increase in meningococcal meningitis incidence in age groups 5-14 and 15-24 was detected, ranging from 0.2 in 2003 to 0.7 in 2006 in the age group 5-14, and from 0.3 in 2003 to 0.7 in 2006 in the age group 15-24. Out of the total of 433 adult patients with known occupation, 233 (54%) were students, 115 (27%) were retired or unemployed, 53 (12%) were physical workers, and 18 (4%) were office workers. There were 9 cases of meningitis registered among recruits. The incidence of meningococcal disease displayed seasonal variations with an autumn increase starting in October and highest levels in winter months with the peak in January.

Serogroup distribution

Between 1994 and 2006, meningococcal strains from 624 cases (37%) were serogrouped. The number of cases according to serogroups during this period is shown in Figure 4. Among serogrouped strains, 415 (67%) were group B strains and 176 (28%) were group C. Additionally, there were 28 strains (4%) established as serogroup A, but these results were not confirmed by the national reference laboratory and were merged into the group labelled "other", along with two cases reported as I, two as Y, and one reported as serogroup D. The proportion of cases with serogroup C of *N. meningitidis* increased gradually reaching the highest value (51% of serogrouped strains) in 2006. Serogroup B was most common in children under 10 years of age (75%) and adults over 50 years old (83.3%), and the median age of group B cases was 2.0 years. Serogroup C was more common in teenagers and young adults aged between 10 and 24 years (median age of group C cases: 12.5 years).

Clinical manifestation

During 1994-2006, meningococcal meningitis only was diagnosed in 1,325 cases (79%) and meningitis with septicaemia in 351 cases (21%). There were 75 fatal cases (4.5 %), with median age at death being 31.8 years. Table 1 shows case-fatality ratios (CFR) specific to clinical manifestation, stratified by age, gender and serogroup.

Case classification

Out of 1,676 cases, 1,477 (88.1%) met criteria for confirmed cases (Table 2). Cerebrospinal fluid culture was performed in the majority of cases, showing positive results in 1,142 cases (77.3% of the confirmed cases). The number of microbiological examinations per patient increased from 1.1 in 1994 to 2.3 in 2006. Of the 80 cases (4.8% of all cases) classified as probable, 21 were diagnosed as meningococcal infection based exclusively on clinical presentation (Waterhouse-Fridriechsen syndrome or petechial/purpuric skin lesions), 59 had also positive antigen test for *N. meningitidis*. The remaining 119 reported cases (7.1%) had neither microbiological nor clinical compatibility required for case confirmation.

Discussion

Since 1981 the incidence of meningococcal meningitis in Poland had been decreasing, but an increase was noted in 2004, 2005 and 2006. However, the incidence rates are still rather low compared to other European countries [1,9-11]. The systematic decrease of meningococcal meningitis incidence during preceding two decades could be explained by decreasing birth rate and decreasing incidence of meningococcal infections in infants possibly related to improvement of living conditions and health-care services in Poland. The unexpected increase in meningococcal meningitis incidence in 2004-2006 may be related to a real increase in meningococcal disease activity in Poland but can also be simply a result of its improved surveillance. However, the fact that this increase occurred mainly in the teenage age group and was accompanied by a systematic increase in proportion of serogroup C observed in epidemiological surveillance and increasing number of cases of ST11 and ST8 clonal complex reported by the reference laboratory indicates that the epidemiological situation in Poland is changing [12-13]. The increasing proportion of serogroup C meningococci strains isolated from cases in neighbouring countries in previous decades, was accompanied by an increase in disease incidence among adolescents and young adults [1,9,11].

The case fatality rates (CFR) based on Polish surveillance data parallel the epidemiological situation of meningococcal disease in developed countries in the pre-vaccination stage. As in other European studies, case fatality was highest in people over 50 years of age, and in those with concomitant septicaemia [1,14,15]. Unlike in published studies, group B meningococci were associated with higher CFR, compared to group C strains. This can be however related to the low proportion of serogrouped strains during the studied period, and to the higher proportion of group B meningococci diagnosed in adults over 50 years of age, where the case fatality is highest.

In order to assess the possible distortion of these results due to the fact that only data on meningococcal meningitis was available for the entire period of study, a sub-analysis was performed using data on the entire spectrum of invasive meningococcal disease available for 2005-2006 (n = 440). In this analysis the CFR was still found higher among serogroup B, compared to serogroup C cases (12.8% vs. 10.8%). Age-specific case-fatality ratio was highest in group B cases aged 10-14 years (1/4, 25%), 5-9 years (2/14, 14.3%) and 0-4 years (9/64, 14.1%). In group C cases, CFR was highest in adults aged over 25 years (4/11, 36%) and teenagers aged 15-19 years (2/12, 16.7%). A recent emergence of outbreaks caused by serogroup C strains has caused serious media concerns and improvement of surveillance sensitivity, as well as microbiological confirmation of individual cases, with increasing proportion of serogrouped strains.

As the level of underascertainment of meningococcal disease in Poland is not known, further enhancement of laboratory and epidemiological surveillance is needed. Some improvements have already been introduced in 2005, namely the extension of surveillance of meningococcal disease to include all its manifestations and the implementation of case definition. Proper attention must be paid to contact tracing and appropriate administering of chemoprophylaxis in order to prevent the occurrence of clusters of the disease.

TABLE 1

Number of meningococcal neuroinfections, deaths and case fatality according to clinical manifestation, gender and serogroup distribution in Poland, 1994 - 2006

	Clinical syndrome							
	Meningitis				Meningitis with septicemia			
	cases	deaths	case fatality (%)	95% CI	cases	deaths	case fatality (%)	95% CI
Total	1325	50	3.7	2.7 - 4.8	351	25	7.1	4.4 - 9.8
Age groups (years)								
0	355	4	1.1	0.0 - 2.2	99	8	8.1	2.7 - 13.4
1	148	3	2.0	0.0 - 4.3	56	4	7.1	0.4 - 13.9
2	71	0	-	-	34	4	11.8	0.9 - 22.6
3	54	0	-	-	23	3	13.0	0.0 - 26.8
4	22	0	-	-	18	0	-	-
5-9	90	2	2.2	0.0 - 5.3	34	0	-	-
10-14	85	1	1.2	0.0 - 3.5	21	1	4.8	0.0 - 13.9
15-19	144	2	1.4	0.0 - 3.3	35	1	2.9	0.0 - 8.4
20-24	56	1	1.8	0.0 - 5.3	7	0	-	-
25-49	162	13	8.0	3,8 - 12.2	14	3	21.4	0.0 - 42.9
50-64	91	14	15.4	8.0 - 22.8	6	1	16.7	0.0 - 46.5
65+	47	10	21.3	9.6 - 33.0	4	0	-	-
Gender								
Males	775	33	4.3	2.8 - 5.7	191	16	8.4	4.4 – 12.3
Females	550	17	3.1	1.6 - 4.5	160	9	5.6	2.1 - 9.2
Serogroup								
B	313	12	3.8	1.7 - 6.0	102	6	5.9	1.3 - 10.4
C	126	4	3.2	0.1 - 6.2	50	2	4.0	0.0 - 9.4
Other	41	2	4.9	0.0 - 11.5	6	0	-	-

FIGURE 3

Incidence of meningococcal meningitis by age group, Poland 1994-2006

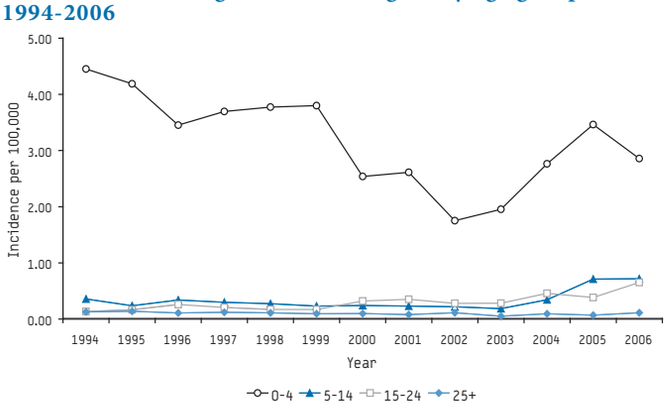


FIGURE 4

Cases of meningococcal meningitis by serogroup, Poland, 1994-2006

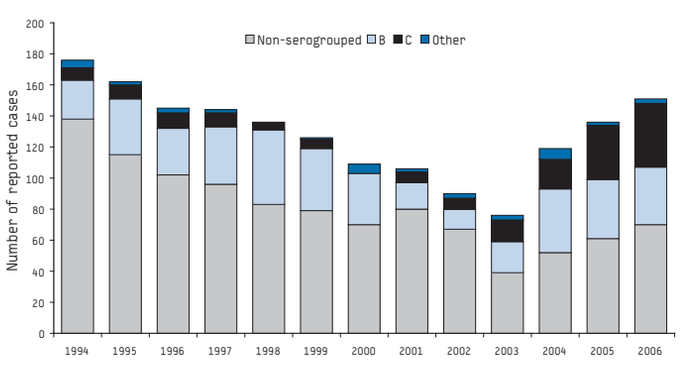


Table 2

Number of cases of meningococcal neuroinfections by case classification and year, Poland, 1994-2006

Year	Confirmed cases					Probable cases	Discarded cases
	Demonstration of gram-negative diplococci	Isolation of N. meningitidis from CSF	Isolation of N. meningitidis from blood	Detection of N. meningitidis DNA by PCR	Total		
1994	44 (30.8%)	94 (65.7%)	6 (4.2%)	0 (0.0%)	143	2	31
1995	48 (34.3%)	113 (80.7%)	8 (5.7%)	0 (0.0%)	140	1	21
1996	62 (44.3%)	115 (82.1%)	19 (13.6%)	0 (0.0%)	140	0	5
1997	48 (36.6%)	100 (76.3%)	19 (14.5%)	0 (0.0%)	131	0	13
1998	32 (26.0%)	106 (86.2%)	23 (18.7%)	0 (0.0%)	123	0	13
1999	47 (41.2%)	92 (80.7%)	16 (14.0%)	0 (0.0%)	114	9	3
2000	23 (24.0%)	79 (81.4%)	21 (21.9%)	0 (0.0%)	97	10	2
2001	34 (34.7%)	74 (75.5%)	21 (21.4%)	0 (0.0%)	98	6	2
2002	26 (32.9%)	64 (81.0%)	10 (12.7%)	0 (0.0%)	79	7	4
2003	20 (30.3%)	50 (75.8%)	18 (27.3%)	0 (0.0%)	66	7	3
2004	32 (33.0%)	71 (73.2%)	32 (33.0%)	0 (0.0%)	97	18	4
2005	34 (27.6%)	97 (78.9%)	35 (28.5%)	9 (7.3%)	123	12	1
2006	25 (19.8%)	87 (69.0%)	48 (38.1%)	9 (7.1%)	126	8	17
Total	475 (32.2%)	1142 (77.3%)	276 (18.7%)	18 (1.2%)	1477	80	119

Detailed and more complete data on serogroups are needed in view of developing evidence-based vaccination recommendations for general public.

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Citation style for this article: Gryniewicz O, Kolbusz J, Rosinska M, Zielinski A, Stefanoff P, . Epidemiology of meningococcal meningitis and changes in the surveillance system in Poland, 1970-2006. Euro Surveill 2007;12(5)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n05/1205-224.asp

Is STI surveillance in England meeting the requirements of the 21st century? An evaluation of data from the South West Region

C Ihekweazu (chikwe.ihekweazu@hpa.org.uk)[1,2], N Maxwell[1], S Organ[1], I Oliver[1]

1. Health Protection Agency South West, Stroud, United Kingdom
2. European Programme for Intervention Epidemiology Training (EPIET)

This study evaluates two sexually transmitted infections (STI) surveillance systems' ability to provide relevant, accurate, and timely information to inform prevention and control activities in England, using data from the South West, the largest of the country's nine regions. The systems were evaluated in terms of timeliness of reporting to subsequent levels; frequency of reporting and feedback; completeness of information in the reports; and representativeness of the reports to the resident population. To determine the usefulness of the system for those responsible for taking public health action, semi-structured interviews of a sample of users of surveillance information were conducted. Timeliness of the two main surveillance systems, laboratory reports and returns from genito-urinary medicine clinics were poor. Completeness of the laboratory system was good for date of birth and sex, but poor for geographical markers. Of the 27 respondents that participated in the survey, only eight were satisfied with the level of detail in the surveillance data they received. Most stakeholders felt that the STI data they received was not representative of the population they served and not useful in responding to emerging problems. Faced with increasing incidence of STIs, existing STI surveillance systems in England are unable to provide adequate epidemiological data for the fulfilment of basic uses of public health surveillance at the local level. Surveillance is inadequate in timeliness, geographical coverage, representativeness, does not allow for the identification of risk factors and conceals variations in sex, ethnicity, and sexual behaviour. Disaggregate data with some geographical and risk-factor information would greatly enhance the usefulness of the data. The goal should be of access to real-time data.

Introduction

Accurate epidemiological information about the occurrence and distribution of sexually transmitted infections (STIs) is imperative for targeted screening, prevention, and control programmes. Recent syphilis outbreaks in the South West region of England [1,2], as well as increasing demands by frontline health staff and Primary Care Trusts for detailed information have highlighted shortcomings in the surveillance data presently available to public health professionals on STIs.

The rates of STIs in England have been on the increase over the past few years [3] and there is a need to understand the factors driving this to inform the public health response. Genital chlamydial infection is the most commonly diagnosed STI in genitourinary medicine (GUM) clinics and genital herpes the most common cause of ulcerative STIs in England. Since 1995, diagnoses of gonorrhoea in England have been rising again after a declining considerable since 1985 [4].

Improving sexual health has been a priority of the UK government and the need for action was reinstated in its recently published white paper, "Choosing Health: Making Health choices easier" [5].

Surveillance of STIs should provide relevant, accurate, and timely information to inform prevention and control activities. It should also be able to provide population estimates for prevalence and incidence, trends, identify risk factors, and present information in a timely and assessable manner [6]. This study evaluates STI surveillance in the South West region of England to ascertain if it is meeting these objectives.

Methods

STI surveillance in England

There are two main sources of STI data in England: genitourinary medicine (GUM) clinics and microbiology laboratories.

Data collected from all GUM clinics, off-shoots of veneral disease clinics, led to the UK's first systematic STI surveillance system [7]. These GUM clinics are open access and offer free, confidential sexual health services. Data statutorily submitted quarterly from these clinics are known as the KC60 returns. KC stands for Korner Code, an abbreviation given to statutory returns from the NHS to the Department of Health; for example, KC62 is breast cancer, KC64 dental activity and KC51 immunisation uptake. This system was initially developed as a tool for workforce planning and monitoring clinic activity. It was set up in 1917 as a system for measuring workload at GUM clinics in the country. This system is supplemented by a second surveillance system called CoSurv. This involves the voluntary laboratory reporting of STIs from the laboratories through regional office to the national centre.

The aim of this study was to evaluate the performance of these two surveillance systems for STIs in England between 1997 and 2004 using data from the South West region in order to determine the systems' ability to provide high quality data in a timely and efficient manner. Our evaluation focused on the needs of local and regional users of STI surveillance information in this region. The flow of data through the two surveillance systems is described below.

As a result of the perceived inadequacies of STI surveillance, the Enhanced Surveillance for Infectious Syphilis Programme, a new national surveillance system, was established to better determine and describe the geographic, demographic and risk factor distribution of infectious syphilis. This initially collected data from all GUM clinics in London with the aim of extending

it to all GUM clinics in England by 2002. However this has not been undertaken due to lack of resources centrally. In response to Syphilis outbreaks in the South West, a similar system was initiated in the region [8]. As this was implemented just before this evaluation, syphilis was excluded from the evaluation due to the likelihood of surveillance artefacts.

The KC60 system

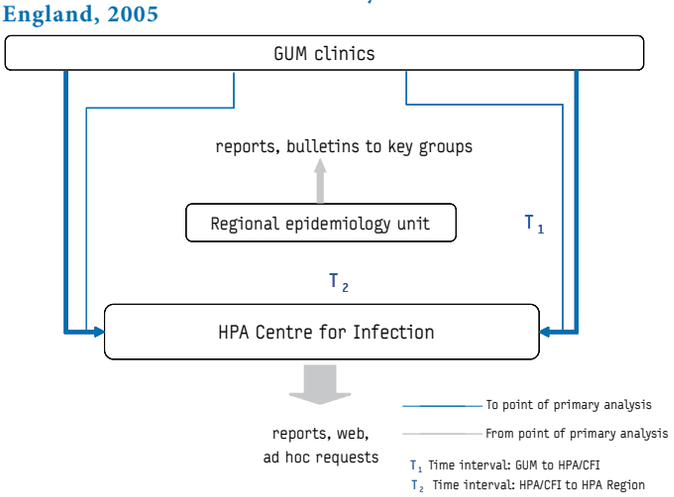
All 206 clinics in England have a statutory obligation to complete an aggregate statistical return on their attendance called the KC60 returns. These data on the total numbers STI episodes seen (individuals may be included more than once) are collected by each GUM clinic. There are 19 GUM clinics spread across the South West. Data are aggregated by age-group, sex and number of cases in men that were homosexually acquired. Each diagnosis is assigned a KC60 code. The data are sent quarterly from the clinics directly to the national Centre for Infections of the Health Protection Agency (HPA) for analysis. The lowest level of geographical data available is the clinic level, for which the catchment populations are unknown. Data are disseminated via an annual STI report, and through ad hoc requests. A subset of data is also sent to the regions annually for analysis and further dissemination to local users.

The laboratory-based system (CoSurv)

Laboratory reports are received from all the 16 laboratories in the South West region. These laboratories receive samples from primary and secondary care providers that cover the entire population accessing the National Health Service in the region.

FIGURE 1

Flowchart of KC60 surveillance system for the South West of England, 2005

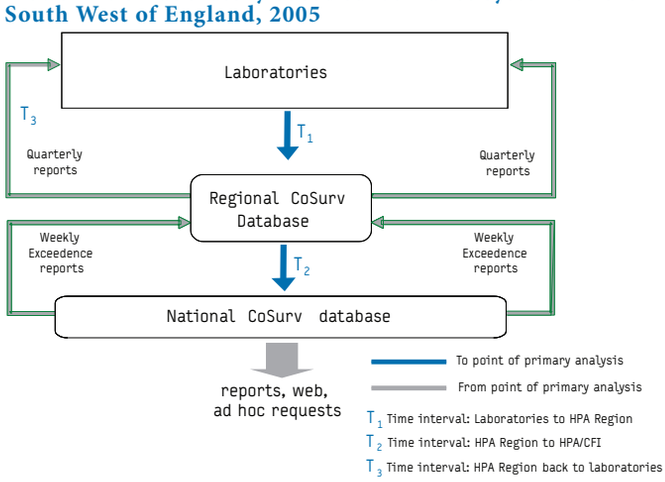


Reporting is electronic and can be done at anytime. These reports are then sent to the HPA Centre for Infection. Staff at the national centre scan the data weekly using specifically designed algorithms to detect increases in the number of reports above what would be expected based on data from the previous five years and produce the "Exceedance reports" [9]. These exceedance reports sent down to the regions weekly alerts staff to temporal and geographic clusters and triggers further investigation.

The US Centers for Disease Control and Prevention's Updated Guidelines for Evaluating Public Health Surveillance Systems [10] was used as the main tool for the evaluation methodology. This tool guides the measurement of the attributes of surveillance systems such as well as the degree to which

FIGURE 2

Flowchart of laboratory based surveillance system for the South West of England, 2005



the data produced is used to stimulate public health action. This evaluation was commissioned South West Sexual Health Task Group. Our evaluation was limited to those attributes that were considered of highest priority to local needs and priorities, the peculiarities of STIs, and the availability of data; these included timeliness, completeness, representativeness, and usefulness.

The timeliness and completeness of data transfer from the collection to dissemination stages were evaluated to ascertain that surveillance outputs are both adequate and timely enough to trigger appropriate public health action. Timeliness and completeness for both systems were evaluated for the period 1997 to 2004.

Timeliness of reports to CoSurv was evaluated by calculating the mean number of days from the date of specimen collection from patients to the date of availability of results in the regional database, the mean number of days until results were available in national database and the number of weeks it took for a report on the data to be available for public health action. For the KC60 system, the mean number of weeks from the end of each quarter until the entry of data into the national database from GUM clinics (T1 in Figure 1) and the time it takes for analysis of the data from GUM clinics to be done at the national level and reported to the regions (T2 in Figure 1) was calculated. Completeness of reports to CoSurv was evaluated by calculating the proportions of reports that had complete information on age, sex, postcode of residence and the GP postcode (the postcode of the general practitioner where the patient is registered).

The representativeness of the KC60 system was evaluated by comparing the data from a similar geographical area to the Avon Surveillance System for Sexually Transmitted Infections (ASSIST) [11, 12]. ASSIST was established as a research project to explore the feasibility of collecting disaggregate data from all STI service providers in the Avon area, which makes up a fifth of the population of the South West region of England. This was done by integrating genitourinary clinic and laboratory data. Postcode information for geographical mapping and small area analysis was obtained by matching pseudo-anonymised data with GP registration databases.

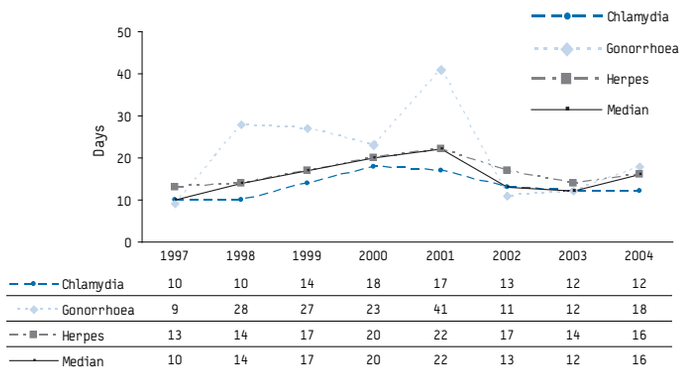
Table 1

Numbers of each stakeholder group interviewed

Group	Number of members of group in SW region	Number surveyed
GUM Physicians	19	5
Consultants in Communicable Disease Control (CCDCs)	12	5
Consultants in Public Health	30	6
Consultant Microbiologists	16	5
Members of the regional epidemiology team	8	3
Total	**85**	**24**

Figure 3

Median number of days between specimen date entry into regional database



	1997	1998	1999	2000	2001	2002	2003	2004
Chlamydia	10	10	14	18	17	13	12	12
Gonorrhoea	9	28	27	23	41	11	12	18
Herpes	13	14	17	20	22	17	14	16
Median	10	14	17	20	22	13	12	16

The usefulness and perceptions of the surveillance systems' attributes were evaluated through semi-structured interviews of a sample of suppliers and users of STI surveillance data. A proportionate stratified random sampling method was used for selecting the respondents for the structured telephone interviews used for this study [11]. We randomly selected approximately 25% of all the members of each group of stakeholders (Table 1) to be interviewed. The respondents were chosen from their professional lists in the South West region. A breakdown of the members in each individual group interviewed is given below. For voluntary organisations working on STIs in the region, we randomly selected three of the nine organisations known to us and spoke to the most senior member of staff on the day we telephoned.

The answers to the structured questions were entered into an Epidata database for descriptive frequency analysis and proportions calculated. The answers to the open-ended questions were reported verbatim and subsequently reviewed and organised into specific themes. These were then reviewed in relevance to the related attribute.

Results

Timeliness

The KC60 system

The mean number of weeks from the end of each quarter until the entry of data into the national database from GUM clinics (T1 in Figure 1) decreased from a mean of 24 weeks in 2003 to 18 weeks in 2004. Considerable variation exists in the timeliness of individual clinics sending in their quarterly returns and as a result, these are collated, and only entered into the national database when the deadline for all clinics to report has elapsed. An analysis of a subset of the data from GUM clinics is done for the regional and clinic level annually at the national level and a report is sent to regions. On average (between 1998 and 2003), this report reached the region 29 weeks after the end of the year. Accounting for the reporting delay for data to get to the national centre (mean = 21 weeks based on 2003/2004 data (T1)), it took an additional eight weeks to report this data to the regional level (T2). Therefore it takes between seven months and 19 months to receive data relating to cases that were reported in the KC60 system depending on which end of the year it was reported.

The laboratory system

Between 1997 and 2004, there were 90,087 reports of genital herpes, gonococcal and genital chlamydia infections in the regional database. The point T1 in Figure 2 illustrates the period between the date of collection of the organism and its entry into the regional database. Over the eight years, the median number of days it took for data to enter the regional database was 15 and an additional two days to enter the national database (T2 in Figure 2). In the South West of England, a report based on the data is produced and sent out to stakeholders at the end of each quarter. The time (T3 in Figure 2) between the end of the quarter and the date of data dissemination through a report is on average eight weeks. In summary, it takes between eight and 21 weeks for laboratory to become available for dissemination.

Perception of timeliness of both systems

Of the 27 stakeholders that responded to the survey, 20 stated that the data they receive is not timely enough to respond to emerging problems. Four respondents were satisfied with the frequency of receiving the KC60 data (sent out annually) while 11 were satisfied with the frequency of the laboratory data (sent out quarterly) received. Most respondents would prefer to receive data quarterly.

Completeness

The KC60 system

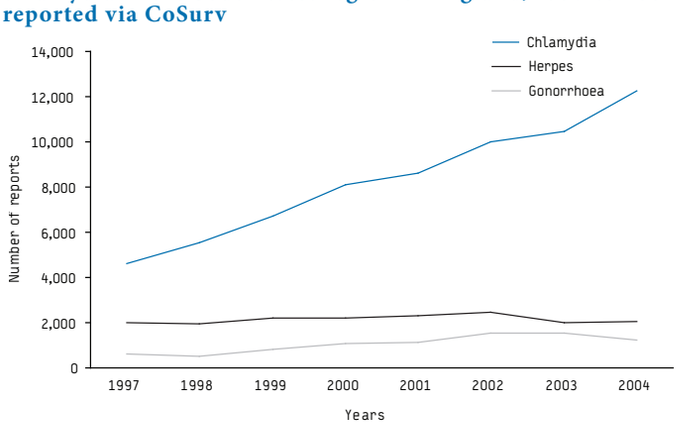
Since data received through this system is in aggregate form, completeness could only be analysed in terms of the number of GUM clinics sending their data to the national level. In this respect, given the generous intervals allowed to GUM clinics to report, completeness is close to 100%. Considering the last two years of the evaluation; 2003 and 2004, 95% of all quarterly returns from the 19 GUM clinics were entered into the national database for each quarter before the deadline for that quarter. Evaluating completeness in terms of individual STIs is only possible by auditing data at the clinic level, which was beyond the scope of this study.

The laboratory system

There were 92,007 reports of genital herpes, gonorrhoea and genital chlamydia cases between 1997 and 2004 from all 16 laboratories in the region (10 for genital herpes). In 2004, 12,282 genital chlamydia cases were reported via the CoSurv system,

Figure 4

New episodes of genital herpes, gonorrhoea and genital chlamydia in the South West region of England, 1997 to 2004 reported via CoSurv



an increase of 265% on the 4,624 cases in 1997. Reports of gonorrhoea also increased steadily since 1997. A total of 1,218 cases were reported in 2004 a 203% increase compared to 1997. The rise in reported genital herpes cases was less marked, with 2,000 cases in 1997 and 2,071 in 2004.

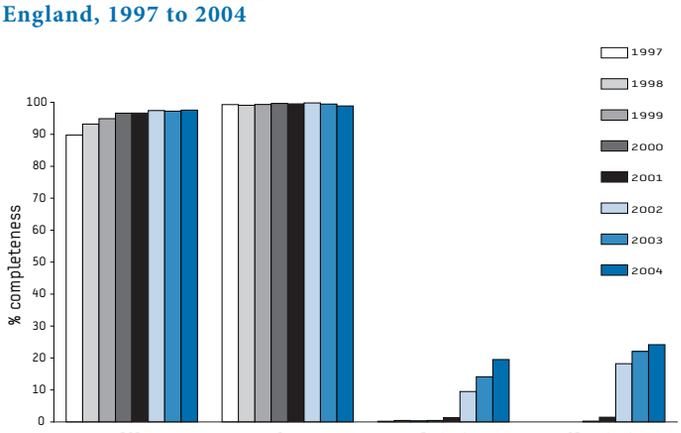
Completeness was evaluated for the information contained in each report. The completeness of reports for gonorrhoea and genital chlamydia infections was assessed for all 16 laboratories and for 10 of the 16 laboratories reporting genital herpes consistently over the past eight years (not all laboratories perform herpes diagnosis). Completeness for date of birth and age was above 90%, but below 30% for the two geographical variables, postcode and GP postcode (see Figure 5), however there has been some improvement in the completeness of these variables in the past five years.

Representativeness

To assess the representativeness of the KC60 system, we compared surveillance data from the KC60 returns to ASSIST for an equivalent population and time period [12]. ASSIST collected disaggregate data from all STI service providers in the Avon area. Results from this project showed that just 31% of genital chlamydia and 64% of gonorrhoea diagnoses were captured by the KC60 returns from GUM clinics alone when compared to data from all sources in the areas served by ASSIST in 2002 [13].

Figure 5

Completeness of genital herpes, gonorrhoea and genital chlanydia reports in regional database, for the South West of England, 1997 to 2004



Perception of representativeness

Most respondents (24/27 for KC60 and 22/27 for CoSurv) felt that the STI data they received was not representative of the population they served. The reasons mentioned for this perception includes that the KC60 data only represents people presenting at GUM clinics with no data from primary care settings. Also mentioned was the perception of significant patient mobility and preference of patients for open-access clinics.

Usefulness

Of the 27 respondents that participated in the survey, 24 received any STI surveillance data and only eight received outputs from both systems. While public health physicians at the local and regional level have good access to outputs of both sources of STI data, GUM physicians only received KC60 outputs while microbiologists only received laboratory outputs, i.e. each group only receiving the data that they are directly involved with. Voluntary organisations involved in activities promoting sexual health were not receiving any outputs from either of the two STI surveillance systems.

Only 13 of the 27 respondents found the geographical level of the data they receive at as adequate. The geographical level at which data was most desired by respondents was the 'Primary Care Trust' level: 11 of the 13. This is the level at which health services are commissioned for the population. The level of detail in the STI data received was satisfactory according to eight respondents. Additional information most desired was additional geographical and risk factor information. Twenty of the 27 said that they discussed STI data regularly at a local forum, often a sexual health strategy group. The use to which the STI data is put is listed below in order of the frequency with which the 27 respondents mentioned it:

Discussion

The main objectives of disease surveillance systems are the efficient collection, collation and analysis of high-quality data, regular provision of feedback to the participants who provided the data (as well as to any relevant stakeholders and decision-makers), in order to enable the implementation of appropriate public health action. In addition to the above, a surveillance system should be

Table 2

Uses for STI data according to 27 respondents in the South West of England

Use	Number of times mentioned*
Monitor trends	8 (30%)
Plan service delivery	7 (26%)
Dissemination	4 (15%)
Plan prevention	3 (11%)
Training	3 (11%)
Use for strategy meetings	3 (11%)
Compare with other areas	3 (11%)
Scan for news stories	1 (4%)
Trigger research question	1 (4%)

*Multiple choices were possible.

able to detect changes in incidence and prevalence in groups of people most at risk of infection, so that targeted prevention and intervention strategies can be developed [7].

For both STI surveillance systems evaluated, timeliness was a major problem. The KC60 data was received at the regional level from the national level annually (midway into the year after it is collected) from where it is further disseminated to users by the regional epidemiology team. The majority of the users we surveyed felt that the data generated was not useful in reacting to emerging problems as a result of the lateness of the reports. This lateness has significantly undermined the confidence of users, as illustrated by the survey.

While completeness of reports was very good for age and sex in the laboratory system, it was extremely poor for the geographical markers. This limits its value for analysis to be done at relevant geographical levels. Primary Care Trusts, which have the responsibility of commissioning prevention services for their populations, need data at this geographical level for the justification and evaluation of programmes/projects.

The dominant view among stakeholders surveyed was that, other than in broad population terms, the data available was poorly representative. The absence of data from primary care settings, and patients' preference for open-access clinics is believed to skew the data. With the increasing burden of genital chlamydia and the increasing access to sexual health services in settings such as pharmacies, the reliance on GUM clinics for STI data might be inadequate for measuring the burden of STIs in the population.

Many respondents wanted information on risk factors, demography, ethnicity and occupation. Studies have shown that the burden of STIs disproportionately affects certain sub-populations [14, 15] and identifying groups at greatest risk will enable interventions to be targeted. The current, aggregate system of STI data collection in England is unable to fully explain these differences and it will be difficult to show progress in all the new initiatives to improve sexual health.

The strength of the KC60 system is in its stability (not explicitly analysed in this paper), its long-standing existence (since 1917) and therefore its reliable trend data. The collection of minimum risk factor information was desired by most respondents as the data at present conceals variations in respect to sex, ethnicity, and sexual preference.

Faced with an increasing incidence of STIs, surveillance in England is not fulfilling one of the fundamental goals of infectious disease surveillance; to provide information for action. Some of these issues might be addressed with the introduction of the minimum data set for STIs when the national programme for information technology is complete [6]. But in the meantime there is a need to provide timely and useful information for planning, prevention and intervention evaluation.

In attempting to address similar problems, some other regions in England have adapted their surveillance by setting up parallel systems to collect disaggregate data from GUM clinics [16]. Elsewhere, Scotland has recently set up a web-based system STISS (STI Surveillance Scotland) providing real-time secure data collection and validation with scalability functions to any number of sites [17]. All clinics were given NHS-net-enabled computers (secure access to the NHS network); and diagnostic codes were revised to introduce service codes, yielding denominator data. This has led to significant improvements in timeliness and completeness. Other advantages include: real-time secure data collection; real-time validation, enhancing data completeness and accuracy; context-sensitive help; flexible revisions to codes; scalability to any number of locations with minimum site visits. [18].

Several other European countries have recently reported improvement since resorting to web-based electronic reporting for all infectious diseases [19, 20]. Significant improvements in timeliness and completeness of surveillance data were reported following the change to an Internet-based reporting system in the Netherlands[18], while an increased detection of outbreaks was reported in Germany[19].

The arrangement in the England which has separate clinics exclusively for the management of STI, would be a perfect example of the scalability of one system across different treatment settings. A web-based surveillance system would ultimately be needed for the capture of data from different types of service providers. Varying access limitation would overcome issues of confidentiality, allowing the collection of disaggregate data. A web interface would also allow for appropriate data extraction and the ability to interactively analyse up-to-date epidemiological data. The goal should be access to real-time data.

The scope of our analysis is limited the use of data from only one of England's nine regions. However, we feel that confident that the findings represent the situation across the country and our data provides a unique perspective of the relevance of a national surveillance system for public health action at the local level.

Acknowledgements

Many thanks to all GUM Physicians, Consultants in Communicable Disease Control, Consultants in Public Health, Microbiologists and members of the South West Regional Epidemiology Unit that responded to our questions and also thanks to Valerie Delpech and Catherine Lowndes for their kind review of our protocol.

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Citation style for this article: Ihekweazu C, Maxwell N, Organ S, Oliver I, . Is STI surveillance in England meeting the requirements of the 21st century? An evaluation of data from the South West Region. Euro Surveill 2007;12(5)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n05/1205-225.asp

Pertussis outbreak detected by active surveillance in Cyprus in 2003

M Theodoridou[1], A Hadjipanagis[2], N Persianis[2], S Makri[3], C Hadjichristodoulou (xhatzi@med.uth.gr)[3]

1. First Department of Paediatrics, Agia Sofia Children's Hospital, University of Athens, Athens, Greece
2. Greece-Cyprus Paediatric Surveillance Unit, Nicosia, Cyprus
3. Department of Hygiene and Epidemiology, Faculty of Medicine, University of Thessaly, Larissa, Greece

Pertussis is a disease of substantial public health importance that still lacks an efficient surveillance system. It has been a notifiable disease in Cyprus since 1930, and has had an incidence rate of 1 per 100,000 persons during the last 10 years. In 2001, the Greece-Cyprus Paediatric Surveillance Unit (GCPSU) was established with the aim of active surveillance for rare paediatric diseases, including weekly data reporting, zero reporting, and obligatory laboratory tests. From November 2002, pertussis has been included in the active surveillance scheme of GCPSU, resulting in a very early detection of an outbreak in June 2003 that led to immediate and successful action.

Introduction

Although the introduction of childhood pertussis immunisation programmes has significantly reduced the occurrence of the disease in children, waning vaccine-induced immunity permits it to affect adolescents and adults, who in turn, transmit the disease to unimmunised or incompletely immunized infants [1,2]. In most developed countries, the incidence rate of pertussis is relatively low, but outbreaks are occurring every 3-5 years, and it is during those outbreaks that most adult cases are reported [1]. In almost all the countries where outbreaks have occurred, difficulties in implementing an efficient surveillance system for pertussis have been recognised. Different countries operate diverse vaccination and surveillance strategies [2,3]. In most European countries, a five-dose vaccination schedule is applied, and the passive notification surveillance system is used. In some countries, laboratory reporting is used as a supplementary surveillance system, while in others it is the only one [4,5]. In every passive surveillance system, an important issue is that the clinical diagnosis alone may not be specific and the laboratory confirmation is not always performed or standardised. Moreover, there is often a clear lack of awareness regarding loss of immunity and occurrence of the disease in adolescents and adults. The ongoing resurgence of pertussis in both developing and developed countries raises the demand for a more efficient surveillance system. The Global Pertussis Initiative [6,7,8,9] is an example of the international medical community's efforts to address this problem.

The GCPSU has been a member of the International Network of Paediatric Surveillance Units (INOPSU) [10] since 2002. The unit conducts active surveillance on rare paediatric diseases and common "target" communicable diseases, in order to evoke prompt public health actions. In Cyprus, there are 150,000 children aged 0-15 years. Eighty percent of these children are provided with a combined acellular diphtheria-tetanus vaccine by the private medical sector and 20 percent receive the whole cell vaccine by the public sector. The pertussis (DTPa) vaccine has been included in the childhood immunisation schedule at ages of 2, 4, 6, and 18 months and at 4-6 years of age since 1996. The coverage for pertussis vaccination of children aged 16-29 months (including DTP1, DTP2, and DTP3) in Cyprus has risen from 48% in 1980 to 97.7% in 1997 and 97.8% in 2003 (Cyprus Ministry of Health) [11]. These coverage rates are comparable to the rates of most developed countries or even higher [2,3]. Pertussis has been a notifiable disease in Cyprus since 1930. Individual data concerning every pertussis patient were mandatorily notified to the Ministry of Health with a delay of sometimes more than a month. Between 1995 and 2002, an average of less than seven pertussis cases per year were reported by the notification system, representing an incidence rate of 1 per 100,000 persons per year. Ninety percent of reported cases occurred in children less than one year of age. This report presents a pertussis outbreak detected and managed by active surveillance (GCPSU) in Cyprus.

Methods

The GCPSU surveillance system consists of all 196 paediatricians working in Cyprus, who voluntarily cooperate by reporting morbidity data. The GCPSU's goal is to support enhanced early detection, quantification, and localization of paediatric diseases of public health concern, on a national level. Real-time reporting is almost impossible, but collecting and analysing ambulatory clinical diagnoses, confirming them with reliable laboratory data and forwarding them for collection and analysis on a weekly basis through GCPSU is feasible, as shown below.

In November 2002, pertussis was included in the GCPSU surveillance scheme. It was considered a rare disease because of low incidence and high vaccination coverage of the population. The initiation of active pertussis surveillance was accompanied by an informative campaign of paediatricians to increase their awareness about the clinical and laboratory diagnosis of pertussis. Paediatricians ere encouraged to report "suspected" pertussis cases of any age, or provide a zero report on a weekly basis. There was a weekly deadline for the report, and physicians were contacted and reminded by telephone if the deadline was ignored. Every suspected case was initially reported, including information regarding sex, age and place of residence. If the case was laboratory-confirmed later, a detailed questionnaire was used to collect additional information on the vaccination status and about the possible source of infection.

For surveillance purposes, a patient that presented with a coughing illness lasting more than 14 days with either paroxysms of cough, inspiratory 'whoop', or post-tussive vomiting, without other apparent cause, was defined as a "suspected" pertussis case and had to be reported. Every suspected case had to be laboratory-confirmed by detection of *Bordetella pertussis*-specific IgA. All laboratory tests were carried out at the same reference laboratory in order to ensure consistency and reliability of the result. During the 2003 pertussis outbreak, case investigations were conducted to identify possible sources of infection among the household contacts.

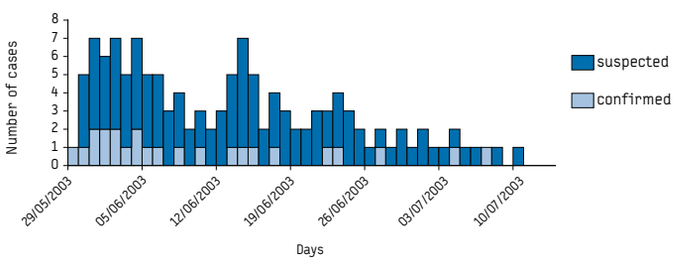
Results

Outbreak detection

During the period between June and early July 2003, the GCPSU recorded 128 "suspected" pertussis cases, 24 of which were confirmed by the detection of positive *Bordetella pertussis*-specific IgA, while the rest were negative. As shown in the epidemic curve (Figure 1), the ratio of the confirmed versus suspected cases was higher during the first days of the outbreak. This could be due to the fact that after the outbreak was registered and was known, paediatricians were more sensitised and did not follow the case definition for the suspected cases exactly, thereby reporting cases not fulfilling the criteria of the suspected cases.

Figure 1

Epidemic curve, pertussis outbreak in Cyprus, 2003 (n=128)



A total of 71 of the suspected pertussis cases presented in Ammohostos (17 of these confirmed), 31 in Larnaka (six confirmed), 17 in Nicosia (one confirmed) and nine suspected pertussis cases (none confirmed) in other areas of Cyprus (Figure 2). The estimated incidence rate of confirmed cases in the most affected area (Ammohostos) was 44.3 per 100,000. The sex distribution of suspected cases was similar to that of confirmed cases while a higher percentage of suspected cases (20%) were younger than 10 years. No major complications were reported; one case was hospitalised, for three days. In the following paragraph, further information for laboratory-confirmed cases is given.

Laboratory-confirmed cases

Three out of the 24 confirmed cases were identified during the case investigation process among close contacts. The majority of

Figure 2

Age distribution of confirmed pertussis cases, outbreak in Cyprus 2003 (n=24)

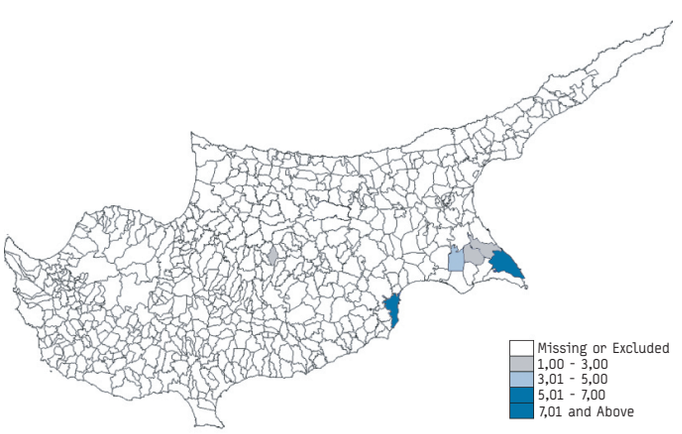
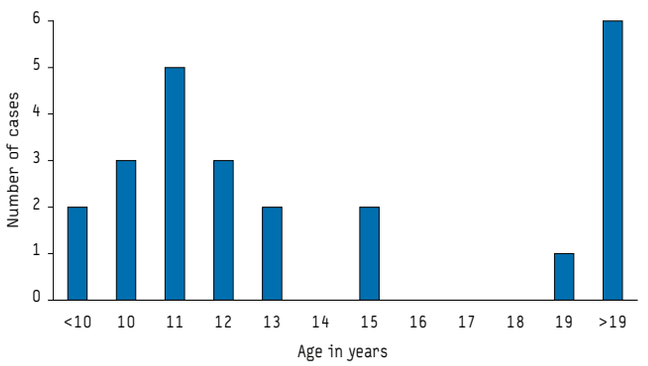


Figure 3

Age distribution of confirmed pertussis cases, outbreak in Cyprus 2003 (n=24)



cases were older than 10 years, two of 24 laboratory-confirmed cases were younger than 10 years, whereas 16 cases were between 10 and 20 years, and six cases were older than 20 years (Figure 3).

