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Editorial

Why a burden of disease study?

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From the time I was appointed as Director of the European Centre for Disease Prevention and Control (ECDC) in 2005, I and the ECDC Governing and Advisory Bodies faced the task of tackling the 46 diseases under mandatory notification in the European Union (EU), as well as severe acute respiratory syndrome (SARS), avian influenza and West Nile virus. The evidence for deciding on relative priorities was limited, especially as the ECDC's first Annual Epidemiological Report (AER) for 2005 describing the Communicable Disease (CD) situation in the EU was in preparation stage.

Furthermore, it was clear that although the public health community "knows" that CD have in general decreased substantially in Europe over the last century, it was also clear that new CDs have started to emerge and old ones re-emerge. However, "evidence" is lacking, both for when the century-old historical decreasing curve started to rise again and for the rate of the current increase. The success in tackling CDs, and hence their burden, has also changed the balance between Communicable and Non-Communicable Diseases (NCDs). CDs are currently estimated to present 9% of the total burden of disease in Europe [1]. This has also had an impact on the direction of priorities between these two broad areas of public health. However, the traditional boundaries between CDs and NCDs are also clearly changing, as present research indicates that many traditional NCDs have infections in their aetiology and should perhaps now be classified as CDs rather than NCDs. Examples are the role of human papillomavirus in cervical cancer [2] and the role of Helicobacter pylori with regards to stomach cancer [3]. In addition, "success" in controlling SARS has in some quarters, especially the mass media, raised questions of "waving shrouds" and the necessity of the considerable expense that was involved. Such doubts may migrate to current avian influenza and pandemic preparedness. These perceptions also need to be rectified with the help of "evidence".

It is now clear that we may only have won a battle against infectious diseases – the war will surely continue

Without the "evidence", it is more than likely that experts in each CD (and NCD) will quite rightly present figures to argue for funds and support that in total would exceed the recorded mortality and morbidity. To some extent, this was one of the rationales for the Global Burden of Disease study initiated by the World Health Organization (WHO) in the1990s and the attempts to develop a composite measure that incorporated morbidity, mortality, sequelae and severity with the ultimate possibility to include direct and indirect costs of the burden of each disease.

The development of composite measures is not new – life expectancy being perhaps the oldest in the health area – and improvements in the underlying data used to develop them are required. Such measures are also most useful when they are designed to be used to identify areas for public health action rather than simple league tables (be they of diseases and/or of countries). The experience of the Global Burden of Disease study has shown that the development and use of such measures can help to bring about significant improvement and attention to the quality and completeness of the underlying data, which have historically perhaps not had the attention and resources required (even given EU Member States' strong historical civil registration systems).

Therefore, in the autumn of 2006 the ECDC decided to explore the potential of the use of composite measures as one element to help guide public health policy and actions in the area of CDs. This was done through the launch of a three-month pilot study together with the Dutch National Institute for Public Health and the Environment (RIVM), which was supported and funded by the Ministry of Health and Welfare of the Netherlands. Given the very short time available (due to the deadlines for the AER), it was clear that this would only be possible by using existing composite measures and generally available data and covering a limited number of CDs. Seven diseases were chosen for inclusion in the pilot, some because work had already been done for these diseases (albeit in specific countries). Other diseases, such as influenza and measles, were selected to ensure that specific difficulties, such as reported data being the "tip of the iceberg" and prevention issues, were considered in the pilot.

The results of this pilot study were welcomed by the technical experts of the ECDC's Advisory Forum in May 2007, who suggested that they be published in an article in a peer-reviewed journal. The Advisory Forum also endorsed the recommendation to launch a full EU-wide burden of communicable disease study covering the full range of CDs with the involvement of all relevant institutions in the EU, researchers with interest in burden of disease, the European Commission and the WHO. Steps are in hand to start such a study in 2008 through a call for tender.

I am personally also very impressed by the initial results of the pilot study, which show both the potential and the difficulties of this issue. However, I believe that the EU public health community will meet the challenge and develop the specific methodologies needed to overcome the identified and yet to be identified challenges. This is because we need to continue to invest in all aspects of the fight against CD.

Forty years ago, the United States' Surgeon General, Dr William Stewart proposed that, with the advent of antibiotics and the broad use of vaccines, the war against infectious diseases had been essentially won, and that we now needed to pay attention to other important health issues, such as chronic diseases. However, it is clear today that we have only won a "battle": the "war" will surely continue. Turning to less aggressive vocabulary, perhaps it is a "never-ending dance" [4] in which the human race needs to constantly find new technologies and tools to keep "in step" with changing and new microbes!

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Editorial

Managing Legionnaires' disease in Europe: the need for international collaboration

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Travel and tourism is an increasingly important economic activity throughout Europe and the rest of the world. For example, the number of visits abroad by British residents in 2006 was estimated to be 69.5 million, compared with 66.4 million in 2005 [1]. Ensuring that this large body of travellers is protected from infectious or environmental sources of disease is a major public health goal in the European Union: travellers should have the same level of health protection as residents within all Member States. The European Working Group for Legionella Infections (EWGLI) is contributing to this goal through its surveillance scheme for travel-associated Legionnaires' disease (EWGLINET), which aims to rapidly detect and respond to clusters and outbreaks associated with hotels and other tourist accommodation sites [2]. The public health challenge of managing cases of Legionnaires' disease associated with travel arises from the fact that diagnosis and treatment of infected persons, and investigations into the source of their infections, usually take place in different countries. Close collaboration between countries is therefore essential to address this important public health issue.

European Guidelines for Control and Prevention of Travel-Associated Legionnaires' Disease were introduced in 2002 by EWGLINET to ensure that every country in the scheme responded to case and cluster reports in a standardized way, in order to ensure that European citizens were being protected from further exposure to infection through specific measures adopted in every participant country. In this issue of Eurosurveillance, Rota, Cano-Portero, Che et al outline the experience of implementing these procedures in Italy, Spain and France respectively [3]. These three countries have frequently topped the list for the largest proportion of cases and clusters reported to EWGLINET annually, and therefore have a great deal of experience in managing the public health response and investigation procedures. The paper not only shows the overall success of their work but also shows how travel patterns vary by country visited and by country of residence of the traveller. On average people stayed longer at cluster sites in Spain, seven days compared with Italy five days, and France two days, but in France, a higher proportion of clusters compared with Italy and Spain comprised their own nationals rather than visitors to their country. Interesting though these differences are, the added value of the legionella guidelines is in their consistency of approach in response to clusters. All should be investigated to the same standards regardless of length of stay or country of residence of the cases involved.

Monitoring the use of the guidelines is an important means of identifying which countries have successfully implemented them and of areas where strengthening is required. The use of environmental sampling is an important tool in this process and since the guidelines were introduced the proportion of sites positive has increased over time [4]. The reason for this is probably a combination of improved surveillance and laboratory diagnosis within countries participating in EWGLINET. However, the persistent lack of clinical isolates from cases of Legionnaires' disease hampers EWGLINET's ability to draw definitive conclusions from these data on sources of infection associated with clusters. Nevertheless, any site whose water system is found to be *Legionella*-positive should have measures applied to it to ensure that the bacteria are reduced to non-infectious levels.

The paper by Rota et al highlights the occurrence of further cases in some cluster sites that may be linked to a re-infection or new infection of the site's water system as a weakness in the control and prevention procedures. These so called 're-offending sites' are likely to be a mixture of probable, possible or no source of further cases. Some of these hotels may be re-identified by chance, simply because they feature in a group of hotels used by persons in the cluster alert. The guidelines state that every accommodation site used by cases within their incubation period must be investigated. If *Legionella* are detected at more than one site, including the 're-offending site', further evidence such as clinical isolates for comparison with environmental isolates would be required to indicate that a 're-offence' had occurred. If no *Legionella* are detected at any of the sites, sensitivity of the detection method may be an alternative reason to a true non-detectable level of organisms, again providing an inconclusive result to the investigations. EWGLINET countries must therefore continue to emphasise the importance of thorough risk assessments at cluster sites, not only to ensure that all potential areas of risk are identified and rapidly dealt with, but also to provide the appropriate context in which to interpret environmental sampling results.

We know from the scheme that infection risks may be higher in some countries than others, and also higher in larger hotels than smaller ones [5]. Tourist resorts such as Bulgaria and Thailand have also recently given rise to outbreaks [6,7,8], suggesting that inexperience of legionella control and prevention and poor or inadequate infrastructures and water systems in rapidly developing resorts may be responsible. However, once countries become aware of Legionnaires' disease and its economic damage when outbreaks occur, effective public health action is planned, leading to new legislation or Codes of Practice. These countries will hopefully emulate the successful actions in Europe to control and prevent travel-associated Legionnaires' disease and contribute to its international management. International collaboration is vital to help increase protection for people travelling in Europe and beyond. Italy, France and Spain have shown how their extensive experience of cluster investigations has successfully contributed to this public health aim.

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Editorial

Chlamydia: a major challenge for public health

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Chlamydia trachomatis is the most commonly reported bacterial sexually transmitted infection (STI) in Europe [1]. Genital chlamydial infection causes cervicitis and salpingitis in women and urethritis and conjunctivitis in both men and women. However, chlamydial infections often produce few or no symptoms (in approximately 70% of women and 50% of men) and may remain undetected and untreated. If left untreated, this STI can progress to cause complications with serious consequences on women's reproductive health, including pelvic inflammatory disease (PID) that may lead to ectopic pregnancy and tubal infertility. Chlamydial infection is easily treated with a single dose of antibiotics and is a preventable disease (safe sex, condom use). An important aspect of prevention involves the evaluation of sexual partners to prevent re-infection and further spread of disease.

In many European countries, the incidence rates of chlamydia infection have increased in the past 10 years. In 2005, over 200,000 cases were reported in 17 European countries (known to be an underestimate) [1]. However, in most European countries it is not a notifiable disease. Because of the asymptomatic nature of infections, screening studies contribute largely to our knowledge of chlamydia. In Europe, prevalence rates have shown to range between 2 and 17% in asymptomatic women, depending on setting, population and country [2,3].

Chlamydia infections are widely diffused in the general population and – unlike gonorrhoea and syphilis – appear not to be restricted to a particular risk group, mainly affecting young people, especially young women. The highest incidence is usually reported in the age group 15–24 years, accounting for more than 60% of all cases, as described in this issue in the article of D. Whyte et al., and also in annual STI reports in the Netherlands and United Kingdom [4,5]. In order to control the chlamydial infection disease burden in Europe, screening programmes targeting young people are crucial for early detection and treatment of all infected individuals and their partners.

Chlamydial infection was detected for the first time in 1907 by Giemsa staining by Halberstaedter and von Prowazek [6]. Ever since, the detection has been improved with respect to sensitivity, specificity, time per assay and the laboratory standardisation. The technical development from culture, enzyme-immuno assay (EIA) and direct fluorescent-antibody assay (DFA) to the more recently developed nucleic acid amplification tests (NAATs) have resulted in easy and quick diagnostics for chlamydial infection both in clinical and screening settings. As of today, NAATs (including polymerase chain reaction – PCR) are regarded as the gold standard for chlamydial infection [7]. Current NAATs are usually targeting genes which are present in multiple copies, like all genes on the cryptic plasmid which is present in 10 copies as compared to the chromosomal genes.

In 2006, a new variant of *C. trachomatis* was reported in and by Sweden, designated either as Swedish CT variant (swCT variant) or new variant of *C. trachomatis* (nvCT) [8-12]. It had been detected following an unexpected 25% decrease in the number of infections observed in Halland county, southwest Sweden. The variant contains a 377 base pair deletion in the cryptic plasmid which is the region targeted by the NAATs manufactured by both Roche and Abbott [8]. Patients infected with this variant of *C. trachomatis* would therefore be given a false negative result if tested by a laboratory that used either of these assays as its diagnostic test. Several other diagnostic kits do not target the deleted region and are therefore able to detect the swCT variant (e.g. Becton Dickinson ProbeTec, GenProbe Aptima Combo2 & Aptima CT).

In Sweden, the swCT variant could spread easily in the counties that primarily used the NAATs unable to detect the swCT variant. As described in this issue of Eurosurveillance (article of I. Velicko et al.), chlamydia infection rates have increased considerably since the diagnostic methods were changed. At the same time, the authors argue that the diagnostics may not have been the only factor that contributed to the recently observed increase.

What does this mean for Europe? Given the increasing amount of international travel, the recent growth of STI rates in young people and sexual activity persisting, a further spread of this variant has been anticipated in countries that used diagnostic assays unable to detect the swCT variant. It is of public health importance to assess the risk of possibly widespread undetected chlamydial infections in Europe. The detection of this swCT variant puts an extra burden on chlamydia control programmes in many countries that already have to face continuous increasing trends.

At the moment, the spread of the swCT variant seems to be restricted to Sweden, as presented in this issue in the article by the European network for the surveillance of STI (ESSTI) and the European Centre for Disease Prevention and Control (ECDC) (article of E.J. Savage et al.). There are a number of single case reports from other Scandinavian countries – Denmark (article of S. Hoffmann et al. in this issue) and Norway [13] – as well as Ireland [14]. In this issue, France also reports a new case of swCT that had an unknown link with Scandinavia (article of B. de Barbeyrac et al. in this issue). The emergence of the swCT variant was followed by individual rapid endeavours of the STI expert community to assess the presence of this variant in other countries (dual-testing, re-testing of samples retrospectively or prospectively (article of S.A. Morré et al. in this issue) [15-17]. Rapid dissemination and the exchange of information and strains were facilitated through

the network of ESSTI epidemiologists and microbiologists (http://www.essti.org) and the ECDC [18]. However, despite these many efforts no evidence has yet been found in many other European countries (article of E.J. Savage et al. in this issue) [19]. Most of the identified patients with swCT variant seem to be linked with Sweden or crucial information on epidemiological characteristics is not available. Given the on-going investigations the news of another discovery will travel fast.

In addition, several diagnostic lessons can be learned. Firstly, cryptic plasmid free strains of *C. trachomatis* were reported in the early 1990s, and in 2007 a plasmid free strain was reported again [20,21]. Developing diagnostic assays based on essential genes only will reduce the chance of diagnostically escaped new CT variants. Secondly, dual target NAATs (in part based on essential genes), could also circumvent the problem of missing new variants and, lastly, as is shown in Sweden, the use of different tests in one country in combination with incidence and prevalence monitoring can also be helpful in identifying potential diagnostic problems [8,12,22].

Although the articles included in this issue raise various questions, in particular why the new variant has so far been confined to Sweden, the collaboration and rapid reaction of the STI community to this possible emerging threat to public health can serve as a good example. The sharing of information facilitates action and inventing solutions of the problem. Finally, it is worth pointing out that the current situation in Sweden provides the possibility of studying in a unique setting the transmission dynamics and network identification of chlamydial infection. However, to date no initiatives have been undertaken to address these topics.

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Results of a Europe-wide investigation to assess the presence of a new variant of Chlamydia trachomatis

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In 2006, a new variant of *Chlamydia trachomatis* was reported in Sweden. Three countries – Ireland, Norway, and Denmark – have detected the variant to date, but very few cases in total have occurred. The European network for STI surveillance (ESSTI) and the European Centre for Disease Prevention and Control (ECDC) assessed the potential spread of the variant in other European countries, and concluded that there is currently no evidence that the variant has spread widely across Europe. However, the variant strain has been reported in between 10% and 65% of infected patients in Sweden. It is too early to tell whether the variant will remain confined to Sweden or whether the number of cases will significantly increase. Enhanced surveillance will need to be continued to address these concerns.

Introduction

In 2006, the occurrence of a new variant of *Chlamydia trachomatis* was reported in Sweden [1,2]. The variant had been detected following an unexpected 25% decrease in the number of infections observed in Halland county, southwest Sweden. The variant contains a 377 base pair deletion in the cryptic plasmid, which is the region targeted by the nucleic acid amplification tests (NAAT) manufactured by both Cobas Amplicor, Cobas Taqman48 and Abbott m2000 (manufactured by Roche and Abbott) [1] Patients infected with this variant of *C. trachomatis* would therefore be given a false negative result if a laboratory used either of these assays as its diagnostic test. Other commercially available NAAT tests such as the the ProbeTec Strand Displacement Assay (SDA) (Becton Dickinson), Aptima Combo 2 (AC2) test (Genprobe), and RealArt CT Kit (Qiagen), target other areas of the cryptic plasmid, the 16SrRNA and omp gene respectively and therefore will detect this variant of *C. trachomatis*.

Genital chlamydial infection is the most prevalent bacterial sexually transmitted infection (STI) in many European countries [2] and any reduction in the detectability of infection has potential implications for public health in Europe. Initial data from Sweden showed that 39% of all chlamydia cases detected during one month were caused by the new variant of *Chlamydia trachomatis* [3]. Although the data from Sweden is so far limited, if this turns out to be the true representative proportion of chlamydial infection by the genetic variant in Sweden and this is then replicated across Europe, an inability to detect such a sizeable proportion of chlamydia infection could have serious consequences. Therefore, the European network for STI surveillance (ESSTI) and the European Centre for Disease Prevention and Control (ECDC) decided to assess the potential spread of the new variant in other countries across Europe [4].

Methods

ESSTI and ECDC designed a short survey to address this issue (A copy of the questionnaire is available upon request from the corresponding author). The questionnaire contained six questions and was sent with a cover letter to all ESSTI collaborators, both epidemiologists and microbiologists, in 25 countries (22 EU member states and Iceland, Norway and Turkey) in February 2007. The survey collected information on the type of NAATs used to diagnose chlamydia, the extent to which NAATs are used for chlamydia diagnosis and also requested information on any actions or investigations that a country or laboratory undertook in response to the appearance of the new variant. Finally, a question asked whether guidelines regarding the diagnosis of chlamydia in the respective countries had been issued or changedissued.

Results

In total, 21 countries had responded to the request by the beginning of May 2007, but only 19 were able to provide any information. Four countries did not respond. Several countries submitted more than one questionnaire, as the survey provided the option of describing information either for the whole country, a particular region or for an individual laboratory; two questionnaires were returned from Portugal and Estonia andthree from Slovenia and England, while Ireland provided results from 17 individual laboratories. Ten countries provided information for the whole country, seven provided information from individual laboratories, Finland gave information from a particular region and Estonia submitted data both from a regional source and an individual

laboratory. Seventy-five percent of respondents (n=24/32) based their answers on actual laboratory data.

Table 1 describes the level of NAAT testing for chlamydia in the countries belonging to the ESSTI network and the number of chlamydia diagnoses. The proportion of chlamydia diagnoses performed by NAAT where information was available for the whole country ranged from 12% in Cyprus to 100% in Iceland, Malta, Netherlands, Norway and Scotland. Malta and Iceland were the only countries that used the Cobas Amplicor or Cobas Taqman48 exclusively, although there was widespread use of this test in individual laboratories in other countries (Figure 1). The Abbott m2000 assay which is also unable to detect the variant was only used in three countries and accounted for only a small number of routine diagnostic tests; France (<5%), Netherlands (5%) and Sweden (3.8%).

Twelve respondents reported that action was or is in the process of being undertaken in their country to assess whether the variant was present. Countries used one or a combination of the following three approaches: Retrospective testing, dual testing and monitoring of surveillance data (Table 2). Retrospective testing of samples was carried out in Denmark, France, Sweden, England, Finland and the Netherlands with varying approaches either by retesting specimens that had tested negative using a test unable to detect the variant or retesting samples that originally tested positive by a test known to detect the variant. New national guidelines for testing were issued in Sweden for laboratories changing from the Cobas Amplicor, Cobas Taqman48 and Abbott m2000 to other tests such as the ProbeTec Strand Displacement Assay (SDA) (Becton Dickinson). In Denmark, the National Board of Health wrote to laboratories recommending that they should either change to a method which could detect the mutant or to forward the specimen to another laboratory.

Table 1

Information provided by country, region and laboratories on proportion of chlamydia testing by NAAT and total number of tests and diagnoses in 2006

Country	Proportion of chlamydia cases diagnosed by NAAT (%)	Proportion based on data or estimate	No. of NAAT tests	No. of chlamydia diagnoses by NAAT	Action taken to investigate presence of variant?
Country Level					
Cyprus	12	Estimate	530	61	No
Denmark	99.9	Data	324431	24866	Yes
France	63[1]	Estimate	500000	NK	Yes
Iceland	100	Data	17202[2]	1641[2]	Yes
Malta	100	Data	1106	46	No
#Netherlands	100	Estimate	57892	5989	Yes
#Norway	100	Data	273741	19973	Yes
#Scotland	100	Data	222709	17289	Yes
Sweden	95	Data	427551	30892	Yes
Turkey	70	Estimate	188	2	No
Region Level					
Estonia 1	85	Estimate	36209	1905	No
Finland	100	Data	53000	3169	Yes
Laboratory Level					
Austria	100	Data	20000	740	Yes
Belgium	100	Data	2075	138	No[3]
England 1	100	Data	22964	1936	Yes
England 2	100	Data	95500	9200	Yes
Estonia 2	100	-	13500	2500	No
[4]Ireland 1	100	Data	20000	2000	Yes
Ireland 2	100	Data	15895	NK	No
Ireland 3	100	Data	8180	666	No
Ireland 4	100	Data	1800	143	No
Ireland 5	100	Data	1361	103	No
Ireland 6	100	Data	2766	99	No
Ireland 7	100	Data	24005	1687	No
Ireland 8	-	-	60	0	-
Ireland 9	100	Data	1320	92	No
Portugal 1	100	Data	2768	222	Yes
Portugal 2	100	Estimate	4200	263	No
Slovak Republic	100	Data	5306	10	No
Slovenia 1	70	Data	1007	122	No
Slovenia 2	48.9	Data	263	27	No
Slovenia 3	12.6	Data	22	NK	No

Data from 2005

[1]Private Laboratories only

[2]Data from 1 lab only. One other lab does chlamydia testing but total number of tests is unknown.

[3]Laboratory routinely screens with SDA ProbeTec and Amplicor. No increase in discordant results seen.

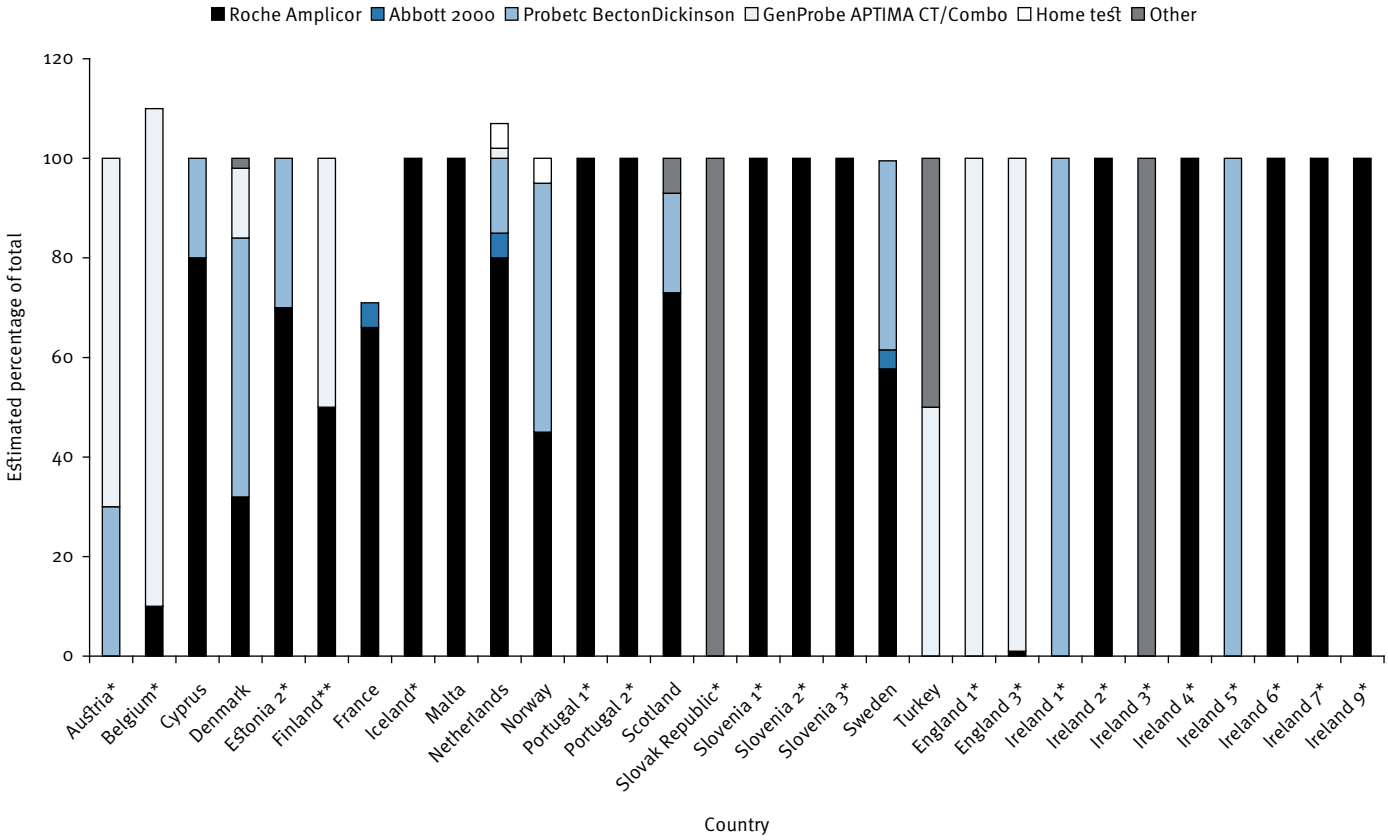
[4] A further 8 labs surveyed in Ireland do not carry out chlamydia testing

- Missing data

NK: Not Known

Figure 1

NAATs used for routine diagnosis of C. trachomatis



Discussion

This survey attempted to assess the potential spread of the new variant across Europe. However, it was not feasible in the available timeframe to survey directly all laboratories, both private and public, that carry out chlamydia diagnostics across Europe. A possible bias in the survey is that data is more likely to have been obtained from public laboratories, but there is no reason why the type of tests used would differ significantly in private laboratories. Although the results of this survey can not be considered comprehensive for all European countries, 10 respondents were able to provide information for the whole country and a further four countries surveyed more than one laboratory. The coverage obtained is therefore considered sufficient to determine whether the variant has spread outside Sweden to a great extent. Since the first report of the new variant, several European countries have undertaken extensive investigations to determine whether the variant is present in their country. Despite this active surveillance, only three countries – Ireland, Norway, and Denmark – have detected the variant to date and very few cases in total have occurred. Two cases of the new variant have been reported in both Norway and Ireland. One of the cases in Norway was of Swedish origin [5]. Similarly, in Ireland, one of the two cases, who were partners, was also of Swedish origin [6]. Since the questionnaire was completed, a single case of the variant has also been detected in Denmark – this case had no known link to Sweden [7]. Further epidemiological information on these cases of the new variant is currently unknown.

There is therefore no existing evidence that the variant has spread widely across Europe even into neighbouring countries and yet in Sweden the variant strain has been reported in between 10% and 65% of the total number of infected patients [8,9]. It is not known when the variant first appeared in Sweden but the increase in prevalence has been both rapid and recent. In Sweden, a considerable increase in chlamydial infection (53%) was reported in the first six months of 2007, compared to the same period in 2006. (Blaxhult, abstract isstdr page 391). It is unclear why the variant is present in such a sizeable proportion of cases in Sweden and yet has not made an impact in other countries. It may be present at very low levels in other countries but the results of the survey suggest that, following the extensive search for the variant by many countries, it would have been detected if it was present in the testing population. A possible reason why the variant does not appear to have spread outside Sweden may be found in a study carried out in one county in Sweden which reported that 79% of all sexual partners of chlamydia cases lived within 100km of each other [8]. Sex abroad may not be a significant risk factor for the acquisition and hence spread of chlamydia infection unlike in the case of other STIs such as syphilis where it is well documented. In Sweden, it has been hypothesised that a number of factors are present that may have resulted in selection of the variant, for example the high number of diagnostic tests carried out almost exclusively by the Roche assay, the lack of contact tracing performed for false negative persons and the treatment of symptomatic patients only [10].

TABLE 2

Details of Investigations carried out across Europe

Country	Type of Investigation	Initial Test Used	Current Test Used	Population or setting	Sample size
Austria	Dual Testing	NK	NK	NK	N=300-400
Denmark	Retrospective Testing of specimens found positive or negative at other laboratories	Cobas Amplicor/, Taqman48 (Roche), (ProbeTec (SDA, Becton Dickinson)	Three SSI Chlamydia trachomatis-PCR methods	5 Departments of Clinical Microbiology	N=1077
	Dual Testing	NK	Three SSI Ct-PCR methods	Since October 2006 3 methods have been used for all Ct-PCRs at SSI, 1 of which can identify the mutant	N=2620
	Data: examine no. positive by month by method from 1 Jan 2004 to 31 Dec 2006	NK	NK	National mandatory surveillance registry of laboratory diagnosed chlamydia	2004: 21624 2005:23854 2006:24866
England	Retrospective Testing of previously negative samples	Cobas Amplicor/, Taqman48 (Roche)	Aptima Combo 2 (AC2) test (Gen-Probe)	1) Newcastle area 2) Genitourinary Medicine clinic	1)n=683 2) n=>1000
	Retrospective Testing of previously positive samples	Unaffected platform	In-house nested block based PCR assay	1) MSM patients from 30 GUM clinics 2) Primarily heterosexual patients from London, Portsmouth, Plymouth, Harrogate, Nottingham	1) n=179 2) n=933
Finland	Retrospective Testing	NK	NK	NK	NK
France	Retrospective Testing of previously negative samples	Cobas Taqman48, (Roche)	Cobas Taqman48, (Roche)and omp2 home test	Male and Female with risk factors	N=40
	Retrospective Testing of previously positive samples	An unaffected platform	Cobas Taqman48, (Roche)	Samples from a private lab which receives nationwide samples	N=500 in 2006
	Dual Testing	NK	Cobas Taqman48, (Roche)and omp2 home test	1)STD/HIV testing clinics in Bordeaux 2) Family planning clinics in Paris 3)Private lab in Paris dealing with mainly MSM 4)Adolescent clinic	1) n=252 male, 199 female 2) n=100 3) n=100 4) n=132
	Prospective testing during 2007	An unaffected platform	Cobas Taqman48, (Roche)	Samples from a private lab which receives nationwide samples	In progress
Iceland	Dual Testing	Cobas Amplicor/, Taqman48 (Roche)	Cobas Amplicor/, Taqman48 (Roche) and Becton Dickinson	All urine samples sent to Dept of microbiology Feb-May 2007	Approx n=4000
Ireland	Dual Testing	ProbeTec (SDA, Becton Dickinson) and Cobas Amplicor/, Taqman48 (Roche)	ProbeTec (SDA, Becton Dickinson) and Cobas Amplicor (Roche)	Department of Microbiology, St James Hospital, Dublin	NK
Netherlands	Retrospective Testing of previously positive samples	Validated in-house Taqman assay	NK	Academic centre	NK
	Dual Testing	NK	Cobas Amplicor/, Taqman48 (Roche)) and ProbeTec (SDA, Becton Dickinson)	High-risk attendees from 3 STI clinics in Amsterdam	NK
Norway	Data: no. tested/no. positive by test method	NK	NK	NK	NK
Portugal	Dual Testing	Cobas Amplicor/, Taqman48 (Roche)	Cobas Amplicor/, Taqman48 (Roche)	1 large private lab	N=4200
	Data: examine no. tested/no. positive by month in 2005 and 2006 Dual Testing when justified by clinical signs	Cobas Amplicor/, Taqman48 (Roche)	Cobas Amplicor/, Taqman48 (Roche) and ompA home test	Chlamydia-Neisseria Laboratory of the Portugese National Institute of Health	N=2768
Scotland	Dual Testing	NK	Cobas Amplicor/, Taqman48 (Roche)and Aptima Combo 2 (AC2) test (Gen-Probe)	1 large testing lab	N=3000
Sweden	Retrospective Testing of previously negative samples	Cobas Amplicor/, Taqman48 (Roche)Taqman48 and Abbott m2000	ProbeTec (SDA, Becton Dickinson)	Some laboratories	NK
	Dual Testing	NK	Cobas Amplicor/, Taqman48 (Roche) and Abbott m2000 and ProbeTec (SDA, Becton Dickinson)	Some laboratories	NK

NK: not known

Conclusions

The presence of a *C. trachomatis* variant that is not detectable, hence causing false negative test results, has serious implications for patient management, care and the transmission of *C. trachomatis* in the population. Therefore, experts in all EU Member States should remain vigilant. More epidemiological information regarding the affected population needs to be collected in order for targeted public health measures to be undertaken. The emergence of the variant suggests it may be more appropriate for any NAAT to include dual targets which is being considered by test manufacturers [8]. It is too early to tell whether the variant will remain confined to Sweden or whether the number of cases will significantly increase. Enhanced surveillance will need to be continued to address these concerns. ESSTI and ECDC aim to repeat the survey at the end of the year to determine if the picture across Europe remains the same.

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Reasons for the sharp increase of genital chlamydia infections reported in the first months of 2007 in Sweden

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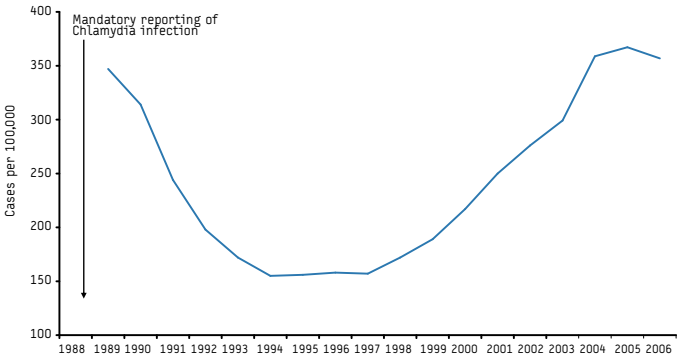
After a continuous increase in the reported chlamydia incidence over the past 10 years in Sweden, the incidence decreased by 2% in 2006. A new genetic variant of Chlamydia trachomatis (nvCT) was discovered in Sweden in October 2006 that could not be detected by some of the commonly used diagnostic tests, which led to underreporting of chlamydia cases. This variant has also been called "swCT" by some authors. After the switch at the end of 2006 to other diagnostic tests that can detect nvCT, the reported incidence rose considerably (75 per 100,000 population) in the beginning of 2007. The objective of this study was to explore alternative explanations for this increase and to propose further action if needed. A data quality check was done in order to exclude double reporting and delayed reporting. To compare the incidence of chlamydia and the proportion of the population that was tested, we divided the Swedish counties into two groups, according to the diagnostic test used. We estimated the chlamydia incidence trend for January and February in the years from 2000 to 2005 by regression model, and predict the chlamydia incidence for the same period in 2006 and 2007. The age and sex distribution of the cases in January and February did not differ between the years 2000 to 2007. The proportion of tested people increased on average by 5% every year. If we assume that the percentage of the population that was tested had been 20% higher in 2007 than in 2006, the incidence predicted by the model for January and February 2007 is exactly the same as the incidence that was actually observed. The change of diagnostic test and an increase in the number of people tested, as well as the increase in the prevalence of CT have probably all contributed to the increased numbers of reported chlamydia cases in January and February 2007. These findings support the need for enhanced prevention campaigns in order to control spread of CT.

Introduction

Reported *Chlamydia trachomatis* (CT) cases have increased substantially in the past 10 years and have become by far the most common sexually transmitted infection (STI) in Sweden (Figure 1) [1]. The number of cases reported to the national surveillance system increased from 13,905 (157 per 100,000) in 1997 to 32,281 cases (359 per 100,000) in 2004, representing a rise of over 120%. In 2005, the annual reported incidence increased only by 2%, and even decreased by 2% in 2006. One reason for this decrease may have been the emergence of a new genetic variant of *Chlamydia trachomatis* (nvCT) in October 2006 that can not be detected by some of the diagnostic tests commonly used in Sweden [2,3]. As a result, chlamydia diagnoses were missed and the national rates of chlamydia cases were underestimated in 2006 [4].

Figure 1

Chlamydia infection incidence in Sweden, 1989-2006



The nvCT was found to be widely spread in Sweden and its proportion varied between counties from 10% to 65%, leading to false negative results [3,5]. Laboratories in 13 of the 21 counties in Sweden had used diagnostic kits in 2006 that did not detect nvCT (Roche Diagnostics and Abbott Laboratories), while laboratories in eight counties had used diagnostic kits by Becton Dickinson that could detect both wild-type CT and nvCT. In order to improve diagnosis of the nvCT, the use of other PCR testing kits (Becton Dickinson or Artus) and/or culture was recommended [6]. An overview by the Swedish Institute for Infectious Disease Control showed that, by March 2007, all laboratories (except one) had switched to one of the suggested diagnostic kits. This change made it possible to diagnose chlamydia infections caused by nvCT and to perform non-interrupted contact tracing, resulting in a renewed increase in reported cases. In the beginning of 2007, the Swedish Institute for Infectious Disease Control noticed a sharp increase in reported chlamydia cases through the electronic reporting system. The incidence of chlamydia in the two-month period of January and February 2007 was 38% higher than the incidence during the same period in 2006. This raised the question: Can this increase be explained only by better diagnosis of nvCT infections? The objective of this study was to explore alternative explanations for the increase and propose further action if needed. Based on available surveillance data several alternative hypotheses were developed. One of the alternative hypotheses is an increase in the testing activity in the beginning of 2007. Another alternative hypothesis is a continued increase in the prevalence of chlamydia infection. Before the hypotheses were tested, we considered the data quality with regards to double reporting or delayed reporting to the system.

Methods

Surveillance system

Genital chlamydia infection is a mandatorily notifiable disease in Sweden under the Communicable Disease Act from 1988 [7]. Partner notification and contact tracing are also routinely performed [7]. The report of a chlamydia case to the national surveillance system contains an individual laboratory notification from the diagnostic laboratory and an individual clinical notification from the health care professional. Notifications do not contain the name of the patient but are coded, based on the social security number (*personnummer*). In addition, all laboratories that perform testing for CT report on a voluntary basis the number of people tested and the number found positive for CT every six months. These data are available in electronical format since 2000.

Quality check for reported cases

Double reporting or delayed reporting of chlamydia cases was checked for every month in 2006 and for January and February in 2007. The time between clinical diagnosis and reporting was compared. Reporting of a clinical case more than one week after diagnosis was defined as a delay. In Sweden, all positive laboratory findings for CT with the same code within a three-month period are considered as new infections.

Grouping of counties according to diagnostic methods

We divided all 21 Swedish counties into two groups based on the diagnostic kits used by their laboratories in 2006: Group A/R used Cobas Amplicor (Roche Diagnostics), Cobas TagMan48 (Roche Diagnostics) or Abbott *m*2000 (Abbott Laboratories) and were unable to detect nvCT. Group BD used the ProbecTec ET kit by Becton Dickinson that is able to detect nvCT. According to this division, 13 counties were included in Group A/R and eight counties in Group BD (including county Västra Götaland, where three out of four laboratories had used Becton Dickinson diagnostic kit and one the Roche diagnostic kit).

Chlamydia cases and incidence

Reported cases in the period of January and February were described in terms of the total number, proportion of males and females, median age, and the reporting county. The incidence of chlamydia was calculated as all reported chlamydia cases per 100,000 population during January and February in the years 2000 to 2007. The national incidence and the incidence per group (A/R and BD) were calculated as geometric means of the incidence of the respective counties.

Testing for C. trachomatis

In order to quantify to what degree the different counties invested in finding new chlamydia cases, we calculated the proportion of the population between 15 and 49 years of age that was tested for chlamydia. This particular age group is tested most frequently and with the highest incidence (ca. 90% of all reported cases). Since it was not possible to obtain the specific data on tests performed in January and February, the annual number of tests was used instead.

Trend estimation

A negative binomial regression model was used to study the time trend of chlamydia cases in January and February in 2000 to 2005. The year 2006 was excluded due to underreporting of nvCT. To model the incidence of chlamydia in January and February, the following variables were included in the model:

a) county group A/R or BD (according to diagnostic kits used),
b) proportion of the population in age group 15 to 49 years tested in each county,
c) year.

We also added an interaction effect of method and time, as differences between the two diagnostic kits could have been exacerbated by the spread of the nvCT over time. The initial model with i=1, ...21 (county) and j=1,...6 (year) was:

$$\log(\text{cases}_{ij} / \text{pop}_{ij}) = \beta_0 + \beta_1 \text{year}_j + \beta_2 \text{proportion tested}_{ij} + \beta_3 \text{group}_i + \beta_4 \text{group}_i * \text{year}_j .$$

All calculations were based on data from individual counties. Based on the model, a prediction of cases was done for January and February 2006 and 2007. Since the proportion of tested individuals is not yet available for 2007, two scenarios were used. The proportion of persons tested in 2007 was assumed to be:

1. 5% more than in 2006 in each county, which represents the average annual increase.
2. 20% more than in 2006 in each county (extreme scenario).

The differences between the observed and predicted incidence were summarized as mean values.

Results

Quality check

The quality check for reported chlamydia cases revealed that every month, 1-2% of cases were reported with a delay. This was consistent throughout the year 2006 and also in January and February 2007. No double reporting of chlamydia cases was discovered.

Description of cases

During January and February 2007, a total of 6,903 chlamydia cases were reported to the national surveillance system. Compared to the same period in 2006, this was an increase of 38%. The distribution of the cases by sex and median age was similar to that observed in the previous years (Table 1). The median age was 21.4 years for females and 24.1 years for males.

Table 1

Characteristics of chlamydia cases in Sweden, January-February period of 2000-2007 (n=36,339)

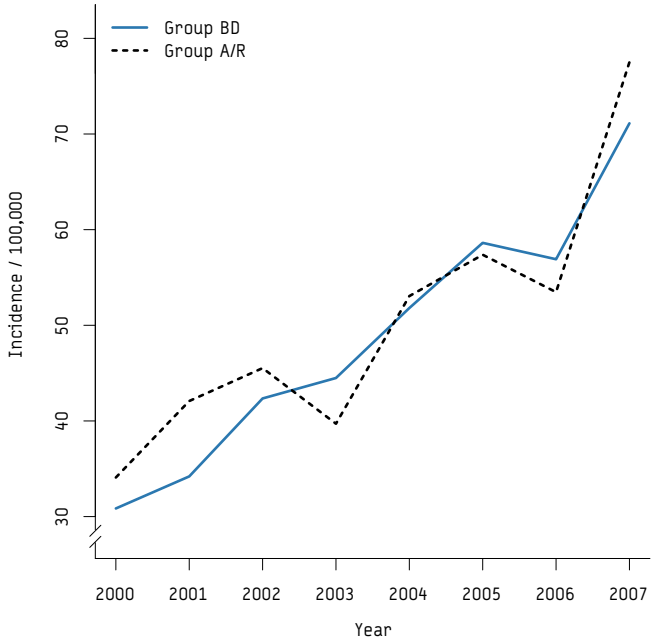
	2000	2001	2002	2003	2004	2005	2006	2007
Number of cases:	2,982	3,542	4,023	3,898	4,880	5,100	5,011	6,903
Female (%)	56.7	55.4	56.6	56.9	56.2	56.2	57.5	57.1
Male (%)	43.3	44.6	43.4	43.1	43.8	43.8	42.5	42.9
Median age (years):								
Female	22.3	22.1	22.2	21.9	21.7	21.9	21.7	21.4
Male	25.0	24.9	24.9	24.5	24.4	24.5	24.8	24.1

Chlamydia incidence

Between 2000 and 2005, the trend of reported chlamydia incidence in the period of January and February was increasing in all counties (Figure 2). In 2006, however, the reported chlamydia incidence decreased both in the counties of group A/R and in those of group BD, and then increased again in 2007.

FIGURE 2

Chlamydia incidence in Sweden (grouping of counties according to diagnostic kit used in 2006#), January-February period of 2000-2007



Group BD: counties that used Becton Dickinson kit.
Group A/R: counties that used Abbot or Roche kit.

Chlamydia cases were reported in all 21 counties (Table 2). Some variation in reported incidence was observed in each county year by year (Table 2). The 2006 decrease in incidence was apparent in 13 counties and in the national incidence, while the increase in reported incidence observed in 2007, affected all counties.

Testing for C. trachomatis

Figure 3 shows the proportion of the population aged between 15 and 49 years that were tested in both groups of counties. From 2000 to 2006 there was, on average, 2% more testing in Group A/R than in Group BD. In both groups of counties there was an upward trend in the proportion of the population tested for chlamydia.

Model estimation

We found that neither the effect for '*group*' nor that for the interaction '*group*year*' were significant in the model, meaning there were no differences in the trend between groups of counties. However, the general trend ('*year*', p-value < 0.001) and the proportion of the population tested (p-value < 0.001) were highly significant. Therefore the final model included only the significant factors, with i=1, ...21 (county) and j=1,...6 (year):

$$\mathbf{log}(cases_{ij} / pop_{ij}) = \beta_0 + \beta_1 year_j + \beta_2 proportion\ tested_{ij} .$$

The model estimated an increase of 8.4% (95% confidence interval 5.8%-11.0%) in incidence per year, given a constant proportion of tested individuals. An assumed increase of 5% in testing in the same year would result in an increase in incidence of 24%. Figure 4 shows the estimated versus the reported incidence for 2000-2005 in all counties in Sweden according to this model.

