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In this edition

Three special issues on

- Vaccination
- Molecular typing
- Hepatitis B and C

Also

- A survey on cases of tick-borne encephalitis in European countries
- Surveillance of air-travel-related tuberculosis incidents, England and Wales: 2007-2008

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See inner back cover

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Contents

Special issue: World Hepatitis Day - a timely reminder of the challenges ahead

SURVEILLANCE AND OUTBREAK REPORTS

RESEARCH ARTICLES

REVIEW ARTICLES

PERSPECTIVES

RAPID COMMUNICATIONS

SURVEILLANCE AND OUTBREAK REPORTS

RESEARCH ARTICLES

EUROROUNDUPS

REVIEW ARTICLES

PERSPECTIVES

RAPID COMMUNICATIONS

LETTERS

Articles published in Eurosurveillance are indexed in PubMed/MEDLINE

European Immunization Week 2008 - time for reflection

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This week's edition of Eurosurveillance is dedicated to European Immunization Week 2008, which will take place from 21 to 27 April. In 2005, the World Health Organization (WHO) organised the first European Immunization Week (http://www.euro.who.int/vaccine/eiw/20050608_1) to increase vaccination coverage by raising awareness about the importance of immunisation, with a special focus on reaching vulnerable and hard-to-reach population groups. During the week, each participating country implements activities to inform and engage key target groups using the slogan "prevent-protect-immunise" and focuses on critical challenges regarding immunisation in their country.

In 2002, the WHO Regional Office for Europe developed a strategic plan for the elimination of measles and the prevention of congenital rubella, which was expanded in 2004 to reach the ambitious target to eliminate both diseases by 2010. 'Elimination' is defined as an incidence of measles less than one case per one million inhabitants per year and an incidence of congenital rubella of less than one case per 100,000 live births. One of the key indicators is to reach vaccination coverage with two doses of the measles, mumps and rubella (MMR) vaccine of at least 95% at national level and at least 90% in all districts.

In 2002, the WHO Regional Office for Europe developed a strategic plan for the elimination of measles and the prevention of congenital rubella,

Although considerable progress has been made since 2002, and vaccine coverage with MMR has increased dramatically, huge outbreaks of these diseases have nevertheless been reported in recent years and are still ongoing in western European countries. There are currently large outbreaks of measles with over 2,000 cases in Switzerland and over 180 cases in Austria, both of which may pose the risk of widespread distribution to other countries during the European football championship (EURO 2008), which will take place in both those countries in June [1].

Enhanced surveillance for measles has significantly improved by the implementation of non-invasive sampling techniques and genotyping. Genotyping provides a good tool for better understanding the epidemiological links of outbreaks and has demonstrated that many of the outbreaks in Europe, especially the recent outbreaks in western countries of the European Union (EU) are connected and often result in the exportation of cases to countries within and outside the EU.

Much effort has been expended, both by EU Member States and the WHO, to strengthen immunisation policy, vaccine safety and quality, surveillance, response and communication. However, despite the development of a new strategic framework plan identifying key strategies, setting annual milestones, targeting hard-to-reach populations, there is still much more to be done if the target of elimination is to be reached.

In recent years, low MMR coverage in hard-to-reach populations has resulted in outbreaks among Roma and Sinti in Italy, and among travellers in the United Kingdom [2,3]. The latter was exported to Israel, resulting in a huge outbreak there, which has been ongoing for several months with around 1,000 cases [4,5].

The decrease of vaccine coverage levels due to the upsurge of objectors against vaccination has been influenced by publications about a non-existent association between the MMR vaccine and autism and Morbus Crohn in The Lancet [6], and a general reluctance by many parents to put their children through vaccination schedules.

In many cases, outbreaks start in environments with a high proportion of susceptibles, for example in anthroposophic groups, which are known for their critical attitudes towards vaccination. These outbreaks may then be exported to the general population, as is currently the case in Salzburg, Austria, where the first cases emerged in an anthroposophic school with very low vaccination coverage.

In this issue, Muscat et al describe the measles situation in Europe with nearly 4,000 cases reported in 2007 and 19 deaths for the period 2005/6 in the EU/European Economic Area (EEA) and EU candidate countries [7]. But as underreporting and underdiagnosis are common, many more cases are likely to have occurred. Further rapid communications provide preliminary information on an ongoing outbreak in Austria (Schmid et al) and its international implications [8] and another current outbreak in Italy (Caputi et al) that highlights the need for improving measles control measures in a hospital setting [9]. An interesting short communication by Spiteri et al. reports on a recent cluster of rubella cases in Malta and results from a cross-sectional study in Northern Greece presented by Fylaktou et al. show lower than expected protection rates against

both measles and mumps in certain age groups, such as infants and young adults, partly due to non-compliance with the second dose of MMR vaccination.

Finally, two articles look at mumps, albeit it from very different angles. Boxall et al report on a large outbreak in the Czech Republic, the cause of which has to be explored among several aspects of the current immunisation program: waning immunity, inadequate cold chain, other causes of vaccine failure [10]. And Kaic et al report an unusual horizontal transmission of the L-Zagreb mumps vaccine strain to parents following children's vaccination [11].

Mumps elimination is not yet a public health goal in Europe, but outbreaks of the disease can be seen as a sign of problems in the MMR immunisation strategy and every issue (including safety) related to mumps vaccination can be a threat to the measles and rubella elimination targets.

Elimination of measles and congenital rubella syndrome (CRS) will only happen with the concerted actions of all stakeholders. This should include the notification of every case, enhanced harmonised surveillance, contact tracing of exposed susceptibles, the communication of every outbreak in all EU Member States, and increasing vaccine coverage. Efforts must also be made to identify populations with low coverage and tailor strategies to address those communities. Different communication strategies must be identified to target these groups, and a strong commitment is needed to ensure that human and financial resources are also provided.

The revised International Health Regulations that came into force in June 2007 are an opportunity to strengthen the battle against measles, which is a highly contagious and dangerous disease. However, in view of the current situation, the elimination by 2010 looks like it may be very hard to achieve.

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Editorials

European Immunization Week 2008: Progress towards regional goals

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The World Health Organization (WHO) Regional Office for Europe established the European Immunization Week (EIW, http://www.euro.who.int/vaccine) in 2005 for three reasons:

1) to raise public awareness of the benefits of immunisation,
2) to support national immunisation systems, and
3) to provide a framework for mobilising public and political support for governmental efforts to protect the public through universal childhood immunisation.

The accomplishments of immunisation programmes in Europe are great – almost 95% of children in the WHO European Region are vaccinated against diphtheria, tetanus, pertussis and measles by their first birthday. However, significant challenges remain: approximately 600 000 infants do not receive the complete three-dose series of diphtheria, tetanus and pertussis (DPT) vaccine by age one, and WHO estimates that approximately 32,000 die each year from vaccine-preventable diseases.

Many will highlight measles and rubella, where major progress has been made toward the regional goal of elimination by 2010,

Although limited human, technical, and financial resources are a factor in some countries, the principal challenges facing Europe's immunisation programmes are changing. While national programmes still face problems delivering services to geographically and socially marginal populations, the effectiveness of vaccinations in reducing the incidence of what were once common scourges has led to a broader public misapprehension. Internet use and a combination of complacency and scepticism have allowed for the persistent propagation of misinformation via anti-vaccination activists. This has resulted in a stagnation or decrease in immunisation coverage in many countries and contributed to recent outbreaks of disease that threaten the health of Europe and other regions of the world. For example, an ongoing measles outbreak in Switzerland, which started in November 2006, has to date resulted in more than 1,400 cases reported in that country and has been linked to local outbreaks elsewhere in Europe and North America [1]. Other examples include recent measles outbreaks in Austria [2] and large epidemics in Ukraine and Romania, which resulted in tens of thousands of cases over the past five years. Moreover, the geographic distribution of measles in Europe is shifting. While once more common in the East, by 2007 the countries with the most cases, and the lowest vaccination rates, were located in the West [3].

Over the past three years, EIW has come to be seen as an effective vehicle for addressing the broad range of issues faced by different countries. With nine Member States of the WHO European Region participating in 2005, the inaugural year, and 33 countries taking part in this year's EIW* from 21-27 April 2008, it is clear that Member States increasingly regard it as an important opportunity to place immunisation communication and advocacy at the top of the public health agenda. Member States recognise the need to focus communication and advocacy on local challenges, be they public complacency, safety concerns, misinformation, or hard-to-reach or vulnerable groups. For EIW 2008, Member States have planned a wide range of activities that reflect these local priorities and strategies to reach their unimmunised populations. While using common logos, slogans (Prevent. Protect. Immunize.), promotional material and, where needed, technical and financial assistance from WHO, EIW remains an event conducted for and by Member States.

Thousands of promotional materials, television and radio broadcasts, writing contests and seminars for journalists, hot lines and web sites will spread the message about immunisation during the Week, highlighting the interactivity of the event. A number of countries have chosen to focus on hard-to-reach groups such as migrant and minority communities (Albania, Bosnia and Herzegovina, Greece, Romania, Slovakia), while Belgium will direct special attention to religious objectors which have seen outbreaks in the past year. Focusing on urban populations, Poland is planning social promotion campaigns in Warsaw central station and underground stations, and will promote vaccination to parents through the distribution of information in kindergartens, as will Germany and Kyrgyzstan. Other countries are choosing different venues and mechanisms for advocacy to parents. Health-care workers, the gatekeepers of health information for many, constitute a target group in countries where further training about immunisation is required. Elsewhere, efforts will include journalists, who often lack knowledge and access to balanced and trustworthy sources. Bosnia and Herzegovina, Bulgaria, the Czech Republic, Kyrgyzstan, Serbia and Tajikistan will engage politicians along with other key policy-makers through initiatives such as parliamentary discussions and round-table discussions.

Working towards national and regional goals

Many countries will focus on boosting immunisation in general while others will use EIW as a means of promoting specific aspects of their national immunisation plans such as new vaccine introduction or linking their efforts to regional goals. Many will highlight measles and rubella, where major progress has been made toward the regional goal of elimination by 2010, but more remains

to be done. Twenty-nine of the 53 countries in the European Region reported measles incidence below the elimination threshold of < 1 per million population in 2007. However, these countries account for only 33% of the Region's population and last year measles incidence remained well above the threshold in many of the largest countries, including Germany, the United Kingdom, Italy, Ukraine, and Spain.

Another important regional goal is to sustain the polio-free status achieved in 2002. Serbia is among those that will focus on this during EIW 2008. Others, such as Georgia, will use EIW to improve record-keeping and reporting to strengthen information systems for management and surveillance. Others will address narrower immunisation interests. Azerbaijan will focus on diphtheria, Croatia on DTP, inactivated polio (IPV) and Haemophilus influenzae type b (Hib) vaccines, and Kazakhstan on Hib vaccine introduction. Turkey will conduct a catch-up Hib vaccination campaign and Uzbekistan a mop-up DTP and DTP-IPV vaccine campaign.

The goal of EIW is not to vaccinate as many people as possible during one week (although almost 1.5 million immunisation doses were given during EIW 2007 [5]). The primary indicator of success will be the increase in advocacy and communication. The hope is that the increased awareness will lead to sustained increases in the number of immunised children. There is a sister initiative to EIW, the Vaccination Week in the Americas organised by the Pan American Health Organization, which has resulted in additional vaccinations of close to 200 million people since its inception six years ago. This year the two initiatives will be synchronised as a first step towards a future global immunisation week.

* Albania, Armenia, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, France, Georgia, Germany, Greece, Hungary, Ireland, Kazakhstan, Kyrgyzstan, Latvia, Malta, Poland, Romania, Russian Federation, Serbia, Slovenia, Slovakia, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, United Kingdom and Uzbekistan.

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Editorials

Tick-borne encephalitis: rounding out the picture

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What is now known as tick-borne encephalitis (TBE) was first recognised as a distinct disease entity in 1931 in Europe by H. Schneider and described as 'meningitis serosa epidemica' of unknown etiology [1]. A disease with similar clinical symptoms was reported in the Far East in 1934 and briefly thereafter – in 1937 – the etiologic agent was isolated in Russia and its transmission by ticks could also be demonstrated [2]. In Finland, TBE was initially described as 'Kumlinge disease' in the 1940s [3] and the first European TBE virus was isolated in Czechoslovakia during an epidemic in 1948 [4].

Since those historic days, the scientific development in the area of TBE and flaviviruses in general has been enormous. Today, we are experiencing an explosion of new information, both on the structure and molecular biology of these viruses and the biological principles underlying their natural cycles [5]. It is especially pleasing to see that the purified inactivated vaccine available on the market [6] has an excellent profile of field effectiveness as well as safety, and vaccination therefore proved to be an extremely successful measure for preventing disease [7].

Nevertheless, there are several aspects in the context of TBE that have not yet been satisfactorily dealt with, including the question of different clinical disease pictures induced by the three TBE virus subtypes (European, Siberian, and Far Eastern), the lack of standardisation of case definitions, laboratory diagnosis, reporting and documentation of the disease as well as of endemic areas. The latter issue, of course, relates to possible changes of the distribution of natural TBE virus foci because of climatic changes, and we are only at an early stage of understanding in which way complex biological systems control the maintenance of the virus in nature [5,8].

A critical review of the present surveillance systems for TBE in different European countries – as presented in this issue's article by O Donoso Mantke *et al* [9] – is therefore most welcome, and pinpoints those areas that need to be addressed in further activities of investigation.

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Editorial

World Hepatitis Day: a timely reminder of the challenges ahead

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Following on the heels of World Hepatitis Day on 19 May 2008, this week's issue of Eurosurveillance is a special issue on viral hepatitis, highlighting the various aspects and challenges related to hepatitis B and C. World Hepatitis Day was launched in 2007 to increase awareness and political commitment to tackling the significant problems viral hepatitis B and C pose to public health and to call for more control and prevention activities. In particular, chronic hepatitis B and C infections are a significant threat to public health, and are considered to be the leading causes of liver cancer worldwide. Hepatitis B and C occur with a very high burden of disease.

In particular, chronic hepatitis B and C infections are a significant threat to public health, and are considered to be the leading causes of liver cancer worldwide.

In hepatitis B, acute illness can have mild to severe symptoms. The majority of severe sequelae occur in patients who are chronically infected with hepatitis B virus (HBV); a significant proportion develop liver cirrhosis or hepatocellular carcinoma. Moreover, those chronically infected serve as a reservoir for continuing HBV transmission. In hepatitis C, up to 90% of cases are asymptomatic and are detected most often in active screening settings or coincidentally in a routine check-up. The evidence suggests that high proportions (possibly as much as 50-80%) of those infected with hepatitis C virus (HCV) could go on to develop a chronic infection state, and a further proportion of these (possibly up to 70% of chronic infections) may eventually develop liver cirrhosis or cancer.

HBV is transmitted by percutaneous or mucosal contact with infectious blood or other body fluids (serum, semen, saliva). For infants and children, the main sources are perinatal transmission from infected mothers and horizontal transmission from infected household contacts. Adolescents and adults are mostly infected through sexual activity, sharing needles in case of injecting drug use (IDU), or accidental needle stick injuries in healthcare settings. Today, transmission via blood transfusion and use of plasma-derived products is rare. HCV is also transmitted by infectious blood; the risk of perinatal transmission is estimated between 5-15%, and sexual transmission is infrequent. Since 1994, transmission via blood transfusion and the use of plasma-derived products has been rare, as routine HCV tests have become widely available.

In the European Union (EU), the most common mode of transmission for hepatitis B seems to be sexual transmission, and for hepatitis C injecting drug use. Statistics and the epidemiology are difficult to interpret and may be biased due to the lack of reliable and comparable data for hepatitis B and C. In addition, the number of infections in immigrants from high-endemic countries contributes to a changing epidemiology, as suggested in the paper by Rantala and Van de Laar in this issue. To reduce the numbers of new hepatitis C cases, preventing infections in IDUs is a priority in the EU, notwithstanding the relative decrease during the last decade due to the impact of "new" drugs consumption. This is highlighted in the papers by Dubois-Arber et al on results from a behavioural surveillance system in Switzerland, the paper by Duberg et al on the on-going epidemic of HCV in IDU in Sweden, and the article by Wiessing et al analysing the outputs from the European Monitoring Centre for Drugs and Drug Addiction. However, it is important to bear in mind that the number of undiagnosed HCV infections is probably high; varies across countries; and may reflect the intensity of screening activities rather than true incidence of infection.

The facts stated above highlight the importance of preventive measures. Hepatitis B is a vaccine-preventable disease and vaccination is currently the most effective way to prevent HBV infection apart from education regarding infection. No vaccine has yet been developed for hepatitis C, because of the large and frequent genetic variation. Screening and testing of blood and organ donors, virus inactivation of plasma-derived products, good infection control, strong education programmes and injection safety practices in healthcare settings are currently the most effective preventive measures for hepatitis C, but also apply for hepatitis B to reduce the individual risk of transmission. Deeper knowledge of acute HCV infections is still lacking. Irving et al are of the opinion that the "failure to address acute transmission of HCV infection will undermine long-term attempts to reduce HCV-associated disease burden". Moreover, spending more resources in this direction would also allow the identification of iatrogenic and nosocomial infections, which are still occurring and are largely unrecognised. A coordinated multi-level approach is a priority, as underlined by Goldberg et al in their report on the launch of the Scottish Hepatitis C Action Plan.

There are some treatment options for both HBV and HCV, so that in certain cases the disease outcome could be improved. Access to treatment is limited in many EU countries. Upscaling treatment services to prevent progression to severe liver disease

requires substantial resources, which may not be available in many EU countries.

An important basis for effective prevention and control measures is a good and reliable analysis of the epidemiological situation. However, reliable epidemiological data on hepatitis B and C in the EU are not available. EU-wide surveillance of hepatitis B and C is urgently needed to gain a better understanding of its changing transmission patterns and to identify the most effective ways to contain the disease. The harmonisation and strengthening of EU-wide surveillance is a priority, as reported by Rantala and van de Laar in their review of European systems. Considering the wide heterogeneity in surveillance systems, data sources and healthcare systems in EU Member States, this will be a major challenge for the coming years.

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Editorials

Molecular typing for public health purposes

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In this issue, seven networks/projects are presented that are dedicated to the molecular typing of bacteria (SeqNet: *Staphylococcus aureus*; MLVA-Net: *Salmonella Typhimurium, Enterobacter sakazakii, Listeria monocytogenes*; HARMONY: *Staphylococcus aureus*; DIPNET: *Corynebacterium diphtheriae*) or viruses (HepSEQ: hepatitis B virus; FBVE: noroviruses and other gastrointestinal viruses; MeaNS: measles). They represent only a few of an increasing number of typing networks. However, they illustrate a couple of relevant issues that need to be considered before implementing these methods for different public health purposes.

By providing appropriate discriminatory analyses, molecular typing can foster rapid and – depending on the method – even real-time early detection of dispersed international clusters/outbreaks, the detection and investigation of transmission chains, the relatedness of strains, and the emergence of antimicrobial resistance and new evolving pathogenic strains. Molecular typing of infectious diseases, if routinely applied, can also complement traditional epidemiological surveillance. Moreover, analysis of molecular typing data can aid in studying the characteristics of a particular pathogen and its behaviour in a community of hosts, such as its spread over time and space, disease transmission dynamics, virulence factors influencing recurrence of infections, mutations and antigenic drifts of strains over time, and the development of drug resistance across strain generations.

Molecular typing of infectious diseases, if routinely applied, can also complement traditional epidemiological surveillance.

Whereas the application of molecular typing during outbreaks and for the investigation of transmission chains is widely accepted, the use of these methods for routine surveillance is more debated, although there are successful examples, such as PulseNet in the United States [1]. However, before transferring a typing method from a research setting into wider use, a number of criteria proposed for the evaluation and validation must be considered.

Among those criteria are typeability, discriminatory power, epidemiological concordance and reproducibility. These characterise the "technical" appropriateness of a method for the typing of a specific pathogen [2]. For the implementation of an appropriate method into practice, a number of aspects need to be taken into consideration: the flexibility (to be used for more than one species); the rapidity; accessibility and overall cost; the ease of use, which includes the workload but also the interpretation of results; the amenability to computerised analysis and incorporation in electronic databases, which is important to combine the typing data with other epidemiological information [2].

For the inclusion of molecular typing data into surveillance at EU level, a few additional considerations are required before a typing method could be suggested for routine application:

- Typing data should provide essential information to achieve the surveillance objectives for the specific disease.
- The typing method should provide real-time information.
- The specific typing method/pathogen combination needs to be agreed upon among the laboratory experts.
- The molecular typing method is standardised in terms of the typing protocol and the nomenclature (or this standardisation is feasible), which allows comparison of data across laboratories and countries.
- External Quality Control needs to be established and regularly carried out.
- All Member States should have access to the agreed molecular typing method/pathogen, either by building up the capacity in their own country or by getting support from those Member States who have already developed the capacity.

The full synergy of combining molecular typing data and routine surveillance information and interpreting them jointly can contribute to improving and better targeting existing infectious disease prevention and control measures, and thus presents a clear benefit for public health and public health policy. However, the introduction of any of these methods will require a careful discussion between all involved stakeholders, which the European Centre for Disease Prevention and Control will encourage and foster, according to its mandate.

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Editorials

Rabies – a recurrent danger to European countries from dogs introduced from endemic countries

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Although vaccine-preventable, rabies remains a worldwide-occurring disease of major public health concern. Globally, rabies is responsible for about 55,000 human deaths per year, mainly in Asia and Africa, and 30-50% of the cases are in children, most often following an infection transmitted through the bite of a rabid dog [1]. Annually, around 10 million people receive treatment after exposure to animals in which rabies is suspected. However, in the absence of such treatment, the disease is fatal.

Although the incidence in humans is very low in Europe, several rapid communications in Eurosurveillance in recent years have documented the tragic outcomes following dog bites in travellers returning from countries with urban rabies [2,3,4,5,6,7]. For example, in 2003 a three-year-old who had probably been infected when playing with unvaccinated dogs during a visit to Gabon died in France [2]. In 2004, a young Austrian tourist died after being bitten by a dog in Morocco [6], and a young German woman died after a bite from a dog in India. In 2005, a British man died who had been bitten by a dog while on holiday in Goa, India [5]. In 2007, a German national died on his return to Germany after being bitten by a stray dog in Morocco which had been fighting the man's own dog [7]. All the deceased had not been vaccinated.

around 10 million people receive treatment after exposure to animals in which rabies is suspected.

In addition, the regions of Europe that are considered 'rabies-free' according to the the World Organisation for Animal Health (OIE) criteria still face a risk of illegal introductions of potentially infected domestic animals, primarily pet animals. This illustrates the need for continued vigilance and strict compliance with European Union (EU) control measures [8]. For example, in February a dog that had never left the country was diagnosed with rabies in France. The investigations of the case revealed that the likely source of the infection was a dog that contracted rabies from another dog that had been illegally introduced from Morocco in late 2007 [9]. In this and last week's issue, two timely communications by V Vaillant et al and M Catchpole et al on recent illegal introductions of rabies-infected dogs into EU Member States point out the danger and highlight challenges associated with the illegal introduction of dogs from rabies-endemic countries. In the recent case of a dog introduced from Gambia to France via Belgium [10], the requirements for the introduction of pet animals from countries not listed in the Annexes to Regulation (EC) No 998/2003 of the Council and the European Parliament [8] were not complied with by the owner of the dog. Although the dog was certified as primo-vaccinated before entry into Belgium, it had neither undergone the required antibody titration test demonstrating a protective immunity, nor the mandatory three-month waiting period before movement to exclude any possible pre-vaccination exposure to the virus.

As a result, this required complicated investigations by the relevant public and animal health authorities in France and Belgium, leading to substantial public expenditure and post-exposure vaccination in France and Belgium alone.

The picture is completely different in the case of a dog that died in a quarantine facility in the United Kingdom [11]. This dog was legally introduced from a non-listed third country in accordance with the transitional measures laid down in Regulation (EC) No 998/2003 and consequently placed in quarantine. However, even in this case three individuals connected to the quarantine were bitten and required post-exposure treatment.

These examples show that, in the case of rabies, continuous vigilance is needed in order to ensure that animals entering the EU are properly vaccinated, and where required by legislation, tested for their immune response. Furthermore, all those intending to introduce dogs, cats or ferrets into the EU need to know that such animals might be infected with rabies and should not be imported unless full prevention and control measures have been carried out [8].

In addition, travellers to endemic countries should be aware of the danger of contracting rabies and be advised to take precautionary measures, such as avoiding contact with mammalian animals, and furthermore be informed about the possibility of pre- and postexposure vaccination.

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Surveillance and outbreak reports

Measles and mumps immunity in Northern Greece, 2004-2007

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A cross-sectional study was conducted in order to determine the prevalence of mumps and measles antibodies in a representative sample of the general population in Northern Greece between January 2004 and May 2007. Overall, 900 healthy individuals participated in the study. The great majority were found to be protected against measles. The total protection rate against mumps was significantly less (87% versus 72%, respectively; $p<0.01$). Compared to all other age groups, statistically significantly lower protection rates were found in children younger than 1.5 years ($p<0.01$). The lowest rates of all adult groups were found in the age group of 21 to 30 years (86% and 68% for measles and mumps, accordingly). In conclusion, protection rates against both measles and mumps seem to be lower than expected in certain age groups, such as infants and young adults.

Introduction

Outbreaks of communicable diseases may occur many years after a period of low incidence following the introduction of vaccination, if a significant number of susceptible individuals has gradually accumulated. Serological surveillance studies can monitor changes in the prevalence of antibodies and possibly predict disease transmission by mathematical models [1].

Measles and mumps occur worldwide, but their incidence has decreased since the introduction of the measles, mumps, rubella (MMR) vaccine. Serious clinical complications such as encephalitis or orchitis are not rare [2-3]. Despite immunisation, mumps and, especially, measles outbreaks are still reported in Europe, even in highly vaccinated populations [4-8].

In Greece, measles vaccination was introduced in the early 1970s, when vaccines became commercially available. Vaccination at the age of 15 months was introduced in the national immunisation schedule in 1981; the MMR vaccine was introduced in 1989. Previous immunisation rates with the monovalent vaccines were significantly lower and the vaccine was given on a voluntary basis. Vaccination with a second dose of MMR at the age of 11-12 years was introduced in the national immunisation schedule in 1991, and since 1999 this second dose has been administered between the ages of four and six years. The national immunisation policy currently includes two doses of the combined MMR vaccine, one at 12-15 months, and a second at 4-6 years.

Since the introduction of vaccination, the reported incidence of measles and mumps has declined. According to the Greek Child Health Institute, mumps and measles outbreaks have become very rare [9,10]. However, periodic outbreaks of both diseases continue to occur, and the last outbreak of measles was reported in 2005 [11-13], with 171 cases recorded between September 2005 and March 2006. Of the 171 patients, 159 (93%) were from Northern Greece [12]. The aim of the present cross-sectional study was to determine the prevalence of mumps and measles antibodies in a representative sample of the general population in Northern Greece.

Methods

Study population

The study population was recruited from the outpatient clinics of Papageorgiou General Hospital, Thessaloniki, Northern Greece. The sample included healthy individuals who underwent blood tests as part of a routine check-up between January 2004 and May 2007. Informed consent was obtained from all participants or their parents or guardians. Information including name, sex and date of birth was exstracted. Data on vaccination history were not obtained as they were not available in the original data set. Subjects were excluded from the study if they presented with acute infections or had received blood transfusions in the three months prior to the study. The study did not require ethical approval by the Ethical Review Board of the Papageorgiou General Hospital.

Ten age groups were composed as follows; infants younger than six months and 0.5-1.5 years old, children 1.5-5, 5-11, and 11-20 years-old, adults 21-30, 31-40, 41-50, and 51-60 years-old, and elderly individuals over 60. Sample size was set to be proportional to the age-specific population size of Northern Greece, an estimated 2.77 million people, representing approximately 25% of the total population in Greece [14].

Sample analysis

Blood samples were obtained by venous puncture and centrifuged. The sera were stored at -20°C and used only once after thawing. Serological analysis was carried out at the microbiology/virology/biochemistry laboratory of the Papageorgiou General Hospital, Thessaloniki, Northern Greece. Blood serum levels of measles and mumps immunoglobulin G (IgG) antibodies were determined by commercial IgG-specific enzyme-linked immunosorbend assays (Genzyme Virotech GmbH, Rüsselsheim, Germany) according to the manufacturer's instructions. The coefficient of variation of the method used was <9%. IgG levels of >12.0 Virotech Units (VE) were considered as the minimum protective level. Each serum titre was determined in duplicate.

Statistical analysis

The antibody prevalence was calculated for both sex and age groups. The chi square test was used to compare proportions. The Fisher's exact test was applied when the expected frequencies were below five. All calculations were carried out using SPSS version 14.00 (SPSS, Chicago, IL, USA).

Results

Overall, 900 healthy individuals participated in the study. The age-stratified population consisted of 428 males and 472 females (48% and 52%, respectively). The demographic distribution of each study group was similar to that of the entire northern Greek population. In particular, 6% of the tested individuals were younger than six months old, 6% were 0.5 to 1.5 years-old, 6% were 1.5 to 5, 6% were 5 to 11, 12% were 11 to 20, 14% were 21 to 30, 14% were 31 to 40, 14% were 41 to 50, 12% were 51 to 60, and 10% were 60 years-old (>1/10,000 representation in all age groups, except for the age group over 60 years). A total of 900 serum samples, collected during the study period, were analysed. The population distribution, according to age and sex, and the seroprevalence results are presented in Table 1.

The majority of our study population was found to be protected against measles (87%). Although most individuals were protected against mumps, too, the total protection rate against mumps was significantly lower (72%) ($p<0.01$). The levels of protective antibodies against both diseases were higher in those older than 1.5 years. The protection rates found in children younger than 1.5 years (i.e. in the first two age groups) were statistically significantly lower than in all other age groups ($p<0.01$).

Table 1

Mumps and measles seroprevalence, Northern Greece, January 2004 - May 2007

Age Groups	No. Tested			Measles [No (%) IgG positive]			Mumps [No (%) IgG positive]		
	F	M	Total	F	M	Total	F	M	Total
<6months	24	30	54 (6%)*	18 (75%)	18 (60%)	36 (67%)	10 (42%)	6 (20%)	16 (29%)
0.5-1.5 years	24	30	54 (6%)*	6 (25%)	8 (27%)	14 (26%)	2 (8%)	6 (20%)	8 (15%)
1.5-5 years	24	30	54 (6%)*	20 (83%)	26 (87%)	46 (85%)	18 (75%)	22 (73%)	40 (74%)
5-11 years	32	22	54 (6%)*	30 (94%)	20 (91%)	50 (93%)	26 (81%)	18 (82%)	44 (81%)
11-20 years	44	64	108 (12%)*	40 (91%)	58 (91%)	98 (91%)	32 (73%)	52 (81%)	84 (78%)
21-30 years	82	44	126 (14%)*	70 (85%)	40 (91%)	110 (87%)	54 (66%)	32 (73%)	86 (68%)
31-40 years	76	50	126 (14%)*	74 (97%)	48 (96%)	122 (97%)	64 (84%)	38 (76%)	102 (81%)
41-50 years	60	66	126 (14%)*	56 (93%)	62 (94%)	118 (94%)	54 (90%)	50 (76%)	104 (83%)
51-60 years	60	48	108 (12%)*	54 (90%)	48 (100%)	102 (94%)	50 (83%)	44 (92%)	94 (87%)
>60 years	46	44	90 (10%)**	44 (96%)	42 (95%)	86 (96%)	34 (74%)	34 (77%)	68 (76%)
Total	**472**	**428**	**900 (100%)**	**412 (87%)**	**370 (86%)**	**782 (87%)**	**344 (73%)**	**302 (71%)**	**646 (72%)**

F: Females; M: Males.
* representing >1:10,000 age-stratified individuals in the general population.
** representing <1:10,000 age-stratified individuals in the general population.

Figure 1

Measles IgG antibody-positives by age group and sex, Northern Greece, January 2004 - May 2007

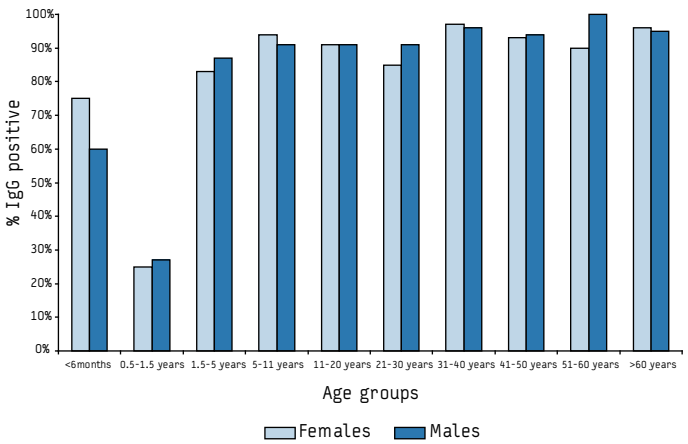
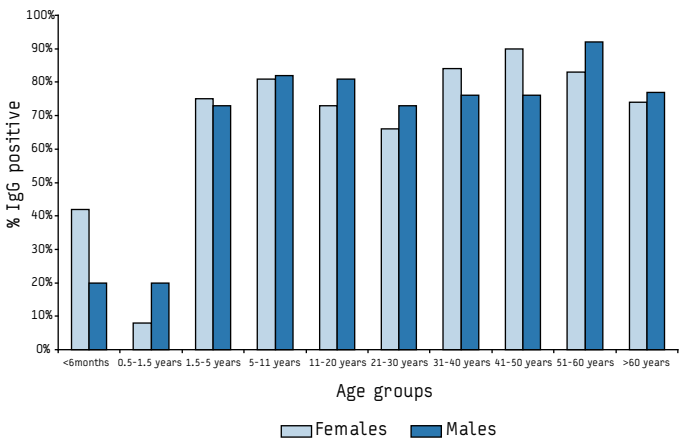


Figure 2

Mumps IgG antibody-positives by age group and sex, Northern Greece, January 2004 - May 2007



Those younger than six months old had higher seropevalence rates against both diseases compared to the 0.5-1.5-year-olds (Table 1 and Figures 1 and 2). The average prevalence of mumps IgG in this group (29%) was lower than that of measles IgG (67%) and also lower than the average prevalence in all adults groups (e.g. 81% and 97%, respectively, for the 31-40 year-olds).

Another interesting finding was the low proportion of protected individuals in the group of 21- to 30-year-olds (87% and 68% for measles and mumps, respectively). This age group had the lowest seroprevalence rates of all adult groups (Figure 1), although overall, the measles and mumps IgG seroprevalence showed a continuous increase from pre-school age to adulthood. This difference was statistically significant ($p<0.05$).

There was no significant difference in the levels of anti-measles IgG between males and females in all age groups ($p>0.05$): 86% of the tested males and 87% of the tested females had protective antibody levels against measles. In addition, 71% of the tested males and 73% of the tested females had IgG-positive antibody titres against mumps. However, in the case of mumps, a statistically significant difference in the protection rate between males and females was found in those younger than six months old (42% versus 20%, respectively; $p<0.01$) and the 41- to 50-year-olds (90% versus 76%, respectively; $p<0.05$).

Discussion

During the past 25 years, measles and mumps incidence in Greece has been steadily declining, due to the MMR active vaccination programme. Vaccination coverage of pre-school children, school children and adolescents with one dose of MMR vaccine is >95% [9]. The second dose covers approximately 60–80% of the indigenous child population – a significant increase compared to the coverage 10 years ago which was only 36.5% [9]. However, two-dose vaccine coverage has been found to be very low, only 2–12%, in certain minority populations [15]. According to a recently published study, the vaccination coverage in adolescents is not satisfactory, mainly due to non-compliance with the second vaccine dose [10].

The most interesting finding of the present study was that 13% and 28% of the Northern Greek population are not protected against measles and mumps, respectively. This is probably due to the relatively low coverage with the MMR vaccine, which is reflected in an insufficient proportion of individuals in the general population who are positive for MMR-specific antibodies. The total protection rate for mumps was significantly lower than for measles. These findings are consistent with other European studies, which showed that different patterns are observed between measles and mumps seroprofiles [16,17]. In particular, as recent outbreaks have proved, the low vaccine coverage has reduced, but not completely stopped viral circulation amongst infants, resulting in the accumulation of a pool of susceptibles amongst older children and adults compared to the prevaccination aera [16].

In addition, we noticed a difference in the seroprevalence of antibodies against measles and mumps, although both vaccines are administered simultaneously. This may be attributed either to primary or secondary MMR vaccine failure or to problems regarding the standardisation procedure of the laboratory assay used to determine the antibody levels [17]. On the contrary, the mumps and measles virus antibodies prevalence reported in European countries with a low incidence of the diseases, such as Finland [16] or Luxembourg [18], is significantly higher. These countries seem to be near the elimination of both diseases. However, importation and circulation of wild virus strains in clusters of religious or minority groups can not be excluded even there.

The origin of antibodies – whether due to infection or to vaccination – could not be defined as data on vaccination status or past history of measles or mumps infection were not obtained. Children younger than 1.5 years (the two first age groups), had significantly lower protection rates against both diseases, compared to all other groups. The sub-cohort of those younger than six months old, however, had higher seropevalence rates against measles than the 0.5-1.5-year-olds (67% versus 26%, respectively). This was to be expected due to the rapid decline of the maternal antibody levels within the first six months of life. For measles, loss of detectable maternal antibodies seemed to follow a slower pattern in time. These findings confirm previous studies showing that a window of susceptibility to both infections exists between the decay of passively acquired maternal antibodies and the start of the immune response elicited by vaccination [19]. To propose a change regarding the right timing for the administration of the first dose of the MMR vaccine and the vaccination of women of reproductive age, a balance between the need to minimise the length of the window period and the development of an optimal immune response to the vaccine should be determined.

The proportion of protected individuals was considerably lower in the age group of 21-30-year-olds (87% and 68% for measles and mumps, respectively). Lower immunity among young adults, especially males of reproductive age, has been frequently reported [4-6, 8, 20-22]. Older adults seem to be better protected, probably due to the fact that they have developed natural immunity the aera before MMR vaccination was adapted in a nationwide scale. For young Greek adults born between the years 1975-1986, low MMR vaccine coverage during the first vaccination decade and the lack of booster vaccinations, as well as the coverage by the general community immunity, are possible additional explanations of low seroconversion rates, especially because the extent of natural booster is not well known.

To reach disease elimination, all susceptible individuals need to be immunised. Several alternative strategies could be launched to achieve this goal, such as offering measles vaccination to all age groups without a history of natural disease, or providing all age groups who have only received one dose of MMR vaccine a second dose in order to avoid breakthrough infections. Such strategies would include compulsory vaccination of children entering day-care facilities and/or primary school and of adolescents before entering middle school [23]. In addition, such supplemental immunisation activities targeting the population younger than 25 years (undergraduate and postgraduate students) should be expanded to those older than 25 years, provided that they belong to a "high risk" group (teaching staff, army, police, border troops, staff members of hospital units). Factors that impede children from hard-to-reach populations, such as the Roma and immigrant communities, from being immunised must be adequately addressed and special strategies should be developed to reach these populations on a regular basis.

We did not find a statistically significant difference in the seroprevalence rates against measles between males and females against measles in any of the age groups. However, it would be interesting to investigate the difference in protection rate against

mumps that we noticed between males and females younger than six months old and the group of 25-50-year-olds, a fact that could possibly be attributed to the small sample size.

The present study has certain drawbacks. Firstly, the cross-sectional type, while useful for generating hypotheses, does not permit hypothesis testing and is prone to late-look bias. Secondly, we tried to ensure that our sample was representative of the general population. The individuals included in the survey were selected randomly after stratification into age groups. The size of each age group was supposed to be proportional to the size of the same age group in the general population. However, this was not possible for all age groups. In particular, serum samples for the over 60 year-old group were extremely difficult to obtain. Moreover, our samples came from hospitals and not from municipalities (e.g. schools). As only people coming to the clinic voluntarily were included in the study, people from hard to reach communities – with probably lower vaccination rates – were not investigated, making our study vulnerable to selection bias. Nevertheless, the study population consisted of healthy individuals, undergoing blood tests as a part of a routine check-up or to obtain health certificates. Finally, the lack of clear international standards for laboratory seroprevalence testing [24] made it extremely difficult to compare our serology results with those from other countries, in which the extent of vaccination coverage and booster vaccinations varies greatly.

Conclusion

In conclusion, Northern Greece seems to remain an intermediate susceptibility country for both mumps and measles. Although the prevalence of measles antibodies is clearly higher than that of mumps, the measles outbreak in 2005-2006 revealed that indigenous disease is still present. In certain age groups such as infants and young adults born in the 1970s and 1980s, protection rates against both diseases are low. As non-compliance with the second MMR dose seems to be one of the main causes of inadequate adolescent vaccination coverage and, consequently, of the low seroprevalence rates observed in this and other studies, special attention must be paid to strengthen the two-dose MMR vaccination programmes and to improve surveillance schemes. Concrete measures to be taken in order to improve the current situation and to make progress towards elimination targets include: sustaining routine immunisation services, providing supplementary immunisation activities for susceptible population subgroups, strengthening surveillance by rigorous case investigations and laboratory confirmation, and improving the availability of high-quality information for both health professionals and the general public on the benefits and risks associated with immunisation.

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Surveillance and outbreak reports

An increase in the number of mumps cases in the Czech Republic, 2005-2006

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The Czech Republic has had a two-dose measles, mumps and rubella (MMR) vaccination programme since 1987. The last outbreak of mumps was reported in 2002, but an increase in the number of mumps cases was observed in 2005, starting in October that year. We analysed routinely collected surveillance data from 1 January 2005 to 30 June 2006 to show the magnitude of the increase and describe the most affected groups in order to better target prevention and control strategies. In the 18-month period examined, 5,998 cases of mumps were notified, with a peak incidence in May 2006. No deaths were recorded, but 21% of cases were hospitalised. Incidence was lowest in the Plzeň region (1.9/100,000) and highest in Zlín (118.6/100,000). There were more male (61.8%) than female cases. The age of the cases ranged from 0 to 80 years. The highest incidence rate was observed in the age group of 15 to 19 years, in which 87% of cases had received two doses of mumps vaccine. The average age of unvaccinated cases was 22.9 years, while for cases vaccinated with two doses it was 14.5 years. Although vaccine effectiveness could not be calculated from the data available, possible reasons for highly-vaccinated cases occurring are discussed.

Introduction

Routine two-dose mass vaccination against measles, mumps and rubella (MMR) was introduced in the Czech Republic in 1987. The first dose is administered at 15 months of age, and the second dose is given six to 10 months later. Since 1984, the MMR vaccine used in the Czech Republic has been a Jeryl Lynn/genotype A vaccine TRIVIVAC produced by Sevapharma Inc. The mumps component produces antibody response in 70% in minimal titre 1:2 and 91% in titre 1:1 in haemagglutination-inhibition test (HIT). According to the manufacturer's information, after two doses given in a span of more than six months, the vaccine produced antibody in 100% subjects [1].

Mumps has been a notifiable disease in the Czech Republic since 1955. It was initially reported as aggregated number, then, as of 1982, as data aggregated by age groups (preschool, school children, youngsters and adults), and since 1993 as case-based data. Prior to the introduction of routine vaccination, disease incidence was highest in the 5-9 years age group [2]. In the last two decades, outbreaks of mumps occurred in 1995-6 (11,680 cases) and 2002-3 (1,501 cases). This paper presents the most recent outbreak in 2005-6 that was detected through routine surveillance.

Methods

The regional public health offices (Krajská hygienická stanice) notify individual cases of mumps in the Czech communicable disease notification system (Epidat) to the National Institute of Public Health (Státní zdravotní ustav). Epidat contains all laboratory-confirmed cases and cases that meet the clinical case definition with an epidemiological link to a laboratory-confirmed case [3]. The clinical case definition for mumps is a person with an illness of acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland, lasting two or more days without other apparent cause.

Epidemiological data of all notified cases of mumps in the Czech Republic reported between 1 January 2005 and 30 June 2006 were extracted and described in time, by region of notification, vaccination status, sex and age-group using Microsoft Excel. Cases were considered unvaccinated if they had no vaccination reported. Vaccinated cases were those who reported one or two doses of vaccination. In a small proportion of cases, the information about the number of doses or the vaccination status was not given. Reported complications included orchitis, meningitis, pancreatitis, encephalitis, and inflammation of the ovaries (oophoritis). Population data used for calculating incidence rates was prepared by the Czech Statistical Office (Český statistický úřad, http://www.czso.cz/csu) extrapolating forward each six months using birth, death, immigration and emigration figures available from the 2001 census. Vaccination coverage estimates for the entire population of the Czech Republic, not stratified by region for the period 1980-2006, were used as reported to World Health Organization [4,5].

The economic impact of mumps in the Czech Republic is potentially large, as persons with mumps are to be excluded from work for nine days (period of infectiousness being up to nine days after the onset of parotitis). We tried to estimate one important element of the economic impact of mumps by calculating the number of working days lost due to illness in people over the age of 19 years. We calculated the days (years) lost from work by multiplying the number of cases over 19 years by the number of days of exclusion from work. Complications were excluded from this calculation due to the variety in recovery time needed.

Results

Between 1 January 2005 and 30 June 2006, a total of 5,998 cases of mumps were notified in the Czech Republic (Figure 1). The numbers reported increased until mid-May 2006, when they started to slowly decrease. During weeks 1-30 of 2006, a total of 4,206 cases of mumps were notified; 2.8 times more in comparison with the same period in 2005 (1,456 cases). In the 18-month period studied, 1,209 cases of mumps (21.1%) were hospitalised, and no deaths were recorded.

Among the cases, 3,683 (61.8%) were males (Table 1). The age of cases ranged from 0 to 80 years (mean age was 17 years, median – 16 years). The highest incidence was in the age group 15-19 years.

Data on vaccination status were not available for 15 cases, and for a further 50 cases that had been vaccinated the number of doses was not specified (Figure 2). Over half of the cases had been vaccinated with two doses (4,187 cases, 69.8%). Their mean age was 14.5 years (median 15 years). Only 63 cases (1.0%) had been vaccinated with one dose. The unvaccinated cases were 1,683 (28.1%). The mean age of the unvaccinated cases was 22.9 years (median 21 years).

In the age group 15-19 years, in which most mumps cases occurred and the incidence was highest (230.1 per 100,000 per year), 87.1% of the cases were vaccinated. Incidence was also high in the 10-14 years age group (166.4 per 100,000 per year), born between 1992 and 1996, again a highly vaccinated population (99.6%). In addition to these highly vaccinated populations affected, the birth cohort born between 1981 and 1985 with low vaccination coverage had a quite high disease incidence of 101.8 cases per 100,000 per year.

In all, 910 cases developed complications (15.2%). Complications were more frequent among unvaccinated than vaccinated cases (32.3% versus 6.6%).