Most cases in the outbreak had previously been vaccinated for pertussis. Thirteen of the confirmed cases had received five vaccination doses and were correctly vaccinated. Six of the cases had received three to four doses, two cases one to two doses, and three cases were unvaccinated. The interval between the cases' last immunisation and the onset of disease was also estimated. Nine of the affected patients had received their last immunisation over 11 years previously, five cases eight to 11 years previously, nine cases four to seven years previously, and only one of the cases had received the last immunisation less than four year previously.

Control measures

The GCPSU, in close collaboration with District Public Health authorities, managed to control the outbreak by timely application of the appropriate control measures. As soon as the outbreak was registered, it was decided to vaccinate all close contacts (family members, schoolmates, friends etc) of cases who were considered not to be fully protected by the immunisation doses they had received so far. The following individuals were given a booster dose immediately:

- Children younger than seven years old who had received less than three vaccination doses,
- Children who had received their third vaccination dose more than six months ago, and
- Children who had received their fourth vaccination dose more than three years ago.

Moreover, preventive chemoprophylaxis using erythromycin (40-50 mg/kg per day for two weeks) was administered to those close contacts who were potentially susceptible. None of these developed pertussis. Finally, cases and their close contact persons were informed about the nature of the disease and the ways of transmission. It took approximately one month to control the outbreak.

Discussion

In 2003, a pertussis outbreak with 24 laboratory-confirmed cases among 128 clinically suspected cases was reported through active surveillance (GCPSU) in Cyprus. It took one week for the

GCPSU to register the beginning of the outbreak and to start applying control measures, whereas more than a month would normally be required for the mandatory notification system of the Ministry of Health. By that time and with the implementation of corrective actions by the GCPSU in collaboration with the District Public Health authorities, the outbreak was already almost over. By investigating this outbreak, we had the opportunity to assess the epidemiological patterns of pertussis in Cyprus and document the usefulness of an active surveillance system.

We cannot exclude that some of the suspected cases with negative serological tests were actually "true" pertussis cases, or vice-versa, since the IgA test has a satisfactory sensitivity and lower specificity due to cross-reactions. Culture (high specificity) and PCR with both high specificity and sensitivity were only available as part of a research protocol but not on a routine basis. As the aim of our project was to sensitise paediatricians in pertussis diagnosis, it was decided to use the test that would be routinely available to them after the end of the project, i.e. the IgA test, despite its limitations mentioned above. Moreover, the usual ratio of confirmed versus suspected cases was not known at that time of the outbreak since the GCPSU started operating in 2001 and pertussis was included in its surveillance scheme only in 2002. This ratio can now be calculated by using data from the syndromic surveillance of the Ministry of Health.

Pertussis is still a significant cause of morbidity globally, with a shift of the age distribution of reported cases to adolescence and adults as reported by notification systems of most developed countries [12]. This shift in age distribution was also detected during the outbreak in Cyprus in 2003. The age distribution of confirmed cases (most of the cases >10 years old) was similar to other investigated outbreaks in highly vaccinated populations, while in poorly vaccinated populations most of the cases were in children less than 10 years old [13,14]. Waning immunity in fully immunised individuals (54.1% in this study) or incomplete immunisation (45.9% in this study) are considered responsible for the documented shift in age distribution of pertussis cases in many studies.

Continuous improvement of immunisation (for example adolescence immunisation) and other preventive actions are being discussed and gradually applied worldwide, but considering the nature of the disease and the insufficient registration monitoring of epidemiological information on pertussis, it is clear that the introduction of a more functionally active surveillance system is also required. Reporting individual data on a weekly basis to a central data collecting unit and performing laboratory tests in reliable standardised laboratories proved to be very efficient in this outbreak. Even more effective was the decision to involve every possible primary or institutional paediatrician in the detection and registration of pertussis, by contacting and informing them systematically. Cyprus is a small island with around 150,000 children and a relatively small number of paediatricians (196). Thus, it is easy to motivate the paediatricians to report individual data immediately. In countries with larger populations, the involvement of only a geographically representative sample of paediatricians would be more appropriate.

The immediate implementation of corrective actions, which was only possible because of the early detection, made it possible to restrict the outbreak within very tight limits. One of the drawbacks of the GCPSU surveillance scheme for this specific disease was the fact that the system could not cover the adult cases and take into consideration the epidemiological patterns of pertussis in recent years This was one of the reasons why the Cyprus Ministry of Health decided to include pertussis in the syndromic surveillance system in which General Practitioners are included. The GCPSU is still functioning, but pertussis is no longer included in the diseases under surveillance. The aim of a paediatric surveillance unit is to initiate surveillance activities for rare diseases for a fixed time period and with specific objectives. Thus, the diseases under surveillance are changing. The objectives of pertussis surveillance were achieved by showing that the epidemiological patterns of pertussis documented worldwide are the same in Cyprus. Moreover, it was a useful experience to promote the initiation of syndromic surveillance in the Ministry of Health.

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Citation style for this article: Theodoridou M, Hadjipanagis A, Persianis N, Makri S, Hadjichristodoulou C, . Pertussis outbreak detected by active surveillance in Cyprus in 2003. Euro Surveill 2007;12(5)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n05/1205-226.

Cryptosporidiosis surveillance and water-borne outbreaks in Europe

JC Semenza (Jan.Semenza@ecdc.europa.eu)[1], G Nichols[2]

1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
2. Environmental and Enteric Diseases Department, Health Protection Agency Centre for Infections, London, United Kingdom

Cryptosporidium causes diarrhoeal disease that can be particularly severe in immuno-compromised individuals. Cryptosporidiosis is a notifiable disease at European Union level, and surveillance data are collected through the European Basic Surveillance Network. The disease distribution in Europe for 2005 showed 7,960 cryptosporidiosis cases reported from 16 countries. The crude incidence rate was 1.9 cases per 100,000, although there were considerable differences in the rates of cryptosporidiosis between countries. Infection was more commonly reported in young children. A pronounced seasonal peak was observed in the autumn of 2005, with 59% of the cases reported between August and November, although Ireland and Spain experienced a peak in spring and summer, respectively. Cryptosporidiosis outbreak investigations and analytic studies have associated the disease with drinking water supplies, animal contact, travel, and swimming pools. Contamination of the source water for drinking water supplies, as well as inadequate water treatment can be responsible for cryptosporidiosis outbreaks. Routine cryptosporidiosis surveillance from North West England over 17 years showed that the cases occurred predominantly in spring and autumn. British drinking water regulations and improvements in drinking water treatment have coincided with a decline in cryptosporidiosis incidence. Improvements in cryptosporidiosis surveillance such as detection, recording and reporting will help to recognise outbreaks and monitor interventions.

Introduction

Cryptosporidium is a genus of protozoan parasites. Some species infect mammals including cattle, sheep, rodents, cats and dogs, but also birds, fish and reptiles. It can cause diarrhoea in humans, and protracted diarrhoea in people with an immune deficiency. Faecal-oral transmission can occur directly through person-to-person and animal-to-person routes or indirectly through environmental vehicles including water and food. Outbreaks have been reported in healthcare facilities and daycare centres, within households, among bathers and water sports participants in lakes and swimming pools, and in municipalities with contaminated public water supplies or people served by private water supplies [1]. The disease in humans is predominantly caused by the species *Cryptosporidium hominis* and *C. parvum*, although a number of other species are also pathogenic for humans.

Cryptosporidium oocysts can resist harsh environmental conditions (heat, cold or chemical insult) for extended periods of time and can survive for months in moist soil or water. Furthermore, oocysts can survive most common water disinfection procedures, including chlorination [2]. Water distribution systems and swimming pools are particularly vulnerable to contamination with *Cryptosporidium* and thus pose a considerable threat to public health. Oocysts can, however, be effectively removed by well operated filtration, or killed by UV treatment.

Surveillance of cryptosporidiosis in Europe

Data on cryptosporidiosis cases are collected and recorded by health agencies in several European countries, and the confirmed cases from 16 countries reported to the European Basic Surveillance Network (BSN) in 2005 are presented in Table 1. The reporting is based on the case definition described in EC decision 2002/253/EC, i.e. a clinical description characterised by diarrhoea, abdominal cramps, loss of appetite, nausea and vomiting, or laboratory confirmation of oocysts in stool, intestinal fluid or small-bowel biopsy specimens, or antigen in stool. A total of 7,960 cases were reported to the BSN in 2005, with 70% reported from the United Kingdom. However, the highest incidence was observed in Ireland with 13.7 cases per 100,000. Only five of the 16 countries reported age specific incidence, which revealed an elevated risk among individuals younger than five years of age (5.7 cases per 100,000) and five to 14-year-olds (2.5 cases per 100,000) compared to older age groups (incidence =<1 cases per 100,000) (Figure 1).

Table 1

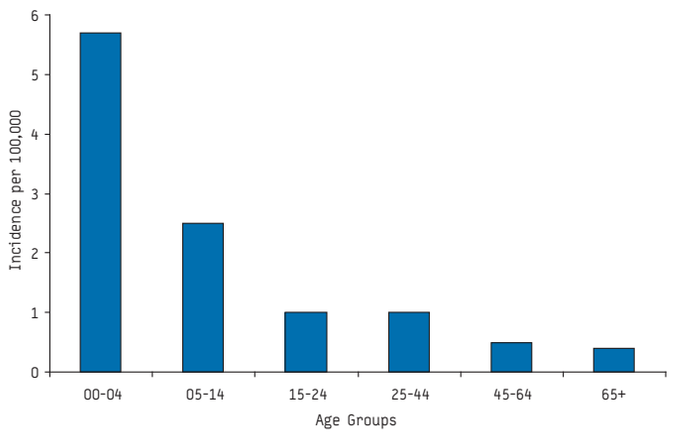
Reported cryptosporidiosis cases and incidence by country, 2005 (Source: Basic Surveillance Network).

Country	Confirmed Cases	Incidence*
Belgium	357	3.4
Cyprus	0	0.0
Czech republic	1	0.0
Estonia	0	0.0
Germany	1284	1.6
Hungary	0	0.0
Ireland	565	13.7
Latvia	0	0.0
Lithuania	0	0.0
Malta	6	1.5
Poland	0	0.0
Slovakia	0	0.0
Slovenia	9	0.5
Spain	108	0.3
Sweden	69	0.8
United Kingdom	5561	9.3
Total	**7960**	**1.9**

*Incidence per 100,000 population (confirmed cases only).

FIGURE 1

Age-specific incidence rates of confirmed cryptosporidiosis cases, 2005. (Source: basic Surveillance Network).



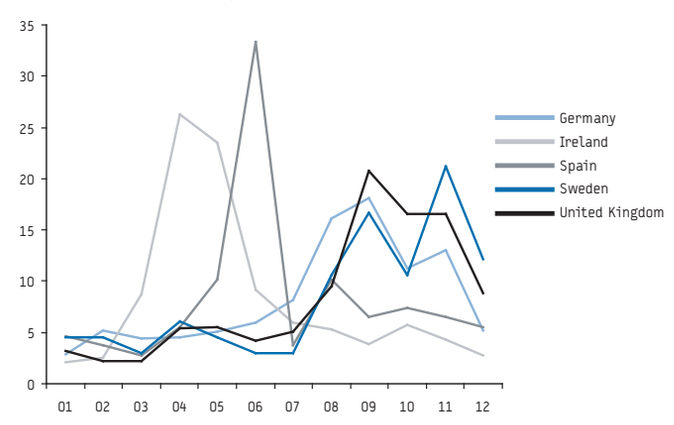
It is difficult to compare counts and incidence between countries due to differences in detection, investigation, case definitions, recording and the procedural/legal basis of reporting. The extent to which routine diagnostic laboratories around Europe screen for *Cryptosporidium* is unclear, but it is likely that there are substantial differences in ascertainment between countries. Furthermore, the reported cases are likely to underestimate the actual burden of cryptosporidiosis due to the insensitivity of passive surveillance. Thus, the currently available data represent only 60% of European countries, and are likely to be biased by the conditions of reporting.

Seasonality

Figure 2 illustrates the percentage of cryptosporidiosis cases per month for individual countries. While this shows differences between months, the data are for a single year only and do not necessarily reflect regular seasonal trends. A peak is observed in the autumn for most countries. However, Ireland saw an increase in spring, and the number of cases in Spain peaked in summer.

FIGURE 2

Monthly percentage of total annual cryptosporidiosis notifications* for selected countries, 2005 (Source Basic Surveillance Network)

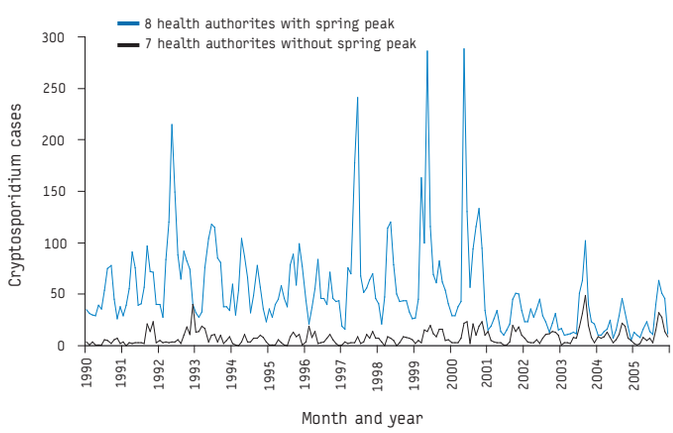


N=6,807 for which seasonal data were available.

For certain countries, the available data are sparse (reflecting limitations in laboratory testing and surveillance in these countries). Surveillance data for multiple years would be necessary to confirm the seasonality of the results, but such data are not available on a European level. An attenuated increase in spring cases is observed in the United Kingdom and Sweden. Evidence from England and Wales suggests that cases of cryptosporidiosis in the spring have mainly been caused by *C. parvum*, while cases in the autumn are frequently caused by *C. hominis* [3,4]. The seasonality of cryptosporidiosis has changed over the years within England and Wales and the spring peak has substantially decreased since 2001 [3,4]. The autumn cases may be caused by holiday travel and swimming pool use, but the evidence is poor.

FIGURE 3

Cryptosporidium cases in two groups of Health Authorities in North West England 1990-2005.



Routine surveillance in North West England over 17 years showed that the majority of cases occurred in spring and autumn [4,5]. The introduction of *Cryptosporidium* drinking water regulations in 1999 that came into effect in 2000/01 together with substantial additional investment in drinking water treatment has led to a reduction in the cases in the spring, but had only a negligible effect on the cases in late summer. Data from eight health authorities in North West England that had previously had regular spring increases have shown a dramatic reduction in these spring cases since 2001, compared to seven control health authorities, where there had never been a regular spring increase (Figure 3). This suggests that improved water treatment such as filtration of previously unfiltered water has resulted in a substantial reduction in the disease [4,5].

Major documented outbreaks via public water supplies

A relatively small proportion (2%) of the sporadic and epidemic cases of gastrointestinal infections suffered in Europe is estimated to be waterborne [1], and the case count differs by country (Table 1). The number of reported waterborne infections varies greatly and is probably affected by the quality of the public water supply and sewage disposal systems, and the nature of the surveillance systems for these diseases. Several *Cryptosporidium* outbreaks associated with public water supplies in Europe have been reported in the literature and selected examples are presented in Table 2.

Table 2

Selected reports of Cryptosporidium outbreaks associated with drinking water

Country	Study description	Ref
Denmark	A nosocomial outbreak of cryptosporidiosis involved 18 HIV-positive patients who were admitted as in-patients to a Hospital in Copenhagen in 1991. The source of the outbreak was identified as ice from an ice machine, contaminated by a patient with cryptosporidiosis picking out ice for cold drinks. Of the infected HIV-positive patients, eight died after prolonged diarrhoea.	6
England and Wales	In 2000, 58 cases were confirmed after heavy rainfall and flood alerts. Cryptosporidium oocysts infiltrated the reservoir from springs and persistence in the water distribution system after the municipality had chosen a different water source. This persistence may have been due to oocysts being entrapped within biofilm on the surface of the water pipes.	7
England and Wales	After heavy precipitation a Cryptosporidium outbreak involving 47 cases occurred in North West England in 1993 one water source was found to drain surface water directly from a field containing livestock faeces, thereby bypassing natural sandstone filtration. A case-control study showed significant association with drinking unboiled tap water, and after withdrawal of the original water supply, the outbreak rapidly subsided.	8
France	An outbreak in 2001 in Dracy Le Fort, Burgundy caused gastroenteritis in 563 of the 1,100 inhabitants. C. hominis was detected in 19 patients. Tap water consumption was the only risk factor associated with the cases, and oocysts were identified in the water-supply.	9
Ireland	A rise in the number of laboratory-notified cases of cryptosporidiosis in 2007 alerted public health officials of an outbreak involving 182 cases in the city and county of Galway. Exceedences to the guideline of less than one oocyst/10 litres observed in the final treated water was linked to the heavy precipitation of historic proportions and the water source reaching the highest lake level on record.	10
Italy	A waterborne outbreak occurred in a drug rehabilitation community in Northern Italy in 1995. The attack rate was 13.6% among HIV-negative individuals and 30.7% among HIV-positive individuals, although in the latter, it varied according to CD4 cell count. Oocysts were identified in sediment from drinking water storage tanks.	11
Northern Ireland	Between 2000 and 2001, 347 laboratory-confirmed cases were linked to contamination of the drinking water supply. Human sewage from a septic tank and wastewater from a blocked drain seeped into the drinking water distribution system.	12
Northern Ireland	In 2002, an increase in Cryptosporidium cases (29 confirmed cases, linked to the same water supply) was noted by the health board. Oocysts were detected in raw and treated water, and in the environment surrounding the lake in the watershed. An epidemiologic, environmental, and microbiological investigation indicated agricultural practices which could have resulted in contamination of the water source with manure.	13
Russia	In 1999, the seroprevalence of Cryptosporidium was assessed in 50 community-recruited adults and 50 blood donors from Cherepovets, Russia. Over a follow-up period, drinking non-boiled water from shallow draw-wells was associated with an increase in seropositive blood samples.	14
Scotland	An outbreak of waterborne cryptosporidiosis in Ayrshire in 1988 affected 27 people. Hundreds of people had suffered from diarrhoea. Cryptosporidium oocysts were detected in the water supply, and the contamination had originated in a break-pressure tank.	15
Spain	An outbreak in 1998 in Guadarrama (Madrid, Spain) affected 21 children. Cryptosporidium oocysts were detected in eight cases. A case control study found a statistically significant association between tap water consumption and gastroenteritis. Deficiencies were observed in water treatment but no oocysts were found in the water.	16
Sweden	In 1991, a cross-connection to a contaminated creek led to contamination of the community water supply, causing 600 infections including cryptosporidiosis.	17

In 208 of 710 waterborne disease outbreaks officially reported in Europe between 1986 and 1996, the causative agent was identified through epidemiological investigations; of these, Cryptosporidium was implicated in one outbreak in Croatia, 13 in England, one in Spain, and one in Sweden [1]. Cryptosporidium has been linked to drinking water supplies in a number of European Union member states. This issue was examined as part of the European project MedVetNet called Cryptnet (http://www.cryptosporidium.it/index.php?id=04). A recent report on cryptosporidiosis in England and Wales identified 149 cryptosporidiosis outbreaks between 1983 and 2005, 55 of which were linked to municipal drinking water supply, six to private water supplies, 43 to swimming pools, and 16 to contact with animals [3].

Preventing cryptosporidiosis infections

In most European countries chlorine is used to disinfect drinking water and to prevent bacterial growth in the water distribution system. Alternative methods such as ozone (O_3) or UV are also very effective processes of inactivation. In addition, chlorine dioxide is currently used in drinking water in Belgium, France, Germany and Italy to inactivate *Cryptosporidium*. Although standard chemical disinfection has limitations, flocculation (a process by which fine particulates are caused to clump together into floc) and filtration can remove *Cryptosporidium* oocysts if carried out properly. Particles suspended in water tend to be negatively charged and repel each other. Coagulation with aluminium sulfate, iron (II) sulphate or iron (III) chloride eliminates this natural charge so that oocysts attract each other and coagulate, building larger particles that will eventually precipitate. Sedimentation and filtration can then provide

an effective barrier for *Cryptosporidium*. Membrane filtration can further improve the quality of the drinking water. Heavy rainfall can cause water drainage systems to overflow and strain water treatment capacity, leading to *Cryptosporidium* contamination of the water supply, treatment plant, or distribution network [2]. Water catchment management and temporary abandonment of water sources have both been useful in reducing the contamination of source waters, and the World Health Organization (WHO) Water Safety Plans are being used to improve drinking water quality.

In summary, cryptosporidiosis can be a life-threatening disease in immuno-compromised individuals and is of concern in young children. The seasonal BSN data and the longitudinal surveillance from England indicate recurrent exposure of the general public to *Cryptosporidium*. However, evidence from North West England shows that improvements in drinking water treatment can substantially reduce the number of cryptosporidiosis cases. These data illustrate opportunities for communicable disease control of this rarely reported, but potentially severe disease. Improvements in investigation, detection, case definition, recording and reporting of cryptosporidiosis are important in assessing the disease burden and in identifying outbreaks. Targeted interventions such as upgrading drinking water treatment plants require timely and complete surveillance data in order to assess risks using Water Safety Plans and to monitor the effectiveness of interventions [18,19].

Acknowledgements

The authors would like to thank Dr. Edward van Straten from the Surveillance Unit at the European Centre for Disease Prevention and Control for technical assistance with the data. We would also like to thank the anonymous reviewers for their detailed comments and critical feedback.

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Citation style for this article: Semenza J, Nichols G, . Cryptosporidiosis surveillance and water-borne outbreaks in Europe. Euro Surveill 2007;12(5)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n05/1205-227.asp

Incidence of Beijing genotype of Mycobacterium tuberculosis in Elche, Spain: A 13-year surveillance study

E Garcia-Pachon (egpachon@Gmail.com)[1], I Escribano[2], JC Rodriguez[2], M Ruiz[2], JM Ramos[3], JF Navarro[4], and G Royo[2]

General University Hospital and University Miguel Hernandez Elche, Spain:
1. Section of Pneumology
2. Section of Microbiology
3. Infectious Diseases Unit
4. Section of Preventive Medicine

Strains of the Beijing genotype family of Mycobacterium tuberculosis have been associated with outbreaks and multidrug resistance. We performed a retrospective thirteen-year surveillance study (1993 – 2005) on the occurrence of this strain in Elche, Spain. Only one of the available isolates from 332 cases of tuberculosis tested positive for Beijing strain. The case, detected in 2001, was that of an immigrant patient from Senegal with pulmonary tuberculosis. The strain was not drug resistant and besides six close contact persons that were infected no secondary cases of this strain were detected. In the Elche area, the incidence of Beijing strains is very low and there is no evidence of transmission or higher virulence.

Introduction

Molecular epidemiology studies have revealed a genotype of *M. tuberculosis* strains that seem to possess selective advantages compared with other strains, have increased virulence and are sometimes associated with multidrug resistance [1,2]. This genotype has been called 'Beijing' or 'Beijing/W' family [1,2] and it is widespread around the world. The fact that this family of strains is widespread and, in some situations, associated with multidrug resistance has led to concern that these strains may be spreading and may have a predilection for acquiring drug resistance [2].

The detection of the Beijing genotype in a particular region and the study of trends over time is of great interest. However, reports from Western Europe (countries with low incidence of this strain) are very scarce. We performed a 13-year retrospective surveillance population-based study in our area in order to detect any possible isolation of *M. tuberculosis* Beijing genotype and to analyse its clinical and epidemiological characteristics.

Methods

Population and data collection

Elche Health District is a region in the southeast of Spain with a population of about 265,000 people during the study period. All microbiological investigations were performed at the regional hospital microbiology laboratory, which is the only laboratory that performs culture-based tuberculosis diagnosis in our region. A search for Beijing/W family strains was performed among 332 *M. tuberculosis* isolates obtained from tuberculosis patients from beginning 1993 to end of 2005, which represent 73% of isolations during this period, and clinical and epidemiological data for each isolate was obtained. The remaining 27% were not available for analysis due to problems during their frozen conservation.

Identification of Beijing Strains

The identification of Beijing strains was performed as proposed by Warren et al. [3]. To identify a Beijing strain, the DNA was subjected to four amplifications with different primers using a polymerase chain reaction (PCR) method based on comparative genomic data. A positive amplification product of 393 base pairs (bp) and 239 bp, respectively, indicated the presence of an IS6110 insertion in Rv2820 that is unique to the Beijing evolutionary lineage. A positive amplification product of 569 and 308 bp, respectively, indicated the presence of M. tuberculosis strain(s) belonging to non-Beijing evolutionary lineages. All tests were performed in duplicate. As a control we used a strain of the Beijing family that was provided by the Mycobacteria Laboratory of Zaragoza University, Spain.

Results

In the study period a total of 455 cases of TB were laboratory diagnosed in the Elche region and isolates for 332 patients were available for further investigation. Of those 332 patients 72% were men, and the mean age was 42 (standard deviation 24). Two hundred and seventy-five patients were of Spanish origin and two were from Western Europe. The origin of 55 immigrants with tuberculosis was Africa for 26, South-America for 17, East-Europe for 10 and Asia for two patients. All 27% of isolates that were unavailable for analysis were obtained from patients of Spanish origin.

We performed two PCR assays in each isolate allowing us to classify the strains into two lineages: Beijing and non-Beijing. Only one isolate of the *M. tuberculosis* Beijing family was obtained, in 2001. The patient was a 24-year old, HIV-negative male from Senegal with pulmonary tuberculosis with cavitations in both lungs. Bacilli were obtained in three sputum samples. The isolate was susceptible to the five antituberculous drugs tested. The patient had close contact with six individuals: three from Senegal and Gambia at the patient's home, and two from Senegal and one Spaniard at work. On investigation all showed a tuberculin skin test higher than 20 mm. Chemoprophylaxis with isoniacid was prescribed for all six contact persons and none of them developed tuberculosis during the follow-up.

Discussion

In this 13-year population-based study in the southeast of Spain, we found a very low occurrence of the Beijing strain of *M. tuberculosis*. Only one case of this strain was found in 332 patients

with laboratory-confirmed tuberculosis. However, it should be noted that 27% of the strains in our area were unavailable for analysis. Interestingly, although all six close contact persons examined were infected, we found no secondary cases. This finding is important because in another report from Spain (Gran Canaria island) an immigrant patient from Africa with laryngeal tuberculosis was the origin of a dissemination of this strain that only five years later was responsible for more than 20 percent of all cases of tuberculosis in the island [4]. The experience in our region is very different to that reported in other regions. Although the study does not report a high number of infections due to the Beijing type strain, we feel that is important to present our findings because they show the differences in the distribution of this strain. In a recent publication that includes patients from 49 studies in 35 countries, the authors describe four patterns for Beijing genotype tuberculosis:

- endemic not associated with drug resistance,
- epidemic associated with drug resistance,
- epidemic but drug sensitive, and
- very low level or absent [5].

Our population can be included in the fourth group, which is the most common in Europe.

Studies on time trends of this genotype are scarce. It has been reported that all Western European sites analysed except London showed a slight increase in Beijing strains over time. In St Petersburg, Okayama, Buenos Aires, Sao Paulo and San Francisco, no significant change occurred over time, but the studies only covered a few years [5]. In Cape Town and Malawi, significant increases occurred over time and were unchanged after adjusting for age [5].

In Western Europe, the Beijing genotype is more common among immigrant patients than in indigenous patients [5]. Reports from Spain are scarce but show that infections with the Beijing strain are almost exclusively found in immigrant patients [4,6,7]. In our region, the proportion of recent transmission is high (established by molecular epidemiology) [8,9], and immigration has markedly increased during this period [10]. For this reason, we expected to find more cases of tuberculosis belonging to the Beijing family in recent years. However, no cases have been detected after 2001. We can assume that the immigrant population in our area, which is now an important origin of newly diagnosed cases of tuberculosis, is not infected by *M. tuberculosis* Beijing strain, probably because they come mainly from regions with no predominance of this strain.

Our study shows a very low occurrence of Beijing genotype of M tuberculosis in the Elche region, without evidence of secondary cases. Continuous control of the possible presence and characteristics of this strain will provide further information on the true epidemiological situation of the Beijing genotype.

Acknowledgements

This study was funded by the Escuela Valenciana de Estudios para la Salud (Valencian School for Health Studies, EVES), Spain.

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Citation style for this article:

Garcia Pachon E, Escribano I, Rodriguez J, Ruiz M, Ramos J, Navarro J, and al. Incidence of Beijing genotype of Mycobacterium tuberculosis in Elche, Spain: A 13-year surveillance study. Euro Surveill 2007;12(5)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n05/1205-229.asp

Toscana virus meningitis in Portugal, 2002-2005.

L Santos (lursantos@net.sapo.pt)[1], J Simões[2], R Costa[2], S Martins[2], H Lecour[3]

1. Infectious Disease Service, School of Medicine and Hospital S. João. Alameda Professor Hernâni Monteiro, Porto, Portugal
2. Department of Microbiology, Hospital S. João. Alameda Professor Hernâni Monteiro, Porto, Portugal
3. Institute of Health Sciences, Universidade Católica Portuguesa (Portuguese Catholic University, UCP), Porto, Portugal

Toscana virus infection is endemic in Italy, but has also been documented in other Mediterranean countries. Our aim was to investigate the occurrence of Toscana virus (TOSV) meningitis in children and young adults in a metropolitan area in the north of Portugal. Cerebrospinal fluid samples from 308 patients with the diagnosis of meningitis and with negative bacterial culture were tested for enteroviruses and herpesviruseses by reverse transcription PCR. Those samples that proved negative for enterovirus and herpesvirus were tested for Toscana virus with a commercial reverse transcription nested PCR assay. In total, we investigated 106 samples, collected between May and September during the four-year period between 2002 and 2005 from patients younger than 30 years old. Toscana virus was the cause of meningitis in six (5.6%) of the cases, three children and three young adults. All had a benign course and self-limited disease. Since a first case report of TOSV infection 1985 and another in 1996, both in foreign tourists, these six cases of Toscana virus meningitis are, to our knowledge, the first diagnosed in Portuguese inhabitants, and they underline the need for more studies on the prevalence of this virus in Portugal.

Introduction

With the improvement of diagnostic techniques such as PCR, it is now possible to rapidly diagnose viral meningitis through identification of the pathogen [1]. In Portugal, enteroviruses are the most frequent cause of aseptic meningitis but, despite thorough testing, a significant number of patients are discharged from the hospital without an etiological diagnosis [2,3]. The inclusion of Toscana virus (TOSV) diagnosis in the laboratory tests for enterovirus- and herpesvirus-negative samples was an attempt to improve the knowledge about aseptic meningitis. Viral meningitides, including TOSV meningitis, are non-notifiable diseases in Portugal and are characterised by non-specific symptoms. Consequently, their seroprevalence is unknown.

TOSV belongs to a group of sandfly fever viruses are arboviruses, transmitted by the sandfly (genus *Phlebotomus*), and classified in the *Bunyaviridae* family, genus *Phlebovirus*. Three sandfly fever viruses have been identified in Mediterranean area: sandfly fever Naples virus, sandfly fever Sicilian virus, and Toscana virus. The latter is endemic in central Italy and described as the most frequent cause of aseptic meningitis in children in that region [4,5]. As a consequence of the life cycle of *Phlebotomus*, TOSV is more frequent during summer, with a peak in August. The most common presentation is an acute febrile illness or meningitis, and more rarely a meningoencephalitis [5-7]. Most of the studies on TOSV have been done in central Italy, but the occurrence of TOSV in other countries such as France, Spain, Slovenia, Greece, Cyprus, Turkey and Egypt, has also been reported recently [8]. TOSV can be identified by culture of cerebrospinal fluid (CSF), a time-consuming method with low sensitivity, but very useful for virus characterisation and genetic studies [8]. Immunoenzymatic tests, (IgM by IFA or ELISA) are rapid and sensitive; however cross-reactivity can occur. Nowadays, reverse transcription (RT)-PCR is considered the method with the highest sensitivity and specificity for virus detection [8,9]. Many vectors implied in human diseases, including *Phlebotomus*, are present in Portugal [10]. The aim of this study was to investigate the occurrence of TOSV meningitis in children and young adults in an urban area in the north of Portugal.

Methods

During the period 2002 to 2005, we have investigated the occurrence of TOSV in CSF samples of aseptic meningitis patients. Aseptic meningitis was defined by a CSF cytosis greater than six leukocytes/ml and a negative bacterial culture. RNA was extracted from the samples with the Qiamp viral RNA mini kit (Qiagen). Samples that were PCR-negative for enterovirus and herpes virus and that had been taken from patients younger than 30 years and hospitalised between May and September each year were tested for TOSV with a nested RT-PCR assay purchased from Amplimedical SpA (Toscana, N prot Kit). Each run included a negative control (water) and a positive control (Toscana virus positive control, Amplimedical SpA). Some negative samples (n=26) were tested with an 'in-house' nested RT-PCR protocol with published outer and inner primers [11].

Results

Over the four-year period (2002-2005), 308 patients were admitted to the emergency department of our hospital with aseptic meningitis and hospitalised for observation and study. They were analysed by RT-PCR for the presence of a number of viruses known to cause meningitis (enterovirus, herpes simplex virus (HSV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and West Nile virus) during the acute phase of the disease. The results are indicated in the Table.

RT-PCR for enterovirus and herpes simplex virus were done in an order determined by the patient's mental status at admission. CSF samples from patients with a normal level of consciousness or with somnolence (Glasgow Coma Scale >=14) were analysed first for enterovirus, and if this was negative, subsequently for HSV. Samples from patients with further impaired mental status (Glasgow Coma Scale <14) were first analysed for HSV, and then, if negative, for enterovirus. RT-PCR for CMV and EBV was performed only in cases with a negative result for HSV and enterovirus. RT-PCR for West Nile virus was done only in 15 patients aged over than 60 years without aetiologic diagnosis. It was negative in all of them.

For this study, we chose 106 of those 308 samples to be tested for TOSV using the Amplimedical SpA nested RT-PCR

Table

Diagnosis of aseptic meningitis by reverse transcription PCR in cerebrospinal fluid samples, Portugal, May-Sept 2002-2005 (pool of samples = 308)

PCR	No. of positive samples	No. of negative samples
Enterovirus	110	178
Herpes simplex virus	20	178
Epstein-Barr virus	5	173
Cytomegalovirus	3	175
West Nile virus	0	15
Toscana virus	6	100
Total no. of viral meningitis cases*	**144 (47%)**	

* positive for one of the six viruses analysed

assay. This included only samples from patients who had been admitted between May and September in the years from 2002 to 2005 and had been negative for enterovirus, HSV, EBV and CMV when tested upon hospital admission. All patients were younger than 30 years of age (range 2.5 months to 30 years). TOSV was detected in six (5.6%) of those 106 samples. Three were children – one aged four years and two aged eight years – and three were young adults, aged 16, 23 and 30 years. Three of the patients were male. All six patients live in an urban area, and none of them had a recent history of travelling abroad.

All cases had occurred between May and July, two cases in 2002, three in 2003 and one in 2005. Admission symptoms were fever, headache and vomiting, and lasted between one and five days. On admission, meningeal symptoms were present in all patients and somnolence in three. Two of them had brain-computed tomography that was normal. CSF cytosis ranged from 70 to 1,090 cells/µl, with normal glucose and protein levels. The blood leukocyte count varied from 5.6 to 11.8x10^9/L, and C-reactive protein was normal in all patients. All underwent only supportive treatment with antipyretics and intravenous fluids and had a benign and self-limited disease. They were discharged between four and seven days after admission. Twenty-six of the 106 samples were examined only by an 'in-house' RT-PCR assay. The sensitivity of this assay was comparable to the commercial RT-PCR when tested using TOSV-positive clinical samples. All 26 samples that were only tested by this method were negative.

Discussion

In the Mediterranean countries, especially Italy and Spain, the interest in TOSV has increased in recent years [12-14]. PCR is the most frequent method used for TOSV diagnosis. It can be complemented by immuno-enzymatic tests, which are rapid and sensitive [8,11], or culture, which in combination with PCR is useful for genetic characterisation of the virus. Most of the reported cases of TOSV infections occur throughout the summertime in the central region of Italy, particularly in the Siena province, in children [4,5,9,15]. A study by Valassina *et al*. [5] describes the analysis of 277 meningitis cases that occurred in Tuscany between 1995 and 1998. TOSV was identified as the cause for 58% of the cases admitted in the period between June and September, and for 10% of the cases admitted from May to October, reflecting the seasonality of the infection. Other studies investigate the seroprevalence of TOSV in humans in southern Europe [8]. More recent reports have demonstrated the occurrence of TOSV in Spain, in the Granada and Madrid provinces [8,16-18]. A study by Navarro *et al*. shows that this virus is responsible for 7% of aseptic meningitis cases in Spain [16]. In another Spanish study using samples collected between 1988 and 1996, TOSV was the cause of 8% of aseptic meningitis cases; these authors analysed 1,268 serum samples from adults and children for the presence of antibodies against TOSV, and found a prevalence of 26.2% [17]. Echevarria *et al*. [18] identified TOSV as the cause of 8.6% of aseptic meningitis cases in the region of Madrid, where 5% of the healthy population were shown to have had a past infection. Another Spanish publication on the seroprevalence of TOSV in the community of Madrid, comparing two periods (1993 to 1994 and 1999 to 2000) found past infections in 7.2% and 5.7%, respectively. It further showed that seroprevalence is age dependent, with the antibody prevalence increasing with age [14]. Two TOSV cases have been identified in southern France, one of aseptic meningitis and the other of influenza-like illness [19,20]. In addition, several reports have been published on TOSV infection in travellers returning from Mediterranean countries [21-24].

The climate conditions in Portugal favour *Phlebotomus* survival. Two infections with TOSV, acquired in Portugal, have been reported in the past. Both were in male tourists, one Swedish and one German, returning from their holidays in Portugal in 1985 and in 1996, respectively [25, 26]. One of them had documented meningitis. Studies on the occurrence of TOSV in Portugal have so far not been done, and the six cases of TOSV meningitis reported here are the first cases diagnosed in Portuguese inhabitants. Thus, in our opinion, the investigation of TOSV in summer cases of meningitis in Portugal should be continued in the future, as it is done in other Mediterranean countries, even though the prevalence of TOSV appears to be lower in Portugal. Serological surveys are planned to document the prevalence of antibodies against TOSV in all age groups of the Portuguese population, in order to gain a clearer picture of the occurrence of this form of viral meningitis.

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Citation style for this article: Santos L, Simões J, Costa R, Martins S, Lecour H, . Toscana virus meningitis in Portugal, 2002-2005. Euro Surveill 2007;12(6)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n06/1206-222.asp

Sentinel Surveillance: an option for surveillance of infectious intestinal disease

C Gauci (charmaine.gauci@gov.mt)[1], T Melillo Fenech[1], H Gilles[2], S O'Brien[3], J Mamo[4], I Stabile[4], N Calleja[5], F Ruggeri[6], L Cuschieri[1]

1. Disease Surveillance Unit, Department of Public Health, Malta
2. University of Liverpool, United Kingdom
3. University of Manchester, United Kingdom
4. University of Malta, Malta
5. Department of Health Information, Malta
6. Istituto Superiore di Sanitá, Rome, Italy

Sentinel surveillance systems offer advantages over passive surveillance which is known to have limitations due to incomplete reporting. Sentinel surveillance gathering data from selected sources was piloted as an option for surveillance of infectious intestinal disease (IID) in Malta. Between October 2004 and May 2005, 22 general practitioners (GPs) voluntarily participated in the study and reported on the number of IID cases (by age and sex) and all primary care encounters in their practice. The GPs' reporting activity lasted for 35 weeks, covering a total of 55,425 primary care encounters, of which 1.95% concerned IID. For every case reported via the routine passive notification system, seven cases would be picked up by this enhanced sentinel surveillance.

Introduction

Surveillance is fundamental for public health decision-making and subsequent action. Over the past few decades, communicable disease surveillance has undergone considerable development. The more commonly used passive surveillance systems, which rely on disease notifications from physicians and laboratories, are known to have limitations due to incomplete reporting [1]. One of the diseases most prone to under-reporting is infectious intestinal disease (IID). To date, the main source of data on IID in Malta has been the passive surveillance system in which doctors and medical diagnostic laboratories report cases to the national surveillance system. Mandatory reporting of cases of salmonellosis, campylobacteriosis, *Escherichia coli* infections, giardiasis, cryptosporidiosis and shigellosis is required from both medical practitioners and laboratories [2]. However, there is no obligation to report cases of IID when food is not the suspected source. As a result, the impact of this illness in terms of the frequency of IID in Malta is not known.

In 2004-2005, a cross-sectional age-stratified study on a random sample of 3,504 persons was performed, with the aim of determining the prevalence of IID at community level, [3,4]. This study estimated a period prevalence of 3.18% of persons suffering from IID in the 28 days prior to the interview and a rate of 0.42 (95% CI 0.09-0.77) episodes of IID per person per year [3,4]. However, such a study cannot be carried out over a long period of time due to limited economic and human resources [5]. Instead, a different form of surveillance is required to estimate the frequency of IID on a continuous basis. One option is sentinel surveillance – an active surveillance system that collects data from selected, targeted groups or networks of health-care providers created for specific purposes [6] and covering a subset of the population. These active sentinel sites can be medical clinics, hospitals, emergency departments [7], health centres and/or general practitioners [8]. General practitioner (GP) sentinel networks are often used for surveillance of communicable diseases such as influenza [9-12], gastroenteritis [13,14] and other diseases [15-18].

In Malta, general practitioner sentinel surveillance of influenza has been underway for several years [19]. During the influenza season of October 2004 to May 2005, the sentinel surveillance of IID by participating GPs was introduced in addition to the ongoing sentinel surveillance of influenza.

Methods

Objectives of study

The main objectives of the sentinel surveillance study were:

- to estimate the proportion of primary care encounters with IID;
- to describe the epidemiology of IID at the GP level;
- to determine the magnitude of under-reporting of IID at the GP level;
- to pilot the introduction of sentinel surveillance as a form of active surveillance of IID in Malta.

Study design

The study was a cross-sectional sentinel active surveillance study involving a number of GPs who reported on IID cases in their practices. They were invited through the local journal of the College of Family Doctors and via personal encouragement to participate in a sentinel surveillance system for IID, influenza and vaccine preventable diseases. Of 1,302 doctors registered with the Malta Medical Council (Direct Communication: registrar of medical council, September 2005), approximately 300 (direct communication with Soler JK. Malta College of Family Physicians, September 2005) are GPs. Twenty-two GPs volunteered to take part in the study.

Case definition

A case of IID was defined as a person presenting with a new episode of acute IID, defined as at least three loose stools or vomiting in 24 hours or diarrhoea or vomiting with two or more additional symptoms in 24 hours. Additional symptoms included

abdominal cramps, abdominal pain, fever, nausea, blood in stool or mucus in stool.

Proportion of IID

The frequency of IID in this study was estimated as the proportion of IID in all primary care encounters. Each participating GP reported the number of cases presenting with IID as well as the total number of patient visits during each reporting week. The former was used as nominator and the latter as denominator in calculating the proportion of IID in the primary care encounters. To show changes in the number of reported IID over time, the actual number of IID cases seen by GPs was taken into consideration, rather than the proportion of IID cases in the primary care encounters, because a possible seasonal change in the overall number of primary care encounters (denominator) would bias the result.

Sentinel surveillance reporting

Participating GPs were provided with specific forms to report on cases with a new episode of IID seen in their practice, including patients seen during home visits. Zero reporting was implemented meaning that GPs submitted forms on a weekly basis even when IID cases were not recorded. Information on IID cases included age, sex, use of antibiotics and whether stool samples were requested for laboratory analysis. GPs also provided basic data (age and sex) on all patients seen over the same period for any condition, i.e. all primary care encounters in their practice. The forms were collected by a courier on a weekly basis and forwarded to the study coordinator.