We predicted the national incidence in 2006 to be 63 per 100,000 population, using a proportion of tested individuals reported in that year. The model overestimated the reported incidence in almost all counties, as well as at national level (observed incidence 55 per 100,000 population). The mean error, however, was smaller among BD counties with –3.6 compared to –10.1 in A/R counties.

TABLE 2

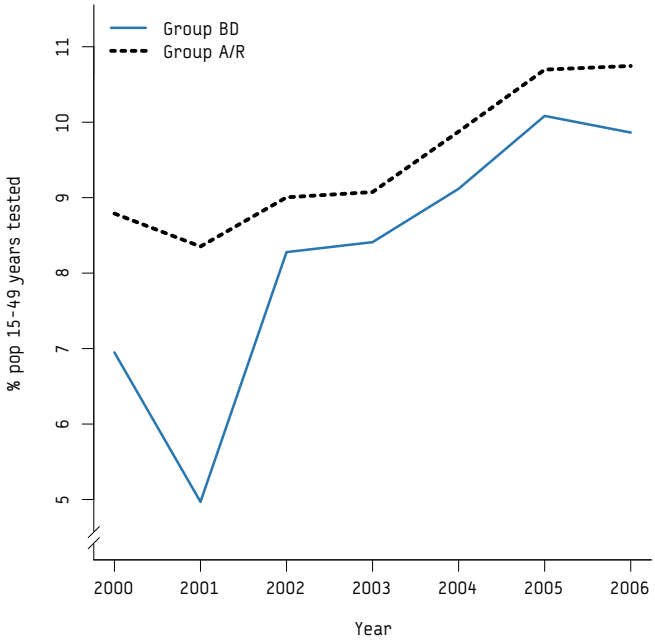
Reported chlamydia incidence per 100,000 population in Sweden by county, January-February period of 2005-2007

County	2005	2006	2007
Group A/R#			
Dalarna	58.7	44.2	170.8
Gotland	52.2	71.6	73.3
Gävleborg	69.6	57.7	66.0
Halland	58.4	46.7	67.5
Kalmar	54.3	45.8	91.1
Kronoberg	51.6	36.2	59.6
Skåne	60.0	57.0	76.1
Stockholm	56.4	59.5	76.8
Södermanland	66.8	62.0	122.0
Värmland	63.7	61.8	65.5
Västernorrland	46.4	52.9	68.9
Örebro	51.8	48.0	56.7
Östergötland	60.5	62.7	66.0
Group BD#			
Blekinge	53.1	52.8	65.4
Norrbotten	76.7	50.4	56.4
Uppsala	68.0	58.5	80.6
Västerbotten	44.6	45.8	56.7
Västmanland	62.4	72.0	92.6
Västra Götaland	43.9	48.4	66.3
Jämtland	74.8	85.8	88.2
Jönköping	55.1	51.6	71.8
Geometric mean of Incidence (Sweden)	**57.8**	**54.8**	**75.0**

Group BD: counties that used Becton Dickinson kit. Group A/R: counties that used Abbot or Roche kits.

Figure 3

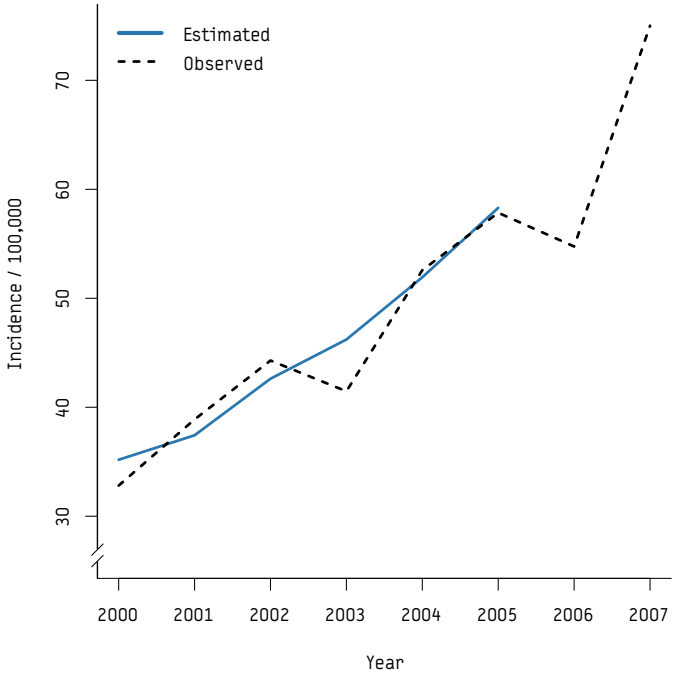
Proportion of 15- to 49-year-olds tested for *Chlamydia trachomatis* annually in Sweden by county group#, 2000-2006



Group BD: counties that used Becton Dickinson kit.
Group A/R: counties that used Abbot or Roche kit.

Figure 4

Observed chlamydia incidence in Sweden, January-February 2000-2007 and estimated chlamydia incidence in Sweden, January-February 2000-2005



The incidence for 2007 was estimated using two scenarios. When it was assumed that 5% more people were tested in each county in 2007 than in 2006, the model estimated a national incidence of 70 per 100,000 population in January and February. When it was assumed that 20% more people were tested in 2007, the predicted incidence was 75 per 100,000 population. The latter gives a prediction close to what was actually observed this year (mean error per county: 2.5).

Discussion and conclusions

The emergence of the new genetic variant of *C. trachomatis* (nvCT) in 2006 led to a temporary decrease in the number of diagnosed cases. In early 2007, a renewed increase in chlamydia incidence was observed. This was expected after the change to diagnostic kits that were able to detect nvCT. The cases did not differ from previous years in terms of age and sex distribution or geographical distribution. We also excluded the possibility of delayed and double reporting as a reason for the increase. However, our comparison of counties using different diagnostic kits showed that the sharp increase in 2007 could not be solely explained by switching the diagnostic method, since rising numbers of CT were also noted in those counties that had already in 2006 used kits that can detect nvCT. This suggests that other factors could have played a role, such as a higher number of persons being tested and/or a higher CT prevalence in the population.

In almost all counties, our statistical model predicted a higher incidence for 2006 than that actually observed. This supports an effect of underreporting due to undetected cases of nvCT already in January and February 2006. When we assumed that 20% more people were tested in 2007 than in 2006, the predicted incidence for January-February 2007 was the same as the observed incidence. The situation with the newly emerged CT variant was widely covered by mass media in Sweden by the end of 2006, contributing to better knowledge on chlamydia diagnostic problems and possible false negative results. This could have led to increased testing for CT in the beginning of 2007, induced both by health professionals and patients themselves.

An additional explanation for the higher incidence could be a continuous increase in the prevalence of chlamydia in the population, as has been described earlier in Sweden [8]. This explanation was also supported by our model.

Several limitations could influence our results. Firstly, our model did not take into consideration size of population, age distribution, testing policy, or the degree of partner tracing in the different counties, which could influence our results. In addition, we assumed that the number of tests performed during the entire year was proportional to the number of tests performed in the period of January and February. Neither did we investigate other possible explanations such as a change in sexual behaviour that could contribute to increased spreading of CT.

The sharp increase in January and February 2007 is misleading if compared to the same period in 2006 without taking into consideration the underestimated rates in 2006. Due to the fact that the diagnostic methods failed to detect nvCT in 2006, cases remained undiagnosed and as a result the contacts of these cases were not traced. This led to an accumulation of chlamydia cases and further spread. We can expect to see this effect in those 13 counties in Sweden that had used diagnostic kits unable to detect nvCT. However, more active testing due to the reasons described above or an increase in the prevalence of CT are likely to have contributed to the increased incidence in January and February 2007.

Published reports from other European countries have so far shown limited evidence of spread of the nvCT outside of Sweden [9,10]. Sporadic cases were reported from neighbouring countries such as Denmark and Norway [11,12]. However, sexual contacts during international travels could lead to spread of this genetic variant to other countries as well. Detection of the nvCT through the surveillance system can take time, as was the case in Sweden where the decrease of chlamydia notifications in some counties was masked by the overall national rates. Therefore epidemiological and laboratory vigilance are important not only at national but also at local level. Continuous evaluation of diagnostic tests is necessary. Sexual health promotion needs to be intensified in order to effectively control the spread of sexually transmitted diseases in general. Sweden has intensified prevention campaigns with information in mass media, Internet and cinemas, condom distribution to teenagers, etc. in the summer of 2007 [13].

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Mutant Chlamydia trachomatis in Denmark

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A mutant Chlamydia trachomatis variant was detected in Sweden in 2006 and has since also been diagnosed in Norway, but not in Ireland or the Netherlands. This paper describes a study aimed at assessing the presence of the new variant in Denmark. Between November 2006 and April 2007 we tested 3,770 specimens using methods capable of detecting the new variant and distinguishing it from the wild type. In late March 2007 we found one case of the new variant in a 19-year old Danish woman without any known relationship to Sweden. It is surprising that the spread of this sexually transmitted pathogen into Denmark and within Denmark has been so low in view of its rapid and substantial spread within Sweden.

Background

During late summer 2006, the presence of a mutant variant of *Chlamydia trachomatis* (CT) was discovered in Sweden, after a decrease in the number of CT PCR positive urogenital specimens was observed in one county (Halland) between November 2005 and August 2006 [1]. The routine diagnostic method of this county's laboratory was PCR targeting the cryptic plasmid. Subsequent analyses conducted with a different method (Artus) targeting the major outer membrane protein (MOMP) chromosomal area revealed a CT prevalence corresponding to the usual level. Successive sequencing of specimens found positive with the latter method showed that a new clone of CT had emerged, differing from the usual CT strains by a 377 base pair deletion in the cryptic plasmid.

Several commercially available test kits for the laboratory diagnosis of CT are unable to detect the new variant because they target this specific area of the cryptic plasmid: Roche Taqman 48, Roche COBAS Amplicor, and Abbott m2000. Two other diagnostic kits employ other targets and are therefore able to detect the new variant: Becton Dickinson ProbeTec, and GenProbe Aptima Combo2 and Aptima CT.

To date, several reports have documented the spread of the new variant to other counties in Sweden [2-4] and various initiatives have been undertaken to detect its possible spread to other countries. In Ireland [5] the new variant was not detected in any of 8,797 samples collected between July and December 2006. In the Oslo area, Norway, the new variant was diagnosed in two female patients, one Swedish and one Norwegian, among 409 patients who had been tested between late November 2006 and early February 2007 [6]. In Amsterdam, the Netherlands, a study published in 2007 reported no detection of the new variant among 515 visitors to an outpatient STI clinic [7].

In Denmark, the mandatory laboratory CT surveillance is based on quarterly submission of data on specimens found positive for CT at the diagnostic laboratories in each county. The data include the total number of samples examined per quarter and the number of positive results. For the latter, additional information is provided on patient's sex and age, body site the sample was taken from (cervical, urethral, anorectal) and the date it was collected, as well as type of the health care provider and laboratory method used. An analysis of these data stratified by month and laboratory method for the period from January 2004 through December 2006 did not suggest a decline in the number of positive specimens that could be attributed to the diagnostic method as described above in case of Sweden. Nevertheless, in order to closely monitor the possible emergence of this variant in Denmark a surveillance plan was arranged in co-operation with some of the diagnostic laboratories.

Methods

Sampling

The 15 counties in Denmark, with a total of 5.4 million inhabitants, are served by 17 laboratories performing CT diagnostic assays. Nine of these employ methods incapable of detecting the new variant. From 1 November 2006 through 3 April 2007, i.e. for about five months, a voluntary surveillance system was employed in which specimens initially assayed in other laboratories were subsequently tested in our laboratory at Statens Serum Institut (SSI). One laboratory using the ProbeTec method capable of detecting the new variant submitted 50 positive and 50 negative specimens in November 2006, and 50 positive ones in March 2007. Four other laboratories using Roche methods incapable of detecting the new variant submitted a total of 977 negative specimens and 23 positive specimens. During the study period, further 2,620 samples were sent for routine testing at SSI directly by clinicians.

Diagnostic method

Our standard CT diagnostic method has been described previously [8]. In short, the cryptic plasmid was amplified with primers identical to those used in the Roche Amplicor assay and all positive results were confirmed with primers amplifying a part of the 16S rRNA gene. Both assays contained an internal control for inhibition. Samples were tested with both primer-sets, thus allowing detection of the new variant. For the purpose of documenting that the lack of amplification with the plasmid primer was due to the mutation present in the new variant, a PCR using primers flanking the deletion in the new variant was applied [9]. This assay was originally designed as a dual-probe real-time assay, but we used it without the probe in a conventional gel-based assay where the new variant and the wild-type could be distinguished by the difference in size of the amplified product.

Results

During the five-month period from 1 November 2006 through 3 April, 2007, a total of 3,770 specimens (2,620 samples received for routine testing and 1,150 submitted by other labs) were examined in our laboratory with both plasmid and 16S rRNA gene PCRs. Only one case of the new CT variant was detected (Table). It was found in late March in a specimen from a Danish 19-year-old woman from the Copenhagen Capitol area, who had tested positive also with the ProbeTec CT-assay (Becton Dickinson) at the primary laboratory. She reported having had a steady relationship for one year and no contact to Sweden. No specimens were available from the partner.

Table

Number of specimens submitted for CT testing at Statens Serum Institut, Denmark, between 1 November 2006 and 3 April 2007

Origin of specimens	Number of laboratories	Results at submitting laboratories	Number of specimens		
			Submitted to our laboratory	Positive with our standard assay	Positive with our supplementary assay (*)
Laboratories using methods incapable of detecting the new variant	4	Positive	23	23	ND
		Negative	977	3	ND
Laboratories using methods capable of detecting the new variant	1	Positive	100	100	1
		Negative	50	1	ND
Sent directly from clinicians	Not applicable	Not applicable	2,620	255	ND
Total			3,770	382	1

(*) Positive in PCR using deletion-flanking primers giving rise to a PCR product of smaller size [9].

Among the 1,027 specimens that had tested negative at other laboratories, four were positive in both assays of our standard methods. Among the 123 specimens that had been diagnosed as positive for CT at other laboratories, all were positive with the 16S rRNA gene assay whereas the one new variant strain was negative in the plasmid PCR.

Discussion and conclusion

Sexually transmitted infections are unlikely to respect national borders, especially in an extended period of time. It was therefore an unexpected finding that only one case of the new CT variant was detected among 3,770 specimens tested during a five-month period. The samples were submitted from the whole of Denmark, although the majority came from the Copenhagen area. Considering the intense daily traffic between the Copenhagen area in Denmark and southern parts of Sweden, it is surprising that the spread occurred so late. One reason could be that the vast majority of CT testing in the Greater Copenhagen area is performed with assays capable of detecting the new variant, consequently leading to containment of the new variant. However, this explanation is not valid for Northern Jutland, where the new variant was not detected either and the traffic between Denmark and Sweden is also quite intense.

The emergence of a new bacterial variant capable of escaping laboratory diagnosis emphasises the need to avoid reliance on a single assay and to use genes of known and essential function as targets for NAATs. Although the prevalence of the CT variant outside Sweden is still low, its occurrence in Norway and Denmark indicates dissemination. It is therefore likely that it will also appear soon in other European countries.

Added in proof

In June 2007, i.e. after the submission of this report, the new CT variant was found in a first void urine specimen collected from a 62-year old man on Bornholm, a Danish island near Sweden.

Acknowledgements*

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Monitoring the potential introduction of the Swedish Chlamydia trachomatis variant (swCT) in the Netherlands

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This report describes the actions of public health experts in cooperation with specialists in sexually transmitted diseases (STD), epidemiologists and (molecular) microbiologists to investigate the possible introduction of the swCT variant in the Netherlands:

1. Investigating trends in CT epidemiology

Result: STD surveillance and laboratory surveillance did not show any evidence of the introduction of the swCT variant in Holland.

2. Retesting samples by TaqMan PCR

Result: Roche CT-negative samples suspected to be CT-positive on the basis of the clinical picture were retested by swCT TaqMan but did not harbour the swCT variant

3. Screening sample pools for the presence of the swCT variant

Result: Four different sample pools covering a wide geographical range were tested by specific swCT Taqman assay, but the swCT variant was not detected in any of them.

In conclusion, to date the swCT variant has not been found in the Netherlands. However, ongoing monitoring is needed until Roche and Abbott have adapted their CT nucleic acid amplification tests (NAATs) to detect the new variant.

Background

Recently, in the county of Halland, Sweden, a new *Chlamydia trachomatis* variant (swCT variant) with a deletion of 377 bp in the cryptic plasmid has been reported [1,2]. This swCT variant has also been designated as new variant *C. trachomatis* (nvCT). The deletion was found in the target area for two commercial CT nucleic acid amplification tests (NAATs) (Roche and Abbott) leading to false negative results when screening patients infected with this new Swedish variant [2]. In some regions in Sweden, a 24-78% reduction in the CT prevalence was found when Roche diagnostics was used as compared to Becton Dickinson (BD) ProbeTec [1,2,3]. So far no epidemiological characteristics have been described.

Several studies [4,5] have been published regarding monitoring of the swCT variant outside Sweden and, as expected, the first cases have been described recently in Denmark and Norway [3,6]. Since false negative test results lead to under-treatment and continuing transmission, the detection of the swCT variant in the population is essential. This report describes the actions of public health experts in cooperation with specialists in sexually transmitted diseases (STD), epidemiologists and (molecular) microbiologists to investigate the possible introduction of the swCT variant in the Netherlands.

Introduction

In December 2006, the Preparedness and Response Unit (LCI) of the Centre for Infectious Disease Control of the Dutch National Institute for Public Health and the Environment (RIVM) established a study group whose task has been to increase awareness among STD specialists, molecular biologists and microbiologists about the swCT variant and to define methods for investigating whether this new variant had been introduced in the Netherlands. "Inf@ct", an electronic message system operated by LCI, has been used as an important communication channel through which information could be shared instantly.

The study group proposed the following main actions and strategies to detect the potential presence of swCT variant in the Netherlands:

1. Investigating trends in CT epidemiology
2. Retesting samples by TaqMan PCR
3. Screening sample pools for the presence of the swCT variant

Methods

1. Investigating trends in CT epidemiology

According to laboratory data, in the Netherlands around 80% of *C. trachomatis* infections are diagnosed by Roche Diagnostics assays. This means that if the swCT variant were present in the Netherlands, it would go largely undetected. The other 20% of positive tests are performed mainly with GenProbe, BectonDickinson

ProbeTec and so-called "in house" assays. A few years ago, one of these in-house assays, a Real-Time PCR (TaqMan), was developed by the VU University Medical Center, Amsterdam and subsequently implemented in 10 laboratories (both public and private hospitals) in the Netherlands for the diagnostics of *C. trachomatis*. Sequence analyses of the primer-probe region inside the CT-plasmid showed that this PCR detected the swCT variant, validating the diagnostic setting.

Sexually transmitted infections (STI) surveillance

The STI surveillance in the Netherlands is based on registration of STI consultations at STI clinics and public health services. Consultations have been registered in SOAP (an internet-based application) since 2003. The data reported includes demographic variables, history of STI and HIV testing, laboratory tests and diagnoses of STI. Based on these variables, positivity rates for STI, including chlamydia, can be calculated.

Laboratory surveillance

Laboratory surveillance (Infectieziekten Surveillance Informatie Systeem – ISIS) collects information on tests and test results with demographic characteristics from nine laboratories in the Netherlands. For the purpose of this study, nucleic acid amplification tests (NAAT) ISIS-based positivity rates per year were calculated. A test that was performed during the two months following a former positive test in the same patient was not counted.

2. Retesting samples with TaqMan PCR

In the period January-May 2007, laboratories in the Netherlands using Roche diagnostic assays for CT detection were urged to send patient samples for retesting at the VU University Medical Center in Amsterdam in cases when clinical presentation in combination with sexual risk profile of the patient did not correspond with a CT negative laboratory result. The samples were retested for the presence of CT with the TaqMan Real-Time PCR which besides all standard CT strains detects also the new swCT variant strain. In addition, a real-time TaqMan assay detecting only the swCT variant was developed [7]. Results of this retesting were sent within a week to the laboratory which had provided the specimen.

3. Screening sample pools for the presence of the swCT variant variant

Sample pools were selected for retesting with the TaqMan PCR method detecting both the wild-type CT strains and the swCT variant [4], as well as with the new real-time swCT variant TaqMan [7].

Results

1. Investigating trends in CT epidemiology

STI surveillance

In Figure 1, the number of individuals tested for chlamydia in the period 2003-2006, and the positivity rates, are displayed. Since 2003, the number of tests for chlamydia has increased in all groups – heterosexual men and women, as well as men having sex with men (MSM). The positivity rates have slightly increased among heterosexual males but stayed more or less the same in MSM.

Laboratory surveillance

Figure 2 shows the positivity rates of NAAT in the laboratory surveillance from 2004 until mid-2007. Among men (M) the positivity rates were higher than among women (F); however, there was no clear trend in either men or women, suggesting a lower prevalence than observed in Sweden. Unfortunately, sexual preference was not registered in this system.

Based on the available STI surveillance data from STI clinics and laboratories, there are no indications for a declining number of chlamydia diagnoses in the Dutch population. This overall stable trend does not preclude a proportion of diagnoses being missed due to reduced diagnostic sensitivity, as the overall detected prevalence could also be affected by changes in populations (although no direct evidence for this was found) or by changes in registration systems.

FIGURE 1

The number of individuals tested for *Chlamydia* and positivity rates among heterosexual men, women and MSM, the Netherlands, 2003-2006 (Source: STI sentinel surveillance network)

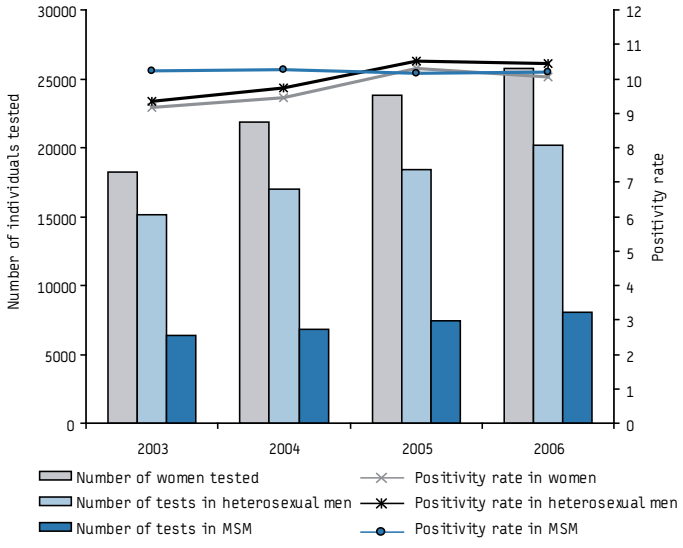
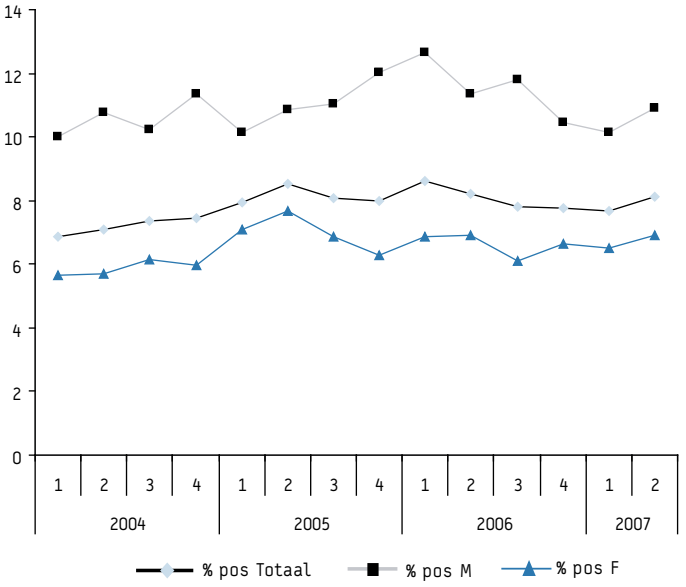


FIGURE 2

Positivity rates of nucleic acid amplification tests (NAAT) for *Chlamydia trachomatis* in the laboratory surveillance (Source: STI sentinel surveillance network)



2. Retesting samples through the TaqMan PCR

During the five months between January and May 2007, a total of 58 samples previously tested CT-negative with Roche (but suspected of being infected with CT on the basis of the clinical picture) were sent to the VU University Medical Center in Amsterdam and retested there for CT and swCT variant. All samples were CT-negative and also swCT variant-negative. This enhanced surveillance system therefore did not reveal the presence of swCT variant in the Netherlands.

3. Screening sample pools for the presence of the swCT variant variant

The following sample pools were retested for the presence of swCT:

1. Random samples of 515 patients attending an STD clinic in Amsterdam, including 75 samples tested CT-positive with Roche Diagnostics (not detecting the swCT variant).
2. 30 samples tested CT-positive in house real-time PCR (detecting also the swCT variant) were selected from the Department of Medical Microbiology and Infection Prevention, VU University Medical Center, Amsterdam, the Netherlands (population: CT prevalence 1.8%).
3. 57 samples tested CT-positive with Becton Dickinson (BD) ProbeTec (detecting also the swCT variant) were selected from the Department of Infectious Diseases, South Limburg Public Health Service, Heerlen, the Netherlands (population: CT prevalence 7.3%).

None of the samples from the three above pools were positive for the swCT variant when tested using the new swCT variant TaqMan. (Table)

The following sample pool surveillance is still ongoing:

4. Since May 2007, in Groningen, during one week in each month all diagnostic clinical samples (n= around 400) have been screened specifically for the swCT variant. In May, 443 samples were tested with both the Abbott M2000 and the VUmc TaqMan PCR. There were 18 positive samples, and no discrepancies. In June-July, another 618 samples were tested in a similar way, with 43 positive test results in both tests and no discrepancies. (Table)

Discussion

Last year Sweden notified a new CT variant which was not detected by the regular Roche and Abbott PCR tests. Since these tests are also commonly used in the Netherlands, there was reason to monitor the potential introduction of this variant there, as well. A swCT study group, set up for this purpose, initiated a number of actions aimed at detecting the new variant in the Netherlands.

To date, however, neither the enhanced laboratory surveillance nor analyses of the epidemiology of CT indicate the presence of swCT in the Netherlands. Although its broad spread in the Netherlands within a short term is not likely, small scale introduction cannot be ruled out. As single cases of swCT variant have been detected outside Sweden, the introduction and further spread of swCT to other countries including the Netherlands is still a realistic scenario. The Dutch swCT study group therefore continues to monitor the situation with the following specific actions:

1. In Groningen, one week per month all diagnostic clinical samples (n=around 400) are being screened specifically for the swCT variant.
2. In Amsterdam, every three months a group of patients presenting at VU University Medical Center and Municipal Health Service (n=around 200, unselected) will be screened for the presence of the swCT variant.
3. Further trend analysis will be performed using the national surveillance dataset from STD clinics and laboratorial results (ISIS) for epidemiological changes in chlamydia cases.

This monitoring system will continue until the manufacturers Roche and Abbott have adapted their *C. trachomatis* diagnostic assays to detect the swCT variant.

Table

Overview of sample pools tested for the swCT variant in the Netherlands

City	CT + (n)	swCT variant (*)	Reference	Remarks
Amsterdam (Municipal Health Service)	75	Not detected	4	Total 515 samples, not selected #
Amsterdam (VU University Medical Center)	30	Not detected	7	Selected CT- positive samples
Heerlen	57	Not detected	7	Selected CT-positive samples
Groningen	61	Not detected	--	To date 1061 samples tested, not selected #

*: swCT: Swedish Chlamydia trachomatis variant identified in Sweden

#: All Roche test CT-negative samples were also negative in the swCT variant TaqMan assay

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Surveillance report

French situation concerning the Swedish Chlamydia trachomatis variant

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In 2006, a plasmid deletion mutant of Chlamydia trachomatis was identified in Sweden that can not be detected with those commercial tests targeting the deleted area. In order to study the spread of this strain in France, a laboratory-based surveillance system was set up by the National Reference Centre for Chlamydiae and the Institut de Veille Sanitaire. Among 1,141 C. trachomatis-positive specimens from all over France, the new variant was only detected in one case. This case was a non-French resident consulting a sexually transmitted infections clinic. Although the new variant does not seem to be established in France as yet, surveillance based on the testing of C. trachomatis-positive samples from all over France continues.

Introduction

A *Chlamydia trachomatis* variant that harbours a 377 bp deletion in the cryptic plasmid has been identified in patients in Sweden [1]. This deletion is unfortunately located in the region targeted by commercially available PCR tests that diagnose urogenital *C. trachomatis* infections, such as the Cobas Amplicor or Taqman tests (Roche Diagnostics) which are frequently used in France, and the Abbott Real Time CT and CT/NG assays. As a consequence, these commercial kits generate false negative results for patients who are infected with the deletion variant of *C. trachomatis*. Currently, the spread of the new variant to other countries seems to be very limited. It has been detected in two patients in Norway (one Swedish, one Norwegian), and recently in Denmark and in Ireland [2-4]. The new variant had not been detected among 8,797 specimens in an earlier study in Ireland, nor in 515 samples from an outpatient sexually transmitted infections (STI) clinic in Amsterdam, The Netherlands, nor in 1,066 *C. trachomatis*-positive specimens in England and Wales [5-7]. As for other parts of the world, recent studies suggest that the plasmid mutation is not present in the Midwest region of the United States nor in Melbourne, Australia [8,9].

Following the European alert, the French Health Products Safety Agency published an alert bulletin in February 2007 to inform their health correspondents of the situation [10]. Moreover, both companies, Roche and Abbott, informed their customers that their commercial tests generated false negative results with the new variant strain. They recommended to use a different test that is able to detect this strain in those cases in which *C. trachomatis* infection was suspected but in which the Roche or Abbott tests had given a negative result. In order to establish whether the Swedish *C. trachomatis* variant was circulating in France, a laboratory-based surveillance system was set up by the French National Reference Centre for *Chlamydiae* (NRC) and the Institut de Veille Sanitaire (InVS). In France, about 1,500 laboratories perform *C. trachomatis* diagnostics on urogenital specimens. A majority (about 70%) of the diagnostic are done using nucleic acid amplification test (NAAT), 70% of which are the Roche tests.

Material and methods

The National Reference Centre for *Chlamydiae* tested samples from three different sources:

1. All consecutive genital specimens from high risk groups consulting four STI centres in two cities (Bordeaux and Paris) in November 2006 that were tested by both Cobas Taqman assay and an in-house real-time PCR assay targeting a 129 bp region of the chromosomal *omp1* gene [11].
2. All samples determined as positive by the Pasteur Cerba laboratory between July 2006 and June 2007 using the CT real-time PCR kit Qiagen Artus targeting the *omp1* gene, a commercial test that is able to detect the new variant *C. trachomatis*. The Pasteur Cerba laboratory is a central laboratory that receives specimens (on average 3,500 specimens per month) from all over the country including the French overseas territories (West Indies, Guyana, Polynesia). The proportion of positive samples is approximately 3.9%. These samples were tested at the NRC using either the new variant-specific real-time PCR described by Ripa or an in-house real-time PCR targeting the deleted region of the plasmid [11,12].
3. All endocervical and male urethral specimens tested routinely in the NCR laboratory located in Bordeaux that were tested by cell culture and Cobas Taqman. Most of those samples came from an STI clinic located in Bordeaux.

Results

A total of 1,141 *C. trachomatis*-positive samples were analysed for the presence of the new Swedish variant:

1. 62 specimens from 784 consecutive genital samples from STI clinics in Paris (n=332) and Bordeaux (n=452) sampled in November 2006. None of those samples contained the Swedish variant *C. trachomatis*.
2. 1,049 samples from 1,040 patients (613 women and 427 men) provided by the Pasteur Cerba laboratory. The Swedish variant was not found among those. However, seven samples failed to amplify and were therefore not typable. This may have been due to differences in the sensitivity of different NAATs, to low concentrations of *C. trachomatis* DNA, or to degradation of the DNA during storage.
3. 30 culture specimens from 650 samples cultivated at an STI centre in Bordeaux since July 2006. Among those, one

new variant was detected in an isolate from a woman consulting the centre in March 2007. The endocervical sample had been positive in culture and negative in the Cobas Taqman assay. The strain belonged to serovar E as determined by PCR-RFLP of the *omp1* gene and as described by Ripa for the Swedish strain [13]. The presence of the 377 bp deletion was verified by sequencing and by using the new variant-specific real-time PCR [12]. Unfortunately, since consultations at STI centres in France are anonymous, detailed information about this case is not available and contact tracing was not possible. The only information available is that the patient was a citizen from a northern European country, visiting Bordeaux at the time of consultation.

Discussion

Our results confirm that the new variant *C. trachomatis* seems currently to be restricted to the Scandinavian countries. Among 1,141 *C. trachomatis*-positive samples from all over France, only one case of the new Swedish variant *C. trachomatis* was detected. This sample stemmed from a non-French resident consulting a French STI clinic. Surveillance of the spread of this variant strain in France was feasible as a result of the cooperation of a private laboratory that performs diagnostics with a technique able to detect the new variant strain. If this had not been the case, it would have been much more difficult to implement a surveillance system, as most (about 50%) of the French laboratories are using assays that are not capable of detecting the new variant.

In Sweden, a decrease of 25% in diagnosed *C. trachomatis* infections was noted at the beginning of 2006. In contrast, the number of *C. trachomatis* infections diagnosed in France, which has been rising between 1998 and 2005 [14], continued to increase in 2006 and 2007 (InVS unpublished data), although the methods of detection of *C. trachomatis* remained the same. Our current knowledge about the spread of this Swedish strain in France does not permit us to recommend the exclusive usage of tests amplifying other targets than the deleted region of the plasmid. Roche Molecular Diagnostics [15] and Abbott Molecular are developing new assays that will be able to detect wild-type as well as plasmid-mutant strains by incorporating a new target region, either on the chromosome or in a region of the cryptic plasmid not affected by the deletion, in addition to the original primers directed at the mutated region on the cryptic plasmid. These dual target tests will include detection of the Swedish *C. trachomatis* variant but will not allow to identify cases caused by these plasmid-mutant strains specifically. Presently, multiple tests are needed for each specimen to identify the new variant *C. trachomatis* in order to be able to distinguish it from the wild-type and to study its spread.

The new variant-specific real-time PCR test described by Ripa, developed on the LightCycler 1.0, detects only the mutant strain because the FRET probes were designed to bind to the sequence flanking the deletion. The result is positive (presence of deletion) or negative. A negative result is not conclusive because it indicates either the presence of the non-deleted strain, or the absence of any strain, or atechnical problem.

A new method that characterises nucleic acid samples by comparing their dissociation (melting) temperature, High Resolution Melting (HRM), seems to be promising [16]. The HRM profile discriminates amplified fragments according to their sequence, length, and GC content, and can distinguish between wild-type and mutant strains. Our first assays show perfect discrimination between the two. This method will be used in the NRC laboratory on positive *C. trachomatis* samples sent by the Pasteur Cerba laboratory. Continued surveillance based on testing positive samples by this method will be very useful in detecting the variant strain in France.

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Surveillance report

Trends in genital chlamydia infection in the Mid-West of Ireland, 2001-2006

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Genital *Chlamydia trachomatis* (GCT) infection is the most common bacterial sexually transmitted infection (STI) in Ireland. A retrospective analysis of 2,087 laboratory-confirmed GCT patient episodes from 2001 to 2006 in the Mid-West of Ireland was undertaken in conjunction with statutorily notifiable data that were reported by the Sexually Transmitted Disease/Genito-Urinary Medicine (STD/GUM) services in the region and used in national surveillance. Data were analysed by year, source, sex and age. The annual incidence of GCT in the Mid-West is increasing. A substantial proportion of GCT infections were diagnosed in the non-STD/GUM setting. The issue of sexually active young people seeking STI screening is a sensitive one, and delays increase the potential for transmission and the possibility of long-term complications when the disease is not treated. Based on this sample, national surveillance would significantly underestimate the burden of disease in Ireland, due to under-reporting. This would have implications for any national chlamydia screening programme. Among those who sought testing, women aged 15 to 19 years are five times more likely to be found positive than men in the same age group. Of those diagnosed in the non-STD/GUM setting, 83% were women. General practitioners and clinicians might consider targeting those aged 15 to 29 years for opportunistic screening and sexual health advice. Contact tracing and follow-up in the non-STD/GUM setting, as well as access for general practitioners to ongoing education on STIs are challenges to be addressed.

Introduction

Chlamydia trachomatis is the most common bacterial sexually transmitted infection (STI) in Ireland [1]. The burden of genital *C. trachomatis* disease in Ireland is a major public health concern. In a previous study in the Mid-West of Ireland, the prevalence of chlamydia in men aged 17–35 attending an orthopaedic clinic and a university sports arena was estimated to be 5.9% [2].

In males, infection can manifest as urethritis or epididymitis, with complications such as Reiter's syndrome in those genetically predisposed [3,4]. Infection in women may present with urethritis, cervicitis, bartholinitis, or salpingitis and, if left untreated, the infection can become chronic and result in ectopic pregnancy, pelvic inflammatory disease and infertility [3].

Up to 70% of women and 50% of men with chlamydia infections do not show symptoms of the disease, resulting in a 'silent epidemic' [5,6]. Individuals unaware of their infection increase the risk of transmission of chlamydia in unprotected sexual contacts. Delays in seeking a diagnosis and treatment can result in increased transmission of chlamydia infection and its consequences. STI testing may be embarrassing for individuals and therefore those accessing diagnostic services may seek care outside their usual area of residence. Currently, there is no national chlamydia screening programme in Ireland. This study examines two sources of data on reported chlamydia and the origins of positive cases in the Mid-West of Ireland.

Methods and Materials

Two sources of data are available on genital chlamydia infections in the Health Services Executive (HSE) Mid-West: (a) data from the aggregate quarterly notifications of the free and confidential Sexually Transmitted Diseases (STD) or Genito-urinary Medicine (GUM) Clinics to the Department of Public Health; and (b) data on laboratory-confirmed infections from the Department of Medical Microbiology, Mid-Western Regional Hospital, Limerick. This laboratory performs all diagnostic chlamydia testing for the region covered by the HSE Mid-West, i.e. the counties of Clare, Limerick and Tipperary North. The region has a population of 339,591 (Census 2002), of which 214,402 are aged 15 to 59 years. STD/GUM services are not available in all regions of Ireland, and therefore cases of positive individuals outside the above catchment area may be included.

From March 2000 to December 2006, all laboratory-confirmed positive results were identified using one Nucleic Acid Amplification Technique (NAAT), i.e. ligase chain reaction (LCR) or polymerase chain reaction (PCR). From March 2000 to January 2004, the Abbott LcX (Abbott Laboratories, USA) was the diagnostic method used. It was replaced from January 2004 by the ABI Prism 7000 (Artus Hamburg GmbH) and Artus *C. trachomatis* PCR kit, which targets a region on the cryptic plasmid that is not affected by the deletion in the Swedish variant. The Microbiology Department at the Mid-Western Regional Hospital participates in an external Quality Control programme (National External Quality Assurance Scheme, NEQAS). Methods before 2000 were non-NAAT.

Data on all positive results for *C. trachomatis* were extracted from the Laboratory Information System of the Mid-Western Regional Hospital Microbiology Department and examined by sex and date of birth. While public health notification of chlamydia by laboratories became mandatory only in 2004, the data analysed here are comparable across all years as they are not based on public health notifications but on laboratory results. Duplicates, defined as two or more positive results on individuals with the same date of birth and sex within an interval of three months, and probable referrals (contemporaneous positive results from non-GUM/STD sources and GUM/STD Clinics, based on date of birth and sex) were excluded. Apparent re-infections, defined as two or more positive results more than three months apart were included. Duplicates and re-infections were classified as *definite* or *probable* based on the data available on each case. Codes used in STD/GUM services allow only date of birth and sex to be compared, therefore data may underestimate cases (where date of birth and sex are the

same but the individual is different) and hence classification can only be *probable*. No data on sexual orientation was available in this dataset.

Results

Cases notified by STD/GUM clinics

Data reported by the STD/GUM Clinics to the Department of Public Health from 1998 to 2005 show a rising incidence of new chlamydia cases diagnosed from 1998 to 2002, and then a decline from 2003 to 2005 (Figure 1). Genital chlamydia infection was more common in women than in men in all years with the exception of 2000.

Laboratory-confirmed cases

There has been a steady rise in the number of requests for chlamydia testing in the HSE Mid-West over the last four years (Figure 2). Of 7,521 laboratory samples tested for chlamydia in 2006, 377 (5%) were GCT patient episodes. This percentage was consistent over the years studied (Table 1).

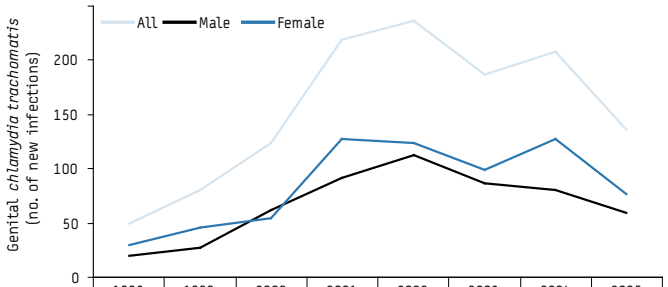
From January 2001 to December 2006, there were 2,328 laboratory-confirmed reports of chlamydia infections in total. Annually, there were up to between two and six cases of ocular chlamydia infections with a total of 26 cases over the period studied and these were excluded from the analysis. Also excluded were 215 'duplicates' or 'referrals' (129 definite and 86 probable), leaving 2,087 patient episodes of genital chlamydia infection. There were 213 cases classified as 're-infections' (84 definite and 129 probable) over the six-year period. Table 1 highlights the number of patient episodes of infection in men and women in the region from January 2001 to December 2006. In women there appears to be a steady increase in the number of genital chlamydia infections up to 2005 (Figure 2). The rate of infection in women is consistently almost twice the rate in men.

The rate in Table 1 is based on sex-specific population aged 15 to 59 years. Table 2 illustrates the age-specific incidence of genital chlamydia infection by sex, annualised for the six years studied.

Young women (15 to 29 years) bear the greatest burden of disease in the region. Among those who sought diagnostic services, females aged 15 to 19 years were five times more likely to be found positive than males of the same age.

FIGURE 1

Notifications of new genital chlamydia infections in HSE Mid-West 1998 – 2005 from STD/GUM Clinics, all ages# (n=1,242)



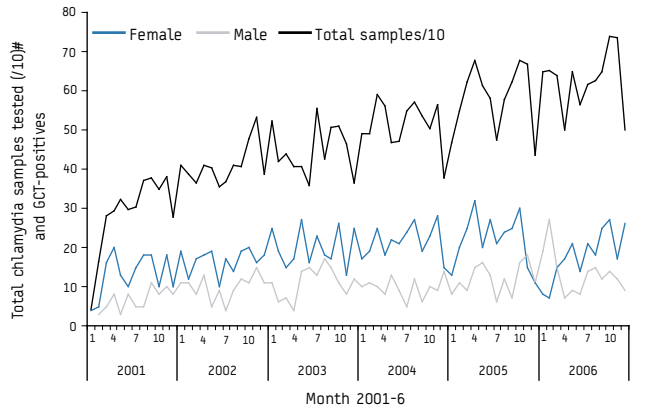
	1998	1999	2000	2001	2002	2003	2004	2005
All	50	81	124	219	237	187	208	136
Male	20	27	62	92	113	87	80	59
Female	30	46	54	127	124	99	128	77

Year

Breakdown by sex not always available in reported data

FIGURE 2

Samples tested for chlamydia (/10)# and number of male and female genital *Chlamydia trachomatis*-positive (GCT-positive) by month at Mid-Western Regional Hospital January 2001 – December 2006



Total samples tested for chlamydia reduced by factor of 10 for ease of presentation on chart

TABLE 1

Number and sex-specific rate# of laboratory-confirmed genital chlamydia infections, 2001-2006, HSE Mid-West

Year	% positive samples	Female (n)	Female (rate#)	Male (n)	Male (rate#)	Unknown sex (n)	All	All (rate#)	Female: Male ratio##
2001	6.8	157	149.4	74	67.7	4	**235**	**109.6**	**2.2**
2002	6.5	199	189.3	119	108.9	0	**318**	**148.3**	**1.7**
2003	7.0	241	229.3	133	121.7	0	**374**	**174.4**	**1.9**
2004	6.1	258	245.4	117	107.1	1	**376**	**175.5**	**2.3**
2005	5.8	263	250.2	142	129.9	2	**407**	**189.8**	**1.9**
2006	5.0	247	235.0	130	119.0	0	**377**	**175.8**	**2.0**
Total		**1,365**		**715**		**7**	**2,087**		

per 100,000 population aged 15 to 59 years
ratio based on incidence rates

Table 2

Number and annualised# age-specific incidence rate (ASIR) of laboratory-confirmed genital chlamydia infections, by sex, 2001-2006, HSE Mid-West

Age	15-19y	20-24y	25-29y	30-34y	35-39y	40-44y	45-59y	Total
Female cases	235	613	319	122	48	16	11	1,364
ASIR	289.9	744.1	434.6	166.2	65.6	23.3	6.2	
Range Min/Max	200-355	510-910	335-515	65-245	25-131	17-44	3-10	
Male cases	47	301	221	91	34	11	7	712
ASIR	54.3	350.4	290.5	120.3	44.6	16.8	3.8	
Range Min/Max	28-104	233-433	158-379	63-167	24-81	8-34	0-10	
Total cases#	**282**	**914**	**540**	**213**	**82**	**27**	**18**	**2,076**
ASIR	**168.8**	**546.1**	**361.2**	**142.9**	**55.7**	**19.2**	**4.9**	
Range Min/Max	114-211	371-653	245-426	64-205	25-106	13-30	1-10	

ASIR – age specific incidence rate per 100,000 population
#cases 2001-6, divided by six years

Sex/age not known in 10 cases. One case not shown.