For cases vaccinated with one dose only the odds ratio (OR) for complications was 6.6 and for unvaccinated cases OR was 7.9 as compared to the fully vaccinated cases (Chi2 for trend=806; p for trend<0.00).

The most frequent complications were: orchitis in males (554 cases, 9.2% of all males), meningitis (166 cases, 2.8% of all cases), pancreatitis (121 cases, 2.0%) and encephalitis (16 cases, 0.3%). There were also three recorded cases of inflammation of the ovaries (oophoritis).

In the age group 25-34 years, the birth cohort with low vaccination coverage, 40.8% of the cases developed complications.

Regarding the geographical distribution of cases, the lowest incidence was reported in the Plzeň region (1.9 per 100,000) and the highest in the Zlín region (118.6 per 100,000) (Table 2, Figure 3).

In an attempt at estimating the economic impact of mumps, we calculated that 42 working years were lost as a direct result of the isolation of cases during this outbreak.

Table 1

Number of notified mumps cases and average annual incidence rates per 100,000 population, by age group and sex, Czech Republic, 1 January 2005 – 30 June 2006 (n=5,998)

Age group (years)	Number of cases			Incidence per 100,000/year		
	Male	Female	Total	Male	Female	Total
0	2	0	2	2.8	0.0	1.5
1 – 4	63	21	84	22.9	8.1	15.7
5 – 9	226	189	415	56.9	50.1	53.6
10 – 14	878	720	1,598	178.5	153.6	166.4
15 – 19	1,411	900	2,311	274.6	183.5	230.1
20 – 24	863	346	1,209	142.5	59.5	101.8
25 – 34	159	69	228	12.9	5.8	9.5
35 – 44	50	42	92	4.9	4.2	4.6
45 – 54	29	21	50	2.5	1.8	2.1
55 – 64	2	4	6	0.2	0.4	0.3
65 – 74	0	2	2	0.0	0.3	0.2
75 +	0	1	1	0.0	0.2	0.1
Total	**3,683**	**2,315**	**5,998**	**49.5**	**29.5**	**39.2**

Figure 1

Number of notified mumps cases, by week of notification, Czech Republic, 1 January 2005 – 30 June 2006 (n=5,998)

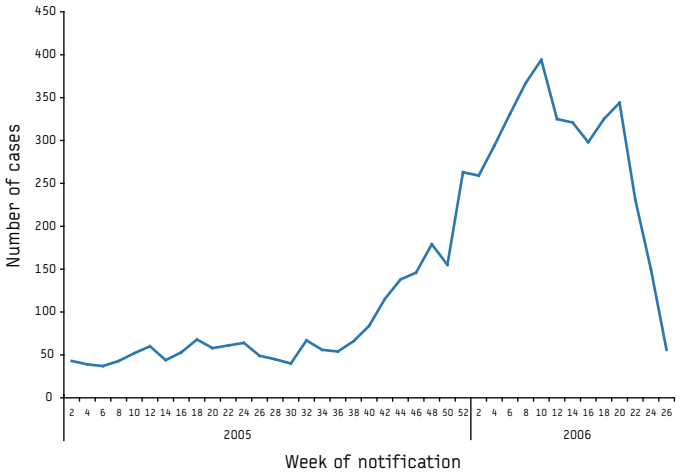
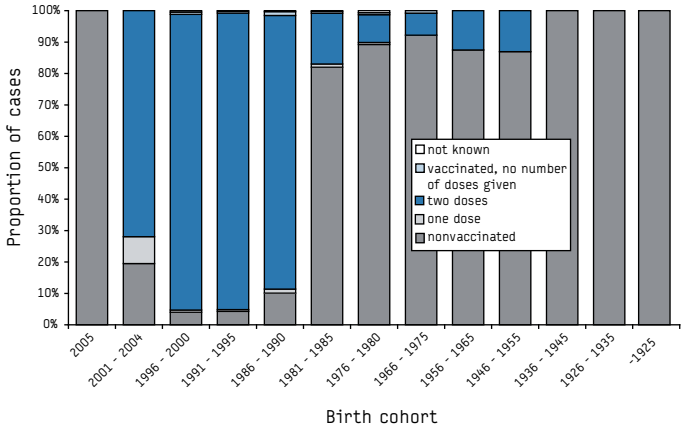


Figure 2

Mumps cases by birth cohort and vaccination status, Czech Republic, 1 January 2005 – 30 June 2006 (n=5,998)



Discussion

The outbreak described here began in late 2005 and continued until mid-2006. It was a regional outbreak that affected mostly the south-east of the Czech Republic. The outbreak affected mainly two different groups of people: a highly vaccinated birth cohort (1986 – 2004), and a birth cohort with low vaccination coverage (1971 – 1985), at considerable cost to the country.

We have described surveillance data alone; no analytical study was undertaken to examine the reasons for possible vaccination failure in the highly vaccinated birth cohorts that were affected. From the data available, we are unable to calculate the vaccine effectiveness.

The Czech Republic uses the live attenuated Jeryl Lynn strain of mumps virus for vaccination since the introduction of routine mumps vaccination. The strain is reported by the manufacturer to be highly safe and efficacious for vaccine use, and both more stable and immunogenic than alternative strain-based vaccines [1]. Though the reported data indicate high vaccine coverage achieved (97-100%), in a seroprevalence survey conducted in 2001, the prevalence of antibodies against mumps in age group 1-15 years (average 79%, range 70-86%) failed to correspond with declared mumps vaccination coverage rate of 97-100% [6]. The herd immunity induced is considered insufficient to prevent epidemics of mumps [7].

Formal epidemiologic studies are required to investigate whether there has been a reduction in vaccine effectiveness over time. It is possible that vaccine effectiveness is lower than expected amongst the highly vaccinated birth cohorts born between 1986 and 2004. We remain uncertain as to what caused the outbreak amongst the younger vaccinated cohorts (born 1996-2004). Further studies are required to investigate risk factors for vaccine failure, such as whether the type of vaccine used (monovalent, bivalent or trivalent) affected the occurrence of the outbreak, or if there may have been failures in the cold-chain during vaccination. For the older vaccinated cohort (born 1986-1995) a plausible explanation would be the waning immunity or vaccine failure, as was demonstrated elsewhere [8,9].

The two different reasons for low effectiveness may prompt different intervention strategies. If failure to seroconvert means that 14-30% of the population is susceptible to mumps, then using a vaccine after which more people seroconvert would be of protective value to the community. If it appears that immunity is waning in the older vaccinated cohort, then the benefits of adding a booster vaccination, offered to young adults, should be considered.

Of the unvaccinated cases born between 1971 and 1985, all were born too early to have received the vaccine, but may have been too young to have developed 'natural immunity' following exposure to circulating wild mumps virus [2]. Catch-up vaccination campaigns may be conducted to obtain an immunisation rate of 90%, the recommended population immunity required to interrupt transmission.

Epidemics are seen among the group with low vaccination coverage (born between 1981 and 1990) every four to five years. In 1995-6, 11,680 cases of mumps were reported, most of them amongst this birth cohort living in north east of the Czech Republic. The same cohort was also affected in 2002-3, this time in the south-east of the Czech Republic. Cross border movement through the Austrian and Polish frontiers could partly explain the uneven geographical distribution of the cases as vaccination coverage in these countries is considerably lower than in the Czech Republic. Austria reported less that 80% and Poland less than 40% vaccination coverage in 2003 and similar figures for previous years.

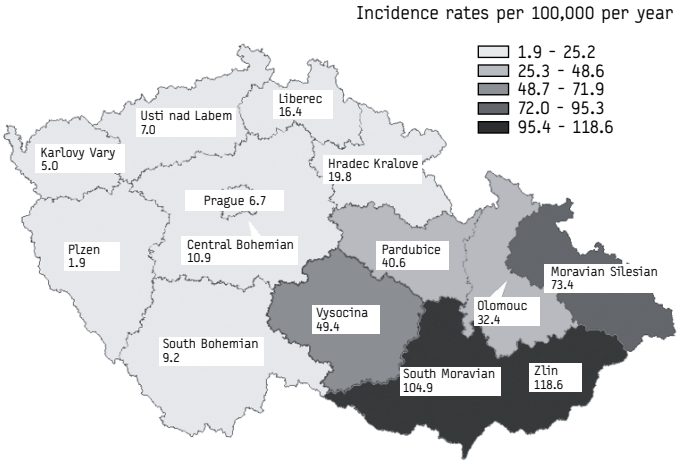
Table 2

Number of mumps cases and average annual incidence rates per 100,000 population, by region, Czech Republic, 1 January 2005 – 30 June 2006 (n=5,998)

Region (name in Czech, main town)	Incidence per 100,000 population/year	Number of cases
Prague, (Praha)	6.7	117
Central Bohemian (Stredocesky, Prague)	10.9	184
South Bohemian (Jihocesky, Ceske Budejovice)	9.2	86
Plzen (Plzensky, Plzen)	1.9	16
Karlovy Vary (Karlovarsky, Karlovy Vary)	5.0	23
Usti nad Labem (Ustecky, Usti nad Labem)	7.0	86
Liberec (Liberecky, Liberec)	16.4	105
Hradec Kralove (Kralovehradecky, Hradec Kralove)	19.8	163
Pardubice (Pardubicky, Pradubice)	40.6	309
Vysocina (Vysocina, Jihlava)	49.4	384
South Moravian (Jihomoravsky, Brno)	104.9	1,767
Olomouc (Olomoucky, Olomouc)	32.4	310
Zlin (Zlinsky, Zlin)	118.6	1,056
Moravian-Silesian (Moravskoslezsky, Ostrava)	73.4	1,392
Czech Republic	**39.2**	**5,998**

Figure 3

Average annual incidence rates of mumps per 100,000 population, by region, Czech Republic, 1 January 2005 – 30 June 2006



[5] Given the periodicity of outbreaks within this specific cohort, one recommendation is to conduct catch-up vaccinations for all of those within the cohort, throughout the country, regardless of vaccination status. Overall, a national intervention strategy that has multiple elements is required to decrease the rate of accumulation of susceptible people within the population.

Our estimation for the economic burden of this mumps outbreak is likely to be an underestimate, as it does not take into account the costs to the health service, or the societal costs within communities. Cases with complications were not included in our calculations, either. A more detailed economic study will inform policy makers of the burden of a mumps outbreak of this size. As the most affected cohort ages, the costs of productivity loss will continue to rise, hence a mass vaccination campaign within this cohort could save costs in the future.

As a result of this outbreak, a voluntary vaccination offer was advertised in the Moravian regions (east of the Czech Republic) and subsequently in the whole country. Males aged 15-25 years were targeted, to decrease the impact of complications, but were required to pay for the vaccination themselves. It is not known how many people responded to this campaign, so it is not possible to evaluate the effectiveness of this control measure. However, the number of cases reported to Epidat after the period described returned to the expected range, indicating that the outbreak had ended.

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Research articles

Transmission of the L-Zagreb mumps vaccine virus, Croatia, 2005-2008

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We report on three cases of symptomatic transmission of the L-Zagreb mumps vaccine virus from three vaccinated children to five adult contacts. The five contact cases were parents of the vaccinated children and presented with parotitis and in one case also with aseptic meningitis. The etiology of the contacts' illness was determined by viral culture, genomic sequencing, serology and epidemiological linking. Two of the vaccinated children developed vaccine associated parotitis as an adverse event three weeks following immunization. Symptoms in contact cases developed five to seven weeks after the vaccination of the children. The five contact cases, as well as the three children with adverse events recovered completely. The children had been vaccinated with MMR vaccine produced by the Institute of Immunology Zagreb, each of them with a different lot. One of the possible explanations for these adverse events is that the very low levels of wild mumps virus circulation in the last decade, combined with waning immunity in those who received one dose of vaccine or suffered from mumps in childhood, resulted in susceptible young adults and that this unique epidemiological situation allows us to detect horizontal transmission of mumps vaccine virus.

Introduction

Vaccination against mumps was introduced into the Croatian vaccination schedule in 1976 for all children at the age of 12 months [1]. In 1994, a second dose of mumps vaccine was added to the vaccination schedule for seven-year-old children [1]. Mumps vaccine is delivered as a trivalent measles – mumps – rubella (MMR) vaccine. The mumps component of the vaccine is prepared from the L-Zagreb vaccine strain. Since the introduction of the vaccine, vaccination coverage has constantly been higher than 90%, ranging from 93 to 98%, both for primary vaccination before the second birthday and for revaccination before the eighth birthday.

Due to high vaccination coverage, the incidence of mumps declined from over 10,000 cases to less than 100 cases annually (Figure). In 2007, only 77 cases of mumps were reported (incidence of 1.7 per 100,000). Mumps cases are subject to mandatory reporting on the basis of clinical suspicion, regardless of the laboratory confirmation.

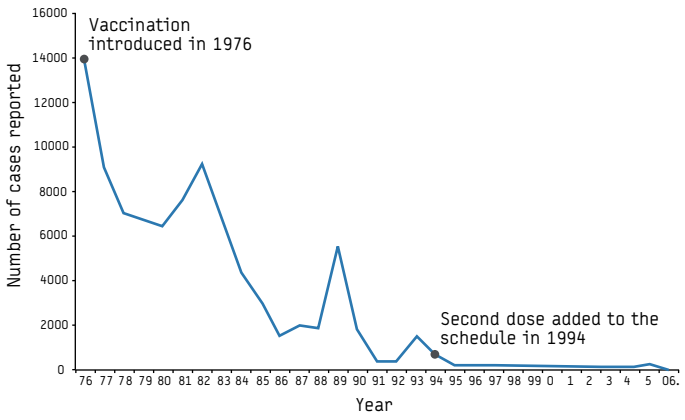
Reporting of adverse events following vaccination is mandatory, as is the vaccination itself. Since 1994, we have recorded annually 50 to 70 cases of vaccine-associated parotitis and five to 15 cases of vaccine-related aseptic meningitis in vaccine recipients. Over 80,000 doses of MMR vaccine are administered annually.

Deascription of cases

The first case was reported in October 2005 from Rijeka. A healthy 14-month-old boy was routinely vaccinated on in mid-September with MMR. Twenty-six days later, he developed unilateral, febrile parotitis. Routine laboratory investigation revealed elevated serum amylases. In late October, six weeks after the child had received the vaccine, his mother was hospitalised due to fever, unilateral parotitis and headache. Lumbar puncture revealed pleocytosis of the cerebrospinal fluid (CSF) and viral meningitis was suspected. By viral culture performed at the Croatian Institute Public Health, mumps virus was isolated on Vero cells from the CSF and confirmed by indirect immunofluorescent assay (IFA) (Light Diagnostics, Temecula, CA). The isolate was subsequently characterised by genomic sequencing and comparing the genome with the reference

Figure

Incidence of mumps in Croatia 1976-2006



sequences (GenBank NIH, Bethesda) performed at the Institute of Immunology Zagreb, as L-Zagreb vaccine strain.

The mother was born in the mid-1970s. According to her medical records, she was not vaccinated against mumps and does not have a history of parotitis. There are no other family members living in the same household. Both mother and child recovered completely. During the last trimester of 2005, there have been no reports of mumps from the Rijeka region.

The second case was reported in October 2007 in Zagreb. A healthy 17-month-old girl was routinely vaccinated in late August. Three weeks later, she had an episode of fever and cough, which was not considered related to vaccination. She had a white blood cell count performed at that time, which revealed leukopenia with relative lymphocytosis. Six weeks after vaccination, the child's mother developed bilateral febrile parotitis, and four days after that the father also developed bilateral parotitis. Sera of the parents, collected three days later, were tested by ELISA for cytomegalovirus (CMV) antibodies and IFA for mumps virus antibodies (Viro-immun) and Epstein-Barr virus (EBV) antibodies. Both parents were IgG positive and IgM negative for CMV and EBV antibodies. The father was IgM and IgG positive, while the mother was low IgM positive and IgG positive for mumps virus antibodies.

The isolation of mumps virus on Vero cells from urine specimens and salivary duct swabs of both parents was attempted at the Croatian Institute Public Health. Mumps virus was only isolated from the mother's salivary gland duct swab, and confirmed by IFA (Light Diagnostics, Temecula, CA). The isolate was subsequently characterised, by genomic sequencing and comparing the genome with the reference sequences (GenBank NIH, Bethesda) performed at the Institute of Immunology Zagreb, as L-Zagreb vaccine strain.

The mother, born in 1970, received all routine childhood vaccinations according to her mother's statement, but no evidence of vaccination was found in medical records. The father, also born in the mid-1970s, had mumps as a child according to his mother's statement, but no medical documentation was found to support that either. There were no other family members living in the same household. Both parents recovered completely. During September and October 2007, mumps activity was very low in Zagreb and its surroundings, with only two cases reported, both geographically distant from the residence of this family.

The third case was reported in January 2008 in Zupanja. A healthy 15-month-old boy was routinely vaccinated in mid-December 2007. Sixteen days later, he developed unilateral, febrile parotitis. No laboratory testing was performed. On 15 January, the mother developed bilateral, painless, afebrile parotitis and three days later, the father developed unilateral afebrile parotitis. Sera of both parents was collected four days after that, and tested by IFA for mumps virus (Vero-immun) antibodies. Both parents were IgG positive and IgM negative for mumps virus antibodies.

The isolation of the mumps virus on Vero cells from urine specimens and salivary duct swabs of the father was performed at the Croatian Institute of Public Health. The mumps virus was isolated from his salivary gland duct swab and confirmed by IFA (Light Diagnostics, Temecula, CA). The isolate was subsequently characterised by genomic sequencing and comparing the genome with the reference sequences (GenBank NIH, Bethesda) performed at the Institute of Immunology Zagreb, as L-Zagreb vaccine strain.

The RT-PCR for mumps virus performed on the father's urine specimen was negative, while the RT-PCR testing of the father's salivary gland duct swab was positive for mumps virus RNA.

There is no information on the vaccination and medical history of the parents.

A three-year old brother of the vaccinated child lives in the same household. He was vaccinated with MMR at the age of one year and was healthy throughout the period between December 2007 and February 2008.

During January and February, there have not been any reports of mumps from Zupanja region. Genetic characterization of the three isolates described above was performed by the sequence analysis of the most variable gene of the mumps virus, small hydrophobic gene, and comparing the nucleotide sequence with the reference sequences (GenBank NIH, Bethesda) as described previously [2,3].

Discussion

We demonstrated horizontal transmission of the L-Zagreb mumps vaccine virus, which resulted in symptomatic illness in contacts.

For three of the five parents who developed parotitis, there is direct evidence of the vaccine strain recovered from the contact cases, confirmed by genomic sequencing of the isolated virus. In the two symptomatic parents without isolation of the mumps virus, the incubation period and the fact that there are no mumps cases in the region are in favour of a causal relationship between the child's vaccination and the parents' parotitis.

Although it is well known that some live attenuated vaccine strains can be transmitted to contacts, e.g. oral polio, varicella-zoster, there are only few reports of transmission of mumps vaccine viruses to contacts [4,5,6]. Searching the literature, we found only two published papers describing horizontal transmission of a mumps vaccine virus, apart from our own report two years ago [6]. Sawada and colleagues demonstrated the asymptomatic horizontal transmission of the Urabe strain [4], while Atrasheuskaya and colleagues demonstrated the symptomatic transmission of the Leningrad-3 mumps vaccine strain [5].

We are exploring possible explanations for the three events reported in this communication. The three cases we described do not represent a cluster, since they occurred in different geographical areas, there is no clustering in time and three separate vaccine lots are involved. Therefore, a mistake in the production of a vaccine lot can be ruled out as an explanation for these events. However, we can not rule out a de-attenuation of the vaccine virus that has been propagated to several lots. The unchanged incidence of other adverse events caused by this vaccine virus (vaccine associated parotitis and aseptic meningitis) does not suggest a general de-attenuation.

It would be useful to know if the rates at which the parents contract disease after having contact with their vaccinated children are increasing, since this would point towards a de-attenuation of the vaccine.

We do not currently have a sufficient number of reports to determine if the described cases represent a rise in incidence. Careful surveillance of adverse events following immunisation will soon provide an answer to this question. Following acknowledgement of the described cases, a letter was sent to all vaccine providers in the country informing them of the possibility of transmission of the vaccine virus to contacts, resulting in illness.

We believe that these events are a consequence of a change in population susceptibility rather than in the properties of the vaccine virus. Our hypothesis is that a horizontal transmission of the mumps vaccine virus has always been occurring at very low rates, but we were not able to detect it.

Owing to the fact that we have a very favourable epidemiological situation with very low levels of wild mumps virus circulation in the population in the last decade, adolescents and young adults who were vaccinated only once are susceptible to mumps because of waning immunity and the lack of natural boosters that natural infection provides. This gives rise to the accumulation of susceptible young adults. Schmid et al. recently reported on a mumps outbreak in Austria and were able to show that 68 of their patients were vaccinated only once [7].

The occurrence of adverse effects requires a critical re-evaluation of the appropriateness of the use of the L-Zagreb strain as a vaccine strain for MMR vaccination in countries with a low level of wild mumps virus transmission. The risk of vaccine side-effects is the leading argument of groups opposing MMR vaccination. It is therefore important to inform the public about the relative safety of the vaccine and of possible complications of mumps, namely meningitis, orchitis and pancreatitis.

In countries with higher levels of wild mumps virus transmission and occasional outbreaks young adults' immunity is boosted through contact with the wild virus. Therefore, in such settings waning immunity following one dose of mumps vaccine can not be demonstrated and, thanks to natural booster, it does not lead to accumulation of susceptible young adults.

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Rapid communications

Measles is still a cause for concern in Europe

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EUVAC.NET is a European Union surveillance network for vaccine-preventable diseases and receives funding from the European Commission (Health and Consumer Protestion Directorate General, DG SANCO) under grant agreement no. 2004205.

Despite efforts to eliminate measles in Europe [1] outbreaks still continue unabated and even cause deaths. In 2006 and 2007 several countries have reported high numbers of cases and outbreaks. The larger outbreaks such as those described in Switzerland [2], Germany [3,4] and Spain [5] mostly involved the general population. Other outbreaks were described primarily affecting particular groups such as the travellers' communities in the United Kingdom [6,7] and Norway [8], Roma and Sinti populations in Italy [9], Roma and immigrant families in Greece [10] and orthodox Jewish communities in Belgium [11] and the UK [7,12]. The groups in the UK are known to historically have low vaccine uptake [13].

Based on preliminary data for 2007 from 31 European countries (Table 1) reporting to EUVAC.NET, a total of 3,826 measles cases was registered. The highest reported indigenous incidence of measles was reported from Switzerland followed by the UK with

Table 1

Reported incidence rates of indigenous measles cases per 100,000 inhabitants by country, 2007*

High incidence (>1.0)	
Ireland (1.62)	United Kingdom (1.64)
Romania (1.62)**	Switzerland (14.06)
Moderate incidence (0.1-1.0)	
Belgium (0.50)	Malta (0.49)
Germany (0.67)	Poland (0.11)
Italy (0.59)	Spain (0.61)
Low incidence (< 0.1)	
Austria (0.04)	Greece (0.02)
Czech Republic (0.01)	The Netherlands (0.04)
Estonia (0.08)	Norway (0.02)
France (0.05)	Sweden (0.01)
No indigenous cases	
Bulgaria (0)	Latvia (0)
Croatia (0)	Lithuania (0)
Cyprus (0)	Luxembourg (0)
Denmark (0)	Portugal (0)
Finland (0)	Slovakia (0)
Hungary (0)	Slovenia (0)
Iceland (0)	

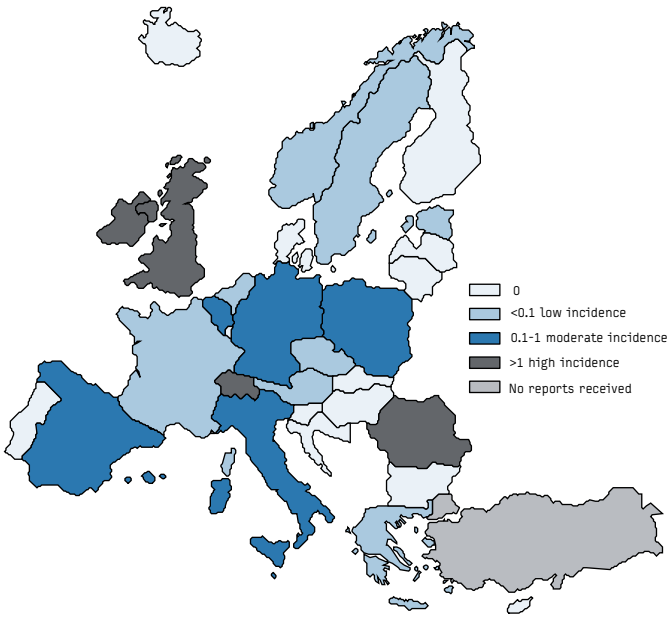
*EUVAC.NET preliminary data. All clinical, laboratory-confirmed or epidemiologically linked cases meeting the requirements for national surveillance were included in this table. The proportion of laboratory-confirmed cases varies in different countries.

** For Romania the crude incidence is quoted in this table as data on importation status of cases was not included in the dataset provided.

Note: To date, no reports were received from Turkey.

Figure

Incidence categories of reported indigenous measles cases per 100,000 inhabitants by country, 2007*



* EUVAC.NET preliminary data. All clinical, laboratory-confirmed or epidemiologically linked cases meeting the requirements for national surveillance were included. The proportion of laboratory-confirmed cases varies in different countries.
Note: For Romania the crude incidence is represented in this figure as data on importation status of cases was not included in the dataset provided. To date, no reports were received from Turkey.

14.06 and 1.64 per 100,000 inhabitants respectively. Thirteen countries reported no indigenous cases (Table 1 and Figure).

As expected, the majority of measles cases were unvaccinated (87%) where vaccination status was known (92%). Although no deaths have yet been reported for 2007 cases, four countries reported 19 deaths for 2005-2006 cases (Table 2), 15 of which (80%) were in children under 5 years of age. Pneumonitis was the established cause of death in 13 cases and acute encephalitis in four cases. In the remaining two cases the cause was unknown or not reported. Overall, for the period 2005-2007, acute encephalitis was reported in 21 cases and distributed in the following age-groups: <1 year (14%); 1-14 years (38%); 15-19 years (19%) and ≥20 years (29%). It was the cause of four deaths mentioned above. In 2007, of the 97% with a known hospitalisation status, 859 cases were hospitalised (23%).

Despite a 53% drop in the number of reported measles cases compared with the previous year for the same 31 countries, the high incidence rates in some countries still cause concern and threaten the success of measles elimination in the region. The World Health Organization Regional Office for Europe reported that in 2007 the majority (60%) of measles cases in the WHO European Region occurred in Western Europe countries [14]. To achieve the goal of eliminating measles in Europe by 2010, greater political will and commitment in these countries are necessary to improve policies that aim to better target susceptible individuals with measles vaccination programmes in both the general population and particular risk groups. These programmes should aim at a minimum of 95% vaccination coverage with two doses of the combined measles-mumps-rubella vaccine (MMR). Such activities will have to be supported by information campaigns highlighting the importance and benefits of the MMR vaccine. Additionally, all suspected measles cases need to be investigated thoroughly to identify transmission patterns thereby enabling better contact tracing and ensuring swift control to limit the spread of the disease.

Table 2

Number of reported measles-related deaths and measles cases by country, 2005-2006*

Country	2005		2006	
	Number of measles-related deaths *(n=13)*	Number of reported measles cases	Number of measles-related deaths *(n=6)*	Number of reported measles cases
Germany	1	778	2	2,307
Romania	11	5,647	3	3,196
Turkey	1	6,206	0	34**
United Kingdom	0	78	1	773

* Only countries reporting fatal cases of measles were included in this table.

** For Turkey, 2006 data consisted of laboratory-confirmed cases only.

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Rapid communications

An ongoing multi-state outbreak of measles linked to non-immune anthroposophic communities in Austria, Germany, and Norway, March-April 2008

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From the second week of March 2008, public health authorities in the province of Salzburg observed an increased number of measles cases compared to previous years. Twenty cases of measles had been were notified Austria-wide in 2007, 24 in 2006, 10 in 2005, and 14 in 2004.

The current outbreak has affected, as of 14 April, 202 people in Austria, 53 in Germany, and four in Norway, bringing the total number of cases related to this outbreak to 259. The initial case series investigation revealed that the common link was attendance of an anthroposophic school and day care centre in Salzburg city. The majority of the pupils were not vaccinated against measles.

An outbreak case was defined as a person who

a) became ill with measles after 1 March, fulfilling the clinical criteria of measles regardless of laboratory confirmation, and
b) was epidemiologically linked to Salzburg city in the period 7 to 18 days prior to clinical onset.

Outbreak investigation

As of 14 April, 183 cases of measles restricted to four public health districts in the province Salzburg, 16 cases from the neighboring province Upper Austria, and one case each in the Austrian provinces Tyrol, Vorarlberg and Vienna fulfilled the preliminary outbreak case definition. In addition, 50 outbreak cases, most of them with residence in Bavaria, three cases of measles in the state Baden-Württemberg in Germany, and four outbreak cases resident in Norway were identified.

Figure 1 illustrates the epidemic curve by onset of rash of 256 notified cases for whom data on clinical onset were available. In 78.5% (201) of these cases a link to the particular school and day care centre in Salzburg city has been identified so far. Questioning of the cases is still ongoing. Figure 2 summarises age and sex distribution of 259 cases.

Since the third week of March 2008, the Austrian health authority has put in place a range of outbreak control measures:

- raising awareness in the overall population and encouraging measles, mumps, rubella (MMR) vaccine uptake, supported by proactive media releases;
- dissemination of information to schools and nurseries;

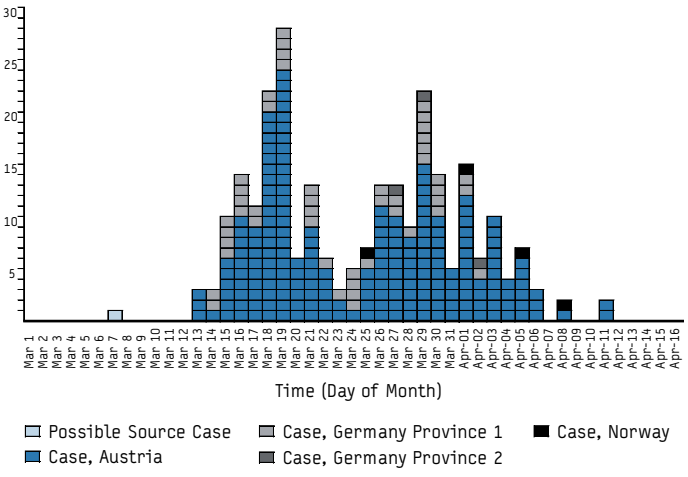
Figure 1

Outbreak cases with date of onset of rash available (N_{total}= 256).

$Cases_{Austria}$: N=202;

$Cases_{Germany}$: N=47 in German province I and N=3 in German province II;

$Cases_{Norway}$: N=4; and the possible source case by date of onset of rash



- closure of the particular school and day care centre for one week;
- post-exposure prophylaxis for contact persons if appropriate;
- control of vaccination documents in all persons of the affected institution;
- access restriction to school for all persons with unclear immune status;
- closure of the particular school and day care centre for one week;
- after re-opening of the anthroposophic school, access restriction for pupils other than those vaccinated at least once and those with serologically documented previous infection;
- offering MMR vaccination free of charge to the population younger than 15 years;
- and alerting health professionals.

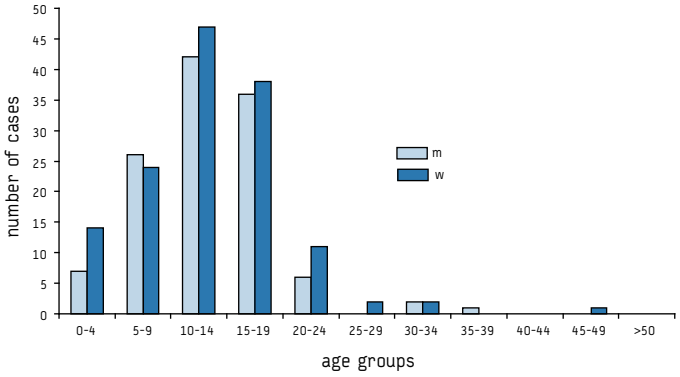
Preliminary results of the outbreak investigation indicate the possible source case – a student from an anthroposophic school in Switzerland who visited the anthroposophic school in Salzburg city with colleagues. That student became ill with measles during their stay in Salzburg on 7 March, a week prior to the primary outbreak case in the anthroposophic school in Salzburg (13 March). Since November 2006, Switzerland is experiencing the largest measles outbreak registered in the country since notification for this disease in 1999 [1].

Conclusions

Recently, ultra-orthodox Jewish communities and travelling communities have been implicated in outbreak of measles [2,3]. The outbreak described here indicates that the anthroposophic community also is an at-risk group of measles spread, because many parents in this group choose not to vaccinate their children with the MMR vaccine [4]. Anthroposophy, based on the writings of the mystic and social philosopher Rudolf Steiner (1861-1925), combines human development with an investigation of the divine spark found in all of nature. The movement has marked education (Waldorf/Steiner schools) and medicine. Anthroposophical doctors emphasise nature-based therapies that support the body's innate healing wisdom. Antibiotics, fever-reducing agents, and vaccinations are used at one's own discretion only [5].

Figure 2

Age and sex distribution in 259 notified measles cases, Austria, March/April 2008



Although measles has been eliminated or is under control in several EU countries, it is still a public health priority [6]. Organisers of large-scale events attended by international travellers, especially youths, should consider documentation of adequate participant vaccination [7]. In view of the current measles outbreak, Austrian and Swiss authorities advise measles vaccination before travelling to the EURO 2008 soccer games, starting on 7 June, 2008 in Austria and Switzerland.

The current multi-state outbreak of measles once again highlights the need to improve the vaccination coverage in Austria, along with disease surveillance and outbreak-control capabilities [8]. Diligent case investigation of every single measles case is a prerequisite to achieve the goal of measles eradication by 2010, planned by the World Health Organization European Office [9].

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Rapid communications

An outbreak of measles including nosocomial transmission in Apulia, south-east Italy, January-March 2008 - a preliminary report

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Between 7 January and 16 March 2008, 16 cases of measles were reported in the region of Apulia in south-eastern Italy (about four millions inhabitants). This outbreak is currently ongoing: we present here a preliminary report.

A case of measles was defined as one that met the clinical case definition (clinical picture compatible with measles, i.e. a generalised rash lasting more than three days and a temperature >38.0°C, with one or more of the following symptoms: cough, coryza, Koplik's spots, conjunctivitis [1].

A confirmed case of measles was defined either as a case that was laboratory-confirmed (by detection of IgM antibodies against measles virus or a positive PCR), or as a case that met the clinical case definition and was epidemiologically linked to a laboratory-confirmed case [2].

Outbreak description

As of 13 April, 16 cases – two adults and 14 children – have been reported; all cases were laboratory confirmed (Figure 1).

Eight cases were not related to a defined cluster. The first reported case was a nine-year-old child who presented with fever (>38.0 °C), coryza and cough and was hospitalised on 7 January. On 10 January, the patient developed a rash. The source of infection remains unknown (the child had not travelled outside their hometown, had any contact with a measles case or any visitors from abroad in the 7 to 18 days before onset of the rash).

The following seven non-cluster cases were reported between 5 February and 19 March: two 11-month-old children, a 17-month-

Figure 1

Distribution of measles cases by age group (N=16). Apulia, January–March 2008

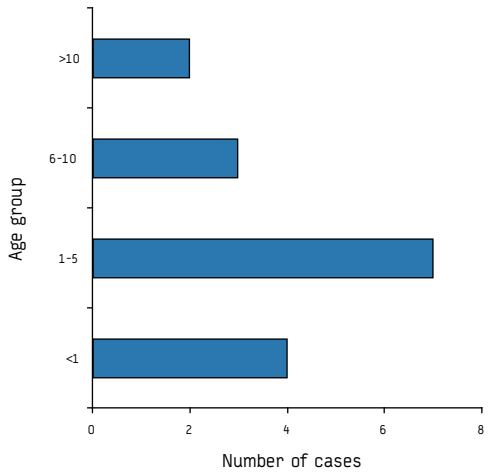
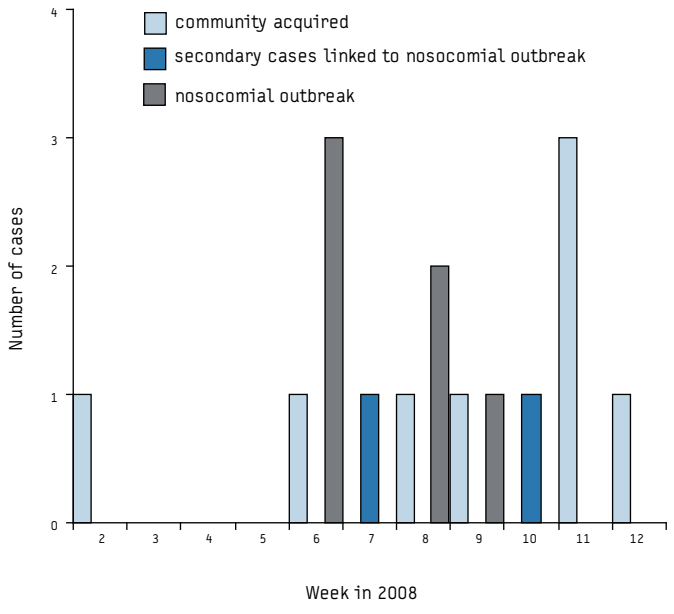


Figure 2

Reported measles cases by week of rash onset and transmission setting (N=16). Apulia, January–March 2008



old child, three children aged between four and nine years and two adults aged 22 and 33 years. Six of them were hospitalised.

Other eight cases were related to a nosocomial outbreak. The first reported case was a five-year-old child who presented with fever (>38.0 °C) and conjunctivitis and was hospitalised on 30 January. On 4 February, the patient developed a rash. The source of infection remains unknown. Further five cases had been in-patients in the same hospital in the Infectious Disease Ward in the seven to 15 days before the onset of the rash, where they had had contact with a measles case. The mean age of nosocomial outbreak cases was four years. Two cases regarded two children younger than 13 months, which is the age established by the Regional Vaccination Schedule for the first dose of the measles, mumps, rubella vaccine MMR. All the cases were hospitalised for measles. Two more cases were relatives of children involved in the nosocomial outbreak:

- a seven-year-old child, a sibling of the nosocomial outbreak index case, who presented with fever (>38.0 °C) and conjunctivitis on 12 February and developed a rash on 15 February;
- a 12-year-old child, a cousin of a 15-month-old child infected with measles in the Infectious Disease Ward of Paediatric Hospital "Giovanni XXIII" in Bari. The case presented with fever (>38.0 °C) and conjunctivitis on 1 March and developed a rash on 5 March.

Neither of the two was hospitalised (Figure 2). The mean age of all the cases notified in Apulia Region during this period was eight years. Three cases regarded three children younger than 13 months. None of the 16 affected patients had ever been vaccinated against measles.

Laboratory results

Thirteen cases were laboratory-confirmed by the regional reference laboratory in Bari (Unità Operativa Igiene Policlinico Bari). Measles virus detection was performed by a nested RT-PCR. The 456-ntsegment of the nucleoprotein (N) gene of these measles virus strains was used for genotyping according to the standardised recommendation of the World Health Organisation. The N gene sequences of the viruses from the outbreak were identical, and belonged to genotype D4.

The other three cases were confirmed by detection of IgM antibodies against measles virus.

Control measures

In response to the outbreak, active surveillance was set up. All susceptible contacts and all susceptible children between two and 10 years of age were vaccinated with a first dose of MMR if previously unvaccinated, or with a second dose if they had already received one dose.

An extensive catch-up vaccination campaign was conducted in order to immunise susceptible children with the combined measles-mumps-rubella (MMR) vaccine as soon as possible.

Discussion

This is the second important outbreak of measles in Apulia since the launch of the national plan for the elimination of measles and congenital rubella [3]. The previous cluster was reported in November 2006-January 2007 when 18 cases of measles belonging to genotype B3 were notified [4].

In the cluster described here, D4 genotype has been identified, which is implicated in several major outbreaks in Europe (Romania, United Kingdom, Spain and Germany) [5,6].

There was a nosocomial outbreak: epidemiological investigation showed that isolation guidelines for measles were not respected and that some children affected with measles and some susceptible children mixed in common areas.

Although nosocomial transmission of measles is well documented [7,8], higher awareness among health professionals of measles diagnosis, appropriate infection control practices to prevent transmission in hospital settings and specific vaccination recommendations for health professionals is needed.

This cluster underlines the need to achieve higher vaccine coverage among children, teenagers and young adults. In 2006, the coverage rate for the first dose of MMR in the 2004 birth cohort was only 88.3% in Apulia Region. Therefore, the target MMR coverage for the WHO European Region (> 95% for both doses) has not yet been reached.

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Rapid communications

A cluster of rubella in Malta, December 2007 - January 2008

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A cluster of rubella has been identified by the Infectious Disease Prevention and Control Unit (IDCU) of Malta in the beginning of January 2008. Two men and a woman aged between 23 and 28 years were affected. The index case had onset of illness on 23 December 2007. The second case had onset of rash on 3 January and the third case displayed symptoms on 6 January 2008. Two of the three cases were laboratory-confirmed (IgM positive), the third displayed typical symptoms and was a close contact of a laboratory-confirmed case but was IgM and IgG negative. None of the affected patients had received vaccination against rubella and there was no history of recent travel abroad. All three cases were linked through a work place. Blood samples were submitted to the World Health Organization (WHO) Regional Reference Laboratory for Measles and Rubella, Luxembourg, for further investigations. None of the cases had any complications. To date no further cases have been identified.

Background

Rubella was declared a notifiable infectious disease in 1978 [1]. During the last thirty years there have been two major outbreaks of rubella in Malta. The first took place in 1985-86, at a time when rubella vaccination was only recommended to young girls, and involved 3,735 persons over two years. The second outbreak occurred in 1995, involved 416 persons, and followed a period when there had been interruptions in the availability of the combined measles, mumps and rubella vaccine (MMR). The last case of congenital rubella syndrome was also reported during that year. Since then rubella has become uncommon. In the period 2002-2006, a total of 13 cases were reported to IDCU (Figure) with ages ranging between 10 months and 62 years (mean 17 years). A third of the cases were female.

Rubella vaccination was introduced in the national vaccination schedule (free of charge) in 1982 [2] and was initially offered to girls aged 11 to 13 years. In 1990, the MMR vaccine was introduced and vaccination was extended to all children at 15 months. In 1991, a second dose of MMR was recommended to children aged 11-12 years. In 2005, the age for the second dose of MMR was reduced to 8-9 years.

Control measures

To control the recent rubella cluster, the health authorities have recommended vaccination against rubella to the cases' work and family contacts if they were not previously vaccinated. In addition, IDCU set up an outbreak control team with the aim of enhancing the surveillance of rubella. This involved informing health-care practitioners about the outbreak to heighten the level of suspicion for any further cases and to report suspected cases of rubella and congenital rubella syndrome for further investigations. Press releases and media interviews served to raise public awareness of the importance of vaccination particularly for women of child-bearing age who were offered vaccination free of charge. The cluster was notified in the forum website of the European Union network for surveillance of vaccine-preventable diseases (EUVAC.NET).

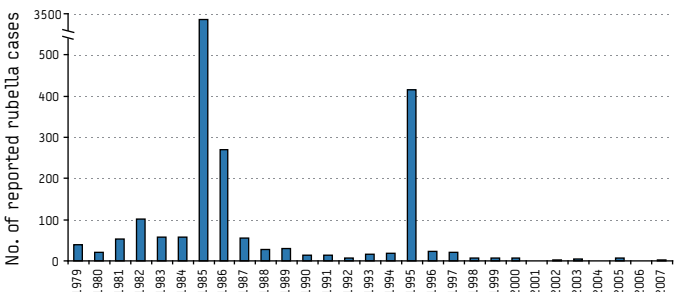
Discussion

This cluster, although small, shows that pools of individuals susceptible to rubella infection still exist in Malta. This should raise awareness of the potential for serious complications to the unborn child, particularly since one female of child-bearing age was affected. The age distribution of the cases in this cluster shows the vulnerability of unvaccinated adults without a history of the disease.

With the current high estimated vaccination coverage rates for the first MMR dose at around 94%, rubella in children is unlikely to occur. However, uninfected individuals who were not vaccinated within the framework of the national immunisation programme in place since the 1980's, either because they were not eligible or because they defaulted, are still susceptible. Indeed, the available data from the late 1980s and early 1990s show levels of vaccine

Figure

Number of reported cases of rubella, Malta, 1979–2007



coverage varying between 20% and 50% for vaccination at 15 months of age and around 70% for school-based vaccination at 11-13 years. These are probably gross underestimates, however, as 4.4% of persons aged 15-39 were seronegative for rubella antibodies according to a study carried out between 1996 and 2004 [3].

The short chain of transmission of the observed rubella cases indicates that the interruption of rubella virus transmission in Malta is being maintained. Currently, the recommended age for vaccination with the first dose of MMR vaccine is at 15 months and with the second dose at 8-9 years of age.

Since rubella, together with measles, is targeted for elimination in the WHO European region [4], every effort is being made to maintain high vaccination coverage with MMR and to enhance surveillance to ensure the interruption of local transmission of these diseases.

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Perspectives

HARMONY – The International Union of Microbiology Societies' European Staphylococcal Typing Network

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2. Sixteen HARMONY participating laboratories (listed in Table 1)

Introduction

The HARMONY typing network was part of the European Union (EU) Directorate General XII (now the Directorate-General for Research) funded project "Harmonisation of Antibiotic Resistance measurement, Methods of typing Organisms and ways of using these and other tools to increase the effectiveness of Nosocomial Infection control", awarded in 1999. Other aspects of the project comprised the exploration of the feasibility of developing a consensual approach to infection control guidelines, examining the issues of antimicrobial susceptibility standardisation and developing a tool to facilitate the establishment of effective antibiotic stewardship [1,2].

Many of the typing group participants were also members of the International Union of Microbiology Societies' (IUMS) Staphylococcal Sub-Committee. This was established in the 1970s to ensure that phage typing was standardised globally and to provide propagating phages for phage-typing [3]. Over time phage-typing had become less useful for some strains of methicillin-resistant and, indeed, methicillin-sensitive, *Staphylococcus aureus* (MRSA and MSSA), as they had become non phage-typable [3]. The IUMS Staphylococcal Sub-Committee now included reference laboratories and centres of staphylococcal research excellence with interests in typing staphylococci by molecular techniques which were more effective than phage for typing some staphylococci. When we started the HARMONY project, it was at a time of tremendous advances in molecular typing methods and we thus added new techniques to the HARMONY assessment process as these became relevant and practical propositions. There were also other aims such as, for example, agreeing criteria for referral of isolates to a typing laboratory and an approach to the nomenclature of MRSA strains.