Pilot study

A pilot study involving 10 GPs for a trial period of one week was performed in order to assess: a) the feasibility and b) the method of collecting and analysing the information. As a result, the questionnaire was finalised and some methodological and technical problems that had been identified during the pilot study were solved before the start of the larger study described in this paper.

Laboratory investigation

Laboratory investigation was attempted in order to confirm the clinical diagnosis, and to identify the aetiological agents responsible for IID at GP level. GPs were expected to ask the patients who fulfilled the case definition for IID to submit stool or vomitus samples (depending on the predominant symptoms) for analysis. Samples were analysed at the Public Health Laboratory in Malta for *Salmonella*, *Campylobacter*, *Shigella* and *Escherichia coli* and at the Virology Department of St. Luke's Hospital in Malta for rotavirus. Further testing for viral IID pathogens (norovirus and sapovirus) was performed at the Istituto Superiore di Sanita in Rome. Intestinal parasites were analysed by means of microscopic examination of fixed samples at St. Luke's Hospital laboratory in Malta.

Data processing

The data obtained from the reporting forms were entered in Statistical Package for Social Sciences Version 12 for Windows. The database and its back-up copy on CD were password-protected and stored in a safe place inaccessible to outsiders. After the data had been collected and the results of laboratory analyses had been communicated to the reporting GPs, all identifiable information was deleted from the database and the reporting GPs were identified only by a study identification number. Results were reported only as aggregate totals, so that no individuals were identifiable (in line with the Data Protection Act, 2001 [20]).

Results

Between October 2004 and May 2005, 22 GPs from various parts of Malta participated in this study. They reported a total of 55,425 primary care encounters. Of these 1,082 met the case definition for IID. Hence the proportion of primary care encounters with IID during the study period was 0.02 (1.95%).

During the same period, the number of cases reported to the national passive surveillance system (Disease Surveillance Unit Database 2004, 2005) [19] was only 146. Hence, the enhanced sentinel surveillance system was able to pick up over seven times more cases than the routine reporting system.

Table

Number of cases of infectious intestinal disease (IID) per age group

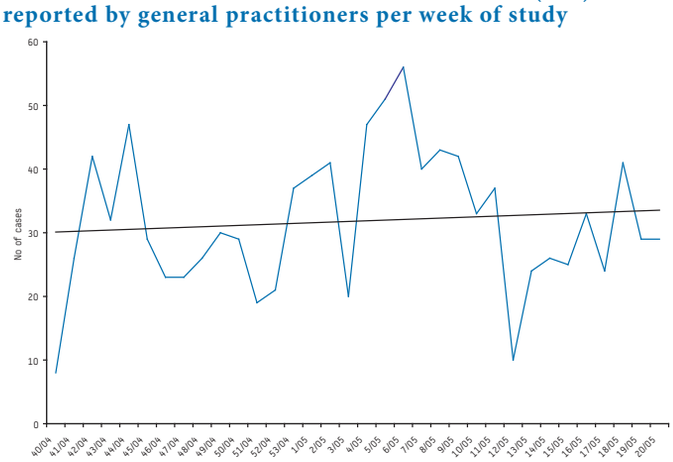
Age group (years)	Number of IID cases	Percentage of all IID cases
0-1	12	1.1
2-4	71	6.6
5-10	99	9.1
11-20	199	18.4
21-30	214	19.8
31-40	163	15.1
41-50	140	12.9
51-60	106	9.8
61-70	49	4.5
71-80	20	1.8
>81	9	0.8

Among the 1,082 cases, there were 533 males and 549 females. Persons aged between 11 and 30 years constituted 38.2% of the cases (Table).

Only 14 out of 1,082 patients with IID (1.3%) were asked by their GP to submit stool samples for microbiological analysis, and only five actually did so. No pathogens were isolated from any of the samples.

Figure

Number of cases of infectious intestinal disease (IID) reported by general practitioners per week of study



The study was carried out between October 2004 and May 2005 (week 40 of 2004 to week 20 of 2005). As expected, during this period, there were minor fluctuations in the number of IID cases from week to week, with a peak in February-March. By plotting the linear line of the regression to the mean, an overall increase was noted as the warmer month of May approached (Figure).

Discussion

The proportion of primary care encounters with IID estimated in this study was 0.02 (1.95%). A patient-related factor associated with the number of cases was the patient's age. The number of cases was highest in the age groups between 11 and 30 years (Table). Several international studies have reported a higher rate of IID in the elderly and children [22]. This was not observed in our study. There was no sex difference in the number of IID cases either, whereas studies in other countries have demonstrated higher rates for women than men [23,24].

The absence of pathogens in samples from symptomatic cases can be explained mainly by the small number of samples obtained, the delay in taking the sample after the onset of symptoms, and prior antibiotic usage.

The study formed part of the sentinel surveillance for influenza. Hence, the period of study coincided with the influenza season between October and May, covering 35 weeks. There were minor fluctuations in the number of cases reported during this period of study; however, a continued surveillance system covering the whole year would be required in order to describe the seasonality of such illness.

Knowing the frequency of IID is essential to be able to target control measures. Ideally, in order to estimate incidence and prevalence rates, cohort or cross sectional studies are carried out respectively. Such studies, however, require considerable human and financial resources. Some countries have opted for sentinel surveillance as a continuous form of surveillance of specific diseases [25,26] However, in order to calculate incidence or prevalence rates on the basis of sentinel surveillance data the exact size of the population covered is needed.

The main problem in Malta is that general practitioners do not have a defined patient population. Patients can refer to any GP they wish, both in private and public sector, and they can even consult different GPs for the same condition. Indeed, taking a second opinion is known to be common. There are no registers of GP's patient lists and even the number of patients seen by individual GPs is not known. There are other countries with the same problem. The Sentiweb system in France [14] extrapolates findings from the sentinel GPs to the total population of GPs in a given region, and uses the population data of that region as the denominator, the same being done on the national level, too. However, this system cannot be applied in Malta because of the differences between various GP practices due to which the population covered by participating GPs may not be representative of the population covered by the rest of GPs of Malta.

Another limiting factor is that most GPs do not keep electronic patient records, hence the list of patients that consult their GP at least once in a given year is not available. This information was used as a reliable denominator in the Belgian Intego register [21]. The Belgian study piloted a method which could be used as a proxy measure to determine the frequency of illness as a proportion of the primary care encounters at GP level, rather than incidence or prevalence rates, in countries where the size of the population (denominator) is not known. One major drawback of using this method is that the proportion of IID obtained in our study cannot be compared to studies in other countries since the denominators used as the basis for the calculations are different. A solution for Malta and other countries with similar problems in determining the size of the population (denominator) would be the development of an electronic database record system for GPs which would facilitate an approach similar to the Intego register and comparisons between countries would be possible since the population denominator would be similar.

Setting up sentinel surveillance is not an easy process. The problems in establishing such a system consist among others in connecting the practitioners to the sentinel system and in coordinating their work. Many GPs in Malta do not keep electronic patient records and hence computer reporting is not feasible. During our study, the reporting was done on paper and the forms were collected from GPs by a courier, increasing the human resources required to carry out this type of surveillance. Since the time available for an average consultation is short, GPs may have difficulties in accurately collecting and reporting information for surveillance purposes on a voluntary basis. It is vital that the forms used are simple and require as little time to fill in as possible, therefore in this study GPs were only asked to tick boxes in a questionnaire, rather than fill in data.

Our study highlighted also difficulties in making laboratory diagnosis for IID. It enrolled highly committed GPs and yet very few submitted stools for analysis. However, the GPs are at the best stage to perform testing since the patient is still symptomatic and hence the identification of pathogens is more feasible. Sentinel surveillance requires consistently high motivation for GPs throughout the entire period. This needs to be maintained by periodic visits from field staff, feedback on data collected, continued medical education meetings and publication of results [27]. In our study, GPs were given initial training and regular updates to ensure that the data being collected was comparable and of the best quality. However, since many doctors do not keep records of visits, validation of data was not possible.

GPs participated in the study on a voluntary basis, and therefore selection bias was inevitable. In order to ensure better representativity, the number of participating GPs should be increased. However, it is also important to make sure that sentinel GPs are easily accessible to surveillance staff.

Conclusion

The estimate of seven cases being reported by this sentinel system for every case notified to the national routine surveillance system confirms the high under-reporting of IID in Malta. Sentinel surveillance that relies on GPs commitment to notify is able to identify more cases than routine passive surveillance.

With appropriate electronic record systems at GP level, the sentinel surveillance would be more feasible and incidence rates could be estimated and compared with other countries.

The findings described here underline the important role that both private and public sector physicians can play in disease surveillance and in the advancement of our understanding about the patterns of common diseases in a population. Ongoing surveillance

conducted by sentinel physicians with appropriate coverage of the population is feasible and could make an important contribution to the surveillance and control of IID in the future.

Acknowledgements

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Citation style for this article: Gauci C, Melillo Fenech T, Gilles H, O'Brien S, Stabile I, Calleja N, and al. Sentinel Surveillance: an option for surveillance of infectious intestinal disease. Euro Surveill 2007;12(4)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n04/1204-227.asp

Seroprevalence of antibodies to poliovirus in individuals living in Portugal, 2002

M Pires de Miranda[1], M Carmo Gomes[2], H Rebelo de Andrade (h.rebelo.andrade@insa.min-saude.pt)[1]

1. Unidade de Vírus Respiratórios e Enterovirus, Instituto Nacional de Saúde, (Unit of Respiratory and Enteroviruses, National Health Institute, INS), Lisbon, Portugal
2. Faculdade de Ciências, Universidade de Lisboa (Faculty of Science, University of Lisbon), Lisbon, Portugal

The last case of poliomyelitis in Portugal caused by indigenous wild poliovirus occurred in 1986 and the country was declared polio-free in 2002. High levels of immunity must be maintained to prevent the importation of wild poliovirus. In this study, we determined the immunity against poliomyelitis of the Portuguese population in order to identify possible immunity gaps. A representative sample of 1,133 individuals older than two years residing in mainland Portugal was studied. Logistical difficulties regarding quick sample transportation precluded the Portuguese islands (Madeira and the Azores) from this study. Sera were collected in 2002 from individuals attending health clinics throughout the 18 districts of Portugal. Levels of neutralizing antibodies against poliovirus types 1, 2 and 3 were determined and a titre of >= 1:8 was defined as indicative of protected immunity. Results were expressed in international units. The antibody prevalence and the geometric mean antibody concentration (GMAC) was 91.6% (GMAC: 2.96 IU/ml), 94.2% (GMAC: 5.03 IU/ml) and 75% (GMAC: 0.53 IU/ml) for poliovirus types 1, 2 and 3, respectively. For poliovirus types 1 and 2, antibody prevalence was close to or above 90% in the majority of age groups. For poliovirus type 3, antibody prevalence was below 80% in teenagers and young adults. Our study shows that the Portuguese are well protected against poliovirus types 1 and 2. For poliovirus type 3, the suboptimal antibody levels observed in teenagers and young adults suggest the need for a booster dose to minimise the risk of wild poliovirus importation.

Introduction

Global immunisation campaigns against poliomyelitis promoted by the World Health Organization (WHO) have resulted in the elimination of this disease from several regions [1]. In Portugal, the last case of poliomyelitis caused by indigenous wild poliovirus occurred in 1986 and the country was certified polio-free in 2002 [2]. Despite imminent eradication, small reservoirs of indigenous transmission persist in Africa and Asia [1]. Thus, there is still a danger of importation of wild poliovirus to polio-free countries, as reported recently [3,4]. Portugal, in particular, could be at risk if protective immunity levels are not sufficiently high, given its close ties with several African countries, including Angola and Cape Verde where outbreaks of poliomyelitis occurred in 2005 and 2000, respectively [4,5].

Mass immunisation against poliomyelitis in Portugal began with a vaccination campaign in 1965, when children aged from three months to nine years were offered two doses of live, attenuated, trivalent oral polio vaccine (tOPV). Subsequently, the national vaccination program has included the administration of three doses of tOPV in the first year of life and since 1990 a tOPV booster at 5-6 years of age. Vaccination coverage has gradually increased since 1965, and since 1991 has reached > 90% of the population at one year of age [6]. The last reported case of vaccine-associated paralytic poliomyelitis (VAPP) occurred in 1995. To prevent further VAPP cases and the circulation of neurovirulent vaccine-derived polioviruses, tOPV was replaced by inactivated polio vaccine (IPV) in the childhood immunisation schedule in January 2006.

High vaccination coverage and the effective surveillance of acute flaccid paralysis are essential for preventing the re-emergence of wild poliovirus. Additionally, serological surveys are useful for identifying groups with low-immunity that could be at risk of infection. We have determined the immunity of the Portuguese population against poliomyelitis. This study was part of a national serological survey conducted in 2002 aimed at assessing the immunity of the Portuguese against vaccine-preventable diseases [7].

Methods

Study population

The national serologic survey aimed at estimating the percentage of the Portuguese population with antibodies against 15 etiologic agents. The target population, estimated to be 10.3 x 10^6 by the 2001 census [8], was stratified by eight age groups: 2-4, 5-9, 10-14, 15-19, 20-29, 30-44, 45-64, and >64 years old. Sample sizes aimed at estimating the prevalence of seropositives, p, were computed assuming that p has a normal sampling distribution. If a maximum absolute error of d=0.05 is tolerated with 95% probability ($z_{alpha/2}$=1.96), when estimating the proportion of seropositives at age group i, then an *a priori* conservative estimate of p=0.5 leads to a sample size of $n_i = z^2_{alpha/2}p(1-p)/d^2$=384 [9]. With eight age groups, this prompts a theoretical total sample size of n=(384x8)=3072 individuals. For each age group, the theoretical sample of 384 was distributed to the 18 geographic districts of mainland Portugal, in proportion to their population size.

As part of the national serological survey in 2002, blood samples were collected from individuals attending a network of health-care clinics present throughout the 18 districts of mainland Portugal where routine blood tests are carried out. An extra 10 ml of blood were collected from individuals older than 10 years and 2 ml from children aged two to 10 years. Individuals were randomly sampled as they arrived in order to fulfil the required sample size by age group in their district. Eligible individuals had to be older than 24 months and resident in the district for the past six months. All participants or their guardians (for individuals younger than 18 years) gave written consent allowing extra blood to be taken for this study. Data regarding birth date, sex, nationality, previous known diseases and reason for showing up at the clinic were collected for each donor.

Table 1

Number of collected samples for each age group compared to the required sample size (n=384), mainland Portugal, 2002

Age group	2 - 4	5 - 9	10 - 14	15 - 19	20 - 29	30 - 34	45 - 64	> 64	Total
Sample available	327	435	402	340	520	582	541	378	3525
Difference to 384	**-57**	+51	+18	**-44**	+136	+198	+157	**-6**	+453

Table 2

Number of samples used for each age group for measuring anti-polio antibodies compared to the required sample size (n=138), mainland Portugal, 2002

Age group	2 - 4	5 - 9	10 - 14	15 - 19	20 - 29	30 - 34	45 - 64	> 64	Total
Sample available	159	135	136	136	152	146	128	141	1133
Difference to 138	+21	**-3**	**-2**	**-2**	+14	+8	**-10**	+3	+29

A total sample of n=3,525 serum samples was collected, larger than the theoretical n=3,072, but not fulfilling the required sample size for every age group (Table 1). The need to survey 15 etiologic agents from a relatively small blood sample per person, plus the values in deficit shown in Table 1, led us to consider more realistic a priori values for p in the population. In the case of polio, given that mass vaccination is universal since 1965 and that the vaccination coverage is high [6], we set an *a priori* estimate of p=0.9. A tolerated error of d=0.05 in the estimated proportion of seropositives for polio, at age group i, thus leads to a theoretical sample of n_i=138 by age group. A total of 1,133 serum samples (475 from males and 657 from females) were screened for the presence of anti-polio antibodies. The distribution of this sample falls close to the theoretical requirement of n_i=138 per age group (Table 2).

Antibody neutralization assays

The titre of neutralizing antibodies against poliovirus types 1, 2 and 3 was determined by microneutralization assay [10]. Sera were diluted two-fold beginning from 1:8 to 1:1024, in duplicate, and each dilution was incubated for three hours at 36°C with 100x50%-cell culture infectious dose of poliovirus strains Sabin 1, 2 or 3 (NIBSC, UK). The virus-serum mixtures were added to Hep-2 cells and, after a five-day incubation at 36°C, the cytopathic effect was assessed by phase contrast microscopy. Titres were calculated as the reciprocal of the highest dilution that protected 50% of the cultures against challenge virus and a titre >=1:8 was defined as indicative of protective immunity. Titres were converted to IU/ml by comparison with the titre of an in-house reference serum (IHS) of known potency. The potency of the IHS was determined by comparison with the titre of an International Standard Serum (NIBSC, UK) as described previously [10]. Titres of test serum were converted to IU/ml by dividing the serum titre by the geometric mean titre (GMT) of the IHS and multiplying by the potency of the IHS.

Data analysis

Data were inserted into an Access database. Analysis of the results consisted of the determination of relative frequencies of protective immunity, geometric mean titres and respective 95% confidence intervals using SPSS 11.01 software.

Results

Our data indicated that a titre of 1:8 corresponded to 0.331 IU/ml, 0.667 IU/ml and 0.151 IU/ml for poliovirus types 1, 2 and 3, respectively, and the geometric mean of antibody concentration for test sera were 2.96 IU/ml (95% confidence interval (CI): 2.73-3.20) for poliovirus type 1, 5.03 IU/ml (95% CI: 4.68-5.41) for poliovirus type 2 and 0.53 IU/ml (95% CI: 0.50-0.57) for poliovirus type 3.

The overall antibody prevalence was 91.6%, 94.2% and 75.1% for poliovirus types 1, 2 and 3, respectively (Table 2). For poliovirus types 1 and 2 the antibody prevalence was highest in children

Table 3

Age-specific antibody prevalence for poliovirus types 1, 2, and 3 in individuals residing in mainland Portugal, 2002 (n=1,133)

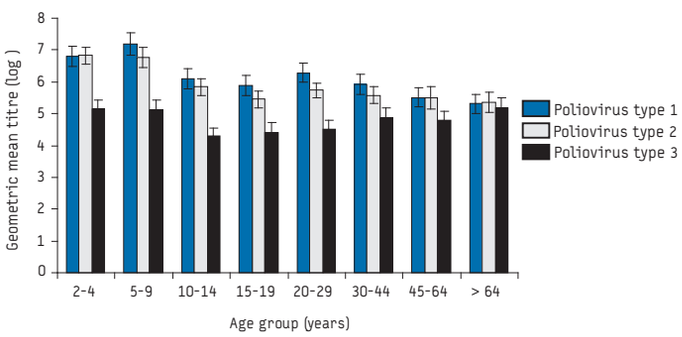
		Poliovirus type 1		Poliovirus type 2		Poliovirus type 3	
Age group	n tested	%	95% CI*	%	95% CI*	%	95% CI*
2 - 4	159	93.1	88.0 - 96.5	98.7	95.5 - 99.8	84.9	78.4 - 90.1
5 - 9	135	99.3	95.9 - 100.0	100.0	97.3 - 100.0	83.7	76.4 - 89.5
10 -14	136	93.4	87.8 - 96.9.	95.6	90.6 - 98.4	68.4	59.9 - 76.1
15 - 19	136	91.2	85.1 - 95.4	95.6	90.6 - 98.4	56.6	47.9 - 65.1
20 - 29	152	93.4	88.2 - 96.8	98.7	95.3 - 99.8	73.0	65.2 - 79.9
30 - 44	146	87.7	81.2 - 92.5	95.2	90.4 - 98.1	72.6	64.6 - 79.7
45 - 64	128	88.3	81.4 - 93.3	82.0	74.3 - 88.3	80.5	72.5 - 86.9
> 64	141	86.5	79.8 - 91.7	85.8	78.9 - 91.1	80.1	72.6 - 86.4
Total	**1133**	**91.6**	**89.8 - 93.2**	**94.2**	**92.6 - 95.5**	**75.1**	**72.5 - 77.6**

* CI= confidence interval

aged 5-9 years and was close to or above 90% in the majority of age groups (Table 3). For these two serotypes, antibody titres were highest in children (5-9 years), then decreased in teenagers, but were relatively stable thereafter (Figure). For poliovirus type 3 we observed lower antibody prevalence in all age groups and this was mirrored by lower antibody titres against this serotype (Table 3 and Figure). The antibody prevalence was close to 85% in children younger than 10 years and then decreased to levels below 70% in teenagers (10-19 years) or and to 70%-80% in young adults (20-44 years) (Table 3). Antibody titres were lowest in persons aged 10-29 years and reached highest levels in children up to nine years and persons older than 30 years (Figure).

FIGURE

Figure. Age-specific geometric mean titres, mainland Portugal, 2002. Whisks represent 95% confidence intervals



We considered three birth cohorts: persons born before 1956 who were not eligible for childhood vaccination; persons born between 1956 and 1964 who represent the first vaccinated cohorts; and persons born after 1964 who would have followed the complete vaccination schedule since birth (Table 4). For poliovirus types 1 and 2 antibody prevalence was highest in persons born after 1964, whereas for poliovirus type 3, the percentage of seropositives was highest in persons born before 1956 (Table 4).

Although there were no overall differences between seroprevalence of male and female individuals, we found that women older than 30 years had better protection than males against all polioviruses (data not shown).

Discussion

Our results show that the Portuguese are well protected against poliovirus types 1 and 2 in most age groups. Additionally, children had very high antibody prevalence and presented the highest antibody titres, consistent with a good response to immunisation and high anti-polio vaccination coverage. The decrease in titre observed in teenagers is most likely due to waning immunity, which is faster in the initial years following vaccination [11]. However we can not exclude the possibility that these lower titres are due to a failure in receiving a booster dose at 5-6 years of age.

Lower prevalence and antibody titres were observed for poliovirus 3. These results are similar to those of other European countries such as Greece [12], Germany [13], the Netherlands [14] and Italy [15] and with the lower seroconversion rates observed for poliovirus type 3 following vaccination with OPV [16]. These observations may be explained by a lower potency of poliovirus type 3 antigens in the vaccine. For this serotype, suboptimal levels of protection were observed, particularly in teenagers and young adults. This has been reported in other countries in Europe [12, 15]. Nevertheless, seroprevalence in children was high as expected under high vaccination coverage. Furthermore, we retested all negative sera at a single dilution of 1:4 and found that for poliovirus type 3 the seroprevalence increased significantly (88.9% seropositives) and was closer to or above 90% in most age groups (Table 5). These results suggest that despite the lower antibody levels against poliovirus type 3 a large proportion of individuals had been primed. The suboptimal antibody prevalence observed in teenagers and young adults is therefore most likely due to waning immunity. It is generally accepted that the presence of antibodies at a dilution of 1:8 confers immunity against polio. Individuals with lower or undetectable antibody levels may be protected from disease by memory immunity that provides a rapid immune response to infection. However, they may be susceptible to re-infection [17]. Examples of importations in Albania and Namibia stress the risk of an age-dependent immunity gap [18,19]. Thus to improve immunity to poliovirus type 3 and minimize the risk of wild poliovirus importation a booster dose in teenagers may be required.

For poliovirus types 1 and 2, antibody prevalence was highest in individuals who most likely acquired immunity through vaccination (persons under 37 years in our study), rather than contact with wild poliovirus, which reinforces the success of anti-polio vaccination in Portugal. Still, a large proportion of persons who would have acquired immunity naturally were seropositive, suggesting that naturally-induced immunity is long-lasting, as described previously [14,20]. Interestingly, for poliovirus type 3, the antibody prevalence was higher in groups born before the vaccination era and the elderly (>64 years) had antibody levels similar to recently vaccinated children. A possible explanation for this result is that immunity

TABLE 4

Antibody prevalence for poliovirus types 1, 2, and 3, according to birth cohort, mainland Portugal, 2002 (n=1,133)

	Poliovirus type 1		Poliovirus type 2		Poliovirus type 3	
	%	95% CI*	%	95% CI *	%	95% CI*
cohort						
Born 1955 (n=261)	**87.7**	83.1, 91.5	**83.9**	78.9, 88.1	**79.7**	74.3, 84.4
Born between 1956-64 (n=90)	**87.8**	79.2, 93.7	**93.3**	86.1, 97.5	**74.4**	64.2, 83.1
Born 1965 (n=782)	**93.4**	91.4, 95.0	**97.7**	96.4, 98.6	**73.7**	70.4, 76.7

• CI= confidence interval

Table 5

Analysis of age-specific seroprevalence using a 1:4 titre[a], mainland Portugal, 2002 (n=1,133)

		Poliovirus type 1		Poliovirus type 2		Poliovirus type 3	
Age group	n	%	95% CI*	%	95% CI*	%	95% CI*
2 - 4	159	95.0	90.3 - 97.8	98.7	95.5 - 99.8	92.5	87.2 - 96.0
5 - 9	135	100.0	97.3 - 100.0	100.0	97.3 - 100.0	93.3	87.7 - 96.9
10 -14	136	94.9	89.7 - 97.9	97.1	92.6 - 99.2	86.0	79.0 - 91.4
15 - 19	136	92.6	86.9 - 96.4	96.3	91.7 - 98.4	80.9	73.5 - 86.6
20 - 29	152	95.4	90.8 - 97.8	98.7	95.3 - 99.6	94.1	89.1 - 96.9
30 - 44	146	93.2	87.9 - 96.2	97.9	94.1 - 99.3	86.3	79.8 - 91.0
45 - 64	128	93.8	88.2 -96.8	91.4	85.3 - 95.1	90.6	84.3 - 94.6
> 64	141	97.2	92.9 - 99.2	95.7	91.0 - 98.4	86.5	79.8 - 91.7
Total	1133	95.2	93.8 - 96.4	97.1	95.9 - 98.0	88.9	86.9 - 90.7

[a]Results combine previously seropositive results at 1:8
*CI= confidence interval

induced by exposure to wild poliovirus type 3 antigens, circulating before mass vaccination, is stronger than vaccine-induced immunity.

This study allows one to draw conclusions on the seroprevalence of the whole Portuguese population. However, important subpopulations, such as immigrant communities, were not specifically examined. We can not exclude the existence of low-immunity pockets in the population that were not detected in our study. Surveys aimed at determining anti-polio immunity in subpopulations as well as in the general population, to evaluate the impact of introducing IPV, should be carried out. We have expressed results as titres and in international units, to facilitate comparison of our data with that of future studies.

Acknowledgements

We would like to thank Colin E McVey, Guilherme Gonçalves and Elsa Vasco for their advice; Sara Rabiais and Paulo Nogueira for help with statistical analysis; and Simone Chrystello, Alcina Gaspar Costa and Anabela Costa for their excellent technical help.

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Citation style for this article: Pires de Miranda M, Carmo Gomes M, Rebelo de Andrade H, . Seroprevalence of antibodies to poliovirus in individuals living in Portugal, 2002. Euro Surveill 2007;12(6)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n06/1206-224.asp

Stagnating influenza vaccine coverage rates among high-risk groups in Poland and Sweden in 2003/4 and 2004/5

MW Kroneman (m.kroneman@nivel.nl)[1], GA van Essen[2]

1. Nederlands instituut voor onderzoek van de gezondheidszorg (Netherlands Institute of Health Services Research), Utrecht, The Netherlands
2. European Scientific Working group on Influenza (ESWI), and Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands

This paper examines influenza vaccine coverage rates (VCR) in Poland and Sweden during the 2003/4 and 2004/5 influenza seasons. An average sample of 2,500 persons was interviewed in each country and each season. Questions regarded age and possible chronic diseases, as well as information on whether they had had an influenza vaccination in the given season. Those who had not received the vaccine were also asked to give reasons for non-vaccination. About one in four (Sweden) to one in three (Poland) of the persons surveyed belonged to high-risk groups (>=65 years of age or suffering from chronic diseases). In the 2004/5 season, 17% (CI 12-19%) of the Polish elderly and 45% (CI 39-50%) of the Swedish elderly were vaccinated. In Poland, 9% (CI 7-12%) of respondents younger than 65 years of age with a chronic condition were vaccinated, whereas in Sweden the corresponding rate was 12% (CI 9-16%). In both countries, the VCR did not change significantly from the previous season. Personal invitations resulted in a higher VCR. In Sweden, the most frequently mentioned reasons for not being vaccinated were the assumption of not qualifying for a vaccination and perceived resistance. In Poland in both years, perceived resistance to flu and the cost of the vaccination were the most often mentioned reasons. The influenza vaccination rates in Poland and Sweden remain far below World Health Organization (WHO) recommendations for the high-risk population. No increase in VCR as demonstrated in this study may indicate that these two countries will not be able to meet the 2010 WHO target, if no further action is taken concerning vaccine uptake.

Introduction

Influenza continues to be a significant health risk for the elderly (>=65 years of age) and people with chronic conditions (e.g. cardiovascular or respiratory diseases, diabetes mellitus, renal failure, impaired immunity due to disease or treatment). All European countries have introduced recommendations for influenza vaccination of these high-risk groups [1]. Despite relatively uniform recommendation policies, influenza vaccination coverage rates (VCR) vary considerably between European countries [2,3]. The WHO recommended vaccinating 50% of the high-risk population in 2006, and increasing this rate to 75% in 2010. Studies carried out in eight European countries (Germany, France, Italy, the Netherlands, Poland, Sweden, Spain and the United Kingdom) revealed that Sweden and Poland had a VCR among the high-risk population below 50% in the 2003/4 influenza season [4-6]. In order to reach the WHO target for 2010, a significant increase in VCR would be needed in both countries. To determine whether there was a change in VCR, the study on vaccine uptake in Sweden and Poland was repeated in the 2004/5 season. The purpose was also to see what reasons the non-vaccinated high-risk persons in these countries have for not being vaccinated.

Methods

Data collection

For the purpose of this study, we used an existing short survey with questions about influenza vaccination uptake, personal invitation from general practitioners (GPs), chronic conditions and reasons for refraining from vaccination. The questions were defined and no open-ended questions were used. For the self-reported chronic conditions, we asked whether these were confirmed by a physician. The questionnaire was tested for validity in the Netherlands [6], and has been applied in several other European countries since then [4].

The survey was conducted in Poland and Sweden in April and May 2004 (2,000 and 2,500 respondents respectively) and in March and April 2005 (3,000 and 2,500 respondents respectively). It was carried out by TNS, an international market research agency that subscribes to the ICC/ESOMAR International Code of Marketing and Social Research Practice and has offices both in Sweden and Poland. Our questionnaires were included in Omnibus Public Opinion Polls – large surveys carried out on a regular basis and on different and changing subjects. Our survey made part of the omnibus only until a predefined number of respondents had answered the questions. In Sweden, the survey was carried out by means of a telephone interview, whereas in Poland the questions were asked face-to-face. In both countries, the respondents were aged 15 years and older. In Sweden, the upper age was 74 years, whereas in Poland no upper age limit was applied. Non-response rates were not available, but in order to establish whether the sample was representative, we compared the age and sex distribution of the sample with the relevant distribution in the actual population according to data from Eurostat. Similarly, the VCR of the sample was compared with the VCR of the total population estimated on the basis of vaccine sales data [3].

Terminology

In this paper we use the term 'diseased' for the group of people who suffered from a chronic condition, like cardiovascular diseases, respiratory diseases, diabetes mellitus, renal failure, impaired immunity due to disease or treatment and who are younger than 65 years of age. The 'elderly' are defined as those aged 65 years and older. The total high-risk group is both groups ('elderly' and 'diseased') combined. For the group of people younger than 65 years of age who did not suffer from a chronic condition (as mentioned above), we use the term 'healthy'.

The reasons for non-vaccination were divided into perceived misconceptions and perceived barriers. The perceived misconceptions were associated with knowledge about influenza

and influenza vaccination, whereas perceived barriers included practical problems preventing one from having a vaccination.

Statistical analyses

To calculate the confidence intervals we used Fleiss quadratic 95% confidence intervals in the statistical package EpiInfo 6. In order to make the study population comparable with the real population of each country, weight factors provided by the TNS offices were used. Since the omnibus polls differ per country, the variables used for the weight factor also differ. For Poland, community size, age, sex and household size were included, while for Sweden, region, age and sex. The data presented in this paper are the weighted data.

Results

Representativity of the samples

The sex distribution in our samples is comparable with the situation in the actual population (based on Eurostat data) (Table 1). The elderly in our samples are overrepresented compared to the actual population in both countries and both seasons. The Macroepidemiology of Influenza Vaccination (MIV) Study Group [3] estimated the vaccination coverage rates of the total population on the basis of vaccine sales data in 2003. The vaccine coverage in our 2003/4 Polish sample is slightly higher and in the Swedish one slightly lower compared to the MIV-group data. For the coverage rate of the elderly, no data were available on Poland. For Sweden, the coverage rate based on a national survey [7] was comparable to our results.

To establish the consistency between both seasons, we also calculated the rate of chronic diseases per person in the samples. In Sweden, 0.15 chronic conditions per person were reported in the total sample for both years. In Poland, 0.25 chronic conditions per person were reported in 2004 and 0.18 in 2005, which is significantly less (t= 4.32, df = 5026, p=0.00). The decrease was mainly due to a 5% drop in reported heart diseases.

Vaccination rates

In the 2004/5 season, 17% (CI 12-19%) of the Polish elderly and 45% (CI 39-50%) of the Swedish elderly were vaccinated (Table 2). Among those younger than 65 years of age with a chronic condition, 9% (CI 7-12%) were vaccinated in Poland and 12% (CI 9-16%) in Sweden, in the same period. In both countries the VCR did not change significantly compared to the previous season.

In Sweden, in both seasons, the VCR of the elderly was much higher than that of the 'diseased' (over three times higher), and that of the 'healthy' (around 10 times higher). In Poland, the differences between the VCR of the three groups were much smaller (Table 2).

Personal invitations

Persons at high risk for influenza who had received a personal invitation from their GP were more likely to be vaccinated than those who had not received such an invitation (Table 3). This was the case in both countries and both seasons. Between 2003/4 and 2004/5 the number of people in the high-risk groups who received

Table 1

Age and sex distribution and vaccine coverage rates (VCR). Data obtained in the study compared with estimates for the actual population

	Season	Poland			Sweden		
		Study group	95% CI	Total population	Study group	95%CI	Total population
Females [%]	2003/4	52.2	*50.0-54.4*	51.6[2]	49	*47.1-51.0*	50.5[2]
	2004/5	52.3	*50.5-54.0*	51.6[2]	48.6	*46.6-50.6*	50.5[2]
Elderly (>=65 years of age[1]) [%]	2003/4	15.6	*14.0-17.3*	12.9[2]	12.6	*11.3-14.0*	8.3[2]
	2004/5	16.8	*15.5-18.2*	13.1[2]	11.9	*10.7-13.3*	8.4[2]
VCR (overall) [%]	2003/4	10.2	*8.9-11.6*	7.9[3]	11	*9.8-12.3*	12.7[3]
VCR (of elderly) [%]	2003/4	--		--	46	*40-51*	51[4]

1) For Sweden: 65-74 years of age
2) Eurostat data
3) Macroepidemiology of Influenza Vaccination (MIV) Study Group. The macro-epidemiology of influenza vaccination in 56 countries, 1997--2003. Vaccine 2005; 23(44):5133-5143.
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Table 2

Distribution of risk groups in the study sample and vaccination coverage rates (VCR) per group in Poland and Sweden

Country	Season	Elderly					Diseased					Non-risk group				
		Total		Vaccinated			Total		Vaccinated			Total		Vaccinated		
		n	%1	n	%2	95% CI	n	%1	n	%2	95% CI	n	%1	n	%2	95% CI
Poland	2003/4	307	16	55	18	*14-23*	405	21	40	10	*7-13*	1254	64	105	8	*7-10*
	2004/5	487	17	74	16	*12-19*	439	15	40	9	*7-12*	1972	68	158	8	*7-9*
Sweden	2003/4	316	13	144	46	*40-51*	332	13	43	13	*10-17*	1859	74	87	5	*4-6*
	2004/5	298	12	133	45	*39-50*	313	12	38	12	*9-16*	1890	76	82	4	*3-5*

1) Percentage in the total study sample
2) Percentage of vaccinated persons within the group

Table 3

Distribution of personal invitations among high-risk group (elderly and diseased combined) and vaccination coverage rate for those who have and have not received a personal invitation

Country	Season	Received a personal invitation?	Risk group (elderly and diseased combined)			Vaccinated risk group (elderly and diseased)		
			n	%[1]	95% CI	n	%[2]	95% CI
Poland	2003/4	Yes	191	27	*(24-30)*	67	35	*(28-42)*
		No	521	73		24	5	*(3-7)*
	2004/5	Yes	192	21	*(18-24)*	84	44	*(37-51)*
		No	734	79		27	4	*(3-7)*
Sweden	2003/4	Yes	94	15	*(12-18)*	50	53	*(43-63)*
		No	554	85		134	25	*(22-29)*
	2004/5	Yes	95	16	*(13-19)*	56	59	*(48-69)*
		No	516	84		114	22	*(19-26)*

1) Percentage of persons who received/did not receive a personal invitation within the risk group
2) Percentage of *vaccinated* persons among those who received/did not receive a personal invitation?

a personal invitation to be vaccinated decreased significantly in Poland and stayed the same in Sweden.

Reasons for non-vaccination

Those non-vaccinated in the high-risk groups were asked to state why they had not had a vaccination. In Sweden, the reasons mainly had to do with misconceptions concerning influenza. The most frequently mentioned reasons were the assumption of not qualifying for a vaccination and perceived resistance to influenza. In the 2004/5 season, significantly more people mentioned not qualifying (2003/4: 15%, 95%CI: 12-18; 2004/5: 35%, 95% CI: 30-39) and significantly fewer persons cited having sufficient resistance than a year before (2003/4: 33%, 95%CI: 29-37; 2004/5: 20%, 95% CI: 16-24). In Poland, in both seasons misconceptions as well as barriers were mentioned: perceived resistance to flu and the cost of the vaccination being the most often cited reasons. There were no significant differences between reasons mentioned by the elderly and those given by the respondents with chronic diseases in either of the countries. Table 4 displays the reasons in both seasons combined.

Discussion

Results

In 2004/5, the VCR of the Swedish elderly was just under the threshold of the WHO recommendations for 2006. For Poland, the VCR of the elderly was far below this figure. In both countries, no difference in VCR was found between the two seasons in the study. VCR of the diseased under the age of 65 in both Poland and Sweden remained well below the WHO recommendations, and no increase was noted between the two seasons. This is a cause for concern, since without an increase in VCR the recommendations for 2010 will certainly not be met. In Poland, no difference between the VCR of the diseased and the VCR of the healthy population was noted, which may imply that there is no (successful) strategy of vaccinating people with chronic diseases.

Table 4

Reasons for not having a vaccination. Combined results for 2003/4 and 2004/5 by risk group and country (in %)

	Poland		Sweden	
	Elderly (n=653)	Diseased (n=761)	Elderly (n=335)	Diseased (n=563)
Misconceptions				
I do not qualify for influenza vaccination	6	7	**22**	**26**
I have sufficient resistance to flu	**34**	**36**	**29**	**25**
Influenza is not a serious illness	4	4	7	13
Barriers				
The vaccination is too expensive	**24**	**24**	3	2
It slipped my mind	6	8	6	6
I was unable to attend at the given time	1	1	1	2
I have had bad experiences with flu in the past	2	4	9	5
On principle, I am against vaccination	12	9	6	5
The GP or public health worker was too far away for me	3	2	1	1
Miscellaneous				
My physician considered it unnecessary	3	4	2	3
Other	12	13	**26**	**24**
Don't know	4	2	3	4

Note: Percentages may add up to more than 100%, since it was possible to choose more than one answer.

When looking into the reasons why high-risk persons refrained from vaccination, in the case of Sweden, it was mainly misconceptions that seemed to matter. The number of people who thought they did not qualify for influenza vaccination increased significantly between the first and the second season – from 12.8% (95%CI: 8.4-19.0) in 2003/4 to 32.1% (95%CI: 25.4-40.1) in 2004/5 with the elderly, and from 15.7% (95%CI: 11.7-20.4) to 36.4% (95%CI: 30.8-42.5) with the diseased, respectively. The number of people who thought they had sufficient resistance to flu, however, decreased over time – in case of the elderly from 36.5% (95%CI: 28.6-43.4) to 21.3% (95%CI: 15.5-28.6), in case of the 'diseased' from 31.2% (95%CI: 25.9-36.9) to 18.9% (95%CI: 14.6-24.2). No significant differences between the seasons were noted for the other reasons.

In Poland, both misconceptions and perceived financial barriers played a role, with no differences between the seasons. Issues concerning perceived resistance and perceived non-qualification may be tackled by means of information campaigns. However, to solve the problem of the out-of-pocket payments, the authors think that the Polish government should consider changing its policy.

Receiving a personal invitation for a vaccination remains an effective way of increasing the VCR. It is therefore worrying that the number of people receiving personal invitations in Poland fell significantly between 2004 and 2005.

There was no difference in VCR within the different disease groups in either of the countries. The pattern found earlier in Germany [4] and the Netherlands [6] that persons with cardiovascular disease and diabetes were vaccinated more often than those with pulmonary disease was not valid for the two countries in this study. This may be related to the low VCR for the 'diseased' in Poland and Sweden compared to Germany and the Netherlands, which do not allow the detection of any significant differences.

Validity of data

In Sweden a telephone survey was used, whereas in Poland the respondents were contacted in their homes. It would have been preferable had the same interview method been used in both countries, but we had no choice of the method, as our surveys had to be included in existing omnibus polls due to financial constraints. However, since the number of households with telephones in Poland is about half that of Sweden, it is probable that the face-to-face interviews in Poland provided a better random sample. However, they may have also led to a higher proportion of elderly and chronically ill in the sample, because these persons can be expected to be at home more often than healthy people. It is not clear whether this method results in more socially desirable answers compared to the telephone interviews. However, even if there is a bias, it does not affect the comparison between the two seasons within the individual countries, since the same method was used in each country for both seasons. The interviews were held in March and April, although it would have been better to have a shorter period of time between the vaccination season and the survey. However, in both years, the data collection took place in the same period so there should be no systematic variation between the two seasons due to different timing of data collection.

The data concerning vaccine uptake and chronic conditions are based on self-reported information from the respondents. Although research into self-reported data compared with medical records revealed a satisfactory reliability for self-reported medical conditions, there may still be over-reporting as well as under-reporting [8-10]. In our validation study in the Netherlands, we found a systematically lower VCR (approximately 10%) from the self-reported data for high-risk persons compared to registered influenza vaccinations at GP practices [6], although the results were comparable with a previous survey in the Netherlands [11]. However, a recent study on self-reported influenza vaccination uptake of the elderly in the past year in the UK showed a high level of concurrence with GP records [12]. We have no explanation for the decrease in reported heart diseases in Poland. There may have been a bias in the selection of respondents between the two years, although the system of data collection and the company that conducted the data collection remained the same.

The findings of this study are supported by the results of the research on the VCR in the total population carried out by the Macroepidemiology of Influenza Vaccination Study Group (MIVSG) in the 2003/4 season. This study group also found hardly any increase in VCR in either country for both seasons (personal communication by GA van Essen).

Conclusion

The most important finding of this study was the lack of increase in VCR of high risk groups in Sweden and Poland, which may indicate that these two countries will not be able to meet the 2010 WHO recommendations if no further action is undertaken concerning vaccine uptake. Personal invitations were found to increase the chance of being vaccinated significantly; therefore the decline of the number of personal invitations in Poland needs to be addressed in the future. The fact that out-of-pocket payments in Poland are mentioned as a barrier may be a result of the economic situation in this country, where the price of the vaccination appears to be a relatively large burden for the average household budget.

Competing interests

This study was financed by the European Scientific Working group on Influenza (ESWI) for the 2003/4 season and by the European Vaccine Manufacturers (EVM) for the 2004/5 season. EVM is a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA).