The median age of men at the time of infection was 25 years (Range: 16 to 56 years) and in women it was 23 years (Range: 15 to 53 years). The median age of women attending STD/GUM Clinic settings was 1.5 years younger than of women attending non-STD/GUM settings, although the overall age distribution for both men and women between STD/GUM and non-STD/GUM settings was similar.

General practitioners, family planning clinics (FPC) and hospital clinicians diagnosed 49% of chlamydia infections in the region. Females made up 65% of cases during the period 2001-2006. Of those cases diagnosed by non-STD/GUM clinics, 83% (856 of 1,027) were female, as shown by data from the HSE Mid-West (Table 3). This is markedly different from the data from STD/GUM Clinics, where similar numbers of males and females are seen and notified.

Discussion

Until recently, complete data on genital chlamydia infection in Ireland have been difficult to establish because there was significant under-reporting by clinicians outside the STD/GUM Clinics. Irish law places a statutory requirement on STD/GUM Clinics to provide aggregate quarterly STI data to the (regional) Medical Officer of Health in the Department of Public Health. The obligation to report

Table 3

Number of genital chlamydia infections# by sex, 2001-2006, according to diagnostic source in HSE Mid-West

		Source of GCT+ cases by year (%)				
Year	Sex	Family planning clinics	General practitioners	Hospital Clinician	STD/GUM Clinic	All
2001	Female	16 (10%)	36 (23%)	40 (25%)	65 (41%)	157
	Male		2 (3%)		72 (97%)	74
2002	Female	10 (5%)	57 (28%)	41 (21%)	91 (46%)	199
	Male		19 (16%)	2 (2%)	98 (82%)	119
2003	Female	24 (10%)	90 (37%)	38 (16%)	89 (37%)	241
	Male		36 (27%)		96 (73%)	132
2004	Female	13 (5%)	120 (47%)	29 (11%)	96 (37%)	258
	Male		30 (26%)	1 (0.5%)	86 (73.5%)	117
2005	Female	19 (7%)	127 (48%)	27 (10%)	90 (34%)	263
	Male		42 (29.5%)	4 (3%)	96 (67.5%)	142
2006	Female	16 (6%)	119 (48%)	34 (14%)	78 (32%)	247
	Male		33 (25%)	2 (2%)	95 (73%)	130
2001-6	Female	98 (7%)	549 (40%)	209 (15%)	509 (37%)	1,365
	Male		162 (23%)	9 (1%)	543 (76%)	714
Total		**98 (4.7%)**	**711 (34.2%)**	**218 (10.5%)**	**1,052 (50.6%)**	**2,079**

STD/GUM: Sexually Transmitted Disease/Genito-Urinary Medicine; GCT+: confirmed genital C. trachomatis cases
Excludes 8 cases – sex or source not known

cases of genital chlamydia infection was introduced for laboratories in 2004 and should allow a clearer assessment of the epidemiology of chlamydia infection in Ireland [7].

National data in Ireland, based on STD/GUM Clinic data, show an increase in the number of cases in Ireland, from seven per 100,000 population in 1995 to 86 per 100,000 in 2005 [1]. This is likely to be directly related to factors such as better surveillance methods, increasing incidence, greater awareness and screening, but also to more sensitive laboratory diagnostic techniques. Data on trends from the Mid-West are consistent with published data in other countries, with the rate of infection rising particularly in young women [8,9]. The lower rates in males may be due to infrequent contact with health services in general in contrast to females who attend for contraceptive advice, smear testing and pregnancy.

It is not appropriate to compare published data from national sources to data in this report, as only STD/GUM Clinic aggregate data are included nationally. Half of all chlamydia infection in the region is diagnosed by GPs, FPC and hospital clinicians (predominantly obstetric/gynaecology clinicians), with the remainder being diagnosed in regional STD/GUM Clinics. General practitioners and, to a lesser extent, hospital-based clinicians diagnose an increasing number of chlamydia infections, especially in women. Therefore general practitioners are in a position to offer opportunistic screening to women attending their practices given the increasing burden of infection in the community. One review suggests that women actively seeking health care are amenable to screening [10]. Under-reporting has a significant bearing on assessing the burden, surveillance and control of chlamydia infections in Ireland. This study in the Mid-West suggests that national data, which are based solely on aggregate returns from STD/GUM Clinics in Ireland, would underestimate the burden of chlamydia, more particularly the incidence in women. The data highlight those at greatest risk of chlamydia infection based on age and sex. With increasing numbers of diagnoses in the community, GPs and clinicians might consider targeting this group for opportunistic screening and sexual health advice. The large proportion of cases seen by clinicians outside STD/GUM Clinics, especially in the community, has implications for public health in terms of complete follow-up, partner notification and contact tracing. General practitioners should have access to ongoing education on STIs.

It was not possible to determine whether genital chlamydia positive cases diagnosed outside the STD/GUM Clinic setting were offered or received full STI screening. It appears that only a small number of such positive genital chlamydia cases are probably referred to the specialist STD/GUM service in the region (4%) indicating that management of the chlamydia infection in the non-STD Clinic setting was mainly by family doctors. The reasons for 're-infections' are unclear, and it is possible that a source of infection has not been identified and remains a reservoir for infection post-treatment. A debate on the need for a national chlamydia screening programme in Ireland, as introduced in other countries, is to be welcomed [11].

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Research article

The burden of infectious diseases in Europe: a pilot study

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The main objectives of this pilot study were to test the potential use of the disease burden concept in the field of infectious diseases, including data quality and availability; to recommend future studies; and to stimulate a debate. The disease burden of seven infectious diseases (influenza, measles, HIV, campylobacteriosis, infection with enterohaemorrhagic *Escherichia coli*, salmonellosis and tuberculosis) in Europe was estimated by calculating Disability Adjusted Life Years (DALYs), a composite measure that attempts to combine mortality, incidence and sequelae, taking duration and severity into account. The results show that the relative burden of diseases as measured by DALYs differs from that only measured by incidence or mortality. Several limitations regarding data availability and quality have been identified, resulting in an underestimation of the true burden of disease in this pilot. Notwithstanding these, HIV-infection, tuberculosis (TB) and influenza are estimated to cause the highest burden in Europe among the selected diseases. The burden of foodborne diseases (campylobacteriosis, infection with enterohaemorrhagic *Escherichia coli* and salmonellosis) and in particular of measles is lower. A consideration of the relative comparison of burden between diseases can be useful when tackling the difficult, sensitive but necessary task of identifying priority actions. A low burden stresses the need for continued support for prevention and control whereas a high burden indicates the need for additional interventions. Following this pilot project, a generalised burden of disease study for infectious diseases in Europe is recommended. Such a study would benefit from an approach that identifies and combines several methods of investigation, including epidemiological modelling, and it should be done in collaboration with other international efforts in this field.

Introduction

Assessments of disease burden are often based on singular health metrics, such as incidence, prevalence or mortality data alone. However, as diseases and their consequences are heterogeneous in terms of morbidity and mortality it is difficult to get an overall estimate of disease burden. Composite health measures attempt to overcome this by combining mortality, incidence (and/or prevalence) and the sequelae associated with a disease. The Disability Adjusted Life Years (DALYs) is such a composite measure that could be helpful in prioritising diseases. Other priority-setting criteria are incidence, the severity of a disease, its potential to spread among the general population, its associated socioeconomic burden, its preventability, its potential to drive public health policy, the perception of risk related to the disease, changing patterns in time [1] and perceived outbreak potential.

The European Centre for Disease Prevention and Control (ECDC) has a responsibility to identify, assess and communicate current and emerging threats to human health from infectious diseases [2]. As part of its work to fulfil this mandate, the ECDC has produced the first Annual Epidemiological Report on Communicable Diseases in Europe [3]. This report provides a comprehensive overview of the threat of infectious diseases in the European Union (EU) in 2005. It analyses incidence trends and patterns of the 46 diseases under mandatory surveillance, as well as severe acute respiratory syndrome (SARS), avian influenza and West Nile virus. The trends identified give an indication of which diseases require priority action; additional indications would be given by including mortality, prevalence (only few data are available) and sequelae. The ECDC aims to evaluate whether a composite measure could be useful to inform its decision-making process. If so, it could be used to gain insight into the current burden and the expected trends of these 49 infectious diseases in order to guide public health policy and action. As a first step, a pilot study was carried out to illustrate the potential of the disease burden concept, to explore data availability and quality, to recommend future studies and to stimulate a debate. This study was conducted by the Dutch National Institute for Public Health and the Environment (RIVM).

Methods

The pilot study was performed between October and December 2006, to fit into the schedule of the production of ECDC's Annual Epidemiological Report on Communicable Diseases for 2005. Due to time and resource limitations, it was decided to include only generally available data, such as those of the Statistical Office of the European Communities (Eurostat), the World Health Organization (WHO) and dedicated surveillance networks. Seven diseases were included in this pilot: influenza, measles, infection with Human Immunodeficiency Virus (HIV-infection), campylobacteriosis, infection with enterohaemorrhagic *Escherichia coli* (EHEC-infection), salmonellosis and tuberculosis (TB). These diseases were mainly selected based on the availability of incidence and mortality data and previous experience with disease burden calculations at RIVM so that comparisons could be made.

The DALY methodology used in this study has been described by Murray and co-workers in the Global Burden of Disease (GBD) project, [4,5] using the following equation:

DALY = YLL + YLD

YLL is the number of years of life lost due to mortality and YLD is the number of years lived with a disability, weighted with a factor between 0 and 1 for the severity of the disability. The YLL due to a specific disease in a specified population is calculated by summation of all fatal cases (d) due to the health outcomes (l) of a specific disease, each case multiplied by the expected individual life span (e) at the age of death:

$$YLL = \sum_{l} d_l \times e_l$$

YLD is calculated by the product of the duration of the illness (t) and the severity weight (w) of a specific disease, accumulated over all cases (n) and all health outcomes (l):

$$YLD = \sum_{i} n_i \times t_i \times w_i$$

Applying the DALY methodology involves making several choices on details of the analysis, which should reflect value choices that are relevant to the decision-maker. Value choices, such as disability weighting, age-weighting and discounting, imply that life years are assigned different value depending on the age and the health state they are in. Disability weighting means that each outcome of a disease is assigned a different value (severity weight) on a scale from 0 (perfect health) to 1 (death), see Table 1 for some examples.

For this pilot project, taking into consideration its short duration, the following (value) choices were made in consultation with the ECDC:

- to use incidence rather than prevalence data;
- to focus on all the relevant health outcomes that can be attributed to one particular infectious agent (an agent-based approach), rather than focussing on clinically defined categories of diseases (ICD-codes) irrespective of their cause (an outcome-based approach);
- which outcomes to include for each of the diseases;
- to use the European life expectancy rather than the life expectancy of a standard life table;
- not to apply discounting and age-weighting (both are debated [7,8,9]);
- to use severity weights based on period profile if available (in contrast to annual profile).

More detailed information on the background of the choices made is included in a full report published by the RIVM.10

Depending on data availability, as many as possible Member States of the European Union plus Iceland, Liechtenstein and Norway were included in the pilot study. The sources of generally available data are displayed in Table 2.

More detailed information on data and assumptions used for calculating baseline estimates of disease burden is included in the full RIVM-report [10]. Due to time limitations, a true sensitivity analysis could not be conducted. However, when alternative morbidity or mortality estimates or severity weights were available, other scenarios were calculated (=scenario analysis) to explore the uncertainty resulting from different limitations. Furthermore, the disease burden estimates were compared with those of previously published more detailed studies [20,21,22].

Results

The potential use of disease burden estimates in guiding public health policy and actions The relative burden of diseases as measured by disease burden is different to the relative burden as measured only by incidence or mortality data (Figure 1). Based on incidence data alone, foodborne diseases cause the greatest relative burden of the seven diseases studied, while mortality data demonstrate the relatively high burden of TB.

Table 1

Disability classes and severity weights according to the Global Burden of Disease study [6]

Disability class	Severity weights	Examples
1	0.00-0.02	Vitiligo on face, low weight
2	0.02-0.12	Watery diarrhoea, severe sore throat, severe anaemia
3	0.12-0.24	Infertility, heumatoid arthritis, angina
4	0.24-0.36	Amputation, deafness
5	0.36-0.50	Down syndrome
6	0.50-0.70	Depression, blindness
7	0.70-1.00	Psychosis, dementia, quadriplegia

Table 2

Generally available data sources used for the disease burden pilot study, RIVM 2007 [10]

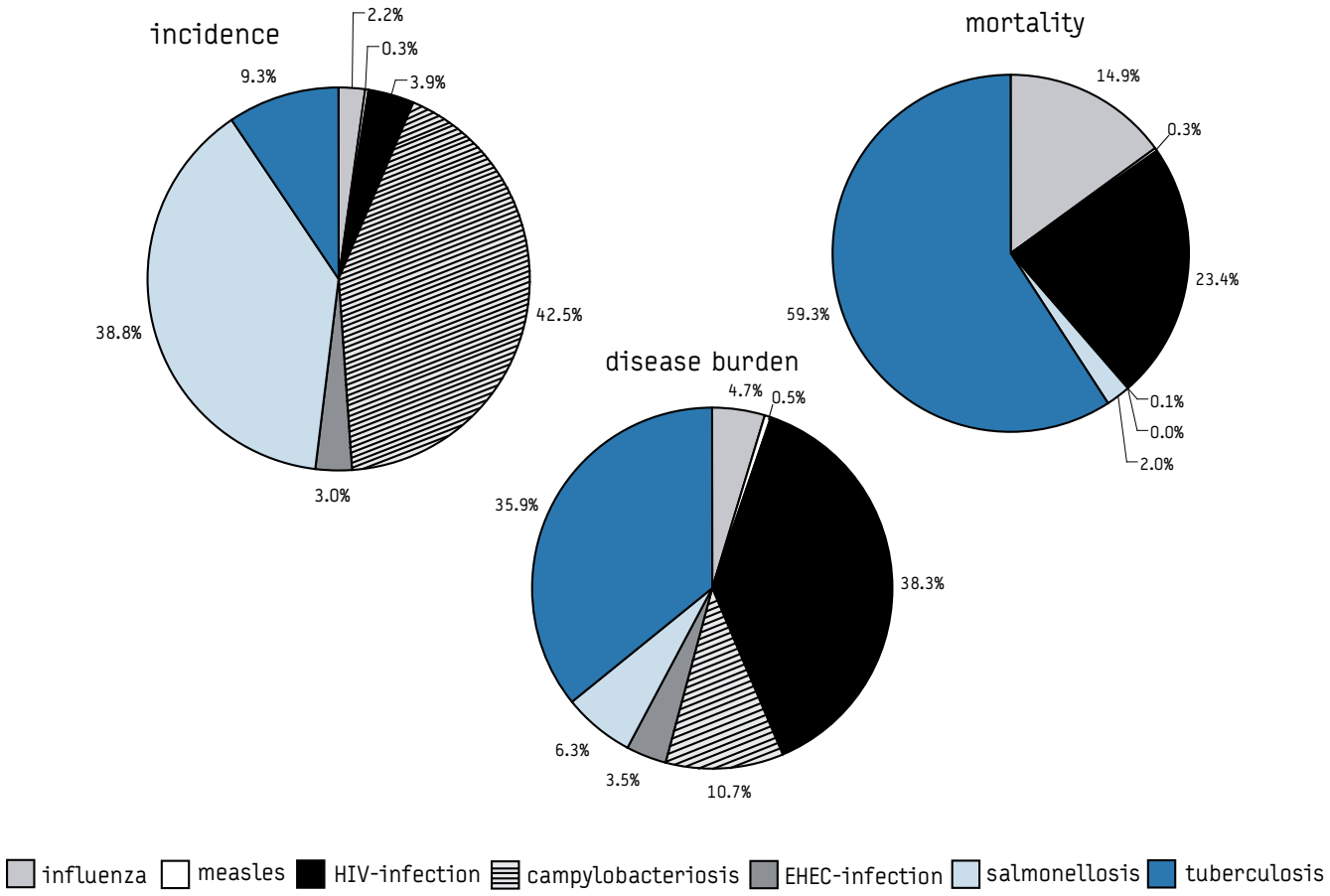
YLL	*D*	= Number of fatal cases	Mean number of deaths 2003-2004 reported to Eurostat/WHO [11,12] CD-10 codes: influenza (J10-J11), measles (B05+A81.1), HIV-infection (B20-B24), campylobacteriosis (A04.5), EHEC-infection (A04.3), salmonellosis (A02) and tuberculosis (A15-A19+B90)
	E	= Life expectancy at age of death	European life expectancy 2004 (calculation based on total mortality and average population data 2004 [11])
YLD	*N*	= Number of cases of illness	Mean incidence 2003-2005 reported to - EuroHIV [13] (HIV-infection) - EuroTB [14] (tuberculosis) - EISS [15,16,17] (influenza, mean 2002/2003-2004/2005) - Eurostat [18] (other diseases)
	T	= Duration of illness	Literature (mainly Global Burden of Disease study [19])
	W	= Severity weights	Literature (mainly Global Burden of Disease study [6])

YLL = number of years of life lost due to mortality

YLD = number of years lived with a disability, weighted with a factor between 0 and 1 for the severity of the disability

Figure 1

Relative burden of the seven selected diseases based on different indicators:
- incidence (mean number of reported new cases per year in the period 2003-2005)
- mortality (mean number of reported deaths per year in the period 2003-2004)
- disease burden (DALYs per year based on above-mentioned incidence and mortality), RIVM Study 2007[10]



Based on data for twelve countries (data available for all seven diseases): Austria, Czech Republic, Germany, Ireland, Latvia, Lithuania, the Netherlands, Poland, Slovenia, Sweden, United Kingdom, Norway

According to our study, disease burden based on DALYs shows a different picture, with a relatively high burden of HIV-infection and TB. Figure 2 shows an estimate of the total disease burden per 100,000 population for the seven selected diseases, for those countries for which DALYs could be calculated. An analysis based on 12 countries for which the disease burden could be calculated for all diseases shows a fairly similar picture. HIV-infection and TB have the highest disease burden in Europe, measles the lowest.

Scenario analysis

The scenario analysis focused primarily on the limitations of incidence data for the Netherlands. Figure 3 suggests that the disease burden of influenza is seriously underestimated (especially morbidity). For HIV-infection the information on long-term outcomes of current infections and the effect of Highly Active Anti-Retroviral Therapy (HAART) is incomplete. Furthermore, morbidity and in particular mortality of foodborne diseases (campylobacteriosis, EHEC-infection and salmonellosis) were likely to be underestimated due to underreporting. Estimates of the burden of measles and TB appeared to be more certain. The scenario analysis for influenza and TB are discussed in more detail below. Further detailed information on the scenario analysis is included in the full RIVM-report [10].

Influenza

Figure 4 shows the baseline scenario for influenza in the Netherlands. In this scenario (scenario one), the number of respiratory specimens tested positive for influenza reported to the European Influenza Surveillance Scheme (the only generally available data at that moment) was used as an estimate of the influenza incidence. However, the disease is usually self-limiting and diagnoses are generally not laboratory-confirmed. Therefore, the true incidence of influenza is considerably higher.

In scenario two, the mean number of general practitioner (GP) visits because of influenza-like-illness in the seasons 2003/2004 to 2005/2006 [23] was used as the incidence estimate. This incidence was corrected on the assumption that only 30% of the influenza patients in the Netherlands visit their GP24 and only 32.2% of influenza-like-illnesses in the Netherlands can be ascribed to influenza [25] (based on laboratory confirmation for the

Figure 2

Disease burden per 100,000 population: total for countries for which data are available for at least one disease (for each disease the number of countries is different), RIVM Study 2007[10]

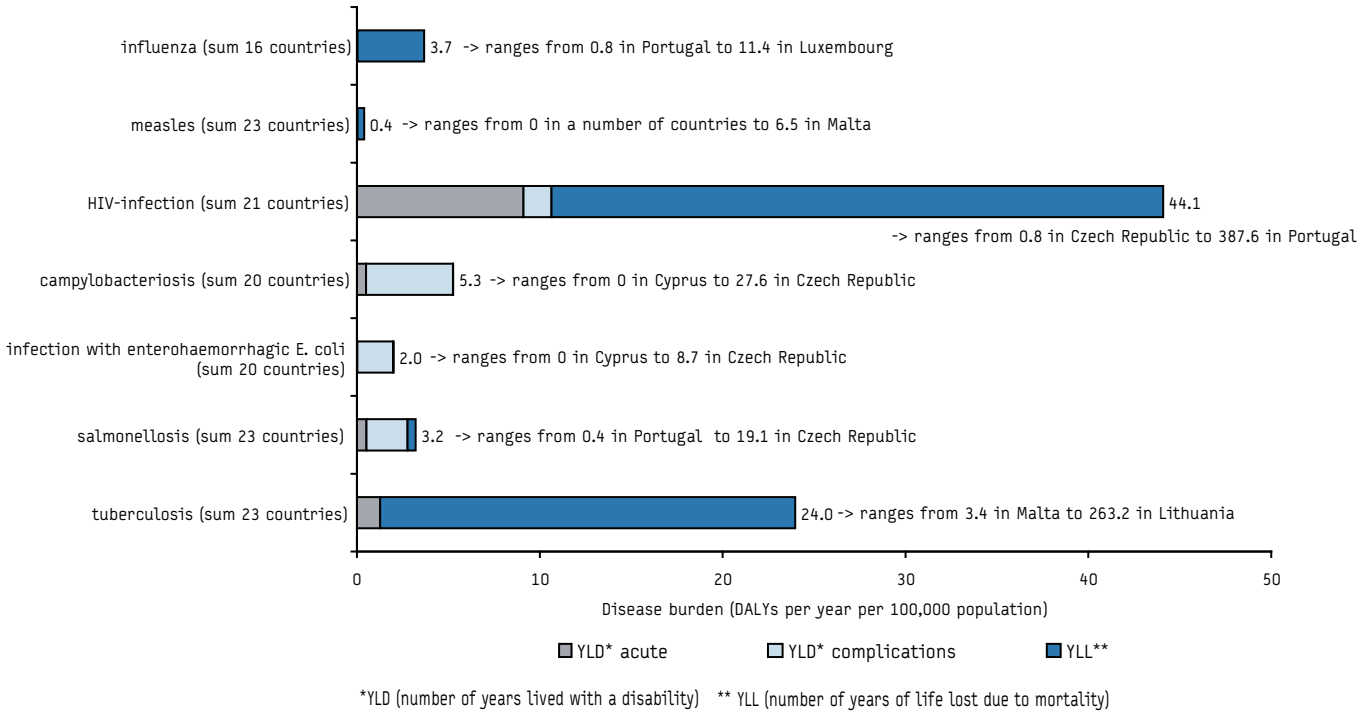
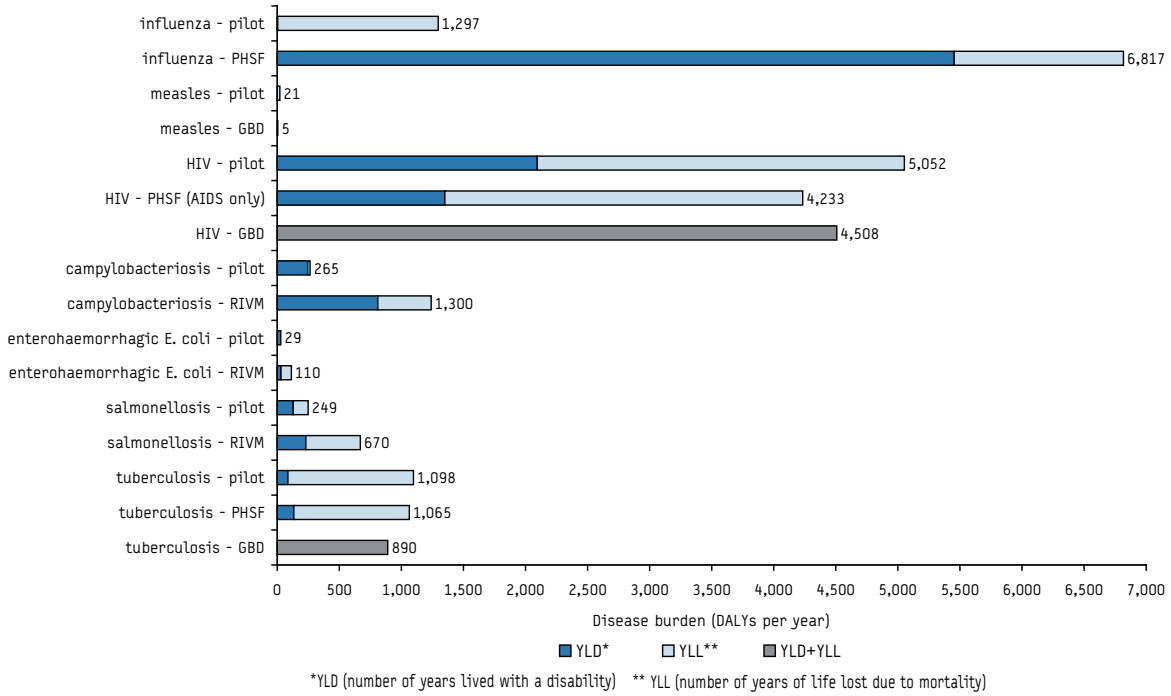


Figure 3

Disease burden of seven selected diseases in the Netherlands: comparison of results from the pilot study with previously published more extensive studies, RIVM Study 2007[10]



Pilot = pilot study on behalf of ECDC (data 2003-2005; agent approach)
GBD = Global Burden of Disease study conducted by WHO (data 2002; outcome approach);
PHSF = Public Health Status and Forecast studies conducted by RIVM for the Netherlands (data 2003; outcome approach);
RIVM = extensive studies on foodborne pathogens conducted by RIVM for the Netherlands (data 2004; agent approach)

influenza season 2005/2006). For the Netherlands, the influenza incidence in this scenario was 279,770 cases per year, compared to 400 in the baseline scenario. This difference has a considerable impact on the morbidity estimate that changes from four YLD in the baseline scenario to 2,808 YLD in scenario two. In England and Wales, approximately 800,000 GP consultations for respiratory illnesses each year are attributed to influenza [26], resulting in 8,030 YLD, compared to 20 YLD for the United Kingdom in the baseline scenario.

In scenario three, the incidence was based on the assumption that the clinical attack rate of influenza during epidemics ranges between 10-20% in the general community [27] In this scenario, the lowest estimate of 10% was used because in half of the cases the infection is subclinical. For the Netherlands the influenza incidence in scenario three was 1,628,178 cases per year (compared to 279,770 in scenario two and 400 in the baseline scenario), whereas the YLD estimate was 16,342.

For the Netherlands, Sprenger et al. estimated that in the period 1967-1989 the overall impact of influenza on mortality was greater than the officially registered influenza mortality by a factor of 3.6 [28]. In scenario four the registered mortality in all age groups was therefore multiplied by 3.6, which resulted in a mortality estimate of 4,654 (compared to 1,293 in the baseline scenario). The number of deaths may have been overestimated this way because the influenza virus seems to have been less virulent in recent years [25] and vaccination coverage today is considerably higher than it was between 1967 and 1989. Furthermore, YLL was probably overestimated because it is likely that people dying from influenza have an underlying disease and therefore a lower life expectancy. In the study of Sprenger et al., almost half of the non-registered influenza deaths were registered as deaths from heart disease, approximately 25% were attributed to lung disease and approximately 30% to other diseases [28].

Tuberculosis

In contrast with the disease burden estimate for influenza, the estimate for TB seems to be more certain. Figure 5 shows that results of this pilot are in line with the estimates of the WHO's Global Burden of Disease study (2002). However, multidrug-resistant TB should be taken into account in future disease burden estimates, especially for countries with a relatively high number of such cases (e.g. the Baltic States).

Discussion

In this pilot study, considerable limitations with regard to both data availability and quality were encountered. Major limitations in data availability were: inconsistent data on morbidity and/or mortality reported by some countries and/or for some years;

- very limited information on the age-distribution of morbidity for most diseases;
- no reporting of the incidence of complications and chronic sequelae;
- no consistent set of severity weights.
- Major limitations with regard to data quality were:

Figure 4

Disease burden of influenza in the Netherlands: scenario analysis (description of scenarios in the text), RIVM Study 2007[10]

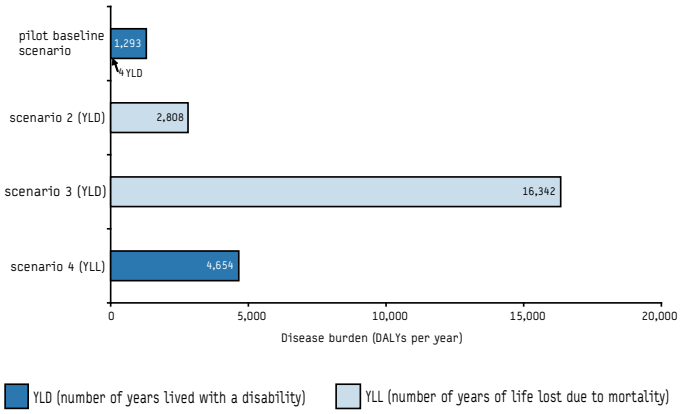
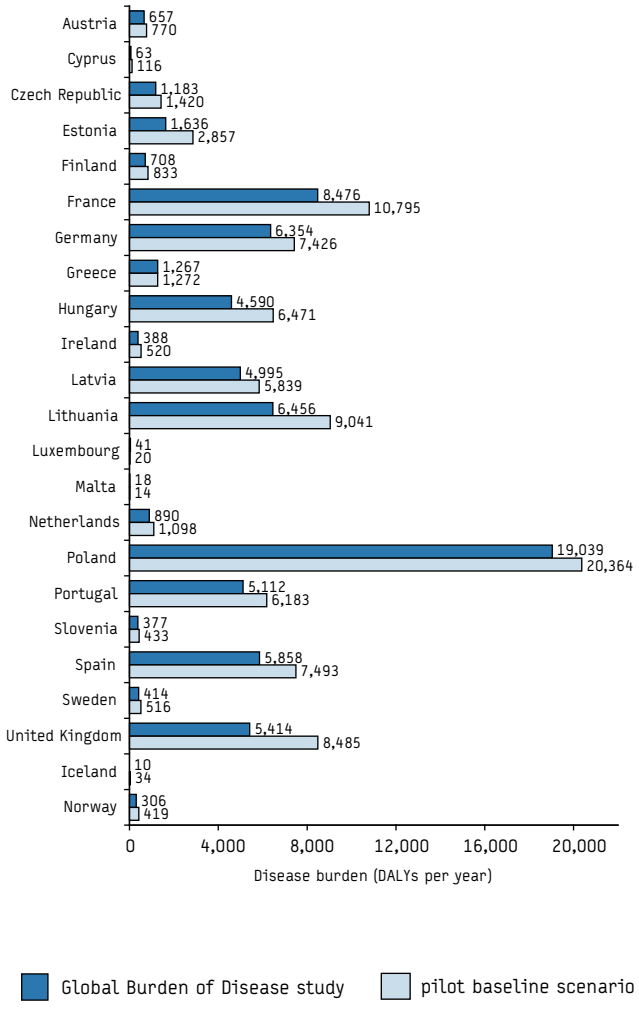


Figure 5

Disease burden of tuberculosis: comparison of results from the pilot study's baseline scenario with the Global Burden of Disease study (2002), RIVM Study 2007[10]



- no information on underreporting of morbidity and mortality;

- no information on the possible variation between countries of the duration, severity and rate of complications and chronic sequelae;

- differences between reports from different sources (national data, Eurostat and the WHO).

The authors are aware that the results of this preliminary study, based on generally available information, do not reflect the full disease burden of the selected infectious diseases in Europe, mainly due to potential underreporting in the available data on morbidity and mortality. Even the current relative comparisons of disease burden may be biased, as the extent of the potential underreporting varies between diseases and countries. Furthermore, not all relevant disease outcomes could be included in this preliminary assessment. Although it seems controversial to weigh health outcomes, a Dutch study on toxoplasmosis indicates that disease burden estimates are more affected by using different data sources than different severity weights [29]. Comparisons of the results of this pilot project with other more extensive studies could only be very general, since the methodological choices differed for each of the studies.

The relative burden of diseases as measured by disease burden is different from the relative burden as measured by incidence or mortality data alone. Based on data for 2003-2005 when available, the disease burden in Europe was estimated to be highest for HIV-infection and TB, followed by campylobacteriosis, influenza and salmonellosis, and lowest for measles and EHEC-infection. Scenario analysis limited to the Netherlands suggested that this ranking is not likely to be affected by better data. However, the relative burden of influenza is likely to increase.

Based on the presented scenarios two (YLD) and four (YLL) combined, the disease burden of influenza in the Netherlands may have been underestimated in the baseline scenario by a factor of at least five. It is likely that the disease burden of influenza was also underestimated for other countries. The number of respiratory specimens tested positive for influenza is not a suitable incidence indicator for disease burden calculations, because laboratory testing is not a general practice (this applies to all the selected diseases, but to influenza in particular). Future morbidity estimates for influenza should concentrate on GP consultation data in combination with virological data to estimate the percentage of influenza among influenza-like-illnesses (scenario two), which give a more reliable incidence estimate than laboratory data. An alternative mortality estimate could be the excess all-cause mortality during periods of high circulation of influenza [30,31], like the example in scenario four.

The current disease burden reflects the balance between threats and the effectiveness of preventive strategies. A low burden stresses the need for the continued support of these strategies. A high burden indicates the need for additional interventions. Disease burden estimates provide an integrated representation of the burden of infectious diseases. For priority-setting, however, other factors – such as threats and trends, costs and perception – should also be taken into account.

Recommendations

It would be worthwhile to extend the calculation of disease burden (e.g. based on DALYs) to other infectious diseases as well, because this composite measure gives more insight into the burden of diseases than single incidence or mortality data. A complete burden of disease study for a wider range of diseases is recommended although it needs to be explored if this is relevant to all 49 diseases. The selection of relevant diseases should be part of a complete burden of disease study. Such a study would benefit from an approach that identifies and combines several methods of investigation, including epidemiological modelling. In this short-term pilot project, pragmatic choices had to be made; however, a more comprehensive study should include a systematic and critical review of other disease burden estimates and of issues such as the most suitable data sources, the extent of underreporting, severity weights, outcome trees etcetera for each of the diseases under study. Furthermore, there needs to be a general agreement on methodological issues, like using a standard life table instead of the European life expectancy that changes over time or showing both discounted and undiscounted results in the future. Where possible, a full burden of disease study should join other international efforts in this field (i.e. the WHO update of the Global Burden of Disease for the year 2004). With regard to priority-setting, other aspects besides disease burden should also be taken into account, such as economic costs or presumed outbreak potential.

In order to obtain better insight into the epidemiology of infectious diseases in general, and into the disease burden in particular, the following recommendations are made:

- to improve the completeness and consistency of reporting of the morbidity and mortality rates in Europe, including information on the age-distribution;

- to conduct cohort studies on the incidence of complications and chronic sequelae, including possible variability between countries and factors associated with that variability;

- to analyse the sources of underreporting of morbidity and mortality in order to calibrate the data and to decrease inconsistencies in reporting between countries;

- to improve quantification of the mortality risks due to infectious diseases by cohort-studies;

- to integrate mathematical modelling to better understand the current and future burden of diseases, in particular for the HIV/AIDS epidemic, including the impact of HAART;

- to promote the collection of standardised data on disease severity and duration across Europe;

- to conduct studies on severity weights and to obtain consensus on the protocols for such studies, including national differences;

- to develop a standardised approach to value choices inherent in disease burden calculations.

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Research article

Exploration of cost effectiveness of active vaccination in the control of a school outbreak of hepatitis A in a deprived community in the United Kingdom

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In January 2006, an outbreak of hepatitis A occurred in a socio-economically deprived area of Liverpool, in the United Kingdom (UK), where extensive community outbreaks of hepatitis had previously occurred. A total of nine cases were confirmed. Five of these were linked within a primary school. The outbreak initially occurred among a close social contact group, but there was evidence of subsequent person-to-person transmission within a local primary school. The school was attended by 221 pupils (age range 4-12 years) with a total of 37 teaching and other staff (age range 22-71 years). Following local risk assessment, mass hepatitis A virus (HAV) vaccination was offered to all staff and pupils, as all were judged to be likely to have been in close contact with the affected pupils. A total of 188 of 217 eligible children (87%), and 33 of 37 staff (89%) were vaccinated. A salivary seroprevalence survey was conducted at the same time as vaccination to assess the benefit of this intervention in the school population. The survey confirmed high levels of susceptibility to hepatitis A in this setting (97.8%, 95% CI 91.6 to 99.62). The direct costs of intervention were estimated as £5,000. The cost effectiveness of intervention varies widely (£60.50 to £2,099 per case avoided) depending on the expected attack rate, which is difficult to estimate due to heterogeneity in published studies.

Introduction

This paper describes the course of an outbreak of hepatitis A in a socio-economically deprived community in Liverpool in the UK. There were five linked cases within a primary school, and mass vaccination of the schoolchildren and staff was undertaken. At the same time we undertook a seroprevalence survey and we use these data to estimate the cost-effectiveness of active HAV immunisation in the control of the outbreak.

Background

Study population and incidence of hepatitis

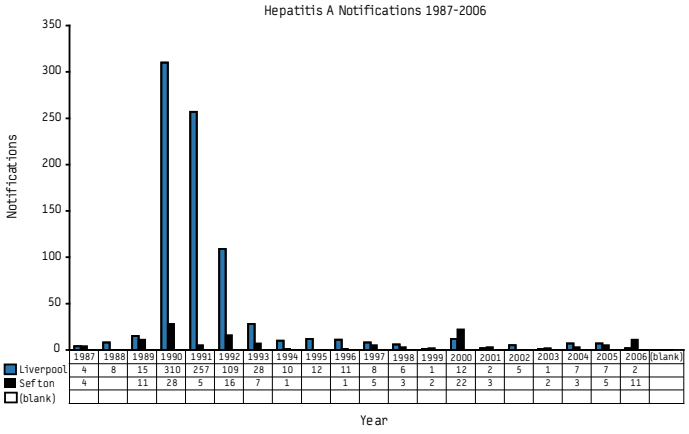
The incidence of HAV in the UK has fallen progressively over the last century, and there has been a marked drop in seroprevalence since the late 1980s [1]. Age-specific seroprevalence rates for 2000-2001 are available from a salivary survey in England and Wales [5]. The overall prevalence in the study rose steadily from 4.0 (95% CI 3 to 5) percent in children 1-4 years of age to 10.6 (95% CI 7 to 12.5) percent and 14.1 (95% 11-17.5) percent in persons aged 5-14 and 15-19 years, respectively.

The outbreak occurred in the borough of Sefton, to the north of the city of Liverpool, with an estimated population of 281,600 people in mid-2003 [2]. The area is poor white British, and has high levels of drug abuse [3,4]. The primary school involved had a population of 221 children, aged 3-11 years, and 37 staff members.

Over recent years, notification rates for hepatitis A in Sefton have been low, but widespread community outbreaks have been described in the locality in the past. Over 300 cases of hepatitis A were notified during the last epidemic year of 1990 in the neighbouring city of Liverpool, with previous community-wide outbreaks occurring at intervals of between six and 11 years [6]. Recent trends in hepatitis A notifications to public health authorities in Sefton and Liverpool are outlined in Figure 1.

Figure 1

Hepatitis A notifications in Liverpool and Sefton, United Kingdom, 1987-2006 (n=944)



Case definitions

The following definitions were used in the outbreak:

- A probable case was defined as a contact of a person with acute hepatitis A, with diarrhoea and/or vomiting and/or jaundice, with onset after 1 January 2006, excluding those with history of foreign travel.

- A contact was defined as a household member, a visitor who stayed overnight or shared food, kissing contact, or a child in the same class.

- A confirmed case was defined as the same as a probable case, but with serological evidence of acute infection based on measurement of HAV IgM and IgG.

Description of outbreak

Between January and February 2006, a hepatitis A outbreak was identified in the Sefton area of north Liverpool in the northwest of England. There were nine confirmed cases, five of them linked within a primary school, and this paper primarily concerns these children. The index case was a 12-year-old girl who was believed to have contracted hepatitis A from a family friend who was notified in early November 2005. The outbreak was initially based among the family and friends of the index case. Contact tracing in this group revealed 12 symptomatic contacts, who were offered serological testing. Five of these contacts were confirmed serologically to have acute hepatitis A (three were immune, two were negative and two did not accept the offer of testing). Three of these cases were school-children. Two attended the same primary school.

An outbreak control meeting was convened at the end of January 2006, where it was decided that active surveillance, provision of information on hand hygiene and environmental infection control measures were the most appropriate actions in the context of a community-based outbreak. Vaccination was offered to close contacts of cases, in line with UK guidelines [1]. The use of hepatitis A vaccine (HAV) is recommended in the UK for preventing secondary cases in people who are close contacts if it can be given within seven days from the onset of illness in the primary case [1].

Subsequent to this, three more symptomatic cases were identified in late February 2006 (Figure 1). Two of these cases were siblings attending the primary school, one of whom attended the same class as one of the previous cases. The other case was the mother of these children. The only risk factor identified was the link to the primary school and this suggested person-to-person spread within the school.

Following a second outbreak control meeting in March 2006, the decision was made to vaccinate the children and staff in the primary school. A public health risk assessment indicated that all children and staff attending the school should be considered as close contacts due to the small size of the school and the open plan design of classrooms. At the same time, a salivary seroprevalence survey was conducted. This was undertaken in order to identify asymptomatic cases, which are common in children, and also to determine the degree of immunity in this population to inform the management of future outbreaks.

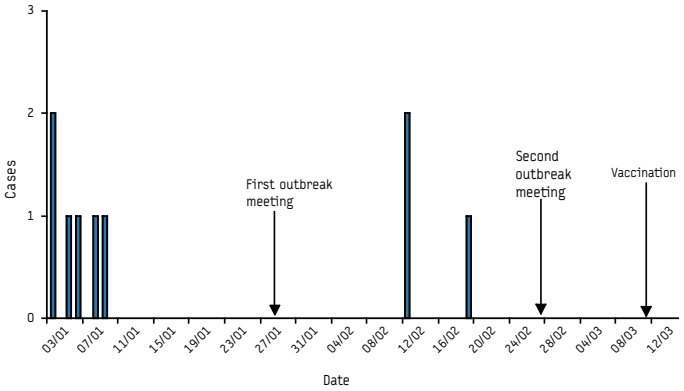
Methods

Vaccination and salivary survey

Hepatitis A vaccination (HAV) was offered to all of the staff and pupils in the school. This involved vaccinating 217 eligible children (four symptomatic cases excluded) in nine classes aged between 4 and 12 years old. Vaccination was undertaken by school nurses and occupational health services over two consecutive days in early March.

FIGURE 2

Epidemic curve of hepatitis A outbreak, Sefton, United Kingdom, 2006, showing number of cases against date of onset (n=9)



The Health Protection Agency (HPA) Centre for Infections (CfI) agreed to process a maximum of 100 saliva tests. Salivary sampling was undertaken in the two classes of children where there were acute cases, and in the two other classes that mixed most closely with these. The children in these classes were aged between 6 and 12 years old. The salivary sampling was undertaken at the same time as delivery of vaccination. Salivary sampling has been validated as an alternative to serology [7]. Furthermore, it has been used successfully to aid the epidemiological investigation of a number of outbreaks in the UK [8-11]. When compared to serum assays, the salivary technique using the antibody capture assay has been found in various studies to be between 100% and 98% sensitive and specific, respectively, for the detection of IgG and IgM anti-HAV antibody [12]. Anti-HAV IgG and IgM testing was calibrated against in-house standards (0-100 arbitrary units) which provide consistency of measurement and aid interpretation. Equivocal and reactive samples were re-tested to confirm reactivity.

Exploring cost-effectiveness

We estimated the observed attack rate in the outbreak, using the results from the salivary survey. We then intended to estimate cost-effectiveness by determining the number of cases avoided through intervention, on the basis of the difference between observed and expected attack rates. This was informed by a literature review of previous school based outbreaks (Search strategy: Pubmed searched using terms hepatitis A and attack rate). In the event, published attack rates were too heterogeneous to allow estimation of expected attack rate.