Criteria for referral of isolates to a typing laboratory

When the project started, only two centres had such criteria. These were important in ensuring that typing was being used optimally to investigate suspected outbreaks or emerging new virulent strains or strains resistant to new or multiple antimicrobials. It would also enable comparison of workloads in centres within and between countries. There was thus much interest in developing a consensus regarding such criteria. One of the centres (England) had been particularly successful in reducing MRSA referrals from ca. 48,000/year to ca.12,000/year between 1995 and 2000, and these were therefore the criteria that the group considered [4]. Table 2 shows the final set of criteria that were agreed upon. There were certain caveats to this. Firstly, they were developed before the emergence of community-acquired MRSA (CA-MRSA) in some EU countries and would therefore need to be adapted to ensure that customers were aware of the characteristics of Panton-Valentine leukocidin (PVL) related MSSA and MRSA syndromes [5]. The English laboratory has used separate information forms for toxin-related disease for many years and these have been modified to take into account PVL-positive strains since the project was completed.

Secondly, some countries with a non-endemic MRSA situation requested referral of all individual patient isolates of MRSA to their centre (even those just colonising patients or staff). One centre requested all bacteraemia *S. aureus* isolates be sent to it where results were used for national surveillance purposes. Several centres, of course, also received referrals from their European Antimicrobial Resistance Surveillance participating hospitals and one of these centres also typed these [6]. The existence of such criteria does not mean that they are being implemented correctly and the group emphasised the importance of reviewing and perhaps auditing these criteria regularly. For example, when the criteria were audited in 1998 in England and Wales [4], although the infection control team usually wrote the referral policy and reviewed the results, there were many variations, and often junior or non infection control personnel were involved in making the decisions on referring isolates. If a member of the infection control team was involved, the laboratory was statistically significantly more able to describe the numbers of isolates sent and to reduce these. Those sending less than 150 isolates in a year were also significantly more accurate in estimating what had been sent and less likely to send unnecessary multiple isolates.

Harmonisation of MRSA typing

Initially, all the HARMONY participating centres were using pulsed-field gel electrophoresis (PFGE) to type MSSA and MRSA. The network collected together, for the first time in the EU, important or epidemic MRSA strains. In-house protocols from 10 laboratories in eight European countries were compared by each centre with an agreed "gold standard" PFGE protocol in which many of the parameters had been standardised [7]. Isolates were later added from other countries (Ireland, Scotland, Slovenia, Poland and Portugal).

Table 1

HARMONY International Union of Microbiology Societies (IUMS) typing laboratory network participants

Participants	Organisation	Country
G. Coombs (Resistotyping lead)	Royal Perth Hospital, Perth	Australia
M. Struelens, A. Deplano R. de Ryck	Hôpital Erasme - Centre for Molecular Diagnostic (CMD), Brussels	Belgium
R. Skov, V. Fussing (to 2002)	Statens Serum Institut, Copenhagen	Denmark
B. Cookson (Co-Ordinator), A. Lynch, S. Murchan, P. Kaufmann	Laboratory of Healthcare Associated Infection, Health Protection Agency, London	England
S. Salmenlinna, J. Vuopio-Varkila (Ribotyping lead)	National Public Health Institute, Department of Bacteriology, Helsinki	Finland
N. El Solh (deceased)	Institute Pasteur, Paris	France
W. Witte, C. Cuny	Robert Koch Institute, Wernigerode Branch, Wernigerode	Germany
P.T. Tassios, N.J. Legakis	National and Kapodistrian University of Athens, Athens	Greece
A. Rossney , B. O'Connell	National MRSA Reference Laboratory, St James's Hospital, Dublin	Ireland
W. Hryniewicz	National Medicines Institute, Warsaw	Poland
D. Morrison	Microbiology Department, Stobhill Hospital, Glasgow	Scotland
M. Mueller-Premru	University of Ljubljana, Medical Faculty, Ljubljana	Slovenia
J. Garaizar	Dept. Immunol., Microbiol. y Parasitol., F. Farmacia, UPV/EHU, Vitoria-Gasteiz	Spain
A. Vindel	Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid	Spain
S. Hæggman, B. Olsson-Liljequist	Swedish Institute for Infectious Disease Control, Solna,	Sweden
A. van Belkum W. van Leeuwen (Binary typing lead)	Erasmus MC, Center, Rotterdam	The Netherlands

Table 2

Criteria for referral of isolates to a typing laboratory

Introductory statement To enable us to maintain our current low turn round times and improve the quality of the service, please:
1) Request typing only if you intend to act upon the results.
2) Ensure that the Consultant Microbiologist and/or Infection Control Team have confirmed there are good reasons for submission.
3) For all requests, state hypothesis to be tested, i.e. how typing will make a difference.
4) If in any doubt contact us and ask.
5) In outbreaks ("a temporal and spatial cluster above the normal baseline") please send the minimum number of isolates needed to inform local practice (this should rarely be more than half), and store temporally related isolates.
6) Give priority to isolates that cause invasive or serious infection during the course of an outbreak, but avoid sending multiple isolates from **single patients** or environmental isolates, without discussion with us.
7) Wherever possible, use surrogate markers such as biochemical tests e.g. urease and antimicrobial resistances and include representative isolates with significantly different phenotypes e.g. in antibiotic susceptibilities, pigmentation and/or haemolysis.
8) In endemic situations ("where a hospital is constantly challenged with MRSA in patient re-admissions and inter-hospital transfers"), if surrogate markers are being used to identify any locally endemic strains we are willing to check a few representative isolates for you from time to time, e.g. five isolates every six months.
9) Toxic shock and endocarditis. We would like to receive an isolate from every case of suspected staphylococcal toxic shock and endocarditis for toxin-testing and MIC testing respectively.
10) Anomalous isolates.Please state the anomaly/resistance to be investigated eg slide coagulase negative MRSA, and please check for mixed culture, coagulase, catalase and Gram stain before sending.
11) Antibiotic resistance. Request antibiotic susceptibility tests only when necessary to assist your local studies, e.g. anomalous or doubtful test results, unusual or clinically significant results, necessary quantitation (e.g. MIC of first encountered mupirocin-resistant isolates), unexpected resistance e.g. to vancomycin).

From these discussions, and by testing different reagents and protocols in the central laboratory and then in other centres, it was found that it was not important to standardise some elements of the protocol, such as the type of agarose, DNA block preparation and plug digestion. Other elements were shown to be more critical; namely, a standard gel volume and concentration of agarose, the DNA concentration in the plug, the ionic strength and volume of electrophoresis buffer used the temperature, voltage and switching (pulsing) times during electrophoresis [7]. This "harmonised" approach proved to be extremely successful in establishing agreement, in that members were reluctant to abandon methods that they had developed over many years without good reason.

Exchanges of scientists between laboratories enabled the identification of some of these important variables (e.g. where the temperature of the buffer was monitored). The new "harmonised" protocol was agreed, and further modified in a pilot study between two laboratories (Brussels, Belgium and London, England), which resulted in a good compromise between electrophoresis times and strain discrimination [7]. Again, this was made possible by the funded exchange of workers between these two laboratories. Seven laboratories' gels were found to be of sufficiently good quality to allow comparison of the strains using a computer software program, while two out of twenty gels could not be analysed because of inadequate destaining and DNA overloading. These issues were to a certain extent due to the employment of less experienced student workers, which made the group aware of the importance of a more accreditation-oriented approach. Good quality gels and inclusion of an internal quality control strain (NCTC 8325) were found to be essential before attempting inter-centre PFGE comparisons. We were finally able to track a number of clonally-related strains in multiple countries throughout Europe [7,8] summarised in Table 3. This highlighted the need for closer international collaboration to monitor the spread of current epidemic strains as well as the emergence of new ones.

We also characterised these MRSA strains with a number of other techniques e.g. antimicrobial susceptibility, phenotyping, resistotyping, ribotyping, binary typing [9] and toxin gene detection [7]. We then collaborated with Mark Enright from Imperial College, London, United Kingdom (UK) to analyse a representative sample of MRSA from 11 European countries to compare our standardised PFGE typing to two other typing methods: sequencing of the variable repeat region in the protein A-encoding *spa* gene, and multilocus sequence typing (MLST) combined with PCR analysis of the staphylococcal chromosomal cassette containing the *mec* gene (SCC*mec*) [8]. A high level of discrimination was achieved using each of the three methodologies, with discriminatory indices ranging between 89.5% and 91.9%, with overlapping 95% confidence intervals.

There was also a high level of concordance of groupings made using each method. MLST/SCC*mec* typing distinguished 10 groups, each containing at least two isolates. Interestingly, these corresponded to the majority of nosocomial MRSA clones described in the literature. PFGE and *spa*-typing resolved 34 and 31 subtypes, respectively, within these ten MRSA clones. Each subtype differed only slightly from the most common pattern using each method. PFGE analysis at a 65% cut-off corresponded to the MLST Clonal Complex (CC); PFGE similarity by 85% or above corresponded to the same MLST Sequence Type (ST). Strain relationships determined by *spa*-typing were likewise concordant with MLST ST designation. PFGE and *spa*-typing could therefore be used as frontline typing systems for multicentre surveillance of MRSA and most members of HARMONY are also members of the *spa*-typing network "SeqNet" [10].

From this work, SCC*mec*, together with MLST was recommended by the HARMONY group to characterise MRSA clones [8]. However, several countries still wanted to use their own names for their strains [8]. In Table 3 examples of nomenclature used in UK are listed and many more are now described (see the utility section below). Experience with *spa*-typing has grown since the project started [11], although for countries with fewer circulating strains its reduced discrimination compared with PFGE is a disadvantage and sequence typing of other genes will most probably be needed [12,13]. Its major advantages over PFGE are ease of interpretation, automation, speed and ability to export results between centres. There is some concern that occasional "violations" of MLST CC assignment by *spa*-typing [14] can occur and so various groups are examining additional genes [12,13]. At present, *spa*-typing may be complemented by the use of additional techniques such as PFGE, MLST, SCC*mec*. This may be supplemented with toxin gene or *agr*-typing depending on the epidemiological or other questions that are being posed and the strains present in a country. International work is underway at standardising the SCC*mec* approaches and this will further increase the discrimination of the techniques, although robust validation will be required.

Table 3

Examples of multi-country clones of methicillin-resistant *Staphylococcus aureus* (MRSA)

HARMONY MRSA nomenclature: MLST Clonal Complex (CC) ; SCC*mec* Designations	Countries and exemplar of English EMRSA nomenclature
MLST CC 5; SCC*mec* I	Belgium, Finland, Germany, Slovenia, Poland, UK; EMRSA-3*
MLST CC8; SCC*mec* IV	Belgium, Finland, France, Germany, Greece, Ireland, Poland, Slovenia, Spain, Sweden; "Iberian Clone"
MLST CC22; SCC*mec* IV	Belgium, Finland, Germany, Ireland, ,Sweden, The Netherlands, UK; EMRSA-15*
MLST CC30; SCC*mec* II	Australia, Belgium, Finland,The Netherlands, Sweden, UK; EMRSA-16*
MLST CC45; SCC*mec* IV	Belgium, Finland, Sweden

* Countries have national names for many of these strains, those for the UK are listed here with an*.
See reference [8] for further details of PFGE and *spa* typing examples; EMRSA = Epidemic methicillin-resistant *Staphylococcus aureus*

Utility of the HARMONY PFGE database

Several countries found the HARMONY experience particularly timely. The PFGE database and protocol was made publicly accessible at: http://www.harmony-microbe.net/microtyping.htm (last accessed 10 April 2008) and has been used by many people from within and outside the EU. In Sweden, the isolates provided made it possible to build a national MRSA-PFGE-database in 2000. It included PFGE patterns of a selection of HARMONY strains and compared, consecutively, incoming PFGE patterns of all Swedish MRSA isolates. Awaiting an international consensus on PFGE pattern nomenclature (which we proposed but did not achieve with other IUMS centres), the Swedish database drew on the HARMONY pattern designations used at the time, adding Swedish designations

when needed [15]. The Swedish MRSA database, including PFGE patterns, normalised against *S. aureus* NCTC 8325, as well as *spa* types (from 2006 and onwards) and MLST STs, providing a national overview, and facilitated exchange of data with laboratories around the world.

Finland established a similar database in 2000, with PFGE still used as the initial typing approach [16]. Interestingly, the lack of transfers of patients between cities in Finland until 2000 was a major factor contributing to MRSA being more contained in this country [16]. Increasingly, patients in many countries are travelling between cities for treatment, either because they think they can get better service elsewhere [17], or because the procedures prescribed are not available in their own city hospital [16,17]. There is also an increased exchange of patients between nursing homes and hospitals, with MRSA increasingly spreading within these healthcare establishments [16,17]. It is therefore plausible to ask whether these factors could perhaps explain the more recent spread of MRSA between cities in Finland [18], as happened earlier in the case of epidemic MRSA-16 in the UK (UK EMRSA-16) [19].

In an impressive initiative, Denmark collaborated with Sweden and Finland to compare MRSA isolated in these three Nordic countries during 2003-2004, again including the HARMONY strains in the comparisons [20] and utilising the HARMONY PFGE protocol.

Several countries with a low incidence of MRSA experienced importation of epidemic MRSA from endemic MRSA countries. The HARMONY database enabled them to confirm that these MRSA strains were indeed indistinguishable from those described in their countries of origin. This enabled the international community to reflect on how the same MRSA strains were behaving in different healthcare settings and patient types. A recurring observable fact in these situations was the rapid spread of these epidemic MRSA strains on affected wards. Some of the infection control teams commented to HARMONY centres that it was far in excess of what they had encountered previously. Audits of infection control in these countries found that the spread was particularly prominent in places where hand hygiene was poor and there were also comments stating that excessive workloads and sub-optimal staffing had been a major driver.

Coagulase negative staphylococcal quality assurance exercise

In 1999, seven of the HARMONY participating laboratories requested another external quality assurance exercise for coagulase negative staphylococci (CNS). Three centres were already considering adopting the new HARMONY PFGE MRSA typing protocol to type CNS and they wanted to know if its discriminatory power was sufficient. For CNS the commonest epidemiological problem is exploring whether pairs of isolates (e.g. isolates from the bloodstream and an intravenous canula from the same patient) are distinguishable. Comparisons are thus needed on the same gel rather than several different gels, as is often the case for MRSA typing referrals. The central laboratory thus sent out 12 isolates of four different species to these seven laboratories in a blinded manner. These included two pairs of duplicate isolates. The results were interpreted in each laboratory, and also objectively in a software program by the coordinating centre. The results were quite remarkable, in that only one centre failed to identify exactly two isolates (a one band difference between two of the isolates probably due to poor gel staining). In addition, the HARMONY protocol proved to be at least equal to the various in-house CNS typing PFGE protocols. This was an important finding, in that the use of a single protocol for all staphylococci would facilitate training, avoid potential confusion and enable inter-centre comparisons, should these be necessary (e.g. exploration of multi-antibiotic-resistant CNS outbreaks following the transfer of patients between different specialised paediatric care (including neonatal) units).

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Perspectives

A European laboratory network for sequence-based typing of methicillin-resistant *Staphylococcus aureus* (MRSA) as a communication platform between human and veterinary medicine – an update on SeqNet.org

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7. Department of Clinical Microbiology, Hvidovre Hospital, Hvidovre, Denmark
8. 44 participating European laboratories (listed in Table 1)

Introduction of SeqNet.org

SeqNet.org is currently an initiative of 44 laboratories from 25 European countries and one laboratory from Lebanon (Table 1), founded in 2004, in collaboration with the Robert Koch Institute at the University of Münster, Germany (http://www.SeqNet.org). Since then, its main objective is to establish a European network of excellence for sequence-based typing of microbial pathogens, having its main focus on *Staphylococcus aureus* [1]. SeqNet.org comprises a large number of national reference laboratories as well as university laboratories. The principle goal of SeqNet.org is to generate unambiguous, easily comparable typing data in electronic, portable form to be used by infection control at a local level as well as national and European surveillance of sentinel micro-organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA). *spa*-typing has been shown to be a useful tool in molecular hospital epidemiology [2,3]. Veterinary laboratories have recently joined the SeqNet.org initiative as MRSA has become an emerging problem in veterinary medicine [4,5]. *spa*-typing data from human and veterinary medicine can be compared using the *spa* server database [6].

SeqNet.org objectives

1. Organisation and participation in seven international workshops contributed to the harmonisation of sequencing methods for sequence-based typing of MRSA and the capacity for building DNA sequencing in diagnostic microbiology. Further meetings and workshops are planned.
2. SeqNet.org rules require that SeqNet.org laboratories (Table 1) undergo at least one certification trial [7] for sequence-based typing of MRSA. Regular proficiency tests are foreseen.
3. Curatorship of the Ridom *spa* server and the development and maintenance of a SeqNet.org web-portal allows the transfer of data at an international level.
4. The excellence of data quality needs to be maintained. This is necessary as the access to the *spa* server will be enlarged in the future.

SeqNet.org database

SeqNet.org is co-ordinated by the University Hospital in Münster and the Robert Koch Institute in Wernigerode, Germany. Besides ensuring the quality aspect, SeqNet.org is responsible for curating the *spa* server for all laboratories using the *spa* server. Currently, the 44 SeqNet.org participating European laboratories (Table 1, Figure) and 148 other laboratories submitting data have synchronised more than 3,816 *spa* types consisting of 222 *spa* repeats from 59,401 *S. aureus* strains of which 93% were MRSA. The analysis of more than 27,000 *spa* server submissions show that the 30 most frequent *spa* types cover 66% of all submissions (Table 2).

Figure

Proportion of strain submissions with complete data set to the *spa* server, by country in Europe, SeqNet.org curated Ridom spa server, 1 April 2004 – 15 February 2008 (n = 32,544)

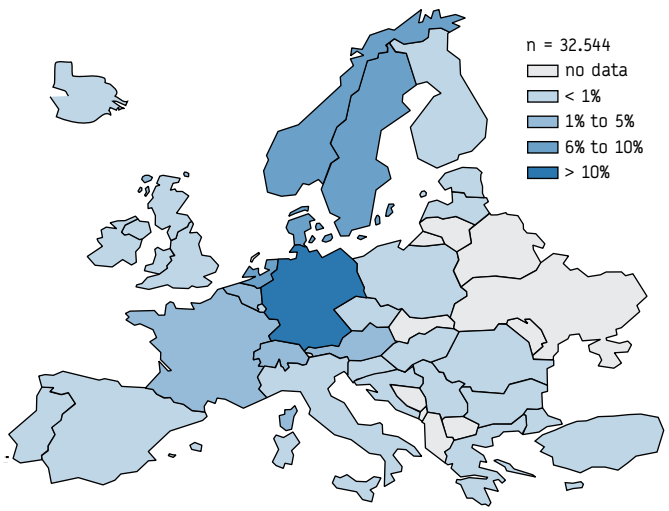

Table 1

SeqNet.org participating medical and veterinary laboratories and institutions (44 in Europe, one in Lebanon)

Nr	Organisation	Veterinary (V) Medical (M)	Main contact person	City	Country
1	Institut für Hygiene, Mikrobiologie und Tropenmedizin	M	H. Mittermayer	Linz	Austria
2	Österreichische Agentur für Gesundheit und Ernährungssicherheit	V	F. Allerberger	Wien	Austria
3	ULB-Hopital Erasme-National Reference Laboratory for Staphylococci	M	M. Struelens	Bruxelles	Belgium
4	National Center of Infectious and Parasitic Diseases	M	T. Kantardjiev, D. Nashev	Sofia	Bulgaria
5	National Institute of Public Health	M	H. Zemlicková	Prague	Czech Republic
6	Clinical and Molecular Microbiology, Clinical Hospital Centre Zagreb	M	S. Kalenic A. Budimir	Zagreb	Croatia
7	Hvidovre Hospital	M	H. Westh (Advisory Board)	Hvidovre	Denmark
8	Statens Seruminstitut	M	R. Skov	Copenhagen	Denmark
9	National Food Institute (DTU)	V	H. Hasman	Copenhagen	Denmark
10	National Public Health Institute	M	J. Varkila	Helsinki	Finland
11	Centre National de Référence des Staphylocoques	M	J. Etienne H. Meugnier	Lyon	France
12	Institute of Hygiene (1), University Hospital Muenster, Clinic for Periodontology (2), University Hospital Münster	M	A. W. Friedrich (1) (Co-ordinator) A. Mellmann (1), D. Harmsen (2)	Muenster	Germany
13	Institute of Medical Microbiology, University Hospital Muenster	M	G. Peters, K. Becker	Muenster	Germany
14	Institute of Hygiene and Microbiology, University of Wuerzburg	M	U. Vogel	Wuerzburg	Germany
15	Robert Koch Institute	M	W. Witte (Co-ordinator)	Wernigerode	Germany
16	Charité – University Medicine Berlin	M	K. Weist	Berlin	Germany
17	Institute of Medical Microbiology and Hospital Hygiene, University Hospital Düsseldorf	M	R. Schulze-Röbbecke	Düsseldorf	Germany
18	Institut für Medizinische Mikrobiologie und Hygiene, University Hospital Tübingen	M	V. Kempf, B. Schulte	Tübingen	Germany
19	University of Athens	M	A. Tsakris E. Piperaki	Athens	Greece
20	"Johan Bela" National Center for Epidemiology	M	M. Fuzi	Budapest	Hungary
21	Microbiology Research Unit, Division of Oral Biosciences, Dublin Dental School & Hospital	M	A. Shore	Dublin	Ireland
22	National MRSA Reference Laboratory, St James's Hospital, Dublin	M	A. Rossney	Dublin	Ireland
23	Istituto Superiore de Sanità, National Reference Laboratory on Antimicrobial Resistance	M	A. Pantosti, M. Monaco	Rome	Italy
24	Istituto Zooprofilattico Sperimentale delle Regioni Lazio e Toscana, National Reference Laboratory on Antimicrobial Resistance	V	A. Battisti, R. Lorenzetti	Rome	Italy
25	P. Stradins Clinical University Hospital	M	E. Miklasevicz	Riga	Latvia
26	Lebanese American University, Microbiology & Biotechnology	M	S. Tokajian	Byblos	Lebanon
27	Laboratoire National de Santé, Microbiology unit	M	J. Mossong	Luxembourg	Luxembourg
28	Laboratorium Microbiologie Twente Achterhoek	M	R. Hendrix	Enschede	The Netherlands
29	National Institute of Public Health (RIVM)	M	X. Huijsdens	Bilthoven	The Netherlands
30	University Hospital	M	E. Stobberingh	Maastricht	The Netherlands
31	St. Olavs University Hospital, National Reference Laboratory	M	T. Jacobson	Trondheim	Norway
32	Akershus University Hospital	M	T. Taennes	Lørenskog	Norway
33	Telelab	M	Y. Tveten	Skien	Norway
34	National Medicines Institute	M	W. Hryniewicz (Advisory Board)	Warsaw	Poland
35	Instituto de Tecnologia Quimica e Biologica (ITQB)	M	H. de Lencastre (Advisory Board)	Oeiras	Portugal
36	National Intitute for Research and Development for Microbiology and Immunology	M	I. Codita	Bucharest	Romania
37	Microbiology Department, Stobhill Hospital	M	D. Morrison E. Giles	Glasgow	Scotland
38	University of Ljubljana/Medial Faculty	M	M. Mueller-Premru	Ljubljana	Slovenia
39	Centro Nacional de Microbiología (Instituto de Salud Carlos III)	M	J. Campos	Madrid	Spain
40	Lund University Hospital	M	A.-C. Petersson	Lund	Sweden
41	Swedish Institute for Infectious Disease Control (Smittskyddsinstitutet)	M	S. Haeggman	Solna	Sweden
42	Sahlgrenska University Hospital, Göteborg	M	Ch. Welinder-Olsson	Goteborg	Sweden
43	Universitätsspital Basel, Mikrobiologie	M	R. Frei	Basel	Switzerland
44	Staphylococcus Reference Laboratory, Health Protection Agency	M	A. Kearns	London	UK
45	Health Protection Agency, Laboratory of Healthcare Associated Infection and HARMONY IUMS co-ordinator	M	B. Cookson	London	UK

Since 2006, the analysis with the BURP (Based Upon Repeat Pattern) algorithm makes it possible to group the *spa* types by means of their relatedness to each other and to a common founder [8,9]. Occasionally, misclassifications between Multilocus Sequence Typing (MLST) and *spa* occur due to intergenomic recombination [10,11] or large chromosomal replacement comprising the *spa* locus, leading to outliers, such as described for ST239 and ST34 [12]. However, BURP analysis shows a correspondence of 92% for pulsed-field gel electrophoresis (PFGE) patterns and 97% for MLST clonal clusters, so that *spa*-typing generated within the SeqNet.org network are comparable with PFGE and MLST databases [10,11]. For example, MRSA strains belonging to MLST type ST398 have been recently associated with pigs. They correspond to the *spa* Clonal Complex t011 (*spa* types t011, t034, t108) and these *spa* types can be used as identifying markers for such strains isolated from humans and animals [5]. The *spa* database is, in its current form, essentially used as a dictionary assuring a common nomenclature, providing molecular typing data in real time, and maintaining excellence of typing data quality. Its data on frequencies of *spa* types can already at this stage provide valuable information regarding wider geographical dissemination (Table 1, Figure). In interpreting raw *spa* data from the *spa* database the following aspects need to be considered:

- Different sampling schemes in different countries. Specifically, a few types might be overrepresented because of focussing on special topics such as: 1) pig farming and MRSA ST398 in Germany, the Netherlands, and Belgium; 2) Panton-Valentine leukocidin-positive (PVL-positive) t044 (ST80) looking especially for presumptive community-acquired CA-MRSA of the European clone; and 3) t084 due to a detailed study on dissemination of MRSA ST8/ *spa* t084 in Denmark. Furthermore, the same *spa* type can designate MRSA and MSSA (methicillin-sensitive *S. aureus*) isolates. Therefore, resistance must always be confirmed before.
- Geographical dissemination. Reporting particular types from many countries is an indicator for epidemic spreading, but it does not necessarily indicate wide geographical dissemination of a special clone. Here, a convergent evolution from a frequent MSSA ancestor is also possible, as already indicated by the possession of different types of SCCmec elements as in t002 (ST5) and t008 (ST8).
- Confirmation with additional testing. Identification of CA-MRSA ST8 ("USA300" clone) is likely when the isolates originate from deep infections of skin and soft tissue [13]. A confirmation of CA-MRSA ST8 should be performed by using PCR for lukS-PV lukF-PV and arcA. Therefore, *spa*-typing can be useful as surrogate marker for highly epidemic and highly prevalent clones [14], but further microbiological characterisation is necessary [11].

Recent developments

In April 2007, the SeqNet.org plenary meeting was held in Rhodes, Greece and was aimed to exchange experiences, discuss and decide on questions which arose during the last three years of sequence-based typing throughout Europe. SeqNet.org participating laboratories presented their experiences in using *spa*-typing as

Table 2

Ten most frequently synchronised *spa* types on the SeqNet.org curated Ridom *spa* server, 59,401 submissions, 1 April 2004 - 6 May 2008

spa-type	Frequency	Countries of origin	*spa*-CC	MLST	Comment and other designations
t003	12.64 %	Austria, Belgium, Croatia, Czech Republic, Denmark, France, Germany, Netherlands, Norway, Sweden, Switzerland, United States	CC001	ST-5, ST-225	CC5, Rhine Hesse MRSA (subclone), EMRSA-3, New York clone
t032	9.78 %	Austria, Belgium, Czech Republic, Denmark, France, Germany, Iceland, Italy, Lebanon, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom, United States	CC032	ST-22	Barnim MRSA (prototype & subclone), EMRSA-15*, prototype of ST-22, CC22
t008	6.94 %	Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Iceland, India, Israel, Italy, Japan, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom, United States	CC024	ST-8, ST-247, ST-250, ST-254	CC8, Northern German MRSA (subclone), USA300 ORSA IV (CA-MRSA** in the US), Archaic/Iberian, ST250 ORSA I
t002	5.99 %	Austria, Belgium, China, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Israel, Italy, Japan, Lebanon, Netherlands, Norway, Romania, Sweden, Switzerland, Taiwan, United Kingdom, United States	CC001	ST-5, ST-231	CC5, Rhine Hesse MRSA (prototype), EMRSA-3*, New York clone, Japan clone, Pediatric, USA100 ORSA II, USA800 ORSA IV, ST 5 ORSA I
t037	3.32 %	Austria, Bulgaria, China, Croatia, Czech Republic, Denmark, France, Germany, Italy, Lebanon, Netherlands, Norway, Poland, South Africa, Sweden, Switzerland, Taiwan, United Kingdom	CC037	ST-239, ST-240, ST-241	CC8/239, Vienna MRSA, Brazilian/ Hungarian, ST239 ORSA III, ST240 ORSA III, EMRSA-1*, -4, -7, -9, -11
t044	2.50 %	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, France, Germany, Hungary, Italy, Lebanon, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom	CC044	ST-80	CA-MRSA** (lukS-lukF +) (CA-MRSA in Europe)
t011	2.19 %	Austria, Belgium, France, Germany, Netherlands, Norway	CC037	ST-398	Pig-associated clone
t001	2.12 %	Austria, Belgium, Croatia, Germany, Israel, Italy, Netherlands, Norway, Slovenia, South Africa, Sweden, Switzerland, United Kingdom, United States	CC001	ST-5, ST-222, ST-228	CC5, Southern German MRSA (prototype & subclone), Rhine Hesse MRSA (subclone), EMRSA-3*, New York clone
t004	1.62 %	Belgium, Denmark, Finland, France, Germany, Israel, Netherlands, Norway, Sweden, Switzerland, United States	CC004	ST-45	CC45, Berlin MRSA (prototype), USA600 ORSA II, USA600 ORSA IV
t015	1.45 %	Austria, Belgium, Croatia, Denmark, Finland, Germany, Indonesia, Italy, Latvia, Netherlands, Norway, Romania, South Africa, Spain, Sweden, Switzerland, Taiwan, United Kingdom	CC015	ST-45	

* EMRSA = Epidemic methicillin-resistant *Staphylococcus aureus*
** CA-MRSA = Community-Acquired methicillin-resistant *Staphylococcus aureus*

first line typing method, besides other typing methods, such as MLST and PFGE. In the following, the most important decisions of SeqNet.org plenary meeting are described.

External quality control standard and proficiency testing

Annual proficiency tests for all SeqNet.org participating laboratories will be performed. Currently only submission of single primer-based results are possible if excellent quality is ensured. Less than five edits are allowed, otherwise no synchronisation with the server is possible. With the existing quality criteria, 99.7% of all current submissions have the maximum quality value of 120 out of 120 (excellent).

***Spa* server as a common strain pool**

The *spa* server provides information on strains originating from various human and veterinary specimens isolated in countries all over Europe and other parts of the world. As it might therefore serve as a decentralised worldwide virtual strain collection, the server is programmed to be searchable for basic information (*spa* type, MRSA/MSSA, PVL, infection/colonisation, human/animal origin). An anonymous strain request system will be available in 2008.

Unique nomenclature

SeqNet.org maintains the curatorship of the *spa* server and is the gatekeeper for all bioinformatic tools using the *spa* server for synchronisation of data. Users of other *spa*-analysing software tools have the possibility to synchronise with the *spa* server, provided they fulfil all given quality criteria. Up to now, agreements have been achieved between SeqNet.org and two developers of *spa*-analysing softwares (Ridom: http://www.ridom.de and Applied Maths: http://www.applied-maths.com). All users of the *spa* server are invited to perform the SeqNet.org certification and annual proficiency test.

SeqNet.org membership, management, organisation and data flow and data property

As local and regional laboratories submit data to the *spa* server, this might lead to a bypassing of national reference laboratories (NRL) which are responsible for regional and especially national molecular surveillance and public health action. A technical software solution could make it possible that, upon mutual agreement between NRL and the local laboratories, all epidemiologically interesting *spa*-typing data could be used in future by the NRL. National or regional data can be made visible by the national reference laboratory. Even cross-border, euregional data can be made visible as it has been done for regional networks such as EUREGIO MRSA-net Twente, Münsterland (http://www.mrsa-net.eu). Nevertheless, it remains up to national initiative to build up such national *spa*-typing networks. It is important to mention that all data on the *spa* server is strictly incrementally synchronised. This means that all synchronised data after having passed quality control and assignment of the *spa* type is stored with a single laboratory identifier. Every submitter using direct submission is able to withdraw his/her data at any time by re-synchronising with the server and indicating the deletion of the submission. Only the *spa* type and the information on quality will remain on the server. International study groups or regional and national networks can choose the option of not making visible their data submission (again, except *spa* type and quality) on the public homepage as long as they wish. In this way, data property of each single submitter is assured at any time.

Collaboration

There is collaboration with other European networks, such as the European Antimicrobial Resistance Surveillance System (http://www.earss.nl). Most of the national reference laboratories are involved in both networks [15]. Furthermore, many members of the HARMONY IUMS are also members of SeqNet.org [16,17]. In 2007, SeqNet.org started a collaboration with the Nosocomial Infection Control Consortium (INICC, http://www.inicc.org) in Argentina, a worldwide network for surveillance of nosocomial infections in developing countries. Most of these countries are interested in external quality control ring-trials for their national laboratories and seek assistance for typing methods. The collaboration with SeqNet.org can foster collaboration between epidemiologists and microbiologists in those countries.

Conclusion

The SeqNet.org initiative is a vivid European-wide network of laboratories for sequence-based typing of microbial pathogens, especially *S. aureus*. It generates high-quality typing data available to all participants and the public through the web-portal. The SeqNet.org laboratory network delivers the tools to detect local, national and international spread of MSSA and MRSA *spa* types. In particular, real-time synchronisation, automatic quality control and data property have made the SeqNet.org curatorship of the *spa* server successful for many years. In consequence, there is a strong need for EU-wide standardised sampling regimen to improve the use of *spa* type data for epidemiological purposes, such as the interpretation of relative frequencies, the time frame, and the geographical spread of *S. aureus spa* types. As the method is employed by both human and veterinary laboratories, typing results can already be used today for interdisciplinary epidemiological studies of MRSA. More laboratories from all parts of the world are welcome to join this initiative. If you are interested in joining SeqNet.org, please contact the coordinators.

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Perspectives

MLVA-NET – A STANDARDISED WEB DATABASE FOR BACTERIAL GENOTYPING AND SURVEILLANCE

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Background

Strain typing is an important aid to surveillance networks and outbreak investigations of infectious diseases [1]. MLVA (Multilocus VNTR Analysis, with VNTR standing for Variable Number of Tandem Repeats) has emerged as a highly discriminatory and widely applicable genotyping method that is now being applied for strain tracking in a growing number of bacterial pathogens [2,3]. The genomic loci containing tandem repeats are often maintained among strains of a bacterial species, while individual strains harbour different copy numbers that can be determined simply by PCR amplification. Similar to sequence-based methods such as Multilocus Sequence Typing (MLST), the MLVA method indexes genetic variation at well defined genomic loci and produces reproducible allelic profiles that can be coded in a simple digital format. Hence, they represent an attractive alternative to banding profile-based methods such as pulsed-field gel electrophoresis (PFGE), which requires dedicated efforts (e.g. http://www.cdc.gov/pulsenet) in order to produce fingerprinting data that are comparable across laboratories. Indeed, to be useful to surveillance networks and for global epidemiology, a genotyping method has to be technically accessible, reproducible and to yield easily portable data. In addition, electronic databases that are made accessible through the Internet can render exchange and comparison of data among laboratories very effective for local, national, and international surveillance.

Existing databases of MLST data accessible through web portals (http://www.pubmlst.org, http://www.mlst.net, http://www.pasteur.fr/mlst) represent a common language for strain typing that has proven extremely useful for collaborative research and global epidemiology of bacterial and fungal pathogens [4]. However, given the much faster evolutionary rate of tandem repeats compared to nucleotide sequences, MLVA markers provide much improved resolution compared to MLST, thus representing a subtyping tool that is especially useful for strain discrimination in genetically homogeneous pathogens, such as M. tuberculosis [5], Bacillus anthracis [6] or Salmonella enterica serotype Typhimurium [7]. Web-accessible MLVA databases are not yet widely used for international collaboration [8], but the development in this area is very active (http://mlva.u-psud.fr/, http://www.mlva.eu/, http://www.miru-vntrplus.org).

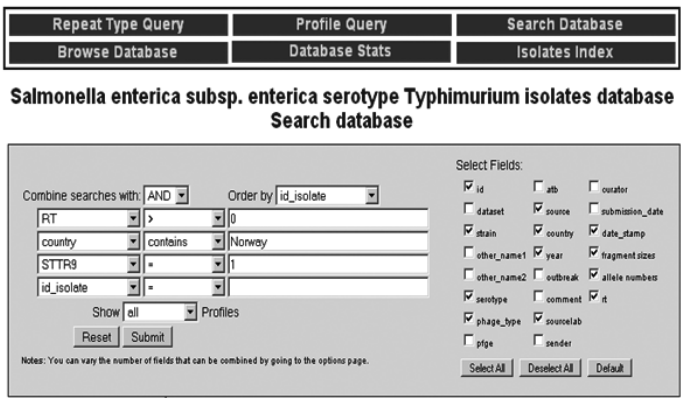
Description of MLVA database

We have developed MLVA-NET (http://www.pasteur.fr/mlva), a web-accessible database system dedicated to the comparison of MLVA genotyping profiles and to retrieval of relevant epidemiological information for the corresponding isolates. An unlimited number of organisms (species, subspecies, serovars or other categories) can be entered into the system. Curators, working through the internet, create and maintain one or several datasets (groups of isolates) for one or more organisms, Individuals who are in charge of data management for a collaborative network can request curator rights from the MLVA-NET administrator. There is no limit to the number of curators and datasets for a given organism.

The database contains two types of data – profiles and isolates – which are accessed through distinct links. Each allele at a given locus is assigned a so-called 'allele number'. When combined over all loci, these numbers make up a numeric code that defines a particular MLVA profile, or repeat type (RT). All MLVA profiles are immediately made public in order to provide the necessary common language for microbial strain typing. In contrast, the curator, in agreement with the person who supplied the data, can decide to keep private the epidemiological information related to isolates, such as isolate name, country or date of isolation. The decision to

FIGURE 1

Example of a MLVA-NET isolates query using the <Search database> menu



keep isolate information private or to make it public is made for entire datasets, not for individual isolates. Hence, the web pages showing information on isolates contain public datasets that are available for all external users, as well as private datasets that are accessible only for registered users through a password-protected identification step. Registered users can either have only reading access, or predefined curator rights that allow them to import or modify isolates.

An important principle of MLVA-NET is to store raw data, i.e. the length of PCR fragments, as determined on agarose gels or capillary electrophoresis. The fragment sizes are automatically translated by the system into allele numbers. Each allele is assigned to a bin, corresponding to PCR fragment lengths ranging between a lower and a higher bound. For each organism, different ways of defining bins ("coding methods") can co-exist according to the preferences of user networks. Therefore, our system retains maximal information (fragment lengths) while providing flexibility and adaptability in the way data can be analysed. For example, the discovery of incomplete repeats in some strains can be taken into account without having to rebuild the database. Because tandem repeats can evolve by stepwise loss or gain of a single repeat, it can be useful to take into account in phylogenetic analyses the difference in the number of repeats between strains. Therefore, a coding method can be defined so that allele numbers correspond to the repeat number, instead of arbitrary numbers (e.g., numbered successively as they are discovered).

The system accepts missing data, which is important given the fact that not all strains contain all possible VNTR loci. The same organism can be analysed by several methods, which can differ by the marker set (number and identity of loci), their order in the allelic profile, and by the definition of bins and alleles. Hence, for a given set of markers, data can be compared across datasets even if contributing laboratories have different preferences for bin definition or allele number assignment.

So far, the database is suitable only for haploid organisms.

Besides download and search functions that give access to the entire public contents of the database, a number of flexible query and comparison functions are available. Notably, they allow strains that have been newly genotyped by the user to be compared to the content of the database. The user can search for all RTs that are identical or similar to a query profile, or retrieve the profile corresponding to a particular RT. An advanced search function is available that allows combining queries with comparison operators (=, >, <, NOT, NOT contains, contains). The search form (Figure 1) allows (i) to enter search criteria in chosen fields, (ii) the way

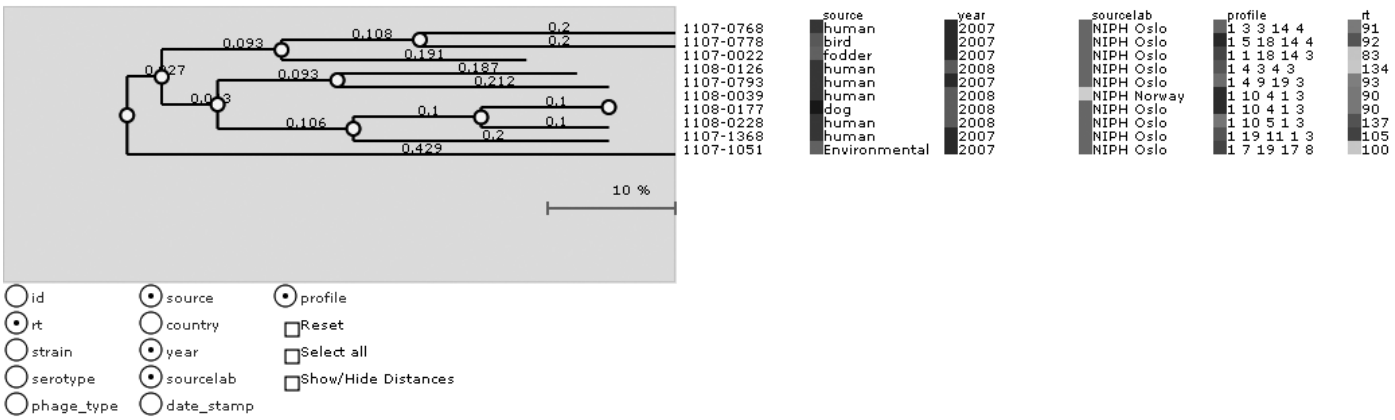
Figure 2

Example of a MLVA-NET results page for S. Typhimurium isolates from Norway with allele number 1 for marker STTR9

Isolates information									Fragment sizes					Allele numbers					RT
id	strain	serotype	phage_type	source	country	year	sourcelab	date_stamp	STTR9	STTR5	STTR6	STTR10	STTR3	STTR9	STTR5	STTR6	STTR10	STTR3	rt
189	1107-0022			fodder	Norway	2007	NIPH Oslo	2007-11-14	162	227	394	363.00	524.00	1	1	18	14	3	83
369	1107-0768			human	Norway	2007	NIPH Oslo	2007-11-22	162	239	300	362	549	1	3	3	14	4	91
377	1107-0778			bird	Norway	2007	NIPH Oslo	2007-11-22	162	252	394	362	550	1	5	18	14	4	92
380	1107-0793			human	Norway	2007	NIPH Oslo	2007-11-22	162	246	348	350.00	523	1	4	9	19	3	93
423	1107-1051			Environmental	Norway	2007	NIPH Oslo	2007-11-22	162	264	305	344	325	1	7	19	17	8	100
457	1107-1368			human	Norway	2007	NIPH Oslo	2007-11-22	162	306	359	356	523	1	19	11	1	3	105
599	1108-0039			human	Norway	2008	NIPH Norway	2008-01-21	162	300	318	356	524.00	1	10	4	1	3	90
603	1108-0126			human	Norway	2008	NIPH Oslo	2008-02-26	162	246	301	393	523	1	4	3	4	3	134
606	1108-0177			dog	Norway	2008	NIPH Oslo	2008-02-26	161	301	319	357	523	1	10	4	1	3	90
608	1108-0228			human	Norway	2008	NIPH Oslo	2008-02-26	162	300	325	356	524.00	1	10	5	1	3	137

Figure 3

Interactive phylogenetic tree on MLVA-NET



criteria are combined, (iii) the order of displayed results, and (iv) the category (complete, incomplete or all) of isolates' profiles that are searched. The buttons on the right panel allow selection of fields that will be displayed on the results page.

It is, for example, possible to search for all isolates from Norway that have allele number 1 for marker STTR9 (Figure 2). From this selection of isolates users can access analysis tools (diversity indices, phylogenetic trees, data export).

The browse database mode gives access to all entries and allows the user to retrieve information for selected fields of interest (e.g. the raw data can be hidden by un-checking the corresponding columns of the table).

Batch functions are available for comparison of large numbers of isolates at once. In the profiles interface, MLVA-NET can assign existing RTs to multiple query profiles from a spreadsheet, and assign allele numbers to raw fragment size data. A specified field can be chosen for ordering the query results. The user can choose to restrict queries to complete profiles (no missing locus information), incomplete profiles, or both.

On the isolates interface, a number of diversity indices can be calculated on the selected datasets and isolates. Unweighted Pair-Group Method with Arithmetic Averages (UPGMA) dendrograms and neighbour-joining phylogenetic tree functions are available to cluster isolates for efficient comparison in an epidemiological context. The resulting interactive graphs can be displayed with the user-defined isolate information attached (Figure 3). The tree can be exported as Newick format for analysis with other tree visualization tools.

Three layouts are possible: phenogram, circular, or radial; each layout includes a re-rooting option. Distances between profiles can be calculated using several evolutionary models such as the saltational (infinite alleles) model or by applying (on user-defined loci) the stepwise mutation model [9,10] which considers alleles with similar repeat numbers as being more likely to be closely related.

Finally, a curator interface allows curators to manage their datasets: insert new isolates one by one or in batch, change or create a new coding method, and change the status (public or private) of datasets. This provides a convenient way for collaborative networks to make datasets public at a chosen date (e.g. once the data have been published).

Conclusion

MLVA-NET, the Institut Pasteur's MultiLocus VNTR Analysis database and web interface system, should help considerably in establishing a common language on microbial strain typing based on MLVA data for large numbers of pathogens. The database structure was tailored to allow distinct access rights to separate datasets. In contrast to alternative MLVA databases, MLVA-NET incorporates raw size data, which extends the possibilities for comparisons across public datasets from distinct networks. Of note, sizing data may vary slightly across distinct experimental platforms, and it is therefore crucial for curators to ensure that size data are normalised before they are entered into the MLVA-NET database.

Our data export functions render it possible to compare MLVA-NET data with data stored in other systems. However, discussions are in progress with the administrators of other MLVA databases to improve harmonisation and avoid redundancy of datasets. The user-friendly design of MLVA-NET was inspired by mlstdbNet [11], a system for MLST databases that used with a large success at pubmlst.org and www.pasteur.fr/mlst. As this design clearly separates profiles on the one hand and isolates on the other hand, the requirement for a common language is ensured by the immediate availability of profiles, even though information on isolates can be kept private for security or confidentiality reasons.

Epidemiological surveillance networks and collaborative networks of microbiologists interested in population biology should benefit from MLVA-NET. It is hoped that this system will contribute to a standardisation of MLVA, allowing the exchange of knowledge on the geographic and temporal distribution of strain types for epidemiology and evolutionary purposes.