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Citation style for this article: Kroneman M, van Essen G, . Stagnating influenza vaccine coverage rates among high-risk groups in Poland and Sweden in 2003/4 and 2004/5. Euro Surveill 2007;12(4)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n04/1204-221.asp

Experiences with the new genetic variant of *Chlamydia trachomatis* in Örebro county, Sweden – proportion, characteristics and effective diagnostic solution in an emergent situation

M Unemo (magnus.unemo@orebroll.se)[1], P Olcén[1], I Agné-Stadling[1], A Feldt[1], M Jurstrand[1,2], B Herrmann[3], K Persson[4], P Nilsson[5], T Ripa[5], H Fredlund[1]

1. Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden
2. Clinical Research Centre, Örebro University Hospital, Örebro, Sweden
3. Department of Clinical Microbiology, Uppsala University Hospital, Uppsala, Sweden
4. Department of Clinical Microbiology, Malmö University Hospital, Malmö, Sweden
5. Department of Clinical Microbiology and Infection Control Halland, County Hospital, Halmstad, Sweden

A *Chlamydia trachomatis* variant that contains a 377 bp deletion in the cryptic plasmid was recently reported in Sweden. This deletion includes the targets for Cobas Amplicor, Cobas TaqMan48, and Abbott m2000. We examined the proportion and characteristics of this variant in Örebro county, Sweden and developed an effective diagnostic solution. In total, 2,401 consecutive *C. trachomatis* culture samples and 536 PCR samples from symptomatic and asymptomatic patients and screened females were included. Culture, Cobas Amplicor, and LightMix 480HT were used for diagnosis. A mutant-specific PCR, plasmid sequencing, *omp*1 sequencing and multilocus sequence typing (MLST) were used to identify and characterise mutants. In total, 162 (6.7%) of the cultured samples were positive for *C. trachomatis*. However, 61 (38%) of those were negative when using Cobas Amplicor, and 60 of these were subsequently confirmed as the new variant. 13 of these mutant isolates were further characterised genetically, and all were of identical genotype E and the unique MLST sequence type: 21, 19, 1, 2, 1. Of all culture-positive samples, 161 of 162 were positive in the LightMix 480HT assay. The single negative sample was only weakly positive in culture, and negative in all PCRs. Of the 536 PCR samples, 37 were positive in both Cobas Amplicor and LightMix 480HT, 13 were only positive in LightMix 480HT (mutants), and two were only positive in Cobas Amplicor. Mutated *C. trachomatis* were prevalent in Örebro county in the period from October 2006 to February 2007, and it appeared to be a single clone. LightMix 480HT seemed sensitive, specific, and enabled high throughput diagnostics. However, rare low positive samples may be false-negative. Frequent surveillance and evaluations of diagnostic methods worldwide are crucial.

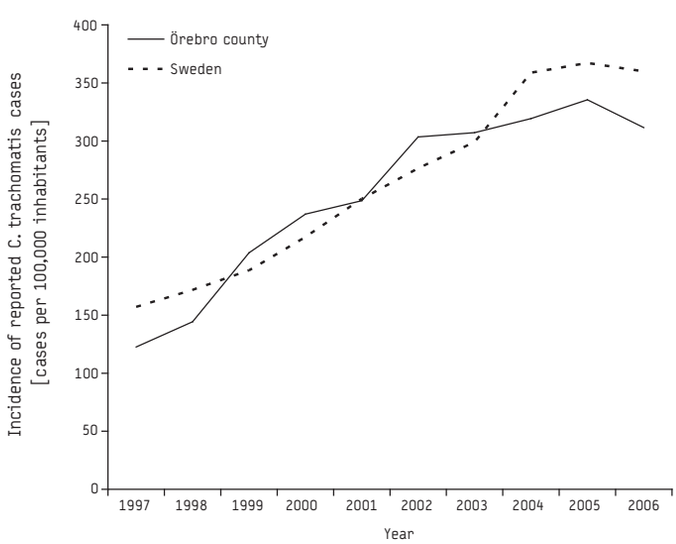
Introduction

In Halland, Sweden, a new variant of *Chlamydia trachomatis* (nvCT) was recently reported, which contained a 377 bp deletion in the cryptic plasmid (GenBank accession no. EF121757) [1]. This deletion includes the targets for diagnostic systems widely used in Sweden and in other countries, i.e. Cobas Amplicor (Roche Diagnostics), Cobas TaqMan48 (Roche Diagnostics), and Abbott *m*2000 (Abbott Laboratories) [1,2]. BD ProbeTec ET (Becton Dickinson), which targets a plasmid sequence outside the deleted region, is used in some of the Swedish counties. Aptima Combo 2 (Gen-Probe), which detects *C. trachomatis* specific *16S rRNA* sequences, is not used in Sweden.

Currently, nvCT have been identified in several counties across Sweden, with reported proportions from 10% to 66% of total *C. trachomatis* true positive samples [unpublished data]. In Örebro County (275,000 inhabitants), all *C. trachomatis* samples are analysed in the Department of Clinical Microbiology, Örebro University Hospital, using nucleic acid amplification test (NAAT), i.e. Cobas Amplicor, or culture (mainly cervical samples). The incidence of clinically reported *C. trachomatis* cases in Örebro county is similar to the national incidence and increased between 1997 and 2005. However, the incidence decreased from 336 cases per 100,000 inhabitants in 2005 to 311 cases per 100,000

Figure 1

The incidence of clinically reported *C. trachomatis* infection, irrespective of diagnostic method, in Örebro county and Sweden from 1997 to 2006



inhabitants in 2006 (Figure 1). Immediately after the first report of nvCT in Sweden, information regarding the diagnostic problem was widely distributed and it was recommended that symptomatic patients and patients with suspected chlamydial infection due to other reasons (contact tracing, etc) should be diagnosed using PCR and/or culture.

The objectives of this study were to examine the proportion and characteristics of mutated *C. trachomatis* in Örebro county, Sweden, and to develop an effective diagnostic solution in an emergent situation.

Materials and Methods

All consecutive *C. trachomatis* samples received for culturing at the laboratory between 5 October 2006 and 15 January 2007 (n=2,401, mainly cervical and urethral specimens) were included in this study. In addition, 536 consecutive PCR samples (urine (n=447), cervical (n=74), urethral (n=7), rectal (n=2), conjunctival (n=1), and unspecified (n=5) specimens) received between 5 February and 28 February 2007 were included. All these samples came from symptomatic or asymptomatic patients with suspected *C. trachomatis* infection, or were screening samples from women.

For diagnosis of *C. trachomatis*, Cobas Amplicor PCR (Roche Diagnostics) and/or McCoy cell culture with subsequent identification using fluorescein-labelled monoclonal antibodies (Phadebact Chlamydia IF Test, Bactus AB) were used. In addition, we evaluated the diagnostic value of a robotised system for automatic DNA isolation with magnetic silica particles (MagNa Pure LC System) combined with the new quantitative real-time PCR assay LightMix 480HT (TIB MOLBIOL) that targets a 136 bp fragment of the *omp*1 gene (together with LightCycler FastStart DNA Master Hybridization Probes, additional MgCl2, and LC Uracil-DNA Glycosylase), performed in 96-well microtiter plates on a LightCycler 480 (Roche Diagnostics). This is the first paper evaluating LightMix 480 HT, with a sensitivity to detect, at least, >=10 copies of *C. trachomatis* DNA (TIB MOLBIOL).

For the genetic characterisation of all suspected mutants, we used a mutant-specific real-time PCR with LightCycler probes flanking the plasmid deletion, and, for selected mutants, we performed plasmid sequencing, *omp*1 sequencing and a new assay for multilocus sequence typing (MLST) [3].

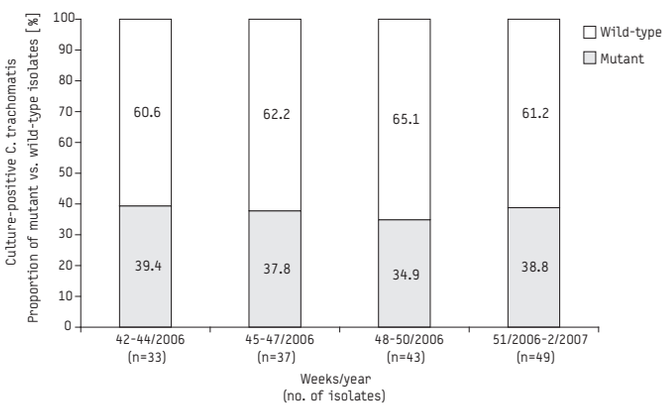
Results

Of the 2,401 cultured samples, 162 (6.7%) were *C. trachomatis* culture-positive. 101 of these 162 culture-positive samples were also positive in Cobas Amplicor PCR. The remaining 61 (38%), however, were negative in the Cobas Amplicor PCR, which only detects "wild-type" *C. trachomatis* and not the nvCT. 60 of those 61 were also positive for nvCT in the mutant-specific PCR, and, in addition, two of those 60 were further analysed by plasmid sequencing and shown to be identical to the mutant previously discovered in Halland [1]. Thus, in Örebro county, based on cultured samples, the proportion of the mutated variant had a mean of 38% (range: 34.9% to 39.4%) during the studied period of 12 weeks (Figure 2).

The mutated isolates were derived from 20 male (mean age: 22 years; range: 17 to 30 years) and 40 female patients (mean age: 21 years; range: 16 to 36 years). There were no obvious differences between the mutated isolates and wild-type isolates, neither with regards to clinical infection nor to growth characteristics in cell culture. 13 of the mutant isolates were genetically characterised

FIGURE 2

Culture-positive *C. trachomatis* and proportion [%] of mutated isolates in Örebro county, week 42, 2006 - week 2, 2007



further and found indistinguishable, i.e. they were all of genotype E, identical to the prototype strain E/Bour [4], and of the unique MLST sequence type: 21 (target region CT046, *hctB*), 19 (CT058), 1 (CT144), 2 (CT172), and 1 (*pbpB*).

For the initial evaluation of the LightMix 480HT diagnostic assay, we used the primary samples of the 162 culture-positive cases described above. 161 (99.4%) of them were positive using LightMix 480HT. Furthermore, we analysed 536 consecutive PCR samples independent of the culture samples. 37 of them were positive in both Cobas Amplicor and LightMix 480HT, 13 were positive in LightMix 480HT only (mutants), but two urine samples were only positive in Cobas Amplicor. Consequently, the proportion of the mutated variant among the PCR samples was 25% (13/52). Overall, according to the quantification available for LightMix 480HT, the load of *C. trachomatis* cells/DNA was similar for the mutated isolates and the wild-type strains (not shown). Furthermore, none of the samples included in this study were inhibited either in Cobas Amplicor or LightMix 480HT according to the internal positive controls.

Discussion and Conclusions

In Örebro county, Sweden, the new genetic variant of *C. trachomatis* was present and the proportion was high and rather constant during the study period (Figure 2). *Omp*1 gene sequencing and MLST, which has a significantly higher discriminatory ability than *omp*1 sequencing [3], strongly indicate that the nvCT is of one single clone that has not been prevalent in the community for an extended time period, at least not in high numbers.

LightMix 480HT seemed to be a sensitive, specific, and fast method for high throughput (96 samples analysed on LightCycler 480 in 1.5 hours) identification of *C. trachomatis*. One culture-positive and two Cobas Amplicor-positive samples were negative using LightMix 480HT. However, the culture-positive sample was reported as only weakly positive in culture, repeatedly negative in all the NAATs (even when using an increased volume of DNA template), and contamination in the culture cannot be excluded. Furthermore, one of the two Cobas Amplicor-positive samples was derived from a woman that already received treatment. However, rare samples with a low *C. trachomatis* load may be false-negative with LightMix 480HT due to its lower sensitivity for wild-type strains compared to Cobas Amplicor. This can presumably be explained by the fact that

the target in LightMix 480HT, *omp*1, is a single copy gene, while the target in Cobas Amplicor is the plasmid, which is present in up to 10 copies per bacterial cell. Moreover, optimised and quality assured culture of *C. trachomatis* remains fairly effective and valuable for the diagnosis of the present or potential other mutants, for NAAT inhibited or extra-genital samples, for antibiotic resistance testing if needed in the future, and for research purposes.

The origin of this nvCT is unknown. Extraordinarily, it has so far only been detected in Sweden and very recently in the neighbouring countries Norway (two cases) [5] and Finland [6]. Studies performed in Denmark [JS Jensen, personal communication], the Netherlands [7], and Ireland [8] did not detect the nvCT. Recently, a study was initiated that is aimed at identifying the diagnostic assays currently used, the presence of the mutant, recommendations for laboratories, and actions undertaken in different areas of Europe [9]. The importance of regular local, national, and international surveillance for possible undetected strains needs to be highly emphasised. In particular, because strains like the nvCT, may already be in a stage of early transmission in many countries. These strains have a selective advantage over wild-type strains and can be transmitted more rapidly if they are not being detected and/or eradicated by treatment. This may explain why the Swedish counties that are mainly using the Roche or Abbott systems are the ones with the highest proportion of the nvCT, as these tests may have resulted in an accumulation of undetected and untreated cases that have escaped the mandatory contact tracing. However, in Sweden and many other countries, symptomatic patients are generally treated independently of the test results. It is also important that any unusual decrease in the *C. trachomatis* incidence in different populations and geographic areas is investigated. In addition, regular and more comprehensive evaluation of different diagnostic methods is crucial for maintaining diagnostic quality. The samples included in such an evaluation should reflect not only currently transmitted strains, but also temporally, geographically and genetically diverse strains. Furthermore, diagnostic assays with a high sensitivity and specificity need to be established and provided, which target at least two different genetic sequences, e.g. a plasmid sequence and a chromosomal sequence such as the *omp*1 gene, or at least two divergent assays based on different targets or principles. This is evident for *C. trachomatis*, and could also be considered for other infectious agents.

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Citation style for this article: Unemo M, Olcén P, Agné-Stadling I, Feldt A, Jurstrand M, Herrmann B, and al. Experiences with the new genetic variant of Chlamydia trachomatis in Örebro county, Sweden – proportion, characteristics and effective diagnostic solution in an emergent situation. Euro Surveill 2007;12(4)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n04/1204-223.asp

Hepatitis B reactivation in an Irish dialysis unit, 2005

L Thornton (lelia.thornton@mailx.hse.ie)[1], F Fitzpatrick[2], D De La Harpe[3], A Brennan[1], N Murphy[1], J Connell[2], H Humphreys[4], E Smyth[4], JJ Walshe[4], M Crean[2], D O' Flanagan[1]

1. Health Protection Surveillance Centre (HPSC), Dublin, Ireland
2. National Virus Reference Laboratory (NVRL), Dublin, Ireland
3. Population Health, Health Service Executive, Naas, Ireland
4. Beaumont Hospital, Dublin, Ireland

In April 2005, a case of reactivation of hepatitis B virus (HBV) infection occurred in a patient undergoing haemodialysis in an Irish hospital. This incident potentially affected patients attending hospitals throughout the country, so a national incident team was set up coordinate the response to the incident. A total of 306 dialysis patients, attending 17 different dialysis centres (14 in Ireland), were identified as having been potentially exposed to HBV as a result of this incident. A programme of HBV serological testing and HBV vaccination was instituted. There was no evidence that any patient acquired HBV infection as a result of cross-infection from the index patient, although 11 patients (3.6%) had evidence of past infection (anti-HBc positive, HBsAg negative). The majority of patients in this cohort were of unknown HBV vaccination status (62.7%), 13.4% were fully vaccinated, 4.6% partially vaccinated and 15.7% unvaccinated. Of 239 tested for anti-HBs, 183 (76.6%) had a titre <10 mIU/ml. Local incidents in dialysis units can have national implications due to the frequent patient transfer between units. This incident highlighted serious deficiencies in current structures and practices, and a lack of appropriate guidelines. However, there were positive outcomes from this incident. The majority of Irish dialysis patients have now been vaccinated against HBV, and lessons learned have been used to develop national guidelines on HBV vaccination and testing and on the management of incidents of blood-borne viral infections in dialysis units.

Introduction

Blood-borne viral hepatitis, in particular hepatitis B (HBV), has been recognised as a hazard for haemodialysis patients and staff since the 1960s [1]. The implementation of guidelines for the prevention and control of HBV infection since the 1970s, including HBV vaccination of patients and staff since the 1980s, has been associated with a reduction in incidence of HBV infection in dialysis settings [1-3]. Investigations of HBV outbreaks in dialysis units since the introduction of these guidelines have indicated that the major factors contributing to cross-infection include significant deficiencies in infection control practices and failure to vaccinate patients [4]. In Ireland, which is a low endemicity country for HBV, infections are notifiable diseases and national guidelines recommend HBV vaccination for patients with chronic renal failure [5,6].

In April 2005, a haemodialysis patient was identified as HBV surface antigen (HBsAg) positive, having tested HBsAg negative on commencing dialysis in November 2004. Laboratory investigation of an archived November 2004 sample, taken before the onset of the first dialysis, revealed that the patient was positive for HBV core antibody (anti-HBc) and tested negative for hepatitis C antibody. Subsequent investigation also revealed that the patient had tested HBV positive in 1976. The April 2005 sample was negative for anti-HBc IgM and contained a viral load of 6.4 x 10^4 copies/ml. It was thought that these findings were caused by a reactivation of a previous HBV infection due to an immunosuppressive illness that developed subsequent to commencing dialysis. The patient was moved to an isolation facility and dialysed on a dedicated machine in April 2005. As the patient was potentially infectious from November 2004 to April 2005 and had been dialysed on several machines in the dialysis ward and was not isolated, there was concern that other dialysis patients may have been exposed to HBV.

A hospital incident team was set up and identified more than 300 adult patients as potentially exposed. A plan of communication, testing and vaccination was agreed on to investigate the incident. Although the majority of patients were still being dialysed in this hospital, some had returned to the care of other units in Ireland and abroad. Therefore, as the incident potentially affected patients in many regions and abroad, a national incident team, which included three members of the hospital team, was set up to co-ordinate the response.

Methods

Potentially exposed patients (primary cohort) were defined as patients haemodialysed in the index hospital, in the time period from the index patient's last negative HBsAg test to the date on which the index patient was isolated. One patient with pre-existing chronic HBV infection was excluded. As some inadequacies were identified in the index hospital's IT system, the national team verified the primary cohort by contacting all Irish adult dialysis units and relevant public health authorities abroad. As a complete list of dialysis units nationally was not readily available, the team compiled this using several sources. The lack of unique patient identifiers and robust IT systems in most units led to delays in identification of patients and necessitated the use of manual lists for organising testing schedules.

Parallel to compiling the list, the hospital incident team contacted each Irish adult dialysis unit to advise on their programme of HBV vaccination and testing. It recommended that all susceptible patients be offered an accelerated HBV vaccination schedule (40 mcg) and that HBV specific immunoglobulin (HBIG) be administered, as appropriate, to susceptible potentially recently exposed patients [1]. In addition, all primary cohort patients were to be tested for HBsAg weekly for 12 weeks from the date of last

dialysis within the exposure period in the index hospital [1]. This universal testing was necessary because information regarding HBV vaccination status and HBV surface antibody (anti-HBs) titre was not readily available for the majority of patients. For primary cohort patients not currently on haemodialysis, monthly rather than weekly HBsAg testing was recommended for patient convenience. In addition, as patients could have acquired HBV and subsequently lost HBsAg, it was recommended that they be tested for anti-HBc to ensure that recent HBV infection had not occurred. Hereafter, the national team contacted each Irish dialysis unit to clarify the recommended testing and vaccination schedules, and to enquire about past protocols and practices for testing and vaccination. In addition, a written protocol for the management of any new cases of HBV infection related to this incident was developed. In June 2005, it became apparent that the full range of recommended tests had not been carried out on all primary cohort patients for a variety of reasons, so the national team recommended that in these cases the last specimen of the testing programme be tested for both HBsAg and anti-HBc.

Data on the primary cohort were collected at intervals during the testing period from dialysis units and laboratories using a unique identifier. Demographics and details regarding dialysis, past HBV infection and vaccination, post-incident vaccination and laboratory investigations were recorded on a Microsoft Access database. Where a full range of testing had not been carried out, an attempt was made to establish the reason for this.

A final status was assigned to each patient as follows:

- HBV-infected (either new positive HBsAg result, new positive anti-HBc result when archived samples were anti-HBc negative or a positive anti-HBc IgM during or after the potential exposure period);
- past HBV infection (negative HBsAg, positive anti-HBc on an archived sample pre-dating November 2004);
- not infected (full range of recommended tests negative);
- other (full range of recommended tests not done).

Results

Some 306 primary cohort patients, in 17 dialysis centres (14 in Ireland and three elsewhere in Europe) were identified. Nearly half were 65 years or older; 190 were male. Two hundred and sixty (85%), were currently on haemodialysis; 18 had resolved acute renal failure, 16 had received a renal transplant, and six were on continuous ambulatory peritoneal dialysis (CAPD). Six were of unknown treatment status.

Previous protocols

A variety of strategies for HBV vaccination and testing were in place in the Irish units prior to this incident. Five units had a routine vaccination programme, seven had none, one had a programme that was not yet activated and one unit routinely asked GPs to vaccinate but few patients had been vaccinated. Regarding pre-dialysis laboratory screening, 13 units tested HBsAg and one tested both HBsAg and anti-HBc. All tested HBsAg every two to three months thereafter. Ten units reported that they had a tracking system whereby patients' dialysis sessions could be tracked to particular machines and staff members. The detail of these systems was not investigated.

Results of laboratory testing

A final HBV serological status was assigned to all patients (Table 1). A total of 2,938 HBsAg tests were performed. Seven patients had vaccine-related weak positive HBsAg test results that occurred within 13 days of vaccination and all were negative for both HBsAg and anti-HBc on follow-up investigation. Apart from the weak positive HBsAg results described above, no patient tested positive for HBsAg over the testing period.

Table 1

Final HBV status of primary cohort patients

Final Status	Patients	%
Not infected	278	90.8
Past infection	11	3.6
Other	17	5,6
HBV infection as a result of the incident	0	0
Total	**306**	**100**

Eleven patients were found to have past HBV infection (anti-HBc positive, HBsAg negative) based upon serological results on archived and recent samples. There was no serological evidence that any patient acquired HBV infection as a result of cross-infection from the index patient

Seventeen patients did not complete the full range of recommended tests. Eleven had no HBsAg tests after the incident (seven had died, three were uncontactable and one refused testing). Two patients who subsequently died each had one HBsAg test after the incident. Two patients had nine and seven HBsAg tests respectively, with the last one more than 10 weeks from the date of last dialysis in the index hospital and it was therefore considered unlikely that they could have acquired an infection. One patient had six and one had two HBsAg tests (the last test six and eight weeks respectively after last dialysis in the index hospital).

HBV vaccination status and anti-HBs titres prior to the incident

Anti-HBs titres at the start of this investigation, or in the three months prior to it, were available for 239/295 (81%) patients (having excluded those who were subsequently shown to have past infection). The majority, 183/239 (76.6%), had an anti-HBs titre <10 mIU/ml; 30 (12.6%) had a titre of 10-99 mIU/ml and 26 (10.9%) >=100 mIU/ml. Only 41 patients were reported to have completed a HBV vaccination schedule prior to the incident and fourteen had a history of partial HBV vaccination (Table 2).

Table 2

HBV Vaccination status of primary cohort patients prior to the incident

Prior HBV Vaccination Status	Patients	%
Full	41	13.4
Partial	14	4.6
None	48	15.7
Unknown	192	62.7
Prior HBV infection	11	62.7
Total	**306**	**100**

Table 3

Anti-HBs results (February-April 2005) of patients with full HBV vaccination prior to the incident

Anti-HBs results (mIU/ml)*	Patients	%
<10	3	7.3
10-99	18	43.9
>=100	18	43.9
Unknown	2	4.9
Total	**41**	**100**

*Anti-HBs levels tested between February and April 2005

Thirteen anti-HBc negative patients, 10 of whom were reported as of unknown vaccination status and three as not having been vaccinated, had anti-HBs levels >=10 mIU/ml and therefore were likely to have been vaccinated previously.

Anti-HBs levels in February-April 2005 were available for 39/41 patients with completed HBV vaccination, with the majority (36 patients) having anti-HBs >=10 mIU/ml (Table 3). Documented post-vaccination anti-HBs levels (within two-four months of the final HBV dose) were available in 16/41 patients. This was >=100 mIU/ml in 10 patients, 10-99 mIU/ml in three, and three did not respond to HBV vaccination. Of the 17 patients with information indicating partial vaccination prior to the incident, seven had anti-HBs levels >=10 mIU/ml.

HBV vaccination following the incident

Thirty-six patients were identified as requiring HBIG: of those, 30 received it, three were offered it but refused, and a further three were not offered it. Regarding the Hepatitis B vaccination, most patients received the higher vaccine dose (40 mcg), and an accelerated preliminary schedule, either 0, 7, and 21 days, or 0, 1, and 2 months. Excluding the 11 patients with past HBV infection, and the 41 who were fully vaccinated before the incident, the vaccination status of the remaining 254 at five months was: 186 (73.2%) fully vaccinated, 10 (3.9%) currently being vaccinated, 14 (5.5%) deceased, 4 (1.6%) not vaccinated as they had protective anti-HBs levels, and 40 (15.7%) unvaccinated patients. Of the 40 unvaccinated patients, 32 were no longer on dialysis, six refused vaccination, one had a reported contra-indication to vaccine and one was not on dialysis anymore and could not be contacted. In addition to the primary cohort, most units had also used this opportunity to vaccinate their other dialysis patients.

Discussion

This incident highlights the fact that a case of HBV infection in one haemodialysis unit may impact on patients in dialysis units throughout Ireland and also abroad. Fourteen of 16 adult dialysis centres in Ireland (87%), and three centres outside the country, were affected.

During the investigation, it became clear that there were difficulties in the identification and follow up of the cohort, due to the lack of unique patient identifiers and suitable national IT systems. As a result, some patients were not tested according to the recommended schedule and some patients who were immune to HBV were tested unnecessarily. We recommend that a standardised national information system be implemented to address the complex needs of haemodialysis patients, including a "Smart card" containing basic demographic data, results of laboratory tests and HBV vaccination status. This will facilitate information transfer during movement of patients between dialysis centres nationally and internationally.

Although guidelines for the prevention and control of blood-borne viruses (BBV) in haemodialysis units published in other countries have served as a resource for Irish practitioners [1,3], the lack of such national guidelines has led to variation in HBV testing and vaccination protocols throughout the country. Most units followed UK guidelines which advise HBsAg, but not anti-HBc, testing before the onset of the first haemodialysis and three-monthly thereafter [1]. In the US, HBsAg and anti-HBc are tested pre-dialysis, with monthly HBsAg for susceptible patients and annual anti-HBs for vaccinated immune patients [3]. Only a third of the Irish units had a programme of routine HBV vaccination in place, despite the recommendation of the national immunisation guidelines that patients with chronic renal failure should receive HBV vaccination [5]. The national team used experiences gained during management of this incident to contribute to detailed guidance on HBV vaccination and testing which was incorporated into a chapter on blood-borne viruses in the haemodialysis, CAPD and renal transplant setting in the national guidelines on the prevention of transmission of BBVs in healthcare settings [4].

Due to the successful implementation of the testing programme following the incident, it was possible to assign a final status for most (94%) patients. There was no evidence that any patient became infected with HBV. This probably reflects the good standards of infection control practices within the Irish dialysis units. Transient weak positive HBsAg results occurred in seven patients post-vaccination. While this occurrence has been previously reported [7-12], it presented specific challenges during this incident, in terms of interpretation of results, patient concern and infection control. Although this problem would have been avoided by testing for HBV DNA, rather than HBsAG, DNA testing was not feasible in this incident due to cost, the need to obtain timely results, and the logistics of collecting suitable samples. Eleven (3.6%) patients were found to have evidence of past HBV infection. This is the first time information has been available on HBV infection in Irish dialysis patients. The identification of previously unidentified patients with past HBV infection raised issues of patient counselling and of the appropriate management of HBsAg negative, anti-HBc positive dialysis patients. This is not addressed in the current UK guidelines [1]. While US guidelines recommend HBV DNA testing, they do not propose any viral load cut-off point above which patients require segregation, but rather recommend that isolation is not necessary once HBsAg remains negative [3]. Neither guidelines proved useful regarding advice on follow-up HBsAg testing. As with the index patient, such patients could potentially reactivate HBV infection due to immunosuppression, have detectable HBsAg and be potentially infectious. We recommended that these patients should be tested monthly for HBsAg but did not need to be isolated once HBsAg remained negative. However, this issue should be addressed in future haemodialysis guidelines; in particular, consideration should be given to the need to dialyse these patients in isolation. We recommend that all patients are tested for anti-HBc pre-dialysis.

The proportion of haemodialysis patients who develop a protective antibody response (>=10 mIU/ml) after HBV vaccination has been reported to be lower than in adults with normal immune status: median 64% (range: 34-88%) after a three-dose schedule and 86% (range: 40-98%) after a four-dose schedule; this compares with a protective anti-HBs response in 90-95% of those with normal

immune status after a three-dose schedule [3]. Our finding that 36/41 (88%) patients vaccinated prior to the incident still had protective anti-HBs, with an anti-HBs level >=100 mIU/ml in half of these, clearly indicates that vaccination of these patients is a worthwhile exercise. Some studies have demonstrated that higher antibody response rates could be achieved by vaccinating patients with chronic renal failure before they become dialysis-dependent [3].

No cases of HBV cross-infection were identified. However, given the susceptibility of the cohort there was the potential for a more serious outcome. The investigation and management of this incident was time-consuming and costly and represented a significant additional workload for hospital, laboratory and public health professionals, much of which might have been avoided by prior vaccination and a national haemodialyis services IT system. The incident highlighted several serious deficiencies in current structures and practices that should now be addressed in order to avoid or minimise the potential for serious BBV transmission in the future. Positive outcomes are that the majority of dialysis patients are now vaccinated, and lessons learned from this incident have informed the updating of national guidelines on HBV testing and vaccination in the haemodialyis setting.

Acknowledgements

Consultant nephrologists, dialysis nurses, infection control nurses, administrative staff, consultant microbiologists and laboratory staff in the relevant hospitals; staff of the HIV/hepatitis laboratory, NVRL; directors of public health and staff in departments of public health; administrative and surveillance staff in HPSC; Ms Kathleen Kelly, Beaumont Hospital, Dublin; Dr Miriam Alter, CDC, Atlanta, GA, USA; Drs Mary Ramsay and Alan Smith, CfI, HPA, London; Drs Stefania Salmaso and Marta Ciofi degli Atti, ISS, Rome; Dr Mike Lilley, Bedfordshire HPU; Dr Massimiliano di Renzi, HPSC and EPIET programme.

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Citation style for this article: Thornton L, Fitzpatrick F, de la Harpe D, Brennan S, Murphy N, Connell J, and al. Hepatitis B reactivation in an Irish dialysis unit, 2005. Euro Surveill 2007;12(4)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n04/1204-224.asp

An Easter outbreak of *Salmonella* Typhimurium DT 104A associated with traditional pork salami in Italy

I Luzzi[1], P Galetta[2], M Massari[2], C Rizzo[2 8] (caterina.rizzo@iss.it), AM Dionisi[1], E Filetici[1], A Cawthorne[2 3], A Tozzi[4], M Argentieri[4], S Bilei[5], L Busani[6], C Gnesivo[7], A Pendenza[7], A Piccoli[7], P Napoli[7], R Loffredo[7], MO Trinito[7], E Santarelli[7], ML Ciofi degli Atti[2]

1. Department of Infectious, Parasitic and Immunological Diseases, Istituto Superiore di Sanità, Rome, Italy
2. National Centre for Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità Rome, Italy
3. European Programme for Intervention Epidemiology Training
4. Ospedale Bambino Gesù, Rome, Italy
5. Istituto Zooprofilattico Sperimentale del Lazio e Toscana Rome, Italy
6. Department of Food and Animal Health, Istituto Superiore di Sanità, Rome, Italy
7. Local Health Units, Rome, Italy
8. Department of Pharmaco-Biology, University of Bari, Italy

Salmonella enterica is a common cause of gastrointestinal illness in Italy. *S.* Typhimurium accounts for approximately 40% of isolates, and most of these strains belong to the phage type DT104. We describe the investigation of an outbreak of *S.* Typhimurium DT104A, a subtype never observed before in Italy, which occurred in Rome during spring 2004. We conducted a matched case control study between 24 July and 9 September 2004. Controls were matched for age and area of residence. Each case had between one and four controls. Odds of exposure to potential risk factors and vehicles for the outbreak were compared between cases and controls. A multivariate analysis was conducted to estimate adjusted Odds Ratios. Sixty-three cases of *S.* Typhimurium DT 104A infection with onset between 1 April and 5 May 2004 were identified. Sixty-one were residents of Rome and two were residents of a neighbouring region. Twenty-six cases (43%) were enrolled in the study. Their median age was 7.5 years. Fourteen of 26 cases and 16 of 62 controls had eaten pork salami (OR= 25.5; 95% CI 1.6- 416.8). No food samples were available for testing. In northern Italy, two months prior to the outbreak, the veterinary surveillance system identified the first isolation of *S.* Typhimurium DT104A in a pig isolate. Both human and pig isolates showed indistinguishable PFGE patterns. It was not possible to trace the pig after the sample was taken at slaughter. The epidemiological evidence on the implication of pork salami in this outbreak suggests that pork products can also be a vehicle for salmonella in Italy and underlines the importance of good manufacturing practices for ready-to-eat foods. This investigation highlights the value of laboratory-based surveillance in identifying community-wide outbreaks of uncommon pathogens. It also underlines the need to improve surveillance timeliness, for promptly detecting outbreaks, undergoing field investigation, and implementing control measures. Moreover, our study shows the usefulness of integrated human and animal surveillance in tracing the possible source of infection.

Introduction

Approximately 10,000 human salmonella cases are notified every year to Italy's mandatory surveillance system of infectious diseases [1]. Circulation of salmonella serotypes is monitored by the laboratory-based surveillance system Enter-net Italy, which is coordinated by Istituto Superiore di Sanità (ISS) and is part of Enter-net, the European network for the surveillance of salmonella and verotoxigenic *E.coli* (VTEC) infections [2]. Enter-net Italy collects epidemiological and microbiological information on salmonella strains isolated in 41 reference laboratories from 15 of the 21 Italian Regions, with the aim of describing the nationwide circulation of different salmonella serotypes. In addition, surveillance involves veterinary laboratories that collect data on isolates from animals and food items of animal origin (Enter-Vet Italy) [3]. Moreover, a sub-sample of strains of *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) and serovar Enteritidis (*S.* Enteritidis) serotyped in the regional laboratories, have been sent to ISS to be phagetyped and genotyped [4,5]. These two serotypes are the most commonly isolated from human infections in Italy, accounting for approximately 80% of total strains.

In 2004, Enter-net Italy reported over 5,000 human salmonella isolates: 41% were *S.* Typhimurium. In the same year, Enter-Vet Italy accounted for 4,600 isolates with 22% belonging to *S.* Typhimurium serotype.

As in other European countries, most *S.* Typhimurium strains in Italy belong to the phage type DT104 [6,7]. Within this phage type there are numerous distinguishable subtypes, identified as A,B,C,H,L [7]. In Italy, most human strains isolated between 2001 and 2006 were 104L and H [6]. We describe the investigation of an outbreak of *S.* Typhimurium DT104A, a subtype never observed before in Italy, which occurred in Rome during spring 2004.

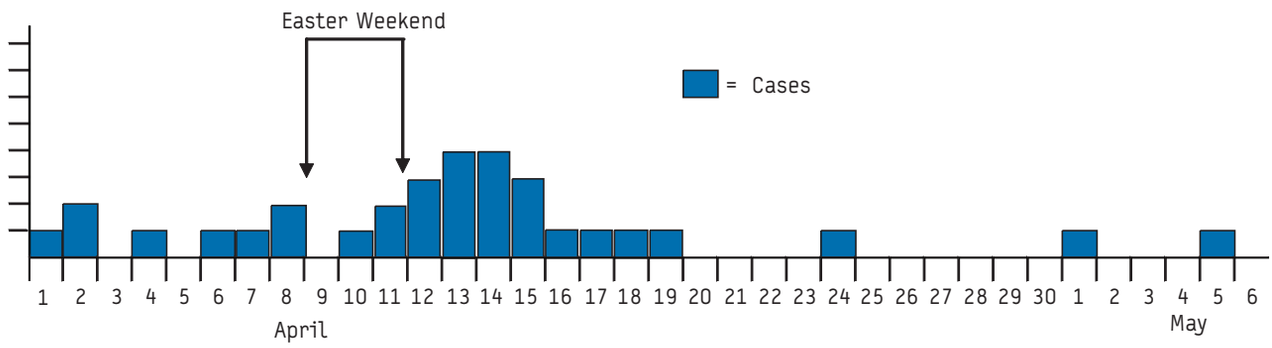
Methods

In June 2004, ISS typed 22 human isolates of *S.* Typhimurium as phage type DT104A [6]. The strains were sent by the Lazio regional references laboratory, and all were isolated by the laboratory of the Bambino Gesù Paediatric Hospital in Rome.

In order to verify if other cases related to the same serotype had occurred, in July 2004 ISS requested to laboratories participating in Enter-net Italy to send all the strains of *S.* Typhimurium isolated between 1 March and 1 June 2004. A request for information on DT104A *S.* Typhimurium strains eventually isolated in animals or food of animal origin were also sent to veterinary laboratories participating in Enter-vet.

FIGURE 1

Cases of *Salmonella* Typhimurium DT104a, by day of onset of symptom, Rome, 2004



***Salmonella* characterization**

Serotyping based on O and H antigens was performed according to the Kauffmann-White scheme [4]; phage-typing was performed in accordance with the methods of the UK's Health Protection Agency [5]. Susceptibility to 11 antimicrobial agents was assessed using the National Committee for Clinical Laboratory Standards (NCCLS) agar disk diffusion method [8]. Pulsed-field gel electrophoresis (PFGE) was performed after digestion of the DNA with XbaI according to a standardized protocol [9].

Matched case control study

In order to investigate risk factors for DT104A *S.* Typhimurium, a matched case control study was conducted between 24 July and 9 September 2004.

A case was defined as a person with a *S.* Typhimurium DT 104A infection, laboratory-confirmed between 1 March and 1 June 2004 in Rome. Demographic information on all cases was obtained from the Enter-net Italy database. We selected up to four matched controls for each case (assuming 25% exposure among controls, 80% power to detect a minimum Odds Ratio of 3.9, alpha error of 5%). We randomly selected controls from each case's general practitioner resident list matched for age (+/- 2 years), sex, and district of residence. Controls were excluded if they reported that they or any of their household members had experienced an episode of gastrointestinal illness (three or more loose stools in a 24-hour period, or vomiting, or abdominal pain) in the seven days prior to the onset of illness in the matched case.

Trained interviewers collected data using a structured questionnaire administered by telephone. The questionnaire collected information on clinical symptoms, food consumption during April 2004 (Easter month, with Easter falling on 11 April), travel (abroad and within Italy), contact with animals, and restaurants and food vendors visited. Interviewers made three attempts at different times of day to contact each case and the corresponding controls. If cases or controls were under 16 years old, parents or guardians were interviewed.

Statistical Analysis

All questionnaires were mailed to ISS, where the data were entered into an MSAccess 2000 (Microsoft, Redmond, Wash) database. Categorical variables were compared using the Chi^2 test; continuous variables were compared using the Wilcoxon Mann-Whitney test. In the univariate analysis, exposure to potential risk factors was compared between cases and controls calculating matched "Mantel-Haenszel" odds ratios (mOR), with exact 95% confidence intervals (95% CI).

A multivariate conditional logistic regression model was then performed to assess independent effects of the exposure variables and to estimate adjusted odds ratio (aOR); risk factors associated

TABLE

Matched univariate analysis (odds ratio: mOR) and multivariate conditional logistic regression analysis (adjusted odds ratio: aOR). Cases of *Salmonella* Typhimurium DT104A infection (n=26) and Controls (n=63) according to investigated risk factors, April-May 2004, Rome, Italy

			Univariate analysis			Multivariate analysis		
Risk factors*	Cases (%)	Controls(%)	mOR	95% CI	*p*-value	aOR	95% CI	*p*-value
Eating at a restaurant	2/25 (8)	17/48 (35)	0.1	(0.01-0.8)	0.03			
Consumption of:								
Crude eggs	5/26 (19)	3/63 (5)	3.4	(0.8-14.4)	0.1			
Sausage	7/25 (28)	33/63 (52)	0.2	(0.1-0.7)	0.01	0.04	(0.01-0.9)	0.04
Ham	3/25 (12)	1/63 (2)	8.9	(0.9-86.3)	0.06			
"Corallina" salami	14/23 (61)	16/63 (28)	4.4	(1.3-14.4)	0.02	25.5	(1.5 – 442.9)	0.03
Snacks	12/26 (46)	39/63 (62)	0.3	(0.1-1.0)	0.05			
Cow milk	12/26 (46)	57/63 (91)	0.1	(0.1-0.4)	<0.01			

**In the univariate analysis, only risk factors with p-value<0.20 are reported; in the multivariate analysis, only variables selected by the conditional logistic model according to a log-likelihood-ratio test for goodness-of-fit are reported*

with the outcome (P<0.20) in the univariate analysis, after testing for multicollinearity, were considered eligible to be included in the multivariate model, and retained in the final model, together with matching variables, according to a log likelihood-ratio test for goodness-of-fit. For each variable, the model excluded records with missing values. Analysis was carried out using STATA 8.2 (Stata Corp, College Station, Texas, US).

Results

Description of cases

A total of 242 *S.* Typhimurium strains were isolated from 1 March to 1 June 2004, and were collected by the Lazio regional reference laboratory in June 2004. Sixty-three (26%) of these strains belonged to DT104A; all were sensitive to the 11 antimicrobial agents tested.

Sixty-one isolates were from residents of Rome and two were residents of a neighbouring region (Umbria). All cases from Rome were distributed within the five districts of the municipality. Of the 63 patient with isolates of *S.* Typhimurium, 34 (54%) were male; the median age, available for 61 cases, was 7 years (range 1-78). Date of onset of symptoms was available for 32 patients (Figure 1) and ranged from April 1 to May 5 with a duration of symptoms of 1-30 days. The cases reported diarrhoea (93%), abdominal pain (73%), and fever (75%).

Matched Case Control Study

Of 61 cases identified in Rome, 35 (57%) could not be included in the case control study: 11 refused to participate, 10 could not be found because interviews took place over the summer period, and for 14 interviewed cases no controls could be identified. In total, 26 cases and 63 controls were enrolled in the study. The 26 cases included in the study did not statistically differ from the 35 cases who did not participate, in terms of sex (P=0.87), median age (7.5 years; P=0.16) and district of residence (P=0.32).

The matched univariate analysis revealed that cases were more likely than controls to have eaten "corallina", a fermented pork salami traditionally consumed during Easter in the Rome region. They were less likely to have eaten at a restaurant, to have eaten sausages or snacks, and to have consumed cow milk (Table).

In the multivariate conditional logistic regression analysis, to have eaten corallina become more strongly associated with illness (OR= 25.5; 95% CI 1.5- 442.9) while only to have eaten sausages (OR= 0.04; 95% CI 0.01-0.9) remained statistically inversely associated with illness.

Food investigation

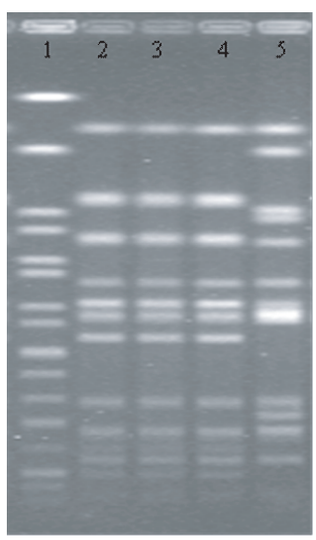
The epidemiological investigation could not identify a possible brand of corallina, as cases could not remember specific brands consumed. No samples of corallina were available for testing at the time of the study.