Instead we estimated the number of cases that could have been expected for a range of possible attack rates, following a review of the literature on previously reported outbreaks. Costing of the intervention was undertaken by calculating the direct costs of delivering the vaccination and environmental infection control measures. We then calculated the cost per case avoided, based on the difference between the observed and estimated numbers of cases, over a range of values.

Results

Vaccination

Children were screened for eligibility for vaccination using a questionnaire prior to the vaccination day. All 217/221 (four symptomatic cases excluded) eligible children were offered vaccination on 13 and 14 of March and 188 were vaccinated (87%). Of 37 eligible staff members, 33 were vaccinated (89%).

Table 1

Estimated direct costs of HAV vaccination and environmental intervention at a primary school in north-west England over the course of an outbreak in 2006

Component	Fixed or variable cost	Number of units	Cost (£) per unit	Total (£)
Vaccine	Variable	188	18	3,384
School nurse time	Variable	4 days	18,000 pa* 50 per day	200
Junior doctor time	Variable	2 days	30,000 pa 82 per day	164
Consultant in Communicable Disease Control	Variable	2 days	80,000 pa 220 per day	440
Teacher time	Variable	2 days	25,000 pa 70 per day	140
School cleaning interventions	Fixed			500
				4,829

* Per annum

Salivary survey

Salivary testing for anti-HAV IgM and IgG was undertaken on 92 of 217 (42%) asymptomatic children with the highest risk of exposure to cases. When screened for IgM and IgG anti-HAV 8 specimens showed some reactivity. These were re-tested and the overall interpretation indicated:

- 1 (1.1%, 95% CI 0 to 5.9%) acute/recent infection (nine-year-old in same class as symptomatic case)
- 1 (1.1%, 95% CI 0 to 5.9%) past infection (nine-year-old in same class as symptomatic case)
- 90 (97.8%, 95% CI 92.4 to 99.7) non-immune children

Estimation of overall attack rate

Five cases were confirmed to have acquired hepatitis A in this outbreak (four symptomatic, one asymptomatic identified on salivary survey). There were 125 children in the school who were not symptomatic, and were not surveyed. However, applying the results of the salivary survey provides an estimate of the number of asymptomatic cases that may not have been identified ([1.1/100] x 125 =1.4 cases, 95% CI 0 to 7.4). The salivary survey also suggests that a similar number in this group may be immune due to past infection (1.4 cases, 95% CI 0 to 7.4). These data were then used to infer smaller and larger estimates for the overall attack rate.

Attack rate = Total cases estimate/ Estimate of number of susceptible persons in the group x 100

= [(5+1.4) / (221 – 1 – 1.4)] x 100
= 2.9 % (confidence limits 2.3% to 5.6%)
= [(5+7) / (221 – 1 – 7)] x 100 = 5.6 % (larger estimate)
= [(5+0) / (221 – 1 – 0)] x 100 = 2.3% (smaller estimate)

Costing

Table 1 shows the estimated direct costs of HAV vaccination and environmental interventions at the primary school over the course of the outbreak.

Literature review

The literature review of HAV outbreaks in open and closed school settings reveals a range of values for attack rates (Table 2).

Table 2

Results of literature review of attack rates in HAV outbreaks in open and closed school settings

Paper	Setting	Age range	Documented intervention	Attack rate
Arnaez 2004 [13]	Nursery day care center, Spain	1-3 years	Active immunisation, Improved hygiene	8.7%
Ang 2000 [14]	'Special needs' school, UK	4-16 years	Active immunisation, Improved hygiene	42%
Bonanni 1998 [15]	Nursery school, Italy	3-6 years	Active immunisation	27%
Panella 1998 [16]	Day care centre, school, nursery	Up to 29 years	Immunoglobulin administration	12%
Leoni 1998 [17]	Primary school, Italy	6-11 years	Improved hygiene	7.9% females, 18.9% males
Stuart 1992 [8]	Infant and junior school, UK	5-7 years (Infant school) 8-10 years (junior school)	Improved hygiene	4.7% infants 2.8% juniors
Tilley 1960 [18]	School, UK	5-14 years	Unclear	20.1%

Discussion

This paper describes a mass HAV vaccine intervention in a primary school near Liverpool in the UK. HAV vaccine is now recommended in the UK instead of human normal immunoglobulin (HNIG) in outbreaks [1]. There are concerns about the transmission of known and unknown infective agents through the use of pooled human blood products. The high uptake rate (87%) suggests that vaccination was an acceptable intervention in this particular community.

We intended to calculate the cost-effectiveness of intervention by estimating an expected attack rate. This proved difficult due to the heterogeneity of published outbreaks. Attack rates from published outbreaks range from 2.8% to 42%. The published outbreaks also differ in terms of age profile, setting and the extent of public health intervention (table 4). It is also likely that there is publication bias favouring outbreaks with higher attack rates. This precludes the estimation of expected attack rate in the absence of intervention, and accurate estimation of cost effectiveness, based on cases prevented. Instead, we estimated the effects of different expected attack rates on cost effectiveness ratios.

The direct cost of our intervention was approximately £5,000. Following the intervention, there were no further cases of HAV in the school, and the final attack rate was low (2.9%). Table 4, however, illustrates how the cost-effectiveness ratio varies widely, from £60.50 to £2,099 over a range of possible expected attack rates. Intervention included environmental infection control measures as well as active vaccination, and it is not possible to determine the relative contribution of each component on the course of the outbreak. This analysis of cost-effectiveness ratios makes the assumption that the intervention changed the course of the outbreak, and reduced the number of subsequent cases, but it is possible that the global attack rate could have been unchanged by the intervention. It is also possible that asymptomatic cases occurred subsequent to vaccination.

There is scant literature regarding cost effectiveness of HAV vaccination in outbreak situations with which to compare these results: Lucioni et al [19] calculated the mean total cost per patient (treatment and indirect costs) involved in an outbreak in Italy to be $US 4,150. Pechevis et al [20] used a decision tree model and estimated that the cost per symptomatic case avoided varies between 700 and 1,300 euros (1 euro = 0.93 US dollars) for vaccination of household contacts in outbreak situations. They also conclude that vaccination of contacts in day care centers and schools results in overall cost-savings in their model. Crowcroft et al [1] estimate the cost of prophylaxis with HAV vaccine or HNIG as less than £400 per case avoided. An economic evaluation of HAV vaccination strategies in Italy concludes that vaccination of contacts, compared to doing nothing, is an economically worthwhile routine measure [17]. These data need to be interpreted in the context of the age group. In younger schoolchildren, cases are often mild or asymptomatic, and the cost implication needs to be considered with this in mind. However, the potential risk to older contacts, including pregnant and other staff and pupils, as well as household contacts is an important consideration. In addition, the economic analysis does not take account of the longer term benefits of vaccinating a highly susceptible group at risk of future outbreaks.

The findings from the salivary survey are consistent with the changing epidemiology of hepatitis A in the UK and globally, reflecting declining seroprevalence and increasing susceptibility [21]. Some 90 out of 92 (97.8%, 95% CI 91.6 to 99.6) children sampled were susceptible to HAV infection. This is similar to figures in a recent formal seroprevalence survey [5] that found susceptibility of around 95% in this birth cohort. The primary school is situated in one of the more socio-economically deprived areas of the UK, where one might expect seroprevalence rates to be higher, since these factors are correlated. It is not surprising, however, that this association is absent here. Since HAV can no longer be considered endemic in the UK, this link may not apply universally. Part of the rationale for the salivary survey was to determine the number of asymptomatic secondary cases, and the sampling was undertaken to cover those children most at risk through contact with a symptomatic case. Only one asymptomatic case was identified (1/92). Thus, of the five cases at the primary school, four were symptomatic. This is perhaps unusual, since many reports state that children are more likely to be asymptomatic at this age (11).

The salivary survey results are consistent with other findings suggesting an increasingly susceptible child population in the UK. Salivary surveys may have value in similar HAV outbreak situations. Salivary surveys appear acceptable and are cheaper than serological surveys. They do not require staff trained to take blood samples, and the collection equipment is cheaper (£2 (3 euros) per person for serology compared to £0.54 (86 euro-cents) for oral swab) [5]. Prompt local risk assessment and timely intervention with HAV vaccination in school outbreaks may be of benefit and help prevent widespread community transmission in areas where prevalence has historically been high. It is difficult to estimate cost-effectiveness ratios for such an intervention, but the range of values calculated in this outbreak (£60.50 to £2,099 per case avoided) is broadly similar to those reported elsewhere.

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Research article

General practitioners' role in the notification of communicable diseases – study in Malta

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General practitioners (GPs) have an essential role in notification of communicable diseases. The main aim of the study described here was to assess the GPs' awareness of and attitudes towards the notification system in Malta, with special focus on infectious intestinal disease (IID). A questionnaire collecting demographic data, information on reporting practices, opinions on the existing notification system and suggestions for improvement was sent to 256 GPs working in either private or public health sector. In all, 150 GPs took part in the survey (response rate 58.6%). The responses revealed that Maltese GPs were aware of their obligations to notify communicable diseases but often did not report them, relying on the hospitals or laboratories to do so. The Disease Surveillance Unit (DSU) website and medical school training were the main sources of information on notification. Notification forms were obtained from health centres and usually kept at the place of work. Most GPs reported filling in the forms during the patients' visits. Private GPs tended to notify earlier than GPs working in public health centers. Among IID, food-borne illness was reported more frequently than person-to-person transmitted gastroenteritis and was considered to be of a higher priority with regard to public health importance ($p<0.001$). The survey highlighted also some areas for improvement, including need of feedback especially by direct communication or a newsletter.

Introduction

Routine surveillance of communicable diseases is fundamental to public health policy and practice [1]. Passive surveillance systems which are the most common depend on statutory reporting of communicable diseases by general practitioners (GPs), hospital doctors and laboratories. In Malta, 67 specified communicable diseases are statutorily notifiable. Notification is mandatory by law for all doctors in both public and private sectors [2] whereby doctors report cases on the basis of symptoms only, not necessarily waiting for lab-confirmation. In addition, a supplementary system is in place which obliges all public and private medical diagnostic laboratories to report laboratory-confirmed cases [3].

In order to evaluate the role of GPs in the notification system and identify areas of improvement, a study was conducted in December 2005. The specific objectives were:

- To assess GPs' current reporting practices.
- To describe GPs' attitudes towards the notification system.
- To collect GPs' views on the notification of communicable diseases, particularly with regard to infectious intestinal disease (IID).
- To ask GPs' opinions on proposed changes in the notification system.

The special focus of the study was on infectious intestinal disease (IID) since it is known that surveillance systems capture only a tiny fraction of the infectious intestinal disease that is actually occurring in the community [4]. This indicates that there must be significant lacunae in information describing the magnitude of infectious intestinal disease, especially at the population level including food-borne illness and infectious gastroenteritis. The study described in this paper formed part of a series of studies to evaluate the surveillance system and to find ways to improve the under-reporting.

Methods

The study employed both quantitative and qualitative research methods, and comprised two phases:

- Phase 1: Survey (postal and hand-delivered)
- Phase 2: Focus group discussion

Phase 1: Survey

Study population

The study population comprised GPs working in the private sector and in publicly funded health centres in Malta. Both types of GPs provide health care service at primary level but patients who consult private GPs have to pay for the service whilst the ones frequenting the health centres do not. To date there has been no official register of all GPs in Malta. For the purpose of this study, a list of private GPs registered with pharmaceutical wholesale dealers (175 GPs) was used. Even though it did not cover all private GPs in Malta, it was considered to be representative of the whole group. The list of health centre doctors (81 GPs), on the other hand, was comprehensive since it was obtained from the Primary Health Care Department which employs them.

Questionnaire

The questionnaire used for this study was prepared on the basis of issues raised during earlier meetings with GPs and on questionnaires used in studies with similar objectives performed

previously in Malta [5], Canada [6], United States [7] and Germany [8], with appropriate permissions obtained.

The questionnaire included:

Demographic Information
Number of years in practice
Type of practice
Access to internet
Sources of information on notification
Reporting practices
Sources of certificates
Where notification forms are kept
When notification forms are filled in
Reliance on laboratory/hospital for notification
Actions taken by Disease Surveillance
Unit in response to notification
Frequency of notification of selected diseases
Criteria used for notification
Ranking of diseases according to public health importance
Attitudes towards notification
Reasons causing physicians not to notify
Proposed suggestions to improve physicians' notification
Feedback expected on reportable diseases
Type of feedback to GPs
Regularity of feedback
Medium to send feedback
Identified subjects for feedback
Participation in sentinel surveillance systems
Infectious Intestinal Disease Cases
Number of patients with IID seen in practice during one month preceding the survey
Symptoms of IID
Stool culture ordering practice for cases
Factors affecting stool culture requests

The questionnaire was sent out by post to all listed private GPs along with self-addressed stamped envelopes to complete and return. In publicly funded health centres the questionnaires were distributed among doctors by their superiors and then collected by hand upon completion. On returning a completed questionnaire, the GPs were included in a prize lottery.

Case definitions

A case of IID was defined as an individual who reported having at least three episodes of diarrhoea (defined as loose stools) within 24 hours or vomiting at least three times in 24 hours, or who suffered diarrhoea or vomiting with two or more additional symptoms. A case of food-borne illness was defined as a case of IID suspected or confirmed to be related to a food source; whereas gastroenteritis was defined as a case of IID in which person to person transmission was suspected.

Phase 2: Focus group discussion

The focus group discussion was conducted after the analysis of the postal survey had been completed, to discuss the main findings of the study and to elaborate on specific areas. For this purpose topic guidelines were developed based on the review of literature and the results of the postal survey.

The focus group consisted of the first author as coordinator, two GPs (one private and one public affiliated), a hospital physician, and a GP with work experience at the Disease Surveillance Unit (DSU).

The ethical approval for the study, including the lottery incentive, was obtained from the Research Ethics Committee of the University of Malta. The data obtained from the postal questionnaire was analysed using SPSS Version 14. Focus group session was audio-taped with the interviewees consent. All tapes were fully transcribed and the information was analysed according to the themes of interest of the study.

Results

Phase 1: Survey

The questionnaire was sent to 175 private general practitioners, of whom 113 replied (a response rate of 64.6%) and 81 health centre doctors of whom 37 returned the questionnaire (a response rate of 45.7%), giving an overall response rate of 58.6% (150 out of 256). The majority of doctors (25.5%) had been practicing for about 16 to 20 years. Access to the internet was available for 66.9% (n=97) of GPs. A further 2.14% (n=30) stated that they planned to have access soon. The major source of information about the responsibility of doctors to notify infectious diseases was the website of DSU, the national centre for surveillance in Malta (31.5%; n=147) while medical school training was the next commonest source (Table 1).

TABLE 1

Sources of information about the responsibility to notify (more than one response option was available per doctor). Survey of general practitioners, Malta, 2005

Source of information	Total number of responses (n= 467)	% of total responses
Disease Surveillance Unit (DSU) website	147	31.5
Medical School training	120	25.7
Department of Health circulars	91	19.5
Infectious Disease notification form	42	8.9
Post-graduate training	22	4.7
DSU newsletter	22	4.7
DSU annual reports	13	2.8
Lectures by DSU staff	8	1.7
Never learned about the responsibility to notify	2	0.4

The GPs who had 11-30 years of practice (62.1% of participants) knew about notification mainly from the following sources: DSU website (31.8%, p=<0.0001); Department of Health circulars (19.9%, p=<0.0001); medical school training (24.3%, p=<0.0001); post graduate training (5.8%, p=0.004); DSU lectures (2.1%, p=0.023) and DSU annual reports (2.7%, p=0.4441).

The majority of doctors obtain notification forms from health centres (41.2%, n=63) and state-owned medical equipment and supplies stores (18.9%; n=29). Other sources included the DSU website (12.4%; n=19); DSU office (9.8%; n=15); St. Luke's

Hospital (7.8%; n=12); another governmental hospital (5.2%; n=8) and local health inspector (1.3%; n=2).

Most GPs (37.3%, n=79), fill in the notification form during the patient's visit; 16.5% (n= 57) of doctors wait till the end of the day; while 15.2% (n=25) complete it immediately after the patient's visit. 10.9% of GPs (n= 18) notify cases at the end of the week, 6.1% (n=10) do so only when prompted by the DSU by means of regular reminders; whereas 14.0% (n=23) rely on laboratories or on hospital doctors to notify. There was a significant association between the group of private GPs and early notification (p= 0.05), indicating that private GPs tend to notify earlier than GPs employed in the public health centres.

Almost half of the GPs (46.2%; n=67) stated that they would always report food-borne illness. However, only 9% (n=13) would do so for gastroenteritis and 34.5% (n=50) admitted they never reported gastroenteritis cases. 48.8% (n= 61) claimed that they reported food-borne illness on confirmation while 75.2% (n=53) claimed to report gastroenteritis on confirmation (Figure). There was a significant relationship between frequency of notification and having confirmed cases of gastroenteritis (p=0.001).

Food-borne illness was rated as a high priority disease according to public health importance by more than half of the GPs surveyed (55.2%; n=80) whilst gastroenteritis was considered a high priority disease by only 15.9% of GPs (n=23). For both food-borne illness and gastroenteritis, there was a significant relationship between the frequency of reporting and the rated public health importance of the disease (p< 0.001) (Table 2).

Table 2

Priority of disease according to public health importance. Survey of general practitioners, Malta, 2005

Disease	High (%)	Moderate (%)	Low (%)
Meningitis	86.2	4.1	0.7
AIDS	83.4	7.6	2.8
HIV	78.6	9	4.8
Legionella	77.9	13.8	2.1
Hepatitis B	74.5	15.9	4.1
Hepatitis C	72.4	17.9	4.1
Acute encephalitis	71	17.2	3.4
Hepatitis A	65.5	21.4	4.8
Typhoid	55.9	26.9	6.9
Food-borne illness	55.2	26.9	6.2
Syphilis	45.5	29	15.2
Dysentery	44.8	36.6	9
Leptospirosis	42.8	39.3	9
Typhus	37.9	37.2	15.9
Pertussis	30.3	42.8	17.2
Measles	29	34.5	25.5
Leishmaniasis	28.3	44.8	18.6
Gonorrhoea	27.6	41.4	21.4
Rubella	24.8	33.8	29
Mumps	22.8	37.2	28.3
Varicella	21.4	33.1	32.4
Gastroenteritis	15.9	33.1	32.4
Chlamydia	13.8	37.2	37.2
Pneumonia	9	38.6	37.2
Erysipelas	8.3	22.8	53.1

Figure

Reporting disease on suspicion or upon confirmation. Survey of general practitioners, Malta, 2005

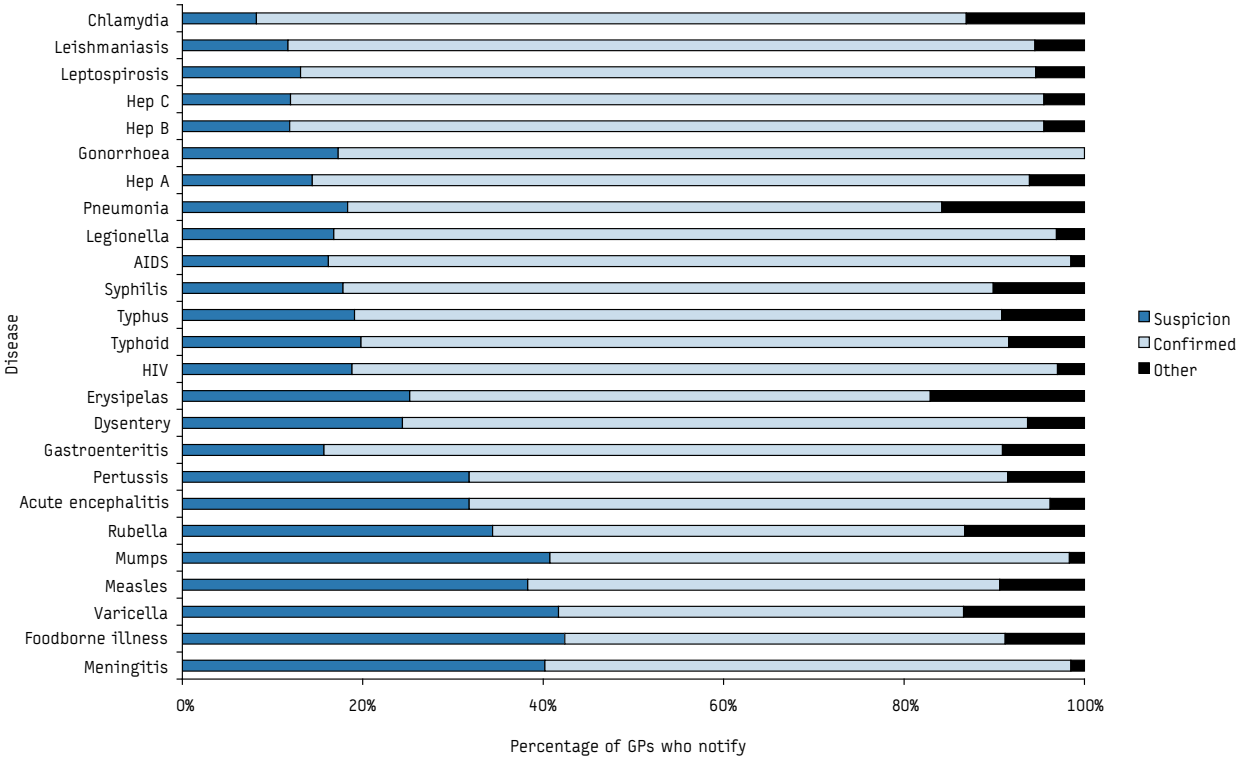

TABLE 3

Reasons for under-notification. Survey of general practitioners, Malta, 2005

Reason for under-notification	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
Expect hospital to notify referred patients	40.7	33.8	13.1	8.3	4.1
Expect laboratory to report	26.2	35.2	13.8	21.4	3.4
No feedback from DSU	15.2	31	14.5	27.6	11.7
No penalty for non-notifiers	11.7	22.8	17.9	24.8	22.8
Violation of patient confidentiality	10.3	29.7	15.9	29	15.2
Expose patient to embarrassment and harassment	9.7	35.9	17.9	23.4	13.1
No remuneration for notification	9	19.3	13.1	25.5	33.1
Pressure from patients not to expose them	7.6	26.9	20.7	33.1	11
No relevance in reporting	4.1	15.9	13.8	35.2	31.0

The commonest reason for under- or non-notification by GPs was the reliance on the hospital or the laboratory to report. Also, GPs felt that notification may expose patients to embarrassment and harassment by public health officers (Table 3).

When asked for views on possible improvements in the notification system, 70.3% of the GPs (n=102) strongly agreed that it would be useful to have diseases that necessitated laboratory confirmation notified only by the laboratories. Emphasising notification responsibilities and practices in undergraduate medical education (69%; n=100 strongly agreed) was also considered to be beneficial (Table 4).

Most GPs considered it important to have some form of feedback on notified cases, with half of the GPs preferring direct communication by the DSU regarding cases investigated (50.00%, n=85), whilst 18.8% (n=32) chose the DSU newsletter. Quarterly feedback was the preferred frequency (60.7%; n= 88), only 6.9% of GPs (n=10) recommended feedback in exceptional cases only. Feedback via the internet (36.2%; n=63) followed by a letter by post (25.3%; n= 44) were the recommended media.

Information on outbreaks was the preferred topic for feedback among 27.4% of GPs (n=132 responses) with other information on trends of communicable diseases (17.4%, n=84 responses),

TABLE 4

Views on proposed interventions to notification system. Survey of general practitioners, Malta, 2005

Proposal	Strongly agree	Slightly agree	Not at all	Do not know
Have laboratory-confirmed cases notifiable by laboratories only	70.3	18.6	8.3	2.8
Emphasise notification responsibilities in undergraduate curricula	69	26.2	4.1	0.7
Telephone confirmation of the outcome of investigations to notifiers	53.1	31	11.7	4.1
Use anonymous reporting for socially stigmatised diseases	52.4	21.4	17.9	8.3
Use set of standard diagnostic criteria	51	29	14.5	5.5
Discretion by DSU in investigations	49	33.1	13.1	4.8
Shorten the list of notifiable diseases	44.8	35.2	15.9	4.1
Award accreditation points to notifiers	44.1	27.6	20.7	7.6
Use telephone/voice mail answering machine reporting	41.4	33.8	19.3	5.5
Link remuneration with notifications	38.6	22.1	28.3	11
Notification on suspicion only	35.2	37.2	19.3	8.3
Send feedback to GPs on national rates to compare with their own data	34.5	46.9	14.5	4.1
Use legal obligation and notification requirements in assessments/exams	30.3	45.5	19.3	4.8
Send reminders to those with low notifications	28.3	41.4	24.8	5.5
Enforce criminal penalties for non-notifiers	20	20	47.6	12.4

vaccination activities (18.5%; n=89 responses), detection of importeddiseases (17.2%; n=83 responses) and recommendations on prevention proposed by (18.3%; n=88 responses) of GPs. The majority of respondents (52.4%; n=76) were not satisfied with the present type of feedback while 18.6% (n=27) could not voice an opinion about it.

GPs are often invited to participate in voluntary sentinel surveillance schemes. In this survey, 40.7% (n=59) of GPs stated that the most important incentive to participate is the easy handling of the system, 33.10% (n=48) indicated reimbursement, and 26.2% (n=38) mentioned feedback of data.

A high percentage of GPs, (90.3%; n=131) had seen a patient with IID in the month preceding the survey. The total number of estimated IID seen in this period by the 131 participating GPs was 2,747. The mean number of cases of IID seen by GPs in the month preceding the survey was 20.9 (95% CI 9.58-32.36). The distribution was skewed however, with a median of eight cases and a mode of 10 cases.

GPs ordered a stool culture in 12.22% (n=16) of cases. The most important reason that influenced the GPs to order a stool culture was the duration of symptoms (37.5%, n=6).

Phase 2: Focus group discussion

The focus group highlighted the importance of hospitals as main sources of information on notification. Although the DSU website was the preferred source indicated by GPs in the survey, yet the focus group pointed out that there are situations where hospital doctors do not use this source since many do not know that they can access the DSU website from the hospital computers. The focus group participants also agreed that notification forms should be at hand: I will notify if I have a notification form in my hand". The members of the focus group stressed that the perceived public health importance of a disease is a significant factor influencing whether to notify or not, which is in agreement with the findings of the GP survey. The focus group also urged for caution by the public health authority personnel in dealing with patients.

Regarding incentives to notify, the focus group recommended reward in the form of continuing medical education points for those who diligently notify as a way to encourage notifications. They also suggested a free phone for notification whereby the doctors could just call to notify without sending in a formal notification.

In addition to the incentives to participate in the sentinel surveillance systems that were mentioned in the GPs' survey, the focus group brought up co-authorship in papers published in scientific journals.

This qualitative part of the study confirmed the reluctance of GPs to ask for stool cultures: "We are not interested in the aetiology!" According to the focus group, the GPs main interest is that of clinically treating the patient. Moreover, GPs usually experience difficulties in both getting a patient to submit a sample and submitting it to a laboratory via the health centre, so that they ask for a sample only in severe cases.

Discussion

The study described in this paper used a combination of qualitative and quantitative methods. The questionnaire used in its first phase was prepared on the basis of issues raised during various meetings held with general practitioners hence it was felt that there was no need to repeat a focus group prior to the initial quantitative study. Instead a focus group discussion was performed to discuss and elaborate the results of the survey.

The questionnaires were distributed mostly by post, which is a cheaper and less time-consuming alternative to face-to-face interviews. This type of study also reduces the observer bias. However, non-response and incomplete response are important biases which should be taken into consideration when interpreting the data [9]. In a study assessing physicians' response to surveys in the United Kingdom it was found that pre-notification of survey recipients, personalising the survey mail-out package and non-monetary incentives were not associated with increased response rates [10]. Yet, monetary incentives, the use of stamps on both outgoing and return envelopes and short questionnaires increased the response rates. It is generally accepted that non-response bias may be of less concern in physician surveys than in surveys of the general public [10]. At any rate, in the study described here a very good response rate was obtained, especially from private GPs.

The demographics of the study population including age, gender and years in practice were not compared to those of the general GP population in Malta since the latter data were not available. However, previous studies have shown that demographic differences have minimal influences on attitudes toward reporting [11].

Taking into consideration the results of the survey and the focus group discussion, a few issues merit some more attention. Lack of awareness of the legal obligation and especially of the notification procedures is a problem which leads to under-notification in many countries [8,12-18]. However, the present survey, as well as a previous study done in Malta [6], show that knowledge of the responsibilities and the procedures of notification is not a problem in our country. Regarding the reporting practices, the survey showed that most GPs tend to fill in the notification forms in the presence of their patients. This is understandable since many GPs do not keep records of patients' visits. It is understandable that the time the GP has available for the patient is limited, hence if they were to invest in electronic record keeping, this would enhance the reporting system. However, a validation system is required if this system is to be introduced [18].

As shown in the survey, the readiness to report and timeliness of notification depend on the perceived severity of the disease and its public health implications. In Malta, although there is a legal requirement for notification, no reporting deadline is mentioned in the legislation. Yet there is general awareness that diseases important from the public health point of view (like meningococcal disease) and/or causing outbreaks are to be reported immediately. For the latter, timeliness of reporting is especially important, otherwise notifications would not be of any use in outbreak identification [19].

A study in the Netherlands has shown that internet-based reporting improves timeliness and completeness of notification [20]. General web-based reporting has been feasible in Sweden using SmiNet-2 since most clinicians in Sweden have access to the internet [21]. It would be useful to encourage such a mode of notification also in Malta and other countries, albeit keeping in mind that at the moment only two thirds of Maltese GPs have access to internet (present survey).

One area of concern highlighted by the survey results is the reliance of general practitioners on hospital physicians to notify when a case is referred to hospital. This issue needs clarification as to who should report such cases. Should it be the referral doctor who is in a position to report earlier, or the hospital physician who can confirm the case at a later stage? Similarly, for diseases which require laboratory confirmation, there is strong reliance by GPs on the laboratories to notify. For some diseases, there is reluctance to notify without laboratory confirmation [22-24]. Medical diagnostic laboratories in Malta are obliged by law [3] to report notifiable diseases upon confirmation. This laboratory-based notification system would be sufficient for certain diseases such as HIV, Hepatitis B, Hepatitis C and other sexually transmitted diseases. However, in cases of food-borne illness, such system could lead to a delay in notification and hence hinder actions to be taken by public health authorities [25].

Among areas for improvement the study emphasized the role of showing practical examples of action taken by the DSU in response to timely notifications. The mainstay of a good surveillance system depends on a strong relationship between the surveillance centre and those who are supplying the information, that is, the physicians both at GP level and at hospital level. It is an established fact that completeness of reporting is directly related to the degree of confidence in the health department [9]. As seen in this study, although many GPs showed confidence in the system and knew that positive action was taken in response to notification, only few knew what was actually done. Many physicians expressed concern over how the patients would react to the investigation being carried out by the public health authorities. This issue is very important, especially for the GPs who take years to build a relationship of trust with their patients, and would not want that trust to be shattered by anyone else. In fact the system foresees that all cases that are notified should be contacted by trained doctors working in DSU who discretely and professionally collect demographic data, clinical information, confirm cases and identify any areas where corrective control measures can be taken. Informing physicians of what is actually done and showing discretion on the part of DSU medical officers should help to overcome these barriers for the benefit of all.

The study showed that some incentives to increase doctors' participation in the notification system are controversial. Remuneration of notifiers was accepted only by one third of GPs, in contrast to other countries where such incentives had stimulated more enthusiasm [17,26]. Acknowledgment of notification in the form of awarding points of continuing medical education was better accepted with relatively more doctors agreeing to it than to monetary remuneration. Also, improving the relationship between the surveillance unit and the GPs has been shown to improve the attitudes of doctors regarding the notification system [27-28].

By including specific questions on IID in the questionnaire, the study has shown that many of the cases that are presenting at GP level remain unconfirmed since relatively few doctors ask their patients to submit stool samples. The results of the survey indicate that GPs ask for laboratory testing in order to improve clinical decisions and not for epidemiological reasons as was found in GP practices in other countries [28-30]. Our study has also demonstrated a relatively high burden of IID in Malta in the period of study [4,31-33]

Conclusion

From this study it is apparent that physicians know about their legal responsibilities to notify yet still many do not notify. Surveillance systems need to identify measures to enhance notification by encouraging physicians to report. A number of recommendations have been put forward in this study, including continuous communication on actions taken by the public health authorities in connection with surveillance data and regular feedback on communicable disease issues, including outbreaks. Many notification systems across Europe rely on notification by general practitioners and it is widely known that there is a high rate of under-notification. The results and recommendations made on the basis of this study can be useful for countries with similar surveillance systems. The methodology applied here can also be used to assess the situation in other countries. Improving notification of communicable diseases in every European country is crucial for the future harmonization of surveillance systems across Europe.

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Pilot scheme for monitoring sickness absence in schools during the 2006/07 winter in England: can these data be used as a proxy for influenza activity?

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During influenza epidemics, school-aged children are amongst the first affected patients. They frequently then spread the virus within their families. Recognising influenza activity in schools may therefore be an important indicator of early activity in the wider community. During 2005/06, influenza B was associated with high levels of morbidity in school-children and over 600 schools outbreaks were reported to the Health Protection Agency by local Health Protection Units. While it is not possible to directly monitor influenza in schools, the feasibility and validity of using sentinel school absenteeism data, as a proxy for influenza in the community can be investigated. From week 02/07 to 20/07, eight primary and three secondary schools from five HPA regions were able, via the Department of Health-funded Health Protection Informatics website, to report daily electronic registration data, relating to absenteeism due to illness. Aggregated absenteeism data due to illness peaked the same week as indices for the age group comparable to that used by the Royal College for General Practitioners and NHS Direct schemes. When illness-defined absenteeism data was stratified into primary and secondary schools, absence in primary schools peaked one week before that in secondary schools and the established schemes for all ages. The start time of the study meant that initial increases in activity could not be measured. These encouraging results justify expanding this sentinel scheme to collect more rigorous evidence of the usefulness of absenteeism as a proxy for influenza activity and a tool to inform policy and trigger local responses.

Introduction

During influenza epidemics, school-aged children are amongst the first affected and then go on to spread the virus through the community [1-3]. Recognising influenza activity in schools could therefore be an important early indicator of seasonal activity in the wider community. During the 2005/06 season, influenza B was associated with high levels of morbidity in school children and over 600 outbreaks in schools were passively reported to the Health Protection Agency (HPA) by local Health Protection Units (HPUs) [4].

While there are considerable difficulties associated with directly monitoring influenza in schools, there is scope to investigate sentinel school absenteeism data as an indicator of influenza activity in the community. A similar study in New York [5] showed little benefit but analysis was based on overall absenteeism rates; absence data coded for illness, as in the United Kingdom (UK), could be a more sensitive tool for surveillance [6]. Following the large number of school outbreaks detected in the 2005/06 influenza season, the Department for Children, Schools and Families (DCSF) agreed to collaborate in a pilot study to test the feasibility of monitoring sickness absence in a sample of schools during the winter of 2006/07.

The main aims of this study were to test the feasibility of collecting school absenteeism data, to evaluate the usefulness of these data as an indicator of influenza activity and to improve the early detection of influenza outbreaks. The predominant circulating virus in the 2006/07 season (October 2006 to May 2007) was influenza A (H3) and indices of activity stayed well within normal limits. Compared to the 2005/06 season, in 2006/07 there were far fewer reported school outbreaks (n=20) to HPA Centre for Infections from HPUs [7], suggesting less influenza activity generally. If absenteeism due to illness could be shown to be an indicator of community activity in a low flu year, then not only would proof of concept of the pilot be achieved but the scheme would have applications beyond high activity, influenza B winters.

Methods

DCSF provided the HPA with a list of 90 schools that kept electronic registers and who could submit daily attendance data of pupils. The recruitment process was two-tiered: a direct approach to head teachers of the listed schools by the Centre for Infections and a request to local Health Protection Units to act as a first point of contact for recruited schools and to find other schools that kept electronic registers and were willing to participate in their area. The recruitment of schools based on DCSF listings was problematic, with the lines of communication from DCSF to HPA to school emerging as a key issue and, as a result, 17 were fully recruited but only 11 regularly provided data. Eight primary and three secondary schools from five of the nine HPA regions participated. Log-ins and passwords were provided to the schools in order for them to submit daily electronic register data for daily absenteeism due to illness, by age, via the Department of Health (DH) funded Health Protection Informatics (HPI) website. "Illness" is used by schools to account for absence when confirmed by parents and included respiratory and non-respiratory illness; absence for any other reason was not considered. Daily aggregated data were collected, episode incidence, i.e. the number of new absences and the duration of absence for an individual, were not collected. These data represent the total number of absentees for every school day in the study period: week ending 14/01/07 (week 02/07) to week ending 20/05/07 (week 20/07).

A number of schools were reluctant to join the surveillance scheme due to concerns of an extra workload, but with the development of clear user guides it was possible to show that this

would involve little resource on the part of the school and could deliver high-impact results. The provision of support for online reporting was felt to be useful during the first few weeks. Although data collection should have started at the beginning of the scholastic year, i.e. the week ending 10/09/06 (week 36/06), due to logistical problems absenteeism data were only collected as of the week ending 14/01/07 (week 02/07).

The primary school population for this study comprised school year groups 1-6 (age group 4-11 years). Nursery and pre-school classes were excluded; they often comprised two groups (one group attending in the morning only and the other attending in the afternoon only). Similarly, school year groups 7-11 (age group 11-16 years) comprised the secondary school returns because the year groups 12 and 13 (age group 16-18 years) tend to be absent more than any other secondary school year groups, due to scheduled study leave. Electronic registering was split into two sessions per day and, accordingly, the HPI website was set up so that the number of sessions in a day would be twice the number of children that attend the school. However, this presumed that all children would be at school for five full days per week and would not accurately record the attendance of children who might only be present for five half days a week or those with scheduled study leave.

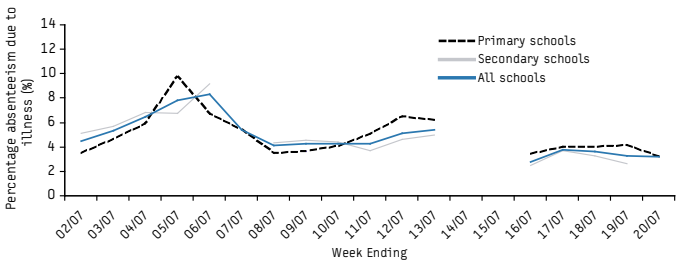
Weekly rates for overall absenteeism and illness-coded absenteeism were calculated and stratified in to primary and secondary schools. These data were then plotted against a number of indices of influenza activity; the Royal College of General Practitioners (RCGP) episode incidence rate (i.e. the weekly number of new consultations from sentinel general practitioners (GPs)) for influenza-like illness (ILI) per 100,000 population for all ages and the 5-14 years age group, comparable to the sample under consideration; the number of positive influenza samples taken by GPs involved in the RCGP sentinel scheme (the number of positive respiratory syncitial virus (RSV) samples were also considered to investigate the possible effect of confounding by this seasonal respiratory virus); the number of outbreaks in schools reported by HPUs; and the NHS Direct proportion of "fever" calls (5-14 years) and "cold/flu" calls (all ages). NHS Direct is a nurse led telephone helpline that can be used as a syndromic surveillance tool. Experience from several years of surveillance of NHS Direct calls has shown that rises in the proportion of "fever" calls in the 5-14 years age group and "cold/flu" calls in all ages may provide an early warning of a rise in influenza and influenza-like-illness in the community [8].

Results

Of the 11 schools involved in the study, at least nine reported data in any given week between week 02/07 and 11/07. Between weeks 12/07 and 20/07 returns were provided by between seven and nine schools. These figures include nil returns made by schools for weeks of school holiday closure. Week 20/07 is regarded as the end of the influenza season; data after this week were not analysed. When illness-defined absenteeism data was stratified into primary and secondary schools, illness absence in primary schools peaked one week before that in secondary schools during weeks 05/07 and 06/07 respectively (Figure 1). The peak illness absence in both school types was of a similar magnitude at 9.8% in primary and 9.2% in secondary schools. The half term break for all recruited secondary schools was in week 11/07 and the Easter break for all recruited schools (both primary and secondary) was in week 14/07 and 15/07. As a consequence, no absenteeism data were collected for the specified school groups in these weeks. Combined illness-defined absenteeism data peaked in the same week as the secondary school data (week 06/07) at 8.3% absence in week ending 10/07.

FIGURE 1

Absenteeism due to illness in primary schools, secondary schools and in both primary and secondary schools combined



Combined illness-defined absenteeism data for primary and secondary schools was assessed against the episode incidence rate for influenza-like illness (all ages) obtained from the Weekly Returns Service of the RCGP, the positive influenza and RSV from this scheme and the proportion of NHS Direct "cold/flu" calls (all ages). The series was extended retrospectively to consider data from these current surveillance schemes from week 48/06. The peak RCGP rate and number of positive influenza samples was one week after peak week for illness-defined absenteeism in week 07/07. According to the RCGP thresholds, influenza was circulating in the community at this time. NHS Direct "cold/flu" calls did not reach the threshold level which was established to give advanced warning of influenza circulating in the community (Figure 2).

Please Note: The threshold for NHS Direct "cold/flu" calls (all ages) is 1.2%

FIGURE 2

Absenteesim due to illness (all schools), NHS Direct "cold/flu" calls (all ages), RCGP ILI episode incidence rate (all ages) and virological data from the RCGP sentinell scheme in 2006/07 Influenza Season

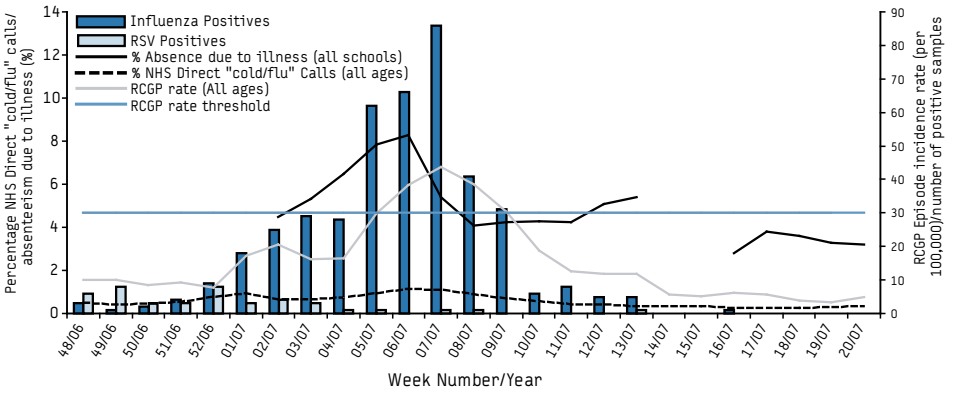
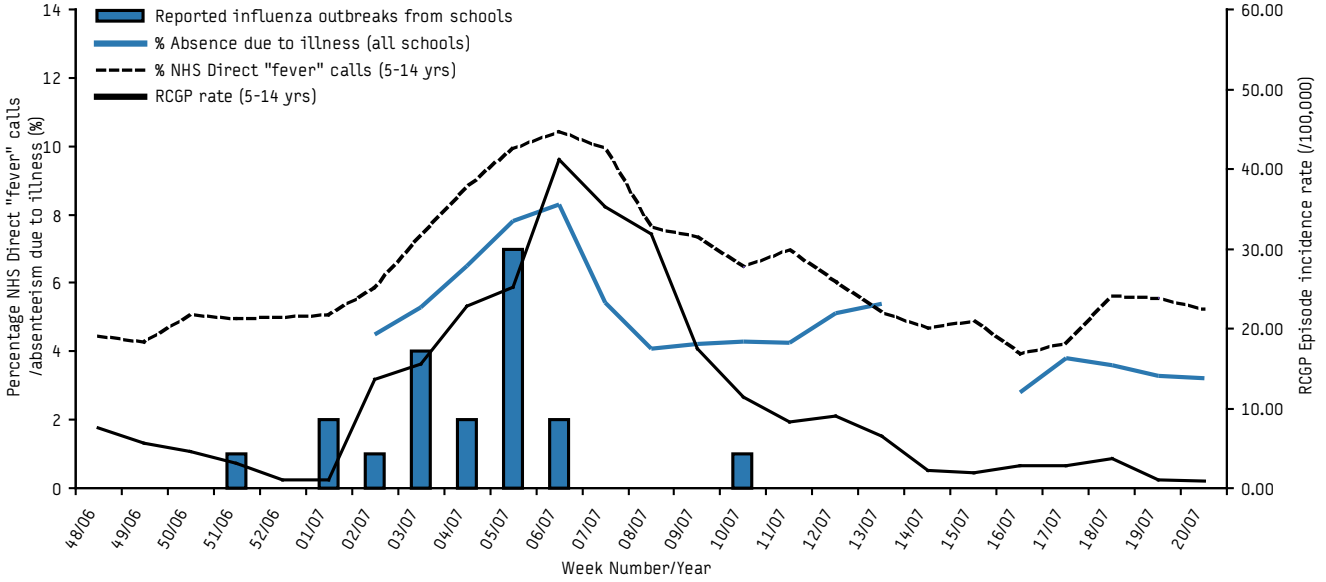


FIGURE 3

Absenteesim due to illness (all schools), NHS Direct "fever" calls (5-14 yrs), RCGP ILI episode incidence rate (5-14 yrs) and in 2006/07 Influenza Season



The threshold for RCGP ILI episode incidence rate (all ages) is 30 per 100,000 population.