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Perspectives

Development of an online database for diphtheria molecular epidemiology under the remit of the DIPNET project

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The Diphtheria Surveillance Network (DIPNET), launched on 1 November 2006, is a 38-month programme bringing together 25 European Union partner countries (24 Member States and Turkey) and collaborating countries beyond Europe in a global dedicated surveillance network for diphtheria and related infections caused by *Corynebacterium diphtheriae* and *C. ulcerans* [1].

Despite the success of mass immunisation, epidemic diphtheria re-emerged in the early 1990s in Russia and the newly independent states of the former Union of Soviet Socialist Republics [2,3]. The European Laboratory Working Group on Diphtheria (ELWGD) was created in 1993 in response to this crisis at the request of the World Health Organization Regional Office for Europe (WHO Europe) [4]. One of the objectives of this collaborative effort was to establish a standard genotyping method for rapid tracking of strains. Since then, several new molecular subtyping methods have been developed, such as ribotyping, pulsed-field gel electrophoresis (PFGE), multilocus enzyme electrophoresis (MEE), random amplification of polymorphic DNA (RAPD) and amplified fragment length polymorphisms (AFLP), and all have been applied to epidemiological investigations of diphtheria, with largely successful results [5-8].

The application of standardised molecular epidemiological tools is essential for monitoring the spread of epidemic clones and to allow for the distinction between epidemic, endemic and imported cases. This also has major implications for timely and adequate preventative measures. Although excellent progress has been made in reducing the diphtheria incidence within the WHO European Regions, several countries such as Belarus, Georgia, the Russian Federation and Ukraine are still experiencing problems [9]. Of particular concern is that in 2006, Latvia experienced a relatively high diphtheria incidence of 1.39 per 100,000 population compared to 0.13 per 100,000 in Russia [personal communication Irina Lucenko]. With this in mind, several basic questions need to be addressed. Could strains associated with the previous European epidemic be differentiated from all other strains currently circulating worldwide? What was it that enabled these strains to cause an epidemic of such proportions within the former Soviet Union? Are we dealing with new, more virulent strains? Has the toxin changed in such a way that the current vaccine may be ineffective?

Molecular subtyping therefore plays a major role in providing the answers to some of these questions. Ribotyping has been evaluated as a discriminatory method for subtyping diphtheria strains and has since been used as the 'gold standard' by several groups. Ribotyping methods have been standardised and disseminated to other centres, and an international nomenclature for *C. diphtheriae* ribotypes has been agreed [10]. A database of ribotype patterns has also been established at the Institut Pasteur, Paris, France, using the software programme Taxotron [10]. Currently, there are 86 ribotypes from 576 strains in the database, and new ribotypes are validated at the Institut Pasteur before designation. In this collection, ribotypes Sankt-Petersburg and Rossija (previously G1 and G4, respectively) were the predominant strains circulating in the Russian epidemic [5]. Definitive and extensive improvements need to be undertaken to enable more rapid and accurate detection of these 'clones' globally, with the establishment of an online international database for automatic, real-time recognition of genotypes.

A key component of DIPNET is an online database providing access to integrated case, epidemiological and genotyping data. The DIPNET website (http://www.dipnet.org) will provide a portal for the DIPNET participants to query and analyse this data. This online surveillance database allows patient, clinical and laboratory data to be integrated with associated immunisation, travel, and case and contact management epidemiological data. Furthermore the database can be securely accessed, updated and modified online in real-time by disparately located participants.

The surveillance database is further underpinned by linking molecular typing results to the ribotype reference strain database. A database of 'reference ribotype patterns' has been integrated into the Bionumerics platform, and automated assignment of ribotypes, through the uploading of ribotype gel-profiles, has been facilitated. This will allow DIPNET participants to analyse the patient, epidemiological and genotyping data simultaneously.

Portability and reproducibility often pose challenges with gel based genotyping methods. Therefore the ribotype strain database will be developed significantly to explore the correlation between more novel, rapid and accessible methodologies such as multilocus sequence typing (still under development) and other new sequence-based methodologies.

Retrospective surveillance data from participating countries collected over the period 2000-2005 on all laboratory-confirmed cases of non-toxigenic and toxigenic strains is being integrated initially. This will then be supplemented by the implementation of a web interface that will allow automated uploading of current case data, expected to go live in June 2008. These data will be subject to agreed data quality standards and formats modelled on the reporting system used by WHO/Europe, but enhanced to incorporate reporting for toxigenic *C. ulcerans* and non-toxigenic infections, with the aim of linking to the ECDC reporting system.

The outputs from this project will enable countries to re-address their strategies for diphtheria and related infections and will establish defined and standardised mechanisms for public health and microbiological surveillance. It is envisaged that the DIPNET online diphtheria genotyping database will attract global users, thus improving communication, standardising genotypes and understanding of the spread of diphtheria.

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Perspectives

On-line Global/WHO-European Regional Measles Nucleotide Surveillance

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Measles virus causes an acute infection characterised by rash and fever. Measles infection is preventable by vaccination, but remains a significant cause of childhood mortality in the developing world with an estimated number of approximately 242,000 deaths by measles in 2006 [1].

The World Health Organization (WHO) is coordinating a global control programme for measles, and all WHO regions have identified targets for control or elimination of transmission of this disease. In the WHO European Region (WHO/Europe) the goal is to eliminate measles by 2010 [2]. Surveillance to document the elimination of transmission is in place, using case-based laboratory confirmation by detection of measles-specific IgM and by sequence characterisation of measles strains from outbreaks and chains of transmission. Measles virus is isolated and/or sequenced by the participating laboratories in the 'Global Measles and Rubella Laboratory Network' [3].

Following the success of HepSEQ [4], a public health database generated by the Centre for Infections of the United Kingdom Health Protection Agency, and a European Union-funded measles network called 'Enhanced Laboratory Surveillance of Measles' (ELSM) [5], we developed a web-based, quality-controlled database with epidemiological and nucleotide data for measles infection in the WHO/Europe region (MeaNS). The major objectives of the MeaNS initiative are to function as an epidemiological surveillance tool and to monitor progress of the measles control programme.

Sequence data from the 450 nucleotide region encoding the C-terminal region of the measles virus nucleoprotein (N) and, optionally, the complete nucleotide sequence of the haemagglutinin (H) gene are deposited into MeaNS, together with epidemiological data. The data is quality checked and curated, first automatically by the database application and then manually by a curator. During the curation, specific identifiers called 'WHO names' [8] are created for each sample unless the names were provided by the depositors. In addition, the deposited sequences are assigned a genotype and a cluster identifying number by matching, respectively, against WHO reference sequences and the unique sequence clusters in the database.

Dynamic reports and graphical charts can be created on any user-selected fields in the MeaNS database (eg: genotype or sequence variation in a geographical location or time period). Relevant data can be exchanged between MeaNS and either GenBank or the WHO database on Surveillance of measles and rubella [6,7]. Bioinformatics tools in MeaNS allow one to find identical or similar sequences, assign a genotype, display phylogenetic trees, and to temporally and spatially track measles transmission chains.

Regional laboratories from the European WHO Measles and Rubella Laboratory Network previewed the development of MeaNS, and the current release was well received. Further testing and development to enable uploading of sequence trace files and quality checking mechanisms are currently being undertaken, with an anticipated release for general use in mid-June 2008. The existing tools and the tools that are now being developed will be useful in the surveillance, sequence analysis, evolution, and genome annotation of measles.

Currently, MeaNS is the only known publicly available global database on measles nucleotide sequences. After registering the purpose of their interest, researchers can access MeaNS at www.hpa-bioinformatics.org.uk/Measles/Public/Web_Front/main.php.

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Perspectives

HepSEQ – an Integrated Hepatitis B Epidemiology and Sequence Analysis Platform

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Hepatitis B virus (HBV) is a major human pathogen. The outcome of acute hepatitis B is variable but usually followed by a complete recovery. A small proportion of infections in adults and a higher proportion of infections in early childhood continue in a chronically infected state in which the virus persists in the liver. Patients with chronic hepatitis B usually have no initial symptoms of infection, but over time the major disease sequelae, cirrhosis and hepatocellular carcinoma, can develop. It is estimated that some 350 million people worldwide are currently chronically infected with HBV, but many more will have been infected and recovered.

HBV exists in its human host as eight clusters of viruses (genotypes A to H [1]), each cluster displaying a similarity of sequences and variable antigenicity (serotypes) [2]. Traditionally, HBV genotypes have a distinct geographical distribution, with genotypes A and D predominant in Europe, the Middle East and India, and genotypes B and C in Asia and the Far East. Genotype E is mainly found in West Africa, and genotypes F and H are associated with Central and South America. There is some evidence that different genotypes may be associated with alternative disease profiles and differing responses to antiviral therapy [3-5]. The influx of non-European HBV genotypes represents increasing population movement or migration and may have a significant effect on management of the disease within Europe. The mixing of genotypes within a European population may also promote increased genetic diversity within HBV (due to recombination), the epidemiological effects of which are impossible to predict. Therefore, surveillance of HBV genotypes is important within a national and a European context.

HepSEQ (http://www.hepseqresearch.org) [6] is a freely accessible web resource for the public health aspects of HBV management, with specific focus on epidemiological, virological, clinical, nucleotide sequence and mutational aspects of HBV infection. HepSEQ is comprised of a relational database with a web-enabled interface, which allows inserting and retrieving epidemiological and sequenced-based information. The database currently contains 1,769 patient records from acute and chronic hepatitis B cases in the United Kingdom (UK) and 2,182 sequences, of which 1,679 cover the surface/polymerase region and 497 cover the X/pre-core/core region. The HepSEQ website also provides access to tools that predict the genotype and characterise the genetic polymorphisms of sequences entered by the user. The HBV genotyper tool assigns a genotype to an HBV sequence provided by the user. Sequence alignment and statistical modelling are used to ensure that predictions of the genotype are accurate. HepSEQ allows rapid and dynamic generation of genotypic data within the database and contains 43.6% A, 5.6% B, 12.4% C, 28.4% D and 9.3% E genotypes. The presence of approximately 20% non-A or non-D genotypes highlights the changing dynamic of HBV sequences within the UK and raises questions about the origins and transmission of these infections.

The majority of countries in Europe have a low prevalence of chronic hepatitis B infection, and the acquisition of hepatitis B is often associated with medical interventions or with specific adult risk behaviour such as sex between men, injecting drug use. As HepSEQ contains information on viruses associated with acute hepatitis B infections, it has the potential to further highlight patterns of disease transmission. The database is currently being enriched by attempting to link in exposure categories so that viruses associated with different routes of transmission in the UK can be identified. This will help to identify the emergence of new variants in specific sub-populations and to evaluate the impact of control measures to reduce the incidence, and therefore the prevalence of specific variants, in these populations.

Antiviral therapy targeting the reverse transcription function of polymerase is increasingly used in clinical practice to suppress viral replication. Six polymerase inhibitors have either been licensed or are in development for treatment of chronic hepatitis B: lamivudine, adefovir dipivoxil, entecavir, tenofovir, telbivudine and clevudine. Not surprisingly, long term use of mono or dual therapy in the face of continued replication is associated with viral mutational escape from the drug and this can be monitored by direct sequencing of the polymerase gene [7,8]. Additional variability in the genome has been shown to arise as a result of the natural emergence of strains which may have a selective advantage during the course of chronic HBV infection in a patient. These include pre-core mutants, deletions in the core gene, and mutations in the preS1 and pre S2 regions [9]. It is speculated that these variants are driven by the immune system but it currently remains unknown which, if any, are clinically significant.

The necessity to recognise and interpret HBV anti-viral resistance mutations has driven the development of a mutation annotation tool within HepSEQ. This publicly available tool takes a polymerase nucleotide sequence as input, performs a genotype assignment and compares both the nucleotide and translated amino acid sequence

to the appropriate genotype consensus sequence. The alignment of both nucleotide and amino acid query sequence and the genotype consensus are displayed within the web browser along with a table of mutations that are recognised as causing resistance to HBV inhibitors. When resistance mutations within the query sequence are detected, these mutations are listed along with the inhibitors that they impact upon and a literature citation for that mutation.

As well as providing the user with additional information, continuous dynamic assessment of the relationships between HBV polymorphisms and treatment histories may allow new resistance mutations to be identified. The mutation annotator tool demonstrates the clinical usefulness of HepSEQ and as a consequence of this we are constantly updating the tool to incorporate new information as it becomes available.

The resistance reporting aspect within HepSEQ has proved hugely successful and we are in the process of developing further the clinical and surveillance aspects of the application. Repeated resistance testing generates longitudinal sequence and clinical datasets for individual patients. HepSEQ has the capacity to capture this repeat testing information and we are designing interfaces that will present temporal data such as viral load, resistance mutations, treatment history and alanine transaminase (ALT) levels for a single patient. This interface will provide a single unified mechanism for collating, presenting and interpreting all available patient data, thus facilitating clinical treatment decisions.

Monitoring the prevalence of HBV drug resistance mutations and their transmission, coupled with correlates of disease progression, requires an extensive epidemiological data set that is representative of the population. At present, only HepSEQ contains such a dataset, which covers only the UK. However, these analyses are critical for the whole of Europe, and we are actively seeking European partners to facilitate this. We envisage that the tools within HepSEQ will provide an invaluable resource for other countries to analyse and interpret these data.

We hope that other national centres in Europe will be encouraged to contribute information on hepatitis B cases. This will allow the tracking of specific strains across Europe, and identify links between specific risk groups due to migration and travel. In addition, the increased use across Europe of selective and universal hepatitis B vaccination and of antiviral therapy may contribute to the emergence of specific mutations. Tracking these strains will have particularly important implications for the prevention and management of hepatitis B in Europe. The identification of increasing numbers of clinically important mutations amongst acute cases in one country may provide warning to neighbouring countries.

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Perspectives

Typing database for noroviruses

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The FBVE network

The FBVE (Food-borne Viruses in Europe) network was initiated during a research project funded by the European Commission (contract QLK1-1999-00594). The aim of the network is to establish a framework for rapid, (pre-publication) exchange of epidemiological, virological and molecular diagnostic data on outbreaks of viral gastroenteritis and acute hepatitis due to hepatitis A and E viruses for both surveillance and research purposes.

Surveillance of (viral) gastroenteritis is not harmonised across Europe as surveillance systems are different in each country. The present FBVE network includes 26 actively participating institutes in 13 countries. Each participating country is represented by at least one virologist and one epidemiologist.

Since the focus of this paper and issue is on typing tools, we do not show extensive documentation on quality of the data (for reference see [1] and [2]).

In September 2001, the FBVE network launched a web-based database for reporting outbreaks of viral gastroenteritis. The FBVE database (www.fbve.nl, password protected) is accessible to all members of the network for online outbreak reporting and to search or download the complete dataset. In addition, sequences can be matched against the complete dataset: the results are presented as a table showing homologous strains detected earlier and their characteristics such as year, country, setting of the outbreak, and mode of transmission. More than 16,000 outbreaks have been entered in the database to date. Another feature is a public genotyping tool that allows 'visitors' to upload partial sequences of specific genomic NoV regions. These sequences are subsequently assigned a NoV genotype (see below).

Norovirus

Noroviruses (NoV) are small single-strand RNA viruses without an envelope and are classified to the family *Caliciviridae*. They are highly contagious and are transmitted via faeces and vomit, either directly through contact with infected people or through objects touched by them, or indirectly via contaminated environmental surfaces. The incubation period is about one to three days. The main symptoms of NoV infections are diarrhoea, abdominal pain and vomiting. Infection can occur at all ages, but young children and the elderly are particularly at risk from dehydration. Currently there are no drugs or vaccines that can control or prevent NoV infections [3].

NoV can be divided in five genogroups (G), of which viruses belonging to GI, GII and GIV cause infections in humans. They are further classified into genotypes or genetic clusters, according to the sequence diversity of their capsids. Most prevalent in humans are NoV of GII, and in this group, genotype GII.4 has in recent years been identified as the cause of global epidemics. From time to time, new variants of this genotype appear and rapidly displace the resident dominant variant [4]. There is some evidence for differences in severity of illness [5] and modes and/or efficacy of transmission between viruses that belong to different genotypes. In addition, GII viruses have been found in animals, which raises questions about their zoonotic potential.

Added value of NoV typing

Genotyping is presently done almost exclusively at the national level as part of surveillance, research projects or outbreak investigations. Several regions of the genome are targeted by a range of RT-PCR assays (Figure). Regions A and C [6]. are most widely used, but other genomic regions have been used as diagnostic targets as well.

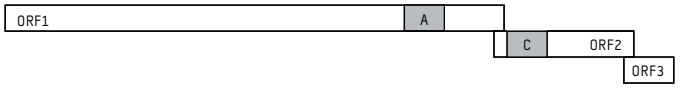
For monitoring trends, region A and C can be used. However, aggregation of data needs to be done with caution because recombination is quite common in NoV, i.e. a recombinant strain may have region A from one genotype and region C from another. Therefore, recombinant strains could erroneously be labelled as distinct, if region A and region C typing results of different strains are compared and sequences from only one of the regions per strain are available.

Typing tool

To harmonise the international comparison of NoV sequences, a quick typing tool was set up by the FBVE network. The availability of a common set of reference sequences with universally accepted

Figure

Norovirus genome and sequencing regions A and C



Open reading frame (ORF) 1: RNA-dependent RNA polymerase
ORF 2: Major capsid protein (VP1)

genotype assignments allows investigators to either rule out or confirm the possibility that a given outbreak is part of a larger (international) outbreak. In the tool, which is publicly accessible at http://www.rivm.nl/bnwww, sequences can be compared to libraries of consensus sequences of regions A and C of different NoV genotypes and variants. The library is regularly updated and newly circulating genotypes or variants are added.

What have we learned through NoV genotyping?

For outbreak investigations, capsid-based typing, based on ORF2 sequencing, provides the highest discriminatory power and can be used to link cases. This has been done on several occasions, e.g. in a transnational food-borne outbreak of NoV in which contaminated raspberries from Slovenia caused infections in Europe and Canada [1].

However, other examples show that this approach may not be as straightforward, particularly in outbreaks in which the source of contamination of food items is sewage in which case multiple strains, and even different virus families, are often present in the same sample. Under these circumstances, often associated with shellfish-related outbreaks, finding dissimilar sequences in patient samples and in the suspected food does not necessarily provide evidence for the absence of such a link, and more extensive analyses are needed [7].

A comprehensive overview of outbreaks in Europe that were reported with combined epidemiological and virological data showed that particular genotypes seem to be more prevalent in certain settings. For example, the winter peaks in outbreaks in hospitals and homes for the elderly and the global epidemics are mainly caused by GII.4 strains, whereas in food-borne infections a relatively high number of GI viruses are found. Typing of NoV can indicate the need for follow-up studies and intervention strategies. If GI or non-GII.4 strains are found, food-borne transmission is more likely, and research and intervention strategies can be focused on source tracing and elimination.

Global exchange of norovirus data through noronet (noronet@rivm.nl)

A recent expert group meeting, convened by the World Health Organization (WHO), the Food and Agriculture Organization (FAO) and the Organization for Animal Health (OIE), stressed the need for better surveillance of possible food-borne viruses, which presently escape detection. This is a cause for concern because microbiological food safety criteria rely on bacterial indicators that clearly do not reflect virus ecology [8]. Therefore, a global initiative was launched to link researchers from the FBVE network to 19 additional institutes across the world, to discuss harmonisation of methods, and allow comparison of NoV epidemiology across continents.

A retrospective analysis illustrated that the observed GII.4 NoV evolution in Europe reflects a global pattern of emergence of novel variants similar to what has been observed for influenza viruses. This suggests that disease activity in one region could potentially be used as an indicator for "hot seasons" with increased NoV activity in other parts of the world, and data are currently analysed to study if such patterns exist.

Future prospects

Within the FBVE network, databases have been developed for the surveillance of hepatitis E virus (HEV) and hepatitis A virus (HAV) in Europe to provide a basis to identify possible sources of these viruses. Both databases contain numerous HEV and HAV sequences but do not yet allow for rapid typing. We are presently developing tools to provide customised overviews of the available data via web-based queries.

Acknowledgement

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Surveillance and outbreak reports

The epidemiology of hepatitis C virus infection in Sweden

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In Sweden, infection with hepatitis C virus (HCV) has been a notifiable disease since 1990, when diagnostic methods became available. Blood donor screening indicated that about 0.5% of the Swedish population (9 millions) had been HCV infected. Here we present the Swedish hepatitis C epidemic based on data from all the HCV notifications 1990-2006. During this time about 42,000 individuals (70% men) were diagnosed and reported as HCV infected. The majority (80%) were born in 1950 or later, with a high percentage (60%) born in the 1950s and 1960s. Younger people, 15-24 years old at notification, were reported on the same level each year. The main reported routes of HCV transmission were intravenous drug use in 65%, blood transfusions/products in 6%, and sexual in 2%, though unknown or not stated in 26%. Approximately 6,000 of all notified individuals have died during the study period. To conclude, the Swedish HCV epidemic is highly related to the increase of intravenous drug use in the late 1960s and 1970s, with a high proportion of people now chronically infected for more than 25 years, resulting in an increase of severe liver complications in form of cirrhosis and hepatocellular carcinoma. Furthermore the unchanged number of notifications of newly infected younger people indicates an ongoing HCV epidemic.

Introduction

Hepatitis C virus (HCV) infection is a global problem affecting about 140 million individuals, corresponding to an estimated global prevalence of 2.2% [1]. However, there are large geographic variations in the distribution. In southern Europe, the overall prevalence ranges between 2.5% and 3.5%, but in Northern Europe the prevalence is below 1% [2]. In Sweden (which has a population of 9 million), the prevalence of HCV infection was estimated in the beginning of the 1990s, when blood donor screening (introduced in 1991) revealed that 0.2-0.5% of Swedish blood donors had antibodies to HCV infection (anti-HCV) [3,4], and a study of a middle-aged urban population in southern Sweden showed that 0.4% were anti-HCV positive [5]. The chronicity rate in HCV infection is high, about 75% [6], with an increased risk of progression to liver cirrhosis and hepatocellular carcinoma (HCC) [1,7,8].

It has been suggested that the initial spread of HCV infection in southern Europe was iatrogenic and started over 50 years ago, leading to high infection prevalence in older people [2]. In recent decades, the European hepatitis C epidemic has mainly been transmitted through intravenous drug use (IDU) among younger people [2]. In Sweden, non-A non-B (NANB) hepatitis (the majority being hepatitis C) existed but was rare in the 1950s – injecting drug users (IDUs) being also very rare in Sweden at that time. NANB hepatitis became more prevalent in the 1970s as a result of the increase of IDUs during the 1960s and 1970s [9]. In a Swedish study, analyses of stored frozen serum samples from patients with acute hepatitis in 1969-1972 revealed that 52% of the intravenous drug users in the study were anti-HCV positive at that time [10]. In the 1990s, it was found that over 90% of Swedish IDUs were anti-HCV positive by the age of 26 to 30 years [11], and even occasional IDU was associated with a high risk of HCV infection [12,13].

In Sweden, HCV infection is by law a notifiable disease since 1990, when diagnostic methods became available. In this study we present the data on HCV infection, based on the national database of communicable diseases with all diagnosed and notified HCV-infected individuals in Sweden. The aim was to study the dynamics and changes over time with respect to age and route of transmission, and to discuss the impact on the Swedish HCV epidemic.

Patients and methods

In Sweden, both the clinician and the laboratory having diagnosed the HCV infection are obliged to report to the Swedish Institute for Infectious Disease Control (SMI) [14]. The laboratories report all results indicating a present infection, as positive HCV antibodies and/or HCV-RNA analyses. These laboratory results are sent to the clinician who also has to report to the SMI. This clinical notification contains information of epidemiological interest, such as suspected route of transmission, but no information on HCV genotype. The registration does not distinguish acute from chronic HCV infection and in most reports, especially in the beginning of the 1990s, the diagnosis is based on a positive anti-HCV test and therefore some patients with a resolved infection could be in the register. Every Swedish resident has a unique 10-digit personal identification number that is used on these notifications and at all contacts with the healthcare system. The universal use of this personal identification number excludes the risk of double reporting of the same patient.

For this descriptive work, we used the register with all the clinical HCV notifications from year 1990 until the end of December 2006. This closely represents the whole, diagnosed, HCV infected population in Sweden.

Results

Annual reporting

Out of a total of 42,153 HCV notifications during the study period, more complete clinical information was reported for 41,026 individuals. The clinical reporting started with only 459 notifications in 1990, rising to a maximum peak of 4,537 in 1992, over some

Figure 1

Number of notifications of hepatitis C by sex and year of notification, Sweden, 1990-2006

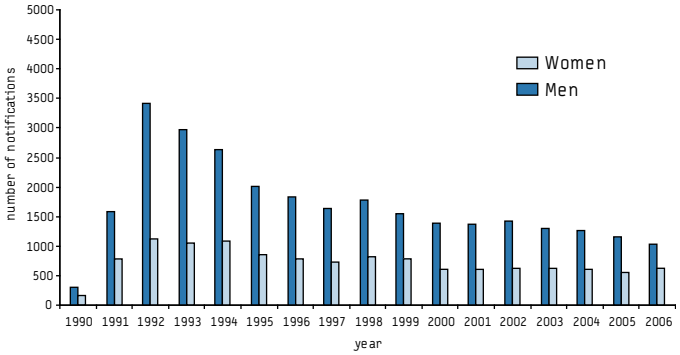


Figure 2

Number of notifications of hepatitis C by sex and year of birth, Sweden, 1990-2006

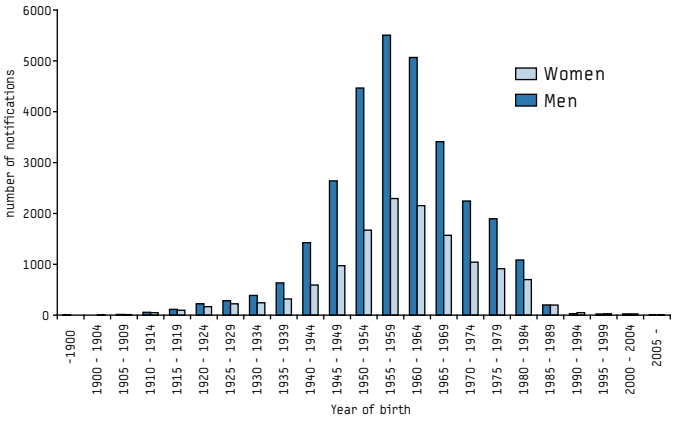


Figure 3

Number of hepatitis C notifications by age at notification and year, Sweden, 1990-2006

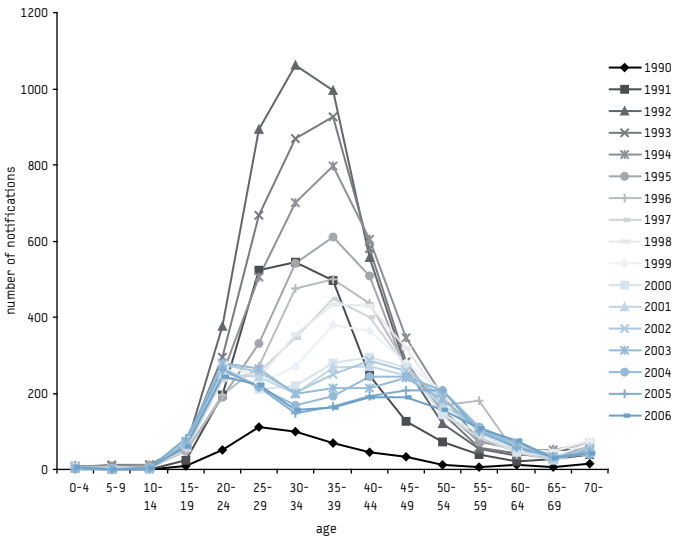
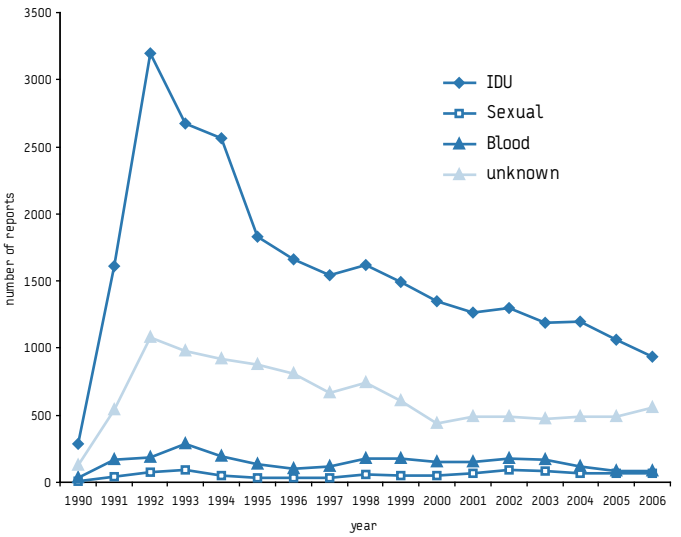


Figure 4

Number of hepatitis C notifications by year and route of transmission, Sweden, 1990-2006



years declining to about 2,000 notifications each year, and then the lowest since 1990 with 1,648 notifications in 2006 (Figure 1).

Demography

Of the 41,026 individuals with a clinically reported HCV infection 12,384 (30%) were women. The majority (80%) were born in 1950 or later, with a high representation of people born in the 1950s (32%) and the 1960s (28%), and the median birth year was 1958 (Figure 2). Until the end of 2006, there were 185 (<0.5%) notifications of people born 1990 or later. Diagnosis and notification were most common at ages from 20 to 50 years (82%) and totally 84% (women 82%, men 87%) were notified before 50 years of age (median age 37 years). Age at notification has changed over the years (Figure 3). In the 1990s, the number of notifications peaked at ages representing the cluster of earlier infected people born in the 1950s and 1960s. However, from 2000 to 2006 there were still high numbers of late diagnosis in people born in those decades. The total number of people notified at age 20-24 was 375 in 1992, but has since then been about the same over the years (ranging from 188 to 294; mean 254 per year), but 20-24 was the most prevalent age at notification in 2006 as the number of notifications of older people had decreased.

According to the reports, 91% of the HCV infected were native Swedes. In patients reported 1990-1996 there were 6% immigrants, and among those reported in 1997-2006 there were 11% immigrants.

Reported route of transmission

According to the notifications, the most probable route of transmission was former or ongoing IDU in 26,772 (65%), transfusion of blood or blood products in 2,534 (6%), and sexual contact in 971 (2%). There were also a few reports on mother-to-child (n=73) and occupational (n=29) transmission, but in 26% the transmission route was unknown or not stated. Notifications by year and reported route of transmission (Figure 4) revealed that in

Table

Number of notifications of hepatitis C by age group and route of transmission, Sweden 1990-2006 (n=42,153)

Age at notification	Reported route of transmission						Total	
years	Blood/blood products	Intravenous drug use	Sexual	Mother to child	Occupa-tional	Unknown/not stated		%
0-4	5	0	0	38	0	29	72	0.2
5-9	22	0	0	9	0	21	52	0.1
10-14	38	2	0	6	0	26	72	0.2
15-19	52	629	31	9	0	190	911	2
20-24	73	3,322	97	8	1	661	4,162	10
25-29	96	4,140	121	1	2	1,160	5,520	13
30-34	145	4,675	143	2	2	1,527	6,494	15
35-39	188	5,103	148	0	6	1,865	7,310	17
40-44	197	4,089	167	0	5	1,775	6,233	15
45-49	262	2,677	128	0	1	1,401	4,469	11
50-54	270	1,490	67	0	7	1,066	2,900	7
55-59	240	580	35	0	2	678	1,535	4
60-64	195	229	15	0	2	475	916	2
65-69	197	62	5	0	1	320	585	1
70-74	144	30	1	0	0	236	411	1
75-79	130	2	0	0	0	159	291	0.7
80-84	81	0	0	0	0	65	146	0.3
85-	32	2	0	0	0	40	74	0.2
Total (%)*	2,367 (6)	27,032 (64)	958 (2)	73	29	11,694 (28)	42,153	100

* Some of the % figures are not exactly the same as in the text where we used the 41,026 notifications.

1992 IDU was reported in 3,200 (70%), this had decreased to 932 (57%) in 2006. Reports of infection through blood or blood products (before 1992) had an absolute peak with 289 (7%) notifications in 1993, but have then declined to the lowest value since 1990, 87 (5%) individuals in 2006. The reported route of HCV transmission by age at date of notification (Table 1) revealed that already at the age of 15-19 years IDU was important, but in high ages (>65 years) transfusion of blood/blood products or unknown/not stated were the most reported routes of transmission.

Discussion

The notification of HCV in Sweden started in 1990 when the first generation of diagnostic tests for anti-HCV became available. In 1991, the second-generation anti-HCV assays were introduced, the blood-donor screening was initiated, and anti-HCV testing became common. People with elevated liver enzymes, liver disease of unknown cause, a diagnosis of chronic NANB hepatitis, or a history of former IDU or blood transfusions, were tested. In 1992, more than 4,000 individuals were diagnosed with an HCV infection and reported to the SMI. This peak was due to testing of people, most of them born in the 1950s and 1960s, who had been infected for a long time without the opportunity to get a correct diagnosis. The annual reporting has then slowly declined to less than 2,000 notifications per year as the number of notifications of persons born in the 1950s and 1960s decreased. However, the number of notifications of younger people, 15-24 years old, has remained the same over the years, indicating that the epidemic has been ongoing with about the same intensity during the last decades.

The spread of HCV in Southern Europe probably started more than 50 years ago, leading to high infection prevalence in older people [2]. In Sweden, 80% of the reported HCV infected individuals were born in 1950 or later and 60% in the 1950s and 1960s. This is consistent with the theory that the spread of HCV in Sweden started with the introduction of IDU in the mid 1960s, with an increase in the 1970s when IDU became more common, mostly among young people, i.e. those born in the 1950s [9]. According to the Swedish report to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, http://www.emcdda.europa.eu), the prevalence of illegal drug use then declined in the 1980s but has increased again in the late 1990s, and so has the number of direct drug related deaths. There is a risk that this increase during the last decade will cause an increase in the spread of HCV, though still not apparent in the surveillance system. The dominance of men in the HCV-infected population is due to the high percentage of IDU that is more common in Swedish men than women according to the EMCDDA.

The percentage of immigrants (9%) in the HCV infected population was somewhat lower than in the general population of which 12.9% (December 2006) were born in another country than Sweden (http://www.scb.se/templates/tableOrChart____26040.asp). This is in contrast to reports from other European countries where immigrants from high endemic countries are considered to account for a large proportion of the HCV population [2]. However, also in Sweden a high proportion of immigrants have come from countries with a high HCV prevalence and the low percentage among reported HCV infected individuals could indicate a lower

screening activity among immigrants or a selection of immigrants with a lower HCV prevalence than the general population of their former home countries.

In 26%, no probable route of transmission was given on the notification. This could to some extent be explained by the fact that many notifications were made at the time of diagnosis after only brief contact with the infected individual. A probable route of transmission could have been identified later on, for example sporadic IDU, but the notification will usually not be corrected. However, there is also a possibility of unknown routes of transmission and iatrogenic transmission associated with medical procedures. In Sweden, a few outbreaks of HCV transmission through medical procedures have been reported [15-19] – in some of these, the most likely route of transmission was contamination of saline multidose vials.

The risk of HCV transmission through blood transfusions and blood products is very low as a result of the introduction of blood donor screening in 1991. However, some patients receiving intravenous immunoglobulin were HCV infected until February 1994, when contaminated batches of immunoglobulin were recalled and exposed patients traced [20]. Recently, the National Board of Health and Welfare recommended that all people who during childhood have been treated with blood transfusions during 1965 to 1991, because of heart surgery, neonatal exchange transfusion, prematurity, or cancer, should be identified and tested for HCV infection (http://www.socialstyrelsen.se/Publicerat/2007/9775/2007-130-6.htm).

A recent study on cause of death in HCV-infected individuals in Sweden revealed that approximately 14% of those notified in 1990-2003 were dead by December 2003 [21]. This study demonstrated an increased all-cause mortality about six times higher than the general population, with a 30-40 times excess mortality from liver disease in higher age groups, both in people infected through IDU and blood/blood products, and a great excess mortality from psychiatric (drug-related) and external causes (as injuries, intoxication, suicide) in younger people. This indicates that about 5,800 of the HCV infected in the population presented here may be dead, leaving about 36,000 diagnosed, living, anti-HCV positive individuals in Sweden. However, there are also individuals with an undiagnosed HCV infection; the size of this population is not known but is supposed to be substantial. In the study on cause of death, 16% of all deaths (not included in the statistical analysis) occurred less than six months after HCV diagnosis and the HCV infection was possibly diagnosed because of a lethal disease [21]. In a Swedish study on HCV and liver cancer, a high proportion had the HCV diagnosis close to liver cancer diagnosis [8], indicating that there is a significant population with an undiagnosed HCV infection. Therefore, it seems realistic to estimate the anti-HCV positive population currently alive in Sweden at around 45,000 individuals, i.e. an anti-HCV prevalence of 0.5% as discussed in the early 1990s [4,5], some with a spontaneously resolved infection but the majority with a chronic infection. The treatment for HCV has improved during the last decade, but there are no official statistics on how many have been treated and cured.

The impact of the HCV epidemic is the morbidity and mortality in the long run of this chronic infection. People diagnosed and eligible for treatment are at little risk for spreading the disease, but treatment is important in order to diminish the long-term complications such as liver cirrhosis and hepatocellular carcinoma. The incidence of liver cancer in Swedish HCV patients was recently studied [8]. During the study period, 1990-2004, the primary liver cancers in the HCV cohort represented about 5% of all primary liver cancers in Sweden (approximately 500 per year). In the later years of the study period, as the HCV cohort grew older, about 10% of the liver cancer patients were found in the HCV cohort. The relative risk for liver cancer was about 40 times higher than in the general population in people who had been HCV infected for more than 25 years (age-, sex- and calendar year-specific incidence rates were used). The absolute risk of developing primary liver cancer within 40 years of HCV infection was 7% in the HCV infected population. In the study on cause of death [21], the risk of death from liver cancer was 35 times higher in all HCV infected (20 times among those infected through blood/blood products) than in the general population. HCV related liver cirrhosis is the most common indication for liver transplantation in Europe and the United States. Also in the Nordic countries, according to the Nordic Liver Transplant Registry (www.scandiatransplant.org), the number of transplanted patients with hepatitis C associated cirrhosis has increased markedly over the last 10 years. There have been more than 1,800 liver transplantations performed in Sweden since 1984, of which about 20% were in patients with HCV related cirrhosis, with or without HCC. In 2005, 30% of liver transplantations carried out in Stockholm were in patients with HCV-related liver disease [22]. The number of patients with serious complications to the HCV infection is increasing in spite of new and better treatment opportunities. This could be related to the age distribution in the HCV cohort: the large group infected in the 1970s have now been chronically infected for 25-35 years, which is the reported latency time to develop liver complications [7,8].

Conclusions

To conclude, the spread of HCV infection in Sweden is highly related to the increase of IDU in the 1970s. The prevalence of anti-HCV in the general population is about 0.5% and a large proportion of the HCV infected in Sweden are born in the 1950s and 60s and have now an increasing risk of morbidity and mortality from liver complications. As a result of a decline in the prevalence of IDU in the 1980s, the epidemic spread probably declined in the 1980s, but is still of the same magnitude as it was in the beginning of the 1990s, and could increase again due to an increase in IDU during the last decade. This will have an overwhelming effect on the healthcare system, a problem that can only partially be met by treating those at risk of developing progressive liver disease. The greatest efforts should be aimed at diminishing the spread, i.e. combating the IDU.

Sweden is a low-prevalence country for HCV infections. The results of this study would likely be relevant also for other low-prevalence European countries. They clearly demonstrate that a full understanding of hepatitis C epidemiology in a country requires a detailed trend analysis of age structures and transmission routes in the notified patients.

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Surveillance and outbreak reports

Hepatitis B virus transmission from a nurse to a patient, France, 2005

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Introduction

Infection by the Hepatitis B virus (HBV), which is often asymptomatic at the acute phase, can progress to chronic liver disease, particularly when infection occurs early in life.

Hepatitis B is mainly transmitted sexually or through blood or body fluids. Episodes of healthcare-associated transmission of HBV have been previously described [1-3]. Transmission of HBV results either from patient to patient through invasive healthcare procedures with improper disinfection of devices used between patient care or from a patient to a healthcare worker (HCW). Transmission can also take place from a chronically infected HCW to a patient. In those episodes, breaches in healthcare practices and standard precaution play a major role.

Prevention of HBV transmission in healthcare settings also relies on the immunisation of HCW, which has been mandatory in France since 1991. HCW are considered immune if they have documented proof that they were vaccinated before 13 years of age, or if a positive anti-HBs antibody test is provided [4].

Description of the episode

In 2005, the Institut de veille sanitaire (InVS) in France was notified of a case of HBV seroconversion in a 35 year-old-female patient who had been operated on twice in a healthcare facility for a bilateral cirsectomy (excision of a section of a varicose vein) in the lower limbs. The implicated healthcare facility reported the case after being informed by the patient of the occurrence of acute laboratory-confirmed hepatitis B 11 weeks after the two operations. An epidemiological investigation was immediately conducted by the regional unit for nosocomial infection control and district and regional health authorities, together with methodological support and guidance from the InVS.

The investigation initially focused on confirming the absence of other modes of exposure to HBV in the patient by interviewing regarding risk factors. The serological status of the patient's partner was controlled and was negative. The only potential risk factor for the case in the six months preceding the diagnosis of acute hepatitis B was dental care.

We then investigated a potential transmission through healthcare, for which the source could have been either an infectious patient hospitalised at the same time as the case or an HCW involved in treating the patient. All patients (n=5) who had surgery at both surgical sessions as the index patient were recorded and screened for HBs Ag and anti-HBs Ab. All results were negative. We audited hygiene practices in the operating room based on a standardised questionnaire. Breaches in the implementation of standard precautions were documented, particularly as regards to appropriate hand washing. Procedures for disinfecting medical devices had not been updated (in particular those concerning laryngoscope blades). The results of the audit were presented to all HCWs of the hospital to stress the importance of strict compliance with standard precautions.

The remaining hypothesis to investigate was transmission from an infectious HCW. No exposure to blood or blood products had been reported while the case was hospitalised. The list of current HCWs involved in caring for the patient, either in the surgery room, the recovery room or the hospital ward was established. Screening for HBV proposed to, and done by the 22 health and paramedical workers did not identify any chronic carrier of HBV.

Meanwhile, the investigation revealed that an anaesthetic nurse who was on sick leave at the time of investigation had participated in one of the two surgical procedures for the case. This HCW had been vaccinated for hepatitis B in the early 1990s by the occupational health service. Following a serological control in 1992, the nurse had been considered to be a 'healthy carrier' with clinically healed hepatitis B requiring no follow-up. A date of infection could not be established. Clinical investigations had revealed a chronic hepatitis B with a high level of viral replication. The anaesthetic nurse who had been working in the healthcare setting since 1995, mainly in orthopaedic and vascular surgery, performed anaesthesia with the laying and management of venous perfusions and vertebral anaesthesia. During interview she reported not wearing gloves and needle sticks on several occasions without ever notifying any past blood exposure to the occupational health services.

After obtaining the HCW and the patient's consent, a molecular and phylogenetic analysis of the viral strains was performed. The analysis was carried out on independent regions of the HBV genome (gene S and gene C), and showed 99.8% sequence homology of an HBV strain of genotype D in both subjects.

Discussion

According to published data, over 50 HCW have been involved in HBV transmission to patients during care since the 1970s. Most were surgeons, obstetricians or dentists who performed invasive procedures [3,5,6], and only one episode was linked to a nurse [7].

Our epidemiological and molecular investigation strongly suggests HCW-to-patient transmission. It was not possible, however, to identify the exact mode of transmission. The audit of hygienic practices indicated breaches in hand hygiene. Carrying out invasive care, such as laying or handling peripheral i.v. devices, may have contributed to HBV transmission considering the high viral load of the HCW.

This incident shows that the full and strict adherence to standard precautions must be stressed even in situations which may seem 'ordinary' at first sight. This episode also stresses the importance for occupational health services to document and strictly follow-up HCW immunization status. The most recent immunisation recommendations of the French Ministry of Health define precisely the working conditions for HCW regarding hepatitis B [4].

The discussion on how to manage HBV-infected HCW continues. Different guidelines are implemented in European countries to exclude HCW from performing exposure-prone procedures. A European consensus group produced recommendations for preventing HCW to patient transmission of viral hepatitis in 2003 and agreed that each country may define its own HBV DNA cutoff level [8].

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Research articles

Trends in drug consumption and risk of transmission of HIV and hepatitis C virus among injecting drug users in Switzerland, 1993-2006

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As a part of the HIV behavioural surveillance system in Switzerland, repeated cross-sectional surveys were conducted in 1993, 1994, 1996, 2000 and 2006 among attenders of all low threshold facilities (LTFs) with needle exchange programmes and/or supervised drug consumption rooms for injection or inhalation in Switzerland. Data were collected in each LTF over five consecutive days, using a questionnaire that was partly completed by an interviewer and partly self administered. The questionnaire was structured around three topics: socio-demographic characteristics, drug consumption, health and risk/preventive behaviour. Analysis was restricted to attenders who had injected drugs during their lifetime (IDUs). Between 1993 and 2006, the median age of IDUs rose by 10 years. IDUs are severely marginalised and their social situation has improved little. The borrowing of used injection equipment (syringe or needle already used by other person) in the last six months decreased (16.5% in 1993, 8.9% in 2006) but stayed stable at around 10% over the past three surveys. Other risk behaviour, such as sharing spoons, cotton or water, was reported more frequently, although also showed a decreasing trend. The reported prevalence of HIV remained fairly stable at around 10% between 1993 and 2006; reported levels of hepatitis C virus (HCV) prevalence were high (56.4% in 2006). In conclusion, the overall decrease in the practice of injection has reduced the potential for transmission of infections. However as HCV prevalence is high this is of particular concern, as the current behaviour of IDUs indicates a potential for further spreading of the infection. Another noteworthy trend is the significant decrease in condom use in the case of paid sex.

Introduction

Drug consumption, especially by injecting drug use, is a significant problem in Switzerland which culminated in the early 1990s with open drug scenes. Switzerland also had the highest rate of newly diagnosed HIV infections in Europe in the late 1980s [1]. The HIV epidemic is concentrated in IDUs and men having sex with men with estimated prevalences of more than 5%. Many harm reduction services and treatment options for IDUs have been progressively developed in Switzerland since the 1980s in response to the HIV/AIDS epidemic:

- Low threshold facilities (LTFs), characterised by easy access, anonymity and no treatment offered, with needle exchange programmes including or not supervised drug consumption rooms for injection or inhalation;
- Permission for sale of injection equipment in pharmacies; and
- Vaccination programmes against hepatitis B, methadone substitution/maintenance treatment, and treatments with medically prescribed heroin [2].