Veterinary data

Two months prior to the outbreak, the veterinary surveillance system Enter-vet identified the first isolation of *S.* Typhimurium DT104A in a pig isolate, among 1021 animal and food *S.* Typhimurium isolates. This strain came from the intestinal content of a pig slaughtered in north-eastern Italy (Veneto region) in January 2004 during a monitoring program on the presence of *Salmonella* in swine herds. Both human and pig isolates showed indistinguishable

FIGURE 2

Pulsed-field gel electrophoresis profiles of three strains (two from patients and one from a pig) of *S.* Typhimurium DT104A after digestion with XbaI (Line 1:Molecular reference marker '*S.* Braenderup strain H9812'; Lines 2,3: *S.* Typhimurium DT104A human isolates; Line 4: *S.* Typhimurium DT104A pig isolate; Line 5: *S.* Typhimurium DT104L with the common penta-resistance pattern)



PFGE patterns (Figure 2). It was not possible to trace the pig after the sample was taken at slaughter.

Discussion

This widespread outbreak of new emerging phage type of *S.* Typhimurium involving 63 cases was identified through laboratory-based surveillance using serotype and phage typing.

The pattern of the epidemic curve, the long period over which the reports of confirmed cases increased and the geographic distribution of cases supports the hypothesis that the outbreak was due to a common source rather than a point source (e.g. food served at a large gathering). The common source could likely be a food product with a long shelf life that was widely distributed across the Lazio region. We suspect that it may have been a ready-to-eat item that did not require cooking, since food-borne infection with *Salmonella* species can usually be prevented with adequate refrigeration and cooking temperatures, and proper handwashing and food preparation practices [10].

The most likely hypothesis supported by the findings of this epidemiologic investigation was that illness was associated with corallina salami. However, just over half of the cases reported eating corallina. There are a number of possible explanations for cases not reporting having eaten the implicated salami. Despite the questionnaire listing a series of food items, interviews took place two to five months after the outbreak period, so it is possible that some cases could not remember their precise food consumption during the period of exposure. Six of the cases who did not report eating corallina were children aged between two and eight years and parents or guardians who answered may not have been aware of all food items eaten during a holiday period associated with social gatherings.

A further limitation of this investigation was the low proportion of cases who were enrolled in the case control study (43%). Even if their demographic characteristics did not statistically differ from patients who did not participate, this could have caused a selection bias.

It should also be noted that consumption of sausages was inversely associated with disease onset, which could be due to the fact that cases who did eat corallina salami were less likely to eat sausages.

Corallina pork salami is a plausible vehicle for infection as pig herds are frequently infected with *Salmonella* in Italy [11,12]. Several studies have shown that contamination of pork sausages with salmonella is common [13-16]. Salami are dry fermented sausages traditionally considered safe due to low pH, low water activity and high salinity, but *Salmonella* can survive fermentation and drying steps if the manufacturing process or fermentation periods are inadequate [15]. Survival of organisms in ready-to-eat products has the potential to cause illness, and salami has been previously identified as the food vehicle for *S.* Typhimurium in two geographically widespread outbreaks in northern Italy (PT 193) and England (definitive type 124) [12-13]. It is reasonable to assume that the corallina salami was commercialised before the optimal fermentation period, because of the high demand for this particular item during Easter banquets in the Lazio region.

A limitation of laboratory-based surveillance is that detailed microbiological analysis is performed on a periodic basis with a delay in recognising uncommon strains. Delays also occur when local laboratories wait to send in ISS samples or strain data until the end of the month or when there are an adequate number of samples.

In this outbreak, cases occurred during Easter, outbreak detection was in June and investigation was conducted during summer, the most difficult period to trace people for interview. As a result, no samples of the suspected salami were available for testing. We could not identify the brand, as cases could not remember which brands had been consumed. Furthermore, the 63 cases identified are probably an underestimation of the outbreak.

In conclusion, although food safety can be assured by good manufacturing practices and standards, the effectiveness of these practices should be monitored by sensitive surveillance of human cases, especially when dealing with the production of ready-to-eat foods. This outbreak highlights the need for timely surveillance and work is now underway to develop an online surveillance system in Italy enabling laboratories to input strain data immediately into the Enter-net Italy database. Finally, the usefulness of integrated human and animal surveillance was clear during this investigation, and is in line with the recent European directive [10].

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Citation style for this article: Luzzi I, Galetta P, Massari M, Rizzo C, Dionisi A, Filetici E, and al. An Easter outbreak of Salmonella Typhimurium DT 104A associated with traditional pork salami in Italy. Euro Surveill 2007;12(4)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n04/1204-226.asp-

Cluster of *Salmonella* Enteritidis in Sweden 2005-2006 – suspected source: almonds

L Ledet Müller (luise.ledet.muller@smi.ki.se)[1,2], M Hjertqvist[1], L Payne[1], H Pettersson[1], A Olsson[1], L Plym Forshell[3], Y Andersson[1]

1. Smittskyddsinstitutet (Swedish Institute for Infectious Disease Control, SMI), Stockholm, Sweden
2. European Programme for Intervention Epidemiology Training (EPIET)
3. Livsmedelsverket (National Food Administration), Uppsala, Sweden

Previous outbreaks of *Salmonella* Enteritidis in Canada and the United States have been associated with the consumption of almonds. From December 2005 to August 2006 a cluster of 15 cases of *Salmonella* Enteritidis NST 3+ was reported in Sweden. A case-control study was performed to identify the source of transmission. Three controls per case were randomly selected, matched on sex, age and place of residence. Cases and controls were interviewed by telephone and data were analysed with a conditional logistic model. The results showed that eating almonds was a risk factor for infection with *Salmonella* Enteritidis NST3+ (unmatched odds ratio 45.0, 95% confidence interval: 4.8-421.8). No *Salmonella* was isolated from almonds tested in the study. In conclusion, almonds could be the source of the outbreak and should be considered when investigating outbreaks as well as sporadic cases of *Salmonella* Enteritidis.

Introduction

From December 2005 to August 2006, a total of 15 non-travel-related cases of *Salmonella* Enteritidis NST 3+ were reported in Sweden (*NST means that in Sweden this pattern has no specific name, 3+ means that the isolate reacts with three different phages*). This phage type is unusual, with a total of four sporadic cases previously reported in Sweden, including the first two cases that were identified in western Sweden in January 2003 (SMI statistics - unpublished).

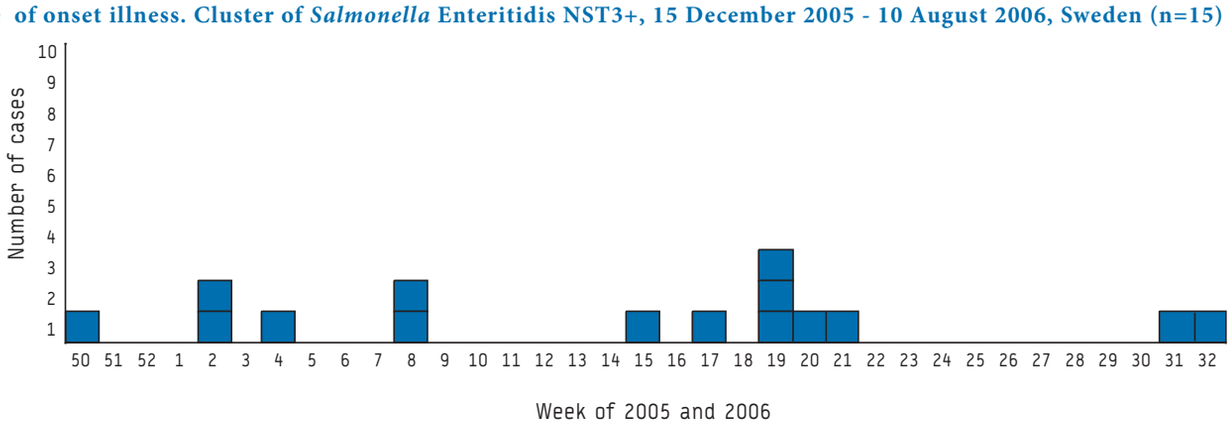
Following an alert to Enter-net on 22 February 2006, information was obtained indicating that no similar increase of *Salmonella* Enteritidis NST 3+ was reported within the network under the same time period. However, in Canada a large outbreak of *Salmonella* Enteritidis had previously been reported with the same phage type pattern (called *Salmonella* Enteritidis phage type 30) in the winter 2000-2001 [1]. In the Canadian outbreak, 168 cases were reported, including 11 cases in United States citizens, and the outbreak was related to almonds originating from California with a calculated odds ratio (OR) of 21.1 (95% CI: 3.6-∞). It was the first time almonds were identified as the source of a food-borne outbreak. Another *Salmonella* Enteritidis outbreak associated with almonds occurred in 2003-2004 in Canada and the United States with 29 confirmed cases [2]. The Swedish isolates from the recent cluster, however, had a different PFGE pattern than the ones in previous outbreaks reported in Canada and United States.

Methods

To investigate the cluster seen in Sweden, the patients were interviewed with a general (trawling) questionnaire regarding exposure to a variety of food items two weeks prior to the date of onset of illness. The first six patients were interviewed in March when the cluster was detected, whereas the other cases were questioned as soon as they were reported. On the basis of the initial results a few exposures to particular food items were suspected as the possible source of infection and an abbreviated version of the questionnaire was made. A case-control study with three controls per case was conducted for 12 of the cases in cooperation with the County Medical Offices. The first controls were interviewed in March when the study began and the rest were interviewed when cases were reported. Controls were randomly selected from the population register matched on sex, age and place of residence, and questioned about the food items eaten during two weeks prior to the interview.

Figure

Date of onset illness. Cluster of *Salmonella* Enteritidis NST3+, 15 December 2005 - 10 August 2006, Sweden (n=15)



Table

Intake of food items among cases and controls (analysis of 12 cases). Cluster of *Salmonella* Enteritidis NST3+, 15 December 2005 - 10 August 2006, Sweden

	Cases who ate the food item n=12 (%)		Controls who ate the food item n=34 (%)		Matched odds ratio (95% confidence interval)		P value
Eggs							
Soft-cooked eggs	2	(18)	14	(41)	0.4	(0.1-2.1)	0.26
Scrambled eggs/omelette	5	(45)	6	(18)	5.4	(1.0-29.0)	0.05
Raw eggs	2	(17)	4	(12)	1.7	(0.2-14.0)	0.64
Hard cheese	11	(92)	32	(94)	0.8	(0.1-8.6)	0.83
Pork/pork steak/pork sausage	6	(55)	29	(85)	0.3	(0.1-1.7)	0.18
Cooking sausage/cocktail sausage/ Frankfurter	8	(73)	24	(71)	1.6	(0.3-9.1)	0.59
Nuts/seeds							
Almonds	10	(83)	6	(18)	**45.0***	(4.8-421.8)*	<0.01*
Hazelnuts	3	(25)	7	(21)	1.3	(0.2-7.6)	0.76
Walnuts	1	(9)	3	(9)	1.0	(0.1-9.6)	1.00
Pistachio nuts	0	(0)	3	(9)	-		-
Pine nuts	0	(0)	3	(9)	-		-
Sesame seeds	1	(11)	5	(16)	0.5	(0.1-5.0)	0.55

*Unmatched analysis

The final data analysis was performed in October 2006. Items in the abbreviated questionnaire were individually analysed with a conditional logistic model to take into consideration the matching. For items where we could not find any case with a discordant control (i.e. an exposed case with at least one unexposed control, or an unexposed case with at least one exposed control), unmatched odds ratio where calculated instead. Unmatched odds ratio in a matched design will be biased towards the null hypothesis of OR=1. Proc Logistic in SAS v.9.1 was used for calculating all odds ratios.

Salmonella identified in the stool samples provided by case-patients were serotyped and phagetyped at the reference laboratory at SMI. Cultures from almond samples and isolates from the cases were tested by serological assays according to the Kauffmann-White scheme and phage typing according to the HPA Colindale method.

Results

The 15 patients came from seven different regions in the south and centre of Sweden and were aged between 11 and 87 years, with an average age of 46 years. Eleven were women. The patients fell ill between 15 December 2005 and 10 August 2006 (Figure). The results of the case-control study are shown in the Table.

Ten patients reported having consumed ready-to-eat untreated almonds and one could not recall eating them or not, whereas among the controls only six had eaten almonds. One patient who had only eaten cooked almonds was considered as unexposed. The controls matched to this case, however, had not eaten almonds either, so we could not find any pairs consisting of an unexposed case and at least one exposed control. For this reason unmatched odds ratio was instead calculated; the estimated odds ratio was 45.0 (P value < 0.01). The almonds consumed by the patients were of various brands. Of the other food items, only scrambled eggs were consumed more frequently by patients than by controls. However, this exposure would only explain 45% of the cases and is more likely to be a chance finding (P value = 0.05).

Thirty-two samples of almonds were tested for *Salmonella*, including samples taken from opened packages from two patients' households, as well as samples taken from unopened packages collected from different supermarkets. No *Salmonella* was isolated from these samples. The *Salmonella* isolates obtained from the cases were sent to the Laboratory of Enteric Pathogens at the Health Protection Agency in Colindale, United Kingdom, where it was found that the phage type was the same as the phage type from the outbreak of 2000-2001 in Canada and the United States.

Discussion

This case-control study showed a high OR for almonds, which suggests that almonds were a risk factor for infection with *Salmonella* Enteritidis NST 3+. Even though the patients consumed different brands of almonds, it has been indicated that the majority of almonds sold in Sweden originate from California, the region where nearly 80% of the world production of almonds come from and where outbreaks of *Salmonella* Enteritidis with the same phage type have previously occurred [2]. In the outbreak described in

this paper, no *Salmonella* was isolated from the almonds, however, only a few samples could be collected directly from the patients' households.

The first patients were interviewed several weeks after the onset of disease, which could lead to recall bias. To reduce recall bias for controls, they were asked about exposure to specific food items in the period of two weeks prior to the interview. This could have led to a seasonal variation between the first cases and their controls. However, due to the small number of cases this is not considered to have significantly influenced the results. Almonds as a possible source of transmission of *Salmonella* should be considered when investigating outbreaks as well as sporadic cases. Interventions to control *Salmonella* in almonds are well motivated and accordingly the Agricultural Marketing Service at the US Department of Agriculture is currently proposing a mandatory program to reduce the potential for *Salmonella* bacteria in almonds [3].

We conclude that almonds could be the source of infection for the cluster of *Salmonella* Enteritidis NST 3+ recently reported in Sweden. However, as no *Salmonella* was detected in the tested almonds and the statistical analysis was interpreted with caution because of the small sample size, no control measures were putin place. No further cases of *Salmonella* Enteritidis NST 3+ have been reported in Sweden after August 2006.

Acknowledgements

We would like to thank the County Medical Offices in Stockholm, Skåne, Västra Götaland, Halland, Östergötaland, Jönköping, Uppsala and Örebro for their contribution to the study.

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Citation style for this article: Ledet Muller L, Hjertqvist M, Payne L, Pettersson H, Olsson A, Plym-Forshell L, and al. Cluster of Salmonella Enteritidis in Sweden 2005-2006 – suspected source: almonds. Euro Surveill 2007;12(6)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n06/1206-225.asp

Outbreaks of monophasic *Salmonella enterica* serovar 4,[5],12:i:- in Luxembourg, 2006

J Mossong (Joel.Mossong@lns.etat.lu)[1], P Marques[2], C Ragimbeau[1], P Huberty-Krau[3], S Losch[4], G Meyer[4], G Moris[5], C Strottner[6], W Rabsch[7], F Schneider[1]

1. Microbiology Unit, Laboratoire National de Santé (National Health Laboratory, LNS) Luxembourg
2. Centre de Recherche Public – Santé (Research Centre for Health, CRP- Santé), Luxembourg
3. Health Inspection Unit, Direction de la Santé (Health Directorate), Luxembourg
4. Administration des Services Vétérinaires (Veterinary Services Administration), Luxembourg
5. Food Control Unit, Laboratoire National de Santé (National Health Laboratory, LNS), Luxembourg
6. Administration des Services Techniques de l'Agriculture (Technical Services for Agriculture Administration), Luxembourg
7. Robert-Koch Institut (RKI), Wernigerode, Germany

A monophasic *Salmonella enterica* serovar 4,[5],12:i:- phage type DT193 emerged as the dominant serovar in Luxembourg in 2006, when it caused two major outbreaks involving 133 laboratory-confirmed human cases, 24 hospitalisations, and one death. The outbreak strain had an uncommon pulsed-field gel electrophoresis pattern STYMXB.0031 and antibiotic resistance profile ASSuT. A high proportion of cases were clustered in institutions for the elderly and in day-care centers. Strains identical to the outbreak strain were recovered from two control meals, a nappy changing table, retail sausages and caecal porcine samples at an abattoir. Locally produced pork meat is strongly suspected to have been the vehicle for the outbreaks, although the precise mechanisms remain unclear.

Introduction

Salmonella enterica is one of the most common causes of foodborne gastroenteritis. Reflecting the trend in Europe as a whole, most human cases in Luxembourg have recently been due to serovars *S.* Enteritidis (typically associated with eggs or chicken) or *S.* Typhimurium (typically associated with pork) [1]. Between 2000 and 2004, an annual average of 360 laboratory-confirmed *Salmonella* isolates were referred to the National Health Laboratory in Luxembourg. Of those, 66% were *S.* Enteritidis and 20% were *S.* Typhimurium.

In recent years, the emergence of a *Salmonella enterica* monophasic serovar 4,[5],12:i:- has been described that was responsible for human cases in New York [2], Spain [3], Brazil [4], Thailand [5] and Taiwan [6]. The strains are called monophasic because they lack the second-phase flagellar antigen, represented by the '-' after the second colon in the antigenic formula 4,[5],12:i:-. Genotypic, biochemical and phenotypic characterisations indicate that such strains usually represent monophasic variants of the serovar *S.* Typhimurium [7]. Between 2000 and 2005, human cases with this monophasic serovar 4,[5],12:i:- were rare in Luxembourg, with on average two to three cases reported annually. However, *Salmonella* serovar 4,[5],12:i:- was responsible for the two large outbreaks in 2006 that are described in this report and is now the dominant human serovar in Luxembourg.

Methods

The microbiology unit of the National Health Laboratory in Luxembourg is the reference laboratory for human salmonellosis and member of the European Enter-net surveillance network [8]. Human *Salmonella* isolates from all private and hospital laboratories as well as veterinary isolates from food safety, animal feed control and animal pathology laboratories in Luxembourg are characterised by serotyping, antibiotic resistance typing (disk diffusion method) and, since 2003, also by pulsed-field gel electrophoresis (PFGE) using the Pulsenet protocol [9]. In 2005, the cooperative research project EPIFOOD was initiated between all public institutions involved in food safety in Luxembourg. It systematically conducts enhanced sampling of different levels of the food chain and compares bacterial pathogens in the food chain with human isolates using molecular typing methods. In particular, routine sampling of bovine and porcine caecal contents was started in all three abattoirs in Luxembourg with the aim of isolating *Salmonella*. On those farms where the routine programme detected *Salmonella*, additional samples were taken.

During the investigation of the 2006 outbreaks, the patients were contacted and sent a detailed questionnaire on medical symptoms and food consumption prior to illness. In supermarkets and catering facilities of institutions in which patients were staying, samples were taken from food items that were considered at risk.

Results

An unexpected increase in gastrointestinal disease was noted in the *Salmonella* reference laboratory during a three-week period

Figure 1

Weekly number of human monophasic *Salmonella* cases in Luxembourg in 2006, based on date of stool sample collection

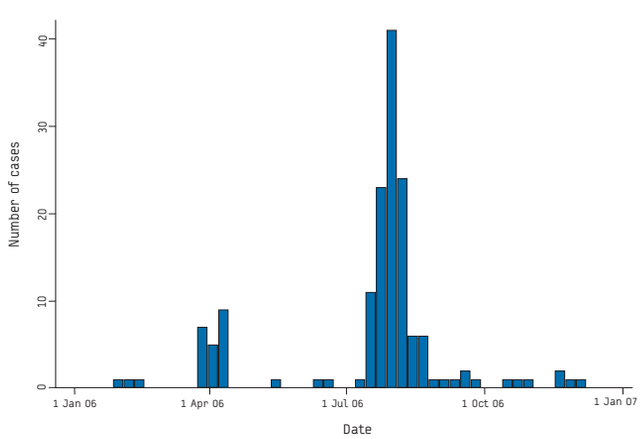
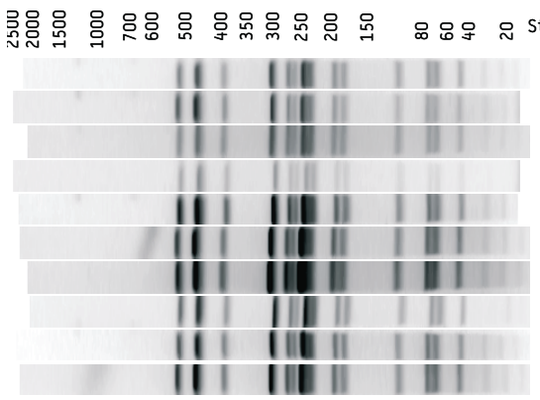


Figure 2

Pulsed-field gel electrophoresis profiles of human, food and veterinary strains implicated in the outbreaks in Luxembourg, 2006



Strain ID	Date	Strain origin
C060533	April 06	Human feces
C061153	July 06	Human feces
C061233	July 06	Cooked ham, institution for elderly
C061272	July 06	Control meal with ham, day care centre
C061273	July 06	Control meal, day care centre
C061314	August 05	Nappy changing table, day care center
E060804	August 06	Mixed barbecue meat, butcher shop
E050287	December 05	Porcine feces, abattoir
E060510	June 06	Porcine feces, abattoir
C061323	August 06	Porcine feces, farm

in spring 2006. Initially, *S. enterica* monophasic serovar 4,[5],12: i:- was confirmed in 21 human cases by the National *Salmonella* Reference Laboratory (Figure 1). Almost all strains isolated from patients had the pulsed-field gel electrophoresis (PFGE) profile STYMXB.0031 (Figure 2) and antibiotic resistance type (R-type) ASSuT, i.e. were resistant to ampicillin (A), streptomycin (S), sulfonamides (Su) and tetracycline (T) [10-12]. The PFGE and antibiotic resistance profiles of this outbreak strain were identical to strains isolated during a monitoring programme in late December 2005 from caecal contents of swine slaughtered at one of three abattoirs in Luxembourg (Abattoir A).

The outbreak investigation did not reveal any common sources of exposure or other risk factors. No unexpected increase was reported in other countries through the European Enter-net surveillance network, although a few concurrent human cases of this monophasic serovar with the same antibiotic resistance pattern were reported in Germany, Hungary (N Nogrady, personal communication), Scotland (D Brown, personal communication) and Switzerland (H Hächler, personal communication). Strains with the same PFGE profile and R-type were also found in pork food samples of German origin in Germany and Denmark (M Torpdahl, personal communication). The initial spring outbreak in Luxembourg eventually stopped in mid-April (Figure 1). No additional public health measures were taken. No common source or food vehicles were identified, although the local and international circumstantial evidence suggest that the cause was probably a pork product.

A much larger outbreak of *S. enterica* started in mid-July, involving 112 cases over a period of six weeks (Figure 1). Again, almost all strains had phage type DT 193, PFGE profile STYMXB.0131 [10-12] and the antibiotic resistance profile ASSuT. The outbreak investigation revealed that approximately half of the cases were clustered in institutions for the elderly or handicapped, and in a day-care centre for young children. 24 patients (21%) were hospitalised and one person aged 64 years died of bacteraemia. The hospitalisation rate of 21% is similar to those reported for all *Salmonella* serovars in Denmark (mean 18%) [13], and for multidrug-resistant *Salmonella* outbreaks in the United States (median: 26%) [14]. Following the identification of the outbreak, 145 food samples were obtained either from the kitchens of institutions that were linked to patients (one hotel, three institutions for the elderly, one restaurant and one day-care centre for children), or directly from retail outlets (five supermarkets and one wholesale store linked to the institutions mentioned above). Strains identical to those isolated from the patients could be recovered from two control meals: the first at an institution for the elderly, the second at a day-care centre in which the same strains were also recovered from a nappy changing table (Figure 2). The day-care centre was closed temporarily for professional disinfection, and hygiene procedures were reinforced through staff education programmes. Most *Salmonella*-positive food samples could be linked to meat from Abattoir A .

An identical *S. enterica* strain had again been recovered, three weeks prior to the July outbreak, from porcine caecal contents at Abattoir A as part of the monitoring programme (Figure 2). During the veterinary inspection, Abattoir A reported problems with hygiene procedures during the summer due to a combination of unusually hot weather and temporary staff during the holiday period.

In addition, on two occasions in August the outbreak strain was recovered at a farm from porcine faeces that had been found positive at the abattoir. No *Salmonella* could be isolated from animal feed used on this farm. Following the main outbreak wave in July/August, a further 22 sporadic human cases were reported in the nine month period between 1 September 2006 to 31 May 2007. This suggests that the outbreak is still ongoing due to continued presence of the *Salmonella* serovar 4,[5],12:i:- in the food chain, albeit at lower levels than during the summer of 2006.

Discussion

To our knowledge, this is the first report of a human outbreak of multidrug-resistant *Salmonella* monophasic serovar 4,[5],12: i:- phage type DT193 with resistance pattern ASSuT. Phage type DT193 with the antibiotic resistance pattern ASSuT has previously been reported only in swine in Spain and the United States [15]. It represents the largest *Salmonella* outbreak recorded in Luxembourg in the last 20 years. As a result, the monophasic serovar 4,[5],12: i:- has become the dominant serovar in 2006, surpassing both *S.* Enteritidis and *S.* Typhimurium in frequency.

The reasons behind this large outbreak in summer were probably multi-factorial and included a high prevalence of the strain on pig farms prior to the outbreaks and poor compliance with hygiene procedures at an abattoir during the holiday period and by catering staff of the institutions involved in the human outbreaks. However, the precise details of what went wrong in the abattoir or further

down along the food chain, and how it could be prevented in the future, remain unclear. Equally unclear are the reasons behind the prevalence of this *Salmonella* strain on pig farms in Luxembourg. July 2006 was an exceptionally warm month in Luxembourg, and hot weather has been linked to an elevated incidence of *Salmonella* infections before, even in the absence of particular outbreak situations [16].

Our outbreak investigation was clearly helped by genotyping methods. The outbreak strain had an uncommon antibiotic resistance and PFGE profile. Moreover, we were able to detect the outbreak strain at an abattoir several months prior to the major outbreak, which facilitated the identification of a likely vehicle of the outbreak. One practical implication for laboratories in the human, food safety and veterinary field is that testing the second phase of the flagellar antigen is essential in order to identify this serovar correctly and to distinguish it from *S.* Typhimurium.

The emergence of this monophasic serovar also has implications with regards to public health reporting, nomenclature and food safety regulations. Genetically, phenotypically and in terms of pathogenicity, the monophasic serovar should be considered a variant of *S.* Typhimurium [3]. Regarding it as distinct from serovar *S.* Typhimurium could imply that it is a rare and unusual serovar, and its public health importance could easily be underrated.

We believe that routine comparison of food chain and human *Salmonella* isolates using molecular typing tools is a powerful tool for monitoring food safety and protecting public health. However, close cooperation between all veterinary, food safety and human public health sectors is key to quick detection and successful control of both well-known and newly emerging foodborne pathogens.

Acknowledgements

We would like to thank Enter-net coordinators and Enter-net members for their valuable assistance during the outbreak investigations. This study was supported through the EPIFOOD project by the National Research Fund (FNR) and the Salmonella PFGE typing project by the Public Research Centre for Health (CRP-Santé). We would also like to thank Arthur Besch, Fabienne Clabots, Fabrice Dulac, Jos Even, Patrick Hau, Françoise Mori, Marion Rommes, Danielle Ruckert, Jos Schon and Jessica Tapp for their contributions.

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Citation style for this article: Mossong J, Marques P, Ragimbeau C, Huberty-Krau P, Losch S, Meyer G, and al. Outbreaks of monophasic Salmonella enterica serovar 4,[5],12:i:- in Luxembourg, 2006. Euro Surveill 2007;12(6)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n06/1206-226.asp

Cross-border investigation of a *Shigella sonnei* outbreak in a group of Norwegian tourists after a trip to Russia

B Schimmer (basc@fhi.no)[1,2], H Meldal[1], NG Perederij[3], L Vold[1], MA Petukhova[3], D Grahek-Ogden[1], K Nygård[1]

1. Folkehelseinstituttet (Norwegian Institute of Public Health, FHI), Oslo, Norway
2. European Programme for Intervention Epidemiology Training (EPIET)
3. Department of epidemiological surveillance, Regional Directorate of the Federal Service for Surveillance on Consumer Rights Protection and Human Well-being, Murmansk county, Russia

In early September 2006, the Norwegian Institute of Public Health was alerted to an outbreak of *Shigella sonnei* infections (shigellosis) among 23 Norwegian passengers who had taken a bus tour from Kirkenes, Norway to Murmansk, Russia. The trip lasted from 27 to 31 August, and the group stayed in various hotels and visited several restaurants in both Kirkenes and Murmansk during this period. Stool samples from three ill passengers yielded *S. sonnei*; an additional 10 passengers had gastrointestinal symptoms with diarrhoea or loose stools with abdominal pain. An investigation was initiated in collaboration with the department of epidemiological surveillance in Murmansk. We sent a questionnaire to the work e-mail addresses of all passengers asking about symptoms and exposures. Two restaurants and a hotel visited by the Norwegian tourists in Murmansk were inspected and sampled. Of all the food and beverage items mentioned in the questionnaire, only cured meat consumed in restaurant A in Murmansk on 28 August was associated with the risk of developing illness. Inspections of the restaurants in Murmansk identified some hygienic shortcomings and inadequate routines. However, *S. sonnei* could not be isolated from food samples or the personnel. Improved routines were implemented.

Introduction

Shigellosis has been notifiable in Norway since 1977 and is primarily an imported disease, mostly from countries in the Middle East and South-East Asia. Approximately 150 cases are notified annually, with *Shigella sonnei* being the predominant serogroup. Shigellosis can be transmitted via contaminated food or water, and outbreaks occur predominantly in families, in child day-care institutions or in connection with imported food items, especially raw vegetables [1]. Outbreaks of shigellosis are rare in Norway. In 1994, imported iceberg lettuce from Spain was the source of an international outbreak of *S. sonnei* [2], and a domestic *S. sonnei* outbreak occurred in a kebab restaurant in Oslo in 2001 [3]. There have been three outbreaks involving Norwegian citizens abroad: one among tourists visiting Tunisia in 2003 and two large *S. sonnei* outbreaks among Norwegian soldiers stationed in Afghanistan in 2004 [4] and in 2006.

On 5 September 2006, the Norwegian Institute of Public Health (NIPH) was notified by a municipal medical officer of an outbreak of gastroenteritis among a group of 22 employees of company A. The group had met on 27 August and travelled by bus from the city of Kirkenes (6,000 inhabitants) in north Norway to Murmansk (320,900 inhabitants) in north-west Russia, a distance of 250 kilometres. The group left Kirkenes on the morning of 28 August, stayed for two days in Murmansk, and returned to Kirkenes on the evening of 30 August. Company A reported that half of the participants developed diarrhoea after their return. Stool samples taken from three hospitalised participants yielded *S. sonnei*. NIPH started an investigation in collaboration with the local public health authorities in Kirkenes and Murmansk with the aim of describing the outbreak, identifying the source and implementing control measures.

Methods

We carried out a retrospective cohort study. A case was defined as a person who: *(1) participated in the bus tour organised by company A from Kirkenes to Murmansk and back from 28-30 August; and (2) had diarrhoea and/or abdominal cramps (i.e. loose stools or bowel movements at least once during any 24-hour period) during the trip or within 72 hours after returning to Norway.* The investigation focused on common food exposures after the participants arrived in Kirkenes on 27 August. We collected information on the travel route, restaurants and hotels visited by the group during 27-30 August. A questionnaire was sent by e-mail to all bus passengers (22 employees of company A) and the bus driver. The questionnaire focused on demographic information and symptoms, and included a detailed list of food and drinks that were served during each group meal (breakfast, lunch, dinner) at a hotel in Kirkenes (hotel X) and in Murmansk (hotel Y), as well as two restaurants in Murmansk (restaurants A and B) and Kirkenes (restaurants C and D). The data were entered and analysed using Epi Info version 3.3.2 and Episheet (Nov 2005 version). We calculated food-specific attack rates and relative risks (RR) with 95% confidence intervals, and Fisher exact p-values for every dining place visited and every food and drink consumed. Stool samples were collected from the hospitalised cases at the University Hospital of North Norway and were tested for enteric pathogens. All *S. sonnei* isolates were sent to the National Laboratory for Enteric Pathogens at the NIPH for serogroup verification. Multiple-locus variable-number tandem repeat analysis (MLVA) was used to genotype the isolates. On 15 September, the NIPH contacted the department of epidemiological surveillance in Murmansk and asked about information on possible locally ongoing outbreaks. Based on epidemiological findings, the Centre for Hygiene and Epidemiology in Murmansk conducted an environmental inspection and took food and drinking water samples from the two restaurants and the hotel visited by the tourist group. Stool and serum samples were taken from foodhandlers, including kitchen staff, barkeepers, and waiters, and tested for enteric pathogens. The local Food Safety Authority in Kirkenes was informed about the outbreak, and they checked the records from recent inspections at hotel X.

Results

Epidemiological investigation

During the outbreak period, there were no cases of *S. sonnei* reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) among people living in or visiting the region of Kirkenes. Moreover, the municipal health physician in the Kirkenes region and the laboratory of medical microbiology at the University Hospital of North Norway had no reports of domestic cases of shigellosis in this region.

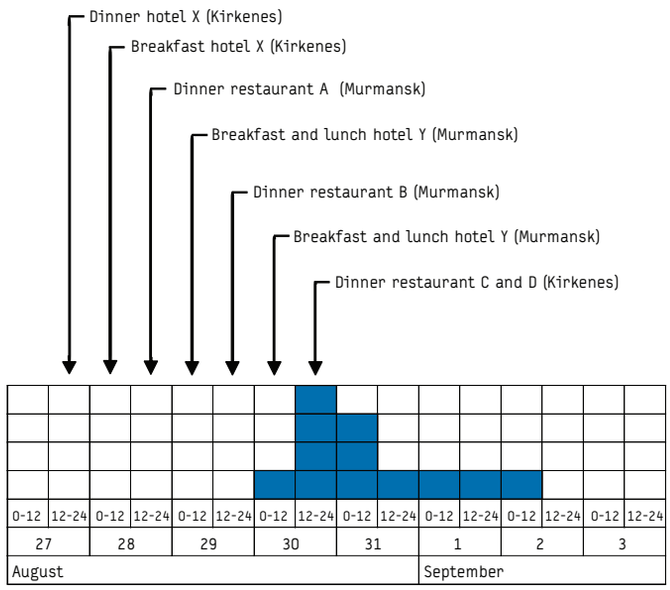
Twenty of the 23 people contacted by e-mail returned the electronic questionnaire (87%). Among these 20 respondents, ages varied between 35-64 years, and 16 (80%) were men. Thirteen cases (11 males and two females) were identified (attack rate 65%). The median age of the cases was 50 years. The first case fell ill on the morning of 30 August, and most others fell ill during the afternoon or evening of 30 August and in the early morning of 31 August. Three people became ill in the first two days of September (Figure). Besides diarrhoea, abdominal cramps were one of the most common symptoms, reported by 62% of the cases. Low grade fever was reported by 31% of the cases. None had bloody diarrhoea. Three cases (7%) were hospitalised. Illness duration varied between 1 and >=7 days, with a median of 6 days. Five cases were still ill at the time of the interview. No secondary cases were reported.

The percentage of cases exposed to the separate meals (breakfast, lunch, dinner) consumed in different dining locations varied between 15% and 100%. All 13 cases participated in the lunch in the bus, the dinner in restaurant A on 28 August, and the dinner in restaurant B on 29 August. Relative risk analysis for the separate meals showed no association with illness when analysed individually for each dining location. No relative risks could be calculated for the lunch in the bus and the dinner in restaurant B as everyone in the cohort was exposed.

Further analysis by food items showed that cured meat consumed in restaurant A on 28 August was significantly associated with illness (relative risk ∞, p=0.02). It was not possible to calculate a relative risk for kebab, as all participants were exposed (Table). The cured meat was served cold as a starter and was consumed by all 13 cases and three of six non-cases. Based on information on time of illness onset and the attack rates by food item, we suspected cured meat consumed at restaurant A to be the most likely food vehicle for this outbreak. This information was sent to the epidemiological department in Murmansk on 21 September.

FIGURE

Cases of gastroenteritis among travellers from company A by time of illness onset (n=12)† in Kirkenes and Murmansk, 27 August to 3 September 2006



†One of the 13 cases mentioned in the text is not included in the figure because the date of illness onset is unknown

Laboratory investigation

Four cases submitted stool samples to the laboratory of medical microbiology at the University Hospital of North Norway. Three out of four samples showed presence of *S. sonnei* and all tested negative for bacterial and viral pathogens such as *Salmonella*, *Yersinia*, *Campylobacter*, *Yersinia*, rotavirus and adenovirus. The sample that was negative for *S. sonnei* was taken from a case under antimicrobial treatment. All three isolates had an identical MLVA-profile.

Environmental investigation

The Food Safety Authority (FSA) in the Kirkenes region indicated that there were no reports of gastrointestinal illness in this period linked to hotel X, where the Norwegian tourists had stayed. Moreover, this hotel had been inspected shortly before by the regional FSA and had received good reports.

TABLE

Proportion of cases exposed, number of cases by exposure status, and relative risks (RR) for food items consumed during dinner at restaurant A, Murmansk, 28 August, 2006 (n=19) ‡

Food item	Cases exposed	Exposed		Not exposed		RR	95% CI	p-value
		Ill	Total	Ill	Total			
Cured meat	100 %	13	16	0	3	∞*	-	0.02
Vegetable noodle soup	92 %	12	18	1	1	0.67	0.48-0.92	1.00
Kebab	100 %	13	19	0	0	-	-	-
Dessert	54 %	7	12	6	7	0.68	0.39-1.20	0.24
Table water in jar or glass	54 %	7	8	6	11	1.60	0.88-2.92	0.15
Other drinks	100 %	13	18	0	1	∞*	-	0.32

‡ *19 of the 20 people who responded to the questionnaire had taken part in the dinner at restaurant A on 28 August 2006*

The department of epidemiological surveillance in Murmansk reviewed recent data on infections with *S. sonnei* in their region and asked recent cases with laboratory-confirmed shigellosis if they had frequented the same restaurants and hotels as the Norwegian group. No cases had been registered in August. However, there were 13 *S. sonnei* cases in Murmansk in September and one in October. Of the 13 cases diagnosed in September, one had visited restaurant B and one hotel Y, while the other cases had eaten in other places than those visited by the Norwegian group. The environmental inspections showed bad hygienic conditions and inadequate routines in restaurants A and B, and hotel Y. No specific information was collected on how the suspected food items were processed or prepared. Contamination with faecal indicator bacteria was shown in six out of 26 food samples, of which four were taken in hotel Y, one in restaurant A and one in restaurant B. Environmental samples and samples taken from tap water were within the normal range. It was not possible to sample the suspected cured meat served on 28 August in restaurant A because there were no leftovers. Stool and serum samples were obtained from 78 foodhandlers (nine from restaurant A, 22 from restaurant B, and 47 from hotel Y) and all tested negative for *S. sonnei*. One foodhandler at hotel Y had an unspecific serologic reaction for *Shigella flexneri* infection. At the time of inspection, there were no reports of gastrointestinal illness in foodhandlers working in the inspected premises and all indicated they had not experienced fever or digestive problems during the previous month.

Control measures

Administrative measures were taken and five penalty fines and regulatory orders were imposed. This encouraged the restaurants to implement appropriate control or prevention measures and correct the hygienic breaches identified. Two restaurants (A and B) and hotel Y were revisited in the week following the first inspection, and this second visit showed improved hygiene practices. According to the department of epidemiological surveillance, the outbreak was probably caused by poor hygienic conditions in one of the restaurants or hotels visited by the Norwegian group. No specific food vehicle or infected foodhandler could be identified microbiologically.

Discussion

This report describes an outbreak of shigellosis among a group of Norwegians after a bus tour to Russia. Investigation of this outbreak in collaboration with colleagues in Russia led to a rapid implementation of control measures. The environmental inspection at the different sites showed inadequate hygiene practices, and measures were immediately taken to improve the hygiene. The results of our investigation suggest that cured meat served in a restaurant in Murmansk, Russia on 28 August was the probable source of the outbreak. This food item could explain all the cases, and the time of consumption falls within the most likely time of exposure based on back-calculation of the median incubation time of shigellosis (48 hours, range 12-96 hours) [1,5]. Cured meat served as a cold cut platter is a plausible food vehicle of a shigellosis outbreak. Unlike for *Salmonella*, humans are the only host for *Shigella*, with food that is served raw or handled after cooking being the most likely vehicle of transmission. However, we cannot exclude other potential sources of infection during the stay in Murmansk as we only studied common meals consumed by the group, and for some food items the whole group was exposed, which is typical for group travel. Due to small numbers in the cohort, and since all were exposed to several of the meals and food items, relative risk analysis was not fully conclusive. A dose response analysis was not performed. Another limitation in this outbreak investigation was a potential misclassification of symptomatic cases that were not laboratory-confirmed.

Food eaten after the return to Kirkenes was less likely to be the source of the outbreak, since one case had already fallen ill on the morning of 30 August before arrival in Kirkenes. While the cases could have become infected in Kirkenes at the beginning of the journey, this was considered unlikely, as no other cases of shigellosis were reported in the region at the time, and no gastrointestinal illnesses were linked to hotel X.

Recent surveillance data from Murmansk showed that the shigellosis outbreak in this group was not part of a larger outbreak in Murmansk. Another outbreak of shigellosis occurred in Murmansk in 1997 and involved *S. flexneri* 3a. That outbreak was limited to Murmansk city, the neighbouring municipality Kola and possibly the municipality of Sevoromorsk. The sources of the outbreak were sour milk products (cream and cottage cheese) from a dairy farm near Murmansk [6]. In 2000, Finland reported that a tourist group contracted *S. sonnei* gastroenteritis while staying overnight in a hotel in south-eastern Finland near the Russian border. The epidemiological investigation suggested that the source of the infection was in the hotel, but failed to reveal the origin [7].

This outbreak investigation illustrates the importance of good international networks and open communication in cross-border outbreak investigations. Timely exchange of information on possible sources of outbreaks and close collaboration between health departments and food safety authorities is important for an efficient alert and response when a foodborne outbreak is suspected in tourists. With increasing international travel, outbreaks and imported infections are more likely to occur in travellers, highlighting the need for early detection and cross-border collaboration in outbreak investigations and surveillance. Other authors have also highlighted the importance of prompt detection and efficient management of gastroenteritis outbreaks, and the difficulty of detecting these outbreaks at an early stage [8].

Norway, together with the other Nordic countries, has a long tradition of collaboration in communicable disease epidemiology and control with the Baltic countries and north-western part of the Russian Federation through the EpiNorth network. Since 1999, EpiNorth has collected epidemiological data of different notifiable diseases from the countries in the Barents region, including several regions in north-west Russia [9]. The incidence of shigellosis in the Murmansk region varied between 30.5 and 93.5 per 100,000 population in the last five years, but was lowest in 2005 with 258 registered cases. The incidence rate is much higher in the Murmansk region than in Norway, which had an incidence rate of 3.7 per 100,000 population the same year, of which 90% were acquired during travel abroad. Risk estimates for contracting travel-associated shigellosis from different regions in the world have been carried out for Swedish travellers. The risk of shigellosis being notified in returning travellers was estimated to be 16 per 100,000 travellers to Russia and former USSR countries [10]. The existing links through EpiNorth with epidemiological units in different counties in north-west Russia, among them the Murmansk region, clearly facilitated the close collaboration in the investigation of this outbreak.

Conclusion

A joint approach, sufficient resources and close collaboration among regional and national health-care departments and food

safety agencies is needed if gastroenteritis outbreaks in tourist groups are to be investigated This approach is important when investigating cross-national outbreaks within Europe, but it is equally important to establish close links between European countries and the Russian Federation. The Russian Federation is the largest neighbour of the European Union (EU) and has been brought even closer to the EU by the 2004 enlargement. It is especially important for countries that directly neighbour the Russian Federation, such as Norway, Finland, Estonia, Latvia, Lithuania and Poland, to establish close links in order to collaborate in the field of infectious disease surveillance and the thorough investigation of cross-border outbreaks.