School illness-defined absence data peaked during week ending 11/02/07, the same time as the RCGP rate for the 5-14 years age group and NHS Direct calls for "fever" in the 5-14 years age group,(Figure 3). This data and the other indices of influenza activity for school aged children peaked one week later than outbreak reports submitted to CfI.

Please Note: The threshold for NHS Direct "fever" calls (5-14 yrs) is 9%

No threshold for RCGP ILI episode incidence rate has been set for specific age groups.

School illness-defined absence data was broken down by HPA region (data not shown). In all regions, illness absence peaked in the same week or one week prior to the peak RCGP regional episode incidence in the 5-14 yrs age group. In two regions, illness absence peaked one week after that of the NHS Direct regional rate for "fever" calls in the 5-14 yrs age group while in the remaining three regions it peaked in the same week or one week prior.

Discussion

It is very encouraging that, in a year of low influenza activity [7], a small number of schools demonstrated that illness-defined absenteeism could be correlated with established indices of influenza activity, similar in age structure to the sample under consideration. As with other indices that look at school age children, school illness-defined absenteeism data peaks before that of the general community, i.e. indices of influenza activity based on all age groups. Virology data would suggest that early increases in school absenteeism, RCGP episode incidence rate and proportion of NHS Direct "fever" calls for 5-14 years age group data reflect influenza activity. The results suggest that expanding this scheme to collect more rigorous evidence of how illness related school absenteeism could be used as a proxy for influenza activity would be worthwhile. With a larger cohort, the data would better represent national illness-coded school absence, would allow more extensive analysis and, with a few seasons' data, establish baseline activity from which control charts could be developed. Such control charts could be used to alert HPUs of any larger than normal increase in absenteeism for that time of year, enabling the early implementation of control measures to be applied.

A more extensive analysis on a larger prospective cohort would be useful for examining whether peak illness-defined absenteeism in primary schools was significantly earlier compared to secondary schools alone and primary and secondary schools combined. Although illness-defined absenteeism peaked a week earlier than established indices, because data was not collected during the period of initial increase in influenza activity, one cannot assume that the initial increase would also have been identified earlier, but it would seem to warrant investigation as to whether this may be the case. If proven, then surveillance of primary school illness absence data alone could give an earlier indication of influenza activity than current established surveillance schemes. The requirement for ever more timely data is in part driven by the possibility of an influenza pandemic situation, where early detection of influenza in schools could be crucial in informing policy such as school closures and the move by local resilience fora to start their emergency-only mode of operation.

Given that fewer people with influenza-like symptoms now seek consultation with a GP than in the past, alternative systems for monitoring influenza, such as this, may become progressively more indicative of the disease burden experienced in these age groups. Different surveillance schemes for monitoring influenza activity will produce different estimates of influenza activity. A strength of school illness-defined absenteeism is that it can be used to differentiate between primary and secondary school populations unlike other surveillance schemes where there is stratification into age groups that transcend the schooling type. However, a weakness of this scheme compared to others is that it is unable to accurately gauge the true burden of disease, given the effect of

other non–respiratory diseases also coded as "illness". This could be addressed if respiratory disease was coded separately but there are currently no plans to do so. Considering data from several routine surveillance sources for a given period allows one to gain an estimation of influenza that is closer to true activity than any single system. This model may have applications in the surveillance of other seasonal diseases and could be used as a basis for similar surveillance schemes in European countries where timely illness-coded data was electronically available and was deemed to be culturally appropriate.

One of the key limitations to using school illness-defined absence data is that key periods of influenza activity are missed during holidays. Unlike respiratory virus infections with a more predictable season, such as RSV, influenza activity peaks at different times from one winter to the next. These missing weeks will therefore cause varying levels of difficulty when extrapolating influenza activity from illness-defined absence data. However, a larger cohort of schools would overcome this to some extent, since half term weeks vary across the country.

It was not possible to collect absenteeism data prior to week 02/06. Information on the background rate of illness-defined absenteeism throughout the scholastic year would have allowed inferences to be made on the significance (and specificity) of the peaks observed and on the sensitivity of this surveillance tool. The inclusion of pre-season months (i.e. October-December) would have allowed one to observe data for the start of influenza activity. This would have better allowed examination of any possible confounding effect that RSV circulation may have, although the declining number of positive RSV samples during the period of increasing and raised illness-defined absenteeism would suggest that this was negligible. In addition, RSV reports to the HPA mainly relate to illness in the <1 year age group and is therefore of questionable relevance to this study.

In order to improve detection of local outbreaks and possibly the start of influenza activity in the community, geographical representation is essential; currently lacking in the small number of schools recruited. While the pattern of absenteeism varies between regions, it is important to note that in two regions (Yorkshire and Humber and West Midlands) only one school participated in this pilot scheme. Therefore, little useful interpretation could be made from the comparison of school absenteeism data at HPA regional level against incidence data for the specific population of students under consideration (RCGP rate for the 5-14 years age group and NHS Direct "fever" calls for the 5-14 years age group) for a given region. With a larger cohort, breakdown of data to both region and HPU could be a useful tool in evaluating the effect of influenza on absenteeism at these levels.

With appropriate geographical representation, these data could be used to provide a real time public health response by informing Health Protection Units (HPUs) when and where to investigate. In the seasonal situation, early detection of influenza in a local community would trigger investigation and virological sampling by local HPUs which would allow us to analyse the evolution of the virus, to identify important drift variants, and to contribute information for vaccine recommendations and vaccine candidate viruses. It is likely to lead to prophylaxis or treatment being offered where appropriate, reducing morbidity and spread of infection. Ideally, virological investigation should be part of such a scheme, with samples taken from a proportion of participants when activity increases. Not only does it provide key virological information as previously described but it underpins the epidemiological information collected. However, due to finite resources such sampling was not undertaken and potential outbreaks in schools, as indicated by the absenteeism data, were not investigated.

School outbreaks reported to CfI from HPUs peaked before all other indicators of activity in the school age group. However, it is worth noting that due to the passive nature of the reporting of these outbreaks, they are unlikely to be representative and given that they are not consistently laboratory confirmed would be no replacement for routine sampling of a proportion of schools involved in this scheme in the future.

It is clear that good communication with the schools is essential if recruitment and compliance are to be maximised. Established relationships between the schools and local health protection units are also crucial; recruiting and supporting the schools centrally was more labour intensive than anticipated. The pilot also identified some required changes in relation to the dataset and recording and retrieving of information through the website, which are being addressed jointly by the HPA and the DH web team. With more obvious returns for the schools, in terms of local responses by HPUs, it is likely that more would sustain regular reporting even during weeks outside of the winter, vital in generating a dataset from which control charts could be developed.

During the 2007/08 season, the HPA will continue to work closely with both the DCSF and HPUs to identify schools who could participate in this surveillance scheme. Recruitment will be increased with a focus on primary schools and improving geographical representation throughout England. Securing access to retrospective illness absenteeism data from a large cohort would provide sufficient power to carry out a quantitative analysis of the relationship between illness absenteeism and influenza activity, as denoted by the indices described in this paper, and further investigation in to the usefulness of a scheme such as this.

Acknowledgements

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Risk groups and uptake of influenza and pneumococcal vaccine in Ireland

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In Ireland, influenza and pneumococcal vaccines are recommended for adults aged 65 years and over and for those with chronic illness or immunosuppression. Influenza vaccine is recommended for healthcare workers (HCWs) and residents of long stay care facilities. Influenza vaccine uptake is only available for those aged 65 years and over. We conducted a survey to estimate the size of risk groups between 18 and 64 years of age, influenza and pneumococcal vaccine uptake in this group, and to determine possible factors influencing vaccine uptake to improve targeted immunisation programmes. Among respondents aged 18-64 years, 136 of 1,218 (11%) belonged to a health risk group; uptake of influenza and pneumococcal vaccine in these risk groups was 28% (95% CI: 20.9-35.4) and 11% (95% CI: 6.7-17.2) respectively. Uptake among persons aged over 65 years was 69% (95% CI: 62.2-74.4) and 41% (95% CI: 35.0-47.9) for influenza and pneumococcal vaccine, respectively. Influenza vaccine uptake among HCWs was 20% (95% CI: 13.1-28.7). Half (47.6%) of influenza-vaccinated respondents reported that their family doctor had recommended it; 60% of non-vaccinated respondents, for whom influenza vaccine was indicated, saw themselves at low risk of influenza.

Background

Vaccination is the main public health intervention to prevent influenza and invasive pneumococcal disease (IPD). The National Immunisation Advisory Committee (NIAC) in Ireland recommends influenza and pneumococcal vaccine to the following adult risk groups: those 65 years and over; persons with chronic illness and immunosuppression. Influenza vaccine is recommended for all residents of long stay care facilities and health care workers (HCWs) [1]. Both vaccines are free of charge for persons in risk groups. Campaigns for the public and HCWs promoting the vaccines are organised every year before the influenza season.

Currently in Ireland, there is no system for estimating the uptake of influenza and pneumococcal vaccine in risk groups except for persons aged 65 years and over. All adults aged 70 years and over and 50% of those aged 65-69 years receives free medical care. Payments made by health services to family doctors for vaccination is recorded. Uptake is based on these data.

The proportion of the Irish population aged 18-64 years who belong to health risk groups is unknown. A United Kingdom study found that 6% of the study population aged 15-64 years belonged to risk groups [2]. In both Germany and Poland, one fifth (20% and 21%, respectively) of respondents under 65 years of age were in high-risk groups. In Spain and Sweden the proportion was less, 10% and 13% respectively [3].

In May 2003, the World Health Assembly recommended the following targets for influenza vaccine uptake among people at health risk and those aged 65 years and over: 50% uptake by 2006 and 75% uptake by 2010 [4]. The Irish national target for influenza vaccination in those aged 65 and over for 2006/2007 was 65%.

Factors associated with influenza vaccine uptake are identified in international studies. Family doctors have been found to strongly influence vaccination uptake and public perception of vaccine safety has also been shown to be correlated with uptake [5,6].

We conducted a survey to estimate the uptake of influenza and pneumococcal vaccine in Irish adults who belong to risk groups for the 2005/2006 influenza season, to provide baseline information and to improve targeted immunisation programmes. The secondary objective was to estimate the proportion of persons who belonged to health risk groups in the study population aged 18-64 years and to determine possible factors influencing vaccine uptake.

Methods

We undertook a cross-sectional retrospective telephone survey. We selected a sample of non-institutionalised Irish adult population, based on age and sex. A respondent was defined as a person aged 18 years and over, residing in Ireland and living in a household with a landline telephone.

We estimated the sample size using Statcalc (EpiInfo Version 6.04). We assumed that 6% of the population between 15 and 64 years of age belong to risk groups for influenza and pneumococcal disease [2]. Using a power of 80%, a confidence interval (CI) of 95% and a precision of ±1.5%, a sample size of 1500 persons was required. Persons living in institutional settings and non-private dwellings, or those unable to complete the telephone interview due to language or speech difficulties were excluded.

The questionnaire was designed to be used as a computer-assisted telephone interview (CATI) and piloted. We sought information on influenza and pneumococcal vaccination; factors influencing vaccination; demographic information (including Health Service Executive (HSE) area of residence) and the health status of the respondent. To identify HCWs, questions about working in health care facilities were asked.

We obtained ethical approval for the study. Oral informed consent was obtained from respondents. Trained interviewers undertook the fieldwork using a generated telephone list. The interviews were conducted in June 2006 during weekdays, evenings and weekends. The data was analysed using SPSS. Prevalence proportions with 95% CI were calculated using the Fleiss quadratic method.

Table 1

Study group and Irish population distribution by age, sex and health service area. Influenza and pneumococcal vaccine uptake survey, Ireland, June 2006 (n=1500)

	Number of respondents in survey	Study population (%)	General population (CSO data) (%)*
Age group			
18-24	205	13.7	16.0
25-34	299	19.9	21.0
35-49	408	27.2	28.0
50-64	345	23.0	20.0
65+	243	16.2	15.0
Female	770	51.3	50.3
HSE area**			
HSE East	281	18.8	36.0
HSE Midland	56	3.7	6.0
HSE Mid West	89	5.9	8.0
HSE North East	100	6.7	9.0
HSE North West	84	5.6	5.0
HSE South East	152	10.1	11.0
HSE South	193	12.9	15.0
HSE West	113	7.5	10.0
HSE area not known by respondent	432	28.8	

*CSO – Central Statistics Office 2002 census

** Health Service Executive

Results

Response rate and demographic profile of respondents

A total of 4,936 contacts were made by telephone. Of all respondents, 1,766 refused in principle to participate, 1,176 refused because they were busy and 494 refused for no cited reason. Eventually, 1,500 valid interviews were conducted (response rate 30%). Table 1 outlines the respondents' demographic profile in comparison with national demographic data from the Central Statistics Office (CSO).

Size of health risk groups

Of 1,218 respondents (11.2%; CI: 9.5-13.1) aged between 18 and 64 years, 136 reported one of the health conditions attributable to health risk groups. Chronic respiratory illness was the most common self-reported condition (6,6%) (Table 2)

Influenza vaccine uptake

In total, 1439 of 1500 respondents (95.9%) were aware that influenza vaccine was available: 280 (19.5%; CI: 17.5-21.6) said they had been vaccinated against influenza before or during the 2005/2006 season; among these 208 (74.3%) were vaccinated in September or October 2005. Vaccine uptake among those aged 65 years and older was 68.6% (CI: 62.2-74.4); among health risk individuals aged 18 to 64 years, 27.6% (CI: 20.9-35.4) and among HCWs, 20.0% (CI: 13.1-28.7).

Table 2

Self-reported health condition of respondents aged 18-64 years. Influenza and pneumococcal vaccine uptake survey, Ireland, June 2006 (n=1218)

	Number of respondents (proportion %)	95% CI
Chronic respiratory disease	81 (6.6)	5.3-8.2
Chronic heart disease	9 (0.7)	0.4-1.4
Diabetes	20 (1.6)	1.0-2.6
Chronic renal disease or nephrotic syndrome	0 (0)	0
Chronic liver disease, including cirrhosis	3 (0.2)	0.06-0.8
Sickle cell disease	1 (0.08)	0.004-0.5
Weakened immune system due to illness, medicines or treatment	19 (1.6)	1.0-2.5
Removed spleen or malfunctioning spleen	3 (0.2)	0.06-0.8

Table 3

Reasons for getting influenza vaccine. Influenza and pneumococcal vaccine uptake survey, Ireland, June 2006 (n=208)

	Number of respondents	Proportion (%)*	95% CI
Ongoing chronic disease	55	26.4	20.7-33.1
Aged 65 years and over	44	21.1	16.0-27.5
GP/Doctor recommended	99	47.6	40.7-54.6
Health care worker	20	9.6	6.1-14.7
Because of my job	18	8.6	5.4-13.5
For prevention/protection	50	24.0	18.5-30.5
Have got it before, found it good	10	4.8	2.5-8.9
Advertised, advised, recommended to get it	9	4.3	2.1-8.3

*Adds to >100% as respondents could indicate more than one answer

Role of family doctors and reasons for getting influenza vaccine

Among the 280 vaccinated respondents, 257 (91.8%) received the vaccine from their family doctor and 18 (6.4%) at their workplace, 3 (1.1%) in hospital and 2 (0.7%) reported another source. Family doctor recommendation was the most commonly cited reason (47.6%) for getting the flu vaccine (Table 3).

Reasons for not getting influenza vaccine among risk groups

We asked non- vaccinated respondents in risk groups to indicate the main reason for not getting the flu vaccination. Low self-perceived risk was the commonest reason stated by all risk groups, including healthcare workers (Table 4).

Pneumococcal vaccine uptake

In total, 144 of 1,448 respondents (9.9% CI: 8.5-11.6) had received pneumococcal vaccine at some time. Vaccine uptake among persons aged over 65 years, was 41.3% (CI: 35.0-47.9) and among health risk individuals aged 18-64 years, 11.0% (CI: 6.7-17.2). Among those vaccinated with pneumococcal vaccine, 53 (36.8%) received it during the previous 12 months, 74 (51.4%)

Table 4

Reasons among risk groups for not being vaccinated. Influenza and pneumococcal vaccine uptake survey, Ireland, June 2006

	HCWs (n=92)		Aged 18-64 with health risk (n=97)		Aged 65 and over (n=74)	
	No.	(%)	No.	(%)	No.	(%)
Low risk/low perceived relevance:	64	69.6	64	66.0	44	59.5
Only good for elderly people	13	14.1	19	19.6	0	0
I don't get the flu/rarely get the flu/I seldom fall sick	19	20.7	16	16.5	22	29.7
I don't need it	32	34.8	29	29.9	22	29.7
Problems with vaccine / injection / side-effects	12	13.0	13	13.4	21	28.4
Problems with awareness / access / affordability	9	9.8	14	14.4	3	4.1
Medical condition / advice	0	0	1	1.0	0	0
Other reason	7	7.6	5	5.1	6	8.1

between 12 months to 5 years prior to the survey; and 17 (11.8%) had received it over 5 years before the survey.

Discussion

The estimated influenza and pneumococcal vaccine uptake among persons aged 65 years and older who took part in the survey was 68.6% and 41.3% respectively. Eleven percent of our study population aged between 18-64 years belonged to health risk groups. The uptake among this group was 27.9% for influenza and 11.0% for pneumococcal vaccines. HCW influenza vaccine uptake was 20.0%. Almost half of vaccinated respondents stated that their family doctor recommended getting the influenza vaccine. Influenza vaccine uptake in those aged over 65 years in our survey reached the World Health Assembly target and surpassed the recommended national target for Ireland. It was similar to influenza vaccine uptake reported for a similar age group in the US (63.3%) in 2005 but less than that reported in Australia for this age group (79.1%) in 2004 [7,8].

Our study identified a low pneumococcal vaccine uptake for those aged 65 and over. This compares unfavourably with US and Australian studies which reported pneumococcal vaccine uptakes of 63.7% and 51.1% respectively [7,8]. As pneumococcal vaccine is recommended for all adults over this age this finding is disappointing, highlighting the need for raising awareness among healthcare professionals and the public.

Vaccine uptake among respondents aged between 18 and 64 years with a health risk was low for both vaccines. They are at increased risk of complications from influenza and pneumococcal disease and should be vaccinated. A recent UK population-based telephone survey estimated that 56.8% of UK residents aged less than 65 years with a health risk had received influenza vaccine, approximately double our findings [9]. A recent German study reported a rate of 39.6% for the same age group [10].

Influenza vaccine is recommended to HCWs because they can transmit infection to vulnerable patients [1]. Influenza uptake among HCWs in our study was low and remained similar to that reported in an Irish study in 2001 which estimated an uptake of 17.5% [11]. Our results suggest that influenza vaccination status among Irish HCWs has not changed substantially since 2001. Achieving high influenza vaccine uptake rates among HCWs is difficult. A UK study which looked at influenza uptake during the 2002/2003 and 2004/2005 seasons reported uptakes of 20.4% and 34% respectively [9]. A German study (undertaken in 2003/2004) found an uptake of 18% among health professionals [10]. Influenza vaccine uptake in other countries is similar or even lower than the rate reported in Ireland.

The results of our study confirm that general practitioners play a pivotal role in promoting vaccination. Respondents were more likely to get influenza vaccine if the family doctor recommended it. It is therefore important to raise awareness of the need to vaccinate risk groups against influenza and pneumococcal infections among family doctors and practice nurses.

Low self-perceived risk of getting influenza was the main reason for non-vaccination stated by two thirds of all health risk groups. This misconception needs to be addressed. A European study in 2004 reported a few other reasons for non-vaccination, such as sufficient resistance to flu; cost of vaccination; forgetfulness, having had a bad experience in the past or objecting to vaccination [3].

Our study has several limitations. The low response rate is common for unsolicited telephone surveys [5]. We were unable to determine if our sample was representative of the regional distribution of Irish population, as one third of respondents were not able to state the HSE area.

Currently it is estimated that about 88% of Irish adults/households have a fixed line phone [12]. This implies that we could not reach 12%, which could result in some selection bias. There is no register for mobile phones probably leading to under representation in younger age groups. However the use of a sample representing the Irish population by age and sex addressed this issue.

Ten percent of the Irish population are foreign born [13]. This study excluded those unable to complete a telephone interview conducted in English due to language, speech or hearing problems. However, it is unlikely to have influenced the results as only three percent of respondents were excluded on these grounds suggesting that this selection bias was minimal.

Recall bias is possible. This study was cross-sectional and data were collected retrospectively for the preceding nine months. The fact that 74% of respondents specified that they had been

vaccinated in September or October 2005 is encouraging, but it does not exclude recall bias. We would recommend that similar studies in the future be undertaken during the influenza season to minimise this bias.

Estimation of influenza and pneumococcal vaccination uptake and health status was based on self-reported information, which was not validated. The validity of self-reported information for pneumococcal vaccine is lower than for influenza, because pneumococcal vaccine is not given annually, increasing the likelihood of recall bias [7].

To increase vaccine uptake additional work is needed to raise awareness among family doctors, relevant healthcare professionals and staff working in immunisation programmes. Wide dissemination of the survey results should help in this respect. Additional efforts are also needed to increase influenza vaccine uptake among HCWs themselves. Information targeted at this group should emphasise the benefit to the individual HCWs as well as their vulnerable patients. Focused health promotion campaigns for medical staff can improve knowledge and awareness. Increasing influenza vaccination rates among HCWs is particularly important, as they are one of the priority groups for the pandemic vaccine. Setting targets for uptake in this group should be considered. Development of a national immunisation information system and chronic disease registers should also be a priority. Such information systems are critical for accurate measurement of performance in relation to vaccine uptake. Investment in such systems is cost-effective considering the public health importance of immunisation in preventing morbidity and mortality.

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Clusters of travel-associated Legionnaires' disease in Italy, Spain and France, July 2002 - June 2006

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For several years, over 50% of the cases of travel-associated Legionnaires' disease (TALD) reported to the European Working Group for Legionella Infections (EWGLINET) have been among travellers to France, Italy, and Spain. We describe clusters of TALD cases reported in these countries during a four-year period. We analysed data from EWGLINET and from the individual countries. In all three countries, upon notification of a cluster, local health authorities are alerted by the national collaborator and immediately begin an environmental investigation at the accommodation site, which includes risk assessments and analysis of water samples.

From July 1, 2002 to June 30, 2006, 2,101 accommodation sites were associated with TALD cases and reported by EWGLINET to Italian, Spanish and French collaborators. Of these, 252 sites (12%) were associated with clusters: 13.8% (96/697) in Italy, 13.2% (81/615) in Spain and 9.5% (75/789) in France. Overall, 641 cases were reported. Hotels, camping sites and ships and other sites represented respectively 83%, 10% and 7% of the total accommodation sites, with similar proportions in the three countries. In 99% of the sites, samples were collected; 62% of them were found to be positive for *Legionella*.

The findings of this study highlight that disinfection and long-term preventive measures were correctly implemented by the large majority of sites. However, additional efforts must be made to further reduce the percentage of re-offending sites so as to reduce the number of accommodations that are contaminated by *Legionella*.

Introduction

The European Working Group for Legionella Infections (EWGLINET) was established in 1987 to identify cases, clusters and outbreaks of travel-associated Legionnaires' disease (TALD). Collaborators in the scheme are usually national or regional representatives from the public health and microbiology institutes in each country and they report cases of travel-associated legionnaires' disease to EWGLINET's coordinating centre in London. National surveillance schemes detect and follow up each case within the country of residence and then report the case, travel and microbiology details to the EWGLINET coordinating centre at the Health Protection Agency's Communicable Disease Surveillance Centre (CDSC) in London. The details are entered onto a database, and the database is searched to check whether that case should form or become part of a cluster, or whether it is a single case.

The number of cases reported to EWGLINET has increased, from 11 in 1988 to 916 in 2006, in part due to the increase in the number of collaborating countries, which is currently 35 with 62 collaborators from 52 centres [1] and improvement in legionnaires' disease (LD) surveillance in most countries. For a number of years, over 50% of the reported cases have been among travellers to France, Italy, and Spain, while the remaining cases occurred mainly in Turkey, Greece, United Kingdom, Germany, and the United States.

Before July 2002, the procedures for responding to and reporting clusters of TALD were not standardized. To standardize these procedures, a group of experts began to prepare European guidelines in 2000 [2], which were approved and endorsed by the European Union's Committee for the Epidemiological Surveillance and Control of Communicable Diseases in the Community [3]. In this article, we summarize the findings of the epidemiological investigations performed according to these guidelines, for clusters identified in France, Italy, and Spain in the past four years.

Methods

We considered cases reported to France, Italy and Spain in the period from 1 July 2002 to 30 June 2006. The data used were those collected by EWGLINET and from the individual countries. The incubation period for LD usually ranges from 2-10 days. According to the European guidelines, a cluster of TALD is defined as two or more cases represented by persons who stayed at or visited an accommodation site between two and 10 days before onset of illness and whose onset was within the same two-year period. Sites in which a cluster occurred and which were associated with additional cases after a report was sent to EWGLI to say that investigations and control measures had been satisfactorily carried out were defined as 're-offending' sites.

When a cluster is identified, an immediate response is required, including risk assessment, sampling and control measures. The European guidelines also require that two reports are sent by the national collaborator in the country of infection to the EWGLINET coordinating centre in London, one within two weeks of the notification of the cluster alert and one within six weeks [4]. These reports have to confirm that measures have been taken to minimize the risk at the site. If one or both of these two reports are not received, or they state that control measures have not been taken or are not appropriate, EWGLINET publishes the name of the accommodation site on its public website (www.ewgli.org). This notice is removed only once satisfactory reports of control measures are received.

Italy and France have applied this procedure since July 2002 and have notified EWGLINET of all cases of TALD, whether acquired internally or abroad. Due to legal issues, Spain only began to apply this procedure in January 2006 and prior to this date only notified EWGLINET of the cases acquired by Spanish citizens abroad, although the cases acquired within Spain were fully investigated in accordance with the European Guidelines. In any case, in the present analysis, data on all Spanish clusters for the entire study period were available.

In countries participating in EWGLINET, when a cluster is identified, local health authorities are alerted by the national EWGLINET collaborator and immediately begin the environmental investigation, which includes identifying the risk and collecting and analysing water samples. Water samples are analysed by accredited regional or local environmental laboratories, and the isolation of *Legionella* is based on standard methods (ISO 11731). Local authorities report the results of the investigation to the EWGLINET collaborator, who in turn notifies the EWGLINET coordinating centre. Lastly, available clinical and environmental strains are compared by the national Legionella reference laboratories by performing molecular analyses [pulsed-field gel electrophoresis (PFGE) of genomic restriction fragments, sequence-based typing, amplified fragment length polymorphism, etc.), to confirm that the site is the source of the cluster.

Results

In the study period, 2,101 accommodation sites were associated with TALD cases and reported by EWGLINET to the Italian, Spanish and French collaborators. Of these, 252 sites (12%) were associated with clusters; 13.8% (96 of the 697 sites with cases) in Italy, 13.2% (81/615) in Spain and 9.5% (75/789) in France. Overall, in the period 2002-2006, from 48% to 61% of the clusters reported to EWGLINET were located in Italy, France and Spain.

The distribution of the clusters, by year and country during the study period is shown in Figure 1. Overall, 641 cases were reported to be associated with the 252 accommodation sites; in particular, 276 cases reported to Italy, 179 cases reported to Spain, and 186 cases reported to France. The median number of days of stay of cases was five in Italy, seven in Spain and two in France; the mode was one day in Italy and France and seven days in Spain.

A large proportion of clusters consisted of French nationals travelling within France (39%), whereas in Spain and Italy this proportion was lower (28% and 24%, respectively). The proportion of clusters involving only foreign citizens was lower in France (19%) compared to Italy and Spain (56% and 58%, respectively) (Figure 2). Of the 252 clusters, 85 consisted of a single case reported by two or more different countries.

In the three countries, the size of the clusters did not greatly vary; the majority of clusters (68%) involved just 2 cases. In only 4% of the sites, more than four cases were involved.

FIGURE 1

Clusters of travel-associated Legionnaires' disease in Italy, Spain and France, July 2002 - June 2006: distribution of cluster notifications by year and country

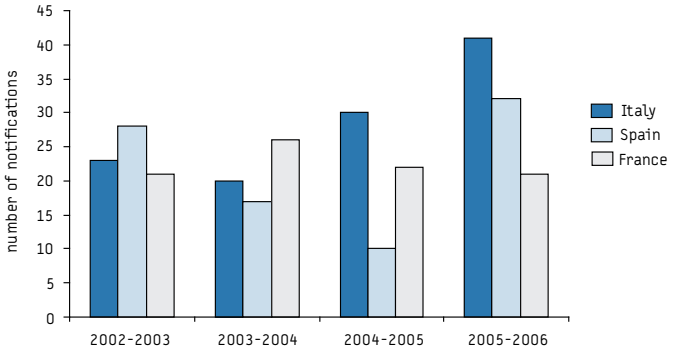
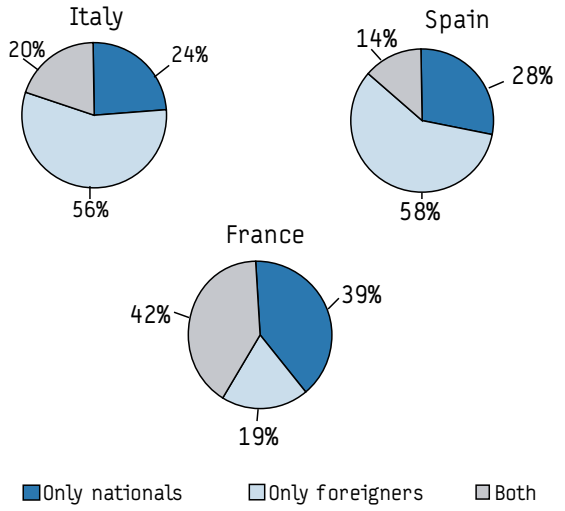


FIGURE 2

Clusters of travel-associated Legionnaires' disease in Italy, Spain and France, July 2002 - June 2006: country of origin of cases



Hotels, camping sites and ships and other sites represented, respectively, 83%, 10% and 7% of the total accommodation sites, with similar proportions in the three countries. For 38 (15%) of the sites with a cluster, an additional case was reported within two years of the last case (thus increasing the size of the cluster); for five (2%) sites, more than one additional case was reported.

Environmental investigations

In all three countries, environmental investigations were started within one to two days after cluster notification, and control measures were implemented or reinforced in all of the accommodation sites. In some cases, investigations were already ongoing before the EWGLI notification. The results of the environmental investigations are summarized in Table 1. In nearly all of the sites (99%), samples were collected. In Spain, in one site water samples were not collected because the hotelier had already carried out disinfection before health authorities performed their inspection; in France, the information was not available in one site.

In more than one third (36%) of the sites, no legionella was found. In Spain, for 46% of the sites, the concentration of legionella was not known, compared to 3% of the sites in Italy and 5% in France. Concentrations of legionella equal to or greater than 1,000 cfu/litre (the threshold set by European Guidelines as requiring actions) were found in 50% of the sites in Italy and in France and in only 9% in Spain.

In Italy, five sites (5.2%) were temporarily closed for implementing control measures; one (1%) site was closed shortly after the investigation for renovation and 19 (20%) accommodation sites were seasonal and were closed during the winter season. In Spain, four (5%) of the sites were temporarily closed; two (2.5%) were closed for renovation; and two (2.5%) were seasonal. In France, 10 sites (13%) were closed for renovation, 12 (16%) sites were closed for the winter season. For all of the sites that had closed, the local health authorities conducted another environmental investigation before re-opening.

TABLE 1

Clusters of travel-associated Legionnaires' disease in Italy, Spain and France, July 2002 - June 2006: number of sites sampled by country and by result

Country	Number of sites	Sites sampled No. (%)	Negative samples No. (%)	Positive, but unknown Legionella concentration No. (%)	Legionella concentration CFU/L $<10^3$ No. (%)	Legionella concentration CFU/L $>10^3$ No. (%)
Italy	96	96(100)	36 (37)	3 (3)	6 (7)	51 (53)
Spain	81	80 (99)	33 (41)	37 (46)	3 (4)	7 (9)
France	75	74 (99)	20 (27)	4 (5)	14 (19)	36 (49)
Total	**252**	**250 (99)**	**89 (36)**	**44 (18)**	**23 (9)**	**94 (37)**

The names of eight French sites (seven hotels and one campsite), two Italian hotels and no Spanish sites were published on the EWGLI website during the study period for failure to comply with the European guidelines.

Microbiological investigations

Clinical isolates were available for 20 of the 186 cases (9.3%) in France, for four of the 234 cases (2%) in Italy, and for two of the 179 cases (1%) in Spain. In France, clinical isolates were available from patients who visited 18 sites (24%), and in 10 sites environmental isolates were available for comparison with clinical isolates. Comparison was made by PFGE or Sequence Based Typing (SBT), and in each instance the environmental and clinical isolates were found to have had identical genomic profiles. Two clinical isolates were obtained from two cases who stayed in the same accommodation site; in one site, all isolates were identical and in another site the clinical isolates were compared and found to have been identical by SBT, but no environmental isolates were available for further comparison [5].

In both Spain and Italy, clinical and environmental isolates were also available for two sites, and the comparison showed a similar genomic profile.

Discussion

The results of the analysis reveal some differences among the three countries considered. In Italy and France, the length of stay in each accommodation site was shorter than that observed in Spain. In Spain and Italy, there was a higher proportion of clusters comprised exclusively of foreigners than in France, which probably indicates different patterns of tourism in the three countries. However, the investigations performed and the results were very similar: in fact, though a huge number of accommodation sites were reported to the three countries during the study period, epidemiological and environmental investigations were carried out in more than 99% of clusters, and control measures were satisfactorily implemented in 96%, as demonstrated by the negligible number of sites published on the EWGLI website. Criteria for closure of accommodation sites are not identified in the European guidelines, and the decision is left to individual countries, according to their national laws; this explains the differences found among the three countries.

Overall, more than 60% of the sites sampled were found to be positive for legionella, and, in particular in Italy and France, where the concentration of legionella was known for most sites, approximately 50% of them were found to be positive at concentrations greater than 1,000 cfu/litre. Although disinfection and long-term preventive measures were correctly applied by most sites, 43 sites (17%) reported additional cases after the cluster and thus required further investigation during the study period. This indicates that additional efforts must be made to further reduce the percentage of 're-offending' sites, so as to reduce the number of hotels that are contaminated by *Legionella* [6]. The fact that no legionella was found in more than one third of the investigations could be because culture of water samples for *Legionella* spp may not be highly sensitive, or because cases did not acquire infection in the accommodation site under investigation.

Between 2002 and 2006, there appears to have been a trend of increase in notifications for Italy and Spain. The increase in the number of clusters in these two countries seems to reflect the improved reporting and ascertainment of cases in 2005-2006, both at the national level (in Italy and in Spain) and at the European level, as demonstrated by the increased number of TALD cases reported to EWGLI. The matching of environmental *Legionella* strains with clinical strains was only possible for a very limited proportion of cases in Italy and Spain, and in a slightly higher proportion in France. This is due to the low proportion of clinical isolates available, as a result of the diagnosis of legionellosis mainly being performed by urinary antigen detection. Efforts should therefore be made to encourage practitioners to collect clinical specimens.

The findings of this study highlight the importance of collaboration among all European countries, given that the surveillance network detected 33% more clusters than would have been detected by individual countries alone. Furthermore, the European guidelines have led to a more standardised approach to investigations across all European countries and to a greater awareness of the importance of proactive interventions. It is thus expected that in the next few years, in spite of the continuously increasing number of travellers, there will be a decline in the number of accommodation sites associated with clusters.

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Results of a 12-month long enhanced surveillance of listeriosis in Italy

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Since 1993, the reporting of listeriosis has been mandatory in Italy. The surveillance system based on case notifications from physicians is managed by the Ministry of Health. The information collected includes only gender, age and case distribution by region. To gather more information, an active surveillance was conducted for 12 months (2002-2003). All hospital microbiological laboratories in Italy (n=103) were given clinical and food questionnaires and were requested to report positive cases and send strains for testing. A higher number of cases of listeriosis were reported by this active surveillance compared to the mandatory notifications. In addition, information on risk factors, clinical symptoms and outcomes of 77 reported cases were analysed. In one case it was possible to trace the source of infection.

Of the 77 cases of listeriosis, 41 *Listeria monocytogenes* isolates were characterised by serotype and pulsotype.

More than 95% of the strains belonged to serotypes 1/2a, 4b and 1/2b; molecular analysis revealed 23 different AscI pulsotypes.

The information collected is very important for understanding the real situation of listeriosis in Italy. It can be used to take effective actions in improving food safety and to provide dietary advice to individuals at greater risk of infection.

Introduction

Listeria monocytogenes (*L. monocytogenes*) is a ubiquitous Gram-positive facultative intracellular food-borne pathogen that causes listeriosis. In pregnant women the disease primarily causes preterm delivery, miscarriage and stillbirth, whereas in newborns it leads to sepsis, pneumonia and meningitis. In elderly and in immunocompromised individuals listeriosis causes sepsis, meningitis and focal infections. Foodborne transmission of *L. monocytogenes* can also cause a self-limiting acute febrile gastroenteritis in healthy adults [1,2]. Listeriosis is an infection of great concern to public health due its clinical severity and high case fatality.

Since 1993, the reporting of listeriosis has been mandatory in Italy. Physicians notify listeriosis cases on a notification form that is sent to the Ministry of Health and archived in a database. The notification form includes information only on gender, age and region. The mandatory surveillance does not comprise sending clinical and food strains to the National Centre for Food Quality and Risk Assessment (Centro Nazionale per la Qualità degli Alimenti e per i Rischi Alimentari – C.N.Q.A.R.A.) for characterisation. To gather more information on the listeriosis situation in Italy, an enhanced surveillance was conducted between February 2002 and January 2003 in all 20 Italian regions. All hospital microbiological laboratories in Italy (n=103) were given clinical and food questionnaires and were requested to report positive cases and send strains for testing.

The objectives of this enhanced surveillance were: to estimate the incidence of listeriosis and compare it to the incidence calculated on the basis of mandatory surveillance, and to describe risk factors, clinical symptoms and outcomes associated with cases of listeriosis. Furthermore *L. monocytogenes* isolates were characterised by serotyping and PFGE, and epidemiological investigations were performed in order to trace source of infection.

Methods

Case definition

The case definition of invasive *Listeria* infection was based on the Commission Decision 2002/253/CE [3]; the case definition of Listeria gastro-enteritis was based on the "Proposed case definitions for a European surveillance network of listeriosis" [4]. A case is considered maternal/neonatal (MN) when diagnosed in a pregnant woman, foetus or a newborn below one month of age. When *L. monocytogenes* is isolated from both the pregnant woman and her newborn child or foetus, it is considered a single case. If a case does not apply to any of these, it is considered as non-maternal/neonatal (non-MN)

Enhanced surveillance

An enhanced surveillance was conducted for a 12-month period (from February 2002 to January 2003), targeting the whole Italian population. A clinical and food questionnaire was prepared with the collaboration of the National Centre for Food Quality and Risk Assessment (C.N.Q.A.R.A.) and the National Centre for Epidemiology Surveillance and Health Prevention (C.N.E.S.P.S.) of the Istituto Superiore di Sanità (ISS). The standardised questionnaires were sent to 103 hospital microbiological laboratories in Italy. The clinical questionnaire included information on gender, age, region, risk factors (underlying disease or condition), clinical symptoms, outcome of patients. The food questionnaire asked to provide a list of food items consumed within two months before the onset of illness. The laboratories were asked to report on all positive cases of listeriosis, with the information requested in the questionnaires, and to submit *L. monocytogenes* isolates to the C.N.Q.A.R.A. All data were obtained through the standardised questionnaires, and not via face-to-face or telephone interviews.

Serotyping

The isolates were serotyped using commercial *Listeria* antisera (Denka Seiken, Japan), in accordance with the manufacturer's instructions, with a few modifications [5].

PFGE

DNA isolation and pulsed-field gel electrophoresis (PFGE) were performed following the PulseNet Protocol [6], with *Asc*I

as restriction endonuclease. The gel was digitally photographed with Gel Doc 2000TM (Bio-Rad, USA). The TIFF images were compared using the Applied Maths BioNumerics software package (Version 4.0, Applied Maths, Saint-Martins-Latem, Belgium), and normalization was carried out by aligning the bands with database global standard *Salmonella* Braenderup strain H9812, loaded in 4 lanes in each gel. Pattern clustering was performed using algorithms within BioNumerics application: the unweighted pair group method using arithmetic averages (UPGMA) and the Dice correlation coefficient with a position tolerance of 1.0%. Strains with the same number and band position were considered indistinguishable.

Results

During our enhanced surveillance 40 hospital microbiological laboratories of 10 regions reported 77 sporadic cases of listeriosis, corresponding to an incidence of 1.3 cases per 1,000,000 inhabitants/year, which was higher than the incidence reported by the Ministry of Health (0.8 cases per 1,000,000 inhabitants/year) in the same 12-month period. The most common underlying conditions among cases were cancer (24 cases, 31%), solid organ transplantation (24 cases, 31%), dialysis (7 cases, 9%), and pregnancy (6 cases, 8%). 16 cases (21%) were over the age of 65 years. The most common clinical manifestations were septicaemia (29 cases, 38%), meningitis (19 cases, 25%) and meningo-encephalitis (16 cases, 21%); less frequent were newborn with septicaemia (7 cases, 9%), miscarriage (3 cases, 4%) and febrile gastroenteritis (3 cases, 4%). The number of deaths reported was 15 (20%).

Only in one listeriosis case, the source of infection was identified [7].

Of the 77 cases of listeriosis, 41 isolates were sent to C.N.Q.A.R.A and were characterised by serotyping and PFGE. More than 95% of the strains (Table) belonged to serotypes 1/2a (18 isolates, 44%), 4b (13 isolates, 32%) and 1/2b (8 isolates, 20%). Molecular analysis revealed 23 different *Asc*I pulsotypes among the 41 strains. Isolates possessing identical restriction patterns were also recovered from different geographical areas, indicating that strains were not correlated (Table). Only in two regions (Lombardia and Puglia) and in a six-month period we found clusters of isolates with indistinguishable *Asc*I profile in the same hospital. In Lombardia it was one MN case and one non-MN case with *Asc*I profile 2 and serotype 4b, and in Puglia there were three non-MN cases with *Asc*I profile 7 and serotype 1/2b, and two non-MN cases with profile 7 and serotype 4b.

Discussion and conclusion

The epidemiological data based on mandatory notifications show the incidence of listeriosis in recent years (2004-2006) to be about 0.8 cases per 1,000,000 inhabitants per year. The enhanced surveillance described in this paper allowed the collection of more precise and complete information about this infection thus responding to the challenges underlined in the "Annual Community Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Antimicrobial Resistance in the European Union" with regard to a mortality rate of 8.3% for listeriosis. The Report pointed out that "the lower than expected reported mortality rate might be due to a lack of data on patient outcomes after the initial notification", and therefore "to assess the burden of listeriosis in the EU community better harmonisation of data collection systems is required" [8].

Table

***Listeria monocytogenes* strains isolated during enhanced surveillance, Italy 2002-2003**

Region	Serotype	*Asc*I
Trentino Alto Adige	4b	2
	1/2b	3
	1/2b	4
	1/2a*	5*
	4b	7
	1/2a	12
Piemonte	1/2b	1
	1/2a	6
	1/2a	15
	1/2c	4
	1/2b	21
Friuli Venezia Giulia	1/2a	17
Lombardia	1/2a	4
	4b#	2#
	4b*#	2*#
	1/2a*	13*
	1/2a	14
	1/2a*	15*
	1/2b	19
Veneto	4b*	2*
	1/2a	18
	1/2a	22
	1/2a	20
	1/2a	23
Toscana	4b	8
	4b*	9*
	4b	7
Lazio	4b	16
Puglia	1/2b#	7#
	4b#	7#
	Not typable	10
	1/2a	11
	1/2b#	7#
	4b#	7#
	1/2b#	7#

* MN cases (the remaining ones, i.e. without*, are non-MN)
# Cases occurred in the same hospital, in the same six-month period

With the exception of one case related to the consumption of gorgonzola cheese [7], no clear source of infection was identified during the enhanced surveillance. There are a number of problems in collecting food items consumed by patients, including the potentially long incubation period (up to 91 days) [9], and the difficulty to collect food samples from homes or from where they were purchased.