Within the framework of both the evaluation of the Swiss government measures – introduced in 1991 – to reduce drug-related problems [2] and the evaluation of the Swiss HIV/AIDS prevention policy [1], five successive national surveys of LTF attenders [3] were conducted, in 1993, 1994, 1996, 2000 and 2006. In this way, a behavioural surveillance system was established among LTF attenders who had injected drugs in their lifetime (named here IDUs) [4]. The decision to concentrate on this group in LTFs reflects the intention to follow up on trends regarding the possible transition from injecting to non-injecting drug use. As all LTFs offering inhalation rooms were included, it is possible to find in these locations injectors currently not injecting but still consuming drugs by inhalation. This article presents the evolution over time of the main indicators included in this system.

Methods

Behavioural surveillance among IDUs is based on a periodic survey of LTFs, using a questionnaire in German or French, proposed to all users of the facility during five consecutive days. Each LTF was eligible for the survey. However, participation varied over time, the number of LTFs included increased: 13 in 1993, 15 in 1994, 16 in 1996, 23 in 2000 and 22 in 2006. In 1993, 1994 and 2000, the three LTFs based in the canton of Zurich did not participate, while local studies were being conducted over the same period. In 2000, Zurich provided data from a local study using most of our indicators. In 2006, the LTFs were located in 10 cantons; half of these included a supervised drug consumption room for injection or inhalation.

Each survey was conducted at the same period of the year, at the end of the first semester (May, June) except for 1996 (autumn). Over five consecutive days, two specially trained interviewers asked all LTF attenders to answer an anonymised questionnaire.

The questionnaire was structured according to three topics:

- Socio-demographic characteristics;
- Drug consumption: frequency of heroin and cocaine use during the previous month, injection during the previous six months and the last month, number of injections in the last week, current substitution treatment; and
- Health and risk/protection behaviour: perceived health, HIV testing and results, hepatitis B and C testing and results, borrowing of injection material (injecting with a syringe/needle already used another person) during the previous six months and the last month, condom use during the previous six months with occasional sexual partners, steady partner(s), or clients in case of paid sex.

The first part of the questionnaire, including socio-demographic characteristics, drug consumption and injection practice was undertaken via a face-to-face interview; the second part, including questions on sharing of injection material, sexual behaviour and condom use, and social integration, was self-administered or undertaken face-to-face if the respondent so wished. The last part, on health status, including testing history and HIV/HCV status, was self-administered and there was no control over the completion of this part by the interviewer.

Questionnaires declared as unreliable by the interviewers – usually questionnaires with many inconsistencies – were excluded from the analysis (32 in 2006). The number and characteristics of non-participants (sex, estimated age, reason for refusal) were documented by the interviewers, except in 1993.

Bivariate analysis used Pearson's chi-square test and trend analysis was conducted on annual aggregated data. Trend significance was assessed using the nptrend test (nonparametric test) available on Stata.

Results

Participation and selection

The participation rate of LTF attenders was 76% in 1994, 81% in 1996, 69% in 2000, and 66% in 2006. It varied across cantons (from 45% to 79%) and was lower when the LTF was a mobile unit (bus), which only distributed material. The surveys included 1,119 individuals in 1993, 764 in 1994, 944 in 1996, 924 in 2000, 1,083 in 2006. Participants and non-participants did not differ according to age and sex.

The analyses presented were restricted to IDUs having ever injected drugs, as defined above: 993 in 1993, 677 in 1994, 855 in 1996, 832 in 2000, and 817 in 2006. This selection represents about 90% of 1993 to 2000 respondents and 75% of the 2006 sample.

Socio-demographic characteristics of IDUs

Around three quarters of the IDUs are men. This proportion remained stable over time. The median age in all IDUs increased significantly, from 26 years in 1993 to 36 in 2006 ($p<0.01$) and the proportion of IDUs aged 25 years or younger decreased from 39.3% in 1996 to 7.5% in 2006. This trend is observed in both sexes. A stable proportion of one third of IDUs completed compulsory schooling. Employment during the last month, part- or full-time, decreased over time, from 44.8% in 1993 to 36.8% in 2006 ($p<0.01$); over the same period, people receiving revenue from social insurance such as disability pension or unemployment benefit or from social assistance increased from 8.8% in 1993 to 35.4% in 2006, respectively 27.8% to 45.0% ($p<0.01$ for both situations). The proportion of IDUs living without fixed abode during the last month decreased from 11.4% in 1993 to 6.2% in 2006 ($p<.01$).

Consumption

Almost all IDUs, have consumed heroin (98%) or cocaine (95.5%) in their life. However, current consumption (in the last month) changed over time: for heroin from 60.5% in 93 to 43.1% in 2006 and for cocaine from 23.7% in 1993 to 63.5% in 2006 (for both cases, $p<0.01$). Furthermore the proportion of IDUs on methadone treatment among IDUs in LTFs increased from 37.2% in 1993 to 59.1% in 2006; 5.1% are on medically supervised heroin treatment (11.2% in 1996).

About half of the IDUs reported having ever had an overdose (52.3% in 1996, 48.2% in 2000, 54.7% in 2006, $p=0.240$.)

Injection practice and risk exposure

Current injection practice is decreasing: 95.1% of IDUs had injected during the past six months in 1993 versus 74.2% in 2006 (see Table 1). The proportion of "new injectors" having begun to inject in the last two years, is also decreasing: from 18.7% in 1993 to 3.3% in 2006.

For current injectors, the median number of injections performed in the last week by was halved between 1996 and 2006, from 14 to 7. Most injections took place at home (56.4% in 2006) or in a supervised drug consumption room (32.8% in 2006).

Almost half of IDUs have borrowed used injection equipment (syringe/needle) at least once during their lives, and almost one in ten did so in the past six months. This proportion has been quite stable since 1994, after a decrease between 1993 and 1994. Sharing of other injection paraphernalia such as spoons, filters and water, is more common, although on the decrease since 1996 (except for cotton sharing). In 2006, 23.4% reported having had an abscess in relation with injection in the past six months.

Sexual risks

In 2006, about half of the IDUs had sexual intercourse with a steady partner in the past six months (56.9% in 1993, 54.4% in 1994, 50.8% in 1996, 54.5% in 2000, 51.9% in 2006, $p=.127$) and less than 30% of them systematically used condoms (25.5 in 1993, 25.5 in 1994, 26.7% in 1996, 28% in 2000, 28.5% in 2006, $p=0.211$). About 30% reported sexual intercourse with occasional partner(s) in the past six months (31.8% in 1993, 28.4% in 1994, 30.9% in 1996, 31.4% in 2000, 27.3% in 2006, $p=0.122$), the proportion of those declaring systematically using condoms in this situation increased (59.5% in 1993, 70.8% in 1994, 64.4% in 1996, 71.1% in 2000, 71.8% in 2006, $p<0.01$).

The proportion of women reporting paid sex in the past six months remained stable (16.4% in 1993, 23.7% in 1996, 18.9% in 2000, 19.8% in 2006, $p=0.98$.) and condom use with clients decreased significantly (90.0% in 1994, 94.4% in 1996, 74.4% in 2000, 81.4% in 2006, $p=0.030$).

HIV/HCV testing

Over 90% IDUs have already had an HIV test (see Table 2). In 2006, 62.4% had been tested during the past two calendar years. The reported HIV prevalence among those tested remained

Table 1

Injection practice and risk exposure (in %) among injecting drug users*, Switzerland , 1993-2006 (n=4,174)

	1993**	1994**	1996	2000	2006	nptrend ; p=
N	993	677	855	832	817	
Injection						
Injection in the last 6 months	95.1	95.1	95.0	86.8	74.2	p<0.01+
New injectors***	18.7	16.4	7.4	*3.2*	3.3	p<0.01+
Median number of years injecting	6	7	9	*12*	15	**** p<0.01+
Median number of injections in the last week (among the last 6 months injectors)	-	-	14	*7*	7	**** p<0.01+
Most frequent place for injecting						p<0.01+
Private place	-	47.4	58.4	*60.7*	56.4	
Public place outdoors	-	18.2	5.5	*6.0*	3.1	
Public place indoors	-	2.6	3.0	*3.4*	2.0	
Supervised drug consumption room	-	29.8	28.6	*24.4*	32.8	
Non response	-	2.0	4.6	*5.5*	5.6	
Risk exposure						
Ever borrowed used equipment*****	39.1	37.1	43.3	44.6	42.7	0.029+
Borrowed in the last 6 months ***** (among the last 6 months injectors)	16.5	8.9	10.7	11.5	8.9	p<0.01+
Borrowed in the last month (among the last month injectors)					4.9	
Lended equipment in the last 6 months		9.2	9.4	8.6	7.8	0.308
Sharing of material serving to prepare the injection in the last 6 months (among the last 6 months injectors)						
Spoon	-	-	67.1	*49.9*	31.9	p<0.01+
Filter	-	-	42.5	36.2	21.1	p<0.01+
Cotton	-	-	3.1	*6.1*	2.0	0.115
Water	-	-	-	*24.6*	15.8	p<0.01+

+ p<=0,05 significant (statistical significance of trends after exclusion of missing data)
* participants who had injected drugs during their lifetime
** Zurich not included
*** % of persons having begun injecting in the last 2 years
**** Pearson chi-square
***** Syringe or needle already used by other person

italics : no data available from Zurich in 2000

stable between 1993 and 2006 at about 10% (lowest value 8.8% in 1994, highest 11.4% in 1996 and 2000, p=0.560). In 2006, 71.8% of persons tested HIV positive were on antiretroviral treatment.

In 2006, 88.4% had ever been tested for hepatitis C, 58% of them during the past two calendar years; reported prevalence of HCV was 56.4%, out of those 16.7% were currently on treatment.

Persons tested positive for HCV were compared to those HCV negative or untested (see Table 3). HCV-positive IDUs were older, more likely to be HIV-positive and more often declared a bad or quite bad health status. They were also more likely to be active injectors than untested or HCV-negative persons. The proportion of "borrowers" in the past six months among HCV was not significantly different from that of the other group, although a higher proportion of them had shared material serving to prepare injection. However, they were more likely to have used a condom at last intercourse.

Discussion

Switzerland is one of the Western European countries, along with France [5,6], Italy [7], Germany, the Netherlands (cohort data) [8], Spain [9], and the UK [10,11], where surveys or other types of data collection on behaviour in IDUs have been conducted repeatedly. Recruitment in LTFs allows us to reach a particularly vulnerable and marginalized population of IDUs. A study on hard-to-reach IDUs conducted in Switzerland showed that the majority do attend LTFs [12].

However, our study has limitations. The type of clients attending LTFs may vary in the course of the day (there was no data collection in 1996 and 2000 in the evening or during week-ends) or over the year. Services offered and opening hours can vary across the LTFs and from year to year. Attendance and participation varied between surveys: the proportion of participants contributed by each town differed from survey to survey. The conditions surrounding the completion of the questionnaire are difficult per se (stress in the premises, persons under the influence of drugs or withdrawal

Table 2

HIV and hepatitis C testing performed and HIV / hepatitis C reported prevalence among injecting drug users* (in %), Switzerland, 1993-2006 (n=4,174)

	1993	1994	1996	2000	2006	nptrend ; p=
N	993	677	855	832	817	
Ever been tested for HIV	90.2	92.5	93.7	96.2	95.8	p<0.01+
HIV status at last test						0.560
HIV positive	10.8	8.8	11.4	11.4	10.9	
HIV negative	87.2	89.3	86.5	86.5	87.0	
non response / unknown	2.0	1.9	2.2	2.1	2.2	
Ever been tested for HCV	-	-	-	*79.8*	88.4	*** p<0.01+
HCV status at last test						*** 0.064
HCV positive	-	-	-	*61.5*	56.4	
HCV negative	-	-	-	*34.3*	40.4	
non response / unknown	-	-	-	*4.2*	3.2	

+ p<=0,05 significant
* participants who had injected drugs during their lifetime
** Zurich not included
*** Pearson Chi-square

italics : no available data from Zurich in 2000

Table 3

Characteristics of hepatitis C positive intravenous drug users versus others (in %), Switzerland, 2006 (n= 817)

	Not tested or VHC-negative	VHC-positive	Chi-square P=
N	410	407	
Female	25.6	28.4	0.371
35 years old and more	52.3	65.4	p<0.01+
Unemployed last month	61.5	64.9	0.314
Education: compulsory school	27.2	33.3	0.058
Private housing last month	84.9	85.8	0.725
Injected last week	56.8	66.3	0.005+
Borrowed in the last 6 months	7.1	10.5	0.150
Sharing of material serving to prepare the injection in the last 6 months			
spoon	27.1	36.8	0.011+
filter	17.8	24.8	0.040+
cotton	3	1.2	0.137
water	13.7	18.3	0.133
Used condom at last intercourse	46.9	54.2	0.041+
HIV status			p<0.01+
non tested	6.2	0.7	
HIV-positive	7.2	13.8	
HIV -negative	84.6	83.2	
Self evaluated health status / bad, rather bad	20	30.9	0.001+

+ p<=0,05 significant

symptoms) and are difficult to maintain strictly stable (degree of quietness in the premises, proportion of persons preferring to complete the second part of the questionnaire with the interviewer, etc.). Furthermore, LTF attenders may not be representative of all IDUs in the towns surveyed: migrant IDUs insufficiently proficient in the two languages of the questionnaire (French and German) were not included as for example in Geneva in 2006 with a group of young eastern European migrant IDUs. The survey does not include IDUs living in smaller cities without LTFs, and the results may therefore not be representative of all IDUs in Switzerland. In spite of these limitations, the type of recruitment in all Swiss LTFs over the same time and period of the year and with the same procedures provides a reasonable approximation of a national representative sample of all attenders of this type of structure.

Over a 13-year period (1993-2006), the average age of IDUs rose by 10 years; there are increasingly fewer young and new IDUs in LTFs. This may be for several reasons: a change in the type of consumption which would delay the transition to intravenous (i.v.) drug use and attendance of LTFs, a decrease in the capacity of LTFs to attract young IDUs, an increase in the number of IDUs entering treatment early in their drug consuming career, or a true decrease in the number of persons having ever consumed heroine or cocaine by injection.

It seems unlikely, however, that this trend is due to limited access to LTFs among juveniles or new users, since a Swiss study of drug users not in treatment, recruited at home or in public places, showed that following their transition to i.v. drug use, they rapidly made contact with an LTF [13]. There has been an increase in the number of persons entering methadone substitution treatments over the period, although without decrease in the average age at entry (see below). A real fall in the number of new IDUs is however highly probable since ageing has also been observed among other populations of IDUs: during the same period the average age of persons entering methadone outpatient treatment, residential treatment and heroin substitution treatment rose in Switzerland [2,14,15].

IDUs attending LTFs tend to be severely marginalised and their social situation has shown little improvement. Even if the percentage of homeless IDUs has decreased, the rates of unemployment and of IDUs receiving social benefits have increased.

Types of drug consumed and mode of consumption show significant changes over time: heroin consumption decreased along with an increase in cocaine consumption whereas i.v. drug use, the proportion of new injectors and the number of injections in the past week among injectors decreased sharply. Similar trends have been observed in Catalonia, Spain [9] and in several European countries [16]. However, there are differences between cities: e.g. in Geneva, new populations of injectors, younger, heroin consuming, some of them migrants, are appearing [17].

Although over half of IDUs attending LTFs are undergoing substitution treatment, they probably represent a minority of all persons in treatment: about 17,000 in 2005 for the whole of Switzerland [18]. Swiss methadone treatment policy has evolved towards a variety of approaches differing according to individual needs and including maintenance. In this case, persistence of consumption is generally not a reason to exclude patients [19]. An unknown proportion of these patients, still consuming drugs such as heroin or cocaine, also visit LTFs.

Trends in indicators of risk exposure regarding HIV or HCV differ: the borrowing of used equipment in the last six months still exists in a minority of current IDUs, the proportion of those doing so remaining rather stable around 10% in the last three surveys, being one of the lowest rates reported in Europe. For example, sharing ie. passing on or borrowing used syringe or needle in the last month was between 28% to 39% in England in 2000 [20], 13% of IDUs declared having borrowed equipment in the last month in France in 2004 [8] and between 15.6% and 19.8% in the past six months in Barcelona in 2005 [9].

Sharing of material serving to prepare injection remains higher, although decreasing. This practice is of particular concern in regards to HCV: sharing paraphernalia is an important route for HCV transmission and reported prevalence of HCV infection is high among IDUs and a high percentage of HCV-positive IDUs share this type of material with other IDUs (Table 3).

A relative stability is observed regarding sexual risk exposure and protection. About one quarter of the IDUs report systematic condom use with steady partners, and more than two-thirds with occasional partners, a level of protection comparable to that observed in the general population [21]. A significant decrease in protection through the use of condoms in the case of paid sex is nevertheless reported.

Most IDUs have undergone HIV testing and the reported prevalence remained stable over time at about 10%.

HCV testing seems to be increasing and levels of reported HCV prevalence are high. Since the beginning of the nineties prevalences between 13% and 80% in IDUs have been reported in Switzerland [3]. Reported HCV prevalence is probably underestimating true prevalence, as it was demonstrated in France [6]; on the other hand, reported HIV prevalence was more similar to biological prevalence.

High levels of hepatitis C seroprevalence, with lower or decreasing HIV prevalence among drug users have also been observed in many countries: France [22], England [23], Italy [24], Norway [25], European Union in general [26, 27], Canada [28], USA [29], Australia [30].

Conclusions

In conclusion, the overall decrease in i.v. drug use in Switzerland has reduced the potential for transmission of HIV and HCV, in spite of the persistence of injection material sharing by a minority of IDUs. Newly diagnosed HIV infections in IDUs notified in Switzerland decreased sharply during the 1990s. This decrease continued in recent years with a stabilisation in 2006 and 2007 (respectively 60 and 61 new cases)[31]. However, the epidemiological situation needs to be monitored carefully since a new increase in heroin consumption and i.v. injection is possible with the increase in production observed in recent years [16].

To address some of the short comings from our survey, other methods of data collection for behavioural surveillance (including collection of biological samples) may be considered, in particular methods including a recruitment extending outside LTFs – such as respondent driven sampling - in order to explore the existence of populations of injectors, especially young ones, possibly not using LTFs. Furthermore, to better take into account the fact that part of their clientele is on substitution treatment, LTFs should consider new ways of linking with treatment centres. Special attention needs

to be paid regarding HCV. The reported prevalence is high and current behaviours of HCV infected IDUs, in particular the sharing of material serving to prepare injection, suggest a potential for further spreading of the infection.

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Review articles

Surveillance and epidemiology of hepatitis B and C in Europe – a review

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Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are frequent causes of acute and chronic hepatitis worldwide and leading causes for hepatic cirrhosis and cancer. There is a distinct geographical variation in HBV and HCV incidence and prevalence in the European Union (EU) and European Economic Area/European Free Trade Association (EEA/EFTA) member states and neighbouring countries. The HBV carrier prevalence ranges from 0.1 to 8.0% and that of HCV from 0.1 to 6.0%. Within the last few years, the HBV incidence has decreased while the HCV incidence has increased. Both diseases are concentrated in certain subpopulations, such as injecting drug users, with tens of times higher prevalence than in the general population. Most EU and EEA/EFTA countries have a surveillance system for HBV and HCV infections, but due to differences in system structures, reporting practices, data collection methods and case definitions used, the surveillance data are difficult to compare across countries. The harmonisation and strengthening of HBV and HCV surveillance at the European level is of utmost importance to obtain more robust data on these diseases.

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are frequent causes of acute and chronic hepatitis worldwide and they create a significant burden to healthcare systems due to the high morbidity and mortality, and costs of treatment. According to the World Health Organization (WHO) estimates, one third of the world's population have been infected with the HBV virus and more than 350 million have chronic infection. Regarding HCV, it has been estimated that 170 million persons have chronic infection and that 3 to 4 million new infections occur each year [1,2]. In the European Union, the occurrence of both HBV and HCV is known to differ across countries but the interpretation of this heterogeneity is difficult [3]. Within the last two years, a number of initiatives aimed at raising awareness of viral hepatitis have been undertaken in the European Union. In 2006, the harmonisation process of surveillance of viral hepatitis in the EU was identified by the European Parliament as one of the priorities for the European Centre for Disease Prevention and Control (ECDC). With the aim of strengthening the surveillance of HBV and HCV the ECDC has started on: 1) reviewing available information on surveillance systems and epidemiology of HBV and HCV in the EU and 2) drafting a proposal for EU-wide surveillance for hepatitis B and C. The objective of this paper is to summarise the main results and conclusions of the first of these projects.

Materials and methods

Data about existing surveillance systems were collected from the former Eurohep.net project funded by the European Commission Directorate-General for Research (DG Research) (available at: www.eurohep.net), the first annual epidemiological report of the ECDC (available at: www.ecdc.europa.eu) [3], and the 2006 annual report on the state of the drugs problem in Europe of the European Centre for Drugs and Drug Addiction (EMCDDA, available at: www.emcdda.europa.eu)

Information on current vaccination schedules were obtained from EUVAC.NET (available at: http://www.euvac.net/graphics/euvac/vaccination/vaccination.html). Country-specific data on the number of reported HBV and HCV cases are based on the background data sent by countries and used by ECDC for the first epidemiological report.

To summarise the epidemiology of the HBV and HCV infections in Europe a literature review was performed in September 2007 – February 2008. Articles indexed in the PubMed database were searched by using the following key words: hepatitis B and/or hepatitis C, incidence, prevalence, surveillance, Europe. Country-specific information was searched by adding a country name to the search. The search was restricted to EU and EEA/EFTA countries, Switzerland, countries of the former Yugoslavia and Albania. To obtain information on risk groups or other epidemiological features of these diseases, the following auxiliary terms were added to the search: injecting drug users (IDUs), men having sex with men (MSM), sex workers, prisoners, tattooing, immigrants, HIV, haemodialysis, blood transfusion, blood donors, health care workers. The search was restricted to publications written in English. Both review articles and original research reports were included. Papers published during recent years (2000-2007) were preferred.

Results

Hepatitis B surveillance

Eurohep.net was a feasibility project funded by DG Research in 2002-2005. The aim of the project was to take stock of, co-ordinate, strengthen and standardise the country-specific surveillance systems and prevention activities of the vaccine-preventable viral hepatitis A and B [4]. A survey was carried out on existing hepatitis A and B surveillance systems; here, only information concerning hepatitis B is summarised. A surveillance system for HBV infections was in place in all 19 European countries that responded to the survey. The objectives for surveillance were revealed to be very similar. Eighteen countries indicated that underreporting of cases was possible. Source of data, the variables, data availability at central level, and frequency of reporting and analysing the data varied between the countries (Table 1). Sixteen countries reported the use of ten different types of age categories [5].

Table 1

Summary of hepatitis B surveillance in 19 European countries* in 2002-2004, according to EUROHEP.NET survey (http://www.eurohep.net)

Characteristics of surveillance	Number of countries
Hepatitis B included in national surveillance	19
Type of surveillance	
active	6
passive	16
Surveillance data based on	
acute clinical cases only	12
acute clinical cases and chronic cases	6
data missing	1
Data source	
hospital data and laboratory reports	5
hospital data only	4
laboratory data only	4
none of these or data missing	6
Objectives for hepatitis B surveillance system	
to detect outbreaks	19
to monitor trends	19
to monitor changes in disease distribution and spread	18
to facilitate planning and control measures evaluation	18
to improve knowledge on the disease epidemiology	18
Type of information collected	
age and sex	18
place of residence	18
country of birth	7
risk factors	16
symptoms	10
date of onset	18
hospitalisation	16
outcome	14
Availability of data on central level	18
individual	13
aggregated	13
Frequency the clinical data is reported to central level	
continuously	10
weekly	6
monthly	6
Frequency of the data analysis at the surveillance centre	
continuously	8
weekly	7
monthly	7
Possibility for underreporting of cases	18

* Data presented only from 19 European countries participating in the first phase of the Eurohep.net study: Austria, Belgium, Bulgaria, Czech Republic, Estonia, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Romania, Slovakia, Slovenia, and United Kingdom

Table 2

Characteristics of different hepatitis B surveillance systems (n=39) in 27 European countries* participating in the ECDC survey in 2006

Characteristics	Number of surveillance systems	Percentage of total
Number of surveillance systems having national coverage	32	82%
Mandatory surveillance	28	72%
Passive surveillance	31	31%
Active surveillance	8	21%
Case based data	34	87%
Aggregated data	5	13%
EU case definition used	20	51%
Other case definition used	14	36%
No case definition used	5	13%
Category of case definition	33**	
clinical+laboratory+epidemiological	17	52%
clinical+laboratory	3	9%
laboratory+epidemiological	3	9%
clinical only	2	6%
laboratory only	8	24%
Source of reporting	37***	
laboratory+physician+hospital+other source	4	11%
laboratory+physician+hospital	9	24%
laboratory+physician	6	16%
laboratory+hospital	2	5%
laboratory only	2	5%
physician only	5	14%
other source, with or without combination of above sources	9	24%

* Data from: Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom;
** Data available from 33 surveillance systems;
*** Data available from 37 surveillance systems.

In 2006, the ECDC conducted a survey on surveillance systems in 27 EU and EEA/EFTA countries. All 27 countries responded to the survey and all of them declared having a mandatory reporting system for HBV (Table 2). Altogether 39 different HBV surveillance systems were described in the survey: 21 countries had only one surveillance system, whereas six countries had 2-6 different systems. At the national level, the EU case definition for HBV was used in 16 countries. Nine countries used other case definitions, and data were missing from two countries. At the surveillance system level, the EU case definition was used in 20 out of 39 surveillance systems [3]. The category of case definition used and the source of reporting varied greatly between the surveillance systems. The characteristics of HBV surveillance systems are presented in Table 2.

TABLE 3

The incidence of reported hepatitis B cases in 27 European countries in 1995-2005 (ECDC, 2007)

Country	Incidence (cases / 100,000 inhabitants) Year										
	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Austria	2.6	2.8	2.6	3.1	4.0	3.3	2.6	4.2	6.4	7.1	7.0
Belgium	0.7	3.2	3	1.3	1.2	2.5	5.2	6.9	7.0	*	5.3
Cyprus	0.2	0.3	0.2	0.7	1.0	0.6	0.4	0	0.7	1.5	0.8
Czech republic	5.8	6.6	5.4	5.6	6.2	5.9	4.5	4.0	3.6	3.8	3.5
Denmark	2.1	1.9	1.9	1.8	1.1	1.2	0.9	1.2	0.7	0.8	0.5
Estonia	10.6	18.6	40.2	35.5	20.3	31.8	32.8	17.9	12.8	9.4	5.8
Finland	2.2	5.6	6.1	4.8	5.0	4.6	2.5	3.4	2.0	1.1	
France											0.2
Germany	7.5	7.4	7.4	6.3	5.6	5.5	2.9**	1.7	1.6	1.5	1.4
Greece	1.7	1.3	1.5	5.7	2.6	2.1	2.0	1.6	1.3	1.6	0.8
Hungary				1.8	1.6		1.6	1.6	1.4	1.3	1.2
Iceland	4.1	6.7	7.8	5.5	16.3	17.6	21.5	13.6	8.0	13.4	11.2
Ireland	0.3	0.3	0.8	4.2	4.3	4.9	8.9	11.7	13.8	18.0	1.8**
Italy	4.6	4.0	3.5	3.2	3.0	2.7	2.6	2.4	2.2	2.0	1.8
Latvia	19.8	17.5	15.3	16.4	18.9	30.1	35.5	21	14.5	9.2	7.4
Lithuania	14.5	14.3	12.0	13.2	10.6	9.9	11.0	7.9	5.1	5.4	4.1
Luxembourg	20.0	12.1	19.4	13.0	14.5	7.4	18.7		0.2	0.4	1.1
Malta	1.9	0.8	2.4	0.8	1.1	1.1	1.3	0.8	0.5	1.5	3.0
Netherlands	1.5	1.5	1.6	1.8	4.3	9.7	10.2	11.5	11.7	11.6	1.7
Norway	2.3	2.2	4.2	10.6	10.6	5.9	4.5	4.0	4.5	4.0	3.2
Poland	23.4	16.7	12.7	10.5	9.1	7.3	6.3	5.3	4.7	4.1	1.2
Portugal	9.9	8.3	6.8	5.7	4.0	2.8	2.0	1.5	1.1	0.9	0.8
Slovakia	6.3	5.6	4.8	3.7	3.9	3.1	2.8	2.6	2.6	2.1	2.3
Slovenia	2.2	1.8	1.2	1.8	1.5	1.3	0.9	0.8	1.2	1.2	0.9
Spain			2.9	2.9	2.3	2.2	1.9	2.0	1.9	1.8	1.5
Sweden	3.3	2.1	1.7	1.5	2.4	2.5	2.4	3.2	4.2	2.8	2.4
United Kingdom	1.4	1.4	1.5	1.6	2.0	1.8	1.6	1.5	1.1	0.7	0.7

* Blank cells indicate that data are not available. Comparing figures between the countries should be done cautiously because some notification systems do not distinguish between acute and chronic cases.

** Abrupt changes in the HBV incidence are most probably due to changes in reporting and/or surveillance system (e.g. from 2001 onwards Germany and from 2005 Ireland focused on notification of acute cases). However, country specific information on changes performed in surveillance systems is scarce at the moment.

Epidemiology of HBV in Europe

The incidence of reported HBV cases in the EU and EEA/EFTA countries has declined over the past ten years from 6.7 cases per 100,000 population in 1995 to 1.5 cases per 100,000 population in 2005. In 2005, a total of 6,977 new HBV cases were reported. The most affected age group was 25-44 year-olds followed by 15-24 year-olds. Men were 1.8 times (range 1-3) more frequently affected than women. Country-specific incidences for the period 1995-2005 are shown in Table 3 [3].

The prevalence of hepatitis B surface antigen (HBsAg) in the general population varies widely between European countries with intermediate to high HBsAg carrier rates in Turkey (8%) and Romania (6%), followed by Bulgaria (4%), Latvia (2%), and Greece (2%). In the Slovak Republic, Poland, Czech Republic, Belgium, Lithuania, Italy and Germany the HBsAg prevalence was 0.5%-1.5% and in the Netherlands, Estonia, Hungary, Slovenia and Norway below 0.5 %. The estimates are from different years and populations, which makes comparison difficult [5-7]. Estonia is, however, considered to be a highly endemic country because of the high incidence of cases (33/100,000) [8].

The most common HBV genotypes in Europe are A and D of which the former is more prevalent in Northern Europe, and the latter in the Mediterranean region and Eastern Europe [9]. For example, genotype A seems to be the prevailing one in Belgium [10], Iceland [11], the Netherlands [12], and Poland [13], whereas genotype D is dominant in northern Italy [14] and Spain [15]. Also, genotypes B and C which are common in Asian countries, genotype E which occurs in Western Africa, and genotypes F and G which are the main genotypes found in South and Central America, respectively, have been detected in Europe. The prevalence rates

of the different genotypes vary both between and within individual countries, depending on the populations at risk and their ethnic and geographical origins [9,15,16]. For example, in 1999-2004 in south-western France, among HBsAg positive patients, genotype A was most frequent (51%) followed by genotype D (26%) [16] while in another study which included patients from Paris and south-east region of France, the proportion of genotypes D and A were 27% and 24%, respectively [17]. In general, in countries where the population is mixed and consists of groups of different geographical and ethnic origins, a more widespread distribution of different genotypes is observed [9]. Co-infection with two genotypes is also possible, but information on the prevalence of co-infections is scarce in Europe [9]. Several studies suggest that HBV response to treatment may differ between the genotypes. For example, patients infected with genotype B seem to have better response to interferon (INF) treatment than those infected with genotype C. A better response to INF treatment has also been detected for genotype A compared to genotype D. However, more studies on the relationship between patient outcome, treatment and HBV genotypes are needed [18].

Some groups are more frequently affected by HBV infection than the general population. The prevalence of HBsAg in IDUs ranges from 0 to 21% and the prevalence of antibodies to hepatitis B core antigen (anti-HBc), which indicates past infection, ranges from 20 to 85% [19]. Concurrent infections with HBV and/or HCV and HIV are common [20,21], especially among IDUs [22]. In Spain and in England, the HBsAg prevalence among sex workers varies between 6-7% [23,24]. In many European countries immigrants from highly endemic regions are 5-90 times more frequently affected by HBV than the general population [25-29]. Other populations at high risk of HBV infection are MSM, and those having multiple sex partners [30,31].

Transmission routes and prevention of HBV

In countries with intermediate to high HBV endemicity (HBsAg ≥ 2%) the most common transmission routes are mother-to-child transmission and horizontal transmission via close household contacts. In low endemic countries HBV is usually acquired via injecting drug use, sexual contacts, or body piercing activities [1]. There is evidence, at least from Denmark and the Netherlands, that the number of HBV infections transmitted by sexual contact has recently been increasing [32,33] but injecting drug use is a major mode of transmission in many countries [32,34]. In the past, HBV was frequently transmitted via blood transfusion, but due to improved testing of blood donors the estimated residual risk of acquiring HBV infection ranges from 1 to 10 per million transfusions in Europe [35-39]. The transmission of HBV infection may also occur through needle stick injuries, which is why health care workers can be at higher risk of getting the HBV infection. However, data from Denmark, Germany, Turkey and Albania showed that HBsAg prevalence among health care workers was at the same level as in the general population [20,40-42].

According to the most recent information from EUVAC.NET [43], 21 out of 30 EU and EEA/EFTA countries have implemented a universal vaccination programme for infants or adolescents or both. Eight countries (Denmark, Finland, Iceland, Norway, Sweden, the Netherlands, Ireland and United Kingdom) with low HBV prevalence have chosen a selective vaccination programme against hepatitis B targeted at risk groups. Information on one country was missing [43]. Most countries have implemented additional prevention programmes for different risk groups, most commonly targeted at those at increased risk of acquiring HBV infection via occupational exposure. For example, the Eurohep.net survey showed that 19 out of 19 countries had a vaccination programme for those at increased occupational risk of HBV infection. The next most common risk group targeted by vaccination programmes were the household contacts of HBV patients (17/19), neonates born to HBsAg-positive mothers (17/19), followed by dialysis patients (16/19) and IDUs (14/19). Vaccination of MSM or patients visiting STI clinics was offered in 10 and 9 countries, respectively. A screening programme for pregnant women was in place in 15 countries [5].

TABLE 4

Characteristics of hepatitis C surveillance systems (n=38) in 27 European countries* participating in the ECDC survey in 2006

Characteristics	Number of surveillance systems	Percentage of total
Number of surveillance systems having national coverage	30	79%
Mandatory surveillance	27	71%
Passive surveillance	29	76%
Active surveillance	9	24%
Case based data	33	87%
Aggregated data	5	13%
EU case definition	21	55%
Other case definition	12	32%
No case definition or information lacking	5	13%

* Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom

HCV surveillance in Europe

All 27 European countries which responded to the ECDC survey in 2006 reported having a surveillance system for HCV infection (Table 5). In 25 countries the reporting was mandatory. Altogether there were 38 different HCV surveillance systems in 27 countries. Six countries had more than one system: Belgium (n=3), Cyprus (n=2), France (n=5), Italy (n=2), the Netherlands (n=3) and Portugal (n=2). The EU case definition was reported to be used in at least one of the surveillance systems in 17 of the 27 countries. Eight countries used other case definitions and two countries did not provide information on this topic. Surveillance data were collected from laboratories, physicians, hospitals, and other sources, or different combinations of these. Twenty countries collected data from laboratories as part of their surveillance system. Seven countries did not include laboratory reporting in the HCV surveillance [3]. The characteristics of HCV surveillance systems are shown in Table 4.

HCV epidemiology in Europe

Almost 250,000 HCV cases were notified by 24 EU and EEA/EFTA countries in 1995-2005. During this period a steady increase in the incidence of reported HCV cases was observed (Figure).

As hepatitis C is often asymptomatic and could easily be missed for diagnosis, cases reported to national surveillance systems could be either newly diagnosed prevalent cases or new incident cases.

Table 5

The incidence of reported hepatitis C cases in 27 European countries in 1995-2005 (ECDC, 2007)

Country	cases / 100,000 Year										
	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Austria	2.0	2.1	3.9	4.8	7.1	5.1	4.4	7.2	13.2	11.8	10.9
Belgium	*	1.7	0.8			4.2					8.9
Cyprus									1.3	1.0	0.5
Czech republic	2.1	2.7	2.6	4.3	6.2	6.2	7.8	8.4	8.3	8.5	8.3
Denmark	1.0	0.3	0.3	0.5	0.3	0.2	5.1	4.2	4.5	4.7	5.7
Estonia	4.5	6.5	19.3	26.3	17.7	26.6	22.4		11.4	9.2	6.0
Finland	26.6	34.7	37.1	35.0	34.0	33.6	28.8	26.4	24.3	23.7	23.8
France											
Germany				4.7	4.7	4.3	10.5	8.2	8.4	11.0	9.5
Greece	0.5	0.3	0.3	1.1	1.5	1.4	1.1	0.6	0.5	0.2	0.1
Hungary				0.8			0.4	0.4	0.3	0.4	0.2
Iceland	15.7	19.0	19.6	24.2	30.5	31.2	27.5	23.7	13.2	21.3	14
Ireland							1.7			28.2	35.0
Italy	2.6	2.0	1.6	1.5	1.4	0.4	0.9	0.7			
Latvia	2.4	3.3	4.2	6.9	10.3	12.5	8.7	6.4	5.2	4.9	4.8
Lithuania	2.5	2.8	3.1	3.1	3.4	3.0	5.7	3.7	2.8	2.4	2.0
Luxembourg	20.2	11.7	16.1	13.5	22.7	12.9					4.0
Malta			1.9	0.5	0.5		0	0.3	0	0.5	2.0
Netherlands					1.6	3.2	3.5	3.4	2.6	0.2	0.9
Norway		0.4	0.5	0.5	0.6	0.5	0.8	0.5	0.8	0.8	0.7
Poland			2.8	4.4	5.1	5.4	5.1	5.2	5.9	5.6	7.9
Portugal	4.6	4.0	4.8	6.9	4.0	2.0	2.4	2.0	0.7	1.5	0.9
Slovakia			0.7	0.8	0.6		1.3	0.9	0.7	0.4	0.5
Slovenia	1.7	1.7	2.4	2.6	2.3	2.6	0.5	0.4	0.6	0.7	0.5
Spain			2.0	2.8	2.5	2.1	1.6	1.8	1.6	0.7	0.6
Sweden	32.6	29.6	52.1	45.0	39.5	38.8	39.3	37.9	36.0	33.2	29.0
United Kingdom	4.9	6.6	7.9	11.2	13.2	12.3	11.4	13.2	14.5	12.5	17.5

* Blank cells indicate that data are not available. Comparison of figures between the countries should be done cautiously because some notification systems do not distinguish between acute and chronic cases. Abrupt changes in the HCV incidence may reflect changes implemented in surveillance systems.

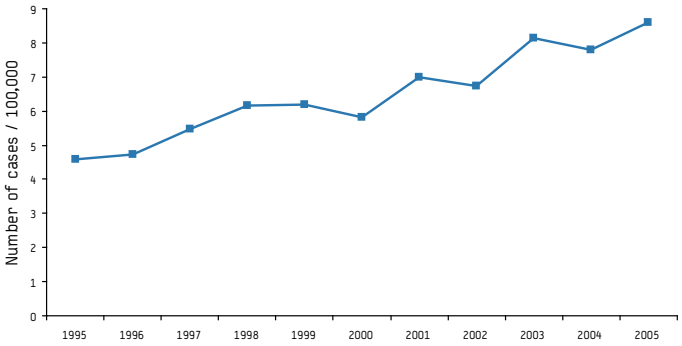
In 2005, a total of 29,243 HCV cases were reported in EU. The rate was highest in the age group of 25-44 year-olds followed by 15-24 year-olds. In men, the rate was twice as high as in women [3]. The incidence of reported HCV cases by country in 1995-2005 is shown in Table 5. According to the WHO, the HCV prevalence in Europe is estimated to be approximately 1% [44]. Compared to other geographical areas in the world this figure is relatively low [2]. The available data from Europe indicate a wide variation in HCV prevalence between the countries, ranging from 0.1 to 6.0%. The lowest HCV prevalence (≤ 0.5%) estimates are from Scandinavian countries, Austria and the Netherlands, and the highest (≥ 3%) from Bulgaria, Greece, Italy and Romania [44].

Types 1a, 3/3a and 4 are commonly found in IDU-related infections whilst 1b and 2 genotypes are linked to blood transfusion or nosocomial transmission [44]. Genotype 4 has also been associated with having a tattoo [45]. As a result of improved blood transfusion safety serotypes associated with blood transfusions are being replaced by other serotypes especially those related to injecting drug use [44]. Prisoners often have prevalence rates of antibodies to HCV comparable to those of IDUs due to a high proportion of IDUs among this group [46-54]. In Germany, Spain and in UK the anti-HCV prevalence in sex workers ranged from 0.7 to 9.0 %; with the lowest estimate in Germany [20,23,24]. In Germany, Spain and in the UK the anti-HCV prevalence in sex workers ranged from 0.7 to 9.0 %; with the lowest estimate in Germany [24]. However, these figures are difficult to compare due to methodological and timeframe differences.

HCV infections in sex workers have been shown to be associated with injecting drug use [55]. A north to south gradient in anti-HCV prevalence among hemodialysis patients in Europe was described based on samples from the 1990's [55]. According to samples from 1997-2001, the anti-HCV prevalence (adjusted for age, gender, race, time on end stage renal disease, and alcohol or drug abuse), was 22% in Italy and Spain, and lower in France (10.4%),

Figure

The incidence of reported hepatitis C cases in EU and EEA/EFTA countries in 1995-2005



Germany (3.8%) and UK (2.6%) [56], although these figures do not necessarily represent the country-specific incidences in general. Data from different studies indicate that there is a remarkable variation between and within individual countries in the anti-HCV prevalence in HD patients. However, it is likely that many of the populations in these studies have been chronic cases exposed to the virus in the past, before screening and testing was widely available, so most likely these results do not reflect the current situation. It should also be noted that the anti-HCV prevalence does not indicate what proportion of the population are HCV RNA carriers and thus infective. The presence of virus (being RNA-positive) can be confirmed in 40-90% of those who are anti-HCV-positive [19].

Transmission routes and prevention of HCV

HCV infection is mainly associated with injecting drug use (blood-blood contact, sharing syringes and needles), blood transfusion, nosocomial transmission, or other parenteral exposure such as needle stick injuries, body piercing or tattooing. In many countries, including France, Germany, Austria, Greece, Sweden and Italy, the most common risk factor is injecting drug use, which accounts for 30-59% of all HCV infections. The second most common risk factor is blood transfusion performed before 1991. In 10-54% of cases the risk factor is unknown [44]. Mother-to-child transmission and transmission of HCV by sexual contact seem to be rare [2] although it has been observed that high-risk sexual behaviour among MSM may predispose to HCV infection probably via permucosal route, especially in HIV-infected MSM [57-59]. The implementation of effective virus inactivation procedures and of anti-HCV testing methods in the late 1980s and early 1990s, as well as the recent introduction of HCV RNA tests significantly improved the safety of blood products [44]. The estimated residual risk for acquiring HCV via blood products ranges from 1 to 40 per 10 million transfusions in Europe [35-39].

There is no vaccine against HCV infection. The cornerstones of preventing and reducing the burden of HCV are early diagnosis, effective preventing programmes, and appropriate treatment [44,60]. It is known that a large number of individuals carrying the HCV virus are not aware of being infected due to the high proportion of asymptomatic infections [2,61]. Thus it is necessary to target the screening of HCV at the risk groups and to provide appropriate testing facilities, also for hard-to-reach populations. However, personal and institutional barriers may reduce the uptake of HCV testing, especially in prisons. Thus further research and development of testing strategies is needed [47]. Needle and syringe exchange programmes, may be useful in reducing the incidence of HCV infection among IDUs, although the impact may be limited, as indicated by the high prevalence of HCV in IDU [19]. In addition, it is vital to encourage education and increase awareness of HCV in the general population, health care providers and policy makers [44].

Discussion

Numerous scientific reports on HBV and HCV epidemiology have been published. The comparability of their results, however, is challenged by differences in objectives, methods, strategies, timeframes, and target populations. Regardless of these limitations, the available data suggest that the epidemiology of both HBV and HCV differ widely between countries and that HBV and HCV infections create a significant burden to health care systems. Viral hepatitis affects the general population disproportionately, with the highest burden on certain risk groups with different epidemiological characteristics across the EU. Prevention and control of HBV and HCV infections require continuous monitoring as well as evaluation of surveillance and prevention strategies. Surveillance and prevention of HCV infection is even more challenging than that of HBV because HCV infections are mostly asymptomatic and may remain undiagnosed for a long time. Also, prevention is challenging as there is no vaccine available against HCV. Despite significant improvements in blood transfusion safety, hygiene practices, screening, education messages, sterile needle and condom availability and blood product treatment, the HCV infection rates continue to rise in Europe. The increasing trend cannot be easily interpreted as it may also partly reflect the results of improved surveillance, intensified screening activities and the availability of accurate testing methods. Nevertheless, HCV can be considered to be an increasing public health concern in Europe in the coming decades, which calls for appropriate public health action.

Comparison of surveillance data is hampered by differences in the surveillance systems, the population under surveillance, the data sources, and the unknown proportion of infections being undiagnosed or missed because asymptomatic or – if diagnosed – unreported. Also, there is no clear distinction in the overall reporting between acute and chronic cases. Abrupt changes in country-specific incidences of reported HBV and HCV cases most probably reflect changes in surveillance systems made by these countries rather than true trends. However, at present, information on these changes is mostly lacking at the EU level and deserves more attention in the future. The differentiation between acute and chronic cases of HBV or HCV infections is a demanding task but will need to be tackled in order to accurately estimate the disease burden. Reporting asymptomatic infections is controversial, but should be discussed as part of a new framework for enhanced surveillance of hepatitis B and C in the EU. Asymptomatic infections may have long term consequences since HBV and HCV infections acquired early in childhood are commonly asymptomatic but may lead to liver cirrhosis, liver failure or even carcinoma at the older age. They can also serve as a reservoir for infection to spread. In the light of these facts non-reporting of asymptomatic infections would underestimate the real incidence and burden of HBV and HCV. To enhance the specificity and comparability of surveillance data between the countries only laboratory-confirmed cases should be reported, but laboratory data need to be supplemented by good quality clinical and epidemiological data. Underreporting of cases also seems to be a common phenomenon. All except one country in the Eurohep.net survey replied that underreporting of HBV was

possible. This applies also to HCV. For example, in England, only half of the HCV cases diagnosed in sentinel laboratories were reported via national surveillance system between October 2002 and September 2003 [62]. In Austria, the reporting activity was even lower since only one fifth of the 10,000 HCV cases in the hospital discharge register were reported to the national surveillance in the period of 1993-2000 [63].