Acknowledgements

The authors thank the local public health and food authorities, the laboratory of medical microbiology at the University of North-Norway, the National Laboratory for Enteric Pathogens at the NIPH and the EpiNorth secretariat for their assistance in the outbreak investigation.

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Citation style for this article: Schimmer B, Meldal H, Perederij N, Vold L, Petukhova M, Grahek-Ogden D, and al. Cross-border investigation of a Shigella sonnei outbreak in a group of Norwegian tourists after a trip to Russia. Euro Surveill 2007;12(4)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n04/1204-225.asp

Update of *Clostridium difficile*-associated disease due to PCR ribotype 027 in Europe

EJ Kuijper (e.j.kuijper@lumc.nl)[1], B Coignard[2], J Brazier[3], C Suetens[4], D Drudy[5], C Wiuff[6], H Pituch[7], P Reichert[8], F Schneider[9], AF Widmer[10], KE Olsen[11], F Allerberger[12], DW Notermans[13], F Barbut[14], M Delmée[15], M Wilcox[16], A Pearson[17], BC Patel[17], DJ Brown[18], R Frei[19], T Åkerlund[20], IR Poxton[21], P Tüll[22]

1. National Reference Laboratory for Clostridium difficile, Leiden University Medical Centre, Leiden, The Netherlands
2. Department of infectious diseases, Institut de Veille Sanitaire (French National Institute of Health, InVS), Saint-Maurice, France
3. Anaerobe Reference Laboratory, National Public Health Service for Wales, University Hospital of Wales, Cardiff, United Kingdom
4. Epidemiology Unit, Scientific Institute of Public Health (IPH), Brussels, Belgium
5. Centre for Food Safety, Food Science and Veterinary Medicine, University College Dublin, Dublin, Ireland
6. Health Protection Scotland, Section for Healthcare-Associated Infection and Infection Control, Glasgow, United Kingdom
7. Department of Medical Microbiology, University of Warsaw, Poland
8. National Health Laboratory (Laboratoire National de Santé, LNS), Luxembourg
9. Microbiology division, Rue du Laboratoire, Luxembourg
10. Division of Infectious diseases and Hospital Epidemiology, University Hospital, Basel, Switzerland
11. National Reference Laboratory for Enteropathogens, Statens Serum Institute (Danish National Institute of Public Health, SSI), Copenhagen, Denmark
12. Österreichische Agentur für Gesundheit und Ernährungssicherheit (Austrian Agency for Health and Food Safety, AGES), Vienna, Austria
13. Centrum Infectieziektebestrijding (Centre for Infectious Disease Control, CIb), Rijksinstituut voor Volksgezondheid en Milieu (National Intitute for Public Health and the Environment, RIVM), Bilthoven, The Netherlands
14. National Reference Center for Clostridium difficile, Saint-Antoine Hospital, Paris, France
15. Microbiology Department, University hospital Saint-Luc, Brussels, Belgium
16. Clostridium difficile Ribotyping Network for England (CDRNE), Microbiology, Leeds General Infirmary, Leeds, United Kingdom
17. Health Protection Agency (HPA), London, United Kingdom
18. National Health Service (NHS), Glasgow, United Kingdom
19. Microbiology Laboratory, University Hospital, Basel, Switzerland
20. Smittskyddsinstitutet (Swedish Institute for Infectious Disease Control, SMI), Solna, Sweden
21. Medical Microbiology, Centre for Infectious Diseases, University of Edinburgh College of Medicine and Veterinary Medicine, Edinburgh, Scotland
22 European Centre for Disease Prevention and Control (ECDC), Solna, Sweden

Recent outbreaks of *Clostridium difficile*-associated diarrhoea (CDAD) with increased severity, high relapse rate and significant mortality have been related to the emergence of a new, hypervirulent C. difficile strain in North America, Japan and Europe. Definitions have been proposed by the European Centre of Disease Prevention and Control (ECDC) to identify severe cases of CDAD and to differentiate community-acquired cases from nosocomial CDAD (http://www.ecdc.europa.eu/documents/pdf/Cl_dif_v2.pdf). CDAD is mainly known as a healthcare-associated disease, but it is also increasingly recognised as a community-associated disease. The emerging strain is referred to as North American pulsed-field type 1 (NAP1) and PCR ribotype 027. Since 2005, individual countries have developed surveillance studies to monitor the spread of this strain. C. difficile type 027 has caused outbreaks in England and Wales, Ireland, the Netherlands, Belgium, Luxembourg, and France, and has also been detected in Austria, Scotland, Switzerland, Poland and Denmark. Preliminary data indicated that type 027 was already present in historical isolates collected in Sweden between 1997 and 2001.

Introduction

A highly virulent variant of *Clostridium difficile* is emerging throughout Europe. This strain is characterised as toxinotype III, North American pulsed field gel electrophoresis type 1 (NAP1), restriction endonuclease analysis group BI and PCR ribotype 027 [1,2,3]. The type 027 strain carries the binary toxin gene, has an 18bp deletion in the regulatory gene *tcdC*, and a 1bp deletion at position 117 of *tcdC*, resulting in a frameshift mutation that potentially allows for larger amounts of toxins to be produced. It is assumed that the increased virulence of this strain is associated with higher amounts of toxin production [4]. Clinical response rates are reduced following treatment with metronidazole or vancomycin [5,6]. This 027 type strain was first isolated in 1988 in France and is considered a 'historical isolate', since it was susceptible to fluoroquinonoles and erythromycin [7]. It only accounted for sporadic cases of *C. difficile*-associated disease (CDAD) until 2002. It has been suggested that the recent acquisition of resistance to the newer fluoroquinolones by the 027 strain was the major reason for its wide dissemination [1,2] although this phenotype is not uncommon in other *C. difficile* strains [8]. Alternatively, increased virulence resulting in pronounced diarrhoeal symptoms may have promoted spread and cross-infection within healthcare institutions. Since 2002, it had caused major epidemics of CDAD in hospitals in Canada and also in the United States [1,2,3].

Background

CDAD occurs most often in people whose normal gut flora has been disturbed, for example during antibiotic treatment. The

clinical manifestation of CDAD can range from diarrhoea to severe pseudomembranous colitis, with a mortality of up to 30% [1]. CDAD is mainly known as a healthcare-associated disease, but it is increasingly recognised as a community-associated disease. At the 17th European Congress for Microbiology and Infectious Disease (31 March-3 April 2007) in Munich, results of a German pilot study were presented. It revealed a high CDAD incidence of 9.3% among 703 patients with diarrhoea visiting general practitioners in the period from August to December 2006 in Germany. *Salmonella enteritica* was cultured in 4.8% and *Campylobacter* in 3% of those patients [9].

The diagnostic methods routinely employed in different European laboratories today are not standardised and vary significantly [1,10]. Most laboratories prefer to detect *C. difficile* specific toxins in faeces. Faeces toxin detection can be performed either by cell cytotoxicity assay or immunological detection. The former is the gold standard, but requires up to two days. Various enzyme-immunoassays are available for immunological detection of *C. difficile* toxins, but their sensitivity and specificity varies enormously. Therefore, a study funded by the European Union (EU) has been launched in order to improve diagnostics of CDAD (LSHE-CT-2006-037870: European approach to combat outbreaks of CDAD by development of new diagnostic tests).

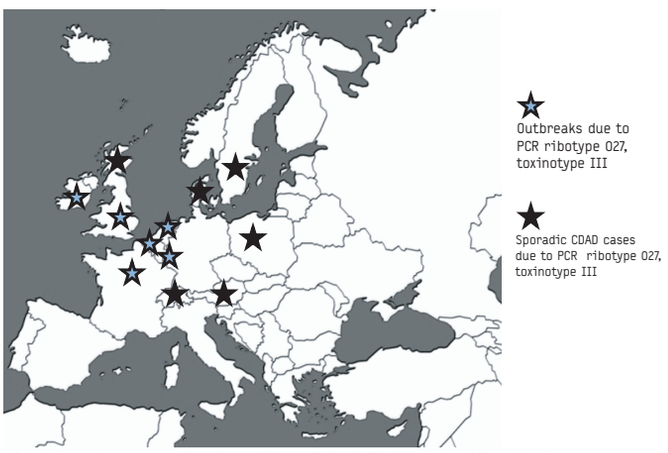
Surveillance efforts

The European Study Group for *Clostridium difficile* (ESGCD) performed a two-month surveillance study in 2005 on the prevalence of CDAD due to *C. difficile* 027 in 12 EU member states [11]. Based on these data and the recently published background document supported by the ECDC, individual countries have developed surveillance studies to the spread of type 027 in their country [1]. *C. difficile* type 027 causes outbreaks in the United Kingdom (UK) (since 2003 [12]), the Netherlands (since 2003 [13,14]), Belgium (since 2003 [15,16]), France (since 2006 [17,18]), and has also been detected in Austria (2006 [19]), Japan (2005 [20]) and Ireland [21]. In addition, it has been found in Switzerland (AF Widmer, R Frei, M Rupnik, personal communication), Luxembourg (P Reichert, E Kuijper, personal communication), Poland (H Pituch, E Kuijper, personal communication), and Denmark [22] (Figure). Preliminary data presented at the 2nd International *Clostridium difficile* symposium in Maribor, Slovenia (6-9 June, 2007) indicated that type 027 was present in three of more than 1,500 historical isolates collected in Sweden between 1997 and 2001. These strains were sensitive to fluoroquinolones and resemble the pre-outbreak type 027 strains in the United States [2] and France [7].

In England, a mandatory surveillance programme of CDAD in people aged 65 years and over has been included in the healthcare-associated infection surveillance system for acute hospital trusts (*UK hospitals are managed by acute trusts; for a detailed definition see:* http://www.info.doh.gov.uk/nhsfactsheets.nsf/vwHelp/Acute%20trusts?OpenDocument) since January 2004. Some 55,681 cases were reported in 2006. This represents an 8% increase in CDAD cases from 2005 to 2006, after a 17% increase from 2004 to 2005. The mandatory surveillance is operated by the Health Protection Agency (HPA) on behalf of the Department of Health (DH). Epidemiological data are collected quarterly from each of the 169 acute National Health Service (NHS) trusts that treat adult patients and yearly reports are produced by the HPA [23]. CDAD incidence rates of individual trusts are publicly reported each year by the DH [24]. Through its network of regional laboratories

Figure

Distribution of *C. difficile* ribotype 027 in Europe* as of June 2007



* Not all countries have performed surveillance studies to *C. difficile* type 027 and this figure may underestimate the number of affected countries

in collaboration with the Anaerobe Reference Laboratory (ARL) in Cardiff, the HPA obtained further isolates of *C. difficile* from symptomatic patients in a structured but random sampling scheme. In an allocated week, local hospitals within each of the nine HPA regions were asked to submit a maximum of 10 *C. difficile* toxin-positive stools to their regional HPA laboratory to culture *C. difficile*. Isolates of putative *C. difficile* were then forwarded to the ARL for confirmation of identity, susceptibility testing against eight antimicrobial agents and typing by the PCR ribotyping method. The findings have recently been published in *Eurosurveillance* [25]. A laboratory surveillance network in England was established in 2007 to facilitate the early investigation of clusters of CDAD, particularly those associated with severe symptoms.

In October 2005, the National Institute for Public Health and the Environment (RIVM) in the Netherlands published specific CDAD ribotype 027 guidelines for infection control and treatment to be used by hospitals and nursing homes in response to the outbreaks in the Netherlands. Diagnostic facilities were increased and made accessible for hospital microbiologists. All laboratories were recommended to culture *C. difficile* from toxin positive faeces samples and to store the isolates. Microbiologists were requested to send strains to the national Reference laboratory from patients with a severe course of CDAD or when an increased incidence of CDAD was noticed. A National Reference Laboratory for *C. difficile* was established at the Department of Medical Microbiology at the Leiden University Medical Center. Strains were characterised by PCR ribotyping, toxinotyping, presence of toxin genes and antimicrobial susceptibility [26]. The results of the first year of surveillance are currently in press [27].

Recommendations for diagnosis, early warning and surveillance of CDAD in France were issued by the French Institute for Public Health (InVS) and the national reference laboratory for *C. difficile* (Hôpital Saint-Antoine, Paris) in May 2006. Hospitals and nursing homes were requested to notify severe cases or clusters of CDAD, which were systematically investigated by local health departments and regional infection control coordinating centres. Culture of faeces was promoted as the diagnostic method of choice for such cases, and a network of six regional laboratories was set up in order

to facilitate characterisation of *C. difficile* strains. The Ministry of Health disseminated recommendations for CDAD prevention and control to all hospitals and nursing homes in September 2006. A national, prospective surveillance of CDAD incidence among hospitals will be implemented in 2007 and will include a sampling scheme in order to better assess the geographical dissemination of *C. difficile* strains.

One case of *C. difficile* 027 was identified in Scotland in 2006 by the UK national reference laboratory in Cardiff. A research study in Western Scotland examined 102 additional strains obtained from nine hospitals from 2006 to 2007. None of these were ribotype 027. Mandatory surveillance in line with the English system has been initiated in Scotland in 2006. Data on the incidence of *C. difficile* 027 in people aged 65 years or older are being collected in healthcare institutions in Scotland and will be published in the public domain by the end of 2007.

In Belgium, the Scientific Institute of Public Health (IPH) and the national reference laboratory (Université catholique de Louvain) set up a laboratory-based surveillance of CDAD clusters in January 2006. Laboratories are requested to send in strains, when two or more CDAD cases occur in the same department within a period of one month. In parallel, a prospective surveillance of CDAD incidence was set up in Belgian acute care hospitals in collaboration with the Belgian Infection Control Society (BICS). Hospitals report clinical and risk factor data on all CDAD cases as well as denominator data on a web-based data entry form during a six month surveillance period. Hospitals are also requested to send strains of five consecutive CDAD patients to the reference laboratory for species confirmation, detection of the *tcdC* deletion and the binary toxin, toxinotyping, PCR ribotyping and determination of antimicrobial susceptibility. National guidelines for prevention and control of CDAD in hospitals and nursing homes were issued by the BICS in June 2006.

Table

***C. difficile* type 027 in 11 European countries (due to differences in surveillance the data cannot be directly compared).**

Country	Survey period	Total number of inhabitants / hospitals / hospital beds	Number of hospitals positive for 027 / number of hospitals investigated for 027	Number of nursing homes positive for 027	Number of 027 strains / Total number of strains tested	Mortality attributable to CDAD	Updates available at:
England and Wales	2005-2006	53.4 million inhab/ England: 172 acute trust hosp/135,794 beds; Wales: 95 /11,500	94/170 (55.3%)	n.a	971/n.a	n.a	http://www.hpa.org.uk/infections/topics_az/clostridium_difficile/default.htm
Scotland	2006-2007	5.1 million/ 261 (incl. 45 acute hosp)/ 29,000	1/9 (11%)	0	1/103 (1%)	n.a	http://www.hps.scot.nhs.uk/haiic/sshaip/clostridiumdifficile.aspx
Ireland	2006	4.2 million/61/10,000	7/7 (100%)	2	81/350 (23.1%)	n.a	http://www.ndsc.ie/hpsc/A-Z/Gastroenteric/CDifficile
France	Jan2006 – April 2007	64 million/ca. 2,800/ca. 460,000	40/164 (24.3%)	4	277/471 (58.8%)	4% (Northern France only)	http://www.invs.sante.fr/raisin
The Netherlands	2005-2006	16.4 million/129/53,000	20/50 (40%)	7	218/863 (25.2%)	6.3%	http://www.rivm.nl/cib/infectieziekten/Clostridium_difficile/Clostridium_difficile_draaiboek.jsp
Belgium	2005-2006	10 million/113/51,640	38/78 (48.7%)	n.a	190/814 (23%)	n.a	http://www.belgianinfectioncontrolsociety.be
Poland	2005	38 million/781/184,000	1/1 (100%)	n.a	1/175 (0.6%)	na	
Austria	2006	8.2 million/ 264/ 63,248	1/20 (5%)	n.a	1/102 (1%)	n.a	
Luxembourg	2006	0.45 million/10/2100	4/10 (40%)	n.a	18/75 (24%)	n.a	
Switzerland	2005-2006	7.3 million/337/28,080	3/11 (27%)	1	4/231 (1.7%)	0%	
Denmark	Nov 2006-March 2007	5.4 million/ 69/22.604	n.a	n.a	6 (pilot study)	Study in progress	

n.a: data not available.

The available results from the surveillance efforts of 11 European countries are summarised in the Table. As methodology, time period and geographical coverage of surveillance differ significantly from one country to another, these results are qualitative and cannot be used for purposes of comparison. A new surveillance study among all European member states, planned for 2007-2008, is currently being developed by ECDC in collaboration with ESGCD, a study group for *Clostridium difficile* set up by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). In addition, a specific surveillance programme (CDAD-KISS) has recently been launched in Germany.

Conclusion

C. difficile type 027 has been detected in an increasing number of European countries. This could either be due to the fact that more countries have started surveillance surveys or an indication that type 027 is spreading rapidly. As yet, type 027 has affected healthcare facilities in 11 EU member states and in Switzerland (Figure). Increased awareness is necessary in all member states and surveillance studies should be performed with uniform definitions, as proposed by ECDC [1]. A guidance document for infection control measures has recently been prepared by international experts together with ECDC [28]. It is unknown how many CDAD cases in nursing homes and the community are due to type 027. The situation in those settings warrants more attention in the future.

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Citation style for this article: Kuijper E, Coignard B, Brazier J, Suetens C, Drudy D, Wiuff C, and al. Update of Clostridium difficile-associated disease due to PCR ribotype 027 in Europe. Euro Surveill 2007;12(6)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n06/1206-221.asp

Haemorrhagic Fever with Renal Syndrome: an analysis of the outbreaks in Belgium, France, Germany, the Netherlands and Luxembourg in 2005

P Heyman[1], C Cochez[1], G Ducoffre[2], A Mailles (a.mailles@invs.sante.fr)[3], H Zeller[4], M Abu Sin[5], J Koch[5], G van Doornum[6], M Koopmans[7], J Mossong[8], F Schneider[8]

1. Research Laboratory for Vector-borne Diseases, National Reference Laboratory for Hantavirus Infections, Brussels, Belgium
2. Scientific Institute of Public Health, Brussels, Belgium
3. Institut National de Veille Sanitaire, Saint Maurice, Paris, France
4. Centre National de Référence des Fièvres Hémorragiques (National Reference Laboratory for Viral Haemorrhagic Fevers, CNRFH), Lyon, France
5. Department of Infectious Disease Epidemiology, Robert Koch-Institut, Berlin, Germany
6. Virology Division, Erasmus Medical Center, Rotterdam, the Netherlands
7. Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and Environment, RIVM), Bilthoven, the Netherlands
8. Laboratoire National de Santé, Luxembourg, Grand Duchy of Luxembourg

This article aims to describe the Haemorrhagic Fever with Renal Syndrome (HFRS) situation in 2005 in five neighbouring countries (Belgium, France, Germany, the Netherlands and Luxembourg) and define the most affected areas. The 2005 HFRS outbreaks in these countries were the most significant in the region since 1990, with a total of 1,114 confirmed cases. The main feature of the epidemic was the extension of the known endemic area in several of the affected countries, with the involvement of urban areas for the first time. A significant increase in the number of cases was noted for the first time in the province of Liège in Belgium and in the Jura department in France.

Introduction

Hantaviruses (family *Bunyaviridae*, genus *Hantavirus*) are rodent-borne, zoonotic, lipid-enveloped RNA viruses, and comprise the aetiological agents of HFRS. HFRS occurs in Europe and Asia, and infection with these viruses can cause a disease characterised by fever, headache, gastrointestinal symptoms and renal dysfunction, the more severe forms with haemorrhagic manifestations [15,20]. Nephropathia epidemica (NE), the mildest form of HFRS, caused by Puumala virus (PUUV), the most common hantavirus, is present in most countries in north-western Europe. Dobrava (DOBV), Tula (TULV), Seoul (SEOV) and Saaremaa viruses also circulate in the region; the first three have been described as causing human disease (DOBV in Germany, Austria and the Balkans region). NE due to PUUV infection has an abrupt onset with fever and myalgias, thrombopenia and sometimes myopia. An acute renal failure occasionally requiring dialysis can occur. The incubation period varies from a few days up to 41 days. The outcome is favourable in most patients and mortality is lower than 0.1%. DOBV causes severe HFRS with a reported mortality rate of up to 20% [20].

The epidemiology of hantaviruses is closely linked to the ecology of their principal hosts. The bank vole is a polyphagous animal that eats seeds, fruits of trees and bushes, and green plants. The multi-annual bank vole population dynamics are therefore directly influenced by the seed production of trees, especially oak, beech and acorn. Years with increased seed production (mast years), mediated by favourable climatic conditions (mild winter), give rise to increased rodent population densities in the following year. The bank vole (*Myodes glareolus*) acts as the main reservoir for PUUV, while the yellow-necked mouse (*Apodemus flavicollis*), the common vole (*Microtus arvalis*), the striped field mouse (*Apodemus agrarius*) and the brown rat (*Rattus norvegicus*) carry and transmit respectively DOBV, TULV, SAAV and SEOV. Transmission of the viruses to man occurs through inhalation of infected animal excreta, i.e. urine, faeces and saliva. Working with wood piles and cleaning long abandoned buildings seem to significantly increase the risk for hantavirus infection.

Outbreaks of hantavirus infections in humans occurred in western Europe in 1985, 1990, 1993, 1996, 1999, 2001 (Belgium only) and in 2003 [4,8,13]. Most cases occurred between March and November, with a peak from August to September. A preliminary report regarding Belgium, France and Germany was published in Eurosurveillance Weekly in June 2005 [11].

Methods

Case definitions in the five affected countries match, as do diagnostic tools (IFA and ELISA are the only validated systems available), so we have compared the data below, with the countries listed separately in alphabetical order.

Belgium:

In Belgium, the National Reference Laboratory for Hantavirus Infections and the Scientific Institute of Public Health (IPH) sentinel laboratory network report data to the IPH. The National Reference Laboratory for Hantavirus Infections applies IgG and IgM ELISA for PUUV and HTN routinely but can if necessary also test for SEOV and DOBV IgG and IgM as well as apply species-specific RT-PCR (traditional or real-time) for the four forenamed serotypes. An HFRS case is considered to be confirmed when the following conditions are fulfilled: detection of IgM antibodies and evidence of seroconversion in a follow-up sample, or detection of hantavirus nucleic acid in a sequenced RT-PCR from blood or urine sediment. Since 1980, more than 1,600 cases have been diagnosed in Belgium. The total number of cases from the 2005 outbreak was 372, which is the so far the most significant epidemic

since the 1996 epidemic. Statistically, an average epidemic year would account for more than 158 cases. The available information on human cases suggests that, in Belgium, a three-year epidemic cycle existed until 1999, after which there was a two-year cycle [6,7]. The reason for this pattern change is not known but could be influenced by changes in the climate.

France:

In France, the Centre National de Référence des Fièvres Hémorragiques (National Reference Laboratory for Viral Haemorrhagic Fevers, CNRFH) is responsible for the surveillance of hantavirus infections in humans [15]. Diagnoses are based on single sera if presence of IgM and IgG (IFA and ELISA) or on paired serum samples if detection of IgM without IgG on the first serum sample. Diagnosis is done in several laboratories (at least three in France) but it is mandatory to send all positive or borderline samples from local laboratories to the CNRFH for confirmation. Only confirmed specimens were included in the study. The total number of cases for the 2005 outbreak was 253 and, as for Belgium, this was the most important outbreak since 1996.

Germany:

In Germany, hantavirus infection became a notifiable disease in 2001. Reports of laboratory-confirmed symptomatic hantavirus infections are transferred to the Robert Koch Institute based on a case definition [17]. The laboratory diagnosis of an HFRS case is considered confirmed when one of the following conditions is fulfilled: detection of IgM- or IgA-antibodies confirmed by IgG-antibodies or marked rise of IgG-antibodies in a paired sample or detection of hantavirus nucleic acid in a sequenced RT-PCR from blood. The average incidence for hantavirus infections over the time period 2001-2004 was 0.25 per 100,000 inhabitants, with an average annual total number of 200 cases. During this period, increased numbers of hantavirus infections were reported in 2002 and 2004. In both those years, the increase was due to outbreaks in a known endemic area of Baden Württemberg in southwestern Germany, the Swabian Alb. In 2004, there was also an outbreak with 38 cases in Lower Bavaria [10].

The Netherlands:

In the Netherlands, hantavirus infections are diagnosed in two laboratories, and data are aggregated for passive surveillance by the Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and Environment, RIVM). With the initial reports of enhanced hantavirus activity in the summer of 2005, regional health services, medical microbiologists and nephrologists were informed actively and were asked to consider hantavirus infections in the differential diagnosis of cases with the appropriate clinical picture. In total, 27 cases were detected. A case is considered confirmed when IgM antibodies are detected and evidence of seroconversion in found a follow-up sample, or by detection of hantavirus nucleic acid in a sequenced RT-PCR from blood or urine sediment.

Luxembourg:

In Luxembourg, laboratory-based hantavirus surveillance began in September 2003 and the Laboratoire National de Santé is the only laboratory in the country carrying out hantavirus serodiagnosis. There was one confirmed case in 2003 equating to a yearly incidence of 0.22 per 100,000 inhabitants. A case is considered confirmed when the following conditions are fulfilled: detection of IgM antibodies and evidence of seroconversion in a follow-up sample, or detection of hantavirus nucleic acid in a sequenced RT-PCR from blood or urine sediment.

Results

Belgium:

The current endemic area in Belgium is situated in the southeast of the country (the provinces of Luxembourg, Liège, Namur and Hainaut). The most affected provinces during the 2005 epidemic were the Luxembourg province (87 cases, incidence 33.8 per 100,000 inhabitants), the Liège province (83 cases, incidence 8.1 per 100,000 inhabitants), the Namur province (78 cases, 17.1 per 100,000 inhabitants) and the Hainaut province (76 cases, incidence 5.9 per 100,000 inhabitants). The 2005 epidemic was the first in which the Liege province (22.3% (83/372) of the cases in 2005) figured as a hot-spot for hantavirus infections. Traditionally, the Belgian hyperendemic area was composed of the provinces Hainaut, Namur and Luxembourg. Based on the residence of the patients, the Flanders region accounted for 7.4% of the total number of cases, while the Walloon region and the Brussels Capital region respectively accounted for 90.1% and 2.5% of the cases. The male-female ratio was 2.4. The median age of the patients was 41.3 years (3-85 years). During the last decade the endemic area, comprising the Hainaut-Namur-Luxembourg provinces has extended substantially and includes now the province of Liège. A significant increase in *Myodes glareolus* (bank vole) population densities was observed in the fall of 2004, coinciding with a beech mast, and during the first 10 months of 2005. In Belgium, *M. glareolus* population density was five to six times higher in April-October 2005 than during the same period in 2004 and seroprevalences in populations that were sampled (P. Heyman, personal communication).

France:

The endemic area is situated in the north-east of the country, along the Belgian and German borders [12,14]. Most cases were noted in the Ardennes district (97 cases, 32.7/100,000), the Aisne district (32 cases, 6.0/100,000), the Nord district (22 cases, 0.9/100,000), the Oise district (15 cases, 2.1/100,000) and the Jura district with 30 cases (12.0/100,000). In the latter district, clusters of hantavirus infection were not observed before and this suggests, as in Belgium, an enlargement of the endemic area. The five most affected districts (see above) in France account for 77.5% of the total number of cases. The male-female ratio was 2.6. The median age of the patients was 42.5 years (11- 81 years).

Germany:

In 2005, the incidence for hantavirus infections increased to 0.54/100,000 persons and in contrast to previous years, the annual number of cases doubled (2005: 448 cases). The weekly number of cases peaked earlier than in the previous years. The season ran from the beginning of May until the end of July. During this time, 15 to 23 infections were reported weekly and nearly half of the cases of 2005 occurred during this period. From mid-October, the weekly number of cases reached the values of the last years. In Germany the hantavirus outbreak of 2005 was mainly due to an increase of cases in several federal states north of the river Main such as Lower Saxony (75 cases, 0.9/100,000), North Rhine Westphalia (143 cases, 0.8/100,000), Hesse (34 cases, 0.6/100,000) and Thuringia (14 cases, 0.6/100,000). In contrast to previous epidemiological findings that hantavirus infections were obtained in rural areas in North Rhine-Westphalia and to a lower extent in also in Lower Saxony, infections were mainly acquired in

urban regions. As in previous years, the highest incidence rate was measured in Baden Württemberg, a known endemic area. In 2005, 110 cases were reported (incidence 1.0 per 100,000 inhabitants) which did not differ much from the previous year (120 cases). In Germany, where the surveillance includes the virus species, most infections were caused in 2005 by the hantavirus species Puumala (n=388; 87%), 7 infections (1.6%) were caused by Dobrava, 1 Hantaan infection was imported from China and for 52 cases the causative virus was not specified (11.5%) [18,19,21]. The male-female ratio was 2.6. The median age of the patients was 41.0 years (6-76 years). The hantavirus outbreak of 2005 was mainly caused by an increase of the reservoir rodent population. According information from experts of agriculture and forestry the reservoir density, especially bank voles, began to rise already in fall 2004 and its increase continued during 2005.

The Netherlands:

In total, 27 cases were detected. One person had become ill while on vacation in Finland, and was considered to have acquired the infection abroad. In all, 78% of cases lived in a region of the country that is known to be endemic for Puumala virus [3,4]. The number of cases was in the same range as has been seen in the past five years, with the exception of 2003, when only 12 cases were diagnosed.

Luxembourg:

There were 14 laboratory-confirmed cases in Luxembourg in 2005 [16]. Two of these patients lived in Belgium and France, close to the border with Luxembourg. The other 12 patients were clustered in the rural region of Mullerthal and surrounding areas in the east of the country, which suggests that the outbreak in Luxembourg was fairly localised. The Mullerthal is an area characterised by beech forests and sandstone formations. The yearly incidence in 2005 of Luxembourg residents was 2.6 per 100,000 persons.

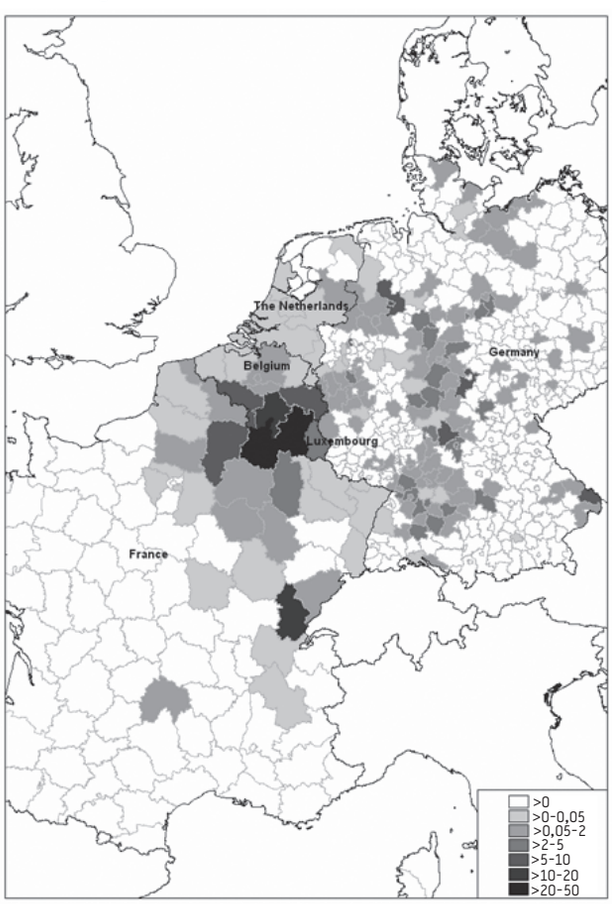
Discussion

The 2005 HFRS epidemic in Belgium, France, Germany, the Netherlands and Luxembourg resulted in a grand total of 1,114 cases. Belgium, France, Germany, the Netherlands and Luxembourg were respectively responsible for 31.4%, 22.7%, 40.2%, 2.5% and 1.2% of the cases according to their respective population sizes (Belgium: 10,263,400; France: 59,039,700; Germany: 82,192,600; the Netherlands: 15,987,100; and Luxembourg: 445,000), the national incidence was 3.6/100,000 for Belgium, 0.4/100,000 for France, 0.6/100,000 for Germany, 0.2/100,000 for the Netherlands and 3.2/100,000 for Luxembourg. Figure 1 displays in more detail the geographical distribution of the incidence.

The main feature of the 2005 epidemic was the extension of the known endemic area in, at least, Belgium, France and Germany. In Belgium, Liège province figured as a new hot-spot, in the Jura region in France a significant increase of human hantavirus cases was noted. In Germany the increase of hantavirus infections was observed in urban regions and areas where hantaviruses were not known to be endemic. The monthly distribution of the cases showed a moderate activity during the first four months of 2005, but the main peak occurred from May to August/September. From October on, the monthly number of cases returned to normal. Exception to this rule were the Netherlands where the majority of the cases occurred in the last four months of the year and where the total number of cases did not significantly increase in 2005 (Figure 2).

Figure 1

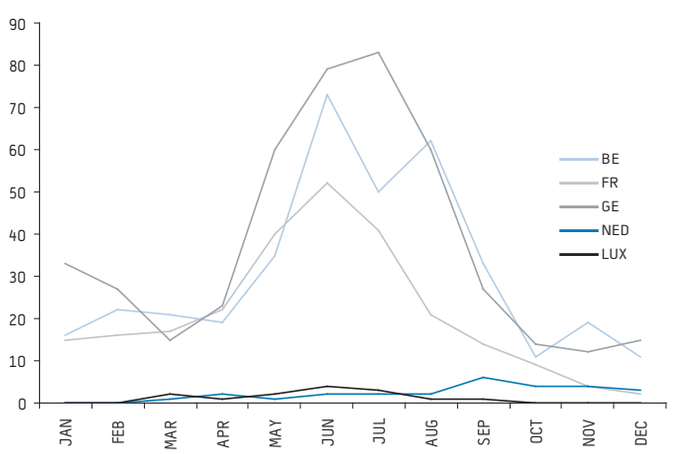
Geographical distribution of human hantavirus cases in 2005 for Belgium, France, Germany, the Netherlands and Luxembourg*



*Colour coding represents the incidence (cases per 100,000 inhabitants) per administrative entity (provinces for Belgium and the Netherlands, départements for France, cantons for Luxembourg, Kreise for Germany) for the respective countries

Figure 2

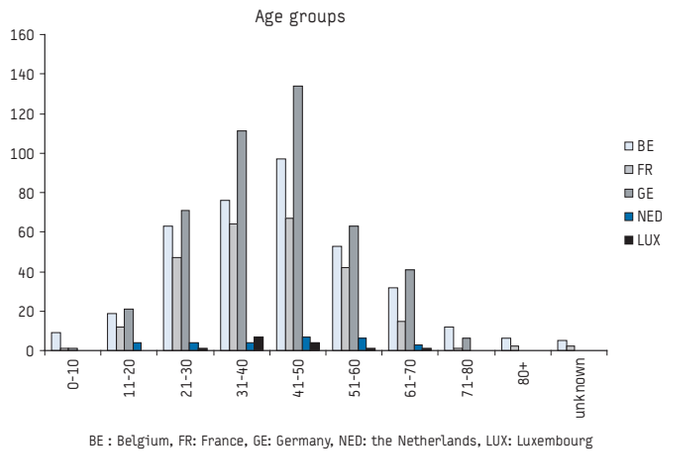
Monthly distribution of human hantavirus cases per month during 2005



BE : Belgium, FR: France, GE: Germany, NED: the Netherlands, LUX: Luxembourg

FIGURE 3

Distribution of human hantavirus cases per age group during 2005



BE : Belgium, FR: France, GE: Germany, NED: the Netherlands, LUX: Luxembourg

TABLE 1

Demographical data of human hantavirus cases during 2005

2005	Cases	M/F ratio	Median age (yrs)	Range (yrs)
Belgium	372	2.4	41.3	3-85
France	253	2.6	42.5	11-81
Germany	448	2.6	41.0	6-76
The Netherlands	27	2.9	42.5	11-68
GD-Luxembourg	14	1.8	37.8	21-70

The age distribution most affected in all five countries were in the range from 20 to 60 years, with the peak in the 41-50 years age group (Figure 3) – this is in line with published risk factors.

The epidemiology of hantavirus epidemics worldwide is determined by the interaction between rodents and humans. And as the rodent population dynamics are directly linked to abiotic factors such as more or less favourable climatic conditions and available food supplies, hantavirus epidemics are triggered by forenamed factors. Hantavirus epidemics in western Europe are not, as in northern Europe, truly cyclic events because of true cyclic rodent population dynamics; they occur after so-called mast years i.e. years in which trees produce more fruits than normal. These mast years normally occur, in western Europe, every four to seven years for oak trees and every three to five years for beech trees. A mast year for beech, oak or acorn will, as a rule, trigger a hantavirus epidemic, but the number of cases seems limited to the duplicate or triplicate of a non-epidemic year; "true" hantavirus epidemics occur when mast years of one or more tree species coincide and there is an abundance of food – and an abundance of various foods – available for rodents.

If this event is strengthened by favourable climatic conditions such as a mild winter, above zero Celsius dawn temperatures in early spring, moderately dry summer, etc. rodent population density may become very high in certain regions. The immediate result is an explosive spread of virus in the population and a significant increase of human cases in the months to follow. The above-described scenario took place in 2004-2005 and the most important hantavirus epidemic ever recorded in western Europe was the result. To date, there exists no coordinated passive or active surveillance in the European for human hantavirus infections and a European early warning system is lacking, although efforts are being made to improve communication through reporting – via the European Network for diagnostics of Imported Viral Diseases (ENIVD) – to the European Centre for Disease Prevention and Control (ECDC). Standardization and evaluation of the available detection methods was done by means of a Quality Control by ENIVD [1,2]. Information on the epidemiology, clinical symptoms and case definition for HFRS can be found at: http://www.enivd.de/VHFDISEASES/fs_vhfdiseases.htm. Advice for the public is available from the websites and publications of the Public Health Institutions in most western European countries.

Acknowledgements

Germaine Hanquet, Scientific Institute of Public Health, Brussels, Belgium; Christian Vandenvelde National Reference Laboratory for Vector-borne Diseases, Queen Astrid Military Hospital, Brussels, Belgium; Tony Vervoort and Marjan Van Esbroeck, Institute of Tropical Medicine, Antwerp, Belgium; Marc Van Ranst, Catholic University of Leuven (KUL), Belgium; Sophie Alsibai, Isabelle Capek, Nicolas Carré, Sylvie Haeghebaert, Jeannine Stoll and Véronique Vaillant, Institut de veille sanitaire and the regional epidemiology units, Saint Maurice, Paris, Lille, Nancy and Dijon, France; Marie Claude Georges-Courbot, National reference laboratory for viral hemorrhagic fevers, Lyon, France; the Federal and Local Health Departments of Germany; and Tineke Herremans, Hans Krul, Diagnostic Laboratory for Infectious Diseases and the Environment, The Netherlands.

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Citation style for this article: Heyman P, Cochez C, Ducoffre G, Mailles A, Zeller H, Abu Sin M, and al. Haemorrhagic Fever with Renal Syndrome: an analysis of the outbreaks in Belgium, France, Germany, the Netherlands and Luxembourg in 2005. Euro Surveill 2007;12(5)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n05/1205-228.asp

Influenza antiviral susceptibility monitoring activities in relation to national antiviral stockpiles in Europe during the winter 2006/2007 season

A Meijer (a.meijer@nivel.nl)[1 2], A Lackenby[3 4], A Hay[3 5], M Zambon[3 4]

1. European Influenza Surveillance Scheme (EISS) Co-ordination Centre, Nederlands Instituut voor Onderzoek van de Gezondheidszorg (Netherlands Institute for Health Services Research, NIVEL), Utrecht, the Netherlands
2. Laboratory for Infectious Diseases and Screening, Rijksinstituut voor Volksgezondheid en Milieu (National Institute of Public Health and the Environment, RIVM), Bilthoven, the Netherlands
3. European Surveillance Network for Vigilance against Viral Resistance (VIRGIL)
4. Respiratory Virus Unit, Centre for Infection, Health Protection Agency, London, United Kingdom
5. World Health Organization Collaborating Centre for Reference and Research on Influenza, National Institute for Medical Research, London, United Kingdom

Due to the influenza pandemic threat, many countries are stockpiling antivirals in the hope of limiting the impact of a future pandemic virus. Since resistance to antiviral drugs would probably significantly alter the effectiveness of antivirals, surveillance programmes to monitor the emergence of resistance are of considerable importance. During the 2006/2007 influenza season, an inventory was conducted by the European Surveillance Network for Vigilance against Viral Resistance (VIRGIL) in collaboration with the European Influenza Surveillance Scheme (EISS) to evaluate antiviral susceptibility testing by the National Influenza Reference Laboratories (NIRL) in relation to the national antiviral stockpile in 30 European countries that are members of EISS. All countries except Ukraine had a stockpile of the neuraminidase inhibitor (NAI) oseltamivir. Additionally, four countries had a stockpile of the NAI zanamivir and three of the M2 ion channel inhibitor rimantadine. Of 29 countries with a NAI stockpile, six countries' NIRLs could determine virus susceptibility by 50% inhibitory concentration (IC50) and in 13 countries it could be done by sequencing. Only in one of the three countries with a rimantadine stockpile could the NIRL determine virus susceptibility, by sequencing only. However, including the 18 countries that had plans to introduce or extend antiviral susceptibility testing, the NIRLs of 21 of the 29 countries with a stockpile would be capable of susceptibility testing appropriate to the stockpiled drug by the end of the 2007/2008 influenza season. Although most European countries in this study have stockpiles of influenza antivirals, susceptibility surveillance capability by the NIRLs appropriate to the stockpiled antivirals is limited.

Introduction

The continued circulation and spread of highly pathogenic avian influenza virus A(H5N1) throughout large parts of Asia and several countries in Europe and Africa underlines the potential of animal (avian) reservoirs to act as the source of the next pandemic of influenza [1]. Since 2003, by 11 April 2007, 291 human cases with a case fatality rate of approximately 60% have been reported by the WHO [2]. Lack of human-to-human transmission has limited the burden of influenza A(H5N1) virus as a human pathogen. However, given the genetic flexibility of influenza viruses, and experience of human morbidity and mortality following previous pandemics, developing counter measures is an important action to minimise the impact of a future pandemic. Many countries in Europe have already stockpiled antivirals as part of their pandemic preparedness plans. The ways in which national stockpiles would be used may vary substantially between countries, according to which drugs are stockpiled and how countries plan to use their resources at different stages of a pandemic [3].

Current licensed antivirals for therapy and/or prophylaxis of influenza fall into two classes, the adamantanes (amantadine and rimantadine), M2 ion channel inhibitors effective against influenza A viruses only, and the neuraminidase inhibitors (NAI) oseltamivir and zanamivir that are effective against both influenza A and B viruses.

During therapy with adamantanes, influenza viruses rapidly become resistant and are readily transmitted [4]. In addition, in many parts of the world, circulating A(H3N2) viruses have become naturally resistant [4]. In Cambodia ,Vietnam and other parts of south-east Asia, a high proportion of A(H5N1) viruses isolated from poultry are adamantane resistant, and although resistance has been detailed in clade 1 A(H5N1) viruses, this is not uniform through all lineages of A(H5N1) [5,6]. More recent clade 2 A(H5N1) viruses have remained adamantane sensitive [5,6].

For the NAI drugs, emergence of resistance to seasonal influenza viruses [A(H3N2), A(H1N1) and B] has been documented, with the highest frequency (18%) being reported in children following oseltamivir treatment in Japan [7,8]. Oseltamivir resistance in severe human A(H5N1) virus infections has also been reported following therapy [8, 9]. However, wide circulation of NAI resistant human strains has not been reported, although these can be detected at very low frequency in seasonal influenza surveillance programmes in countries with high drug consumption [10]. Currently, the ease of transmission of NAI resistant viruses is much less than that of adamantane resistant viruses, mainly because NAI resistance mutations tend to impair virus fitness and such viruses generally show reduced transmissibility in models *in vivo* [11].