Our results show that most of the strains isolated from listeriosis cases belong to serotype 1/2a. In comparison with the results of our previous work [5] in which we studied the distribution of *L. monocytogenes* serotypes in food, environment and human isolates collected in Italy during 1990 to 1999, we have currently observed that the distribution of serotypes among the food isolates has remained the same, while among human isolates, the frequency of serotype 4b has decreased and the frequency of serotype 1/2a has increased. This variation of serotype of clinical *L. monocytogenes* isolates has also been observed in a study conducted in Finland on *L. monocytogenes* isolates from invasive infections during 11-year period [10]. These results support findings in the United Kingdom [11], Denmark [12], Switzerland [13] and Sweden [14] suggesting that serotype 1/2a is replacing serotype 4b in human infections.

Molecular analysis revealed 23 different *Asc*I pulsotypes among 41 strains and this supports the fact that isolates were from sporadic cases. There were only some exceptions of indistinguishable strains for serotype and PFGE profile collected in the same hospital and in a six-month period. In these few cases, epidemiological and microbiological investigations were unable to identify a probable common source of infection.

The following were considered to constitute the possible limitations of this study: participation of only half of the regions and no communication of zero reporting; difficult-to-perform epidemiological investigations; incomplete questionnaires. Notwithstanding these limitations, the information collected during the study is important in understanding the real situation of listeriosis in Italy. It can be used to take effective actions in improving food safety and to provide dietary advice to high-risk individuals in avoiding specific foods (like the consumer information made available by the Food Safety and Inspection Service in the United States – http://www.fsis.usda.gov).

Serotypes and pulsotypes of clinical and food strains collected during our study will be added to the Italian database and to the PulseNet European Network, contributing information useful in detecting compatible cases and tracing probable sources of infection.

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Rubella immunity and vaccination coverage of the population of northern Greece in 2006

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This study was prompted by two rubella outbreaks that occurred in northern Greece in the last decade (1993 and 1999) and by periodic changes to the immunisation strategy. It was designed to determine the current status of rubella immunity and vaccination coverage in this region, eight years after the last outbreak in 1999 and seven years after the last epidemiological study in the area. Among the 685 subjects studied the seroprevalence was 83.7% and the total vaccination rate was 31.3%. In people born before the introduction in 1989 of the measles/mumps/rubella (MMR) vaccine into the national immunisation programme, higher rates of rubella seropositivity (88.1%) were observed compared to those born after 1989 (77.1%). The vaccination rates for these age groups were 14.8% and 58.1%, respectively. The reason for this difference is the lack of vaccination at the time these people were children, and it underlines the need for a vaccination strategy targeting older people as well. Among women of reproductive age (16-40 years), who represented 44.8% of the study population, 13.9% were susceptible to rubella and only 18.5% were vaccinated. These results indicate that there is a great need for a comprehensive policy designed to protect mostly young adults and women of childbearing age in order to prevent congenital rubella infections. This policy should also include competent surveillance systems for rubella and congenital rubella syndrome and an evaluation of existing immunisation programmes.

Introduction

Rubella is usually a mild childhood disease, but when it occurs early in pregnancy it can result in spontaneous abortion, stillbirth and congenital rubella syndrome (CRS) [1,2]. Following the availability of the combined measles, mumps and rubella (MMR) vaccine, most European countries introduced mass childhood vaccination strategies [3].

In Greece, vaccines against rubella, measles, and mumps became commercially available around 1975. Since 1977, prominent Greek paediatricians have recommended that children be immunised with the MMR vaccine at the age of 15 months. This has begun, but only in the private sector. As rubella vaccination was classed as 'optional' by the Ministry of Health at the time, public services only offered rubella immunisation to girls aged 10 to 14 years on request. A limited rubella vaccination programme was introduced in 1980 for adolescent girls and larger groups of young women working or living together.

Vaccination coverage in children was not assessed systematically in Greece. Several published studies show that during the late 1970s and 1980s, the vaccination coverage for rubella increased only slowly, remaining consistently below 50%. It did not reach 50-60% before 1990 [4]. During that period, three rubella outbreaks took place, in 1983, 1986, and 1989, just a few years before the introduction of the MMR vaccine in the national immunisation programme [5].

Mass infant vaccination was introduced in the form of the national immunisation programme in 1989, with a single dose of MMR administered at the age of 15 months. In 1991, a two-dose vaccination scheme was adopted, with the first dose administered at 15 months and the second dose at 11 to 12 years. Two rubella outbreaks followed, one in 1993 and another one in 1999.

The 1993 outbreak mostly affected adolescents and young adults, (64% of cases were 15 years or older), and the incidence of the disease in individuals of childbearing age was higher than in previous epidemics. Twenty-five babies (24.6 per 100,000 live births) with serologically confirmed CRS were identified [6].

During the outbreak in 1999, the age distribution of rubella cases shifted towards older age groups. The average age was 17.1 (SD 5.5) years; 96% of cases occurred among people who had not been vaccinated; 60% of the cases were men. Four confirmed cases of congenital rubella syndrome were reported after the outbreak [7]. According to the World Health Organization (WHO), only six cases of CRS occurred in the last 10 years in Greece [8]. Five were reported in 1999, after the rubella outbreak in Greece, and one in 2000. No CRS case has been reported since 2000.

The vaccination policy was reconsidered after the outbreak in 1999 and now recommends two doses of rubella vaccine, with the first included in the MMR vaccination administered at the age of 15 months, and the second one as a double vaccine against measles and rubella at the age of four to six years [4,9].

According to a national study on immunisation coverage in Greece, carried out in 1996-1997, the proportion of two-year old children vaccinated with the first dose of the vaccine was 63.5%, but only 18.8% had received a second dose at an older age. In 2001, three years after the last outbreak in the area, another national study on immunisation coverage was carried out in two- to three-year old children. It was found that 89% of them had received at least one dose of a vaccine against rubella before their second birthday [10,11].

The aim of this study was to determine the current status of rubella immunity in northern Greece, eight years after the last outbreak in 1999 and seven years after the last epidemiological study in the area [12].

Materials and Methods

Taking into account the current population of northern Greece (2,769,834 inhabitants) as well as the seroprevalence of rubella in

different age groups expected on the basis of previous serological studies conducted in Greece, the minimum sample size for the study was calculated to be 308 with a 5% error and 95% confidence interval [12].

A total of 685 residual serum samples were included in the study. They were collected between October and December 2006 from patients who presented to hospital for reasons unrelated to rubella infection. The study group consisted of consecutive, non selected patients, according to patient registration number in each age group. None of the sera belonged to people suffering from infectious diseases or any known immunodeficiency syndrome. The study was approved by the hospital's ethics committee. Informed consent was obtained from all participants.

The samples were divided into eight age groups (Table 1). They were also divided according to date of birth into two larger groups A and B. Group A consisted of 379 individuals born before the introduction of the MMR vaccine in the national immunisation programme in 1989, and Group B of 306 individuals born after 1989. In addition, the samples were divided according to the origin of the patients (Table 2) into one group of 567 native Greek residents and one group of 118 residents of foreign origin (immigrated from Albany and countries of the former Soviet Union, who now live permanently in Greece and therefore are a part of the Greek population). Of all the 685 samples, 303 were taken form women of reproductive age (16-40 years).

Each individual provided information about age, sex, ethnicity, place of residence and history of rubella vaccination were obtained. Data on rubella vaccination of children was obtained from the parents or guardians All data were cross-checked with the information in each individual's health record, where available. Protective immunity to rubella virus was determined by ELISA (Axsym system Rubella IgG, Abbott). This assay is used by other investigators in other parts of Europe, thus ensuring the quality and comparability of the data [13]. An antibody titre of 30 IU/ml was defined as protective seropositivity against rubella. This titre is three times higher than the cut-off recommended by the manufacturer.

The statistical analysis of the results was done with the SPSS 11.5 programme. The different age groups, seropositivity, vaccination rate, mean age and geometric mean titre (GMT) of antibodies were estimated by means of descriptive statistics. Comparisons were made among different groups using Student's t-test for normally distributed variables, or the Mann-Whitney t-test for non-parametric variables. Odds ratio and univariate 95% confidence intervals were calculated for the seropositivity prevalence estimates and the vaccination rate. The chi-square test was used to compare seropositivity rates among different groups.

Results

For the 685 sera tested, the rate of seropositivity for rubella virus was 83.7%, while the total vaccination rate for all age groups combined was 31.3%. The age-adjusted rates of rubella seropositivity, the antibody GMTs for each age group and the vaccination rate are shown in Table 1.

The seropositivity rate of 66.1% among children aged zero to six months reflects maternal acquired immunity. In the next two age groups, aged between seven and 15 months and between 16 months and five years, the seropositivity rate was 7.4% and 93.3% respectively, following the usual pattern of disappearing maternal antibodies and appearance of vaccine-acquired immunity. In all other age groups (aged from six to over 40 years), seropositivity rates ranged from 83.1% to 92.1% (Table 1).

The rate of rubella seropositivity was higher in people born before 1989 (group A, 88.1%) compared to those born after 1989 (group B, 77.1%), and the difference was statistically significant (p=0.001, odds ratio (OD)=6.69, confidence interval (CI)=1.96-23.0. The vaccination rates for these age groups were 14.8% in group A and 58.1% in group B, with a statistically significant difference (p<0.001, OD= 19.0, CI=4.723-77.65) (Table 2).

Table 2

Rubella seroprevalence, geometric mean titre (GMT) and vaccination rate in people born before (Group A) and after 1989 (Group B), in women of reproductive age, in the native Greek population, and in residents of foreign origin

Category	No. of sera examined	Seroprevalence (%)	GMT	Vaccination rate (%)
Group A	379	88.1*	77.9	14.8*
Group B	306	77.1*	67.4	58.1*
Greeks	567	84.4	67.2	33.5*
Immigrants	118	79.6	114.5	17.7*
Women of reproductive age	303	86.1	99.5	18.5

* statistically significant difference

Table 1

Rubella seroprevalence, geometric mean titre (GMT) and vaccination rate in the different age groups (n=685)

Age group	No. of sera examined	Seroprevalence (%)	GMT	Vaccination rate (%)
0-6 months	59	66.1	39.5	-
7-15 months	67	7.4	48.4	2.9
16 months- 5 years	60	93.3	83.0	91.7
6-10 years	60	92.1	73.4	94.7
11-20 years	70	85.7	77.1	74.3
21-30 years	148	83.1	89.3	23.0
31-40 years	137	89.8	86.5	10.9
>40 years	84	86.5	70.0	2.4
Total	**685**	**83.7**	**68.8**	**31.3**

Among the 118 foreigners (17.2% of all participants) the seropositivity rate was 79.6% (compared with 84.4% among those of Greek origin), while the vaccination rate was 17.7% (compared with 33.5% among those of Greek origin). There was a statistically significant difference between vaccination rate and birthplace (p=0.014, OD=3.762, CI=1.301-10.991), with a higher rate of vaccination among the native Greek population compared with the foreign residents (Table 2).

Among women of reproductive age (16-40 years), the seropositivity rate was 86.1%, while the rate of vaccination was only 18.5% (Table 2).

Discussion

The lowest rate of rubella seropositivity in this study was found in people aged 21 to 30 years (83.1%). This is due to the lack of vaccination at the time these people were children, as the vaccination coverage for rubella remained consistently below 50% during the 1980s [11]. This is also the reason why the last two outbreaks that occurred in Greece, especially the last one in 1999, affected mostly young adults born in the 1980s [4].

In contrast, the highest rates of rubella seropositivity were found in the age group from 16 months to five years (93.3%), followed by the group of six to 10 year-olds (92.1%). The majority of those children were vaccinated (91.7 and 94.7% respectively). According to a serological study that was conducted in northern Greece in 1999-2000, (one year after the last outbreak in 1999), 28.2% of children aged six to 10 years were susceptible to rubella [12]. This is probably due to the fact that children of that age were born late enough to receive mandatory rubella vaccination at the age of 15 months, but too early to be vaccinated with the second dose of the vaccine at the age of four to six years. 23% of the 10 to 15 year-olds were also susceptible to rubella. It is quite remarkable that the same age group (six to 10 years), had a significantly increased level of immunity in our study, seven years after the last epidemiological study in the area. Those children had received both doses of the MMR vaccine, highlighting the importance of the booster vaccination for the development of immunity against rubella.

Previous local and national studies on the coverage with a first dose of rubella vaccine that were carried out in 2001, showed that 89% of two to three year-old children had been vaccinated by the time of their second birthday. Among the two to 12 years-olds, 94-98% were immunised against rubella [11,14-16]. Our data are comparable to the situation in other European countries. In England and Wales, the prevalence of rubella antibodies was above 90% in all age groups above the age of three, while in France, more than 80% of children between three and six years of age are seropositive for rubella. In the former region of West Germany on the other hand, roughly 25% of children aged five to 13 years are estimated to be seronegative for rubella [17].

Women of reproductive age had with 86,1% a high rate of protection. Their vaccination rate, 18,5%, however, was low enough to assume that most of them had acquired immunity through exposure to the wild virus.

In a study from 1999-2000, women of reproductive age had similar rates of seropositivity (89,8%) and vaccination coverage (16,4%) [12]. It seems that the level of immunity has remained almost unchanged for the last 35 years since an older study conducted in 1972 in the same area showed a similar proportion of 81,8% of seropositive women of childbearing age [18]. This can be explained by the fact that young girls vaccinated in 1989 have not yet reached reproductive age. The effects of the introduction of the vaccine in women of reproductive age will become apparent within the next 10 years, as the vaccinated people grow older. These are the reasons why the last two rubella outbreaks in Greece (1993 and 1999) affected also women of reproductive age at a higher rate than in previous epidemics and why they led to an increased number of babies born with CRS [14].

Many seroepidemiological studies carried out in other European countries had similar results. The susceptibility rate among women of reproductive age in the Russian Federation was 16,5% [19]. In Spain, 28,8% of the females aged 15 to 45 years were vaccinated and their seroprevalence was 95% [20]. In France, only 12% of women between 20 and 39 years were susceptible to rubella infection, while only 3% of the women in that age group in Germany were seronegative for rubella antibodies [17].

Conclusions

A very high proportion of the child population in Greece is presently vaccinated against rubella, which contributes significantly to reducing the circulation of rubella virus in the population. On the other hand, most of the people born before the introduction of the MMR vaccine in 1989 have, as expected, a low vaccination coverage, among them women of reproductive age. The lowest rate of seropositivity was found in young adults, aged between 21 and 30 years. Thus, there is a potential for rubella epidemics to occur among those sub-populations.

In addition, the absence of good quality data on rubella activity in Greece is an inherent problem, as the introduction of rubella immunisation was not part of a coherently designed policy and was not accompanied by the establishment of a surveillance system.

Our results indicate that there is a great need in Greece for a comprehensive policy designed to protect mostly young adults and women of childbearing age in order to prevent congenital rubella infections. This policy will need to include immunisation programmes targeted to reach women of childbearing age who have no proven immunity, as well as young adults, a large proportion of whom are susceptible to rubella. In addition, immunisation programmes are needed for post-pubertal males and females living, studying or working in large groups. Special measures are required to attain a high level of vaccinaton coverage for children, making sure that they receive two doses of the vaccine, and also to achieve high vaccination coverage of adolescents. This comprehensive policy will also need to include competent surveillance systems for rubella and congenital rubella syndrome, as well as an evaluation of the immunisation programmes.

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Nosocomial infections and community clusters of pertussis in France, 2000-2005

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Pertussis is not a notifiable disease in France. In addition to a paediatric hospital sentinel surveillance system, pertussis epidemiological data have, since 1996, been gathered through the voluntary notification of community clusters by general practitioners, and since 2001 by the statutory notification of nosocomial infection to the relevant local health authority. The local health authority forwards the information to the French National Institute for Surveillance (InVS). The objective of this study was to analyse pertussis data outside the routine paediatric hospital sentinel surveillance system. We gathered all the information concerning healthcare-associated infections and community clusters of pertussis (specific forms, investigation reports, emails etc.) reported to the InVS between 2000 and 2005. The InVS received and analysed 67 reports with a total of 595 cases. Almost half of the reports (n=31) came from hospitals, and healthcare workers were usually first affected. Control measures were put in place in 22 healthcare facilities and the average duration of an outbreak episode was 48 days. Outside healthcare facilities, clusters were reported also from 17 daycare facilities or schools and five workplaces. Among the 595 cases, six deaths occurred in children under seven months of age. Pertussis is still occurring in France and affects those who are not or who are no longer protected by the vaccine. Infection of infants within the household could be prevented if their parents and siblings were immunised. The number and size of pertussis clusters in hospitals could be reduced through immunisation of health staff, and timely and adequate outbreak management.

Background

The high coverage of childhood vaccination for pertussis during the last 40 years has changed pertussis epidemiology in France [1]. The disease now mainly affects infants who are too young to be vaccinated and adolescents and adults who are no longer protected by booster vaccinations [2]. The vaccine schedule in France recommends an immunisation at the age of two, three, and four months, and two booster doses at the age of 15 to 18 months and 11 to 13 years. Since 2004, pertussis vaccination is recommended for health professionals in contact with children too young to have received all three doses of the vaccine (maternity, neonatology and paediatric ward). During pregnancy, siblings and the father should be vaccinated, and the mother should receive the vaccine after delivery. Adults planning a baby are also urged to get vaccinated before [3].

Pertussis is monitored through a paediatric hospital sentinel surveillance system described in detail in Bonmarin *et al.* (2007) [4]. This system does not allow comparison of the French situation with other European countries as it reflects only a very small part of the epidemiology in the community [5]. In addition to this system, general practitioners are asked to report community clusters of pertussis to the local health authority on a voluntary basis since 1996. Following the implementation of mandatory notification of nosocomial infection events in 2001 [6], nosocomial pertussis infections must now be reported.

As there is no pertussis surveillance in the community, we reviewed and described all the epidemiological data regarding pertussis that were forwarded to InVS between 2000 and 2005.

Methods

Each report provided information on either healthcare-associated events (sporadic cases or clusters) or community events (clusters only). These events were documented by emails, investigation reports or specific forms. A pertussis case was defined as a person with a cough lasting for more than eight days, with a laboratory confirmation (positive culture, PCR or serology) or with a clinical confirmation (cough lasting for more than 14 days with at least one of the following symptoms: whoop, vomiting after paroxysms, apnoeas, cyanosis, lymphocytosis >10,000/mm^3) or with an epidemiological link to a laboratory-confirmed case. A cluster was defined as two or more epidemiologically linked cases (same hospital unit, office, classroom, etc).

For nosocomial infection, defined as a hospital-acquired infection, excluding colonisation, a specific form had to be completed containing a brief description of the healthcare facility, the episode (cluster or sporadic, type of organism, type of units affected), the investigation and the control measures that were implemented. We collected additional information received by email or through investigation reports when available.

Data collection for the community clusters, i.e. outside health facilities, was not standardised. Instead, we gathered the information received by emails and reports. There were no specific criteria for undertaking investigations, but they were carried out by the local or regional health authority in the event of a pertussis-related death or if the community event was prolonged.

We created a datasheet covering the following variables: type of reporting (mandatory system or not), institutions involved (healthcare facility, schools etc.), number of cases per age group (0-15 years and >15 years), number of laboratory-confirmed cases, vaccination status (defined as correct number of doses according to age), number of deaths, date of onset of first and last case, reporting date, and control measures (type and coverage). We analysed all reports received between 2000 and 2005. The duration of an event of clustered cases was calculated from the dates of disease onset of the first and last cases. The alert time was defined as the duration between the date of onset of the first case and the date the local authority was informed. Quantitative data were described as the sum and distribution of the variable and

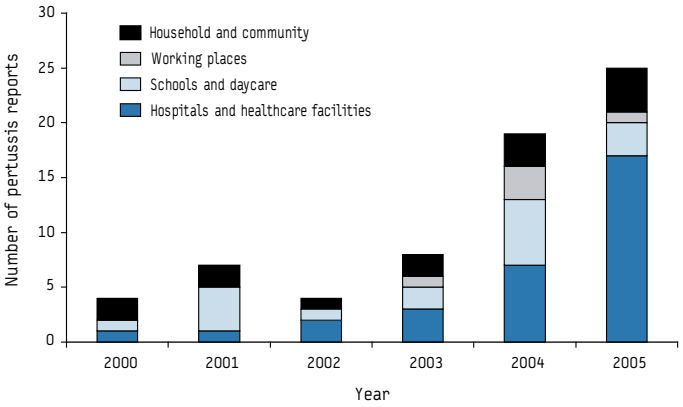
qualitative data as frequencies. We did not analyse variables when the values for them were missing in over 50% of the reports.

Results

Between 2000 and 2005, the InVS received and analysed 67 reports with a total of 595 cases. The annual number of reports increased during that period, particularly for healthcare-associated pertussis (Figure).

FIGURE

Annual number of reports on healthcare-associated events (sporadic cases and clusters) and community clusters (including schools, day care facilities and working places) of pertussis reported at national level, France, 2000-2005



The table summarises the results of the reports according to the age of the patients and the setting in which they occurred (healthcare facility or not).

Healthcare-associated pertussis events

Of the 67 reports, 31 came from healthcare facilities; one from a centre for disabled people, one from a nursing home for the elderly and 29 from hospitals. They accounted for a total of 262 cases 39% of which were laboratory-confirmed. The vaccine status of the cases was missing in most reports, and the pertussis vaccine coverage of the health staff was not known.

The 31 reports covered four sporadic cases and 258 cases belonging to 27 different clusters. The number of cases per cluster varied from two to 91 cases, with a mean of 10 cases and a median of five cases. In 27 of the 31 healthcare-related pertussis events, staff were reported to be infected. In only seven of the 27 clusters the infection originated from patients. In three clusters, patients were secondarily infected. No deaths occurred.

Four reported events did not involve healthcare workers. Three of them affected children hospitalised since birth, infected by relatives or visitors. The source and place of infection for the last one was never found.

Among the 262 healthcare-associated cases, 17 (6%) were under one year of age. The source of infection in five of these infants were the parents, in two further cases it was health workers, and the source in the remaining 10 cases was unknown.

The hospital wards reporting pertussis events among staff or patients most frequently were paediatric (n=6), maternity (n=6) and neonatology wards (n=4). Based on available data from 21 of the 31 healthcare-associated events, the alert time varied from seven to 125 days, with a mean of 48 days and a median of 40 days. The duration of an episode (based on data from 20 of the 27 clusters) ranged from seven to 155 days, with a mean of 48 and a median of 35 days.

Control measures (including at least an attempt of active case finding among exposed individuals) were implemented in 22 of the healthcare facilities. Ten facilities organised large-scale antibiotic

TABLE

Number of cases per age group, laboratory confirmed cases and deaths according to setting, France, 2000-2005

	Cases				Laboratory-confirmed cases	Deaths
	0-15 years	> 15 years	Age unknown	All ages		
Healthcare facilities						
Clustered cases						
Total number of cases	**20**	**228**	**10**	**258**	**100**	**0**
Number of cases per cluster #						
Min	0	1		2	1	
Max	4	90		91	18	
Means	1	9		10	5	
Median	1	3		5	2	
Sporadic cases						
Total number of cases	**2**	**2**	**0**	**4**	**3**	**0**
Outside healthcare facilities						
Total number of cases	**175**	**101**	**57**	**333**	**92**	**6**
Number of cases per cluster #						
Min	1	1		2	0	
Max	26	19		33	11	
Means	7	4		9	3	
Median	4	3		5	1	

The data indicate the minimum/maximum/mean/median number of patients that occurred in a cluster in a given age group

prophylaxis for exposed health staff and patients, whatever the degree of exposition, the risk to develop a severe form of pertussis or the risk to pass it to a vulnerable person (who could develop a severe disease). Healthcare workers in six of the 14 affected wards for which vaccination is recommended since 2004 were immunised following an episode of pertussis infections. The vaccine coverage in the one health facility for which such data was available, was 58% (348 of 596 staff members). Exposed patients, if already discharged, were called back for information and prophylaxis in six of the 16 units taking care of very young children and in two of the 15 other units. The highest number of people contacted by a health facility was 440.

Clustered pertussis events in the community

Of the 67 reports, 36 originated outside healthcare facilities. In total, 333 cases were affected, 53% of which were children under the age of 16, 30% were adults, and 17% were of unknown age. Laboratory data were available for 33 of those reports, and a total of 92 cases (33%) were laboratory-confirmed. Twenty of the children (6% of all cases) were infants under one year of age. The source of infection in five of these infants were the parents, in two further cases it was a sibling, and the source in the remaining 13 cases was unknown.

Clusters occurred in eight primary schools, eight secondary schools and one daycare nursery, affecting a total of 110 children and 38 adults. Information about age was available from three of the eight primary schools, where 26 of the 33 cases were over eight years old. In two other schools, it was reported that the affected pupils were in 4th and 5th grade. The information that was provided regarding the immunisation status of the children was incomplete.

Five clusters occurred in various workplaces. A total of 35 cases were reported in these clusters, and the duration of the episode, known for three of the locations, was 43, 52, and 61 days.

Six deaths occurred, all of them among infants. Two deaths occurred in infants younger than three months-old who had laboratory-confirmed infections. The source of infection for one infant was the mother, and unknown for the other. The remaining four deaths occurred in Guyana, a French overseas district: two infants aged two months, one infant aged three months and one aged seven months. They were among 68 cases reported in two different clusters of pertussis that occurred in Guyana, and the proportion of children younger than 16 years-old in those clusters was 66%.

Discussion

This report analyses data on pertussis outside the routine paediatric hospital sentinel surveillance system. They must be interpreted with caution seeing as clusters among the community are not always reported and local and regional health authorities often only informe the InVS when they need assistance. The nosocomial infections surveillance system, put in place in 2001, is also not exhaustive.

There is an increase in reported pertussis infections, mainly from hospitals. This is mostly due to a more efficient surveillance system and increased awareness of the issue among medical staff [7].

The burden of the disease for healthcare facilities is not negligible. Firstly, despite probable under-reporting, this study shows that outbreaks in healthcare facilities are not a rare event (17 reports in 2005). Secondly, even though the duration of the episodes did not take into account the three weeks of active surveillance following the last case detection (to ensure that the episode is under control), our data confirm that pertussis outbreaks are often prolonged (median 35 days). The economic consequences can be serious, as shown by an outbreak with 91 cases reported in our study that led to medical and productivity costs of 46,661 euros [8]. Our study therefore confirms that pertussis infections are time- and resource-consuming.

Control measures, including active case finding, antibiotic therapy or chemoprophyalxis, and immunisation update, as defined in Floret *et al*. [7] are difficult to assess. Nevertheless, the study highlights several points that could be improved:

- Healthcare staff are often the source of infection in the healthcare-associated pertussis clusters. As most of the clusters originated from units targeted by the 2004 recommendations [3], vaccination of health workers could reduce the burden of the disease in such settings.

- The alert is often late. This is probably due to late diagnosis among health staff and to a delay in reporting to the occupational physician. This needs to be improved, especially as health workers do not spontaneously use a mask when they are coughing and thus coninue to spread the disease.

- The control measures, especially large-scale prophylaxis, can lead to adverse effects, as observed recently in Paris where 33% of the people receiving Azithromycin suffered adverse effects. This can also reduce the compliance even with a short regimen [9,10]. The impact of large-scale prophylaxis is not easy to assess. The 2004 recommendations regarding pertussis vaccination of health professionals in contact with infants could help to lower the risk of pertussis clusters among health workers [3] and could minimise the use of antibiotics to control clusters.

- Of the four clusters involving only patients, two clusters originated from visitors. Visitors should therefore report any illness to the health staff and either wear a protective mask if they have a cough, or postpone their visit.

Following this study, a standardised and detailed form for collecting data regarding pertussis clusters in health facilities was made available on the InVS website (http://www.invs.sante.fr/surveillance/coqueluche/default.htm). This form should improve data collection and help to assess control measures.

Outside healthcare facilities, there was no increase in reported pertussis cases. Among the six infant deaths reported, only one could have been prevented by the vaccine. Apart from infections that occurred in Guyana where infants were probably infected by older children, the source of infection (where known) for infants under one year of age, was mainly the parents of the case. This emphasises the need for protection of parents by immunisation, as recommended in the 2004 vaccine strategies [3]. So far, less than 10% of new parents are immunised against pertussis. In the few districts like Guyana where the three dose-coverage is not yet above 90%, the vaccine coverage among children should be increased to avoid infection of infants by non-vaccinated children. This study, did not allow assessment of the number of cases and deaths among

infants that could have been avoided by adequate and prompt control measures (rapid case detection and antibiotics).

The data have also shown the waning protection after vaccination. This waning effect explains the clusters we observed in schools, with cases aged over eight years. We have little information on the vaccine status of the individual cases in this study, but the coverage for the pertussis booster immunisation among teenagers between 11 and 13 years is lower than 50% in France, which may explain the clusters in secondary schools.

Finally, pertussis also affects adults and the long duration of the outbreaks is probably linked to a late diagnosis. The information collected outside healtcare facilities has been described previously [2] and does not add to the current knowledge. Nevertheless, our data is an opportunity to reinforce the message to clinicians in France who are not all aware of the epidemiology of pertussis today. Pertussis should be suspected when an adult or an adolescent has a cough for more than one week, especially at night, and if there is a suspected source of infection. Infants are the main group at risk: control measures must be put in place rapidly to protect them, even for a single case, and household members must be vaccinated.

Conclusion

Despite very good vaccine coverage, pertussis still occurs in France. Outbreaks occur regularly in healthcare facilities, and the number and size of pertussis clusters in hospitals could be reduced through immunisation of health staff and timely and adequate outbreak management. Infants are the main group at risk and should be protected first through the immunisation of household members.

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Outbreak of salmonellosis in a restaurant in Stockholm, Sweden, September – October 2006

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The largest outbreak of salmonellosis in 25 years in Stockholm County occurred during September - October 2006. A total of 115 persons who had a meal at a restaurant in Stockholm were notified as cases of salmonellosis through the Swedish surveillance system. The probable vehicle of the outbreak was mung beans, soaked in lukewarm water for 24 hours before being served at the restaurant. These mung beans had been included in all dishes served in the restaurant and the outbreak was terminated when they were excluded from the menu. Either *Salmonella* Bareilly or *Salmonella* Virchow were isolated from affected persons. No person was found to have an infection with both serotypes. The majority of affected persons were females with a median age of 34 years. This and similar outbreaks associated with consumption of vegetables and fruits highlight the increasing importance of fresh produce as vehicle for foodborne outbreaks in Europe.

Introduction

Salmonellosis is one of the most important gastrointestinal infections in humans, causing substantial morbidity. The vast majority of Swedish cases of Salmonella are imported, which is due both to the large number of Swedish travellers abroad and the relatively low risk of infection in Sweden compared to other countries, mainly due to effective control programmes implemented in the animal food production. The yearly incidence of domestic-acquired salmonellosis in Sweden is about 7/100,000 inhabitants, compared to 10-390/100,000 in many other European countries [1]. In Sweden about four to 13 outbreaks of salmonellosis are reported every year [2]. However, the number of affected persons in most of these outbreaks is less than 20. This paper reports the largest outbreak of salmonellosis in the Stockholm County in the past 25 years, involving 115 notified cases.

The outbreak

On 18 October 2006, an environmental health officer from the Environment and Health Administration (EHA) in Stockholm City contacted the Department of Communicable Disease Control and Prevention (DCDC) in Stockholm County and informed about a suspected food poisoning at a popular Indian style restaurant situated in the centre of Stockholm. The restaurant manager had called the EHA since 12 persons claimed that they had suffered from food poisoning after having visited the restaurant. The symptoms and incubation time indicated the possibility of Salmonella infection. Before notifying EHA, the restaurant manager questioned the affected guests about the menu items they had eaten and thus established that mung beans were the only ingredient present in all those dishes. The mung beans were bought from a wholesale trader that had imported them from Canada. In the restaurant the beans were put in lukewarm water and left for 24 hours in room temperature, then rinsed and served. Assuming the mung beans to be the possible cause of disease the restaurant manager decided to exclude them from the menu. No mung beans were served from 17 October onwards.

Methods

The Swedish surveillance system

Since 1968, salmonellosis has been a notifiable disease in Sweden. The cases are notified both by clinicians who first see the patients, i.e. clinical notification, and the laboratories which detect the bacteria, i.e. laboratory notification. These notifications are linked together to create a single case using the national identification number (personal identity number – personnummer) assigned to all Swedish citizens. Regarding salmonellosis, a verified case notified from a clinician should be a laboratory-confirmed case of salmonellosis. Notifications are submitted in parallel to the Swedish Institute for Infectious Disease Control (Smittskyddsinstitutet - SMI) (national level) and to the County Medical Officer of DCDC (local level). Clinical notification should contain relevant epidemiological information, including suspected source of infection and country of infection. However, since there is a delay in these notifications outbreaks are usually detected by the Swedish surveillance system two to three weeks after their onset.

Case finding

Upon receiving the information on a possible outbreak in a restaurant in Stockholm the EHA and DCDC launched an investigation. The case finding started with an assessment of all laboratory-confirmed domestic cases of salmonellosis reported in the previous month. All possible cases were contacted by telephone and asked if they had been eating at the restaurant and, if so, the date of visit and the menu item consumed were recorded.

The preliminary case definition included all laboratory-confirmed notified cases of salmonellosis with a history of eating at the restaurant from 1 September 2006 onward. This case definition was later revised to include laboratory-verified and notified cases of *S.* Bareilly or *S.* Virchow with a history of eating at the restaurant from 20 September 2006 onward. Cases with domestic-acquired *S.* Bareilly or *S.* Virchow notified at a later stage of the outbreak were only contacted if information on the source of infection was missing in the notification.

The restaurant declared its willingness to compensate the affected persons for the inconvenience and loss of working days. This communication was forwarded to all persons that were contacted by the public health authorities. The restaurant also registered the name (sometimes also the address), the date of visit at the restaurant and the menu item consumed of each person that complained about food poisoning at the restaurant, and passed this information on to the authorities. This register was later compared with the list of notified laboratory-verified cases. Persons who were

not laboratory-confirmed cases were not contacted and not regarded as a case in the outbreak investigation.

Since action had been taken against the probable vehicle of infection at the restaurant it was decided not to carry out any analytical study. The restaurant guests were therefore not interviewed systematically and thus, a relative risk of illness associated with different food items served at the restaurant was not calculated. However, according to the manager, almost all dishes available in the menu were served with mung beans.

Microbiological investigations

All staff at the restaurant delivered faecal samples that were tested for Salmonella by use of routine diagnostic methods. Several different food items at the restaurant, including mung beans, were sampled and analysed for Salmonella [3]. Furthermore, several batches of mung beans from different wholesale traders and thereby different countries of origin were sampled by the environmental health officer. Modification of the pre-treatment techniques at the laboratory, such as having a part of the mung beans soaked in water and left in room temperature for 24 hours before start of routine culturing, were used in order to detect Salmonella. In total, 34 food samples were analysed in connection with this outbreak.

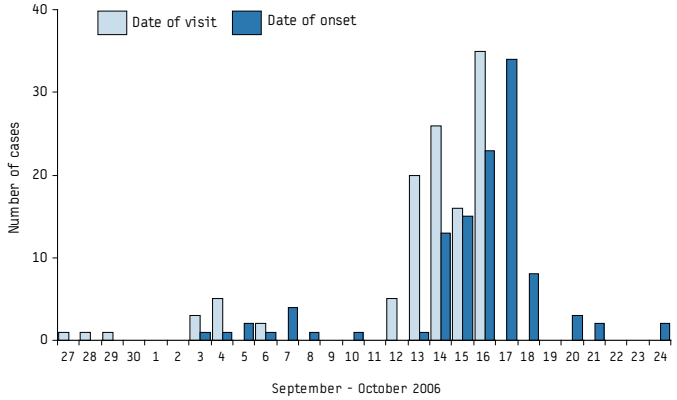
Results

The assessment of domestic cases reported in the previous month yielded three cases infected with *S.* Bareilly. As the source of infection was not given these persons were contacted and it was established that all of them had eaten at the restaurant before the onset of illness. Further investigation revealed several more cases associated with the restaurant but infected with *S.* Virchow. The analysis of laboratory results indicated that cases who reported eating at the restaurant between the end of September and 4 October were infected with *S.* Bareilly, whereas those who visited the restaurant from 6 October onwards were infected with *S.* Virchow. In none of the cases both serotypes were detected.

The total number of affected persons with a Salmonella positive stool culture increased to 115. The outbreak started with a few cases in the end of September and beginning of October and peaked in mid October (Figure 1).

Figure 1

Cases of salmonellosis associated with an outbreak in a restaurant in Stockholm, 2006, by date of visit to the restaurant and date of onset of symptoms (n=115)

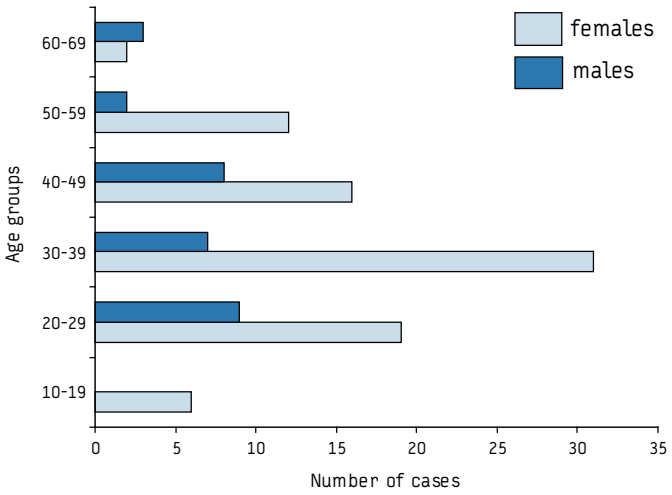


No cases reported visiting the restaurant after 16 October, which strongly supports the hypothesis that the mung beans, which have been omitted from the menu since 17 October, were the vehicle in the outbreak. The exclusion of mung beans from the menu was the only measure taken by the restaurant at the time. The restaurant was inspected by EHA and no major faults in food handling were recorded.

The restaurant, which serves dishes rich in vegetables, attracts mostly young women. This is clearly reflected in the age and gender distribution of cases (Figure 2). There were 86 women and 29 men affected by the outbreak. The median age among females was 34 years and among males 35 years, with the age span from 12 to 67 years.

Figure 2

Cases of salmonellosis associated with an outbreak in a restaurant in Stockholm, 2006, by age and sex (n=115)



Thirteen people living in Stockholm County were hospitalised due to severe disease, and seven of them developed sepsis but no fatal cases occurred.

The register kept by the restaurant showed that 97 persons had contacted directly the restaurant to complain about food poisoning. When comparing their names and addresses with the list of cases notified through the official surveillance system, only 72 persons were found to be present in both sources. Among the 115 notified cases of salmonellosis who were associated with the outbreak, 43 (37%) had not contacted the restaurant. On the other hand, 25 people who complained to the restaurant about having been ill after eating a meal there were not reported as cases.

No Salmonella was found in the food samples despite different pre-treatment techniques used. Nor was any member of staff at the restaurant Salmonella-positive.

An enquiry sent through Enter-net, the international surveillance network for the enteric infections Salmonella and VTEC O157 [4] showed that no other European country had experienced clusters of *S.* Bareilly or S. Virchow in the same period, although S. Bareilly had been isolated from different spices.

Discussion

In the outbreak described here, 115 cases of salmonellosis notified through the routine surveillance system were associated with Salmonella infection in a restaurant in Stockholm, making it the largest outbreak of salmonellosis in the region in the last 25 years. The true number of people affected in this outbreak is likely to have been even higher, considering that the restaurant served about 300 portions each day. It is interesting to note that only 72 of the 115 confirmed Salmonella cases (63%) contacted the restaurant to be eligible for compensation for pain and suffering as well as income reduction. Conversely, 25 persons claiming to the restaurant were not notified as cases of salmonellosis. This could be due to the fact that since the incidence of non-imported salmonellosis in Sweden is low (~7/100,000 inhabitants) clinicians are more reluctant to collect stool samples from patients with domestically acquired gastrointestinal disorders [2]. Some persons associated with the outbreak, but not sampled, have confirmed this suspicion during phone calls to DCDC.

Since action had been taken against the probable vehicle of infection at the restaurant we decided not to carry out any analytical study since it was an outbreak investigation and not a scientific study. The restaurant guests were therefore not interviewed systematically and thus, a relative risk of illness associated with different food items served at the restaurant was not calculated.

S. Virchow and *S.* Bareilly are very rare serotypes in Sweden and during the last 25 years no outbreak of *S.* Bareilly has occurred and only two minor outbreaks have been caused by *S.* Virchow. The vast majority of cases with *S.* Virchow are imported and *S.* Bareilly is seldom recorded among imported cases.

The restaurant involved in the outbreak is regarded as having good management, but this incident shows that one mistake may jeopardise the whole business. If these mung beans had been well rinsed before and under the process and undergone a heat treatment before serving, the growth of salmonella would probably have been minimised, thus preventing the outbreak. We strongly recommended this handling of beans and seeds to be used in the future at the restaurant. However, the manager decided to permanently exclude beans and sprouts from the menu.

An increase in the number of outbreaks associated with consumption of vegetables and fruits has been observed in the last 15 years in Sweden as well as in other industrialised countries [5,6]. Especially bean sprouts have caused numerous outbreaks worldwide and have now become the cause of most vegetable-associated outbreaks both in Sweden and elsewhere [7-10]. In Sweden bean sprouts have caused at least 10 outbreaks in the last 20 years, most of them caused by alfalfa sprouts. The first recognised sprout-associated outbreak in Sweden in 1988 was caused by mung beans and affected at least 195 persons [7]. However, in the outbreak described here the beans were not sprouted, only put in water in order to give them a softer consistency. This and similar outbreaks associated with consumption of vegetables and fruits highlight the increasing importance of fresh produce as vehicle for foodborne outbreaks in Europe.

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Legionnaires' disease in Europe: 2005-2006

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Once a year, every country that participates in the European Surveillance Scheme for Travel Associated Legionnaires' Disease (EWGLINET) is asked to submit a dataset comprising all cases of Legionnaires' disease (not only travel-associated) with date of onset in the previous year. This paper presents the data collected for 2005 and 2006. In this period, 11,980 cases were reported by 35 countries, showing a continued increase compared with earlier years. 214 outbreaks or clusters were reported, involving 1028 cases. 377 cases died, giving a case fatality rate of 6.6%. The highest incidence rates in both years were recorded in Spain, while six countries reported a rate of less than one case per million population in at least one of the years. Incidence rates by age group were included in the dataset for the first time, showing an increase of the overall rate with age. Main method of diagnosis was the urinary antigen test (76.0%), whilst the percentage of cases diagnosed by culture fell from 10.0% in previous years to 8.9% in 2005-2006.

Introduction

Legionnaires' disease is an atypical pneumonic illness caused by the *Legionella* bacteria. These bacteria can be found naturally in environmental water sources such as rivers, lakes and reservoirs, usually in low numbers. The organism favours warm, stagnant waters, and becomes infective when aerosolised. Poorly maintained aerosol-generating devices can act as a source of the disease, and have been responsible for outbreaks affecting up to 400 cases [1]. Wet cooling systems, water systems and spa pools are all well documented sources of Legionnaires' disease [1].

The identification of Legionnaires' disease in 1977 led to the establishment of the European Working Group for Legionella Infections (EWGLI) in 1986. The group aimed to share knowledge and to monitor trends in legionella infections across Europe. Currently, 35 countries are members of EWGLI.

Every year the EWGLI participating countries are asked to submit data on the cases of Legionnaires' disease that have been diagnosed in their residents during the preceding year to the co-ordinating centre in London. This allows for analysis of this disease on a European level and for comparison of trends between countries. Data from the years 1996 to 2004 have been published previously [2-7]. This paper presents the dataset for the years 2005-2006.

Methods

Participating countries submit an aggregated epidemiological and microbiological dataset using standardised reporting forms. The following data is collected: the number of confirmed and presumptive cases diagnosed in the reporting country during the preceding year, how many died, and the population base covered by the reporters; the method of diagnosis and the species and serogroup of any isolates obtained; age group and sex of the cases (age standardised rates were introduced into the dataset for the first time in 2005); category of exposure (nosocomial [hospital-acquired], travel or community); countries of travel for the travel-associated cases; outbreaks by type, size and suspected source.

Cases are classified as confirmed or presumptive, based upon the EWGLI case definitions [8]. If the method of diagnosis is not known, the case is classified as 'diagnosis not known'.

Each case is further categorised by exposure history into 'travel', 'nosocomial' and 'community' cases. This is determined for each case by the country of report according to national definitions. In instances where there is insufficient evidence to allocate a case to one of the existing categories (e.g. cases that spent part of their incubation period both in hospital and travelling), the case is categorised as 'other', and if there is no exposure information available, the case is allocated to the 'not known' category.

Where incidence rates per million population are calculated, they are based upon the reported population size. Regional rather than national incidence rates were obtained for six countries in 2005 (Bulgaria, Croatia, Czech Republic, Lithuania, Romania, Russia) and four in 2006 (Bulgaria, Lithuania, Russia, Romania), and it should be noted that these data may not be representative of the entire country.