Toward harmonisation of EU-wide surveillance

Although there were some differences in methodology and the number of participating countries between the Eurohep.net and the ECDC surveys, both clearly showed that surveillance systems differ in many ways. The objectives of the surveillance systems are very similar and basic data sets (e.g. age, sex, place of residence, date of onset, data on hospitalisation, and risk factors) are collected in most countries, but there is great heterogeneity between surveillance systems regarding the use of EU case definitions, reporting of acute and chronic cases, inclusion of asymptomatic cases in the reporting, data sources, and the legal aspects of reporting. While the availability of electronic data has markedly improved within the last years, many different types and formats of the data are being used. All these issues are likely to pose a major challenge for EU-wide harmonised data collection.

Nevertheless, harmonisation of EU-wide surveillance of viral hepatitis is of utmost importance in order to be able to make true comparisons between trends and epidemiological characteristics of these diseases across countries, to contribute to targeted prevention and control strategies, and to assess the disease burden. The ECDC is currently preparing to strengthen the surveillance of HBV and HCV in the EU.

Conclusion

To conclude, comparable and validated reliable data on HBV and HCV infections are needed in the EU in order to estimate the disease burden of these diseases. However, harmonisation of the EU-wide surveillance of HBV and HCV infections faces many challenges due to differences in surveillance systems between the countries.

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Perspectives

Acute hepatitis C virus infection

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Around 25% of people infected with hepatitis C virus (HCV) are able to clear the infection spontaneously, while the majority become chronically infected, with a subsequent risk for the individual patient of progressive inflammatory liver disease, cirrhosis, hepatocellular carcinoma and liver-related death (Figure 1). Much is known about the epidemiology, pathogenesis, diagnosis and management of chronic HCV infection. In comparison, knowledge about acute HCV infection is patchy. In this article, we will highlight concerns relating to acute HCV infection and suggest that public health bodies responsible for managing the HCV epidemic should redirect at least some of their resources to dealing with these issues.

Natural history of the disease

Most patients with newly-acquired HCV infection do not present with an acute hepatitic illness – most estimates suggest only 10-15% of cases are acutely jaundiced. In the remainder, the infection is either asymptomatic, or may present with mild constitutional symptoms (nausea, loss of appetite, fatigue, vague abdominal pain), with an alanine aminotransferase (ALT) which peaks below 1,000 UI/ml. As a result, few such cases come to medical attention or are tested for evidence of HCV infection [1].

Given the largely asymptomatic nature of the acute infection, as well as the fact that most acute infections occur in injecting drug users (IDUs) who are hard to reach, and that a diagnosis of acute infection can be difficult to prove (see below), most studies of the natural history of acute HCV infection contain relatively few patients. A recent review [2] identified 675 individuals in 31 studies (mean 22 per study, range 4-67). Clearance of infection ranged from 0-80%, with a weighted mean of 26%. Females were more likely to clear infection than males (40% versus 22%), and patients identified because of clinical presentation with acute illness were more likely to clear infection than those identified as a result of screening protocols i.e. in post-transfusion or sero-incident (i.e. demonstration of infection by serial testing and revelation of seroconversion from negative to positive) studies (31% versus 18% and 18%).

Epidemiology

Many countries have surveillance systems that record new diagnoses of HCV infection. In England and Wales, new diagnoses are reported to the Health Protection Agency, which produces annual reports showing trends in the identification of anti-HCV positive sera [3]. In the Netherlands virological laboratories report positive serology and positive HCV RNA to the National Institute for Public Health and the Environment (RIVM). However, these data do not distinguish between acute and chronic infections, and it is highly likely that the vast majority of the reported cases are from patients with chronic infection.

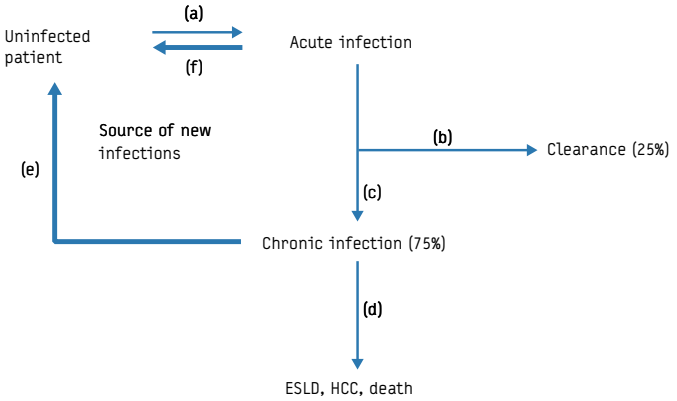
In the United States, there is a reporting scheme for acute viral hepatitis. Reporting is voluntary, and the US Centres for Disease Control and Prevention produce annual reports, the latest of which, published in March 2008, contains data pertaining to 2006 [4]. The case definition for acute HCV infection has both clinical and laboratory components – see Table. Note that this case definition will not discriminate between acute infection and an acute exacerbation of chronic infection. In 2006, 802 cases of acute HCV infection were reported, a population incidence of 0.3/100,000. 41% of these cases were hospitalised, and 66% jaundiced. Taking into account under-reporting, and the fact that the large majority of acute HCV infections do not present with jaundice, this equates to an estimated 19,000 new infections. Risk factors present in acute cases included injecting drug use (54%), surgery (16%), sex with known positive partner (10%) and occupational exposure (1.5%) (some patients had more than one risk factor). The data allow identification of trends, assessment of the impact of preventive strategies, and can highlight areas of concern should these arise. The data show an encouraging decline in the number of cases of acute HCV infection reported since 1992 (Figure 2).

In Europe, the European Centre for Disease Prevention and Control (ECDC) has produced its first Annual Epidemiological Report on Communicable Diseases in Europe [5]. The HCV data within the report demonstrate a steady increase in the "Incidence rate of hepatitis C cases in EU and EEA/EFTA countries by year reported 1995-2004" (fig 4.18.1, page 113), but this clearly does not relate to incident infection, but to an unspecified amalgam of chronic and acute infections, the bulk of which will be chronic. Indeed, the conclusions of the HCV section of the report contains the statements: "There are clear limitations with the HCV surveillance data…", "…the data are inadequate to describe the true HCV infection trend and disease burden." and "The real transmission pattern… should be more thoroughly investigated in the EU…".

Recent papers describing experience with acute HCV demonstrate that, while most patients are IDUs, transmissions are also occurring through other routes. Many reports cite high risk sexual behaviour as

Figure 1

The natural history of HCV infection

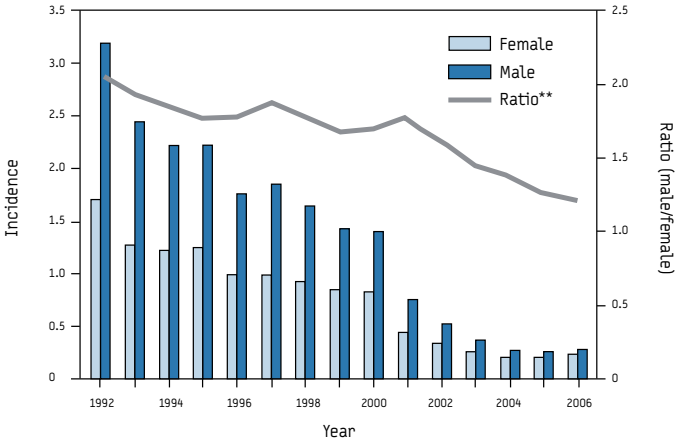


New infections (arrow a) are either cleared spontaneously (arrow b, 25%) or give rise to chronic infection (arrow c, 75%). Chronically infected patients are then at risk of life-threatening complications of liver disease (arrow d). Uninfected individuals acquire infection either from chronically-infected individuals (arrow e), or from other recently infected individuals (arrow f). The relative contributions of these two distinct sources towards incident infection is currently unknown. Control strategies aimed at chronically-infected patients may reduce the likelihood of individuals progressing to chronic liver disease (arrow d), but have relatively little effect on acute transmissions (reducing arrow e but having no effect on arrow f). Focussing on acute infections may allow therapy and thereby prevent chronic infection (arrow c), and may also significantly reduce further onward transmission (arrow f).

* ESLD = end stage liver disease
** HCC = hepatocellular carcinoma

Figure 2

Incidence (per 100,000 population) of acute hepatitis C, by sex and year – United States, 1992 – 2006*



* Until 1995, acute hepatitis C was reported as acute hepatitis non-A, non-B
** The bars indicate the rate per 100,000 population (left y-axis) by sex; the line is the ratio (right y-axis) of the incidence among males compared to that among females.

Taken (with permission) from Wasley et al; Surveillance for acute viral hepatitis – United States, 2006, MMWR Surveillance Summaries 2008; 57(2): 1-24.

Table

Case Definition for Acute Viral Hepatitis C, US Centers for Disease Control and Prevention National Notifiable Disease Surveillance System

Clinical case definition:
acute illness with 1) discrete onset of symptoms (e.g. nausea, anorexia, fever, malaise, abdominal pain) AND 2) jaundice or raised serum alanine aminotransferase (ALT)
Laboratory criteria:
serum ALT higher than seven times the upper limit of normal, AND IgM anti-HAV negative, AND IgM anti-HBc negative, or if not performed, HBsAg negative, AND either anti-HCV or HCV RNA positive

a significant risk factor for heterosexual transmission [4,6,7], while outbreaks of HCV infection amongst HIV-infected men who have sex with men have recently been reported from the UK, France and the Netherlands [8,9,10]. Iatrogenic infection is also reported at alarmingly high rates, with even minor procedures such as receiving an injection while in hospital being significantly linked to acute infection [4,6,7,11,12].

Diagnosis

Current algorithms for the diagnosis of HCV infection involve the detection of anti-HCV antibodies and/or HCV RNA in a serum sample. While such testing is able to distinguish between past, cleared HCV infection, and current infection, it does not allow determination of whether the infection is acute or chronic. The presence of IgM antibodies, the usual serological marker of acute infection, is unreliable in the context of HCV infection [13]. Clinical diagnosis, i.e. in a patient presenting with an acute jaundice and possibly even a history of recent exposure, has an extremely low sensitivity, as the vast majority of acute cases do not present in this way, and will also have a specificity of less than 100% through failure to distinguish acute infection from an acute exacerbation of chronic infection. Diagnosis of acute HCV infection is therefore difficult.

Demonstration of sero- or genoconversion in serial samples taken from the same patient would provide definitive proof of recent acquisition of infection in that individual. However, long-term serial sampling of high-risk populations is notoriously difficult to achieve, especially outside carefully conducted and well-funded research studies, and therefore adoption of such a strategy for monitoring incidence trends is likely to be expensive, subject to considerable sampling bias, and unlikely to generate robust data.

Two approaches to diagnosis of acute infection that are showing some promise are window-period testing, and IgG avidity determination. The former is based on the principle that in an acute infection, there is a window period where HCV RNA will be detectable within the peripheral blood, but anti-HCV antibodies will not. Thus, RNA testing of antibody negative sera should identify acute infection. Knowledge of the length of the window period (best estimates give median duration of 58 days, 95%CI 45-75, ref 15) allows conversion of the percentage of antibody negative RNA positive sera derived from the population under study into an incidence rate. Studies using this approach have recently been published from both the United States and the United Kingdom [14,15], demonstrating widely differing rates according to the nature of the study population. The potential expense of RNA testing on a large-scale for surveillance purposes can be reduced

to some extent by testing of pooled samples, albeit with some loss of sensitivity.

IgG avidity (or antigen-binding force) increases over time following antigen challenge. Thus, virus-specific IgG in the weeks following an acute infection will be of low avidity, while that associated with a chronic infection will have matured into high avidity. Assays can distinguish between low and high avidity antibody, based on the extent to which antigen-antibody binding is disrupted by the presence of a chaotropic agent. Results are usually expressed as an avidity index (AI), calculated as the optical density generated in the presence of the chaotropic agent divided by that produced in its absence. An AI <0.3 (or 30%) equates to low avidity, while anything >0.7 (or 70%) represents high avidity. Such assays perform very well when analysing seroconversion panels [16,17], providing clear cut-off AI values which distinguish samples taken within 20-100 days of infection from those derived from patients with chronic infection. Importantly, samples from chronically infected patients with acute exacerbations have high avidity (as would be expected), increasing the specificity of this approach [17]. However, there is no current standardised agreed methodology for these assays – reports differ in terms of which chaotropic agent is used (e.g. urea, guanidine), at what molarity, and at what stage in the assay it is used (e.g. addition to serum diluate, addition to wash buffer).

Treatment

Interest in this area was stimulated by the seminal study which demonstrated a sustained virological response (SVR) in 43/44 (98%) patients with acute infection using standard interferon, conducted at a time when average SVR rates in patients with chronic infection treated with combination interferon and ribavirin therapy were below 50% [18]. A number of studies have replicated this encouraging finding viz. that early treatment is associated with significantly higher clearance rates, although as would be expected, response rates decline if patients do not adhere to their therapeutic regimens [19]. Some controversies remain. A multi-centre trial from Egypt, USA and Germany demonstrated high response rates using pegylated interferon alone for only 12 weeks, and also showed that, for genotype 2 or 3 infection, delaying onset of therapy until 12 weeks (and possibly longer) after diagnosis, thus allowing patients to achieve spontaneous clearance, did not impact on overall SVR rates, although this was not true for genotype 1-infected patients [20] A separate study from the same group demonstrated better response rates for genotype-1 infected patients treated for 24 weeks as opposed to 12 weeks [21]. European experience suggests that pegylated interferon alone is sufficient, while American recommendations suggest that the use of ribavirin should also be considered on an individual basis [22]. It seems sensible to recommend combination therapy for HIV-infected patients who acquire acute HCV infection, as response rates are generally not as high in this patient group compared to monoinfected patients.

Public health aspects

Although HCV is a transmissible disease, current management of HCV-infected patients for the most part does not reflect this fact. The vast majority of patients attending specialist clinics for assessment and management acquired their infection many years ago, and are likely to be no longer at significant risk of transmitting their infection to others, as their own risk behaviour (e.g. injecting drug use) will have ceased. Thus, there is little point in undertaking standard public health measures to deal with an infectious disease, such as contact tracing and identification of the infectious source, when dealing with a chronically infected patient. However, even for those patients who are still activeIDUs, contact tracing, which may identify other infected individuals who may benefit from therapy, is often complicated and not routine practice.

Considerable effort is expended by governments and health departments on encouraging patients who might have chronic HCV infection to come forward for appropriate testing and therapy, which overall results in around 50% cure. While this is excellent news for the individuals concerned, as it reduces if not entirely prevents their individual risk of suffering progressive liver disease (arrow d in fig 1), the impact of such a strategy on incident infections is hard to gauge. Incident infections arise from one of two sources – individuals with acute infection (arrow f, Figure 1), and individuals with chronic infection (arrow e, Figure 1). The relative contribution of these two distinct sources towards incident infection is not known. The majority of patients with chronic infection undergoing therapy in specialist clinics are no longer IDUs, and therefore we argue that a strategy based on treatment of chronic infection alone will not have a major impact on incident infections.

An alternative approach to the HCV epidemic would be to concentrate efforts on the acutely infected patient. There are cogent reasons for this, although we acknowledge that identification and treatment of acutely infected patients presents considerable challenges:

- Treatment of acutely infected patients is far more effective than for those who are chronically infected. Thus, there is considerable benefit to the individual concerned in being diagnosed and offered therapy at this stage of their infection. Successful therapy also reduces the future numbers of patients with chronic infection (arrow c, Figure 1) and its downstream [?] life-threatening complications;
- Knowledge of who has been recently infected will allow the implementation of standard public health approaches to the control of an infectious disease. Contact tracing will identify other infected individuals, perhaps most likely with chronic infection, but possibly also some with acute infection who would benefit from therapy. It may be possible to pinpoint an infectious source, and thereby interrupt future transmissions (arrow f, Figure 1) e.g. by education/provision of clean injecting materials. The effectiveness and cost-effectiveness of any of these interventions has not yet been adequately studied.
- Mathematical modelling has demonstrated that unless there is a dramatic (e.g. >80%) reduction in the acquisition of new HCV infections, then the numbers of patients presenting with HCV-related cirrhosis, hepatocellular carcinoma, and liver-related death will continue to increase for at least the next 30 years [23]; and
- Accurate data on incident infections would allow appropriate monitoring of trends, recognition of changes in patterns of transmission, assessment of the efficacy of intervention strategies (e.g. public education campaigns) and long-term modelling of and planning for the HCV epidemic.

The implementation of such a strategy would require a reliable means of identifying individuals with acute HCV infection, most of whom would be asymptomatic. As discussed above, laboratory methodologies for this are being developed. Avidity testing of antibody positive sera from high-risk individuals using a standardised laboratory protocol, plus RNA testing of antibody negative sera, would fulfil this requirement. Secondly, patients with acute infection would need to enter appropriate care pathways. This will certainly present a challenge, but a number of centres have reported

successful engagement with and treatment of active IDUs [24-27], so it is clearly not insurmountable. Proper assessment is required of the potential effectiveness and cost-effectiveness of reconfiguring services and resources to dealing with this particular challenge.

Conclusions

It is our belief that an understanding and control of acute HCV infection is important, for the reasons outlined above, and currently not sufficiently studied. We do not wish to belittle the efforts and benefits of strategies aimed at identifying and treating patients with chronic infection, and agree that both approaches (i.e.diagnosing acute and chronic infections) should play an important role in controlling HCV. However, failure to address adequately acute transmission of HCV infection will undermine long-term attempts to reduce HCV-associated disease burden. Iatrogenic and nosocomial infections are still occurring, and are largely unrecognised. Meaningful surveillance of acute HCV infection, especially in Europe, is virtually non-existent and will require careful case definition and adoption of standardised diagnostic assays, such as window period and avidity testing. Treatment of acute infection is effective, but precise regimens are not universally agreed.

Our collective failure to identify patients with newly-acquired infection, combined with a lack of understanding of transmission patterns and dynamics, will ultimately undermine public health efforts aimed at reducing the disease burden arising from chronic HCV infection. In collaboration with the ECDC, the Viral Hepatitis Group of the European Society of Clinical Microbiology and Infectious Diseases is keen to establish European-wide systems of laboratory diagnosis and surveillance of acute HCV infection.

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Rapid Communications

European monitoring of notifications of hepatitis C virus infection in the general population and among injecting drug users (IDUs) – the need to improve quality and comparability

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Background

Hepatitis C virus (HCV) infection is a serious public health problem in Europe, and it is estimated that a large number of people are unaware of their infection [1-3]. HCV infection may lead to symptomatic chronic liver disease after many years of asymptomatic infection. Effective treatment is available for HCV infection; however, the efficacy for many genotypes remains low and therapy is prolonged, involving both weekly injections and daily oral medication, and can be associated with significant adverse effects [4,5]. Where documented, injecting drug use is a major transmission route for HCV infections [1,6,7]. In many European countries, national surveillance of HCV infections has been established relatively recently.

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), a decentralised technical agency of the European Union (EU), is charged with monitoring the drugs phenomenon in Europe. The public health aspects include the surveillance of infections in drug users, which is mainly based on prevalence survey data such as HCV, hepatitis B virus (HBV) and HIV antibody prevalence among injecting drug users (IDUs) in drug treatment and other settings [8,9]. For HCV, these monitoring activities have been complemented by a centralised collection and reporting of available data on notifications of HCV infection. The aim of this is to add information to the data collected through the surveillance of the prevalence of HCV among IDUs, in order to better inform and influence policies at the European level. The monitoring of HCV notifications was initiated at a time when no other institution or expert network collected these data at the European level. Due to limitations in EMCDDA resources and its mandate, this activity has so far been restricted to collecting the data as reported at the national level. However, the need for a European standardisation of national hepatitis C surveillance systems was already identified in 1998 among the then 15 EU Member States [10].

In this paper, we present and discuss the sources of information and data collected so far. This may provide an up-to-date basis to improve the comparability and quality of data reporting and increase their usefulness at the European level.

Methods

The EMCDDA collects data on HCV notifications annually through national focal points in charge of drugs and drug addiction surveillance. The national focal points are either interdepartmental bodies (for example, located in ministries of health, internal affairs or justice) or technical governmental institutions carrying out research and monitoring of the drugs phenomenon at the national level. The national focal points are responsible for the collection and reporting to the EMCDDA of a large number of drugs-related data from different national sources. In the case of HCV notifications, the national focal points use a standard reporting questionnaire (the HCV notifications part of 'Standard Table 9', available from: http://www.emcdda.europa.eu/?nnodeid=1375). They request their responsible health authorities (e.g. virologists or epidemiologists at the national institute of infectious disease surveillance) to provide aggregated data, including the total number of cases of HCV infection notified by physicians, and, if possible, to specify if these are acute or chronic cases; they also request the number of cases with known risk factor and the number attributed to IDUs. From this information, it is possible to observe trends in the total number of notified cases of hepatitis C, as well as the proportion of IDUs among the cases with valid information on exposure category. Data are also available broken down by gender, age group and the time since first injection. Information on methodology, describing the national surveillance systems, include the use of a unique identifier, the need for laboratory confirmation, and the case definition for HCV infection, as well as the name of the principal investigator responsible for the surveillance at the national level, his/her institution (e.g. national institute of infectious disease surveillance) and relevant bibliographic references.

Results

The number of countries providing data has increased from two in 1999 (providing data back to 1992) to 17 (most recent years of reporting range from 2003 to 2006), of 30 countries currently working with the EMCDDA (27 EU Member States, Norway, Croatia and Turkey). One country (the United Kingdom – England and Wales) reported that data were not statutory notifications but laboratory reports, although this information was not collected in a standard way for other countries (Table 1).

Table 1

Definitions of HCV infection used by the different countries in Europe

Country	Year when most recent definition was given	Definition given	Source
Croatia	2006	Individuals positive for anti-HCV	University Hospital for Infectious Diseases
Czech Republic	2006	A symptomatic case that is laboratory confirmed - detection of HCV-specific antibodies, detection of HCV nucleic acid from clinical samples	National Institute of Public Health, CEM
Germany	2006	Laboratory confirmed hepatitis C (either HCV-antibodies, confirmed by NAT or blot) or NAT alone. If clinical signs or symptoms are present, data is collected too.	Robert Koch Institute
Denmark	2008	Acute: Clinical symptoms + Laboratory confirmed hepatitis C (preferably HCV-RNA, but HCV-antibodies are accepted) Chronic: Laboratory confirmed hepatitis C present for more than 6 months OR Laboratory confirmed hepatitis C + histology	Statens Serum Institut
Estonia	2004	Clinical description. Discrete onset of symptoms and jaundice or elevated serum aminotransferase levels. Lab criteria: 1) Detection of HCV-specific antibodies; 2) Detection of HCV nucleic acid from clinical samples. Case classification: Confirmed - A symptomatic case that is lab confirmed.	Health Protection Inspectorate
Finland	2004	HCV Ab-positive, HCV-RNA-positive	National Public Health Institute
Hungary	2006	An illness with discrete date of onset, and (2) jaundice or elevated serum aminotransferase levels greater than 2.5 times the upper limit of normal. Serologic criteria used: + anti-HCV positive	National Center for Epidemiology, Department for Epidemiology
Italy	2006	Case definition is based on clinical and serological criteria: an acute illness compatible with hepatitis and serum alanine transferase levels greater than 10 times the normal value; anti-HCV positive; IgM anti-HAV negative; IgM anti-HBc negative.	Italian National Institute of Health
Lithuania	2006	Symptomatic case, with confirmation from laboratory tests for acute HCV.	Centre for Communicable disease prevention and control
Luxembourg	2004	Self reported HCV test results	CRP-Santé/CES/PF OEDT
Latvia	2005	Cases are confirmed if a symptomatic case is laboratory confirmed.	Public Health Agency
Malta	2005	Acute: detection of HCV-specific antibodies. Detection of HCV nucleic acid from clinical samples. Symptomatic cases that are laboratory confirmed.(Ref: Decision No.2119/98/EC of the European Parliament and of the Council) Chronic: positive result for Hepatitis C without any clinical symptoms or signs	Dept. Public Health, Disease Surveillance Unit
Netherlands	2006	Laboratory confirmation of HCV infection with and without clinical symptoms.	RIVM
Sweden	2006	anti-HCV positive.	Swedish Institute for Infectious Disease Control, Department of Epidemiology
Slovenia	2003	A suspected case which is laboratory confirmed (anti-HCV positive or HCV-RNA positive)	Institute of Public Health of the Republic of Slovenia
Slovakia	2006	Positive: anti HCV, PCR	Regional office of public health
UK - England and Wales	2006	Anti-HCV positive by two EIAs, EIA and RIBA or HCV RNA positive	Communicable Disease Surveillance Centre
UK - Scotland	2005	Laboratory reports of all persons who have been diagnosed HCV antibody and/or PCR positive in Scotland	Communicable Disease Surveillance Centre
UK - Scotland	2003	Persons in Scotland reported to be anti-HCV positive by year of earliest positive specimen	Communicable Disease Surveillance Centre
UK - Northern Ireland	2006	All cases of hepatitis should be reported	Communicable Disease Surveillance Centre

TABLE 2

Number of reported cases of HCV infection, number and percentage of cases with known risk factors, and number and percentage of cases with injecting drug use as the reported risk factor, by country in Europe

Country	Acute, chronic, combined (acute + chronic)	Year of most recent data	Number of cases reported for that year N (a)	Number with known risk factor (b) and % (b/a)	Number with IDU as known risk factor (c) and % (c/b)
Croatia	combined	2006	-	153	82 (54%)
Czech Republic	combined	2006	1022	-	711
Germany	combined	2006	7509	5686 (76%)	1992 (35%)
Denmark	chronic	2006	300	264 (88%)	223 (84%)
Denmark	acute	2006	6	5 (83%)	5 (100%)
Estonia	acute	2004	-	-	54 (71%)**
Finland	combined	2006	1181	694 (59%)	570 (82%)
Hungary	acute	2006	29	15 (52%)	4 (27%)
Italy	acute	2006	137	95 (69%)	40 (42%)
Lithuania	acute	2006	62	30 (48%)	13 (43%)
Luxembourg	combined	2004	395	174 (44%)	129 (74%)
Latvia	acute	2006	105	72 (69%)	9 (13%)
Malta	acute	2006	9	6 (67%)	6 (100%)
Malta	chronic	2006	24	15 (63%)	12 (80%)
Netherlands	acute	2006	30	26 (87%)	8 (31%)
Sweden	combined	2006	1976	1220 (62%)	932 (70%)
Slovenia	acute	2003	11	2 (18%)	2 (100%)
Slovakia	acute	2006	31	25 (81%)	13 (52%)
Slovakia	chronic	2006	239	198 (83%)	108 (55%)
UK* - England and Wales	combined	2006	8774	673 (8%)	647 (96%)
UK* - Scotland	combined	2005	1600	988 (62%)	886 (90%)
UK* - Scotland	chronic	2003	1779	1104 (62%)	1030 (93%)
UK - Northern Ireland	combined	2006	140	19 (14%)	19 (100%)

* Laboratory reports
** Only these numbers were provided

All 17 countries reported requiring laboratory confirmation. In eight countries, HCV-RNA results were reportedly collected. Case definitions were provided by all countries, but varied, and did not always seem to be consistent with the EU case definition [11]. The definitions, as reported to EMCDDA, combined clinical, biological and serological criteria (Table 1). Twelve countries used a unique identifier to prevent double counts.

Seven of the 17 countries provided combined data for acute and chronic cases, four provided separate data, and six provided only data for acute IDU cases.

In 2006, 12 countries reported their total number of notified cases, of which five countries reported a total of 22,050 combined acute or chronic cases, one country (Denmark) reported 300 chronic cases, and seven countries (including Denmark) reported a total of 400 acute cases. Eleven of the 12 countries provided the number of notifications with known risk factors. The proportion of notified cases with known risk factor has increased slightly (from 40% in 2001 to 43% in 2006) but on the whole it has remained very low. In 2006, this proportion varied across countries, from 8% of cases in the UK (England and Wales) to 88% in Denmark (Table 2).

Among eight countries reporting over 50 IDU-related cases in 2006 or the latest year available, the proportion of IDUs among all cases with known risk category ranged between 74% and 100%, with the exception of Germany (35%) and Croatia (54%) (Figure).

Discussion

Many EU Member States are able to report HCV notification data and at least 17 countries can provide the number and proportion of IDUs among reported cases, adding to the information collected on prevalence of infection among IDUs [9].

Methodologically, the national surveillance systems seem to differ considerably in the definition of HCV infection, thus strongly limiting the comparability between countries, even though these data may still provide information regarding trends over time. For a majority of HCV cases reported, the risk factors are unknown or

not available for surveillance purposes thus severely limiting their interpretability.

The EMCDDA recommends that countries provide separate data on acute and chronic cases. Better data on acute cases provide a more accurate picture of the current epidemiology of HCV whereas chronic cases reflect a past epidemiology. However, hepatitis C is often asymptomatic in the acute phase, and therefore not diagnosed. Also, as there are few methods for actually identifying the acute cases and distinguishing them from the chronic ones, it is still not entirely clear if a distinction between these categories is useful. Better methods are needed to identify and diagnose acute cases, and it may also be helpful to concentrate on young age groups (15-19, 20-24 years), where there can be relatively high assurance of recent infection. Moreover, the low proportion (and number) of acute cases that are notified often precludes their use as an indicator of new transmission. A study in Seattle in the United States (US) estimated that less than 5.7% and possibly around 1.5% of IDUs who acquire HCV infection would be notified [12]. On the other hand, a recent report from the US suggests that enhanced surveillance approaches may detect outbreaks of new infections in IDUs [13]. For diagnosed chronic cases in regular contact with the healthcare system, it might be expected that notification rates are very high. However, in Denmark it was recently found that only 50% of these had been notified to the national register [14].

There are thus considerable problems in comparing and interpreting the available notifications data, especially when used as an indicator of true incidence of HCV infection, due to the very large proportion of asymptomatic infections, coupled with under-diagnosis, underreporting and the differences in national notification systems. Following the changes in proportions of specific transmission categories over time (e.g. the percentage IDUs among cases), rather than absolute counts or population rates, may provide more comparable information on trends in hepatitis C infection among different risk groups. Given the limitations of the data, the EMCDDA has so far mainly reported the proportion of IDUs among all cases with known transmission risk [9].

The proportion of IDUs among all cases with known risk factor is high in most countries, indicating that IDUs still constitute a major, in most European countries even the largest, risk group for acquiring HCV infection. In the data presented here, some countries report changes over time in the proportion of IDUs.

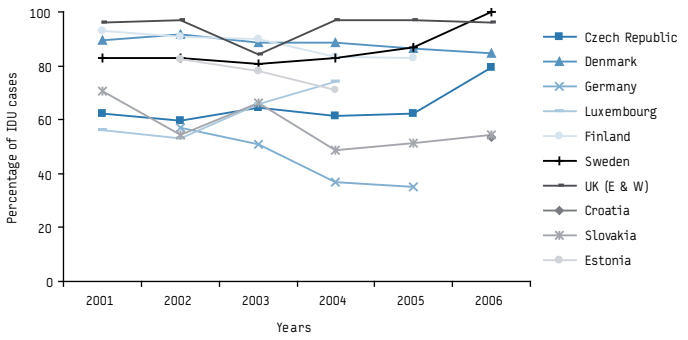
It cannot be excluded, however, that the high proportion of IDUs among cases observed in many countries is partly the result of specific screening programmes among IDUs, resulting in higher detection rates compared to other risk groups. Likewise, some countries that report relatively low proportion of IDUs among the cases with known transmission risk, suggesting differences in the epidemiology of HCV, may practice more intensive screening of other populations at risk than IDUs, the low proportion thus resulting from different HCV screening policies. In addition, there may be differences in the way the transmission risk is being assessed or reported.

An important improvement to the monitoring system would be to obtain further information regarding the legal status of the notification system (mandatory or voluntary), and this information is currently being collected by the European Centre for Disease Prevention and Control (ECDC). Equally important would be to gather information regarding the estimated exhaustivity of the system for reporting incident or prevalent cases. Regarding the unavailable data (e.g. countries reporting only IDU-related cases or providing combined acute and chronic cases), it would be important to know whether more information is available at the country level. Surveillance systems are still heterogeneous and difficult to compare and a minimal standardisation is a prerequisite for an improved European surveillance of HCV infection [10]. There is a pressing need to improve the HCV surveillance systems in Europe and, ultimately, to establish a more standardised European approach, which will be the subject of upcoming expert meetings at the ECDC. A good understanding of the epidemiology of HCV in Europe is not likely to be based on one single method, such as collecting notifications data, but on a combination of complementary surveillance systems [15] focused on both the general population and the specific populations at risk such as IDUs.

The public health importance and the implications of the HCV epidemic are major issues for Europe. An appropriate monitoring of the newly acquired HCV infections, the associated risk factors and the prevalence and burden of infection across Europe is needed. This should help to target prevention and screening programmes at those who are most at risk of infection, specifically the IDU population, and to allocate services for treatment.

FIGURE

Notified cases of hepatitis C related to injecting drug use – percentage of injecting drug users among all cases with risk factor information, 2001 to 2006, countries with 50 or more cases in 2004-06



Note: Estonia reported acute cases only; for other countries acute and chronic cases were combined.

Acknowledgments

We thank all national focal points and colleagues at national level, as well as the EMCDDA expert group on drug-related infectious diseases for providing the data here described. Else Smith, the Danish National Board of Health, having contributed when working at Statens Serum Institut, and Norbert Frost and Danica Klempova, EMCDDA, have provided important contributions.

Note: The EMCDDA collects similar data on national hepatitis B notifications, as well as HCV and HBV seroprevalence data from sentinel and national serological testing in samples of IDUs and it coordinates a European expert network on drug related infectious diseases (mainly hepatitis B, C and HIV) among injecting drug users. For HCV notifications and other infectious diseases data up to 2005 see: http://www.emcdda.europa.eu/stats07/INF

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Rapid Communications

Hepatitis C Action Plan for Scotland: Phase II (May 2008-March 2011)

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In 2004, the Scottish Government recognised that "Hepatitis C is one of the most serious and significant public health risks of our generation" [1] . By December 2006, Health Protection Scotland (HPS) estimated that 50,000 people in Scotland had been infected with the hepatitis C virus (HCV) and that 38,000 were chronic carriers (Figure 1) [2]. Following an extensive consultation in 2005, the Health Minister and Chief Medical Officer launched Scotland's 'Action Plan for Hepatitis C' in September 2006 [3].

Its aims are:

- To prevent the spread of hepatitis C, particularly among intravenous drug users (IDUs);
- To diagnose hepatitis C-infected people, particularly those who would most benefit from treatment; and
- To ensure that those infected receive optimal treatment, care and support.

The plan is a two-phased one. Phase I, undertaken during September 2006 to March 2008, involved increasing awareness about hepatitis C among professionals and gathering evidence through numerous surveys and other investigations to inform proposals for the development of hepatitis C services during Phase II (2008-2011)[4]. This paper presents the key findings of the evidence gathering exercise, recommended actions stemming from the evidence and funding associated with the actions[5].

Phase I

Phase I was co-ordinated by HPS. An Action Plan Co-ordinating Group (APCG), comprising representatives of key stakeholder groups, oversaw the implementation of the Action Plan; the APCG was supported by Working Groups corresponding to the three areas of i) Prevention, ii) Testing, Treatment, Care and Support and iii) Education, Training and Awareness-Raising. Each, during the first half of 2007, oversaw the implementation of actions involving the generation of evidence; during the second half, they translated the evidence into proposed key issues and actions. At a consultation event in October 2007, issues, evidence and proposed actions were presented to nearly 200 stakeholders who indicated their approval/disapproval through a digital voting system. The Working Groups modified the actions in accordance with the findings of the consultation and, by early 2008, they were approved by the APCG. Final approval by Scotland's Minister of Public Health was given for the Phase II Plan to be launched on World Hepatitis Day, 19 May, 2008 [5].

Approaches taken to generate the evidence

The approaches adopted to gather the evidence, involved self-administered questionnaire surveys and face-to-face interviews with service providers, the analysis of existing data held on laboratory and clinical databases, examining scientific literature and undertaking analytical studies to estimate the current and future clinical and financial burden of hepatitis C-related disease in Scotland.

Key epidemiological data

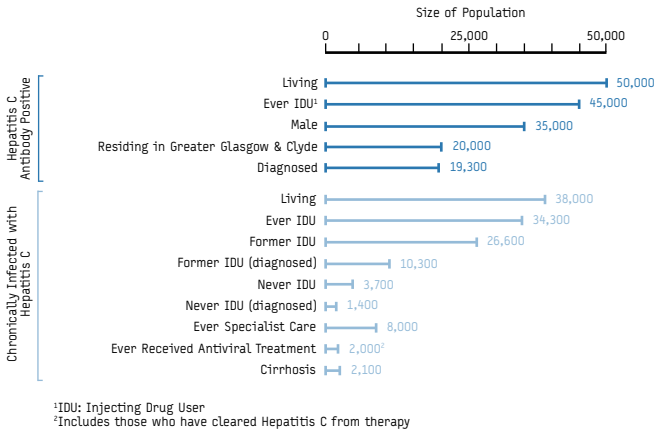
- As of 2006, of an estimated 38,000 living persons in Scotland, chronically infected with hepatitis C, 14,500 have been diagnosed, 8,000 had attended specialist clinical services for chronic hepatitis C and around 2,000 had received antiviral therapy; an estimated 2,100 hepatitis C infected persons had progressed to and were living with, cirrhosis (Figure 1).
- In 2006, an estimated 250 and 110 hepatitis C infected persons, respectively, developed cirrhosis and liver failure.
- It was estimated that if 2,000 persons per year received antiviral therapy over the next two decades, 5,200 and 2,700 cases, respectively, of hepatitis C-related cirrhosis and liver failure would be prevented in the future.
- Of 450 persons initiated on antiviral therapy during 2006, approximately 30 were prison inmates.
- In Greater Glasgow and Clyde, the area in Scotland with the greatest number of IDUs, the incidence of hepatitis C is steady at 20-30 infections per 100 person years of injecting.
- It is estimated that between 1,000 and 1,500 IDUs in Scotland are infected annually.

Summary of evidence: Testing, Treatment, Care and Support

- In recent years, very considerable progress in developing high quality services for hepatitis C infected persons in Scotland has been made; there are, however, several issues which need to be addressed.
- Insufficient numbers of infected persons, particularly former IDUs, are diagnosed.
- Widespread variations in the clinical management of hepatitis C infected persons exist.
- The training of the hepatitis C workforce is sub-standard.

FIGURE 1

Hepatitis C epidemiological landscape (estimates): Scotland, 2006



[1]IDU: Injecting Drug User
[2]Includes those who have cleared Hepatitis C from therapy

- There is a lack of integration among primary care, specialist, addiction, prison and social care services, resulting in many hepatitis C infected persons failing to complete a successful passage through the diagnostic, referral, treatment and care pathway.
- Insufficient numbers of infected persons are being administered antiviral treatment and resources, particularly for specialist clinical management and social care, including the support of persons journeying through the patient pathway, are inadequate.

Summary of evidence: Prevention

- Since the late 1980s, services providing needle/syringes to IDUs have been developed; these have been highly effective in preventing the transmission of HIV among IDUs. In the context of the more infectious and more longstanding (in terms of prevalence) hepatitis C Virus, however, there are many issues which need to be addressed.
- Widespread variations exist in the provision of injection equipment and educational initiatives for IDUs to prevent hepatitis C transmission, due to gaps in co-ordination and guidance.
- A high frequency of injection equipment sharing and incidence of hepatitis C among IDUs is observed.
- Opportunities to evaluate novel approaches to injection equipment provision in community and prison settings exist.
- A dearth of hepatitis C information provision for young people in educational settings is evident.

Summary of proposed actions stemming from the above evidence

- Networks will be established, guidelines and standards produced and plans developed to ensure that approaches to the prevention, and diagnosis and care of persons with, hepatitis C are highly effective and, where appropriate, consistent.
- Initiatives to train the workforce in, and educate young people about, hepatitis C will be implemented and awareness-raising campaigns to promote hepatitis C testing will be undertaken.
- To reduce the numbers of hepatitis C infected persons who will progress to severe liver disease, services in both health and prison settings will be improved to increase the annual numbers of persons of individuals receiving therapy from 450 in 2006 to 1,500 in 2010/11.
- To reduce hepatitis C transmission among IDUs, the nature, quantity and quality of services providing injection equipment, including paraphernalia other than needles and syringes, will be improved.
- To ensure that the performance of the above measures is monitored, several information generating initiatives (e.g. clinical databases, surveys gauging HCV incidence among IDUs) will be established or further developed.

Conclusions/Actions

Thirty-five recommended actions were submitted by the APCG to the Scottish Government for approval. All but one proposed action – the evaluation of community-based needle/syringe dispensing machines for IDUs – were approved by the Health Minister. £43.2 million has been made available over three years, commencing May 2008; £36.7 million will be allocated to Scotland's 14 Health Boards for the development of prevention, testing, treatment, care and support services. The Plan is designed to improve all hepatitis C services ranging from those that provide education to young people in schools about the dangers of drug use to the treatment of infected persons and the associated social support required to support them and their families through what, often, is a challenging journey. The Plan also recognises the crucial role of the voluntary and local authority sectors in providing education, training and social support services and the huge opportunity for hepatitis C-related prevention, diagnosis and treatment in Scotland's prisons. A range of performance indicators will be adopted to monitor the performance of the Action Plan which will be co-ordinated, on behalf of the Scottish Government, by Health Protection Scotland.

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Evaluation prompting transition from enhanced to routine surveillance of lymphogranuloma venereum (LGV) in the Netherlands

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In 2004, a lymphogranuloma venereum (LGV) epidemic among men who have sex with men in the Netherlands motivated the introduction of enhanced surveillance. We evaluated the acceptability of the enhanced LGV surveillance in the Netherlands in 2004-2005 to provide recommendations for future surveillance. Completeness of requested patient information was analysed. All 12 sexually transmitted infection (STI) health services participating in the 2004-2005 STI surveillance completed evaluation questionnaires and rated surveillance system features from 1="very poor" to 5="very good". Information from enhanced LGV surveillance was available for 34 (33%) of 104 cases. For these 34 cases, median proportions of response decreased successively for clinical information (100%), sexual anamnesis (71%) and details about the last sex partners (44%). A median score of 4 ("good") was assigned to simplicity, required resources and surveillance information requested and distributed. Seven respondents favoured continuation of LGV surveillance, whereof six preferred modifications, usually meaning less extensive surveillance. In conclusion, the enhanced LGV surveillance was generally regarded as adequate. However, it was limited by low completeness, underlining the need to keep requested information to a minimum. The routine STI surveillance now includes LGV diagnosis and, following this evaluation, the additional enhanced surveillance was discontinued. However, occasional cases justify alertness and LGV remains under routine STI surveillance in the Netherlands.

Introduction

Lymphogranuloma venereum (LGV) in Europe

Since 2004, LGV has been recognised as a public health concern among men who have sex with men (MSM) in western Europe, particularly in the United Kingdom, France, Germany and the Netherlands [1-6]. Chlamydia trachomatis serovar (genotype) L1, L2 or L3, the LGV causative agent, is associated with more invasive disease than the urogenital serovars D-K [1]. LGV can present with a genital or rectal ulcer or papule, proctitis, mucoid or purulent anal discharge, rectal bleeding, anal spasms, tenesmus, constipation, inguinal lymphadenopathy (buboes), pain and general malaise. The initial alert regarding the present epidemic was based on the observation of a cluster of cases among a subgroup of MSM in Rotterdam [7-11]. Typically, the cases presented with proctitits, were HIV positive, had concomitant STIs and reported having had unprotected sex with many partners in the Netherlands and abroad. To date, nearly 250 cases have been identified in the Netherlands, the majority belonging to the principal risk group [3,12,13].

Enhanced LGV surveillance in the Netherlands

In the Netherlands, a national LGV work group was established in January 2004, a case definition was developed (Table 1), and voluntary enhanced LGV surveillance was launched in March 2004 [7-9]. The objectives of the LGV surveillance were to; 1) assess the magnitude of the outbreak, 2) describe epidemiological aspects and, 3) identify risk factors in order to target prevention activities. A prerequisite for successful LGV surveillance was national awareness with regard to the LGV surveillance, clinical manifestation and diagnosis among STI physicians, human immunodeficiency virus (HIV) treatment centres, gastroenterologists and other. Corresponding information was distributed through email updates, national and international alerts [7-10] and information at the RIVM website.

The enhanced LGV surveillance was integrated with the routine internet-based STI surveillance (SOAP) and applied the case definition in Table 1. In 2004-2005, SOAP was based on 12 STI clinics and municipal health services that reported STI cases to the National Institute for Public Health and the Environment (RIVM) (Figure). As well as LGV being included in SOAP, other health professionals were also invited to report LGV cases in SOAP or on paper to the local municipal health service or the RIVM. The municipal health services and the RIVM exchanged information regarding LGV cases. In addition to the primarily clinical information about other STIs routinely collected in SOAP, the enhanced LGV surveillance requested more detailed information through an LGV-specific patient form. The additional information included LGV clinical manifestation, diagnostics, treatment and detailed information about sexual behaviours and meeting places, primarily during the past six months. RIVM summarised data and distributed feedback information to local and national stakeholders in the form of annual reports, presentations and email updates.

LGV cases have also been identified after the initial cluster, demonstrating that LGV is likely to remain on the public health agenda [12,13]. In this context, we evaluated the acceptability of the enhanced LGV surveillance in the Netherlands in 2004-2005 to provide recommendations for future surveillance.

Methods

Acceptability of the enhanced LGV surveillance in the Netherlands in 2004-2005 was estimated by completeness of requested information and rating of surveillance system features. Epidemiological analyses of the information collected in the enhanced surveillance have been published elsewhere [3].

Completeness

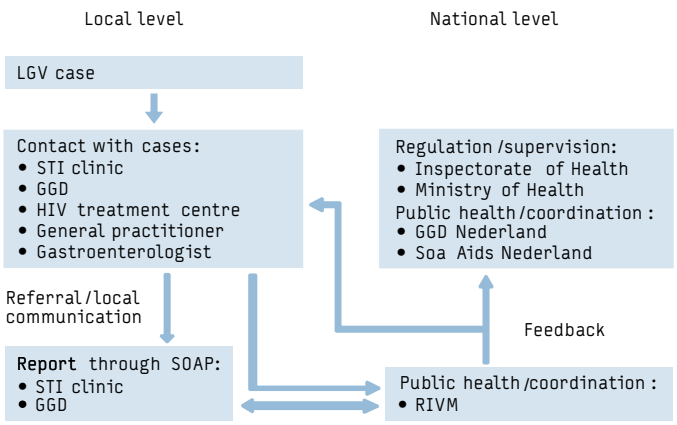
First, completeness of the requested LGV patient information was measured by the proportion of reported patients for whom requested forms had been obtained. Second, for different sections of the LGV patient form, the median proportion of response and the interquartile range (IQR) were calculated (Table 2). Furthermore, timeliness was measured by the duration between symptom onset, patient consultation and creation of a report in SOAP.