In this context, VIRGIL and EISS have been collaborating since 2004 to develop capability and capacity for surveillance of influenza antiviral resistance within Europe [12,13]. VIRGIL (www.virgil-net.

org), is an EU funded network of excellence that integrates and coordinates the activities of physicians and scientists from many institutions in 14 European countries in order to combat current and emerging antiviral drug resistance developments of influenza virus, Hepatitis B virus and Hepatitis C virus. For influenza, this includes the creation of reference laboratories for antiviral susceptibility measurement, development of testing protocols for phenotypic and genotypic analysis, training for laboratory staff and linkage of susceptibility testing to clinical surveillance activities. 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 due to influenza in Europe by active clinical and virological surveillance of influenza, and has been operational since 1996 [14,15]. EISS is currently funded by the European Centre for Disease Prevention and Control (ECDC) and includes 26 European Union countries plus Norway, Serbia, Switzerland and Ukraine (Table 1,2). A total of 35 National Influenza Centres (NIC) recognised by the WHO plus five Influenza Reference Laboratories (IRL) in countries that have currently no NIC (Cyprus, Estonia, Lithuania, Malta and Ukraine), together referred to as NIRL for this paper, participate in EISS (http://www.eiss.org/cgi-files/wiw_cnrl_labs.cgi). These laboratories have functioned within EISS as the Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) since 2003 [12,13]. The NIRLs report virus detection and identification data of respiratory specimens collected by sentinel physicians and of non-sentinel (e.g. hospital or non-NIRL laboratories) sources to EISS and work on improving the virological surveillance, which includes antiviral resistance monitoring.

Since the widespread emergence of antiviral resistance would likely have a significant impact on clinical effectiveness of antiviral therapy and prophylaxis, it is important to track resistance through regional and national surveillance programmes. In addition, it is important that these surveillance programmes are appropriate to the antivirals being stockpiled. Therefore, VIRGIL and EISS, as the European public-funded consortia working on these subjects, carried out this study in order to evaluate the actual and future antiviral susceptibility testing activities by the NIRLs in relation to the national antiviral stockpile in the 30 European countries that are members of EISS.

Method

During a VIRGIL-EISS laboratory workshop on influenza antiviral susceptibility testing techniques at the Health Protection Agency (HPA) in London between 3 and 6 October 2006, the participants who represented 17 NIRLs were asked the following questions:

1. Does your country have a stockpile of influenza antiviral drugs?
2. If yes, which antiviral drugs?
3. Do you do any NAI susceptibility testing?
4. If yes, which tests: genotypic (virus nucleic acid analysis) or phenotypic (virus susceptibility analysis, i.e. determination of 50% inhibitory concentration values)?
5. Do you do any adamantane susceptibility testing?
6. If yes, which tests (genotypic/phenotypic)?
7. Do you plan to either introduce or extend NAI or adamantane susceptibility testing in the season 2006/2007?

The questionnaire was also sent out more widely after the course by the EISS coordination centre in the period October 2006 - January 2007 to all 40 EISS NIRLs for verification and for completion by the remaining 23 NIRLs.

Answers to the questionnaire were processed at the EISS coordination centre and reports were created by laboratory and by country. When a country had more than one NIRL the most positive answer was taken for the report by country. If the answer to a question was: “available”, “if necessary” or “possibly”, these were interpreted in the analysis as no actual testing or no actual plans to introduce or extend testing.

Results

At least one NIRL per country responded to the inventory questionnaire. In total, 33 of the 40 NIRLs in EISS responded. The London NIC reported on behalf of the United Kingdom, which includes also the NICs in Northern Ireland, Scotland and Wales. Of those 33 NIRLs one NIRL did not provide information on sequencing of the neuraminidase gene and 17 NIRLs did not report on actual phenotypic testing for adamantane susceptibility. Tables 1 and 2 summarise the results.

Out of 33 NIRLs representing 30 countries, seven NIRLs (six countries) reported phenotypic testing of NAI susceptibility and 15 NIRLs (13 countries) reported sequencing of the neuraminidase gene. Sixteen NIRLs (16 countries) reported on the capacity for phenotypic testing of adamantane susceptibility, of which only one was testing. Out of 33 NIRLs (30 countries), seven NIRLs (seven countries) reported sequencing of the M2 gene.

All 30 EISS countries apart from Ukraine had a stockpile of antivirals; 22 countries had stockpiled oseltamivir only, four countries had stockpiled both oseltamivir and zanamivir and three oseltamivir and rimantadine. In six out of the 29 countries that had a stockpile of NAI drugs (oseltamivir or zanamivir), the NIRLs were performing the phenotypic analysis to evaluate NAI resistance, and in 13 out of the 29 countries with a stockpile of NAI drugs the NIRLs undertook genotypic analysis of NA genes to assess NAI resistance. For the monitoring of adamantane resistance, only the NIRL of one out of the three countries with a stockpile of rimantadine indicated actual testing of adamantane susceptibility, by genotypic means only.

In 21 of the 30 countries, NIRLs had plans to introduce or extend antiviral susceptibility testing for NAIs and/or adamantanes over the next winter seasons using either phenotypic analysis (17 NIRLs in 14 countries for NAIs and 15 NIRLs in 13 countries for adamantanes) and/or genotypic analysis (22 NIRLs in 20 countries for NAIs and 16 NIRLs in 14 countries for adamantanes), while NIRLs in nine countries had no plans to introduce any testing. Taking into account these planned activities, NIRLs in 14 out of the 29 countries with a NAI stockpile would have the capacity to perform the phenotypic analysis, and NIRLs in 20 countries would have the capacity to undertake genotypic analysis to assess NAI resistance. For the monitoring of adamantane resistance, the NIRLs in two out of the three countries with a stockpile of rimantadine would have the capacity to conduct adamantane susceptibility analysis, by phenotypic and/or genotypic means.

Table 1

Overview of influenza antiviral susceptibility monitoring activities in Europe during the 2006/2007 influenza season

Country(N=30)	National stockpile of antiviral drug	Laboratory(N=33)	Current laboratory antiviral susceptibility activities											
			Neuraminidase inhibitor susceptibility						Adamantane susceptibility					
			Phenotypic testing[1]			Sequencing NA gene			Phenotypic testing[1]			Sequencing M2 gene		
			Yes	No	Remark	Yes	No	Remark	Yes	No	Remark	Yes	No	Remark
Austria	Oseltamivir	NIC, Vienna		X		X				X			X	
Belgium	Oseltamivir	NIC, Brussels		X			X			X			X	
Cyprus	Oseltamivir + Zanamivir	IRL, Nicosia		X			X			X			X	
Czech Republic	Oseltamivir	NIC, Prague		X			X				Available		X	
Denmark	Oseltamivir	NIC, Copenhagen	X			X					Missing	X		
Estonia	Oseltamivir	IRL, Tallinn		X			X				Missing		X	
Finland	Oseltamivir	NIC, Helsinki		X		X					Available		X	
France	Oseltamivir	NIC, Paris	X			X					If necessary	X		
		NIC, Lyon	X			X					Missing		X	
Germany	Oseltamivir + Zanamivir	NIC, Berlin		X		X					Missing		X	
Greece	Oseltamivir	NIC, Thessaloniki		X			X				Missing		X	
		NIC, Athens		X			X				Missing		X	
Hungary	Oseltamivir	NIC, Budapest	X			X				X			X	
Ireland	Oseltamivir	NIC, Dublin		X			X			X			X	
Italy	Oseltamivir + Zanamivir	NIC, Rome		X		X					Missing		X	
		NIC, Milan		X		X					Missing		X	
Latvia	Oseltamivir + Rimantadine	NIC, Riga		X			X				Missing		X	
Lithuania	Oseltamivir + Rimantadine	IRL, Vilnius		X				Missing			Missing			Possibly
Luxembourg	Oseltamivir	NIC, Luxembourg		X			X			X			X	
Malta	Oseltamivir	IRL, Malta		X			X			X			X	
Netherlands	Oseltamivir	NIC/RIVM, Bilthoven	X			X			X			X		
Norway	Oseltamivir + Rimantadine	NIC, Oslo		X		X				X		X		
Poland	Oseltamivir	NIC, Warsaw		X			X			X			X	
Portugal	Oseltamivir	NIC, Lisbon		X		X					Missing		X	
Romania	Oseltamivir	NIC, Bucharest		X			X			X			X	
Serbia	Oseltamivir	NIC, Belgrade		X		X					Missing		X	
Slovakia	Oseltamivir	NIC, Bratislava		X			X				Missing		X	
Slovenia	Oseltamivir	NIC, Ljubljana		X			X			X			X	
Spain	Oseltamivir	NIC, Madrid		X			X				Missing		X	
Sweden	Oseltamivir	NIC, Stockholm	X			X					Missing	X		
Switzerland	Oseltamivir	NIC, Geneva		X			X				Missing	X		
Ukraine	Planned	IRL, Kiev		X			X			X			X	
	Rimantadine - in private pharmacies													
United Kingdom	Oseltamivir + Zanamivir	NIC, London	X		Limited[2]	X[2]					Missing	X		
Total laboratories			**7**	**26**		**15**	**17**		**1**	**12**		**7**	**25**	
Total countries			**6**	**24**		**13**	**16**		**1**	**12**		**7**	**23**	

1 Phenotypic = IC50 determination using fluorescent assay (MUNANA) for NAI, or Cell ELISA or plaque inhibition assay for NAI and adamantanes
2 As part of the VIRGIL project

Table 2

Overview of influenza antiviral susceptibility monitoring activities planned to be introduced or extended during the 2006/2007 influenza season

Country(N=30)	National stockpile of antiviral drug	Laboratory(N=33)	Planned laboratory antiviral susceptibility activities											
			Neuraminidase inhibitor susceptibility						Adamantane susceptibility					
			Phenotypic testing[1]			Sequencing NA gene			Phenotypic testing[1]			Sequencing M2 gene		
			Yes	No	Remark	Yes	No	Remark	Yes	No	Remark	Yes	No	Remark
Austria	Oseltamivir	NIC, Vienna			Possibly	X				X			X	
Belgium	Oseltamivir	NIC, Brussels		X			X			X			X	
Cyprus	Oseltamivir + Zanamivir	IRL, Nicosia		X			X			X			X	
Czech Republic	Oseltamivir	NIC, Prague	X			X			X			X		
Denmark	Oseltamivir	NIC, Copenhagen	X			X			X			X		
Estonia	Oseltamivir	IRL, Tallinn			Possibly	X					Possibly			Possibly
Finland	Oseltamivir	NIC, Helsinki	X			X			X			X		
France	Oseltamivir	NIC, Paris	X			X			X			X		
		NIC, Lyon	X			X			X			X		
Germany	Oseltamivir + Zanamivir	NIC, Berlin	X			X					If necessary			If necessary
Greece	Oseltamivir	NIC, Thessaloniki	X			X				X		X		
		NIC, Athens	X					Possibly		X			X	
Hungary	Oseltamivir	NIC, Budapest	X			X			X			X		
Ireland	Oseltamivir	NIC, Dublin		X		X				X			X	
Italy	Oseltamivir + Zanamivir	NIC, Rome	X			X			X			X		
		NIC, Milan	X			X			X			X		
Latvia	Oseltamivir + Rimantadine	NIC, Riga	X				X		X				X	
Lithuania	Oseltamivir + Rimantadine	IRL, Vilnius			Possibly			Possibly		X				Possibly
Luxembourg	Oseltamivir	NIC, Luxembourg		X		X				X			X	
Malta	Oseltamivir	IRL, Malta		X			X			X			X	
Netherlands	Oseltamivir	NIC/RIVM, Bilthoven	X			X			X			X		
Norway	Oseltamivir + Rimantadine	NIC, Oslo			Possibly	X			X			X		
Poland	Oseltamivir	NIC, Warsaw		X			X			X			X	
Portugal	Oseltamivir	NIC, Lisbon	X			X			X			X		
Romania	Oseltamivir	NIC, Bucharest			Possibly			Possibly		X			X	
Serbia	Oseltamivir	NIC, Belgrade	X			X				X			X	
Slovakia	Oseltamivir	NIC, Bratislava			Possibly		X			X			X	
Slovenia	Oseltamivir	NIC, Ljubljana		X			X			X			X	
Spain	Oseltamivir	NIC, Madrid		X		X			X			X		
Sweden	Oseltamivir	NIC, Stockholm	X			X			X			X		
Switzerland	Oseltamivir	NIC, Geneva		X		X			X			X		
Ukraine	Planned	IRL, Kiev		X			X			X			X	
	Rimantadine - in private pharmacies													
United Kingdom	Oseltamivir + Zanamivir	NIC, London	X			X[2]				X		X		
Total laboratories			**17**	**10**		**22**	**8**		**15**	**16**		**16**	**14**	
Total countries			**14**	**10**		**20**	**8**		**13**	**15**		**14**	**14**	

1 Phenotypic = IC50 determination using fluorescent assay (MUNANA) for NAI, or Cell ELISA or plaque inhibition assay for NAI and adamantanes
2 Pyrosequencing, as part of the VIRGIL project

Discussion

All European countries (except Ukraine) that participated in this study indicated that antiviral stockpiles are available. This is an encouraging observation as it relates directly to national pandemic preparedness activities. However, the number of countries in which NIRLs performed influenza antiviral susceptibility testing appropriate to the stockpiled antivirals was limited.

There is widespread variation in the use of different influenza antiviral drugs within Europe (Intercontinental Marketing Services prescribing data, Oct 2006), and substantial variation in natural susceptibility of circulating influenza strains to adamantane class of drugs in particular [4]. The creation of antiviral stockpiles involves substantial allocation of resources, and in the event of a pandemic it will be important to use such resources efficiently. Emerging information about the potential for the development of resistance against influenza antiviral drugs suggests that information about susceptibility of circulating strains should be taken into consideration for decisions on recommending drug use, in particular in those countries which have stockpiles of adamantane drugs, where the level of resistance is high, but not uniform, among circulating strains [4]. Antiviral susceptibility testing should exist to support the stockpiling of antiviral drugs, to analyse the susceptibility of viruses to the stockpiled antivirals in the early stages of a pandemic and to assess possible treatment failure.

European antiviral susceptibility monitoring is currently achieved through the VIRGIL project, which will finish early in 2008. Representative, but limited, evaluation of both NAI and adamantane resistance of European influenza isolates is carried out in London by the HPA in collaboration with the World Health Organization Collaborating Centre for Reference and Research on Influenza (WHO–CC) at Mill Hill. Subsets of isolates from all European countries that undergo detailed analyses for the annual WHO vaccine recommendations have been analysed, representing approximately 5-10% of virus isolates in Europe each season. Aggregated susceptibility data for winter seasons 2004/2005 and 2005/2006 will shortly be available through the EISS/VIRGIL website and analysis of isolates from the 2006/2007 season is underway.

As the VIRGIL project is limited in time, national testing should be developed. This should be done as a matter of urgency, as our inventory showed that NIRLs in only 13 out of 29 countries with a NAI stockpile were testing for NAI susceptibility. In addition, the NIRL in only one out of three countries with a stockpile of rimantadine was testing for adamantane susceptibility. Therefore, VIRGIL in collaboration with EISS is working on improving this situation. As the NIRLs in EISS process the respiratory specimens collected by sentinel doctors, of whom the patient lists are representative for the population in a country, this existing network offers an excellent opportunity for setting up antiviral susceptibility surveillance programmes [14,15].

Most NIRLs test for NAI resistance by sequencing, indicating that this type of analysis is much more widespread, compared with phenotypic susceptibility testing that is dependent on working with virus isolates. However, phenotypic NAI susceptibility analysis is still necessary to fully evaluate NAI resistance, given the uncertainty of purely genotypic methods for assessment of resistance as only a few mutations conferring NAI resistance have been described so far, and several more are likely to emerge. Therefore, we recommend that if a surveillance programme for NAIs is developed, both genotypic and phenotypic methods are used and data combined from both methods. In contrast, if a surveillance programme for adamantane susceptibility is developed, testing using genotypic methods would be sufficient as the relationship between genotype and phenotype is absolutely predictable so that either method for analysis is suitable. In addition, it will be necessary to ensure that capability for drug resistance surveillance is maintained, testing methodologies and data are shared and harmonised between countries as surveillance for drug susceptibility is expanded.

To facilitate the development of above-mentioned surveillance programmes the following actions have been taken:

► A swabbing protocol has been published in the EISS library that includes a form asking for a minimum set of data i.e. questions about antiviral treatment/prophylaxis of the patient, the kind of drugs that have been used and contacts with family members with flu who used antiviral drugs.

► Standard operating procedures for phenotypic and genotypic analysis of antiviral susceptibility have been published in the EISS laboratory protocol library.

► A laboratory training programme hosted by VIRGIL, the HPA and the WHO-CC, National Institute for Medical Research, London, was held in October 2006 to assist national laboratories in developing their capacity for techniques involved in antiviral susceptibility. This meeting was attended by representatives from NIRLs in 17 countries.

In addition to these activities, our inventory showed that several countries were planning to initiate or extend antiviral surveillance over the next winter seasons. All together, these are the first steps to enhancing capacity and capability for detection of influenza antiviral resistance in Europe.

Conclusion

Although stockpiles of influenza antivirals are available in almost all EISS countries in Europe, surveillance systems to track antiviral resistance necessary to support the use of the stockpiled drugs are not widely available. Through collaborative efforts of VIRGIL and EISS, countries are being facilitated to develop antiviral susceptibility surveillance systems. This will further strengthen the level of pandemic preparedness in Europe as enhancing antiviral susceptibility monitoring capacity and capability will improve ability to deliver rapid information on the appropriateness of using the stockpiled antivirals in case of an introduction of a new, possible pandemic, influenza A virus subtype.

Acknowledgements

The authors thank all colleagues from the participating laboratories, VIRGIL and EISS who provided information.

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Citation style for this article: Meijer A, Lackenby A, Hay A, Zambon M, . Influenza antiviral susceptibility monitoring activities in relation to national antiviral stockpiles in Europe during the winter 2006/2007 season. Euro Surveill 2007;12(4)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n04/1204-222.asp

A CURRICULUM FOR TRAINING HEALTHCARE WORKERS IN THE MANAGEMENT OF HIGHLY INFECTIOUS DISEASES

A Baka[1], FM Fusco[2], V Puro (puro@inmi.it)[2], N Vetter[3], P Skinhoj[4], K Ott[5], H Siikamaki[6], HR Brodt[7], R Gottschalk[8], P Follin[9], B Bannister[10], G De Carli[2], C. Nisii[2], J Heptonstall[11], G Ippolito[2], on behalf of the European Network of Infectious Diseases*

1. Hellenic Center for Disease Control and Prevention, Athens, Greece
2. National Institute for Infectious Diseases L. Spallanzani, Rome, Italy
3. Otto-Wagner-Spital (Otto-Wagner Hospital), Wien, Austria
4. Rigshospitalet (The State Hospital), Copenhagen, Denmark
5. West Tallinn Central Hospital, Tallinn, Estonia
6. Helsinki University Central Hospital, Helsinki, Finland
7. University hospital, Johann Wolfgang Goethe Universität, Frankfurt, Germany
8. Gesundheitsamt Stadt Frankfurt (City Health Service Frankfurt), Frankfurt, Germany
9. Smittskyddsinstitutet (Swedish Institute for Infectious Disease Control), Stockholm, Sweden
10. Royal Free Hospital, London, United Kingdom

The SARS epidemic, the threat of bioterrorism, and recent examples of imported highly infectious diseases (HID) in Europe have all highlighted the importance of competent clinical and public health management of infectious disease emergencies. Although the European Union of Medical Specialists in Europe and the Infectious Diseases Society of America have developed curricula for training in infectious disease medicine, neither of those mentions training in the management of HIDs. The European Network for Infectious Diseases (EUNID, http://www.eunid.com) is a European Commission co-funded network of experts in HID management, created to help improve the preparedness for HID emergencies within Europe. One of EUNID's agreed tasks is the development of a curriculum for such a training. Between April 2005 and September 2006, EUNID developed a curriculum and accompanying training course on the basis of a questionnaire that was sent to all country representatives and discussion, followed by amendment of drafts shared through the project website, and a final consensus meeting. The resulting curriculum consists of a two-module course covering the core knowledge and skills that healthcare workers need to safely treat a patient who has, or who may have, an HID. The first module introduces theoretical aspects of HID management, including disease-specific knowledge, infection control, and the public health response, through didactic teaching and class-based discussion. The second module involves a "skill station" and a clinical scenario, and equips trainees with relevant practical skills, including the use of specialised equipment and teamwork practice in patient management. Together, the curriculum and course contribute to the creation of a common framework for training healthcare professionals in Europe, and although they are designed primarily for clinicians that are directly involved in patient care, they are relevant also to public health professionals and others who may be involved in HID management and emergency response.

Introduction

Recent public health emergencies of global impact involving infectious agents and/or diseases (e.g. the deliberate release of letters containing anthrax spores via the US Postal Service in 2001 and the epidemic of severe acute respiratory syndrome (SARS) in 2002-2003), and incidents in Europe concerning the importation of highly infectious diseases (HID), such as viral haemorrhagic fevers, have drawn attention to the importance of competent clinical and public health management of infectious disease emergencies, and the need to improve preparedness within Europe for emerging health threats [1-5]. The European Commission, within its Public Health and Risk Assessment Programme, is funding a number of activities intended to improve health security, build capacity, and strengthen preparedness for response to infectious disease emergencies. This includes the European Programme for Intervention Epidemiology Training (EPIET, http://www.epiet.org), a network of containment level 4 (P4) laboratories (Euro-P4), European Training in Infectious Disease Emergencies (ETIDE, http://ec.europa.eu/health/ph_projects/2005/action2/action2_2005_2_en.htm) targeting emergency departments, and the European Network for Infectious Diseases (EUNID, http://www.eunid.com) [6].

EUNID was created to exchange information, share best practice, develop training, and improve the connections between national (or regional) isolation units. It is a network of clinicians experienced in the management of HID, who represent national (or regional) infectious disease units designated to the care of patients with HID, including four high-level isolation units (HLIU), in Frankfurt/Main (Germany), Rome (Italy), Stockholm (Sweden), and London (United Kingdom). Most members are infectious disease clinicians, but the group also covers expertise from public health and epidemiology to emergency preparedness, pulmonary medicine, microbiology, infection control, and critical care medicine.

Infectious disease medicine is formally recognised as an independent specialty or subspecialty in most, but not all, countries in Europe [7]. It is still a relatively young specialty - the European Union of Medical Specialists (UEMS), created by statute in 1958 to 'harmonise and improve' the quality of medical specialist practice in the European Union (EU), has had a section of infectious diseases only since 1997 - and there is considerable debate about the ways in which the specialty should evolve and about the degree to which training in infectious disease medicine should be integrated into training in public health/epidemiology, microbiology, and infection prevention and control [8].

The European Union of Medical Specialists has developed a core curriculum for training in clinical infectious diseases and a training logbook to assist countries without a written curriculum in order to facilitate the development of common standards of training in infectious disease medicine within Europe [9,10]. In North America, the Infectious Diseases Society of America (IDSA) published a consensus-based core curriculum for clinical training in adult infectious disease medicine in 1998. [11] The curricula of both organisations are based on training in general medicine, involve clinical and research components, and require experience in medical microbiology, infection control and public health medicine in addition to a commitment to continuing medical education. The European Union of Medical Specialists' curriculum was updated in 2002, and now also requires an understanding of the issues related to the clinical presentation, early recognition, epidemiology, management and control of infections which could potentially be deliberately released into a community for example, smallpox, anthrax, plague, botulism and tularaemia [9]. The need for similar training issues has been recognised by American researchers [12]. Although infectious disease clinicians will be involved, either directly or through consultation, in the management of any patient who has, or might have, an HID, neither model specifically mentions training in the management of HID, or training in preparedness for infectious disease emergencies. Relevant training for other health professionals (e.g. nurses, paramedical staff, infection control practitioners, clinic-managers) in Europe is, where it exists, even less standardised.

EUNID has therefore developed a core curriculum and an accompanying prototype training course that cover the theoretical and practical aspects of the management of patients with HID. Its objective was the creation of a common training framework in the EU in order to provide health professionals with the knowledge and skills needed to safely manage HID. EUNID defines an HID as an infectious disease that

- is transmissible from person to person;
- is life threatening;
- presents a serious hazard in the healthcare setting and the community;
- requires specific control measures.

The definition therefore includes SARS, viral haemorrhagic fevers (eg. Ebola, Lassa, Marburg and Crimean Congo haemorrhagic fevers), multi-drug and extensively-drug resistant tuberculosis (MDR- and XDR-TB) and smallpox. However, it excludes rabies and anthrax, which are lethal and require a specific public health response, but are not easily transmissible from person to person, and measles, which is easily transmissible but rarely lethal in developed countries [13]. This report describes the development and outlines the content of the curriculum and training course.

Methods

In April 2005, a questionnaire was sent to all EUNID partners about current training requirements in their country for healthcare professionals working in high-level isolation units and/or caring for patients with HID. The survey also sought the partners' views on whether formal, standardised training of such professionals in the management of HIDs was desirable, and asked them to list the key elements of an optimal training programme.

The EUNID coordination team then used the data obtained in the questionnaire to develop a draft core curriculum and an outline training course. The course was designed according to "outcomes-based education" principles; working "backwards" from the outcomes to be obtained by the trainees to the elements of the desired course (content, teaching and learning experiences, assessment, and evaluation), and recognising that trainees are more likely to retain information if they participate actively in the learning process, and if didactic teaching is backed up with practical, skills-based, learning [14,15,16].

Results

Representatives from five countries (Germany, Greece, Italy, Sweden and the United Kingdom) reported that some form of training in the management of HID was available in their country. They reported that this training was largely un-standardised, and mostly targeted to high-level isolation unit personnel, as were arrangements for regular updating of knowledge and skills.

Responders identified a need for training in the following key areas:

- disease-specific knowledge, including epidemiology and public health response;
- infection control including the correct use of personal protective equipment (PPE); decontamination, and the safe management of clinical waste;
- providing healthcare in the setting of a high-level isolation unit;
- the use of specialised medical devices and equipment (e.g. patient isolators; respirators) found in this setting.

Responders also suggested as additional training needs:

- bio-security, including safe transport of specimens and safe patient transfer;
- crisis management;
- regular exercises for patient care teams.

All EUNID partners who contributed to the development of the core curriculum and course outline highlighted the importance of practical skills-and-drills based training.

The curriculum therefore has two components: theoretical knowledge (Table 1) and practical skills (Table 2), each of which relate to the areas identified by consensus between EUNID partners as key to the management of HID. The course is designed to be taught over a minimum of three days in the setting of a healthcare facility with an attached high-level isolation unit. It consists of two integrated modules, matching the two components described in the curriculum. Module 1 "knowledge" provides the knowledge and evidence base for Module 2 "practical skills", which offers practical, skills-based training. A detailed course schedule, with outline content and timings is available on the EUNID website, where comments and input can also be given (http://www.eunid.com/index.asp) [17,18].

Table 1

Proposed EUNID core curriculum for management of highly infectious diseases (HID): theoretical knowledge

MODULE 1: KNOWLEDGE	
Topic	**The specialist should be able to describe/explain**
Disease-specific knowledge	• Disease epidemiology and its public health impact • Mode of transmission • Clinical presentation, including early recognition, differential diagnosis, investigation, and management options • Appropriate infection control measures • Pre-and post-exposure preventive measures • Appropriate management of hospital and family contact • Appropriate management of an occupational exposure • Sources of advanced technical advice including relevant national and international guidelines
Public health and HIDs	• The principles of the public health response to HID • Systems for notifying/reporting HID in their own and other countries • Epidemiologic characteristics that may distinguish a naturally occurring outbreak from a deliberate release event • How and when to involve public health authorities in management of HID • The concept of syndromic surveillance • Public health responses to the deliberate release of biological agents
Hospital infection control	• The different types of infection control precautions (standard, contact, respiratory/droplet, airborne infection isolation) and criteria for their use • Country-specific HLIU isolation techniques and the advantages and disadvantages of each • Disease-specific high-risk procedures (e.g. aerosol-generating procedures in SARS) and techniques for risk reduction • Sources of advanced technical advice including relevant national and international guidelines
Personal protective equipment (PPE)	• The different types of respiratory and other PPE available for use by healthcare workers, including specialised respiratory protection, and the principles underlying the selection of appropriate PPE • Sources of advanced technical advice including relevant national and international guidelines
Disinfection, decontamination and waste management	• Categories of disinfectant and their use in management of HID • Safe and appropriate decontamination of patients and equipment • Waste management issues, including resources for assistance • Sources of advanced technical advice including relevant national and international guidelines
Biosafety issues	• Principles of biohazard groupings and risk assessment • Safe transportation of biohazard samples within and between healthcare facilities in accordance with current UNECE guidelines, including different types of triple container • Safe patient transfer within and between healthcare facilities • The procedures for handling a body post mortem • Sources of advanced technical advice including relevant national and international guidelines
High level isolation units (HLIU)	• The design and construction characteristics of a HLIU, including air changes, pressure gradient and air filtering • The different modalities of HLIU in the EU • The differences between an isolation room and HLIU • Criteria for advising patient admission to a HLIU • Sources of advanced technical advice including relevant national and international guidelines on unit design, construction and maintenance

Table 2

Proposed EUNID core curriculum for management of highly infectious diseases (HID): practical skills

MODULE 2: PRACTICAL SKILLS	
Topic	**The specialist should be able to**
Use of respiratory protection	• Distinguish types of respiratory protection against infectious agents available for health care workers (HCW) • Demonstrate the correct selection, use, and safe decontamination/disposal of each type • Conduct a fit test and a fit check • Detect problems with the use of each type of mask or respirator • Show a fellow HCW how to use the mask or respirator
Infection control and use of personal protective equipment PPE	• Demonstrate the correct procedures for hand washing and use of alcohol gels for hand cleaning • Demonstrate the correct use and disposal of needles and sharp instruments • Demonstrate the correct use of aseptic technique • Demonstrate the correct selection, use, and safe disposal of PPE appropriate to the risk • Detect and respond appropriately to problems with the use of an article of PPE • Recognise when PPE is being used inappropriately • Assist/correct a fellow HCW with the proper process of donning/removing PPE
High level isolation unit (HLIU)	• Conduct basic airflow/pressure checks • Check a planned preventive maintenance schedule and its results, and discuss these with the facility engineer • Have participated in patient admission drills/exercises
Team working	• Demonstrate experience of the team work and coordination needed to deal with a HID patient • Respond appropriately to an occupational exposure incident (e.g. blood splash, glove tear) • Have participated in patient admission drills/exercises
Country - specific skills	• Safely use the country-specific HLIU equipment relevant to their home country • Demonstrate an awareness of country-specific HLIU equipment used elsewhere, including its limitations and necessary infection control precautions

The aim of the "knowledge" module is to introduce the trainees to the clinical aspects of HID and their impact on public health, and to the principles of infection control, including selection and use of personal protective equipment, disinfection and waste management, through didactic teaching and class-based discussion. The module consists of a series of 12 lectures, which require a minimum total teaching time of 10 hours. The learning objectives for each lecture or subgroup of lectures match those outlined in Table 1.

The "practical skills" module requires a minimum of eight hours training time. It consists of three skill stations that cover the use of respiratory equipment, PPE, and country-specific medical equipment, e.g. patient isolator. A lecture is incorporated into an on-site tour of a functioning high-level isolation unit and during four clinical scenario exercises the trainees work in small groups to manage a patient. The skill stations are modelled on those offered in internationally recognised resuscitation courses (e.g. ACLS©, ATLS©), where, with the assistance of an experienced trainer, trainees practise a particular skill in groups of four to five people. The clinical scenario exercises are intended to give trainees the opportunity to work together as an interdisciplinary team, to experience working in the setting of a high-level isolation unit, and to use the knowledge and practice the skills they learned during the course.

Learning material (course manual, selected texts, e-learning activities) should be made available to trainees at least six weeks before the course, to encourage their active participation and

ensure that everyone has the opportunity to start the course with the same level of basic knowledge. Trainees are expected to have reviewed all course materials before attending the course.

EUNID partners agreed that the course should be accompanied by an assessment of the performance of trainees and trainers, and an assessment of the training material [19]. The evaluation of trainees should have three elements: a pre-course test, an in-course assessment of performance in skill stations and clinical scenarios, and a post-course test. The pre- and post-course tests would both consist of multiple choice questions, either web- or hardcopy-based, drawn from a pool of questions developed by experts in the management of HID or infectious disease emergencies and piloted to ensure consistency and suitability. The pre-course test should be provided to trainees at the same time as the course material, and completed as part of the pre-course preparation. Trainees should be given their test score by the course organiser at registration, and have an opportunity to discuss issues about which they were uncertain with a trainer. Trainees would take the post-course test on the final day of the course, and the results of the post-course test, coupled with performance at the clinical scenario stations, would form the basis of the final trainee assessment.

Trainees should be given the opportunity to evaluate the training material, the course, the facility, the lectures and the skill stations/clinical scenarios. The training faculty should collectively review these evaluations, which should be used to refine the course content and retained for use in benchmarking future courses.

Discussion

The events of 2001 in the US (e.g. the World Trade Center attack and the deliberate release of anthrax spores) forced a reassessment of global health security, revealing gaps in clinical, laboratory and public health capacity to respond effectively to infectious disease emergencies, including those that involve highly infectious diseases.

Multiple studies support the intuitive association between higher provider practice and better clinical outcomes ("practice makes perfect") [20,21], but few clinicians or public health practitioners working in the EU have first hand experience of highly infectious diseases gained from direct involvement in case management. In the 2002-2003 SARS epidemic, only seven of the current 27 EU member states reported probable cases of SARS: seven in France; nine in Germany; four in Italy; five in Sweden; four in the United Kingdom; one in Ireland; and one in Spain [22,23,24]. Most clinicians now in practice have never seen a case of smallpox. Haemorrhagic fever virus infections are imported to Europe sufficiently often to require preparedness, and but not frequently enough to generate widespread clinical expertise or confidence in their management [25,26,27].

Given this situation, there is a need for continued education and training of the healthcare professionals likely to be involved in diagnosis, management and response to infectious disease emergencies involving HID. Most preparedness and response plans recognise this, and considerable resources have been invested in developing national guidelines, fact sheets, incident response check lists, teaching slide sets, decision-based algorithms for diagnosis, and clinical management pathways for highly infectious diseases.

However, public health preparedness for many nations cannot be achieved by national initiatives alone, but requires a cohesive international programme that includes collaborative training. EPIET aims to improve the response capacity of public health professionals in Europe and neighbouring countries and now also covers bioterrorism and rapid assessment of emergencies [28]. However, there is no equivalent common framework for training in the clinical setting in Europe, where the ways in which highly infectious diseases are managed vary considerably between and within countries.

The core curriculum and accompanying course outlined here are intended to help standardise and augment current training on the management of HID in Europe, and to complement, rather than duplicate, work undertaken by the European Centre for Disease Prevention and Control (ECDC), and to interface with other training programmes in public health and field epidemiology (EPIET, Training Programme in Epidemiology and Public Health Interventions Network – TEPHINET, http://www.tephinet.org). The described training tools have the advantage of being shaped through consensus by clinicians with a broad range of expertise in infectious disease and public health who have experience in identifying and meeting training needs within their own institutions, which include high security isolation units. The curriculum has been designed in a way that, if desired, it could, be integrated into existing training curricula for infectious disease medicine, other medical specialties, or other disciplines. The course is targeted primarily at infectious disease clinicians and other hospital-based healthcare professionals (including hospital infection control practitioners, intensive care personnel, emergency medicine practitioners, nurse-consultants, clinic-managers/administrators), who would be most likely be directly involved in the multidisciplinary management of an infected patient. It also puts a strong emphasis on the public health response to infectious disease emergencies, and could be used to cross-train public health practitioners, and others (e.g. paramedics, laboratory workers, health emergency planning advisors) who might be involved in major infectious disease incident management.

The course as described is intended to be taught over three days on site in a healthcare facility with an attached high level isolation unit, so that trainees can gain exposure to the specialised equipment and techniques used in such units. We believe that a three-day course would, given time and cost constraints, be more accessible to trainees than a longer one, but we recognise that the course is very tightly scheduled. We are convinced that the schedule is feasible provided that trainees undertake the pre-course preparation as intended, and the course itself is well organised.

The development of the curriculum and course in the future will improve the sharing of experience between healthcare professionals from different countries, and the experience of participation in a common European training course, based on a common core curriculum, will facilitate communication and collaboration during a real international public health emergency. We hope that trainees who have completed the course will be able to contribute to health protection in Europe, and to the broader European response to infectious disease emergencies. EUNID intends to apply for European continuing medical education (CME) accreditation for the course from the European Board for Accreditation in Infectious Diseases (EBAID) and will also seek the opinion of the European Union of Medical Specialists Section of Infectious Diseases on the curriculum and course content [29].

* Further members of European Network for Infectious Diseases: Renaat Peleman, Belgium; Ida Gjorup, Denmark; Kuulo Kutsar, Estonia; Christian Perronne, France; Helena Maltezou, Greece; Gerard Shehaan, Ireland; Robert Hemmer, Luxembourg; Andy I. M. Hoepelman, The Netherlands; Kamal Mansinho, Portugal; Antoni Trilla, Spain, Magda Campins Marti, Spain; Boo Jarhall, Sweden. This work was partly supported by the EC grant EUNID (2003207), and by the Ministero della Salute, Italia - Ricerca Corrente, Istituti di Ricovero e Cura a Carattere Scientifico.

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Citation style for this article: Baka A, Fusco F, Puro V, Vetter N, Skinhoj P, Ott K, and al. A curriculum for training healthcare workers in the management of highly infectious diseases. Euro Surveill 2007;12(6)[Epub ahead of print]. Available online: http://www.eurosurveillance.org/em/v12n06/1206-223.asp

Low Pathogenicity Avian Influenzas and human health

Influenza Team (influenza@ecdc.europa.eu)

European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

Human disease due to LPAIs

Influenza A/H7N2 virus, as seen in the poultry outbreak described above, is one of many Low Pathogenicity Avian Influenzas (LPAIs) [1]. These have a genotype associated with causing milder symptoms in birds than the rarer high pathogenicity viruses and are negative on *in vivo* test [2,3]. Outbreaks of LPAIs in birds, both wild and domestic poultry, occur regularly in Europe and are probably more common than recognised. Serological surveys of domestic poultry have found evidence of outbreaks that seem to have been missed [4,5]. Occasionally, it seems that an LPAI transforms in birds to become a high pathogenicity avian influenza (HPAI) strain, but that is thought to be a rare event [4,6].

Human disease due to LPAIs

The fact that an avian influenza is highly pathogenic for birds does not necessarily mean it is pathogenic for humans. However, one notable influenza (type A/H5N1) is both highly pathogenic for birds and humans [7,8]. Influenza A/H7N2 virus infection in humans and all other human infections with LPAIs have only been associated with mild to moderate self-limiting disease, primarily conjunctivitis or flu like illness. Some cases have ended up requiring hospitalisation, but all have recovered. In addition, it is likely that there are asymptomatic infections and infections with mild symptoms that are never diagnosed because LPAI is not suspected and tested for [5]. It is unclear whether or not there has ever been human-to-human transmission of an LPAI virus, although this has happened with some highly pathogenic viruses [9-11]. During case-finding in outbreaks, people are often found to have symptoms compatible with LPAI infection, but turn out not to be infected [6]. This was seen in an influenza A/H7N3 virus outbreak in the United Kingdom (UK) in 2006, when a single poultry worker presented with conjunctivitis and had confirmed infection, but others with similar symptoms were test-negative [12].

Who is at risk from LPAIs?

Following requests from European Union (EU) Member States and the European Commission, the European Centre for Disease Prevention and Control (ECDC) is undertaking a formal risk assessment for avian influenza viruses (excluding H5N1) in relation to human health. We also posted a document examining this outbreak and its implications on our website on 28 May [10],11. After a thorough review of the literature, our assessment was that there is only limited public health risk from LPAIs, but that those who are at risk should nevertheless maintain vigilance and take precautions. The risk of infection with LPAIs is almost entirely confined to people who have close contact with domestic poultry (chickens, ducks etc) or their droppings. Human cases have almost entirely been in this category [11]. People with small domestic and pet flocks are probably most at risk, as they are less likely to be able to take precautions than those working in industry and may be less aware of the dangers. Other groups that have occasionally been infected are veterinarians and people involved in controlling outbreaks in birds (culling) and people who work on industrial poultry farms. Most EU Member States have standard occupational guidance for the latter group, but there are others at theoretical risk who should follow basic precautions, as shown in the table below. However, no infections have been seen in these groups. For the vast majority of people, who have no direct contact with domestic birds or their droppings, the risk of acquiring LPAIs and the risk to health are almost non-existent. Human infection with LPAIs from wild birds has never been reported.

Table

Who is at risk of infection with low pathogenicity avian influenza viruses (LPAI)?

Group 1. Low but real risk – precautions obligatory
• The risk of infection is almost entirely confined to people who have close contact with domestic poultry (chickens, ducks etc) or their droppings. Human cases have almost entirely been in this category[1]. People with small domestic and pet flocks are most at risk as they are less likely to be able to take precautions than those working in industry[2]
• Veterinarians and people involved in controlling outbreaks in birds (culling)
• People who work on industrial poultry farms
Group 2. Theoretical risk – some precautions recommended
There are also those at theoretical risk who may be exposed to the virus and should be advised to take some basic precautions. This includes the following where LPAI may be present:
• Persons with close contact with infected persons: Person-to-person transmission with LPAIs has yet to be described, but occurs with some HPAIs so it should not be excluded as a possibility
• Healthcare workers caring for those with LPAIs
• Those working in laboratories with H5N1 viruses
•People who may have close contact with wild birds, e.g. some ornithologists and hunters
For both Groups 1 and 2 there is greater risk of catching other potentially more serious infections from birds – examples include campylobacter and salmonella infections. Standard hygienic precaution to protect against these infections will protect against LPAIs.
For the majority of people who have no contacts with domestic or wild birds or their droppings, the risk of acquiring LPAIs and the risk to health is effectively non-existent.

1. While theoretically children might be expected to be at higher risk than adults, they have not been observed as infected in the few reported cases [11].

2. They are also probably more likely to be in influenza risk groups (the elderly and those with chronic debilitating diseases) than those exposed occupationally.

What actions should those with domestic poultry take?

The advice from the ECDC has not changed and is the same as for reducing the risk of acquiring infection with HPAIs. People with small domestic flocks in Europe should always look out for ill-health in their birds and promptly report such to the authorities. They and their families should also maintain basic hygiene as this will minimise the risk of them catching LPAIs and the more dangerous pathogens that poultry may carry such as campylobacter and salmonellosis. The ECDC has produced model guidance on this for use by national authorities [12].

What is the risk of a pandemic resulting from an LPAI?

Essentially this risk is unknown and unknowable. It is thought that each of the three pandemics of the 20th century had a link with avian influenza, as some avian genes seem to have appeared in the resulting human pandemic strain. Although there is particular concern about avian influenza H5N1 because of its high pathogenicity in humans and its stability over time in bird populations, there is no *prima facie* reason to imagine that the next pandemic strain will contain genes from a HPAI rather than an LPAI [13,14].

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Citation style for this article: Influenza team (ECDC). Low Pathogenicity Avian Influenzas and human health. Euro Surveill 2007;12(5):E070531.3. Available from: http://www.eurosurveillance.org/ew/2007/070531.asp#3

Short report

Vibrio cholerae O1 strains with decreased susceptibility to fluoroquinolones in travellers returning from India (Rajasthan) to France, April 2007

A Tarantola (a.tarantola@invs.sante.fr)[1], ML Quilici[2] on behalf of the laboratory investigation group*

1. Institut de Veille Sanitaire (National Institute of Public Health, InVS), Saint-Maurice, France
2. Centre National de Reference des Vibrions et du Choléra, Institut Pasteur (National reference centre on vibrios and cholera, Pasteur Institute), Paris, France

Two returning French travellers were hospitalised in late March 2007 for cholera caused by *Vibrio cholerae* serogroup O1 serotype Ogawa. In a separate event, a third case was hospitalised in early April 2007. All three travellers had returned from a trip to India (Rajasthan). They all required urgent specialised care in an intensive care unit and were treated by intravenous rehydration therapy and antibiotics. The *V. cholerae* O1 strains isolated during the first cluster of two cases and the third unrelated case were tested for antibiotic susceptibility. These tests showed resistance to nalidixic acid with decreased susceptibility to ofloxacine and ciprofloxacin. The three isolates were sensitive to tetracycline and doxycycline, and one of them was sensitive to trimethoprim-sulfamethoxazole.