In this report, the term 'outbreak' is used to describe outbreaks in hospitals or community settings, whereas the term 'cluster' is used to describe this type of incident when associated with hotels or other tourist accommodation sites. Every country defines its outbreaks independently, whilst clusters are defined as 'two cases associated with the same accommodation site within two years', based upon EWGLINET's definition.

Results

In 1993, only 19 countries reported a dataset to EWGLI. The response rate has risen significantly since then to 35 countries in both 2005 and 2006. The number of cases reported was 5,700 in 2005 and 6,280 in 2006. In the fourteen years for which this dataset has been collected, 41,627 cases have been reported (Table 1). [Note that in previous publications, the number of cases for 1993 was erroneously reported as 242 instead of 1,242]

Incidence per million population

In both years the highest incidence rates were reported by Spain (28.4/1,000,000 population in 2005 and 30.0/1,000,000 in 2006), followed in 2005 by France (24.8/1,000,000 in 2005 and 23.0/1,000,000 in 2006) and in 2006 by the Netherlands (16.7/1,000,000 in 2005 and 26.9/1,000,000 in 2006). Five countries reported incidences of less than one case per million population in 2005 (Latvia, Malta, Poland, Slovakia and Turkey), in comparison with four countries in 2006 (Latvia, Romania, Slovakia and Turkey). Table 2 shows rates of Legionnaires' disease per million

Table 1

Legionnaires' disease in Europe: total number of reported cases and incidence rate per million population, 1993 - 2006, EWGLI data

Year	Cases	No. of countries contributing data	Population (millions)	Incidence rate per million population
1993	1242	19	300	4.1
1994	1161	20	346	3.4
1995	1255	24	339	3.7
1996	1563	24	350	4.5
1997	1360	24	351	3.9
1998	1442	28	333	4.3
1999	2136	28	398	5.4
2000	2156	28	400	5.4
2001	3470	29	455	7.6
2002	4696	32	467	10.1
2003	4578	34	468	9.8
2004	4588	35	550	8.3
2005	5700	35	551	10.3
2006	6280	35	563	11.2

population for 10 countries, selection based upon their consistent rates, and in order to allow comparison with previous papers.

The overall incidence for Europe was 10.3/1,000,000 in 2005 (based on a denominator population of 550.8 million) and 11.2/1,000,000 in 2006 (based on a denominator of 562.7 million) (Table 1).

Category of cases

For the two years 2005-2006, 629 cases were reported as nosocomial, 7,041 as community cases, 1,395 as associated with travel abroad, 1,227 as associated with travel within the country of residence, 126 as 'other' and 1,562 as 'not known' category of infection (Table 3).

Table 3

Legionnaires' disease: number of cases and proportion by category of infection, 2005-2006, EWGLI data

	2005		2006		Total	
Category of infection	Cases	Percent (%)	Cases	Percent (%)	Cases	Percent (%)
Nosocomial	322	5.6	307	4.9	629	5.3
Community	3353	58.8	3688	58.7	7041	58.8
Travel abroad	691	12.1	704	11.2	1395	11.6
Travel home	589	10.3	638	10.2	1227	10.2
Not known	715	12.5	847	13.5	1562	13.0
Other	30	0.5	96	1.5	126	1.1
Total	**5700**	**100.0**	**6280**	**100.0**	**11980**	**100.0**

Table 2

Legionnaires' disease: number of cases and incidence rate per million population for selected countries, 2005-2006, EWGLI data

		2005		2006	
Country	Population (millions)*	Cases	Incidence rate	Cases	Incidence rate
Belgium	10.5	175	16.8	230	21.9
Denmark	5.4	114	21.1	127	23.4
England and Wales	53.0	340	6.4	544	10.3
France	62.6	1527	24.8	1440	23.0
Germany	82.4	459	5.6	484	5.9
Italy	58.5	869	14.9	800	13.7
Netherlands	16.3	273	16.7	440	26.9
Spain	43.7	1229	28.4	1312	30.0
Sweden	9.1	88	9.7	108	11.9
Switzerland	7.5	157	21.1	176	23.6

*Where the population differs between 2005 and 2006, the 2006 figure is given

Age of cases

A breakdown of cases by age group was available in both years for all countries except Czech Republic, Former Yugoslav Republic of Macedonia, Germany, Iceland, Israel and Portugal. National demographic data on population size by age group were also provided in order to calculate age standardised rates. The peak age group of cases was 50-59 in both years; 1,164 cases in this age group were reported in 2005 and 1,289 cases in 2006. Whilst in both years the number of reported cases in the older age groups decreased with age (60-69 years: 1,076 in 2005, 1,170 in 2006; 70-79 years: 914 in 2005, 1,026 in 2006; 80+ years: 639 in 2005, 726 in 2006), the overall age standardised incidence rates increased with increasing age (60-69 years: 2.6 cases per 100,000 in 2005, 2.86 in 2006; 70-79 years: 2.91 in 2005, 3.32 in 2006; 80+ years: 3.83 in 2005, 4.32 in 2006). This increase in incidence rate with age was seen for some individual countries (e.g. France, Italy), but did not hold for all (e.g. England and Wales, The Netherlands) (Table 4).

Table 4

Legionnaires' disease: age group and age-specific incidence rates for selected countries, 2005-2006, EWGLI data

		2005		2006	
Country	Age group	Number of cases	Incidence rate per 100,000	Number of cases	Incidence rate per 100,000
Belgium	< 20	2	0.08	2	0.08
	20 - 29	6	0.51	11	0.84
	30 - 39	11	0.74	19	1.29
	40 - 49	25	1.57	37	2.31
	50 - 59	50	3.68	43	3.10
	60 - 69	32	3.24	38	3.81
	70 - 79	27	3.15	56	6.55

	80+	22	4.91	20	4.29
	Total	175	1.68	226	2.15
Denmark	< 20	0	0.00	1	0.08
	20 - 29	1	0.16	2	0.32
	30 - 39	3	0.38	4	0.51
	40 - 49	18	2.33	23	2.93
	50 - 59	29	3.87	27	3.65
	60 - 69	36	6.42	31	5.27
	70 - 79	21	5.99	22	6.25
	80+	6	2.72	17	7.63
	Total	114	2.11	127	2.34
England and Wales	< 20	0	0.00	2	0.02
	20 - 29	7	0.11	5	0.08
	30 - 39	15	0.19	29	0.36
	40 - 49	64	0.86	90	1.21
	50 - 59	96	1.43	162	2.41
	60 - 69	99	1.96	146	2.89
	70 - 79	47	1.24	77	2.03
	80+	12	0.51	33	1.41
	Total	340	0.64	544	1.03
France	< 20	8	0.05	2	0.01
	20 - 29	30	0.35	33	0.41
	30 - 39	105	1.18	85	0.95
	40 - 49	244	2.79	214	2.42
	50 - 59	328	4.12	322	3.91
	60 - 69	261	4.92	250	4.66
	70 - 79	301	6.44	293	6.20
	80+	250	9.41	241	8.61
	Total	1527	2.48	1440	2.30
Germany	< 20	11	0.07	6	0.04
	20 - 29	8	0.08	10	0.10
	30 - 39	33	0.27	38	0.32
	40 - 49	77	0.58	98	0.72
	50 - 59	123	1.22	106	1.01
	60 - 69	108	1.04	97	0.97
	70 - 79	99	0.97	129	1.23
	80+				
	Total	459	0.56	484	0.59
Italy	< 20	4	0.04	6	0.05
	20 - 29	12	0.17	8	0.11
	30 - 39	77	0.81	39	0.41
	40 - 49	139	1.62	132	1.54
	50 - 59	164	2.20	153	2.05
	60 - 69	202	3.10	180	2.76
	70 - 79	174	3.32	165	3.15
	80+	97	3.35	117	4.04
	Total	869	1.49	800	1.37
Netherlands	< 20	0	0.00	1	0.03
	20 - 29	4	0.20	6	0.31
	30 - 39	16	0.64	26	1.07
	40 - 49	42	1.67	67	2.65
	50 - 59	84	3.77	121	5.34
	60 - 69	69	4.60	124	8.08
	70 - 79	45	4.34	68	6.49
	80+	13	2.27	27	4.60
	Total	273	1.67	440	2.69
Spain	< 20	12	0.14	6	0.07
	20 - 29	19	0.29	29	0.45
	30 - 39	120	1.64	105	1.41
	40 - 49	216	3.39	219	3.35
	50 - 59	265	5.26	287	5.59
	60 - 69	245	6.15	248	6.14
	70 - 79	207	5.91	270	7.64
	80+	140	7.44	142	7.23
	Total	1224	2.83	1306	2.99
Sweden	< 20	1	0.05	3	0.14
	20 - 29	3	0.28	0	0.00
	30 - 39	4	0.32	4	0.32
	40 - 49	12	0.98	6	0.48
	50 - 59	25	2.07	32	2.68
	60 - 69	15	1.51	30	2.89
	70 - 79	20	3.04	19	2.88
	80+	8	1.64	14	2.86
	Total	88	0.97	108	1.19
Switzerland	< 20	1	0.06	0	0.00
	20 - 29	2	0.22	1	0.11
	30 - 39	10	0.88	7	0.62
	40 - 49	17	1.44	23	1.92
	50 - 59	29	2.98	30	3.07
	60 - 69	32	4.32	43	5.73
	70 - 79	43	8.18	35	6.62
	80+	23	6.91	37	11.00
	Total	157	2.11	176	2.36

Outbreaks

During the two years, there were a total of 214 outbreaks or clusters, detected by 18 countries and involving 1,028 cases, 8.6% of the total dataset (Table 5). Countries reported 408 cases associated with 107 outbreaks in 2005, and 620 cases associated with 107 outbreaks in 2006. The outbreaks ranged in size from two to 146 cases. The largest outbreaks in both years occurred in Spain and were attributed to wet cooling systems; involving 50 cases in 2005 [9] and 146 in 2006 [10]. The number of deaths associated with these outbreaks could not be determined from the information collected in this dataset.

Nineteen outbreaks (8.9%) involving 66 cases were linked to hospitals or healthcare facilities and occurred in Austria, Denmark, England and Wales, France, Germany, Ireland, The Netherlands, Poland, Portugal and Spain. Fifteen of these were attributed to contaminated hot or cold water systems, two to wet cooling systems, and two to an unknown source. These sources are as reported by collaborators, and the standard of investigation may vary between countries.

TABLE 5

Legionnaires' disease: number of outbreaks and associated cases by category of infection, 2005-2006, EWGLI data

	2005		2006		Total	
Category of outbreak	Outbreaks	Percent (%)	Outbreaks	Percent (%)	Outbreaks	Percent (%)
Nosocomial	10	9.3	9	8.4	19	8.9
Community	25	23.4	19	17.8	44	20.6
Travel abroad	54	50.5	40	37.4	94	43.9
Travel home	16	15.0	33	30.8	49	22.9
Other/unknown	2	1.9	6	5.6	8	3.7
Total	**107**	**100.0**	**107**	**100.0**	**214**	**100.0**

Forty-four outbreaks (20.6%) were linked to community settings, and involved 522 cases. They occurred in Austria, England and Wales, France, Germany, The Netherlands, Northern Ireland, Poland, Portugal, Scotland and Spain. Wet cooling systems were identified as the source in 19 outbreaks, five were attributed to hot or cold water systems, four to whirlpool spas, 15 to an unknown source and one to the sediment at the base of a pressurised water tank [11].

One hundred and forty-three clusters (66.8%) were associated with travel; 94 (44%) with travel outside the country of residence, and 49 (23%) with travel within the country of residence. Hot or cold water systems were responsible for 52 of the clusters, a wet cooling system in one cluster, and whirlpool spas in three. No source was identified for the remaining clusters.

Two outbreaks (one in each year) were linked to prisons, and in both the source of infection was identified as the hot or cold water system. One 2006 outbreak was associated with a nursing home, for which the source was not identified, and the remaining five outbreaks (one in 2005, the rest in 2006) were associated with private homes or buildings. In two of these latter outbreaks, the hot water systems were identified as the source; for the remaining three no source was identified.

Travel-related legionella infection

Altogether in 2005-2006, 26 countries reported a total of 2,622 travel-associated cases; 1,395 were classified as 'travel abroad' and 1,227 were associated with travel in the patient's country of residence (Table 3). Nine countries in 2005 and five countries in 2006 reported no travel-associated cases. Travel within Europe accounted for 89.2% of the travel-associated cases in 2005 (1142 cases) and 90.0% in 2006 (1208 cases). Travel on cruise ships was associated with two cases in 2005 and 11 in 2006.

Spain was associated with the most travel-related cases over this two-year period (545 cases), followed by France (497 cases) and Italy (450 cases). These countries may be disproportionately represented as countries of infection because they reported the highest number of cases in general, and the majority of the travel-associated cases in these countries (59.6%, 77.3% and 53.3%) occurred as a result of domestic travel.

A more detailed analysis of travel-associated cases of Legionnaires' disease is published each year from EWGLI's surveillance scheme (EWGLINET) [12]. EWGLINET operates a strict case definition for travel-associated infections, and so not all cases reported as travel in this dataset are reported to the EWGLINET travel dataset. EWGLINET's case definition excludes patients who had stayed in private accommodation, patients for whom travel information was incomplete, or those for whom travel did not fall within the strict 2-10 day incubation period. EWGLINET does not include these cases because it would not be possible to investigate them further or to link them to other cases who shared the same accommodation site.

Main method of diagnosis

EWGLI collaborators allocate a main method of diagnosis to each reported case, taking culture as the 'gold-standard' test. The majority of cases in 2005 and 2006 were primarily diagnosed by urinary antigen detection (9,100 cases, 76.0%), followed by isolation/culture for 1,067 cases (8.9%), single high antibody titres in 716 cases (6.0%), and a fourfold rise in antibody detection levels for 274 cases (2.3%). The remaining cases were diagnosed by respiratory antigen detection, PCR, other methods or the method was unknown (Table 6).

In 2006 compared with 2005, the percentage of cases diagnosed primarily by culture fell from 9.3% to 8.6%, whilst the number of cases with urinary antigen detection as the main method of diagnosis increased from 71.3% to 80.2%. The proportion of cases diagnosed serologically (including both seroconversions and single high titres) fell from 8.8% to 7.8%.

'*Legionella pneumophila* serogroup 1' accounted for 9,219 cases (77.0%) over the two years, '*L. pneumophila* other serogroup or serogroup not determined' accounted for 1,862 cases (15.5%), and 899 (7.5%) were reported as 'other *Legionella* species' or 'species not known'.

Of the 1,067 isolates obtained, 862 (80.8%) were identified as *L. pneumophila* serogroup 1, 94 (8.8%) were *L. pneumophila* serogroups 2-16 and 74 (6.9%) were *L. pneumophila* serogroup unknown. Seventeen isolates were diagnosed as other species of *Legionella*. These were reported as *L. anisa* (1), *L. bozemanii* (2), *L. brunensis* (1), *L. cincinnatiensis* (1), *L. feeleii* (1), *L. jordanis* (1), *L. longbeachae* (4), and *L. micdadei* (6). For 20 isolates, the *Legionella* species was not known.

Deaths

There were 377 deaths reported in 2005 (case fatality rate of 6.6%) compared with 387 deaths in 2006 (case fatality rate of 6.2%). In some countries it is not compulsory to report deaths, and so these figures may underestimate the true mortality attributable to Legionnaires' disease.

Table 6

Legionnaires' disease: number of cases and proportion by main method of diagnosis, 2005 - 2006, EWGLI data

	L. pneumophila sg1		L. pneumophila (other serogroup), or serogroup not determined		Other Legionella species or species not known		All legionella cases	
Main method of diagnosis	Cases	Percent (%)	Cases	Percent (%)	Cases	Percent (%)	Cases	Percent (%)
Isolation/ culture	862	9.4	168	9.0	37	4.1	1067	8.9
Urinary antigen detection	7925	86.0	949	51.0	226	25.1	9100	76.0
Serology: Seroconversion	109	1.2	120	6.4	45	5.0	274	2.3
Serology: Single high titre	272	3.0	346	18.6	98	10.9	716	6.0
Respiratory antigen detection	3	0.0	5	0.3	0	0.0	8	0.1
PCR	27	0.3	106	5.7	62	6.9	195	1.6
Other	13	0.1	3	0.2	1	0.1	17	0.1
Not Known	8	0.1	165	8.9	430	47.8	603	5.0
Total	**9219**	**100.0**	**1862**	**100.0**	**899**	**100.0**	**11980**	**100.0**

(Each case counted once only)

Discussion

The number of cases reported each year to the scheme continues to increase. This rise in case numbers can be partly attributed to increasing ascertainment as national surveillance schemes strengthen. It is especially notable that awareness of Legionnaires' disease is rising in the newer European Union member states. Invitation to submit annual datasets of cases each year appears to be helping in raising the profile of the disease in these countries, whereas comparison of the rates between countries can highlight the extent of the under-ascertainment. EWGLI hopes that the number of cases reported by these countries in the future annual datasets will increase to better reflect the true number of cases.

Every year, the number of nosocomial cases reported to the dataset remains relatively static (between 300 and 350 since 2003 [7]). In the context of increasing overall case numbers this stability is an encouraging trend, especially since case fatality rates are higher amongst nosocomial cases than amongst other categories [13]. Also, the number of large community outbreaks has been decreasing in recent years. Community outbreaks are unpredictable, so it is difficult to determine whether this decrease is real or artifactual. However, more extensive legislation has been introduced across Europe in recent years for the control and prevention of Legionnaires' disease, which is probably having a beneficial effect [14-16]. Authorities should be encouraged to ensure that national or WHO guidelines are being utilised in national health care systems [1].

EWGLI has repeatedly raised the problems associated with a decrease in the number of clinical isolates being obtained but, despite this, the number fell again during 2005-2006 to 8.9% (in comparison with 10.0% in 2003-2004 [6]). Lack of clinical isolates can cause difficulties for public health authorities when investigating clusters; with no clinical isolate to compare with any environmental isolates obtained, the suspected source of the outbreak cannot be microbiologically confirmed. As Legionella is a relatively ubiquitous organism in the environment, microbiological confirmation is an important step in determining the source of infection. As the urinary antigen test becomes ever more widespread, this problem is likely to become exacerbated. The increasing use of the urinary antigen test probably also accounts for the high proportion of *L. pneumophila* serogroup 1 reported to EWGLI, since the test almost exclusively detects these organisms.

The overall incidence rates recorded in this dataset show an increasing rate with increasing age. This is a new variable collected in the dataset and the resulting figures have important implications for Europe's aging population. Countries should expect an increase of case numbers and a greater demand for health services due to Legionnaires' disease in the future. There are some countries that do not show this increasing rate with age, however, it is difficult to determine whether this is due to different testing policies or to true trends in the incidence rates.

In 2010, EWGLINET and the collection of this annual dataset will transfer to the European Centre for Disease Prevention and Control (ECDC). This annual dataset has now been collected for fourteen years, to comprise the largest dataset of cases of Legionnaires' disease in the world and should be continued. EWGLINET itself has been a valuable tool in raising awareness of the disease among members and national surveillance structures, and has contributed to the introduction of regulations and guidelines across Europe. This type of European surveillance is especially important for preventable diseases with environmental sources, as prompt action can tackle these sources as they emerge. With the ageing of populations across Europe, and therefore more people at risk from Legionnaires' disease, EWGLINET's importance will only increase.

EWGLI hopes that the ECDC will encourage countries, especially the new EU Member States, to develop their national surveillance schemes and submit their annual data so that surveillance of the Legionnaires' disease across Europe can continue unabated.

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DIPNET – establishment of a dedicated surveillance network for diphtheria in Europe

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The ninth international meeting of the European Laboratory Working Group on Diphtheria (ELWGD) and the first annual meeting of the Diphtheria Surveillance Network (DIPNET) was held in Vouliagmeni, Greece, in November 2006. The recognition of DIPNET as an established Dedicated Surveillance Network (DSN) by the European Commission (EC) was announced, with the specific objective "to establish a Pan-European network of expertise for the prevention of diphtheria and other related infections". At the meeting, DIPNET participants from the European Union (EU) Member States and associated countries as well as collaborators from countries beyond EU presented the current situation concerning the clinical, epidemiological and microbiological aspects of diphtheria and related infections. Issues highlighted included the need for improving surveillance systems, supporting laboratory diagnostics globally, and undertaking screening and seroepidemiological studies to sustain diphtheria control in the WHO European Region and beyond.

Introduction

At the request of the World Health Organization Regional Office for Europe (WHO EURO), the European Laboratory Working Group on Diphtheria (ELWGD) was formed in July 1993 because of the re-emergence of diphtheria to epidemic levels in the Russian Federation and Newly Independent States (NIS) during the 1990s [1,2]. The main objectives were to form a network of laboratories for microbiological surveillance, to standardise laboratory diagnostic methods in epidemic areas, and to understand the molecular epidemiology and characteristics of epidemic strains at that time. In 2001, the network was expanded through a feasibility study funded by the European Commission Health and Consumer Protection Directorate-General (DG SANCO). The Diphtheria Surveillance Network (DIPNET) integrates both epidemiological and microbiological aspects of diphtheria, and also includes other infections caused by potentially toxigenic corynebacteria [3]. Following the success of the feasibility study, DIPNET was officially recognised by the European Commission (EC) as a Dedicated Surveillance Network (DSN) and was established in November 2006. The main beneficiary and coordinating centre is located at the Health Protection Agency Centre for Infections, London, United Kingdom, where the WHO Collaborating Centre for Diphtheria and Streptococcal Infections is situated. The main purpose of DIPNET is "to establish a network of expertise for the prevention of diphtheria and other related infections" [4] across the EU Member States and beyond. The specific objectives of DIPNET are to:

- Harmonise and enhance surveillance of *Corynebacterium diphtheriae* and *C. ulcerans* within the WHO European Region.
- Determine the disease prevalence and characteristics of toxigenic and non-toxigenic *C. diphtheriae* and *C. ulcerans* in a variety of populations with emphasis upon higher risk countries.
- Expand the DIPNET external quality assurance schemes for laboratory diagnosis to include epidemiological typing and serological immunity.
- Develop novel tools for integrated molecular epidemiological characterisation so as to gain a clearer understanding of the spread of epidemic clones throughout the WHO European Region.
- Undertake serological immunity studies within 'high risk countries' and assessment of serological methodologies across all EU Member States.

These objectives will be achieved through nine specific work packages (Table 1).

DIPNET was launched at the ninth international meeting of ELWGD held in Vouliagmeni, Greece and included participants from 36 different countries, twenty two EU Member States, one associated country, ten countries of the Newly Independent States (NIS) of the former Soviet Union, Canada, Japan, United States of America, as well as the European Centre for Disease Prevention and Control (ECDC) and WHO EURO (Table 2). DIPNET works closely with the ECDC to significantly improve the basis for the exchange of information on diphtheria cases, detection of new disease manifestations and provide essential data for immunisation policies within the EU. Furthermore, DIPNET together with the ECDC will consult and advise WHO EURO in order to strengthen and enhance communication in data sharing and collection within the EU and those countries beyond the EU where the disease is endemic.

This report presents the current status of diphtheria and related infections within the WHO European Region and highlights key areas of discussion from the first annual DIPNET meeting and background data requested from the DIPNET participants.

Current state of diphtheria in the WHO European Region

Over a decade ago, the epidemic of diphtheria in the Russian Federation and NIS peaked at 50,425 cases in 1995 [2]. Following mass immunisation campaigns, additional control measures and support from ELWGD, diphtheria is largely under control in the WHO EURO region, with only 500 cases reported in 2005 [5]. The majority of European countries observed sporadic or no cases in recent years, with 13/25 DIPNET countries not having reported a diphtheria case since 2000 (Figure). The largest number of reports came from Latvia which reported 487 isolates of *C. diphtheriae* between 2000 and 2006. Eight DIPNET countries (Belgium, Czech Republic, Finland, France, Germany, Lithuania, Turkey and UK) reported sporadic cases caused by toxigenic strains of *C. diphtheriae* between 2000 and 2006; 1-10 isolates for the six year period.

Table 1

Nine specific work packages of DIPNET - dedicated surveillance network for diphtheria in Europe.

Work Package (WP)	Specific Objectives
WP1: Coordination of project	• To be responsible for general management and co-ordination. • To manage and coordinate the Steering Committee. • To manage the financial and administrative aspects of the project. • To liaise with the EC, ECDC and other key international bodies. • To ensure that all the milestones and deliverables for each WP are successfully achieved. • To develop and use the DIPNET website to disseminate information to European policymakers, professionals and the public.
WP2: Dissemination of results	• This work package will support the development and integration of sustainable EU systems for collecting, validating, analysing and disseminating epidemiological and laboratory surveillance data and information. • To plan and coordinate all the meetings. • To publicise and promote the activities of DIPNET. • To publish project results in peer reviewed journals, progress reports in Eurosurveillance and periodic reports for the EC.
WP3: Evaluation of project	• To ensure participation is in accordance with the Principles of Collaboration. • To commission regular updates from work package leaders, detailing progress towards objectives.
WP4: Assessment of surveillance and disease burden	• To harmonise and enhance surveillance for *C. diphtheriae* and *C. ulcerans* in Europe, with close working with the ECDC.
WP5: *C. diphtheriae* and *C. ulcerans* detection amongst EU populations	• To determine the disease incidence, prevalence and characteristics of toxigenic and non-toxigenic *C. diphtheriae* and *C. ulcerans* in a variety of populations with particular emphasis upon higher risk countries. • To assess detection rates amongst different populations, establish information on current upper respiratory tract (URT) infections. • To construct a model of transmission for *C. diphtheriae* and *C. ulcerans* in the EU and assess where possible the role of domestic animals as reservoirs of *C. ulcerans*.
WP6: Assessment of Diphtheria Reference microbiology and External Quality Assurance (EQA)	• To harmonise, standardise and enhance surveillance of *C. diphtheriae* and *C. ulcerans* in Europe. • To develop and provide laboratory support to participating countries by expansion of the DIPNET EQA schemes for laboratory diagnosis and to include epidemiological typing and serological immunity. • To support networking and cooperation between European reference centres/facilities for diphtheria in order to ensure compatibility of data.
WP7: Molecular epidemiology of C. diphtheriae and C. ulcerans in Europe	• To evaluate and establish rapid molecular typing methods and create an on line access database for genotypes and epidemiological data. • To develop novel tools for integrated molecular epidemiological characterisation so as to gain a clearer understanding of the spread of epidemic clones throughout the European Region.
WP8: Development of DIPNET integrated database and website	• To provide a dedicated database and website for the implementation of the work packages and as a valuable information resource which would be integrated and exchanged with other EU disease networks and international agencies, ECDC and WHO EURO. • To provide mechanisms for on-line collection and dissemination of information to support the work packages. • To develop and use the DIPNET website to disseminate information to European policymakers, professionals and the public.
WP9: Serological immunity to diphtheria in EU	• To assess methodologies used for serological immunity studies across all member states and associated countries. • T o undertake serological immunity studies within high risk countries.

Table 2

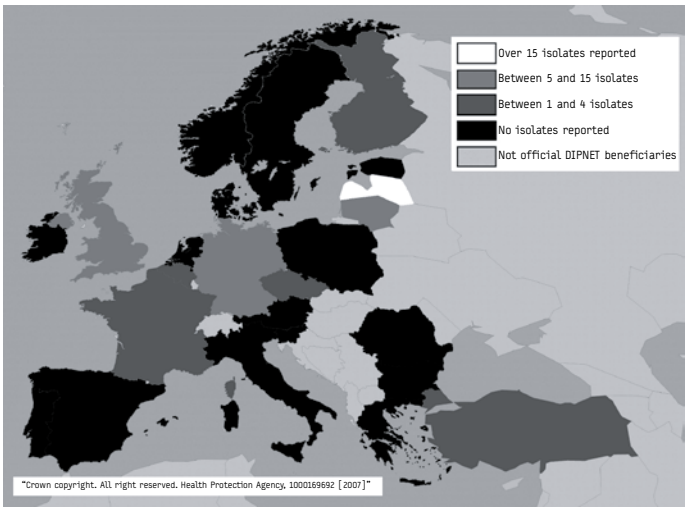
DIPNET members and other collaborating countries, as of November 2006 (n=46)

DIPNET Countries	Collaborating Countries
United Kingdom	Argentina
Austria	Armenia
Belgium	Australia
Bulgaria	Azerbaijan
Cyprus	Belarus
Czech Republic	Brazil
Denmark	Canada
Estonia	Georgia
Finland	India
France	Israel
Germany	Japan
Greece	Kazakhstan
Ireland	Kyrgyzstan
Italy	Moldova
Latvia	Russia
Lithuania	Switzerland
Netherlands	Tajikistan
Norway	Turkmenistan
Poland	Ukraine
Portugal	USA
Romania	Uzbekistan
Slovenia	
Spain	
Sweden	
Turkey	

Seven countries (France, Germany, Italy, Netherlands, Romania, Sweden and UK) reported sporadic cases caused by toxigenic strains of *C. ulcerans*; 1-19 isolates for the six year period (Table 3). These corynebacteria, more commonly found in animals, can

Figure 1

Number of toxigenic *Corynebacterium diphtheriae* isolates in DIPNET countries, from 2000 to 2006



carry the same bacteriophage that codes for the toxin produced by toxigenic strains of *C. diphtheriae*. Human *C. ulcerans* infections are usually acquired through contact with animals or by eating or drinking unpasteurised dairy products [6,7,8]. The reporting of these toxigenic organisms is therefore important to identify and monitor any changes in the epidemiology of the disease and because the data is not currently collected by WHO. However, the proposed ECDC case definition will include cases caused by toxigenic *C. ulcerans* [5, personal communication with ECDC]. In addition, non-toxigenic *C. diphtheriae* are also voluntarily reported in most countries. The UK experiences high numbers, but this is most likely due to good clinical and microbiological awareness and includes mild cases of pharyngitis.

Although excellent progress has been achieved in reducing diphtheria incidence, a few countries within the WHO European Region, such as Belarus, Georgia, Latvia, the Russian Federation, and Ukraine are still experiencing problems [5]. In particular, Latvia, a member of both DIPNET and the EU, has the highest diphtheria morbidity and mortality within the EU, with 143 cases and 14 deaths reported between 2002 and 2006. In addition, there is particular concern in Latvia amongst populations with poor socio-economic status and high-risk groups (e.g., homeless and the military) [9].

Control of diphtheria is still a high priority for the WHO European Region. There are four key strategies to ensure continued prevention and control of diphtheria: primary prevention by ensuring high population immunity, strengthened surveillance, early diagnosis and high quality case management and rapid investigation and management of close contacts [10].

Table 3

Number of toxigenic *Corynebacterium ulcerans* isolates in DIPNET countries, from 2000 to 2006.

Country	*C. ulcerans*
Austria	
Belgium	
Bulgaria	
Cyprus	
Czech Republic	
Denmark	
Estonia	
Finland	
France	19
Germany*	4
Greece	
Ireland	
Italy	1
Latvia	
Lithuania	
Netherlands	2
Norway	
Poland	
Portugal	
Romania	2
Slovenia	
Spain	
Sweden	2
Turkey	
UK#	20

* Data up to 2005

\# Numbers include mild cases of pharyngitis

Surveillance of diphtheria and related infections in DIPNET countries

Reporting of diphtheria cases from countries in the WHO European Region is mandatory; however, the level of reporting varies between countries, indicating that action is needed to enhance awareness and to promote reporting of diphtheria. Also improvements in surveillance and ascertainment at the EU level are essential. This will be undertaken within the remit of DIPNET in consultation with the ECDC, WHO EURO and the EU Member States' Ministries of Health. Surveillance methods vary based on either clinical case data or laboratory-based data, or both. One key objective of DIPNET is to harmonise surveillance in all EU countries. Currently, WHO EURO obtains a minimal set of data fields; if additional information could be collected, this would help inform epidemiologists and clinicians of any changes in disease pattern.

DIPNET will establish an enhanced database for all countries to submit standardised data to capture both clinical details and microbiological characteristics. This will be developed together with the ECDC where an EU-wide disease surveillance is currently

being set up based on the idea of using a common core dataset and then enhancing this with additional fields specific to particular diseases.

Laboratory diagnostics and screening policies for C. diphtheriae and C. ulcerans

It is important to maintain expertise in laboratory diagnostics of diphtheria to detect these relatively uncommon organisms [11]. Most DIPNET countries have diagnostic hospital laboratories that undertake primary isolation, although the real extent of expertise is hard to ascertain in many of these countries. In Slovenia and Turkey, diphtheria diagnostics are only performed in a few regional laboratories. It is envisaged that with the support of DIPNET, laboratory diagnostics will be available in all participating countries. Most DIPNET countries have Diphtheria Reference Laboratories. The main role of the reference laboratory is to confirm the identification of *C. diphtheriae* and other potentially toxigenic corynebacteria, and to test for toxigenicity [12]. The Elek test, a conventional test, based on the immunoprecipitation reaction between toxin producing strains and diphtheria antitoxin [13], is widely used, and the Polymerase Chain Reaction (PCR) detection of the gene encoding toxin production is offered in at least eight countries. Other reference laboratory activities currently undertaken within the EU also include molecular typing and determining serological immunity levels (see below).

The screening of throat swabs for toxigenic corynebacteria is limited within most DIPNET countries due to workload, staff shortage, lack of expertise and the decline of this classical disease due to vaccination. However, if throat swabs are not screened routinely, the diagnosis of cases will be delayed [14]. A few countries (UK, Italy) have developed guidance policies for screening for diphtheria in specific instances only, such as cases with: pharyngo-tonsillitis and a pseudo-membrane; ulcerating skin lesions acquired overseas; any overseas travel, especially to Eastern and Central Europe, Asia, Africa or South America; history of farming or veterinary work; and consumption of unpasteurised dairy products [15]. Other countries (Bulgaria, Estonia, Greece, and Turkey) have performed targeted screening studies. For example, in a Greek study, between 1999 and 2006, throat swabs were taken from 3950 healthy volunteers, which resulted in only two toxigenic isolates of *C. diphtheriae* (carriage rate of 0.05%) [16]. There are only a few countries where routine screening of throat swabs is undertaken and these include the Czech Republic, Lithuania, Latvia and Slovenia. The isolation rate for *C. diphtheriae* is low; in Latvia, where diphtheria incidence is still relatively high, routine screening of 38,157 throat swabs in healthy and non-healthy populations between 2002 and 2006 generated only 140 *C. diphtheriae* isolates (0.4%); 86% were toxigenic strains [9]. Clearly there are differences between countries in the incidence of diphtheria and the caveats applied to throat swab screening.

Diphtheria immunity: strategies and sero-epidemiological studies

One of WHO EURO's key strategies to control and eradicate diphtheria is to "maintain at least 95% coverage with primary immunization (DTP3) by 12 months of age" [17]. However, data obtained from both DIPNET participants and the WHO EURO web-site showed that many DIPNET countries are still falling short of these targets [18]. At least fourteen countries have attained the >95% target, but other countries such as Greece and Turkey have lower coverage rates, 88 and 90% respectively.

Vaccination coverage does not provide an accurate estimation of the population immunity. Immunity to diphtheria, as measured by protective antibody levels in selected populations has been studied in a number of DIPNET countries and has generally revealed a correlation of decreasing protection levels with increasing age [19]. For example, a study in Bulgaria between 2001 and 2005 revealed that 2.2% of children aged 0-15 years had levels of <0.01 IU/ml (no protection) compared to 42.2% of adults aged 56-65 years and 83.3% of adults over 65 years of age [20]. There are still many adults who have inadequate immunity levels and may therefore be susceptible to diphtheria. These poor immunity levels may be explained by the absence of adult boosters in some countries and the fact that only some individuals were born before the introduction of routine vaccination and acquired natural immunity to diphtheria. However, since the introduction of mass vaccination in the 1940s and the WHO Expanded Programme of Immunisation in 1974, diphtheria incidence has declined [20]. The recommendation from WHO EURO "to achieve at least 90% adult vaccination coverage with tetanus-diphtheria vaccine" is unreachable in many countries as adult boosters are not administered [10].

In an effort to standardise methods, DIPNET will undertake an External Quality Assurance (EQA) to assess the different serological immunity methods currently used in selected countries, to ultimately work towards the ability to compare diphtheria immunity levels from country to country. The information from this study will form the basis for new guidelines for serological assays within the EU. Currently, the Vero cell toxin neutralisation assay (VCA) is the only assay that measures functional antibodies and is therefore used as the reference in vitro assay [21]. However, it requires specialised methodology, expertise and is labour intensive, so other improved methods based on enzyme-linked immunosorbent assays (ELISA) or enzyme immunoassays (EIA) would offer significant advantages in terms of cost, speed, ease of use and adaptability to automation [22]. Nevertheless, there are disadvantages with some of these improved methods as they do not all measure functional antibodies and do not correlate well with tissue culture and in vivo neutralisation tests for low titre specimens [23].

In addition to this assessment, sera will be collected from populations in both high-risk and low-risk countries to assess the presence of diphtheria antibacterial antibodies by an EIA developed in the Russian Federation. This novel approach is not based on antitoxin antibodies which measures the immune response against toxigenic diphtheria but on antibacterial antibodies against a non-toxigenic *C. diphtheriae* strain, therefore ascertaining the immune response against all *C. diphtheriae* infections [24].

Immunisation policy for diphtheria and vaccine accessibility

All DIPNET countries have recommendations for childhood immunisation for diphtheria from their Ministries of Health. Infants are primarily given three doses within the first twelve months; the most frequent schedules being 2, 3, 4 months (n=7 countries), 2, 4, 6 months (n=7) and 3, 5, 12 months (n=4). The number of childhood boosters range from two to four doses, and at least 15 countries recommend a booster every 10 years (data also available from EUVAC.NET [25]. Some countries also recommend vaccination for laboratory personnel handling the organism (UK, France, Ireland, Lithuania, and the Netherlands), persons travelling to endemic areas (UK if more than 10 years have lapsed since last dose, France, Lithuania, the Netherlands, Norway and Slovenia) and for wound injury patients (Denmark and Slovenia).

Most vaccines are procured from commercial sources; four countries are known to produce their diphtheria vaccines "in-house" (Bulgaria, Denmark, the Netherlands, and Romania). Diphtheria vaccines are available as combined doses with tetanus, pertussis, Haemophilus influenzae type b (Hib), polio (for example, DTwP, DTaP, DTaP/IPV/Hib, DTaP/IPV, DT and dT). There is, therefore, considerable variation between countries in terms of both the type of vaccines used and the administration schedule. However, surveillance and microbiological data collected by DIPNET should provide a solid background for public health guidelines and may inform future vaccination policies within the participating countries, ECDC and WHO EURO.

Clinical management and treatment of contacts and cases

At least 14 of 25 DIPNET countries follow guidelines for control, management and treatment using published guidelines from their own country, the published UK guidelines or the WHO guidelines [14]. Control measures include isolation of the index case, treatment with appropriate antibiotics and antitoxin, along with contact screening. With changes in the epidemiology of diphtheria, in particular the increased reporting of cases caused by toxigenic *C. ulcerans* from some European countries, it is important to re-address and update the 1994 WHO Guidelines for the Management and Control of Diphtheria [25].

Antitoxin is given to patients to prevent the manifestation of systemic disease due to the circulating diphtheria toxin [14]. However, only nine countries reported an availability of stocks for emergency administration. These countries either manufactured antitoxin using in-house facilities (Bulgaria, Romania and Turkey) or sourced it from other countries such as Australia, Brazil, Croatia and New Zealand. It is of concern that with such limited supplies of antitoxin amongst EU member states, many countries are unprepared to treat sporadic cases with severe symptoms, and to effectively manage an outbreak of diphtheria.

Immediate requirements and areas for improvement

At the first DIPNET meeting, member countries were asked if there were areas relating to diphtheria that required improvement, and many issues were reported which this programme will address. Thirteen countries stated that a more reliable supply of antitoxin, preferably sourced within Europe for convenience and speed, is essential. Laboratory diagnostics and screening were also highlighted as a priority area; at least ten countries required the expansion or improvement in their diagnostic capabilities and ten countries welcomed support for screening studies. Specific examples included the manufacturing of the rapid immunochromatographic strip (ICS) for detection of diphtheria toxin [26] and the development of a more sensitive and selective medium for screening cases and contacts. Surveillance and vaccination policies were also stated as being problematic, with many countries requiring support to improve and promote their surveillance and vaccination strategies, including the enforcement of the case definition at primary care level, and increasing the importance of booster doses in adults. Undertaking enhanced surveillance using seroepidemiological studies was also deemed important by at least six countries. Three countries within northern Europe stated that they could see no need to improve diphtheria diagnostics and surveillance; this view was possibly due to the absence of cases in recent years. However, complacency regarding the detection of diphtheria is potentially worrying, as it is a highly transmissible and life-threatening disease in an inadequately immune adult population [27].One centre reported that they had concerns about the financial support for their diphtheria reference laboratory, as the zero incidence of diphtheria has triggered discussions concerning the existence of this important and active reference centre.

Conclusion

DIPNET has been built upon the firm foundations of ELWGD which was established in 1993. There are many objectives that DIPNET will address. For example, the potential reporting differences amongst DIPNET countries will be assessed, and core and additional data fields will be agreed and harmonised, to establish a European diphtheria surveillance system, with information flows to ECDC and WHO EURO. This database will be integrated with molecular typing data and will function at a web-based level both as a tool for diphtheria surveillance and as a valuable source of information. In order to assure the laboratory data, DIPNET will train key personnel in laboratory diagnostics and ensure microbiological compatibility through EQA schemes for laboratory diagnostics, epidemiological typing and serological immunity. DIPNET also intends to undertake selected screening studies in both high- and low-incidence countries to determine the incidence and characteristics of *C. diphtheriae* and *C. ulcerans* in different populations. A major recommendation for the control and management of diphtheria cases is that all countries must have rapid access to antitoxin, in liaison with the ECDC and the European Medicines Agency (EMEA).

A major output of DIPNET is to update the WHO guidelines on the 'Laboratory Diagnosis of Diphtheria' and 'Control and Management' in liaison with the EU Member States, the ECDC and WHO EURO [12,25]; these guidelines will have impact not only in Europe, but on a global level. DIPNET will also liaise with other European networks involved with vaccine preventable diseases, such as EUVAC.NET and VENICE to deliver a unified European approach to all aspects of this infection.

The eastern European epidemic of the 1990s has clearly shown that diphtheria can always return whenever and wherever immunity levels decrease, further highlighting the importance of microbiological and epidemiological surveillance. DIPNET will endeavour and continue to work to "a collaborative and coordinated approach to the epidemiology and microbiology of diphtheria and related infections".

Further information on DIPNET can be found at: http://www.dipnet.org

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Short report

Identification of Klebsiella pneumoniae carbapenemase (KPC) in Sweden

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A *Klebsiella pneumoniae* expressing carbapenemase type 2 (KPC-2) enzyme has been identified in Sweden. The patient, who had a history of chronic obstructive lung disease, developed a respiratory tract infection while on holiday in Greece. After initial intensive care treatment in Greece, the patient was transferred to Sweden. Upon recovery, the central venous catheter was withdrawn and a multiresistant *Klebsiella pneumoniae* was isolated from the tip. The strain was susceptible to aminoglycosides, tetracycline and tigecycline, but resistant to all beta-lactam antibiotics, including carbapenems, as well as to fluoroquinolones, trimethoprim-sulfa and chloramphenicol.

The isolate was sent to the Swedish Institute for Infectious Disease Control for further investigation and was shown by PCR and sequencing to contain KPC-2. This is a beta-lactamase with carbapenem hydrolyzing activity that has been identified in different types of gram-negative bacteria, but particularly in *Klebsiella pneumoniae* [1]. Four variants of KPC-enzymes (-1, -2, -3 and -4), have been characterized and all are described as plasmid encoded [1-5]. This probably facilitates their spread among different gram-negative species.

KPC-1 was described in the United States as far back as 1996 [6]. The first reports of *K. pneumoniae* with KPC-2 came from New York in 2004 [7]. Subsequently, several hospital outbreaks were described in that area, creating major treatment problems [8-12]. KPC-3, a variant of KPC-2, has also been reported from the New York area [13]. Recently, KPC-2 producing isolates were reported from France, Israel, Columbia and China [1,14,15]. In October 2007, Scotland's Health Protection Agency reported the first Scottish case of *K. pneumoniae* with KPC-enzyme, and in the December issue of Antimrobial Agents and Chemotheraphy a KPC-producing *K. pneumoniae* from Greece, with a resistance phenotype identical to the Swedish isolate, was described [16, 17]. However, carbapenem resistance in enterobacteria in Greece seems to be mainly due to the production of metallo-beta-lactamases (MBL) of the VIM type (1-4) whereas, to the best of our knowledge, this was the first isolation of KPC-producing Klebsiellas in this country [18-21].

It is important to be aware of the low-level resistance to carbapenems among these isolates, potentially making the resistance phenotype difficult to detect. For the Swedish isolate, the primary test was based on disc diffusion, and the isolate was initially classified as intermediately susceptible to imipenem.