Rating of surveillance system features and usefulness

In May-August 2006, all 12 STI health services that participated in the 2004-2005 routine STI surveillance completed evaluation questionnaires. SOAP in general and the enhanced LGV surveillance in SOAP were ranked in terms of simplicity, collected information, feedback information, required resources and training of staff.

FIGURE

The enhanced lymphogranuloma venereum (LGV) surveillance system integrated with SOAP* in the Netherlands in 2004-2005



*SOAP: surveillance system for sexually transmitted infections

Note: Human immunodeficiency virus (HIV); lymphogranuloma venereum (LGV); municipal health service (GGD);

National Institute for Public Health and the Environment (RIVM); sexually transmitted infection (STI); GGD Nederland is a national association for GGDs; Soa Aids Nederland is a national expert centre for STI and HIV.

TABLE 1

Lymphogranuloma venereum (LGV) surveillance case definition in the Netherlands in 2004-2005

LGV surveillance case definition*		
Confirmed case	Probable case	Possible case
Anorectal syndrome OR contact of confirmed case AND positive *C. trachomatis* PCR (urine/rectum) AND positive or unknown *C. trachomatis* serology AND *C. trachomatis* serovar L1-L3	Anorectal syndrome OR contact of confirmed case AND positive *C. trachomatis* serology AND positive *C. trachomatis* PCR (urine/rectum)	Anorectal syndrome OR contact of confirmed case AND positive *C. trachomatis* serology

* As outlined in the user guidelines of the enhanced LGV surveillance

TABLE 2

Median proportions of response in patient forms received for 34 (33%) of 104 cases as part of the enhanced lymphogranuloma venereum (LGV) surveillance in the Netherlands in 2004–2005

Section of patient form	Median proportion of response in percent (interquartile range)
Clinical information	
Section overall	100 (88–100)
Clinical manifestation and anamnesis	100 (70–100)
Diagnostics, treatment and care	100 (83–100)
Sexual anamnesis	
Section overall	71 (50–78)
Basic anamnesis	76 (61–83)
Techniques and meeting places	65 (46–74)
Details about five last sex partners	
Section overall	44 (32–59)
Partner 1	74 (69–74)
Partner 2	59 (56–59)
Partner 3	44 (44–44)
Partner 4	32 (32–32)
Partner 5	32 (32–32)

TABLE 3

Ratings of the sexually transmitted infection (STI) surveillance system SOAP, the enhanced lymphogranuloma venereum (LGV) surveillance and LGV information and knowledge, as reported by the 12 STI health services that participated in the STI surveillance in the Netherlands in 2004–2005

Group of items	Number of scores available / requested (percent)*	Median score (interquartile range)**
SOAP in general***	36/60 (60)	4 (4–4)
LGV in SOAP***	24/60 (40)	4 (3–4)
Distributed information, March-April 2004****	49/60 (82)	4 (4–4)
Distributed information, May 2004-December 2005****	49/60 (82)	4 (4–4)
In-house LGV knowledge, April 2004*****	50/72 (69)	4 (4–4)
In-house LGV knowledge, at present*****	58/72 (81)	4 (3–4)

* Unavailable scores consisted of the answer alternative "don't know" or missing data.
** 5="very good", 4="good", 3="mediocre", 2="poor" and 1="very poor"
*** Included features: simplicity, collected information, feedback, required resources, required training
**** Included features: general impression, usefulness, simplicity, timeliness, completeness
***** Included features: clinical manifestation, risk groups in the Netherlands, epidemic in the Netherlands, diagnostics, aim of surveillance, LGV in SOAP

Distributed information about the enhanced LGV surveillance, including instructions and feedback, was ranked as for general impression, usefulness, simplicity, timeliness and completeness. Further, in-house LGV knowledge was ranked with regard to LGV clinical manifestation, risk groups, epidemic, diagnostic methods, surveillance objective and surveillance in SOAP. The answer alternatives composed a score; 5="very good", 4="good", 3="mediocre", 2="poor" and 1="very poor". The median score and IQR were calculated for each item and group of items (Table 3).

The questionnaire also enquired about perceived usefulness of information collected in the enhanced LGV surveillance and the prospects for future LGV surveillance. To gather further comments on the questionnaire items, we interviewed four STI health services who had diagnosed the majority (79%) of LGV cases in 2004-2005.

Results

Completeness

Of 114 LGV cases in the Netherlands in 2004-2005, 10 (9%) were retrospectively reported and could not be contacted for inclusion in the enhanced LGV surveillance [3]. Of the remaining 104 reported cases, 34 (33%) were reported in the enhanced surveillance with accompanying LGV patient forms. Of these, 31 (91%) were reported to the RIVM through SOAP while three were reported on paper and entered in SOAP at the RIVM. A large number of missing forms was attributed to one large STI clinic that at that time did not use SOAP to report STI cases. However, this STI clinic provided basic information on LGV cases, including consult date, basic demographics, sexual preference, other STI diagnoses and LGV clinical presentation (inguinal or anorectal). Information on detailed symptoms, date of onset, treatment and sexual anamnesis was not available for these cases.

For the 34 received patient forms, the response decreased as the questions became increasingly detailed (Table 2). Median proportions of response for different sections decreased from 100% for clinical symptoms, diagnostics and treatment to 71% for sexual anamnesis and to 44% for details about the five last sex partners. For the latter section, median proportions of response also decreased successively for details of the first to the fifth partner (74%, 59%, 44%, 32%, and 32%). The date of symptom onset was known for seven, estimated for 24 and unknown for three patients. The median duration from onset to consultation was 57 days (IQR 29-96 days). The median duration between patient consultation and creation of a report in SOAP was 20 days (IQR 0-62 days), which is a usual time period for obtaining laboratory results [14].

Rating of surveillance system features

The 12 STI health services provided 266 (69%) of 384 requested scores, while the remainder consisted of either the answer alternative "don't know" or missing data (Table 3). Overall, the ratings of different features of the enhanced LGV surveillance corresponded to a median score of 4 ("good") (IQR 4-4). The items relating to SOAP in general and the LGV surveillance in SOAP generated median scores of 4 (IQR 4-4 and 3-4, respectively). The information distributed about the LGV surveillance in the start-up phase (March-April 2004) and thereafter (May 2004-December 2005) also yielded median scores of 4 (IQR 4-4 and 4-4). The STI health services' initial (April 2004) and present in-house LGV knowledge corresponded to median scores of 4 (IQR 4-4 and 3-4, respectively). The above picture was supported by the interviews. Seven respondents had experience of LGV patients, but results did not appear to differ between respondents with and without LGV experience.

Future LGV surveillance

Of the 12 STI health services, eight regarded the information collected by the enhanced surveillance in 2004-2005 as useful, while one regarded it too detailed and three did not provide an opinion. Six respondents favoured continued LGV surveillance but in modified form, one respondent preferred continued LGV surveillance in its present form, two deemed that there should be no LGV surveillance at all, while three did not provide a preference with regard to future LGV surveillance. Modifications of the enhanced LGV surveillance usually referred to collection of less information as clarified in comment fields and interviews. Downscaling of the enhanced surveillance was motivated by perceptions of limited public health importance and low usefulness outside outbreak situations.

Discussion

The present evaluation of the enhanced LGV surveillance in the Netherlands in 2004-2005 showed that participating STI health services generally regarded the surveillance as adequate. This notion is limited by the occasionally low proportions of response in the evaluation questionnaire (Table 3). This applies in particular to the enhanced LGV surveillance section, probably because not all respondents had direct experience of LGV cases and thus of the enhanced surveillance. The tendency towards satisfied ratings contrasts with the low completeness of requested information, especially the low proportion of received patient forms (33%), which indicates that the enhanced LGV surveillance did not fully function as intended.

Usefulness of the enhanced LGV surveillance

The patient information received through the enhanced LGV surveillance confirmed the initial observation of an epidemic among a high-risk subgroup of MSM [3]. The basic information available for reported cases without the patient form showed a similar picture. This absence of evidence of spill-over into other population groups is important when devising public health responses. In the context of the first surveillance objective, this evaluation offers no reason to suspect that there were considerable numbers of not notified diagnosed LGV cases, although underdiagnosis cannot be excluded. With regard to the other two surveillance objectives, the cases have been described elsewhere [3]. Thus, it can be concluded that the enhanced LGV surveillance provided information according to the stated objectives.

However, the usefulness of the collected patient information was limited by low completeness, notably the low proportion of available patient forms (33%). Moreover, low proportions of response could be associated with detailed questions regarding sexual anamnesis. This may be attributed to the intimate nature of the questions, the time required to complete the patient form and a limited perceived usefulness of the most detailed questions. Low response for detailed behavioural questions has been noted in the corresponding enhanced LGV surveillance in the United Kingdom [4] and France (Anne Gallay, personal communication, 26 March 2007), and the Dutch form stood out in that it asked for more detailed information about the five last sex partners. This evaluation highlights that a prerequisite for efficient surveillance is to keep requested information to the minimum required for public health action.

Future LGV surveillance

In 2006-2007, an increase in LGV cases in Amsterdam confirmed a need for sustained alertness and surveillance [12, 13]. Since 2004, the routine STI surveillance in SOAP has been gradually expanded and now includes LGV diagnosis and serovar. Furthermore, information is presently routinely collected on basic demographics, sexual preference, number of sex partners during the past six months, other STIs, condom use during the last sexual contact and unprotected contacts abroad during the past three months. Thus, the routine STI surveillance alone should presently, in conjunction with alertness among clinicians, provide a sufficient basis for public health action. If deemed necessary, such action may include research on clinical and behavioural characteristics of cases in order to follow the epidemic's development in more detail.

The present evaluation was presented at a national STI expert meeting and a proposal to discontinue the enhanced LGV surveillance was accepted. The revised objective for future LGV surveillance is to monitor and analyse trends in LGV cases in the Netherlands and thus obtain basic information to guide public health action. Furthermore, the Dutch case definition may be adapted according to the standard case definition of the European Centre for Disease Prevention and Control (ECDC), which could reduce differences among European countries [2-5].

Conclusion

The enhanced LGV surveillance was useful to confirm risk groups [3] and the present evaluation indicates that the surveillance was generally regarded as adequate. Public health usefulness was limited by low completeness of information requested through the LGV patient form. The low completeness may be attributed to occasionally low acceptability and too detailed questions, underlining the need to keep requested information to a minimum. The routine STI surveillance has been expanded and now includes LGV diagnosis, reducing the added value of the enhanced LGV surveillance. Accordingly, in July 2007, following this evaluation, the enhanced LGV surveillance was discontinued. However, occasional cases justify alertness and LGV remains integrated in the routine STI surveillance in the Netherlands.

Acknowledgments

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A survey on cases of tick-borne encephalitis in European countries

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The European Network for Diagnostics of "Imported" Viral Diseases (ENIVD) is finalising a project to improve the diagnostic and monitoring of encephalitis viruses in Europe. Part of this study was to analyse the present surveillance situation for tick-borne encephalitis (TBE), which is the most important flavivirus infection of the central nervous system in the European Union (EU) and Russia. A questionnaire was mailed to contact points in all Member States of the EU and three non-EU countries (Norway, Russia and Switzerland) to summarise their TBE surveillance and prevention activities. Information was requested on case definition, type of laboratory tests for TBE diagnostics, investigations regarding tick-transmitted diseases, mapping of endemic foci, vaccination programmes, and recommendations for travellers. The survey gives an overview of the existing epidemiological and laboratory sources of information and the number of TBE cases from 2004 until 2007, but also showed that, in particular, case definitions, diagnostic assays for confirmation, and methods/indicators for mapping risk areas differ widely across the participating countries. The data will help to develop recommendations for the standardisation and quality control of TBE surveillance and diagnostics.

Introduction

Tick-borne encephalitis (TBE) is the most important flavivirus infection of the central nervous system (CNS) in Europe and Russia. The total annual number of cases is estimated to be up to 10,000 in Russia and about 3,000 in European countries [1-4]. According to the International Committee for Taxonomy of Viruses, TBE virus is classified as one species with three subtypes, namely the European subtype (which comprises almost all known isolates from Europe), the Siberian subtype (mainly isolates from Urals, Siberia and far-eastern Russia) and the Far Eastern subtype (mainly isolates from far-eastern Russia, China and Japan).

The three TBE virus subtypes are associated with varying degrees of disease severity [2-4]. Human infections with Far Eastern subtype viruses are usually severe, frequently with encephalitic symptoms (focal meningoencephalitis or polyencephalitis), with an associated fatality rate between 5 and 35%. This type does not cause chronic disease. In contrast, TBE virus infections of the Siberian subtype cause a less severe disease (fatality rate between 1 and 3%), with a tendency for patients to develop chronic or extremely prolonged infections accompanied by diverse neurological and/or neuropsychiatric symptoms. In contrast to these two forms, infections caused by European strains typically take a biphasic course [5]: after a short incubation period (usually 7–14 days, with extremes of 4–28 days), the first (viraemic) phase presents as an uncharacteristic influenza-like illness lasting 2–4 days (range 1–8 days) with fever, malaise, headache, myalgia, gastrointestinal symptoms, leukocytopenia, thrombocytopenia and elevated liver enzymes, often followed by a symptom-free interval of about one week (range 1–33 days). The second phase of TBE occurs in 20–30% of infected patients and is marked by four clinical features of different severity (meningitis, meningoencephalitis, meningoencephalomyelitis or meningoencephalo-radiculitis) and the appearance of specific antibodies in the serum and cerebrospinal fluid (CSF). This is usually the time when patients with high fever and severe headache seek medical advice. The fatality rate in adult patients is less than 2%. However, severe courses of TBE infection with higher mortality and long-lasting sequelae often affecting the patient's quality of life have been correlated with increased age [6-8]. More detailed information on the clinical picture, case definition and other issues of interest are available in a TBE fact sheet on the ENIVD website [http://www.enivd.org].

The epidemiology of TBE is closely related to the ecology and biology of ticks [2,3,9,10]. In nature, TBE virus is propagated in a cycle involving permanently infected ticks and wild vertebrate hosts. Virus transmission occurs horizontally between tick vectors and vertebrates, especially between spring and autumn, with small mammals (mainly rodents) serving as virus reservoirs. In addition, trans-stadial and trans-ovarial transmission of the virus, as well as co-feeding of infected and non-infected ticks on the same host play a major role in virus transmission [11]. In contrast to other tick-transmitted diseases, such as Lyme borreliosis, TBE is distributed in an endemic pattern of so-called natural foci over a wide geographical area focussed on central Europe, the Baltic states and Russia. The distribution of TBE is determined by the occurrence of the respective tick vectors in certain regions [3,10]. While Ixodes ricinus is the prevalent hard tick species across Europe and therefore the most important transmitter of the European TBE virus subtype, Ixodes persulcatus occurs in forest regions of the Urals, Siberia and far-eastern Russia and is the main vector of the other subtypes. Co-circulation of two or all three subtypes could be shown for Finland and the Baltic states where the distribution areas of the two main tick species overlap [12,13].

However, the virus prevalence in ticks as well as the prevalence of infected ticks within the risk areas can vary [4,9,14,15]. Countries with high-risk areas are Russia, Latvia, Lithuania and Estonia. TBE is also a significant issue in Germany, the Czech Republic, Poland, Switzerland, Sweden, Finland, Slovakia, Hungary and Slovenia. Even in Austria, the only country with progressively decreasing

incidences since 1981 (due to high vaccination coverage [16]), the occurrence of TBE may be of relevance for unvaccinated tourists. In France, Italy, Greece, Norway and Denmark, TBE is of minor importance. In the United Kingdom, Ireland, Belgium, the Netherlands, Luxembourg, Spain and Portugal, TBE is not indigenous. Detailed epidemiological statistics from 1990 onwards can be obtained from the website of the International Scientific Working Group on TBE [http://www.isw-tbe.info].

An increase of TBE incidence has been observed in the risk areas (both high- and low-risk) in some of the endemic countries mentioned above, especially in the last decade [15,17-20]. In addition, new TBE foci have appeared in Europe. This is due to a complex interrelation of several factors, such as social (e.g. socio-political changes, human leisure activities), ecological (e.g. effects of climate changes on vectors) and/or technological factors (e.g. advanced diagnostics and increased medical awareness) [20-24]. The collection of epidemiological data is indispensable in order to predict endemic foci and to recommend preventive measures. Several methods can be employed to investigate the epidemiological situation of TBE [10]:

1. examination of ticks and animal reservoirs for the presence of TBE virus (especially by molecular diagnostic techniques);
2. seroprevalence study of people exposed to ticks; and
3. describing clinical cases and their geographical location.

TBE is a growing concern in Europe, but the surveillance and notification schemes are not uniform and not always mandatory and may affect the prevalence estimates for the disease in certain regions [25,26]. Main problems are the lack of a Europe-wide standard case definition, wide differences in the quality of national surveillance of TBE cases, and varying diagnostic procedures. Thus, surveillance data from different countries are difficult to compare. Furthermore, little is known about the true TBE virus prevalence in tick populations or about the circulation of new subtypes in Europe.

Currently, the European Network for Diagnostics of "Imported" Viral Diseases (ENIVD) is finalising a project to improve the diagnostic and monitoring of encephalitis viruses in Europe. Its tasks are being defined in several working groups [27]. Here, the ENIVD-working group for TBE virus describes the results of a questionnaire survey on the present TBE surveillance situation in Europe, which will help to develop recommendations for the standardisation and quality control in TBE surveillance and diagnostics.

Methods

To request information on TBE surveillance and prevention activities in national surveillance systems, a questionnaire with 10 questions was mailed to contact points in all member states of the European Union (EU) and three non-EU countries (Norway, Russia and Switzerland) based on an ENIVD database of expert microbiologists and epidemiologists. The questions were the following:

1. Is TBE a notifiable disease in your country? (Since when?)
2. Is there an official reference base to which the annual number of cases is reported?
3. Does a clear case definition for TBE exist? (If yes, what is it?)
4. What kind of diagnostic assays are used most often to diagnose TBE?
5. Is there an expert or reference laboratory for TBE infections in your country? (If yes, what are their contact details?)
6. What was the annual number of human cases between 2004 and 2007?
7. Are there any regular investigations regarding tick-transmitted diseases? (If yes, what kind of investigations?)
8. Do you map endemic foci/risk areas? (If yes, based on what kind of data?)
9. Is there an official vaccination programme for TBE in your country?
10. Are there official recommendations regarding TBE vaccination for travellers to TBE endemic areas?

Results

Of 30 contacted countries, 19 EU member states and three non-EU countries (Norway, Russia and Switzerland) participated in this survey (recovery rate: 73%) (Figure 1). All contributors are listed in the acknowledgements section. The completed questionnaires were returned during the summer trimester of 2007. The TBE case numbers for 2007 were added afterwards in February/March 2008. Therefore, the results of this survey reflect national surveillance systems and case numbers for TBE up to these dates.

FIGURE 1

Form of notification for tick-borne encephalitis in Europe and Russia (survey participants)

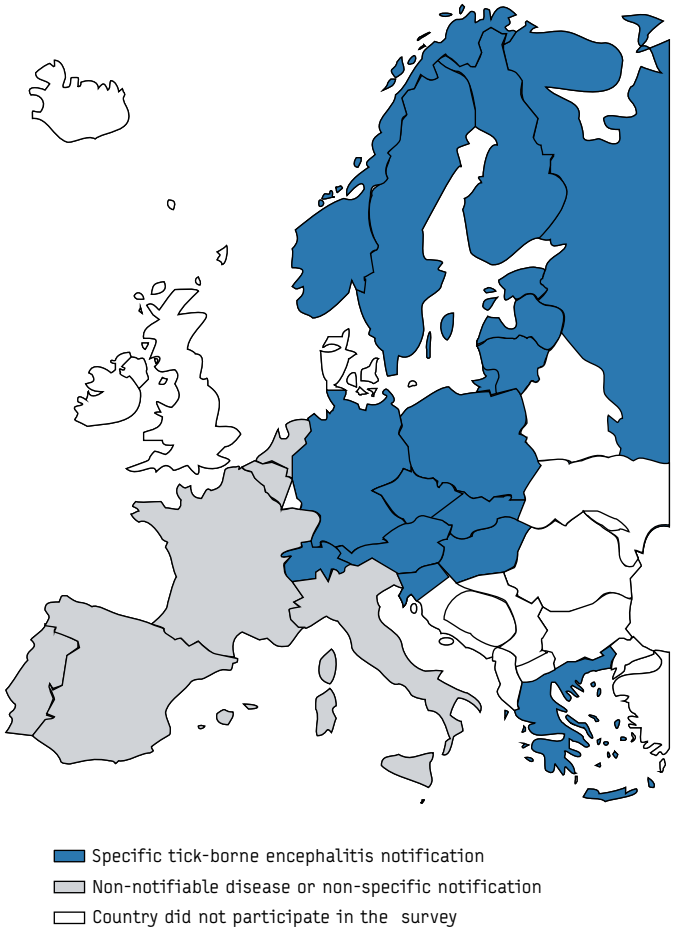


Table 1

Survey data regarding surveillance systems on tick-borne encephalitis in European countries*

Member State	Notifiable disease	Case definition	Diagnostic assays	Investigations regarding tick transmitted diseases	Mapping of endemic foci/risk area	Vaccination programme	Recommendations for travellers
Austria	Yes[1]	Serological proven hospitalised TBE cases are counted	ELISA	Survey on TBE and borreliosis	For human cases	Yes	Yes
Belgium	No	No	ELISA, PCR	Research project on anaplasmosis, babesiosis, TBE (2007-2010)	In development for human cases, vectors and hosts (rodents, roe deer)	No (optional)	Yes
Czech Republic	Yes, since 1971	Clinical and laboratory signs of aseptic meningitis/ meningoencephalitis and positive TBE virus serology	Mostly ELISA, in NRL for arboviruses: CFT and VNT	Tick surveillance in natural foci (TBE and borreliosis)	For human cases and infected ticks	No (optional)	Not known
Estonia	Yes, since 1970	Possible case: typical clinical case history (biphasic course of infection), epidemiological links (e.g. tick bite); Confirmed case: with laboratory confirmation: not less than four-fold increase in antibody titre in pair-sera or IgM-antibodies in serum/CSF or positive PCR[5]	IFA, ELISA, VNT, PCR, SEQ, VI, WB, HIA	Survey on TBE	For human cases	No (optional)	Yes
Finland	Yes, since 1996	TBE virus-IgM positive with suitable clinical and anamnestic data (not exposed to other flaviviruses)[6]	IgM micro-capture ELISA and HIA (PCR only for tick studies)	Tick field surveys (TBE, babesia and anaplasma)	For human cases	Yes, only Åland islands (since 2006)	Yes
France	No	For the diagnosis of TBE, a double check on a pair of serum samples is required (not further specified)	ELISA, VNT only in very few cases (PCR not in routine)	Survey on patients with risk of exposure in infested areas as well as outside	For human cases (only Alsace region)	No (optional)	No
Germany	Yes, since 2001	Clinical CNS symptomatic case with positive PCR in blood/CSF or IgM- and IgG-antibodies in blood/CSF or increase in IgG-antibody titre or intrathecal antibody production[7]	ELISA	Tick surveillance (TBE); surveys on borreliosis and rickettsiosis	For human cases	Yes	Yes
Greece	Yes[2]	Clinical CNS symptomatic case with: positive PCR in clinical sample, increased IgG and IgM antibody titres of, IgM detection in CSF, virus isolation	ELISA, IFA, PCR, VI	Survey on TBE (human cases, serosurvey, ticks); survey on CCHF and on bacterial tick-borne diseases	For human cases and ticks, in northern Greece	No (optional)	Yes, if requested
Hungary	Yes since 1977	Aseptic meningitis, encephalitis or meningoencephalomyelitis confirmed by laboratory tests	IFA, HIA, ELISA	Regular: human cases, serosurvey (TBE); project on tick survey (until 2008)	For human cases and TBE natural foci	Yes, for people at occupational risk	No
Italy	no[3]	No	IFA, VI, PCR, micro-neutralisation	not known	For human cases (only north-eastern Italy)	No (optional)	No
Latvia	Yes, since 1999	No	ELISA	Survey on TBE and borreliosis; tick survey	For human cases and infected ticks	Yes, for children (since March 2007)	Yes
Lithuania	Yes, since 1969	Officially no, but reported cases are serologically proven hospitalised TBE cases	ELISA	Annual tick activity	For human cases	No (optional)	Yes
Poland	Yes, since 1970	Clinical description: typical clinical case history (biphasic course of infection); Laboratory criteria: demonstration of four-fold or greater rise of antibody titre in serum or demonstration of intrathecal antibodies or virus isolation from tissues, blood or CSF (for probable case: demonstration of IgM antibodies in serum with no history of previous flaviviral exposition); classification in possible, probable or confirmed cases[8]	ELISA	Survey on TBE and borreliosis	For human cases	Recommended for high-risk groups, but not reimbursed (optional)	Yes
Portugal	No	No	IFA	Survey on rickettsia, borrelia and arboviruses; tick survey	No	No (optional)	No
Slovakia	Yes, since 1950	Not known	ELISA, HIA (PCR in specific cases)	Survey on TBE and tick survey	No	No (optional)	Yes
Slovenia	Yes, since 1977	A case of TBE is considered to be confirmed by the following findings: fever, clinical signs/ symptoms of meningitis or meningoencephalitis, an elevated CSF cell count (>5x10^5 cells/L), and serum IgM anti-bodies to TBE virus and/or IgG seroconversion	ELISA, PCR	Survey on human cases and in ticks for TBE, borreliosis, rickettsiosis, anaplasmosis and further tick-borne pathogens	For human cases, ticks and reservoirs	Yes	Yes
Spain	No	No	ELISA, PCR	Survey on bacterial tick-borne diseases	No	No (optional)	Yes
Sweden	Yes[4], since 2004	Under discussion, but reported cases are based on clinical picture and positive serology	ELISA	No	Human cases, incidence	No (optional)	No
The Netherlands	No	No	ELISA, PCR	Survey on borreliosis (RIVM, Bilthoven)	For borellia	No (optional)	No
Norway	Yes, since 1975	No	ELISA	Survey on borreliosis	For human cases, serosurvey in dogs (areas of Kristiansand)	No (optional)	No
Russia	Yes, since 1950	No formal case definition	ELISA	Survey on human cases and in ticks forTBE, orreliosis, rickettsiosis, CCHF	For human cases and infected ticks	Federal level: optional; regional level: yes	No
Switzerland	Yes, since 2001	Not known	ELISA	No	For human cases and natural reservoirs	Yes, recommended for high-risk groups	Yes

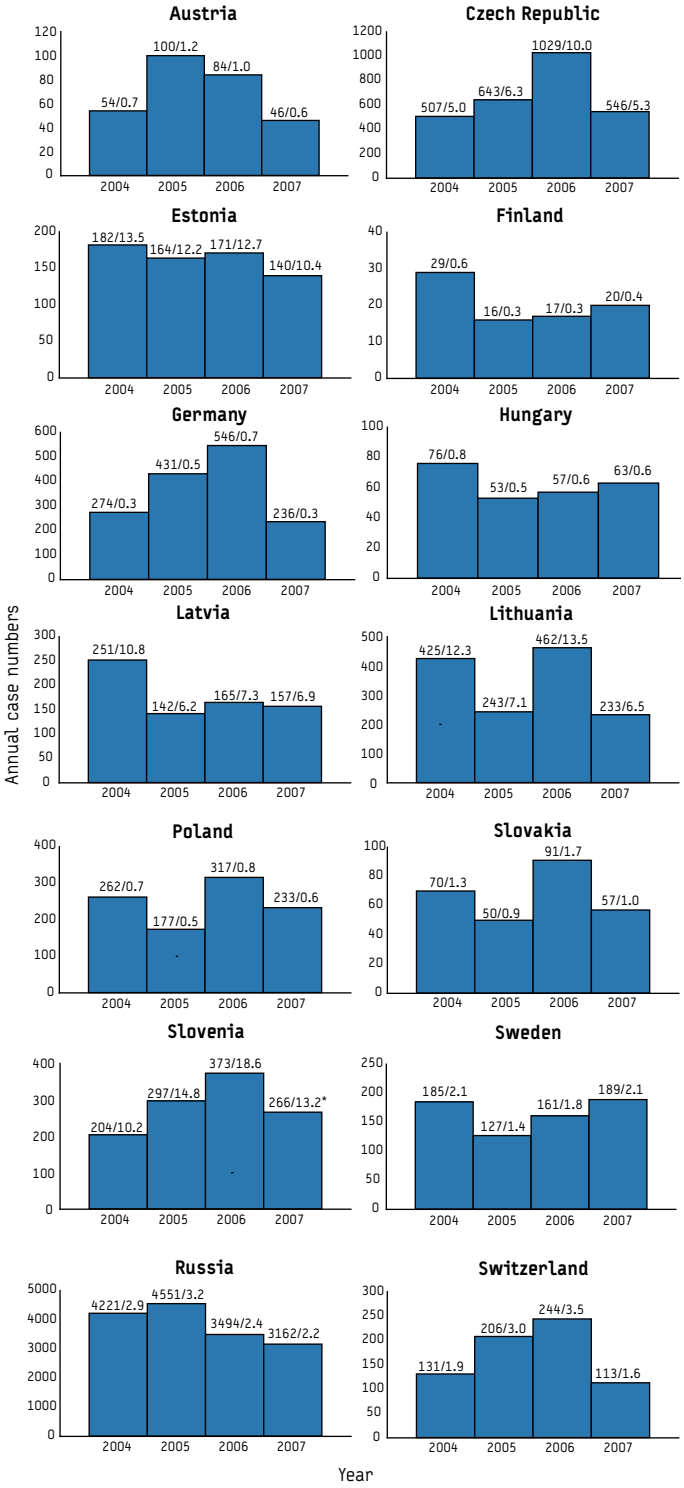
* Data provided by listed contributors.

[1] Notified if meningoencephalitis. Start of notification not further specified.
[2] Notification as arboviral encephalitis since 2002 as part of the Commission decision 2002/253/EC.
[3] Notification of all acute viral encephalitis cases since 1990. Not specifically TBE.
[4] Notifiable 1969-1989, and again from July 2004. Voluntary reporting during the period 1990 - June 2004.
[5] Case definition used since 2004.
[6] A Baltic/Nordic working group on TBE started in October 2007 to discuss an appropriate case definition.
[7] Case definition of the Robert Koch Institute according to the Law for the Prevention of Infections (Infektionsschutzgesetz, IfSG), 2007
[8] Case definition used since January 2005.

CFT: complement fixation test; CSF: cerebrospinal fluid; ELISA: enzyme linked immunosorbent assay; HIA: haemagglutination inhibition assay; IFA: immunofluorescence assay; PCR: polymerase chain reaction; SEQ: sequencing; VI: virus isolation; VNT: virus neutralisation; WB: Western blot. CCHF: Crimean Congo haemorrhagic fever; TBE: tick-borne encephalitis. NRL: National reference laboratory

FIGURE 2

Annual case numbers and incidences (per 100,000 inhabitants) of tick-borne encephalitis in European countries, 2004-2007



* Slovenia 2007. No officially confirmed laboratory data (usually 25% higher than the mandatorily reported cases)

Case reporting

While TBE cases were specifically notifiable in 16 of the 22 participating countries (73%), at the time of the survey, notification of TBE was not mandatory in Belgium, France, Italy, Portugal, Spain and the Netherlands (Figure 1). Of the 16 countries with TBE notification, eight (Austria, Czech Republic, Germany, Greece, Hungary, Poland, Slovenia and Sweden) had a case definition based on clinical criteria and laboratory confirmation, two (Estonia and Finland) also included cases with an epidemiological link (e.g. tick bite), and the remaining six countries (Latvia, Lithuania, Norway, Russia, Slovakia, and Switzerland) had no officially or clearly formulated case definition (Table 1). From Finland and Sweden we know, that the present case definitions are under discussion and will soon be harmonised among the Baltic and Nordic states (the discussion started in October 2007 and is planned to be done by June 2008).

Although clear case definitions were provided by ten countries, differences could be seen in the classification of relevant TBE cases as aseptic meningitis, meningoencephalitis and/or meningoencephalomyelitis (see e.g. classifications in Austria, Czech Republic, Hungary or Slovenia), as well as in the application of laboratory tests for case confirmation (Table 1). Commonly, the routine laboratory diagnosis of TBE is based on the detection of specific antibodies by enzyme linked immunosorbent assay (ELISA) as done in 20 participating countries (91%). Polymerase chain reaction (PCR) is included for particular investigations (e.g. tick studies or severe cases) by 10 countries (45%); followed by other methods like immunofluorescence assay in five countries; haemagglutination assay and virus neutralisation tests in four countries, respectively; and virus isolation in three countries. Other less common methods like complement fixation test, sequencing and Western blot are used in the Czech Republic and Estonia.

Surveillance activities

While for Italy, Sweden and Switzerland information on further investigations regarding tick-transmitted diseases (e.g. TBE, borreliosis, babesiosis, ehrlichiosis, rickettsiosis) were not available, the other 19 countries could provide these data (Table 1). They conduct mainly human serosurvey studies on borreliosis or TBE (10 countries each), followed by surveys on rickettsiosis in five countries. Surveys on the prevalence of TBE virus in tick populations were also performed in seven countries; for anaplasma (the causative agent of ehrlichiosis in Europe) and borrelia in four countries, and for babesia, rickettsia and other relevant pathogens in three countries, respectively. All countries except Portugal, Slovakia and Spain provided information on what kind of data they based their TBE risk assessments on (Table 1). The mapping of risk areas is mainly based on the geographical incidence of autochthonous clinical cases (18 countries), while seven countries also included data on infected ticks in the risk assessment, and only four countries used data from natural reservoirs (e.g. rodents) or indicator hosts (e.g. roe deer, dogs). The Netherlands used this kind of data only for risk assessment of borreliosis.

Trends in TBE incidence

Based on the data from this survey we are able to present an overview of the TBE situation in 14 European countries from 2004 until 2007 (Figure 2). Other participating countries have provided no (Belgium, Greece, Italy, Portugal, Spain) or only few data (France, The Netherlands, Norway).

For the presented period of the past four years certain tendencies/changes in the TBE incidence can be extracted. Following clear increases of the annual case numbers in 2004-2006 (approximately two-fold) in the Czech Republic (with more than 1,000 cases in 2006, the highest reported number since notification began), Germany (with an all-time high of 546 cases in 2006), Slovenia (with 373 cases in 2006, the highest number since 1994) and Switzerland (with the highest number, 244 cases, in 2006) the incidences in these countries declined in 2007. A similar trend in annual TBE case numbers could be observed for Austria. However,

Table 2

Survey data regarding surveillance systems on tick-borne encephalitis in European countries*

Member State	Reference	Expert or reference laboratory†
Austria	http://www.virologie.meduniwien.ac.at/home/virus-epidemiologie/virusepidemiologische-information/lang_1-content.html (Institute of Virology, Medical University of Vienna)	Univ.-Prof. Dr. F. X. Heinz Institute of Virology, Medical University of Vienna
Belgium	http://www.iph.fgov.be/epidemio/epien/index0000.htm (Scientific Institute of Public Health, Brussels)	Dr. P. Heyman Research Laboratory for Vector-borne Diseases, Queen Astrid Military Hospital, Brussels
Czech Republic	http://www.szu.cz/cema/epidat/epidat.htm (National Institute of Public Health, Prague)	Prim. Dr. J. Januška NRL for arboviruses, National Institute of Public Health, Ostrava
Estonia	http://www.tervisekaitse.ee/ (Health Protection Inspectorate, Tallinn)	Dr. I. Golovljova National Institute for Health Development, Tallinn
Finland	http://www3.ktl.fi (National Public Health Institute, Helsinki)	Prof. O. Vapalahti Haartman Institute, University of Helsinki
France	http://www.pasteur.fr/sante/clre/cadrecnr/arboFHV-index.html (National Reference Centre for Arboviruses, Lyon)	Dr. H. Zeller Unit for the biology of emerging viral infectious (UBIVE) Institut Pasteur, Lyon
Germany	http://www.rki.de/DE/Content/Infekt/EpidBull/epid__bull__node.html (Robert Koch-Institute, Berlin)	Prof. J. Süss NRL on tick-borne pathogens, Friedrich-Löffler-Institute, Jena
Greece	http://www.keel.org.gr/ (Hellenic Centre for Infectious Disease Control, Athens)	Prof. A. Papa School of Medicine, Aristotle University of Thessaloniki
Hungary	Yearbook of Health Statistics (National Centre for Epidemiology, Budapest)	Dr. E. Ferenczi NRL for viral zoonoses, National Center for Epidemiology, Budapest
Italy	not provided	Dr. L. Nicoletti Arbovirus Laboratory, Italian National Institute of Health,(Istituto Superiore di Sanitá), Rome
Latvia	http://www.sva.lv/epidemiologija/statistika/ (State Public Health Agency, Riga)	Dr. T. Kolupajeva Infectology Centre of Latvia, Riga
Lithuania	http://www.ulpkc.lt (Centre for Communicable Disease Prevention and Control, Vilnius)	Dr. A. Griskevicius Lithuanian AIDS centre laboratory, Vilnius
Netherlands	not provided	Dept. of Virology, Unit Diagnostics, Erasmus MC, Rotterdam and Laboratory of Virology, National Institute for Public Health and the Environment (RIVM), Bilthoven
Poland	http://www.pzh.gov.pl/epimeld/index_a.html (National Institute of Hygiene, Warsaw)	Associate Professor B. Litwińska NRL for arboviruses, National Institute of Hygiene, Warsaw
Portugal	not provided	Dr M.T. Paixão Centre for Vectors and Infectious Diseases Research (CEVDI) National Institute of Health, Lisboa
Slovakia	Regional Public Health Authority, Banska Bystrica	Ing. Z. Sirotná NRC for arboviruses, Public Health Authority of the Slovak Republic, Bratislava
Slovenia	http://www.ivz.si/ (Institute of Public Health Republic of Slovenia, Ljubljana)	Prof. Dr. T. Avšič-Županc Instituteof Microbiology and Immunology, University of Ljubljana
Spain	http://cne.isciii.es (National Centre of Epidemiology, Institute of Health Carlos III, Madrid)	Dr. A. Tenorio CNM Institute of Health Carlos III, Majadahonda-Madrid
Sweden	Annual report of the Department of Epidemiology, Swedish Institute for Infectious Disease Control	Swedish Institute for Infectious Disease Control, SE 171 82 Solna, Sweden
Norway	http://www.msis.no/emsisexternalweb/Forside.htm#_Welcome_to_the (Norwegian Institute of Public Health, Oslo)	not provided
Russia	Annual (or biannual) Book "Infectious morbidity in the provinces of Russian Federation" (Federal Centre of Hygiene and Epidemiology, Moscow)	Dr. A.E. Platonov Laboratory for arboviruses, Central Institute for Epidemiology, Moscow
Switzerland	http://www.bag.admin.ch/k_m_meldesystem/00733/00804/index.html?lang=de (Federal Office of Public Health, Bern)	Dr. D. Schultze Institute for Clinical Microbiology (IKMI), St. Gallen

* Data provided by listed contributors.
† Further contact information can be provided on request.
NRL: National Reference Laboratory; NRC: National Reference Centre

the incidence in Slovenia changed dramatically from 10.2 cases per 100,000 inhabitants in 2004 to 18.6 cases per 100,000 in 2006, and is now similar to incidences in Lithuania and Estonia, countries that are usually among the countries with the highest incidence rates. In Latvia, the incidence has decreased significantly in 2005 and since remained stable with approximately seven cases per 100,000 inhabitants. Among the Nordic countries, Sweden had the highest incidences with a gradual increase from 127 cases in 2005 to 189 cases in 2007. While Lithuania, Poland and Slovakia showed considerable fluctuations in the annual TBE case numbers, the trends in the remaining countries were more or less stable. However, we found high incidence levels in the Czech Republic, Estonia, Latvia, Lithuania and Slovenia in 2007 (5.3-13.2), considerable incidence levels for Slovakia, Sweden, Russia and Switzerland (1.0-2.2), and incidence levels under 1.0 cases per 100,000 inhabitants for Austria, Finland, Germany, Hungary and Poland. The epidemiological and laboratory sources of information for the TBE surveillance data are listed in Table 2.

Vaccination policy

Only in Austria, Finland, Germany, Hungary, Latvia, Slovenia, Russia and Switzerland, TBE vaccination is included in an official governmental vaccination programme under certain conditions. In the remaining 14 countries, it is available as an optional vaccination, partly recommended, but not reimbursed by health insurance companies (Table 1). In Austria (with a successful vaccination campaign since 1981), Germany and Switzerland, health insurance companies cover the vaccination costs for people who are at risk of exposure to ticks in risk areas [28-30]. In Finland, TBE vaccination has been offered for free since 2006 only for the Åland islands which have the highest incidence rate of the country. Hungary has a programme only for people at occupational risk. Also in Slovenia, vaccination is only obligatory for forest workers, farmers, military personnel and other occupationally exposed people. In Latvia, a free vaccination programme was started for children from regions with high incidences in March 2007. TBE vaccination in Russia is recommended, but currently not financed by federal budget. There are some programmes on regional level based on province budget or other financial sources.

Travel recommendations

Austria, Belgium, Estonia, Finland, Germany, Greece, Latvia, Lithuania, Poland, Slovakia, Slovenia, Spain and Switzerland stated that they had more or less official recommendations regarding TBE vaccination for people travelling to endemic areas, the other nine participating countries did not provide information on this issue (Table 1). Although the responses to this part of the questionnaire suggested that the contact points had not interpreted the question in the same way, it can be deduced that information for travellers is given for following purposes:

a) General information included in national vaccination programmes for citizens coming from non-endemic regions (e.g. in Austria and Poland);
b) Information on the endemic status of a country for citizens and visitors (limited information in the Baltic states, Slovakia and Slovenia, and comprehensive information in Finland, Germany and Switzerland);
c) Information on the endemic status of foreign countries for citizens travelling abroad (e.g. in Belgium and Spain).

Discussion

TBE is an emerging disease which occurs and spreads among central and western European countries, Scandinavia, countries from the former Soviet Union, and Asia where it has a significant impact on public health. The epidemiology of TBE is very complex, and closely related to the distribution of ixodid ticks. Based on this survey which comprises updated information on TBE surveillance in Europe since the last overview published in 2004 [31], TBE is a notifiable disease, namely in Austria, the Baltic states, Czech Republic, Finland, Germany, Greece, Hungary, Norway, Poland, Russia, Slovakia, Slovenia, Sweden and Switzerland.

While we were able to present an overview of the TBE situation in 14 European countries (based on annual case numbers from 2004 to 2007) in which the disease poses a major threat to public health, other participating countries provided no or only very few data for this survey. A reason for this could be that TBE is not indigenous or a disease of minor importance in these countries. However, single cases of TBE have been documented in France in the Alsace region and more recently in Bordeaux [32], in the northern as well as central part of Italy [1], in northern Greece [33], and also in Norway (southern coast area) and Denmark (Bornholm) [34]. Unfortunately, details about the TBE annual case numbers in Romania and other eastern European countries could not be obtained and remain unclear.

To understand the described tendencies and changes in the TBE incidence during the past four-year-period as well as the fluctuation in incidence rates observed particularly during the last decade among European countries, a complex interrelation of several factors has to be considered, such as social, ecological and/or technological factors [15, 17-24]. It seems more appropriate to base a discussion of the TBE epidemiology on these factors – the importance of which can vary depending on the country – rather than on climate change alone. In particular, due to the mild winter in 2006/2007, it was not to be expected that the TBE incidences would decline in 2007 for Austria, the Czech Republic, Germany, Slovenia and Switzerland. Similar observations have been discussed in previous publications regarding the increase of incidence and appearance of new foci, for example in Nordic and Baltic states [24,35]. Thus changes of leisure activities in nature, increasing/decreasing mobility to risk areas, changes in wildlife hosts/tick populations, improved diagnostics or vaccination campaigns may have influenced the quantity and quality of epidemiological data. In the case of Latvia, the observed decrease in incidence from approximately 11 cases per 100,000 inhabitants in 2004 to seven cases per 100,000 in 2005 and the following years, probably reflects the initiation of vaccination activities [36].

Knowledge about endemic foci needs to be expanded (also in countries where TBE is of minor importance) and regularly updated in order to identify the risk for the exposed population and to apply TBE vaccines in an optimal way. For an appropriate collection of epidemiological data, a broad standard case definition including all possible clinical signs of laboratory-confirmed TBE should be used in European countries in order to avoid under-ascertainment of cases and to increase the knowledge on the true incidence of TBE [25,26].

Currently, the routine laboratory diagnosis of TBE is based mainly on the detection of specific antibodies in serum and CSF, usually by ELISA. However, certain limitations need to be taken into consideration when using serological methods [37]: An early diagnosis by detecting only IgM is questionable, since IgM antibodies can persist for up to 10 months in vaccinees

or individuals who acquired the infection naturally. Therefore, confirmation by detection of specific IgG is recommended, but may turn out negative in the first phase of infection. Although it is necessary to monitor IgG titres one or two weeks later for a possible increase, this is rarely done. Moreover, a major problem when using ELISA and IFA are cross-reactions of antibodies induced by other flavivirus infections or vaccinations (e.g. Dengue virus, West Nile virus, Yellow fever virus and Japanese encephalitis virus). It is therefore advised to verify positive results by neutralisation test. Due to the use of infectious virus particles, this requires the handling in biosafety level 3 facilities, making the test time-consuming, expensive and only available in highly specialised laboratories. PCR techniques have also been developed in a remarkable way lately and new publications reveal that RT-PCR methods can be of great diagnostic value in the early diagnosis of TBE and in the discrimination among virus subtypes [37]. However, they are mainly restricted to the first phase of infection. Serological and/or molecular testing should be performed using standard operation protocols (SOPs) among European countries and should be regularly monitored by external quality assurance programmes to guarantee the comparability of data from clinical diagnosis, epidemiological surveillance and surveys on the incidence of TBE virus in ticks and vertebrate hosts [38].

While Lyme borreliosis, another tick-transmitted disease of similar epidemiological importance in Europe, can be treated with antibiotics, no specific treatment for TBE is available to date and the administration of TBE immunoglobulin for a passive post-exposure prophylaxis is highly questionable [39] and not recommended anymore for example in Germany. The last application was discontinued many years ago as the preparations for passive immunisation are no longer produced.