The vast majority of cholera cases worldwide are treated by oral rehydration therapy (ORT) which, when administered in a timely and sufficient manner, has transformed the prognosis of cholera since the early 1960s and remains the mainstay of cholera treatment [1]. A total of 129 imported cases of confirmed cholera were diagnosed in France between 1973 and 2005, with a median of three diagnosed cases per year [2]. An additional two cases were diagnosed in 2006. Although many may go undetected, the number of diagnosed cases is on the decrease. Imported cholera cases, however, are diagnosed increasingly in infants or elderly persons who may not well tolerate massive fluids loss [2,3]. Antibiotics may be a useful adjunct [1] as they have been shown to reduce the duration of diarrhoea [1,4-8], the volume of diarrhoea [5,6,8], the volume of fluids required for rehydration [9,10], the duration of hospital stay [9] and the duration of excretion of *V. cholerae* [4-8]. Although emergence of multiple antibiotic resistance during cholera epidemic outbreaks has been documented over the past 30 years [11,12], there is little data on the prognosis of cholera in patients infected with resistant strains. Available data points to longer-lasting and more severe cholera in patients treated with inappropriate antibiotics [1]. In industrialised countries, treating with inappropriate antibiotics may be associated with increased morbidity in patients and higher costs to the community [1].

In a 2004 publication [13], the World Health Organization (WHO) examined the possible antibiotic regimen indicated when needed in outbreak or highly endemic situations. The WHO recommends single-dose doxycycline or tetracycline qid per three days or erythromycin in young children qid per four days. Although fluoroquinolones are not recommended by the WHO for treating suspected cholera, they are widely used in the first-line treatment of diarrhoea caused by infections acquired in developing countries. *V. cholerae* O1 strains resistant to fluoroquinolones have emerged in India [14] and Bangladesh [15,16] over the past years for a number of reasons. Quite logically, it was only a matter of time before resistant strains were imported to Europe. The impact of emerging antibioresistant cholera strains is greatest on patients in endemic countries but also affects imported cases. Community- or hospital-based clinicians considering antibiotic therapy for cholera in returning travellers before susceptibility testing should bear in mind that at least three cases imported to France from Rajasthan in 2007 showed decreased susceptibility to fluoroquinolones.

*The laboratory investigation group included: Hélène Jean-Pierre, Montpellier University Hospital; Valérie Lalande, Saint-Antoine University Hospital; Patrice Lemaître, Creil Hospital; Christophe Paquet, Institut de Veille Sanitaire; Estelle Ronco, Garches Hospital; Jacques Tankovic, Saint-Antoine University Hospital.

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Citation style for this article: Tarantola A, Quilici M. Vibrio cholerae 01 strains with decreased susceptibility to fluoroquinolones in travellers returning from India (Rajasthan) to France, April 2007. Euro Surveill 2007;12(5):E070503.2. Available from: http://www.eurosurveillance.org/ew/2007/070503.asp#2

Short report

An outbreak of measles among a travelling community from England in Norway: a preliminary report

Ø Løvoll (Oistein.Lovoll@fhi.no)[1], L Vonen[2], T Vevatne[3], E Sagvik[4], K Vainio[1], S Sandbu[1] and P Aavitsland[1]

1. Folkehelseinstituttet (Norwegian Institute of Public Health, NIPH), Oslo, Norway
2. Malvik Municipality, Norway
3. Sola Municipality, Norway
4. Trondheim Municipality, Norway

Between 7 and 14 May 2007, Nasjonalt Folkehelseinstitutt (the Norwegian Institute of Public Health, NIPH) was notified of six cases of measles, all occurring in a group of families from England staying at camping sites in Norway.

Epidemiology of measles in Norway

Measles is no longer considered an endemic disease in Norway [1]. Except for one imported case earlier this year, there have been no cases of measles reported in Norway since 2004 when seven cases, also imported, were notified. The last cases of measles of probably endemic origin in Norway were in 1999. Measles is a notifiable disease in Norway and every case is to be reported individually by both clinicians and laboratories. In addition, the disease is subject to immediate early warning to local and health authorities and the 24/7 doctor on call at the NIPH.

MMR vaccine is included in the national vaccination programme and children are vaccinated at 15 months and 12 years of age. The vaccination coverage for the first dose of MMR was 86% in 2003, but has increased to 91% for 2006. The coverage for the second dose was 91% in both 2003 and 2006. Vaccination is also recommended for non-immune persons within 72 hours of being been exposed to measles.

Outbreak description

On 7 May, the NIPH received a laboratory report indicating measles in a seven-month-old girl (case no. 1) admitted to Stavanger University Hospital in the south-western part of the country. Following up this report, we learnt that the child had onset of fever on 27 April and was examined at the hospital outpatient department the following day. Due to worsening of her condition she was admitted to the paediatric department on 1 May and then developed a rash and was isolated. The measles diagnosis was confirmed by a positive IgM test in serum.

The patient was the child of an English family staying in a caravan at a camping site in the municipality of Sola neighbouring Stavanger. According to the mother the child had been in contact with a child with measles in England shortly before they came to Norway. The Municipal Medical Officer in Sola was notified by the hospital and the NIPH. He visited the camping site and found three to four English families staying there on vacation. Two children of these families, aged five (case no. 3) and nine years (case no. 4), had fallen ill on 8 May and had been to an out-patient clinic. They were later confirmed as having measles on the basis of serology test of serum. They were unvaccinated. The remaining seven children of the English families at the camping site had been vaccinated, according to their parents.

On 10 May, the NIPH was notified by St. Olav University Hospital in Trondheim, a city in central Norway (at least 16 hours drive from Stavanger), of a case of measles in a child 15 months of age (case no. 2). The child fell ill on 4 May with fever and diarrhoea and a rash developed on 7 May. The child was admitted to the paediatric ward on the 8 May and isolated the following day. The child was a cousin of the first case in Stavanger, and had been staying at the same camping site in Sola at the time when the first patient fell ill. The family had later gone with their caravan to a camping site in the municipality of Malvik near Trondheim. The child had not been vaccinated against measles. According to her father, who also was not vaccinated, the girl and her brother of four years had not been vaccinated because the parents feared serious side effects.

On 12 May, the father (case no. 5) of the child in Trondheim (case no. 2) also came down with fever. He became so affected that he was admitted to St. Olavs Hospital on 15 May. The brother of case no. 2 also fell ill with fever on 13 May and had developed a rash when he was seen by a doctor on 17 May. He was also admitted to St. Olavs Hospital on 18 May. The diagnoses for all three cases of this family were confirmed by PCR in throat swab and serology in serum.

Public health measures

NIPH informed general practitioners and public health officers through our biweekly newsletter MSIS-rapport on 8 May, and gave

Table

Table. Six cases of measles in English tourists in Norway, May 2007

Case no	Age	Sex	Onset date	Lab result	Epidemiological information
1	7 mths	F	April 27	IgM pos	Infected in UK
2	15 mths	F	May 4	PCR, IgM pos	Cousin of 1
3	5 yrs	F	May 8	IgM pos	Sola Camping
4	9 yrs	F	May 8	IgM pos	Sola Camping
5	21 yrs	M	May 12	PCR, IgM pos	Father of 2
6	4 yrs	M	May 13	awaiting	Brother of 2

more comprehensive information on the web site from 11 May. An early warning was also issued through EWRS on 11 May. On 15 May, further information was sent to all hospitals in the country.

Both the index patient in Stavanger and the first patient in Trondheim had visited outpatient clinics and paediatric wards during their infectious period. The hospitals could therefore not rule out the possibility that they might have infected other children. Stavanger University Hospital posted information to 30-40 families with children who might have been in contact with the patient. St. Olav Hospital and the municipal Medical Officer in Trondheim traced patient contacts and offered vaccine and gammaglobulin. Three unvaccinated children aged 9-15 months received MMR vaccine and one child below nine months of age received gammaglobulin. Also three adult contacts and six health workers received vaccination. So far, no secondary cases due to contact in the health services have been reported.

The Senior Medical Officers in Malvik, in Sola and in the city of Trondheim were involved in contact tracing. The patients in Trondheim were staying at a camping site in Malvik together with approximately 24 other English families with a total of approximately 75 persons. MMR vaccine was offered to all members of these families. So far, 15 have accepted and received vaccine, and two infants below the age of nine months have been given gammaglobulin.

International investigation

It is not common to see English families with school-aged children on camping holidays in Norway at this time of the year, and there were also indications that the families were reluctant to vaccinate children. As this suggested that the families were from the travelling community, we sought more information from the Health Protection Agency in the United Kingdom (UK). Around 20 cases have been confirmed so far this year among travellers from several sites in the UK, most arising after a large gathering that occurred in south-east London on 3 April. On further interviewing, it appears likely that the index patient in Stavanger attended this event early in April. The mother reported hearing that someone with measles had been at that event, but as the index patient fell ill on 27 April, however, it is likely that she contracted measles following contact in the UK with other travelling children. These details of the intermediate cases remain to be investigated.

Travelling communities in the UK report poorer health than comparable groups of residents from socially deprived inner city areas, other ethnic minorities and rural residents [2]. Outbreaks of measles have indicated that they have lower vaccination coverage than the stable population.

Conclusion

Norwegian health authorities are investigating an outbreak of measles among English nomadic travellers in Norway. The infection is most likely imported from England and linked to other current clusters in the UK. So far, no cases in the Norwegian population can be linked to the outbreak. The investigation of the outbreaks continues and intensified surveillance during the coming weeks will show if the outbreak will continue or not. Due to low vaccination coverage and wide travels, the travelling communities in Europe represent a particular challenge for the measles elimination campaign [4].

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Citation style for this article: Løvoll Ø, Vonen L, Vevatne T, Sagvik E, Vainio K, Sandbu S, Aavitsland P. An outbreak of measles among a travelling community from England in Norway: a preliminary report. Euro Surveill 2007;12(5):E070524.1. Available from: http://www.eurosurveillance.org/ew/2007/070524.asp#1

Short report

Outbreak of measles among Irish Travellers in Norway: an update

Ø Løvoll (Oistein.Lovoll@fhi.no)[1], L Vonen[2], SA Nordbø[3], T Vevatne[4], E Sagvik[5], K Vainio[1], S Sandbu[1] and P Aavitsland[1]

1. Folkehelseinstituttet (Norwegian Institute of Public Health, NIPH), Oslo, Norway
2. Malvik Municipality, Norway
3. Sola Municipality, Norway
4. Trondheim Municipality, Norway

This is an update on the preliminary report [1] of an outbreak of measles in Norway among a travelling community from England.

As of 13 June, 15 cases have been reported. The outbreak is currently confined to several families of Irish Travellers from England who have had contact in two camping sites in Norway. Most of them are now living in a camp site outside Trondheim in central Norway. The date of onset of symptoms ranges from 27 April to 2 June. So far, 12 cases have been confirmed by PCR, IgM antibodies or both. There are 11 female patients. Thirteen are children, all unvaccinated, and aged between 7 months and 9 years (two less than one year, four between 1 and 3 years, six between 4 and 5 years, and one aged 9 years). The two other cases are unvaccinated adult members of the Traveller families.

There are currently no indications that the outbreak has spread to the indigenous population in Norway. Only one other case of measles, imported from Pakistan, has been reported in Norway this year.

The virus strain from one of the patients have been sequenced. It was found to be a D4 strain closely matching the measles strain causing the current outbreak among Irish Travellers in the United Kingdom (UK) [2].

Conclusions

The outbreak in Norway is clearly linked to the ongoing UK outbreak [2]. The cases in Norway belong to the same community, at least one of the cases visited a gathering of Irish Travellers in south-east London on 3 April 2007, and the Norwegian outbreak strain closely matches the UK one. It is too early to declare the outbreak over so we have to face the following public health challenges:

► Some of the Irish Travellers currently residing in Norway seem to fly back and forth to England from time to time. This poses a risk of exposure to infected Irish Travellers in England and subsequent reimportation, and vice versa, i.e. Travellers from Norway infecting people in England.

► Some of the Irish Traveller families have now moved on from their main camp site in Norway: their whereabouts are not known. Members of these families may be incubating measles. There is a possibility of further contact with non-immune people elsewhere in Norway or neighbouring countries and thus a risk of further spread of the disease.

So far, several non-vaccinated contacts within the Traveller community involved in the outbreak have been given the MMR vaccine. The Traveller community has responded favourably to the Norwegian health authorities' interventions.

On June 14, as this article was being prepared for publication, a suspect case of measles (case no 16) with onset on June 10 was notified to the Norwegian health authorities. The patient is an Irish Traveller child who had recently moved from Trondheim to Bergen, over 700 kilometres away.

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Citation style for this article: Løvoll Ø, Vonen L, Nordbø S, Vevatne T, Sagvik E, Vainio K, Sandbu S, Aavitsland P. Outbreak of measles among Irish Travellers in Norway: an update. Euro Surveill 2007;12(6):E070614.2. Available from: http://www.eurosurveillance.org/ew/2007/070614.asp#2

Short report

Outbreak of measles among Irish Travellers in England, March to May 2007

S Cohuet (scohuet@yahoo.fr)[1,2], O Morgan[1], A Bukasa[3], R Heathcock[4], J White[3], K Brown[3], M Ramsay[3], R Gross[1]

1. London Regional Office, Health Protection Agency, England and Wales
2. European Program for Intervention Epidemiology Training
3. Centre for Infections, Health Protection Agency, England and Wales
4. South East London Heath Protection Unit, Health Protection Agency, England and Wales

The Health Protection Agency (HPA) in England has been investigating an outbreak of measles in the Irish Traveller community. Between 23 March and 26 May 2007, 92 cases have been reported from six of England's nine regions: London, East of England, South East, South West, East Midlands, and Yorkshire and the Humber. A further six cases were reported among unvaccinated Irish Travellers in Norway between 7 and 14 May 2007 following a suspected importation by an infected Irish Traveller from England [1]. The outbreak in England is thought to have been associated with a gathering of Irish Travellers in south-east London on 3 April 2007. We describe the ongoing investigation of this outbreak.

Epidemiological investigation

For our investigation, we defined a confirmed case as an individual with a clinical diagnosis of measles and laboratory confirmation of measles IgM or RNA, with date of onset of illness after 3 April 2007, and who is either a member of the Irish Traveller community or who had contact with a confirmed case associated with this outbreak within four weeks of date of illness onset. A probable case was defined as for a confirmed case, but with no laboratory confirmation of measles IgM or RNA.

Between 3 April and 26 May 2007, there were 41 confirmed and 49 probable cases of measles occuring among the Irish Traveller community in England. However, two additional confirmed cases were identified in Irish Travellers from a site in the East of England with dates of onset in late March and with an epidemiological link to the gathering of Irish Travellers on 3 April. These two cases and the subsequent confirmed cases were caused by the same measles D4 strain (MVs/Enfield.GBR/14.07/).

We therefore included these two cases in our investigation, even though they occured before the time period of interest of our case definition. The date of illness onset for the 92 confirmed and probable cases are shown in Figure 1. The average incubation period for measles is 10 days (typical range 7 to 18 days). The first case occured on 23 March, 11 days before the gathering in south-east London. The second sibling case and probably index case, occured on 28 March, six days before the gathering. Four distinct peaks can be distinguished in Figure 1. The first peak of 10 cases occured between 14 and 16 April, 11 to 13 days after the gathering in south-east London. There was a second peak of 19 cases between the 23 and 25 April, nine to 11 days after the first peak. Ten cases occured nine to 11 days later (between 2 and 4 May). A fourth peak of 13 cases between 12 and 14 May occured 10 to 12 days later. This pattern suggests ongoing transmission within the Irish Traveller community.

Figure 1

Probable and confirmed cases of measles [n=92] among travellers by date of onset, England, March - May 2007

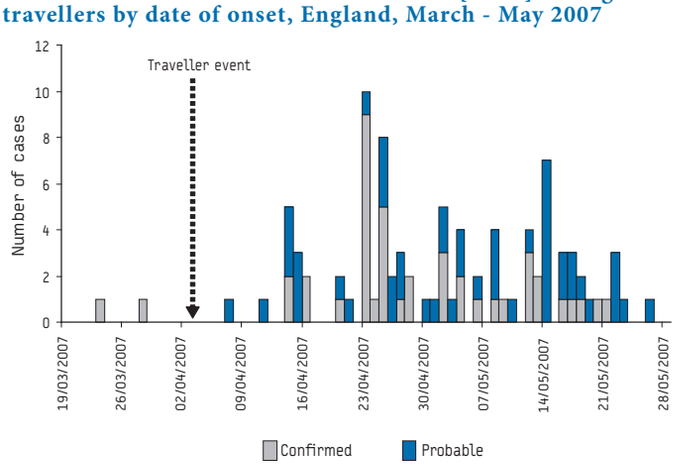

Table 1

Probable and confirmed cases of measles, by region of England, March to May 2007

Region	Probable	Confirmed	Total
East of England	19	22	41
London	16	17	33
South East	3	4	7
East Midlands	7	0	7
Yorkshire and the Humber	2	0	2
South West	2	0	2
Total	49	43	92

Cases were identified as living in one of 10 distinct Irish Traveller sites across six English regions (Table 1). London and the East of England regions have experienced the largest number of cases so far. The smaller number of cases reported from the other regions have occured more recently, suggesting that this outbreak may be spreading to other parts of the country.

Cases were aged between two months and 21 years and were equally distributed between the sexes (Table 2). The majority of cases were between one and 14 years old, with six cases under one

Table 2

Number and percentage of probable and confirmed cases of measles, by age and sex, England, March to May 2007

Age (years)	n	(%)
<1	6	(7)
1-4	20	(22)
5-9	32	(35)
10-14	18	(20)
15-19	11	(12)
20+	1	(1)
Unknown	4	(4)
Total	92	(100)
Sex	**n**	**(%)**
Male	48	(52)
Female	44	(48)
Total	92	(100)

year and 12 cases were 15 years and older. Of 38 confirmed cases for whom information was available, 36 (95%) were unvaccinated at the period of exposure. The two vaccinated confirmed cases received one dose of MMR (measles, mumps and rubella) vaccine, but the date of vaccination was not available.

Clinical symptoms are shown in Table 3. Nearly all cases reported rash and fever, and just under two thirds reported conjunctivitis, cough or coryza. Thirteen cases were admitted to hospital, although no serious complications arising from measles infection were reported.

Public health measures

In affected areas, local Health Protection Units have been working with local National Health Service providers to offer vaccination with MMR to Irish Traveller communities. Traveller education liaison teams from local authorities have been contacted to notify schools with pupils from the Irish Traveller community. Traveller organisations and societies have been contacted to help raise awareness of the importance of MMR vaccination. Information about this outbreak has been distributed nationally and Health Protection Units in non-affected areas have been asked to report any cases of measles that might be linked with this outbreak.

Discussion

Measles is a notifiable disease in the United Kingdom (UK) and the UK childhood immunisation schedule includes one dose of MMR vaccine at 13 months and a second dose between three and five years of age. In England, vaccination coverage decreased after concerns about the safety of MMR were published in 2002. Although, coverage for the first dose of MMR has since increased to 84% in 2006, it is still below recommended levels. MMR coverage may be lower still in some communities, such as Irish Travellers, who report poorer health than comparable groups

Table 3

Symptoms reported by probable and confirmed cases of measles, England, March to May 2007

Symptom	Information available	Yes	(%)
Fever	86	83	(97)
Rash	88	87	(99)
Conjunctivitis	82	47	(57)
Cough	64	39	(61)
Coryza	62	37	(60)

of residents from socially deprived inner city areas, other ethnic minorities and rural residents [2]. There was an outbreak of measles in the Irish Traveller community in England in 2006, resulting in over 700 cases [3,4]. However, this mostly involved a B3 strain, suggesting that this current outbreak is a result of re-introduction of measles into the Irish Traveller community. Low vaccination coverage and frequent movement of travelling communities presents a particular challenge for measles elimination in Europe [5]. This outbreak also emphasises the difficulties in eliminating a disease in its end-phase with the threat of importation/exportation of measles, as happened here with Norway.

Acknowledgements

We thank the following Health Protection Units who provided these data: South East London, South West London and North West London, Essex, Bedfordshire and Hertfordshire, Kent and Surrey and Sussex, East Midlands South, South Yorkshire and Gloucester. We are also grateful to Kate Fitch and Shamma Mutaz for assistance with this investigation.

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Citation style for this article: Cohuet S, Morgan O, Bukasa A, Heathcock R, White J, Brown K, Ramsay M, Gross R. Outbreak of measles among Irish Travellers in England, March to May 2007. Euro Surveill 2007;12(6):E070614.1. Available from: http://www.eurosurveillance.org/ew/2007/070614.asp#1

Short report

Ostreopsis ovata and human health: epidemiological and clinical features of respiratory syndrome outbreaks from a two-year syndromic surveillance, 2005-06, in north-west Italy

P Durando (durando@unige.it)[1], F Ansaldi[1], P Oreste[2], P Moscatelli[3], L Marensi[4], C Grillo[5], R Gasparini[1], G Icardi[1] and the Collaborative Group for the Ligurian Syndromic Algal Surveillance*

1. Department of Health Sciences, Section of Hygiene and Preventive Medicine, San Martino Hospital, University of Genoa, Genoa, Italy
2. Department of Health and Social Services, Liguria Region, Genoa, Italy
3. Chair of Medical Emergency Unit, San Martino Hospital, Genoa, Italy
4. Chair of Hygiene and Public Health Unit, Local Health Unit, Genoa, Italy
5. Regional Agency for the Environmental Protection of Liguria, Genoa, Italy

There appears to be a lack of data regarding the effects on human health of *Ostreopsis ovata*, a marine dinoflagellate species usually living in tropical and subtropical areas but recently found with more and more frequency in the Mediterranean Sea [1-4]. Recently, 28 cases of rhinorrhea with or without mild dyspnea, cough and fever have been associated with the concomitant proliferation of *Ostreopsis ovata* in southern Italy [1].

This paper presents epidemiological and clinical data on more than 200 cases of respiratory syndrome (20% requiring hospitalisation) occurring in patients who had spent time near or on the beach at the specific tracts of the coast near the cities of Genoa and La Spezia, in the north-west of Italy, where the presence of *Ostreopsis ovata* algal blooms has been well documented [4].

In mid-July 2005, clinical-epidemiological and local environmental investigations were launched in Genoa, following the first reports of an unusually high number of patients seeking medical care in several hospital emergency departments, after recreational or working activities on the beach.

A case definition was put together on the basis of the most important epidemiological and clinical data obtained from the patients, including:

- presence at the seaside (<90 m from the shore-line), in concomitance with *Ostreopsis ovata* algal bloom;
- seeking medical care in a hospital emergency department;
- presenting with at least two of the following symptoms: cough, dyspnea, sore throat, rhinorrhea, fever >=38°C, headache, lacrimation, nausea/vomiting and dermatitis.

Patients who fulfilled these criteria were asked to provide detailed information concerning demographics, date of onset of symptoms and possible co-morbidity conditions (e.g. asthma or rhinitis), as well as activities performed and the exact amount of time spent by the patients on the beach.

At the same time, a concomitant superficial proliferation of macroalgal mucilage was described along the part of the coast where most cases occurred. The local environmental protection staff immediately analysed air and water samples to exclude the presence of chemical pollution, and suspected a particular kind of unicellular algae, *Ostreopsis ovata*, detected in high density in the sea water, as a causative agent [4]. Laboratory tests of water, plankton and macrophyte samples demonstrated the presence of "putative palytoxin" [2]. High temperature of the water and high atmospheric pressure, meteorological conditions with no wind and a flat sea, combined with the peculiar typology of the coastline with numerous small inlets, were factors that certainly favoured the algal bloom and its aerosolisation in the days immediately preceding the first recorded cases.

As a result, an algal syndromic network was established, including the Regional Epidemiological Observatory, the emergency departments of the main hospitals in Genoa and the local Public Health Units, and continued the surveillance of respiratory syndromes associated with exposure to algae, throughout the summers of 2005 and 2006.

In Genoa, between 17 and 26 July 2005, a total of 209 patients (73 males - 34.9%, mean age 35.9±20.1 years, range 1-89 years) matched the above-described case definition. The most frequent symptoms were fever, sore throat, cough and dyspnea, variously associated (see tables below).

Mean onset of symptoms was 4 h 33 min (median 7 h, range 30 min - 23 h) after the beginning of exposure. Samples for laboratory analysis were available during the acute phase in 82 patients (39.2%) (in all the hospitalised cases and in patients who expressed their consent): 46.3% of them had leucocytosis (mean white cell count 13,900/mm^3±3,400; range 10,100-23,900), and 40.2% of them had neutrophilia (mean 82.2%±4.7; range 75.2-91.5), but no other significant divergence from normal laboratory values (transaminases, gamma-glutamyl transpeptidase, creatinine and sedimentation rate) was found. All electrocardiogram and chest X-ray tests gave negative results. Overall, 43 (20.6%) out of the 209 patients seeking medical help at the emergency departments needed hospitalisation (hospital

stay range 24-72 h). None of the investigated risk variables (bathing, distance from the sea, length of stay on the beach, etc.) or of the personal and medical histories (age, sex, co-morbidity, etc.) seemed to be associated with hospitalisation.

During the following summer, in the periods between 29 July and 3 August, and 21 and 23 August 2006, concomitantly with new Ostreopsis algal blooms, 19 cases matching the above described case definition were identified by the surveillance network in both cities of Genoa and La Spezia. On the basis of the previous year's experience, immediately following the identification of the first cases, the Genoese local Public Health Authorities ordered access to the beaches and bathing to be forbidden and informed the population of the reasons for this safety precaution. In La Spezia, a different management model was applied: bathing was not forbidden, but a widespread information campaign was conducted about the presence of *Ostreopsis ovata* and associated health risks. The case histories and clinical pictures of the patients notified during the summer season of 2006 were very similar to those observed in the previous year.

Symptoms and their associations recorded during the two investigated seasons in patients who needed medical care at hospital emergency departments and hospitalisation are presented in detail in Tables 1, 2 and 3.

Table 1

Clinical symptoms reported in 228 patients treated in hospital emergency departments in Genoa and La Spezia, during the summers of 2005 and 2006

	2005		2006	
	No.	%	No.	%
All patients	**209**		**19**	
Fever	133	63.6	6	31.6
Sore throat	105	50.2	7	36.8
Cough	84	40.2	14	73.7
Dyspnea	81	38.8	7	36.8
Headache	66	31.6	2	10.5
Nausea	50	23.9	3	15.8
Rhinorrhea	44	21.1	5	26.3
Lacrimation	33	15.8	1	5.3
Vomiting	21	10	1	5.3
Dermatitis	10	4.8	0	0

Table 2

The most frequent associations of symptoms reported in 228 patients treated in hospital emergency departments in Genoa and La Spezia, during the summers of 2005 and 2006

	2005		2006	
	No.	%	No.	%
All patients	**209**		**19**	
PATIENTS WITH 2 ASSOCIATED SYMPTOMS:	80	38.3	18	94.7
Fever and sore throat	17	8.1		
Fever and dyspnea	7	3.4		
Fever and headache	7	3.4		
Fever and cough			5	26.3
Cough and dyspnea			3	15.8
Sore throat and dyspnea			2	10.5
Other associations	49	23.4	8	42.1
PATIENTS WITH 3 ASSOCIATED SYMPTOMS:	47	22.5	1	5.3
Fever, cough and sore throat	6	2.9		
Fever, cough and dyspnea	6	2.9	1	5.3
Other associations	35	16.7	0	0
PATIENTS WITH 4 ASSOCIATED SYMPTOMS:	38	18.2	0	
Fever, cough, dyspnea and headache	5	2.4		
Fever, sore throat, headache and nausea	5	2.4		
Other associations	28	13.4		
PATIENTS WITH 5 ASSOCIATED SYMPTOMS:	24	11.5	0	
Fever, cough, sore throat, dyspnea and rhinorrhea	6	2.9		
Other associations	18	8.6		
PATIENTS WITH MORE THAN 5 ASSOCIATED SYMPTOMS:	20	9.6	0	
Fever, cough, sore throat, dyspnea, headache and nausea	5	2.4		
Fever, cough, sore throat, dyspnea, lacrimation and nausea	5	2.4		
Other associations	10	4.8		

Table 3

The most frequent associations of symptoms in 43 patients requiring hospitalisation in Genoa, during the summer of 2005

	2005	
	No.	%
All hospitalised patients	**43**	
PATIENTS WITH 2 ASSOCIATED SYMPTOMS:	11	25.6
Fever and sore throat	5	11.6
Fever and headache	4	9.3
Other associations	2	4.7
PATIENTS WITH 3 ASSOCIATED SYMPTOMS:	12	27.9
Fever, cough and sore throat	4	9.3
Fever, cough and dyspnea	3	7.0
Other associations	5	11.6
PATIENTS WITH 4 ASSOCIATED SYMPTOMS:	10	23.3
Fever, sore throat, headache and nausea	3	7.0
Other associations	7	16.3
PATIENTS WITH 5 ASSOCIATED SYMPTOMS:	6	14
Fever, cough, sore throat, dyspnea and rhinorrhea	2	4.7
Other associations	4	9.3
PATIENTS WITH MORE THAN 5 ASSOCIATED SYMPTOMS:	4	9.3
Fever, cough, sore throat, dyspnea, lacrimation and nausea	2	4.65
Other associations	2	4.65

The outbreaks of respiratory illness following exposure to concomitant *Ostreopsis ovata* blooms, occurring in Italy over the last few years [1-4], have undoubtedly triggered the discussion on the urgent need to monitor and prevent such events. Setting up a syndromic surveillance network, including the Regional Epidemiological Observatory, the main hospital emergency departments and the local Public Health Units, could represent an efficacious tool for both the rapid detection of the sentinel cases and the implementation of health regulations by the Local Public Health Authorities, for example forbidding bathing in the area, to limit the burden on human health. In addition, collecting information on the clinical symptoms reported by patients exposed to *Ostreopsis ovata* blooms could contribute not only to a better understanding of the effects of the exposure on human health but also to the construction of a more stringent case definition for syndromic surveillance purposes.

* Collaborative Group for the Syndromic Algal Surveillance: Pasquale Di Pietro, Paolo Angelo Cremonesi, Cecilia Brescianini, Angelo Ferrari, Roberto Carloni, Alberto Verardo, Daniela Amicizia, Salvatore De Luca, Laura Sticchi, Federica Compagnino, Jessica Lugarini, Simona Costabel, Floriana Botto, Patrizia Torracca, Alessandra Bertone, Nunzia Melchiorre, Rosella Bertolotto, Barbara Vivaldi.

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Citation style for this article: Durando P, Ansaldi F, Oreste P, Moscatelli P, Marensi L, Grillo C, Gasparini R, Icardi G. Ostreopsis ovata and human health: epidemiological and clinical features of respiratory syndrome outbreaks from a two-year syndromic surveillance, 2005-06, in north-west Italy. Euro Surveill 2007;12(6):E070607.1. Available from: http://www.eurosurveillance.org/ew/2007/070607.asp#1

Letter to the editor

Influenza antiviral susceptibility monitoring activities in relation to national antiviral stockpiles in Europe during the winter 2006/2007 season

Bruno Christian Ciancio, Angus Nicoll (angus.nicoll@ecdc.europa.eu)

European Centre of Disease Prevention and Control (ECDC), Stockholm, Sweden

To the Editor: In their article on antiviral stockpiles and influenza antiviral susceptibility monitoring (http://www.eurosurveillance.org/em/v12n04/1204-222.asp), Meijer *et al.* expressed concern about the discrepancy between nearly all countries in Europe having influenza antiviral stockpiles as part of their pandemic plans and yet only a few having laboratory capacity to perform antiviral susceptibility testing.[1] They go on to recommend that all countries in the European Union (EU) with a stockpile of antivirals should have this testing as a routine at a national level. This is in principle correct, especially if during a pandemic countries would not be able to, or might not wish to share specimens as they normally do through the World Health Organization (WHO) Flunet system or the other mechanisms that work at present [2].

The authors represent the European Surveillance Network for Vigilance against Viral Resistance (VIRGIL), an EU funded research project which is producing important data on markers of antiviral resistance in influenza and other viruses identified in Europe [3]. They do so working with the European Influenza Surveillance Scheme (EISS) and National Influenza Reference Laboratories. The evaluation of both neuraminidase inhibitor and adamantane resistance of European influenza isolates is carried out in London by the Health Protection Agency Centre for Infection in collaboration with one of the four WHO Collaborating Centres for Reference and Research on Influenza [1,2]. Such data are important in informing the choice of clinicians for antivirals especially since the emergence of resistance markers to the adamantanes in a number of countries and a few reports of resistance to oseltamivir in Japan [4,5]. Generating and gathering data relating to anti-viral resistance should become a routine function annually in the EU. However in a pandemic it would be important to quickly determine any resistance and to monitor for it emerging following mass use of antivirals. Currently, Europe has no routine monitoring of antiviral resistance for influenza though there are a number of published individual reports and a global network [6].

We agree that there should be monitoring of influenza antiviral resistance in the EU and support the VIRGIL activities in promoting routine resistance monitoring, however we are cautious in recommending that influenza susceptibility testing should be developed in all 27 EU countries as a priority activity for pandemic preparedness. Therefore this recommendation does not seem to take into account the large differences existing between European countries in term of resources and organisation of the healthcare systems, and hence their need to differently prioritise preparedness activities. Antiviral resistance testing and monitoring is expensive and would inevitably detract from investment in other laboratory work. Secondly, the presence of a national laboratory performing antiviral resistance testing in each country, does not necessarily imply that antiviral resistance monitoring for clinical and public health purposes will be effectively carried out in Europe during a pandemic. For effective monitoring of antiviral resistance, laboratories should be able to:

- routinely collect and test an adequate and representative number of samples;
- continuously provide resistance figures to public health policy makers in a timely way;
- with others gather relevant epidemiological data for monitoring risk factors for resistance should it emerge at a significant level.

This might not be feasible in all countries in Europe in the short term. Therefore in preparation for a pandemic, a possible solution to guarantee an efficient monitoring of antiviral resistance would be to have an agreement between countries so that some pre-defined laboratories can be supplied with a representative number of viruses and then constantly feed information on the drug resistance profile of the pandemic virus to all Europe. This strategy entails that there is prior agreement that samples/virus isolates and data from all countries are shared and tested according to previously agreed protocols. Common shared protocols should form the basis for regulating this collaboration including estimates of the maximum number of samples that can be tested in the different phases of the pandemic. Such approach would also be valuable for countries with difficulties not only in testing but also in collecting samples as they will receive information on the drug resistance profile of the pandemic virus circulating in Europe.

This kind of collaboration exists already between countries in the WHO Global Influenza Surveillance Network where National Influenza Centres collect specimens in their country, perform primary virus isolation and preliminary antigenic characterization, but they ship newly isolated strains to one of the four WHO Collaborating Centres for high level antigenic and genetic analysis, the result of which forms the basis for WHO recommendations on the composition of influenza vaccine for the Northern and Southern Hemisphere each year [2,7].

On a more general perspective, we can expect that during Phase 6 of a pandemic the request for data from policy makers and the politicians to public health institutes will probably run ahead

of what can be delivered. Careful planning is therefore needed to select the information that is of public health value. In this context it would be crucial to distinguish between what data should be collected in every Member State, and what has an EU added value and can be agreed as being done at EU level (in some but not all countries) but the results being fed back to all the Member States. If a pandemic starts in the next few years, antiviral resistance monitoring would probably fall in the latter category as well as other specific surveillance information including those on characteristics of transmission, case fatality rates, antiviral and vaccine effectiveness, etc. This is the subject of work being led by ECDC with a working-group of experts from Member States working on surveillance in a pandemic.

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Citation style for this article: Ciancio B, Nicoll A. Letter to the Editor: Influenza antiviral susceptibility monitoring activities in relation to national antiviral stockpiles in Europe during the winter 2006/2007 season. Euro Surveill 2007;12(6):E070628.4. Available from: http://www.eurosurveillance.org/ew/2007/070628.asp#4

Letter to the editor

Author's reply - Influenza antiviral susceptibility monitoring activities in relation to national antiviral stockpiles in Europe during the winter 2006/2007 season

Adam Meijer (A.Meijer@nivel.nl)[1,2], Angie Lackenby[3,4], Alan Hay[3,5], Maria Zambon[3,4]

1. European Influenza Surveillance Scheme (EISS) Co-ordination Centre, Netherlands Institute for Health Services Research, Utrecht, the Netherlands
2. Respiratory Infections Group, Department of Virology, Laboratory for Infectious Diseases and Perinatal Screening, National Institute for Public Health and the Environment, Bilthoven, the Netherlands
3. European Surveillance Network for Vigilance against Viral Resistance (VIRGIL)
4. Respiratory Virus Unit, Centre for Infection, Health Protection Agency, London, United Kingdom
5. WHO Collaborating Centre for Reference and Research on Influenza, National Institute for Medical Research, London, United Kingdom

To the Editor: In responding to our paper on the current limitations in influenza antiviral susceptibility testing in Europe (http://www.eurosurveillance.org/em/v12n04/1204-222.asp), Ciancio and Nicoll criticise our suggestions for enhanced capacity in individual countries and favour a system that, as at present, relies on resistance monitoring by predefined central laboratories, as they consider this model most effective for clinical and public health purposes during a pandemic [1,2]. They have focussed mainly on the requirements for information about antiviral susceptibility as part of pandemic planning. We, on the other hand, have considered requirements in a broader context and recommended establishing capacity and capability for antiviral susceptibility testing at national level [2], for several reasons:

► The fundamental requirement for knowledge about antiviral susceptibility as part of clinical care.

Clinical management of influenza includes the use of antiviral drugs and requires decisions about the choice of drugs to use during the ongoing management of (seasonal) influenza in immunocompromised individuals and severely ill patients, as well as during an outbreak of 'avian' influenza or an emerging pandemic. It is necessary to know, with sufficient speed to be able to adapt patient management, which drugs can be used and whether resistance has emerged. Such clinically relevant information is usually best delivered by national or local reference laboratories. This was an important lesson learned in the Netherlands during the H7N7 avian influenza outbreak in 2003 [3,4].

► Current susceptibility monitoring systems do not deliver timely data for clinical care.

The global Neuraminidase Inhibitor Susceptibility Network (NISN), the World Health Organization (WHO) Global Influenza Surveillance Network and the European surveillance network for vigilance against viral resistance (VIRGIL), in collaboration with the European Influenza Surveillance Scheme (EISS), routinely monitor antiviral susceptibility in representative isolates, as part of influenza surveillance. However, the flow of virus isolates from National Influenza Centres (NICs) to the regional testing labs in VIRGIL/EISS or the WHO Collaborating Centres, required to develop periodic overview data, usually occurs over a period of weeks or months after virus isolation and is not set up to report in time to adapt patient management.

► Building capacity and capability for pandemic response is best achieved by ensuring both exist at national level.

Within the WHO Global Influenza Surveillance Network and EISS in Europe, the NICs are likely to represent the primary source of expertise in surveillance and response to influenza epidemics and pandemics. Consequently, triggering many of the well-planned interventions described in national pandemic preparedness plans will depend on the efficient and effective functioning of the NICs. National capacity and capability is required to assure rapid detection of antiviral resistance if it occurs during mass use of antivirals in a pandemic. In addition, developing capability for antiviral susceptibility testing in each NIC was emphasized in the recently published WHO document outlining the roles of NICs in interpandemic, pandemic alert and pandemic periods [5]. Although many NICs have made significant progress in preparing for a pandemic, a substantial number currently do not have capacity for influenza surveillance outside the seasonal context. Strengthening NIC function by improving technical capacity and capability can be achieved by the gradual introduction of new technology, as was achieved with the introduction of PCR technology for influenza diagnosis in NICs.

► Antiviral susceptibility testing is not particularly demanding.

Arguments about significant differences in healthcare systems and inappropriate prioritisation of limited resources against the introduction of national antiviral susceptibility testing are misleading. Our inventory showed that 13 out of 29 European countries already carry out antiviral susceptibility testing, and that this number increases to 21 when countries that plan to do so in the coming winter season are included [2]. The reasons for introducing antiviral susceptibility testing have been driven mainly by clinical prescribing needs, not by public health surveillance.

Many European NICs already undertake influenza gene sequencing as part of their surveillance. This is an important element in antiviral susceptibility monitoring. Extending this capability to the genes affected by anti-influenza drugs and the introduction of phenotypic testing techniques are not major technical leaps. Nor do they require substantial financial investments: indeed the financial and technical requirements to introduce this activity are considerably less than the previous barriers to the introduction of PCR in most laboratories. Furthermore, the provision of standard operating protocols, reference reagents and training to support the establishment of national capacity and capability, and of a central database facility for the sharing and interpretation of antiviral susceptibility data are part of the VIRGIL and EISS programmes.

► Appropriate specimen collection is already available in most countries.

In Europe, the NICs collaborate in a Community Network of Reference Laboratories (CNRL) for human influenza, coordinated by EISS [6]. This network, in collaboration with VIRGIL, has a programme for antiviral susceptibility monitoring using routine sentinel clinical and virological surveillance and virus isolates sent to the NICs from several sources, e.g. hospitals and other peripheral laboratories [6,7]. We expect these national systems for specimen and virus isolate collection, as part of NIC responsibilities in the WHO Global Influenza Surveillance Network [5], will still function during a pandemic. In addition, EISS and VIRGIL agreed in 2004 on a minimum required epidemiological dataset, including antiviral use, to be part of the clinical form accompanying specimens taken for virological analysis. Countries fulfilling all requirements increased from one for the 2003/04 season to four for the 2004/05 season and 12 for the 2005/06 season. Countries not fitting the requirements are being stimulated to change their forms and databases to contain these data [EISS, personal communication].

In conclusion, in our opinion antiviral susceptibility testing should take place at the locations where it is most effective for clinical management during interpandemic, pandemic alert and pandemic periods, and that such capability and capacity should be developed nationally. It will also be necessary to sustain central reference laboratory functions to evaluate technically difficult samples, provide standardisation, develop new methods and provide training. We agree that coordination of activities in collaboration with the European Centre for Disease Prevention and Control is essential and that there will be a sustained need for the coordinated aggregation, analysis and interpretation of data and for the development of recommendations.

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Citation style for this article: Meijer A, Lackenby A, Hay A, Zambon M. Author's reply – Influenza antiviral susceptibility monitoring activities in relation to national antiviral stockpiles in Europe during the winter 2006/2007 season. Euro Surveill 2007;12(6):E070628.5. Available from: http://www.eurosurveillance.org/ew/2007/070628.asp#5

Erratum:

In our last print compilation (Vol 12, Issues 1-3), the article 'Ensuring prudent use of antimicrobials in human medicine in the European Union, 2005' contained a paragraph inadvertently taken from another article in the same issue. The paragraph on methods starting at the foot of page 64 should have read the same as it does online, ie:

'The Commission convened representatives from several Member States in a working group on the prudent use of antimicrobial agents in human medicine that developed a template for reporting. This template was designed in the form of a questionnaire to facilitate reporting in a concise and comparable manner, allowing for better collation and analysis of the information. Member States and EEA countries were asked to report to the Commission on the implementation of the Recommendation. Templates were sent to all Permanent Representations that coordinated the response through their national contact points and responsible institutions. During 2004, the Commission received one coordinated reply from every Member State, from Iceland and Norway, and also from the acceding country Bulgaria, which responded voluntarily. Results were summarised by the Commission and recorded with the help of the working group in a report to the Council highlighting the areas of the Recommendation needing further attention. [9] This report is supported by a Commission staff working paper providing a more detailed analysis, as well as tables summarising answers from single Member States. [10] For more details the reader is referred to these Commission papers available on the Commission's website; in this paper, the authors limit themselves to presenting the main findings and recommendations.'

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Epidemiological Surveillance,
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Print version available, online version available soon. Bulgarian, titles translated into English.
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Institute of Public Health, Bucharest.
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TQ-AD-07-002-EN-C

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ISSN 1025 496X
6,000 copies