KPC-producing *Enterobacteriaceae* have now been identified in at least four European countries, and we therefore encourage microbiological laboratories to be observant on abnormal carbapenem resistance phenotypes in order to detect KPC-producing isolates. Based on the New York experience, we stress the importance of early identification followed by intensified infection control measures to prevent the dissemination of Enterobacteriaceae with KPC-enzymes in Europe.

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Short report

A case of *Clostridium difficile*-associated disease due to the highly virulent clone of *Clostridium difficile* PCR ribotype 027, March 2007 in Germany

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Increasing rates of *Clostridium difficile*-associated disease (CDAD) have been reported from North America since 2003. This increase is associated with the emergence and spread of a particular strain of *C. difficile* characterised as PCR ribotype 027 or pulsotype NAP1. This epidemic strain produces toxins A and B and the binary toxin, is resistant to erythromycin and the newer fluoroquinolones, and patients infected with it are more likely to experience severe disease [1]. More recently, the epidemic PCR ribotype 027 strain has spread to Europe. Epidemics of *C. difficile*-associated disease (CDAD) due to this new, highly virulent strain have been detected in England and Wales, Ireland, the Netherlands, Belgium, Luxembourg and France, and isolates exhibiting PCR ribotype 027 (no data on virulence-associated traits available) have been detected in Austria, Scotland, Switzerland, Poland, Denmark and Finland [2-7].

In Germany, a dramatic, nationwide increase of CDAD incidence was observed between 2000 and 2004 [8,9]. However, an association between this increase and the occurrence of the epidemic PCR ribotype 027 strain has not been documented. Here, we report the isolation of *C. difficile* PCR ribotype 027 from a patient suffering from pseudomembranous colitis in Germany in March 2007. The strain was identified during a retrospective PCR ribotyping survey of stored isolates.

Case report

In early January 2007, a 76-year-old man was admitted to a hospital in Stuttgart, in southern Germany, for treatment of an elbow fracture. Postoperatively, the patient developed a wound infection requiring several revisions. Following isolation of *Staphylococcus aureus* from a wound swab culture, the patient was treated with amoxicillin/clavulanic acid, then later with cefalexin. When a second wound swab yielded *Enterobacter cloacae* and an *Escherichia coli*-strain-producing extended-spectrum beta-lactamase, treatment was changed to imipenem/cilastatin.

In late March 2007, the patient developed pneumonia and severe pseudomembranous colitis. *Clostridium difficile* toxins A and B were detected in a stool specimen by enzyme immunoassay. Three days later, the patient died from multi-organ failure and septic shock.

Characteristics of bacterial isolate

Stool culture performed in March 2007 yielded *C. difficile*. Retrospectively, the isolate was further characterised as PCR ribotype 027 at the reference laboratory in Leiden in August 2007. It exhibited a heretofore undescribed MLVA genotype, and, hence, a connection with strains circulating in the Netherlands [10] or the United States [11,12] could not be established. The genome of the isolate contained genes for toxin A, toxin B, and binary toxin. The *tcdC* gene is characterised by an 18-bp deletion and a single nucleotide deletion at position 117, which causes severe truncation of the encoded putative negative regulator of toxin A and B production. This *tcdC* genotype is typical of the epidemic, highly virulent PCR ribotype 027 clone, first isolated in North America [11].

Using E-tests, the isolate was determined as resistant to erythromycin, imipenem and moxifloxacin, and susceptible to metronidazole, vancomycin, clindamycin and doxycyclin. This resistance pattern has previously been reported for the epidemic PCR ribotype 027 strain. In contrast, 'historic' PCR ribotype 027 strains isolated prior to 2001 in Europe and North America were susceptible to moxifloxacin [1,13].

Conclusions

The highly virulent, epidemic strain of *C. difficile* PCR ribotype 027 was isolated from a patient suffering from severe, antibiotic-associated CDAD in a hospital in southern Germany. There was no indication of an outbreak situation. This report indicates that this strain was already present in Germany in March 2007.

This new strain may add to the increase of CDAD incidence that is already occurring in Germany. As a consequence, general practitioners' and public health institutions' awareness of the incidence and severity of CDAD should be enhanced. Hygienic guidelines must be followed to curb transmission of *C. difficile*, especially within hospitals and nursing homes. In case of outbreaks and severe disease courses, bacterial isolates should be obtained from toxin-positive faecal samples to enable resistance determination and investigations about possible clonal spread.

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Short report

Confirmed cases and report of clusters of severe infections due to *Clostridium difficile* PCR ribotype 027 in Germany

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In late September 2007, the local health authorities in Trier, Rhineland-Palatine, in south-western Germany, were informed of four cases with a severe course of *Clostridium difficile*-associated disease (CDAD) on several wards in a local hospital. Three of the four patients underwent colectomy, and two died in the further course due to complications of CDAD and their underlying condition. Further infection control measures were then implemented in this and other Trier hospitals by the local health authorities.

Further exploration revealed that in March 2007, a severe case of a *C. difficile* infection had already occurred in this hospital. The strain isolated from this patient in April could be further characterised as PCR ribotype 027, toxinotype III, PFGE NAP1, and was shown to be PCR-positive for the binary toxin and an 18 bp deletion in the *tcdC* regulatory gene. The strain demonstrated resistance to erythromycin and moxifloxacin, among other antimicrobials, but was susceptible to clindamycin, thereby exhibiting a similar profile to that seen for the highly virulent strains that have recently caused outbreaks in North America and several European countries [1,2,3].

Based on these findings, a retrospective case search was initiated, including a systematic review of patient details, history, and known risk factors for CDAD. In addition, a prospective surveillance system was implemented for all hospitals in Trier. Stool samples of all patients with possible CDAD are now being systematically tested for CDAD, as well as cultured to isolate *C. difficile*. Isolates from positive samples are being ribotyped. The investigations are still ongoing.

As of 5 November 2007, the situation was as follows: since January 2007, eight confirmed and 28 probable cases of *C. difficile* PCR ribotype 027 (definitions of probable and confirmed cases can be found in the box) were identified in six hospitals in the region of Trier (Figure). The cases include 16 male and 20 female patients. The mean age was 74 years. Six patients died due to a cause attributable directly or indirectly to the CDAD. Two small clusters comprising a total of six cases were identified in one hospital. We have not yet been able to establish linkage between the other cases. An additional infection with *C. difficile* PCR ribotype 027 was identified in an asymptomatic carrier.

A neighbouring administrative district in which surveillance has not yet been established, reported another case of CDAD due to PCR ribotype 027.

Box

Definition of probable and confirmed cases of CDAD due to *C. difficile* ribotype 027

Probable case:

This is an inpatient in the administrative district of Trier-Saarburg, Germany admitted to a health care facility as from 1 January 2007 and fulfilling the following criteria:

Diarrhoeal stools or toxic megacolon and a positive laboratory assay for *C. difficile* Toxin A and / or Toxin B in stools or a toxin-producing *C. difficile* organism detected in stool via culture or other means or a patient with pseudomembranous colitis,

and to whom at least one of the following criteria apply:

1. admission to a healthcare facility for treatment of community-associated CDAD;
2. the necessity of readmission to a hospital due to a relapse;
3. admission to an intensive care unit for treatment of CDAD or its complication;
4. surgery (colectomy) for toxic megacolon, perforation or refractory colitis;
5. death within 30 days after diagnosis if CDAD is either the primary or a contributive cause.

Confirmed case:

This is an inpatient in the administrative district of Trier-Saarburg, Germany admitted to a health care facility as from 1 January 2007 and fulfilling the following criteria:

Diarrhoeal stools (more than three unformed stools/24 hours) or toxic megacolon or pseudomembranous colitis,

and

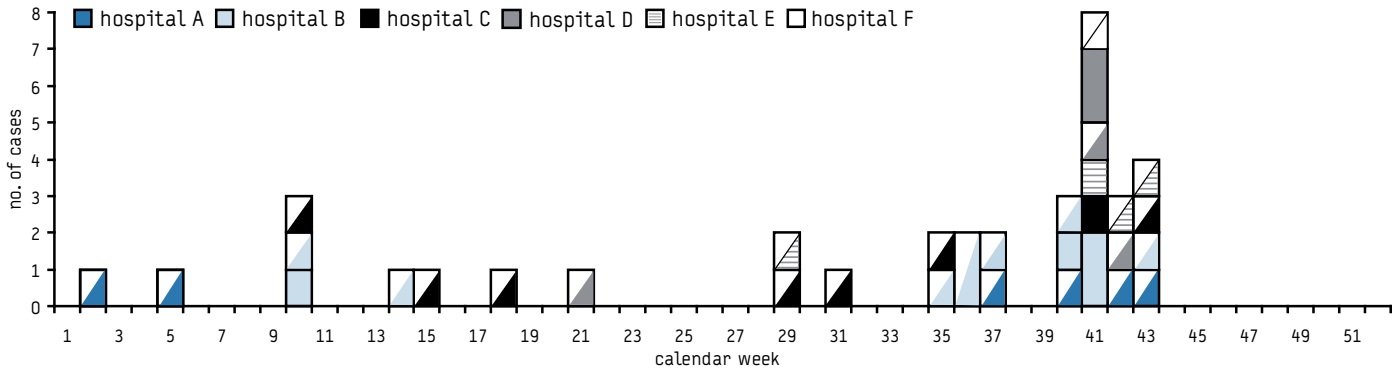
a positive laboratory assay for *C. difficile* PCR ribotype 027.

Agreement was reached upon a nationwide notification of severe cases of CDAD between chief representatives of the public health authorities of the federal states and the consulting experts from the Robert Koch Institute.

As isolates are seldom routinely cultured or typed in Germany, and samples are only rarely sent to the national consultant laboratory or the few specialised laboratories, it is probable that there have been previous cases in Germany before the case reported above (see also [4]). However, *C. difficile* PCR ribotype 027 with the characteristics of the highly virulent strains described above was not found in a set of approximately 900 isolates collected between January 2000 and September 2006 and sent to the consultant laboratory for gastrointestinal infections, Freiburg, Germany [5].

Figure

Epidemic curve of *Clostridium difficile*, PCR ribotype 027 infections by onset of symptoms in the region of Trier, Rhineland-Palatine, Germany, 2007



start of active surveillance: 42nd calendar week
confirmed case: full box
probable case: half box

The results of the investigations performed so far suggest that *C. difficile* PCR ribotype 027 may already be endemic in Germany, at least in the Trier region. Further investigations to determine the extent to which this new strain and possibly other highly virulent strains have spread in Germany are ongoing.

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Short report

Outbreak of Salmonella Weltevreden infections in Norway, Denmark and Finland associated with alfalfa sprouts, July-October 2007

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Between 10 and 15 October 2007, the national reference laboratory at the Norwegian Institute of Public Health (FHI) detected *Salmonella* Weltevreden in samples from four gastroenteritis patients. The patients were all living in the south-eastern part of Norway, and had no history of foreign travel during the month prior to onset of illness.

S. Weltevreden is a common cause of gastroenteritis in south-east Asia [1,2], but is a very rare serovar in Norway. Over the past 30 years, fewer than 10 cases were reported annually, only seven of which were domestically acquired.

In response to the detected cases, an outbreak investigation was initiated on 19 October in order to identify the source of the outbreak. It involved FHI, the Norwegian Food Safety Authority (NFSA), and the municipal medical officers. An urgent enquiry was sent out through the European Centre for Disease Prevention and Control (ECDC) on 22 October. In response to the enquiry, Denmark reported a cluster of 18 cases of *S.* Weltevreden that was under investigation at the time. The onset of illness of the first cases had been in late July. In three cases, it was thought likely that the infection had been acquired abroad. On 26 October, Finland reported a cluster of seven cases that had occurred between 1 August and 1 October.

On 23 October, a salmonella isolate obtained from a major Danish alfalfa sprout producer was serotyped as Weltevreden. The Danish authorities issued an alert through the Rapid Alert System for Food and Feed (RASFF) on the same day. The isolate was later shown to have the same multiple locus variable number tandem repeat analysis (MLVA) and Pulsed Field Gel Electrophoresis (PFGE) profiles as the isolates from the case-patients from Denmark, Norway and Finland. S. Weltevreden has also been verified in the sprouts sold in Finland, but the PFGE result of this strain is pending.

The seeds for growing the alfalfa sprouts had been imported to Denmark in July and August 2007. The Danish producer had then exported part of the batch of seeds to a Norwegian alfalfa sprout producer on 19 September. The batch of seeds used in Denmark and Norway was traded, according to invoices, via retailers in Germany and the Netherlands to Denmark, and probably originated from Italy (further information is pending). No clear link has been found as yet to the seeds used in Finland, except that they came from the same Dutch supplier. A link may appear when the full traceability accounts from the Netherlands are provided through the RASFF system. The batch of alfalfa seeds had been imported to Finland in June. However, sprouts from this batch were not on the market in Finland before August.

The alfalfa sprouts were recalled and withdrawn in Denmark on 18 October, in Norway on 23 October, and in Finland on 28 October (Figure 1).

Outbreak investigation

A case was defined as a person living in Denmark, Finland or Norway, with a laboratory-confirmed infection with a strain of *S.* Weltevreden that matched the PFGE and/or MLVA profile of the outbreak strain, and with onset of symptoms of gastroenteritis July to October 2007.

Figure 1

Cases of Salmonella Weltevreden associated with alfalfa sprouts, by week of sample taken, July-October 2007, Norway, Denmark and Finland (n=45)

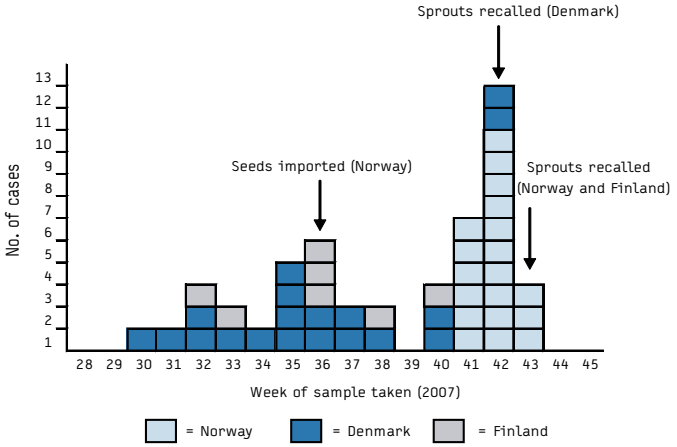

Figure 2

Cases of *Salmonella* Weltevreden associated with alfalfa sprouts, by gender and age group, July-October 2007, Norway, Denmark and Finland (n=45)

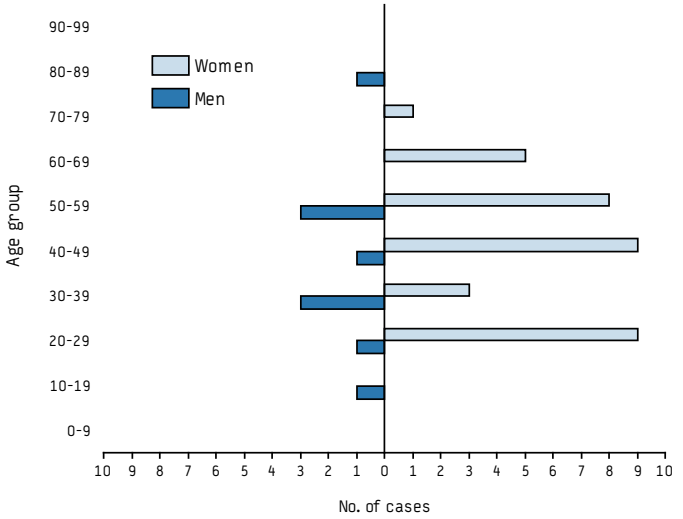

Figure 1 shows the combined epicurve for the three countries of all *S.* Weltevreden cases by week of taking the sample. By 19 November, 19 cases had been reported in Norway, 19 in Denmark, and seven in Finland. The patient's ages ranged from 18 to 83 years (median age 34 years). Thirty-five cases were female and 10 male (Figure 2). The demographic characteristics of the cases are comparable in all three countries: they are adults and predominantly female. The dates of symptom onset for the Norwegian cases range from 28 September to 15 October; two cases were not available for interview. The 14 Danish cases that were available for interview fell ill between 23 July and 20 October. Five of the Finnish cases were available for interview; their disease onset was between 11 August and 30 September.

In Norway, NFSA interviewed the first six cases using a standard pilot questionnaire for foodborne outbreaks, focusing on food items known to be risk products causing gastroenteritis. Five cases had eaten alfalfa sprouts during the incubation period, and one had not eaten this product. As a follow-up, 13 patients identified later were asked whether or not they had eaten alfalfa sprouts: seven remembered having eaten sprouts, three were not sure, and two were not available for interview.

Most of the Danish cases were interviewed several weeks or months after the illness and therefore had difficulties remembering their food consumption in the relevant time period. Only the two cases with recent illness onset clearly remembered buying and eating alfalfa sprouts. The Finnish cases were also interviewed several weeks after onset of illness. Two of them recalled exposure to alfalfa sprouts prior to illness. Alfalfa sprouts are typically part of sandwiches and salad buffets not prepared at home, and it can therefore be difficult to recall consumption of this product.

Conclusions

Based on the available information, it was concluded that alfalfa sprouts grown from contaminated seeds were the source of the outbreak in all three countries. A case-control study will not be conducted, since the source of the outbreak is well documented by other methods. In support of this conclusion, molecular typing of isolates from epidemiologically unrelated cases and of other food sources, including the two different *S.* Weltevreden isolates found in baby corn related to the recent Shigella sonnei outbreak in Denmark [3], showed a number of DNA-profiles that differed from the outbreak strain.

Sprouts are a well-known source of salmonella infections and have been described as the source of a large number of outbreaks [4]. The gender distribution may simply mean more females eat alfalfa sprouts in salads and sandwiches.

In both Norway and Finland, precautionary chlorination had been used to decontaminate the imported seeds. No decontamination process had been used by the Danish producer. The seeds imported to Denmark and Norway were part of the same batch. The seeds traded to Finland came from the same supplier in the Netherlands; they were not from the same batch but probably a related one. More information on traceability concerning a possible link is pending through RASFF. Contaminated seeds may therefore have been exported to other countries and a trace-back investigation is ongoing.

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Short report

STEC O157 outbreak in Iceland, September-October 2007

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From 28 September to 22 October, nine domestically acquired cases of Shiga toxin (Stx)-producing *Escherichiacoli* (STEC) O157 were diagnosed in Iceland, one of which is probably a secondary case. The cases were between two and 61 years of age, five males and four females. All except two were hospitalised, one with elevated creatinine levels. No cases developed haemolytic uraemic syndrome (HUS).

The onset of symptoms was between 23 September and 18 October. The cases reside in different parts of the country: four in the area of Reykjavik, two in the north of Iceland, one in the east of Iceland, and two in the Westman Islands (Figure).

Eight of the nine patients (presumed secondary case was excluded) answered a trawling questionnaire on food consumption, travel and mass gathering; supermarket purchase records were collected from three cases. The results from the questionnaires showed that seven had eaten fish or ham, and six had eaten lettuce. The source of infection is unknown at this point.

Five cases had consumed lettuce packaged and imported from the Netherlands, as verified either by questionnaire (three cases) or by supermarket purchase records (two cases). Intensified surveillance in lettuce with increased sampling began in mid-October and is ongoing. Culture results have so far been negative.

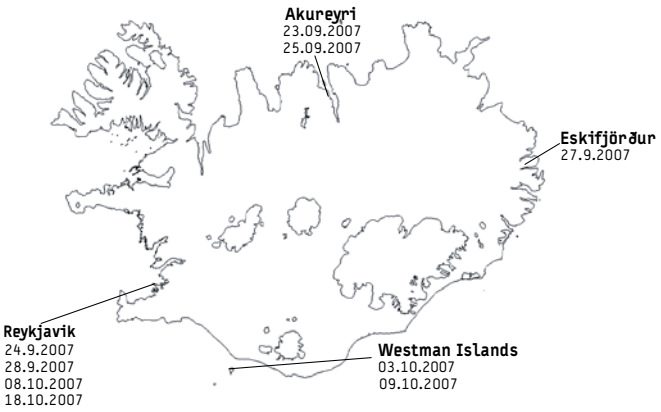
The strain that caused the outbreak in Iceland was identified by the Laboratory of Enteric Pathogens at the Health Protection Agency in the United Kingdom as STEC O157, phagetype 8, carrying the *stx1* and *stx2* shigatoxin genes. The PFGE pattern of all nine Icelandic isolates was identical to the strain that caused the current STEC O157 outbreak in the Netherlands. That outbreak is described in an accompanying article in this issue [1].

Acknowledgements

The authors would like to thank the Laboratory of Enteric Pathogens at the Health Protection Agency in the United Kingdom for typing of the STEC strains.

FIGURE

STEC outbreak in Iceland, September-October 2007, distribution of cases according to onset of symptoms and place of residence (n=9)



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Short report

STEC O157 outbreak in the Netherlands, September-October 2007

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Early in October 2007, an increase in notifications of human cases infected with Shiga toxin (Stx)-producing *Escherichia coli* (STEC) O157 was seen in the Netherlands. All cases reported diarrhoea, and most also had bloody diarrhoea. No cases developed haemolytic uraemic syndrome (HUS). The onset of illness for the first cases was in mid-September (Figure 1).

STEC O157 strains that contained both *stx1* and *stx2* genes were isolated from 36 patients. Subtyping of these isolates by pulse-field gel electrophoresis (PFGE) showed, for 33 cases, an identical pattern not previously observed in the Netherlands. One further isolate was nearly identical to the 33. The two remaining isolates, which were isolated from the siblings of a confirmed case, have not yet been typed.

The PFGE pattern was compared to the pattern found in Iceland, which appeared to be identical. The Iceland outbreak of STEC O157 is described in an accompanying article in this issue [1].

The age and sex distribution of the cases is shown in Figure 2. Most cases (67%) were between 10 and 50 years of age. More females than males were affected in these age groups. The cases were distributed across the whole country, with a concentration of the cases in the western part.

As part of enhanced surveillance, all laboratory-confirmed STEC patients in the Netherlands are asked to fill in a questionnaire on symptoms and exposures in the week before illness onset. For the year 2007, questionnaires were available for 31 cases of the current outbreak and 37 STEC cases that had occurred earlier in 2007. A case to case comparison revealed raw vegetables as the possible source of the outbreak (71% of the outbreak cases had consumed raw vegetables, compared to 49% of the earlier cases, p=0.06).

Municipal health services undertook further trawling interviews with the current outbreak cases, which pointed towards pre-packaged shredded iceberg lettuce purchased at several supermarket chains as the possible source.

The environmental investigation is ongoing. The Dutch Food and Safety Authority (FSA) is investigating the distribution channels of packed fresh vegetables and the individual ingredients. Samples of lettuce and other raw vegetables are being taken, as well as environmental samples at vegetable growers and shredding plants that may be involved. One shredding company for fresh vegetables also cuts and packs lettuce products for Iceland.

An alert was sent by the Dutch FSA to the Rapid Alert System for Food and Feed on 26 October [2].

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Figure 1

Epidemic curve by onset of symptoms of all STEC O157 cases related to the outbreak, September-October 2007, the Netherlands (n=35)

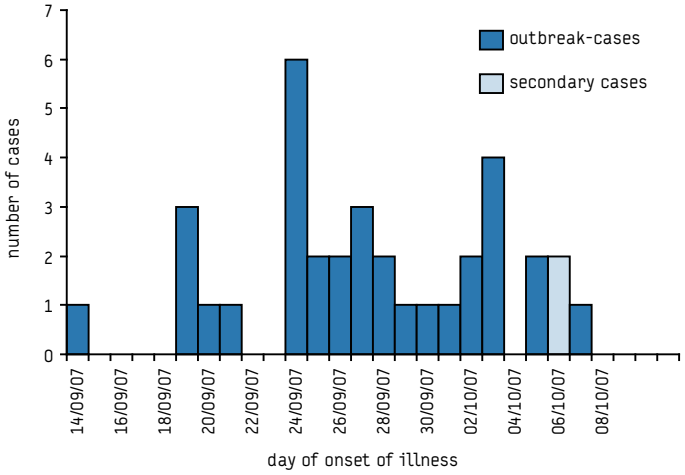
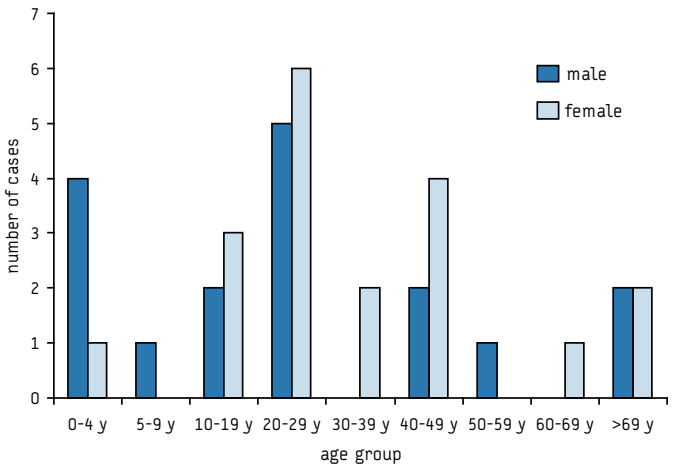


Figure 2

Age and sex distribution of all STEC O157 cases related to the outbreak, September-October 2007, the Netherlands (n=36)



Short report

Contact tracing of passengers exposed to an extensively drug-resistant tuberculosis case during an air flight from Beirut to Paris, October 2006

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Contact tracing of air travellers exposed to cases of multi-drug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) has become an increasingly important issue. The case of MDR (initially diagnosed as XDR) TB in an American citizen who travelled to and across Europe in May 2007 attracted a lot of media attention and raised a number of questions regarding control measures [1]. As travel and trade involving countries where MDR and XDR TB is endemic increase, such situations are likely to become more frequent. Therefore, contact investigation in travel situations involving MDR or XDR TB cases should be addressed more specifically, especially in a context where second line anti-TB drugs are not available in all countries. This paper describes the process of contact tracing of passengers exposed to an XDR TB case during an air flight from Beirut, Lebanon, to Paris, France, in October 2006. This investigation involving an index case with XDR TB in an aircraft was the first to be notified to the World Health Organization (WHO).

Case description

On 18 October 2006, the French Ministry of Health (MoH) was informed of a fatal case of pulmonary TB in a passenger who, on 5 October, had travelled on a five-hour flight from Beirut to Paris. He died 10 days after the journey, despite surgery, from a severe haemoptysis. The patient was travelling with his wife and two children.

The patient's history revealed that he had been treated for TB twice, in 2000 and 2004, for three months on each occasion, while resident in Chechnya (Russian Federation). This raised the clinical suspicion of MDR TB (resistance to at least isoniazid and rifampicin). Drug susceptibility testing confirmed that the *Mycobacterium tuberculosis* strain was resistant to isoniazid, rifampicin, streptomycin, kanamycin, amikacin, capreomycin, fluoroquinolones, ethambutol, and thiacetazone. These results met the WHO case definition criteria of XDR TB [2]. In addition, the case was considered to be highly infectious due to severe cough, cavernous lesions, and smear-positive sputum (10 to 99 acid fast bacilli per high-power field).

Subsequently, pulmonary TB was diagnosed by chest X-ray in the wife of the index case and in one of his children with mediastinal lymphadenopathy, but without bacteriological identification in either case. Latent TB infection was diagnosed in his other child (positive tuberculin skin test).

Since 15 December 2006, the case's wife and one child have been treated with ethionamide, para-aminosalicylic acid (PAS), linezolid, cycloserine and pyrazinamide, and the other child with ethionamide, PAS and pyrazinamide for latent TB infection. No side effects have been notified and the cultures have so far remained negative.

Contact tracing

Advised by an expert group (respiratory physicians, bacteriologists and epidemiologists), the French MoH decided to apply the contact investigation strategy. Although the WHO recommends tracing close contacts only when the duration of the flight exceeds eight hours [2], and this flight was five hours, the investigation was nevertheless carried out, on the grounds that the index case was infected by an XDR strain and that he was highly infectious at the time of travel. Close contacts during the flight were defined according to WHO guidelines [3].

According to the flight details provided by the airline company, 11 passengers were identified as close contacts. All contacts (passengers and cabin crew) were adults. Due to the resistance pattern of the case (XDR), treatment was not considered relevant for latent TB infection in adult contacts of the index case. Screening and medical follow-up was recommended to be mainly based on chest X-ray (0, 6, and 12 months) to all close contacts and information on TB infection was provided.

The final destination was the United States (US) for four contacts, Panama for three, Morocco for two and France for two of these contacts. Contact details have been obtained through the travel agencies only for nine passengers. The French MoH also informed the relevant national health authorities of the countries of residence of these passengers (in the US, Canada, Panama, France and Lebanon) as well as the WHO office for the passengers in Morocco.

At the time of publication of this article, seven of the 11 contact passengers have been informed. For three of them (in the US, Canada and France), results of the initial screening are available, while for one (in France) the results of the follow-up after six months are known. No active TB was diagnosed in any of these passengers. Members of the cabin crew were contacted by the airline occupational health service, but no further information is yet available.

Discussion

This event has raised several questions about the strategy of contact investigation in travel situations. There is no evidence that XDR strains are more contagious than sensitive strains. However, the French experts agreed with the MoH that the prevention of transmission of such a strain through international air travel was

paramount. The contact tracing investigations were decided on with the aim of avoiding important delays in the appropriate clinical management of potential secondary cases. Indeed, Kenyon et al. [4] have described several TB transmissions from a passenger with similar clinical characteristics but in a longer flight, and concluded that both the infectiousness and the flight duration had to be considered.

Regarding the organisation of contact tracing, our case shows that information required to locate and contact the passengers is not always available. Indeed, for some of the passengers it was only possible to ascertain the country in which the plane ticket had been bought. As nine of the passengers' final destination was not France, a press release was not considered suitable. Additionally, such information several weeks after the flight might have caused unnecessary panic, as discussed by Lasher et al. [5]; this kind of measure should be restricted to cases involving diseases with short incubation periods and/or when the contact-tracing approach is not feasible within appropriate time limits and/or when all the exposed passengers cannot be reached using the available data.

As in other contact tracing investigations involving TB cases in airplanes, this event highlights the need to improve international coordination. This would enable the relevant stakeholders to make a joint risk assessment in situations not included in the guidelines but nevertheless considered serious due to the potential risk of transmission of severe TB, and to agree on relevant control measures. When deciding on control measures, in addition to the risk assessment it is important to consider the potential effectiveness of the contact tracing, taking into account several factors. These might include: the time since notification, the number of countries involved and the epidemiological situation in the countries. In order to assess the efficiency of such measures, the results of contact tracing should be analysed in terms of the number of passengers reached, the delays between the flight and screening of contacts, the number of screenings performed and their results. Follow-up assessment of such events is needed to revise existing guidelines, if necessary, or to address the relevance of conducting contact tracing in situations for which no specific guidelines are available.

Acknowledgments

Physicians of the airline company, physicians from the TB control centre (Centre de lutte antituberculeuse), the district health authority of Seine Saint Denis and the clinicians who managed the cases and the contacts (Trousseau and Pitié-Salpêtrière hospitals, Paris).

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Conference report

Meeting report from the Third European Congress of Virology, 1-5 September 2007 in Nuremberg, Germany

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Nuremberg was the third European city to host the European Congress of Virology in September this year (www.eurovirology.org). Some 1,500 scientists from Europe and elsewhere came together to share their knowledge on basic and applied research in clinical, veterinary and plant virology. The main focus was on human pathogenic viruses, providing a platform where basic research and clinical application came into contact. The topics covered all areas of research in virology, from basic molecular biology and immunology to epidemiology, vaccine development, and diagnostics. For this meeting report, the Editorial team has selected some of our highlights out of the many excellent keynote lectures and workshop contributions.

50 years of interferon

The opening session of the congress was dedicated to the discovery of interferon in 1957 by Alick Isaacs and Jean Lindenmann (Mill Hill, London, United Kingdom (UK)). Jean Lindenmann, now 83, gave an account on the early days of interferon research. His lifetime achievements were honoured by the first European Virology Award (EVA) 2007. Two keynote lectures by Otto Haller (Freiburg, Germany) and Richard Randall (St. Andrews, UK) described the advances in interferon research over the past 50 years and the most recent developments in understanding the antiviral activity of interferon, and explained the specialised antagonistic proteins that most viruses have evolved to suppress interferon production or action.

Finally, Michael Manns (Hanover, Germany) reviewed the current state of art in treating patients with *chronic hepatitis C* using interferons and ribavirin. In the future, it may be possible to individualise interferon therapy depending on the HCV strain the patient is infected with. A new drug, the protease inhibitor Telaprevir (Vertex), can lead to the development of escape mutants within two weeks of treatment, but may have an application in combination with interferon, as those mutants are interferon-sensitive.

Emerging viral epidemics

A significant part of the conference was dedicated to the emergence of viral epidemics and the global spread of viruses previously restricted to exotic areas.

Two presentations on chikungunya virus were of particular interest, coming just days after the announcement of the first cases of locally transmitted chikungunya fever in Italy. Isabelle Schuffenecker (Paris, France) gave an overview on the distribution of chikungunya virus and its vectors, and emphasised the importance for increased vector and case surveillance in Europe. *Aedes albopictus*, the vector responsible for the transmission of chikungunya in Italy has, in the last 25 years, moved from Asia to Middle America and southern and central Europe, and was even found in glass-houses in the Netherlands in 2005. In Africa, *Ae. furcifer, taylori, luteocephalus*, and *africanus* are responsible for the sylvatic cycle of transmission, while only *Ae. furcifer*, *taylori*, and *africanus* are known to transmit the infection to humans during rural epidemics. The main vector in urban epidemics is *Ae. aegypti*. In Asia, urban transmission to humans occurs through *Ae. aegypti* and *albopictus*.

Marcus Panning (Hamburg, Germany) described a study on several hundred European patients with imported chikungunya virus infection, all of them travellers returning from the Indian Ocean area. IgG testing was sufficient to confirm the disease from five days after the onset of symptoms. IgM testing does not offer a significant diagnostic advantage, neither being more sensitive nor allowing much earlier detection. Viral RNA could be detected by RT-PCR earlier than five days from the onset of symptoms, and as late as until seven days after symptoms. There are indications for presymptomatic viraemia, which is of importance in the context of blood donations.

An entertaining and informative overview on bats as vectors for viruses was presented by Noël Tordo (Paris, France). Nipah, Hendra, Menangle and Tioman viruses are found in *Pteropus* flying foxes in Asia and Australia. In Africa, Marburg and Ebola can be transmitted by fruitbats of the genus *Pteropus*. In Europe, the Americas, Africa, and Australia, we find rabies virus and bat lyssavirus. The latter can infect frugivorous, insectivorous, and haemivorous bats. All bat species have their own group of lyssavirus genotypes, indicating a strong adaptation between virus and host. Rabies virus and genotype 1 of lyssavirus use carnivores not only as dead end hosts, but also as vectors, while the other genotypes only use bats. In contrast to the paramyxo- and filoviruses, lyssaviruses can occasionally lead to the death of the bat host. From a public health point of view, Tordo considers it sufficient to vaccinate dogs. He concluded with a call for more research on bats in order to determine, for example, what happens to the virus when the bats hibernate.

Dobrava hantavirus infections cause aemorrhagic fever with renal syndrome (HFRS) with very different degrees of severity. Detlev Kruger (Berlin, Germany) reported on a new genetic lineage of Dobrava virus that was isolated from *Apodemus ponticus* mice, a new host for this virus, in southwest Russia. It causes ca. 53% severe disease compared to the variant transmitted by *A. agrarius*, which is common in central Europe and causes ca. 24% severe disease.

The current view on the origin of human immunodeficiency viruses (HIV) was presented by Paul Sharp (Edinburgh, UK). HIV-1 and HIV-2 are phylogenetically different enough to indicate that

they originated from separate simian immunodeficiency viruses. The chimpanzee subspecies *Pan troglodytes troglodytes* from west central Africa has been pinpointed as harbouring the ancestors of HIV-1, but it is their eastern neighbour, *P. troglodytes schweinfurthii*, who transferred HIV-1 to humans. HIV-1 was transmitted not just once, but three times; of the HIV-1 groups M, N and O, M is the one that has spread worldwide. It arose in the south-east of Cameroon, and was probably acquired by humans who captured and slaughtered chimpanzees. The origin of HIV-2 may have been sooty mangabey monkeys in the Ivory Coast.

A new animal model for the study of zoonotic orthopoxvirus infections was introduced by Marit Kramski (Berlin, Germany). It relies on infection of marmosets with calpox virus, which is closely related to cowpox virus. The lethal infectious dose in the marmoset/calpox model is significantly lower than in the two currently approved primate models. The animals can be infected intra-nasally, mimicking the natural route of infection, and develop symptoms comparable to smallpox.

Intervention strategies regarding emerging virus infections were addressed in a talk by Albert Osterhaus (Rotterdam, the Netherlands). He pointed out that after the eradication of variola virus and the halt of vaccination, related orthopoxviruses such as monkeypox and cowpox have started to fill the niche. A similar scenario is conceivable with regard to a potential halt of vaccination against measles in the event of successful elimination of measles virus. Other morbilliviruses that have so far been restricted to animals could fill the niche. Regarding the threat of an influenza pandemic, which is considered by Osterhaus to be realistic, he considers a risk assessment to be impossible at this stage, due to insufficient understanding of the molecular basis of influenza pathogenicity and transmissibility.

Avian influenza and pandemic preparedness

More recommendations for policy formulation regarding a possible influenza A pandemic came from Roy Anderson (London, UK). He presented a model map on the spread of H5N1 influenza virus in the UK, which impressively highlighted the areas that would be most or least affected. Such models can make use not only of population density data, but also of randomised mobile phone data that can be exploited to follow the patterns of people's movements. In contrast to a slow virus like severe acute respiratory syndrome (SARS) virus, containment and isolation will, in Anderson's opinion, not be effective measures against H5N1 influenza virus with a generation time of only four to six days and an incubation period of one to two days. Measures restricting travel would have to be over 96% effective to have some significant effect, something that will not likely be achieved and that he considers a waste of time. One should rather focus on interventions within the country. In his opinion, the closure of schools during a pandemic, if implemented within two weeks, has the potential to slow down the spread and buy valuable time, but depends very much on what the children do instead. In a recent pandemic preparedness simulation exercise in the UK requests for countermeasures such as masks and gloves exceeded the supply within a week, and human resources were swamped very quickly. In a scenario where the district authorities are in charge, the heterogeneity in decisions and measures would cause serious problems. Instead, strict central implementation is needed. Critical are the logistics of drug delivery, since antiviral drugs need to reach the patient within a maximum of two days. Anderson ended with a call for the funding of very basic studies on the effectiveness of very simple public health measures such as masks, hand washing, avoiding handshaking etc.

Claude Muller (Luxembourg) talked about the spread of H5N1 influenza virus in sub-Saharan Africa. The Nigerian-Luxembourg poultry virus surveillance network, established in 2001, has followed outbreaks on several Nigerian farms. Viral sequence analysis was used to determine, based on a calculated constant mutation rate, the evolutionary time needed for the virus from one farm to develop into the virus on another. This exceeded by fourfold the time between the actual outbreaks, indicating that three independent importations of H5N1 influenza virus likely have occurred in Nigeria. The first human cases have meanwhile been reported from sub-Saharan Africa. The Luxembourg avian influenza response team offers interventions and training courses. The network also runs a project on the surveillance of hooded vultures in Burkina Faso. Vultures are common on the African continent and could be used as sentinels for avian influenza. Viral sequence analysis indicates that these scavenger birds may play a role as vectors in this area and could even cause spill-backs from poultry to wild birds if infected poultry carcasses are not carefully disposed.

Vaccination

In a separate symposium new vaccine strategies were presented, for example the use of reverse genetics for the development of better vaccines against influenza by Peter Palese (New York, United States) and a critical analysis of the current situation regarding the development of a vaccine against HIV by Ronald Desrosiers (Southborough, United States).

Harald zur Hausen (Heidelberg, Germany) was awarded the Loeffler-Frosch medal 2007 to for his groundbreaking research on the role of human papilloma viruses (HPV) in the development of cervical carcinoma. Zur Hausen's work on the biology, structure and function of those viruses provided the basis for the development of a vaccine against papilloma viruses that was first approved in Europe in 2006. His award lecture concentrated on new viral vaccination strategies against cancer. The current bivalent vaccine against HPV type 16 and 18 consists of recombinant papillomavirus L1 coat protein of that self-assembles into virus-like particles. It is currently extremely expensive with a cost of around 400-500 Euro depending on the country.

Clinical aspects

New variants of norovirus are associated with increased severity and mortality. Marion Koopmans (Bilthoven, the Netherlands) reported that norovirus can be responsible for up to 900 excess deaths in the Netherlands in one year, which corresponds to ca. 40% of the mortality of influenza. Risk factors are meat, salad, shellfish, and raspberries. As people often eat food containing a mix of human and animal norovirus, this is a perfect scenario for recombination and the development of new norovirus variants.

Christian Drosten (Hamburg, Germany) reported on the isolation of variant parechoviruses. Ten out of 674 diarrhoea samples in northern Germany were positive for parechovirus. Several samples appeared to represent recombinants of types 1 and 3. One virus appeared to be a new type and is identical to a parechovirus found in Japan. Drosten recommends that testing should be done but should focus on young children.

Annika Linde (Solna, Sweden) reminded us that science should not lose sight of the patient in a talk about the role of day-care

in the transmission of respiratory diseases in small children. The proportion of children in day care in Sweden has risen from under 10% in 1964 to over 80% in 2003. 21% of colds, 50% of otitis media, and 85% of pneumonias can be attributed to day-care. While waiting for science to development vaccines, we could focus on simple solutions such as using so-called outdoor day-care centres in which the children spend all day outside and the risk of infection has been found to be significantly reduced.

The congress was organised by Otto Haller (Freiburg, Germany) and Bernhard Fleckenstein (Erlangen, Germany) with the participation of many European virological societies, in particular the European Society for Clinical Virology (ESCV), the British Society for General Microbiology (SGM), the 'Gesellschaft für Virologie' of German-speaking virologists (GfV), and the Federation of European Microbiological Societies (FEMS).

The next Eurovirology conference will be held in Milan, Italy, in 2010.

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National Bulletins

AUSTRIA

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Ministry Website: http://www.bmgf.gv.at

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Quarterly, print and online versions available.
In Dutch. http://www.vlaanderen.be/epibul

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Weekly, online only. In English.
http://www.iph.fgov.be/epidemio/epien/plaben/idnews/index_en.htm

BULGARIA

Epidemiological Surveillance,
National Centre of Infectious and Parasitic Diseases, Sofia.
Print version available, online version available soon. Bulgarian, titles translated into English.
http://www.ncipd.org/bulletin.php

CYPRUS

Newsletter of the Network for Surveillance and Control of Communicable Diseases in Cyprus
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Biannual, print and online versions available.
In Greek.
Ministry website: http://www.moh.gov.cy

CZECH REPUBLIC

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Monthly, print and online versions available, in Czech with some important notifications in English.
http://www.szu.cz/cema/adefaultt.htm
EPIDAT (Notifications of infectious diseases in the Czech Republic)
http://www.szu.cz/cema/epidat/epidat.htm

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Weekly, print and online versions available.
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http://www.ssi.dk

ENGLAND AND WALES

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FINLAND

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Monthly, print and online versions available.
In Finnish.
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GERMANY

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Austurströnd 5
170 Seltjarnarnes
Monthly, Online Only. In Icelandic and English.
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IRELAND

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Monthly, print and online versions available. In English.
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ITALY

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Monthly, online only. In Italian.
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Online. In Latvian.
http://www.sva.lv/epidemiologija/bileteni

LITHUANIA

Epidemiologijos žinios
Užkreciamuju ligu profilaktikos ir kontroles centras
Kalvariju str. 153,
LT-08221, Vilnius.
Online. In Lithuanian.
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NETHERLANDS

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In English.
http://www.cdscni.org.uk/publications

NORWAY

MSIS-rapport
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Weekly, print and online versions available.
In Norwegian.
http://www.folkehelsa.no/nyhetsbrev/msis

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POLAND

Reports on cases of infectious diseases and poisonings in Poland
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Ministry website: http://www.dgsaude.pt

ROMANIA

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Institute of Public Health, Bucharest.
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Insitute website: http://www.cpcbt.ispb.ro

SCOTLAND

Health Protection Scotland Weekly Report
Health Protection Scotland, Glasgow.
Weekly, print and online versions available.
In English.
http://www.hps.scot.nhs.uk/ewr/index.aspx

SLOVENIA

CNB Novice
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Monthly, online only. In Slovene.
http://www.ivz.si

SPAIN

Boletín Epidemiológico Semanal
Centro Nacional de Epidemiología – Instituto de Salud Carlos III, Madrid
Bi-weekly, print and online versions available.
In Spanish.
http://www.isciii.es/jsps/centros/epidemiologia/boletinesSemanal.jsp

SWEDEN

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Smittskyddsinstitutet, Solna.
Weekly, online only. In Swedish.
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