Due to the fact that TBE causes high costs for health care systems (intensive care in hospitals, possible long-lasting cognitive and neuropsychiatric sequelae etc.) TBE vaccination should be recommended and reimbursed for residents of and travellers to TBE endemic areas, who are at risk of tick bites. The Austrian example shows that systematically increased vaccination coverage will result in the decrease of morbidity and therefore hospitalised cases [16]. A further important question of great public health impact, not addressed in this survey, is the diagnosis of vaccine failure [25]. The protective efficacy of the widely used TBE vaccines cannot be properly evaluated if no quality assurance exists for the diagnosis of vaccine failures. Since this is a difficult procedure, the question arises of whether national reference laboratories on CNS diseases should handle the relevant tests and establish widely accepted criteria on how to define a vaccine failure. Furthermore, since awareness among tourists as well as consulting doctors is rather rare [22] recommendations for travellers should be provided by state institutions regardless of whether these institutions are in countries with endemic (e.g. Germany) or non-endemic (e.g. Spain) situation. These can be done using country-specific risk profiles based on the epidemiological data. Today, existing risk maps on this issue are mainly distributed through the vaccine manufacturers. Bringing national data on incidences and prevalence together and distributing such maps may therefore be an important role for a European public health institution.

The participating countries mainly applied the surveillance data from clinical cases as an indicator for predicting endemic foci and for recommending preventive measures. Due to the fact that incidences of human cases may decrease in future because of mass vaccination programmes, alternative indicators for risk assessment are necessary. Therefore, the intro-duction of tick or animal reservoir surveys for prevalence studies of TBE virus have a high priority and should be implemented in national surveillance systems as initiated in previous studies [40-42] . So far, methods for measuring virus prevalence in ticks or animal reservoirs have not been standardised, and reliable tools should be introduced to translate epizootic prevalence data into infection risk for humans.

The implementation of the recommendations given in this report could be helpful, to gain more valuable clinical and epidemiological data on TBE, to improve national surveillance systems and to reduce the incidence rate for the most important flavivirus CNS infection in Europe.

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A food-borne outbreak of hepatitis A virus (HAV) infection in a secondary school in Upper Normandy, France, in November 2006

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In November 2006, six symptomatic cases of hepatitis A in pupils of a secondary school in Upper Normandy, France, were reported to the district health service. This paper describes the outbreak investigation undertaken with the aim to identify the vehicle and source of infection, implement control measures and estimate the size of the outbreak.

A primary case at the secondary school was defined as a pupil or a member of the staff with IgM anti-HAV detected in the serum and with onset of symptoms between 12 and 21 November 2006; a secondary case was defined as a contact to a primary case and who developed symptoms and had IgM anti-HAV two to seven weeks later. We performed a case control study of primary cases, controls being pupils visiting the same school (cases/controls 1:4) and inspected the canteen facilities. All 13 canteen employees were examined for anti-HAV IgM antibodies. A phylogenetic analysis of HAV of cases was performed.

We identified 10 primary and 5 secondary cases. Among primary cases 90% reported eating liver pate at the canteen compared to 62% among controls (OR 5.5, 95% CI 0.62-256.9). One liver pate sample contained markers of faecal contamination. HAV genotypes were of one identical type. All 13 canteen employees were negative for IgM anti-HAV while four had anti-HAV total antibodies. We found deficiencies regarding food preparing procedures and insufficient hand washing facilities.

The vehicle of the outbreak was believed to be the liver pate but the source of HAV could not be identified. Insufficient facilities in the canteen hindered staff from maintaining a high hygiene standard and were subsequently improved.

Introduction

The hepatitis A virus (HAV) is transmitted faeco-orally by direct contact with an infectious person or through contaminated food. The incubation period ranges from 15 to 50 days with a mean of 30 days [1]. Acute hepatitis A is usually diagnosed by detection of immunoglobulin M antibodies to hepatitis A virus (IgM anti-HAV) in the serum. In the past 10 years, surveillance was based on a sentinel physician network, however due to a decline in the number of cases reliable incidence estimates could not be provided anymore [2]. Mandatory notification of hepatitis A was introduced in November 2005. The notification rate in 2006 was 2.2/100,000 [3]. With the decreasing incidence the risk of infection during early childhood declined and teenagers and young adults who lack immunity against HAV are at risk of developing symptomatic hepatitis A if exposed [4]. In France prevention of transmission of hepatitis A person to person relies mainly on hygienic measures like hand washing. Recommendations on vaccinating close contacts of cases are currently under debate [5,6].

Between 17 and 20 November 2006, the district health service in Rouen received reports on six symptomatic cases of hepatitis A in pupils of a secondary school in a town in Upper Normandy. The school is frequented by close to seven hundred pupils aged 10 to 15 years most of whom regularly eat at the school canteen.

On 20 November 2006, the Interregional Epidemiological Unit of Upper Normandy in collaboration with the Institut de Veille Sanitaire launched an investigation to identify the vehicle and source of infection and contributing factors, to devise and implement control measures, and to estimate the size of the outbreak.

Methods

Case definition and case finding

A primary case at the secondary school was defined as a pupil or a member of the staff with IgM anti-HAV detected in the serum and with onset of symptoms between 12 and 21 November 2006.

A secondary case was defined as a family contact of a primary case or a pupil of the school in whose serum sample IgM anti-HAV were found during the period of two to seven weeks after week 46 and 47 (weeks 49 of 2006 to 2 of 2007). We actively looked for cases through two private laboratories in the town where the outbreak took place and the University hospital of Rouen.

Case investigation

On 22 November, we interviewed all primary cases by telephone, using a standardised questionnaire. The questions included a list of symptoms experienced after 1 November and exposures that had taken place between 2 October (50 days before the first cases developed symptoms) and 24 October 2006 (start of school holidays). Pupils of the school use electronic cards to pay at the canteen, which allowed us to determine for each child the exact dates and times of having a meal at the canteen. To generate the epidemic curve we plotted the week of onset of jaundice for each

primary case and, as the date of jaundice was unknown for the secondary cases, the week of blood testing for each secondary case.

Environmental investigation

The veterinary and environmental health service of the district inspected the canteen on 21 November 2006. Water samples were taken for microbiological analyses. Two microbiological analyses of food items are being done routinely each month. Their results were reviewed for the last 10 months.

Microbiological examinations

Blood samples were taken from persons working in the canteen during the exposure period to look for anti-HAV total antibodies and IgM antibodies. Sera of the ten primary cases and one secondary case (mother of a primary case) were sent to the National Reference Centre for virus genotyping and phylogenetic analysis (sera of the remaining four secondary cases were not available for genotyping after the serological examinations had been completed). Viral RNA was extracted using the QIAmp Viral RNA kit (QIAgen, Les Ulis, France) and subjected to reverse transcription and polymerase chain reaction (RT-PCR) by using the One-Step RT-PCR kit (QIAgen). A 508 base-pair fragment encompassing the VP1/2A junction was amplified with the following primers: +2870 5'- GACAGATTCTACATTTGGATTGG-3' and -3381 5'-CCATTTCAAGAGTCCACACACT-3'. The nucleotide sequences were aligned with Clustal X software. Phylogenetic trees were constructed with the MEGA software by the Neighbor-Joining method from a Kimura two-parameter distance matrix, and bootstrap values were determined from 1,000 bootstrap resamplings of the original data. The HAV genotype was determined by comparing the phylogenetic analysis with the reference sequences of different HAV genotypes. GenBank accession numbers were X75215, AB020567, AB020564 and AF357222 for IA; M14707 and M20273 for IB; AY644676 for IIA; AY644670 for IIB; AY644337 and AJ299464 for IIIA and D00924 for V.

Case control study

We conducted a case control study including the ten primary cases. To select controls we asked parents of all children who had eaten at the canteen between 2 and 24 November (n=570) for a written consent authorising us to interview their child. Among children with parental written consent, we randomly selected four controls per case. We interviewed the controls face to face on 8 December. For each food item we calculated the percentage of cases and controls who reported having eaten it during the exposure period and the corresponding odds ratios (OR) with 95% confidence intervals (95% CI). The Fisher exact test was used for statistical inference ($p<0.05$).

Results

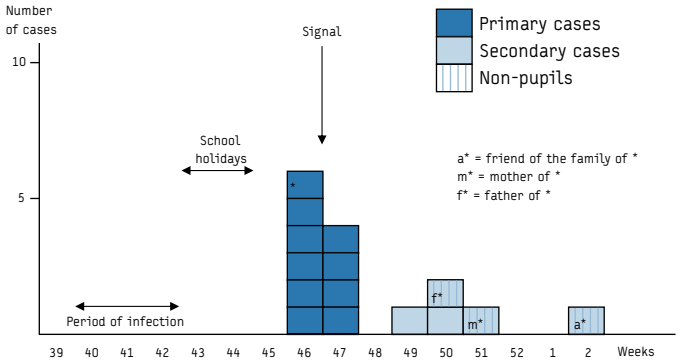
Description of cases

In total, 15 cases of hepatitis A were associated with the outbreak, having occurred during nine weeks from week 46 of 2006 to week 2 of 2007 (Figure 1). The epidemic curve suggested a common source of contamination with secondary transmission. Hepatitis A has been a notifiable disease in France only since November 2005 therefore the number of cases reported in the area during the same period of 2005 was not available. For comparison, in August, September and October 2006 (weeks 31-44) no cases had been declared.

FIGURE 1

Cases of hepatitis A by week of onset of jaundice for the primary cases (week 46 and 47) and by date of blood sampling for the secondary cases (week 49 to 2).

Hepatitis A outbreak at a secondary school in Upper Normandy, France, November 2006.



We identified 10 primary cases among the pupils of the secondary school, aged 10 to 14 years, six of them girls. Six cases were in the sixth grade (11-12 years old) but only two of them attended the same class, three were in the fourth grade (13-14 years old) but all three in different classes, and one was in the third grade (14-15 years old). None of the affected students had travelled during the 50 days preceding the onset of disease and none remembered having been in contact with a jaundiced person. All had febrile jaundice with abdominal discomfort. Three were hospitalised for two days because of a low prothrombin blood level.

The only common exposure identified was having regularly eaten at the canteen. No primary cases outside the school were found. No other cases were identified by the laboratories.

Five secondary cases have been identified, with the onset of symptoms (jaundice) between 9 December 2006 (week 49) and 14 January 2007 (week 2), two of them pupils of the same school who had been in contact with a primary case in their class, and three cases (two parents and a friend) who had been exposed to a single primary case at home.

Environmental investigations

The inspection of the school canteen revealed malfunctioning of equipment (dysfunction of the cold chamber, insufficient food storage capacities, no protection against insects) and deficiencies regarding food preparation procedures (insufficient separation of food items allowing cross contamination, uncovered chocolate dessert bowl, defrosting procedures not following the guidelines). There was no hand washing facility in the cold food preparation area, so food handlers had to cross the hot food preparation area and exit the clean area to access the hand washbasin next to the cloakroom. A liver pate sampled on 23 October had revealed a contamination with faecal coliform bacteria.

Microbiological investigations

Of the 13 persons who worked at the canteen during the exposure period, four were positive for anti-HAV total antibodies, but none of them had IgM antibodies. Serum samples of 11 cases (10 primary and one secondary case) were sent to the National Reference Centre for HAV genotyping. The eleven sequences were identical over an

analysable fragment of 457 bp, and clustered with genotype IB strains (Figure 2).

Case control study

Completed questionnaires were available for 10 cases and 39 eligible controls (n=49). Information on 76 food items were collected and the questionnaires were completed in more than 80% (four or less missing values) by 93% (n=44) of all children. No child left more than nine food item questions empty. Nine of the 10 cases (90%) reported eating liver pate compared to 23 controls (62%, OR 5.5, 95% CI: 0.6-256.9, Table). Liver pate was served on 13 and 23 October. All 10 cases were present at school on these two days and nine (90%) had reported having eaten the liver pate. Of the 37 controls who answered the corresponding question, 21 (57%) were present on 13 October and reported eating liver pate for an OR = 6.9; 95% CI: 0.78-319; and 19 (51%) were present on 23 October and reported eating liver pate for an OR = 8.5; 95% CI 0.97-394.

Control measures

Two information letters were sent to the parents of all pupils attending the school, one on 20 November, shortly after the first cases had been notified, and one on 14 December. The letters described the common manifestations of hepatitis A and the ways to limit the transmission of infection by following basic hygiene rules. Deficiencies regarding the equipment and the food preparation process were reported to the canteen operator in order to prevent future food contamination. A renovation of the canteen and its kitchen in particular was scheduled for the first half of 2007. In line with the French vaccination guidelines it was recommended to check the vaccination status and if necessary to vaccinate individuals with a higher risk of an adverse outcome of hepatitis A, namely patients with a chronic hepatitis B infection or individuals with chronic liver diseases (notably due to hepatitis C virus infection or excessive alcohol consumption). The French guidelines include no recommendations to vaccinate the contacts of cases.

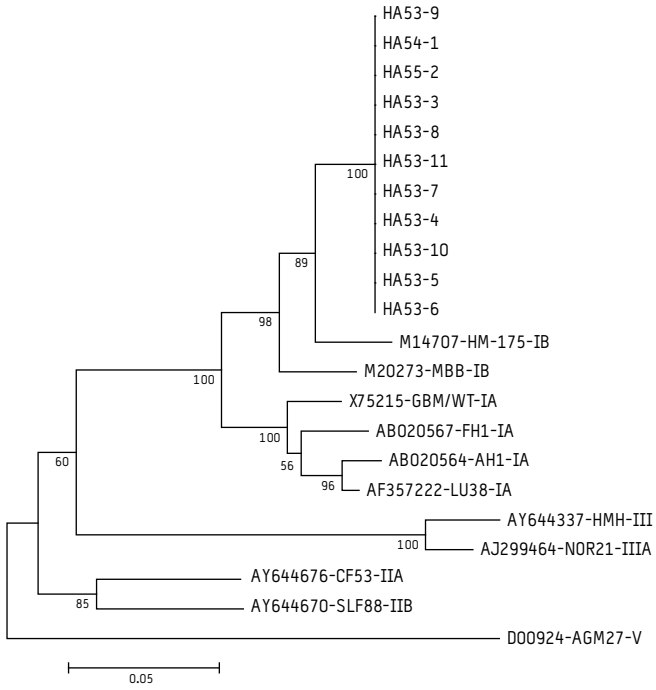
Discussion

We described a typical example of what we believe to be a food-borne hepatitis A outbreak with 10 primary and five secondary cases. Person-to-person transmission as an alternative route of infection can not be excluded, but seems improbable as only two of the 10 cases belonged to the same class and shared the same classrooms. Although most cases of hepatitis A are a result of person-to-person transmission, food-borne outbreaks from a common source still occur in western countries [7-12]. About 5% of all hepatitis A cases between 1997 and 1999 in France were estimated to be due to contaminated food [13]. Contamination of a food item can occur at any point during cultivation, harvesting, processing, distribution or preparation (e.g. through infected food handlers) [8].

Although the results are not statistically significant, our case control study suggests that the vehicle of infection was the liver pate. Faecal contamination found in a pate sample reinforces this hypothesis. The food questionnaires were relatively complete and only two children did not answer the question whether they had eaten liver pate or not. However, due to the long incubation period of hepatitis A the children had to provide information on food items they had eaten six to nine weeks before. Their answers may therefore reflect not only the actual food intake but also the food preferences, and should be treated with caution.

Figure 2

Phylogenetic tree of hepatitis A sequences obtained during an outbreak at a secondary school in Upper Normandy, France, November 2006



Note: The samples of 11 hepatitis A patients (10 primary and one secondary case) were all of one identical type IB hepatitis A virus strain. HA54-1 was the mother of HA55-2, a primary case who had infected both parents and a friend of the family. 53-3 to 53-11 are samples from the other nine primary cases. The strains used for sequence analysis are labelled with their GenBank accession number. The scale bar corresponds to 0.05 substitutions/positions.

The specific source of HAV could not be identified. None of the 13 food handlers working in the canteen had IgM antibodies when serum samples were taken but elevated anti-HAV total antibodies were found in four. HAV RNA has been detected in serum for as long as six to 12 months after infection (mean three months) [14]. In the majority of patients IgM anti-HAV declines to undetectable levels less than 6 months after infection [15]. In a study from 1986, IgM persisted even less than 30 days [16]. In the outbreak investigation described here, one of the four canteen employees who had elevated anti-HAV total antibodies may still have been infectious when the pate was served but the IgM anti-HAV level may have declined under a detectable level when the serum sample was taken six to eight weeks later.

HAV can remain infectious up to one month on environmental surfaces at ambient temperature [17]. Survival is inversely correlated to temperature and humidity favouring survival in refrigerators [18]. HAV can remain infectious on hands for more than four hours and be easily transferred from contaminated surfaces to food items by a food handler, regardless of whether the food handler excretes HAV or not [19]. Hand washing seems to be efficient in reducing the virus transfer to food [20]. The hand washing facilities in the canteen were insufficient. A contamination of the pate at an earlier stage (production process) seems improbable as we did not identify any cases outside the affected school and all primary cases were pupils who ate regularly at the canteen.

Table

Exposure of cases and controls to different food items served at the canteen during the exposure period (2-24 October 2006). Hepatitis A outbreak at a secondary school in Upper Normandy, France, November 2006

Food item	N	Percentage of cases exposed	Percentage of controls exposed	OR (if possible)	95% CI	Fisher exact p-value
Spaghetti Bolognese	49	100	97			1.0
Fried fish	48	100	95			1.0
Mashed potatoes	49	100	85			0.6
Pasta	49	100	90			0.6
Liver pate	47	90	62	5.5	0.62-256.9	0.1
Cordon bleu	49	90	97	0.2	0.003-20.6	0.4
Hamburger	49	90	97	0.2	0.003-20.6	0.4
French fries	49	90	97	0.2	0.003-20.6	0.4
Cheese	48	90	82	2.0	0.21-101.6	1.0
Crêpe with cheese	47	80	68	1.9	0.31-21.0	0.7
Nuggets	49	80	95	0.2	0.01-3.54	0.2
Cheeseburger	49	80	90	0.5	0.05-5.99	0.6
Rice	49	80	90	0.5	0.05-5.99	0.6
Yoghurt	46	100	89			
Chocolate mousse	49	80	74	1.4	0.22-15.4	1.00
"Petits suisses"	49	80	90	0.5	0.05-5.99	0.6
Ice-cream	48	80	71	1.6	0.26-18.0	0.7
Tomatoes	49	70	49	2.5	0.46-16.6	0.3
Cucumber maize	47	60	43	2.0	0.38-11.0	0.5
Tomatoes surimi	48	50	21	3.8	0.66-20.5	0.1
Tomatoes mozzarella	48	50	26	2.8	0.51-14.8	0.3
Cucumber, beet	47	40	32	1.4	0.24-7.18	0.7
Beet, maize	48	40	24	2.2	0.36-11.5	0.4
Lettuce	48	20	29	0.6	0.06-3.86	0.7
Tomatoes, cucumber, feta cheese	45	20	23	0.8	0.07-5.63	1.0
Pasta salad surimi	47	20	16	1.3	0.11-9.22	1.0
Lettuce, gruyere cheese	48	10	26	0.3	0.007-2.94	0.4
Curly endive, goat cheese	48	10	21	0.4	0.01-3.96	0.7
Cabbage red/white	48	10	11	0.9	0.02-11.3	1.0
Grinded carrots, celery	48	10	16	0.6	0.01-6.04	1.0
Exotic salad	46	10	22	0.7	0.007-3.71	0.7

Note: The table contains food items consumed by at least eight of the 10 primary cases (in bold) and all dishes that need manual handling during preparation reported by at least one case (in italic). N is the number of children who gave an answer (yes or not) to a particular food item question.

Since we chose a case control study design we could not directly estimate the attack rate among those exposed. About 570 children regularly eat at the canteen and 62% of the controls stated having eaten liver pate. The number of those exposed to the HAV contaminated pate can therefore be estimated at 353 which indicates a food specific attack rate of about 3 per 1000. Such a low estimated attack rate is in line with relatively low attack rates found in food-borne hepatitis A outbreaks [8] but could also indicate that not all portions served had been contaminated.

Guidelines for prevention of hepatitis A in close contacts of a case vary across western countries and depend on whether or not human normal immunoglobulin (HNIG) is licensed for this use in a given country. On the basis of the results of a randomized trial performed in Italy in which contacts received either the vaccine or no intervention within one week after the onset of symptoms in the index case [21] some countries introduced the use of vaccine for post-exposure prophylaxis. The British guidelines recommend vaccination of close contacts within seven days from the onset of illness in the primary case to prevent secondary cases [22] and

the application of HNIG to close contacts identified too late to be protected by vaccine. In Germany vaccination of persons in contact with hepatitis A cases in collective facilities and schools is recommended. The use of HNIG is recommended in individuals with a higher risk of an adverse outcome due to a chronic liver disease [23;24].

In the United States, until recently guidelines recommended the administration of HNIG within 15 days to all unvaccinated household and sexual contacts of persons with serologically confirmed hepatitis A [25]. Since 2007, single-antigen hepatitis A vaccine is preferred for healthy persons aged 12 months to 40 years. For persons aged >40 years IgG is preferred [26]. This policy change was brought about by a clinical trial suggesting that vaccine performance approaches that of HNIG in healthy children and adults under 40 [27]. The Canadian guidelines prefer the use of active vaccination of close contacts within seven days after exposure and the use of HNIG only in individuals who may not respond to the vaccine such as infants under one year and immunocompromised individuals [28].

In France, HNIG are not licensed for post-exposure prophylaxis of hepatitis A. The French advisory committee for vaccination has recently launched a working group whose task is to make a proposal on the use of vaccine for contacts in household or school settings. In this outbreak, apart from the reinforcement of hygiene, it was recommended that household contacts at higher risk of severe hepatitis A, as defined by the advisory committee for vaccination, should be vaccinated [5]. Considering the age group concerned, the risk of secondary transmission in the school setting was considered to be low.

Conclusion

We concluded that the vehicle of the outbreak was the liver pate but could not identify the specific source of HAV. Insufficient facilities in the canteen hindered staff from maintaining a high hygiene standard and these were subsequently improved.

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Prevalence of hepatitis C and hepatitis B infection in the HIV-infected population of France, 2004

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Our objective was to estimate the prevalence of HCV and HBV co-infection among HIV-infected adults in France and describe the epidemiological characteristics of co-infected patients and their clinical management. A one-day national cross-sectional survey was conducted in 2004. A random and proportional probability sample design was used, based on the number of AIDS cases reported since 1999 by hospital wards. Weighted estimations were computed. HIV-infected adults (out/in-patients) were included after consent. Data were collected on demographic criteria, HIV, HCV and HBV infections, as well as on antiviral therapies. Overall, 1849 HIV-infected patients were included. The prevalence of anti-HCV or HCV RNA positivity (HCV co-infection) was 24.3% [95% confidence interval (CI): 21.3-27.6] and varied from 3.1% in men who had sex with men to 92.8% in injecting drug users (IDUs). The prevalence of positive HCV RNA was 17.0% [95% CI:14.7-19.4]. The prevalence of HBs antigen (Ag) or HBV DNA positivity was 7.0% [95% CI: 5.9-8.1] and varied with the continent of birth from 2.1% in Northern Africa to 10.8% in sub-Saharan Africa. The prevalence of HIV-HCV-HBV co-infection was 1.6% [95% CI: 1.0-2.4], mostly IDUs (83.3%). A severe liver disease (cirrhosis or hepatocellular carcinoma) was diagnosed in 24.7% of the positive HCV RNA patients.This study confirmed the burden of HCV infection in French HIV-infected patients and described for the first time in France the epidemiological characteristics of HIV-HBV co-infection. Furthermore, it stresses the severity of liver disease related to HCV in HIV-infected population.

Introduction

The decline of mortality due to opportunistic infections in HIV-infected patients since the introduction of highly active antiretroviral therapy (HAART) has led to an increase in morbidity and mortality related to hepatitis B (HBV) and C (HCV) virus infections, and end-stage liver disease among HIV-infected patients in France [1;2]. As these infections share similar routes of transmission, co-infection with HIV and viral hepatitis B and/or C is common. Approximately one-third of HIV-infected individuals are infected with HCV and 70% of HIV-infected have prior contact with HBV infection [3;4]. Those coinfections lead to an increase risk of cirrhosis and hepatic failure compared to HCV or HBV-monoinfected patients [5]. Therefore determination of HBV and HCV status is crucial for HIV-infected patients care and for allocations of resources in health care programs. In France, although HCV prevalence among HIV-infected persons was estimated at national level in 2001 (28 % [95 % confidence interval (CI): 27-31]) [6], it was not estimated for HBV yet. In June 2004, we conducted a one-day national cross-sectional survey in order to assess the prevalence of HCV and HBV infections among HIV-infected patients, and describe the characteristics of HIV-HCV and HIV-HBV co-infected patients and their clinical management.

Methods

We used the sampling frame of hospital wards (infectious diseases, internal medicine) based on the number of AIDS cases reported through the Mandatory notification at the national level between January 1999 and September 2003. The 207 wards which had notified more than three AIDS cases and 70 wards randomly selected among the 211 having notified three or less AIDS cases were invited to participate on a voluntary basis.

At the time of the survey, every HIV-infected out or in-patient seeking care in one of the selected wards was enrolled after informed consent, and the number of HIV-infected patients refusing to participate was collected. A standardized questionnaire was used to collect data from medical records on socio-demographic characteristics (age, gender, country of birth), HIV infection (HIV transmission group ie: person infected through high-risk heterosexual contacts, man who has sex with men, injecting drug user, transfusion recipient, haemophiliac; clinical classification, CD4 cell count, viral load, antiretroviral therapy), and on alcohol consumption. The alcohol intake was collected using the number of glasses (or drink) of alcohol drunk per week. It is considered that whatever the kind of alcohol (beer, wine, cocktail …) served, it contains 10 grams of pure alcohol (the standard quantity served varies with the type of alcohol). Excessive alcohol intake was defined as the consumption of more than 21 glasses (210 g of alcohol) per week for women, and more than 28 glasses (280 g of alcohol) for men.

Biological markers of hepatitis C (anti-HCV antibody (Ab), HCV RNA), hepatitis B (anti-HBs and anti-HBc Ab, HBs antigen (Ag), HBe Ag, HBV DNA), and hepatitis Delta status (Ab, Ag) were also collected.

HCV co-infection was defined as positive anti-HCV antibodies or HCV RNA, chronic hepatitis C as positive HCV RNA, HBV co-infection as positive HBs Ag or HBV DNA, and chronic hepatitis B as positive HBs Ag.

For patients with chronic hepatitis B or C, we also collected alanine aminotransferase (ALT) levels, presence of clinical complications of cirrhosis (e.g. ascites, portal hypertension…) and diagnosis of hepatocellular carcinoma. To describe the management of co-infected patients, we collected data on the methods used for diagnosis of liver fibrosis (liver biopsy, serum markers), the METAVIR scores [7] and antiviral treatment (past or current).

Cirrhosis was defined by a METAVIR score F4 (liver biopsy or serum markers of fibrosis) or by the presence of complications of cirrhosis. Severe liver disease was defined as cirrhosis or hepatocellular carcinoma diagnosis.

All data were analysed using Stata 8.2 (Stata Corporation, College Station, TX). The sample design was specified mentioning a weight attributed to each individual, equal to the inverse of his inclusion probability and the stratification. Estimates were calculated from the classical Horvitz-Thompson unbiased estimator using the specific survey functions implemented in the Stata software. Confidence intervals were also estimated using unbiased estimators

Results

Of the 277 randomly selected wards, 167 (60.3%) accepted to participate. Among wards which had notified more than three AIDS cases, the median number of cases notified by the participating wards was higher than those notified by the non-participating ones (30 versus 13, respectively; p 10-4). Among the 2054 eligible HIV-infected patients, 205 refused to participate in the study (9% and 13% of out-patients and in-patients, respectively). Of the 1849 patients who agreed, 78.6% [95% confidence interval: 75.3-81.5] were out-patients and 21.4% [95% CI: 18.5-24.7] were in-patients.

Table 1 shows the main characteristics of HIV-infected patients. The estimated mean age was 42.9 years [95% CI: 42.4-43.5]. Excessive alcohol intake was estimated for 5.3% [95% CI: 4.3-6.6] of the patients (unknown: 11%). Those who acquired HIV through injecting drug use (IDUs) were more likely excessive alcohol drinkers than the rest of the population (respectively, 12.3% and 3.8%; p<10-3).

HIV-HCV co-infection

The prevalence of HIV-HCV co-infection (Table 2) was 24.3% [95% CI: 21.3-27.6] and varied depending on HIV transmission groups (maximum for IDU: 92.8%) and continent of birth (maximum for Northern Africa: 35.1%). The prevalence of chronic hepatitis C was 17.0% [95% CI: 14.7-19.4].

Table 1

Characteristics of medical ward-recruited HIV-infected adults in France, 22 June 2004

N = 1849	%	95% CI*
Sex		
Male	68.2	65.3-71.0
Female	31.6	28.8-34.5
Not documented	0.2	0.1-0.5
Age		
≥ 40 years	60.9	58.3-63.4
< 40 years	38.4	35.9-41.0
Not documented	0.7	0.4-1.4
Country/continent of birth		
France	64.9	59.8-69.8
French overseas territories#	3.1	1.6-5.7
Sub-Saharan Africa	17.4	14.2-21.2
North Africa	5.1	4.0-6.3
Other	8.5	6.3-11.3
Not documented	1.0	0.6-1.8
HIV transmission group		
Heterosexual contact	41.4	37.3-45.7
MSM[1]	30.2	26.3-34.4
IDU[2]	18.8	16.0-21.9
Transfusion recipient/haemophiliac	2.7	2.0-3.6
Undetermined	6.9	5.6-8.4
HIV clinical classification		
Primary infection	0.7	0.4-1.5
Asymptomatic	39.4	35.8-43.1
Symptomatic	24.6	21.9-27.4
AIDS	33.5	30.3-36.8
Not documented	1.8	1.2-2.8
CD4 count		
< 350 cells/mm³	49.7	46.4-53.0
≥ 350 cells/mm³	48.5	45.2-51.7
Not documented	1.8	1.2-2.7
HIV viral load		
Detectable	53.3	50.5-56.2
Undetectable	43.4	40.5-46.4
Not documented	3.3	2.4-4.4
Antiretroviral (ARV) therapy		
Yes	75.1	72.3-77.8
Interrupted	6.0	4.8-7.5
No	18.4	15.9-21.1
Not documented	0.5	0.2-0.9

* Confidence interval
[1] Man who has sex with men
[2] Injecting drug user
French Guyana, French West Indies, Reunion Island

Table 2

Prevalence of HBV and HCV infections by group of HIV transmission and continent of birth, France, 22 June 2004

	HBV$		HCV§	
N = 1849	%	95% CI*	%	95% CI*
Overall	**7.0**	5.9-8.1	**24.3**	21.3-27.6
HIV transmission group				
Heterosexual contact	**5.3**	3.9-7.2	**8.6**	6.5-11.2
MSM[1]	**9.2**	7.1-11.8	**3.1**	2.0-4.7
IDU[2]	**7.5**	5.1-11.0	**92.8**	89.0-95.3
Transfusion recipient/ haemophiliac	**5.9**	1.9-16.6	**47.1**	32.3-62.5
Undetermined	**6.6**	3.3-12.5	**18.0**	11.1-27.8
Continent of birth				
Europe[3]	**6.3**	5.2-7.7	**28.2**	24.9-31.8
Northern Africa	**2.1**	0.6-7.4	**35.1**	25.3-46.2
Sub-Saharan Africa	**10.8**	7.7-14.9	**10.2**	7.2-14.4
Asia	**10.0**	2.4-33.1	**15.0**	4.7-38.5
American continent	**7.4**	2.8-17.9	**2.5**	0.5-10.4

* Confidence interval
$ HBs Ag+ or HBV DNA+
§ anti-HCV + or HCV RNA+
[1] Man who has sex with men
[2] Injecting drug user
[3] Including French Guyana, French West Indies, and Reunion Island

Among the HIV-infected patients with chronic hepatitis C, degree of liver fibrosis was assessed either by liver biopsy for 48.5% or by serum markers for 5.3% and both methods were used for 4.0% of the patients; 32.4 % had no available evaluation at the time of the survey (variable not documented: 10%). Severe liver disease defined by the presence of cirrhosis or hepato-cellular carcinoma was diagnosed in 24.7% [95% CI: 19.7-30.5] of the HIV-infected patients with chronic hepatitis C. Severe liver disease was diagnosed in 33.4% of IDUs with excessive alcohol consumption and in 21.8% of those without (p=.05).

Among patients with chronic hepatitis C, 36.4% [95% CI: 30.7-42.6] were (or had been) treated with anti-HCV therapy. This proportion varied whether liver disease was assessed or not (49.8% and 14.6%, respectively: p<10-3). Anti-HCV treated patients were (or had been) under ribavirin and interferon (pegylated or not) in 79.7%, and under interferon alone in 17.0% (not documented in 3.3%).

HIV-HBV co-infection

The prevalence of HIV-HBV co-infection was 7.0% [95% CI: 5.9-8.1] (Table 2), and varied according to the continent of birth (maximum for Sub-Sahara Africa: 10.8 %). The prevalence of negative HBs Ag associated to negative anti-HBc and negative anti-HBs was 27.1% [95% CI: 24.5-30.0] (Table 3).

Among positive HBs Ag patients, HBV-DNA was positive for 48.5% [95% CI: 38.6-58.4], negative in 27.3% and was not documented for 24.2%. HBe Ag was positive for 33.3%, negative for 45.4% and, was not documented for 21.3%. Among positive HBs Ag IDUs, delta virus serostatus was not documented for 77.0%, positive for 19.2% and negative for 3.8%. Delta status was not documented for 66.7% of positive HBs Ag Sub-Saharan Africans, and was positive for 2.8%.

Among positive HBs Ag patients, the severity of liver disease was assessed in 37.1% of them, depending on the ALT level: in 14.3% when ALT level was equal or below the upper limits of the reference values and in 59.3% when ALT level was greater. A severe liver disease was diagnosed in 26.0% and absent in 33.3% of the overall positive HBs Ag patients with abnormal ALT level.

At the time of the survey, 71.2% of the positive HBs Ag patients were treated for hepatitis B: with lamivudine (31.0%), tenofovir (8.4%) or adefovir (3.8%) alone, and 28.0% with lamivudine and tenofovir. The proportion of anti-HBV treatment varied from 81.8% when patients were on antiretroviral therapy to 11.8% when they were not.

HIV-HBV-HCV co-infection

The overall prevalence of HBV-HCV co-infection was 1.6% [95% CI: 1.0-2.4]. HIV-infected patients with HBV-HCV co-infection were mainly (83.3%) injecting drug users. The prevalence of chronic hepatitis B associated with chronic hepatitis C was 0.8% [95% CI: 0.5-1.3].

Discussion

This survey estimated the prevalence of HBV co-infection (7%) among HIV-infected adults in France in 2004. It also estimated for the first time in Europe, the prevalence of HBV-HCV co-infection (1.6%) and of chronic hepatitis B and C (0.8%) in this population. It confirmed the importance of HIV-HCV co-infection (24.3%), mainly in IDUs. The prevalence of HCV and HBV infections was greater among HIV-infected patients than in the French population in 2004 (0.84% and 0.65%, respectively) [8].

Prevalence rates of HBV and HCV infection in our study were close to those reported in European HIV-infected cohorts at inclusion [9;10]. The estimates of HCV co-infection in 2001 (28%) [6] and 2004 (24%) were slightly different. This could possibly be due to a decrease in the proportion of IDUs between the two studies (22% versus 18.8%, respectively).. Interestingly, although cases of acute HCV infection have been described since 2001 in France among men who have sex with men [11], the estimates of HCV co-infection between 2001 (6%) and 2004 (3%) were not different in this group. However, any comparison of the estimates between the two surveys (2001 and 2004) should be interpreted with caution due to different sampling design. The prevalence of HCV co-infection (10%) among patients born in Sub-Saharan Africa, very close to the HBV's (around 11%), could reflect the overall high prevalence estimates (3%) of HCV in Sub-Saharan Africa [12]. Therefore, HCV screening should be also routinely added to HBV testing and repeatedly included in the follow-up of HIV-infected patients originating from this region.

The proportion of patients with chronic hepatitis C who had a liver fibrosis assessment evaluation increased from 49% [6] to 62% in 2001 and 2004, respectively. This could be related to the development and availability of non-invasive markers of liver fibrosis in place of liver biopsy, since 2001 [13].

Severe liver disease among HCV mono-infected patients is associated with excessive alcohol consumption [14]. In our study, the proportion of severe liver disease among IDUs who had reported excessive consumption was higher than among those who had not. However, the overall proportion of heavy drinkers (12.3%) was three times lower than the 41.3% observed in newly referred HIV-infected IDUs with positive anti-HCV attending hepatology reference centers in France, in 2004 [15].

We found that almost one third of the HIV-infected population had negative biological markers for hepatitis B. A better promotion of anti-HBV vaccination targeting this population should be stressed according to the French recommendations [16].

Even though a higher incidence of liver-related cirrhosis [17], and a deleterious impact of hepatitis delta co-infection on liver fibrosis

Table 3

Prevalence of biological markers of HBV infection among HIV-infected adults, France, 22 June 2004

N = 1849				%	95% CI*
HBs Ag (+) or HBV DNA (+)				7.0	5.9-8.1
Negative HBV markers#				27.1	24.5-30.0
HBs Ag (-)	anti-HBc (-)	anti-HBs (+)		9.4	7.5-11-5
HBs Ag (-)	anti-HBc (+)	anti-HBs (-)	*23.7*		
		anti-HBs (+)	*12.6*	37.6	35.0-40.2
		anti-HBs (?)	*1.3*		
Not documented				18.9	

* Confidence interval
\# HBs Ag (-) anti-HBc (-) and anti-HBs (-)

[18] had been observed in HIV-HBV co-infected patients compared to mono HIV-infected, biological markers (HBs Ag, HBV DNA, HBe Ag, Delta status) and the evaluation of liver disease severity related to chronic hepatitis B were too often not documented. Therefore, the overall proportion of severe liver disease (26.0%) related to chronic hepatitis B could be underestimated.

The proportion of patients being treated for chronic hepatitis B was very high (71 %). A possible explanation is that antiviral molecules against HBV were opportunely chosen when HAART was needed. Since then, European guidelines on treatment of viral hepatitis and HIV co-infections have been issued in 2005 [19]. Criteria to decide whether to treat chronic hepatitis B include HBV-DNA level, liver disease activity, and the evaluation of the presence of cirrhosis. Moreover, the development and the use of less invasive techniques than liver biopsy probably contributed to a better diagnosis of severe liver disease by clinicians in this population.

Our study has several limitations. The results relied on data collected from medical records as the viral hepatitis markers were not measured at the time of the survey. The participation of the wards was lower than expected and may have biased the prevalence estimates. However, it is difficult to draw a conclusion on how it may have affected the results (over or underestimation). A small proportion of the patients did not agree to participate. It is unlikely that the non participation may be related to the HCV/HBV infection status and thus had any effect on our estimates. Also, we were not able to take into account the follow-up frequency of the patients. It is possible that patients with chronic hepatitis B or C were more likely to have been included in the study leading to a potential overestimation of the prevalence figures. However, the HCV and HBV prevalence we found was not significantly different from that reported in European cohorts at inclusion [6,7].

Conclusion

With a longer life expectancy for HIV-infected patients, hepatitis B and C associated co-morbidities are becoming major concerns in terms of health care. This study confirms the burden of HCV infection in HIV-infected patients and also emphasises the severity of liver disease linked to viral hepatitis in HIV-infected patients. The assessment of chronic hepatitis B co-infection in HIV-infected definitely needs to be improved, especially screening for hepatitis delta antibodies and evaluation of liver fibrosis. Since 2004, European guidelines for the management and treatment of chronic hepatitis C and B coinfection in HIV-infected adults have been released and should help the clinicians for a better assessment of chronic hepatitis B and C in HIV-infected patients. Furthermore, vaccination against HBV must be promoted among HIV-infected people with negative biological markers for hepatitis B.

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A local outbreak of quinolone-resistant gonorrhoea in Norway, January 2008

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Since 1994, the incidence of gonorrhoea in Østfold county, Norway, has remained within the range of 1-8 cases per year, with 40% of cases being imported from abroad. On 20 January 2008, a general practitioner in the county diagnosed two seemingly unrelated domestic cases of gonorrhoea in three days and started contact tracing.

A case was defined as a person with clinical symptoms of gonorrhoea who was a part of the sexual network. Available isolates from the samples taken were tested for resistance.

Among 13 contacts identified in the sexual network, eight were classified as cases on the basis of symptoms, four of whom had laboratory-confirmed gonorrhoea. The index case acquired the infection abroad. The three isolated strains were resistant to ciprofloxacin, but sensitive to ceftriaxone which was used for treatment.

In the outbreak described, most cases were diagnosed only after contact tracing although they had had symptoms. A quinolone-resistant strain was imported from abroad and introduced into the population. The Norwegian national treatment guidelines, which still recommend quinolones for empirical treatment, should be updated.

Introduction

Background

Gonorrhoea is a sexually transmitted disease with a high transmission rate and a short incubation period of two to seven days [1]. The risk of male to female transmission is assumed to be as high as 50-70% per sexual intercourse and the risk of female to male transmission is estimated to be 20-30% [2].

The disease most frequently manifests as purulent discharge and dysuria, but up to 50% of women and 2-5% of heterosexual men can be asymptomatic. Rectal and pharyngeal infections are frequently asymptomatic. Untreated patients can be carriers for several months with late complications such as pelvic inflammatory disease, fistula formation and urethral strictures [2].

Culturing of *Neisseria gonorrhoeae* has lower sensitivity than some newer methods [3,4], but obtaining a culture is important for determining antimicrobial resistance [2]. Laboratories and clinicians are obliged to report data on gonorrhoea patients anonymously to the Norwegian surveillance system of communicable diseases (Meldingssystem for smittsomme sykdommer – MSIS) (5). Since 1993, over 90% of the samples from the patients reported to MSIS have been cultured.

With a mean incidence of 5.4 per 100,000 between 2002 and 2007, gonorrhoea is currently a rare disease in Norway. The imported cases represented 30-40% of all cases reported in the same period. In the Østfold county, where the outbreak occurred, a yearly incidence of 1-8 cases has been registered since 1994, with about 40% of cases imported from abroad.

In Norway, the doctor who treats a patient with a sexually transmitted disease is in charge of contact tracing. Patients can opt to notify their contacts themselves or the contacts are notified by the doctor [6]. Treatment is recommended to all sexual contacts of a patient diagnosed with gonorrhoea [6], regardless of symptoms or test results. Control samples should be taken from the patients at least a week after the completed treatment to check whether the treatment was successful and no re-infection from the sexual partners occurred during this time.

The outbreak

On 17 January 2008, a male patient was diagnosed with gonorrhoea by his general practitioner. On 20 January, another man presented to the same general practitioner with symptoms of gonorrhoea. The two patients had no sexual contact with each other and had not travelled abroad recently. Both had a positive culture of *N. gonorrhoeae*. The general practitioner started contact tracing. We describe the results of the investigation.

Methods

Epidemiological investigation

A confirmed case was defined as a person with a positive culture for *N. gonorrhoeae* or a person who was the only possible source of the infection for a culture-positive case.

A probable case was defined as a person who experienced symptoms such as purulent discharge, dysuria or pelvic pain and was sexually linked to a confirmed case.

Every new contact was asked about all his/her sexual contacts. All available sexual contacts were tested for gonorrhoea, hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, chlamydia and syphilis. All cases and contacts were asked about recent sexual exposure and symptoms according to the standard MSIS reporting form for clinicians [5].

Microbiological investigation

All hospitals and general practitioners in the county routinely send their microbiological samples to the same public laboratory at Østfold hospital. Here, swabs from different anatomical locations were cultured on modified Thayer Martin (MTM) agar. Morphologically distinctive cultures were stained by Gram and tested for oxydase. Further identification of *N. gonorrhoeae* was done using commercial identification kit API NH [7] and agglutination in antiserum using the Phadebact Monoclonal GC test [7].

For resistance testing, the isolates were then cultured on Mueller Hinton agar with 1% Isovitalex and 1% haemoglobin supplements. The determination of the minimum inhibitory concentration (MIC) was done by Etest [8].

Results

Epidemiological investigation

In total, 13 contacts were identified forming a sexual network. Among these, six fulfilled the case definition criteria for confirmed case and two were considered probable cases (Figure). The age range of the cases was 19 to 30 years and five out of eight cases were women. Seven out of eight cases were immigrants from different continents, mostly residing in Norway for more than 10 years.

After the initial two cases had been diagnosed on 17 and 20 January, a third one was discovered through contact tracing on 24 January (Figure, contact nr 3). She was symptomatic but tested negative for gonorrhoea. However, it was established that she was the only link between cases 1 and 2 and therefore classified as confirmed case and treated.

Another case (contact nr 4) was identified on 24 January. He was notified by the second case and consulted a doctor. He revealed that he had visited his country of origin in Asia in September 2007, experienced symptoms there and was treated by a local doctor. His symptoms continued in Norway and his general practitioner treated him for urinary tract infection with trimetoprim. The symptoms persisted for several months, yet he did not consult a doctor again. We concluded this case had initiated the outbreak.

The fifth case (contact nr 5) was identified on 25 January through contact tracing. She had visited a doctor due to symptoms on 16 January but was treated for urinary tract infection. Later, the woman developed a clinical picture of pelvic inflammatory disease and tested negative for chlamydia, but gonorrhoea was not suspected. She underwent laparoscopic appendectomy. From the start, she was treated with several antibiotics. Her sample for gonorrhoea was taken only after she had been identified as a contact of a confirmed case.

Two more cases (contacts nr 6 and 7) were found through contact tracing. Both were symptomatic, one had already visited a doctor and although she wanted to be tested for all STDs, a sample for gonorrhoea was taken only after she was traced as a contact. The other had previously received a symptomatic treatment with azitromycin and penicillin, which did not completely improve her symptoms.

The two women (contacts nr 6 and 7) and two men (contacts nr 2 and nr 4 – the index case) met on a single occasion to have sex. Our findings suggest that this was when the infection was transmitted from the index case to three people.

The last case was identified in the wife of the index case (contact nr 8). She was notified by a general practitioner after the index case had resisted informing her. Her mild symptoms started months ago and persisted.

The specific symptoms, experienced by the eight cases are shown in the Table. In addition, five asymptomatic contacts were identified in the sexual network (contacts nr 9 to 13). All cases and most of the asymptomatic sexual contacts were treated and educated about safe sex.

We failed to deliver the treatment to an asymptomatic prison inmate (contact nr 12), whose sample was negative for gonorrhoea, and an asymptomatic woman (contact nr 13), whose partner, belonging to the sexual network, was also asymptomatic and tested negative.

The cases were tested for gonorrhoea again at least a week after the completed treatment and all were negative. Available contacts (1-11) were also tested for other sexually transmitted infections (STI). All were negative except two men who had a past HBV infection.

At the time of writing this article, no other cases have been linked to this outbreak.

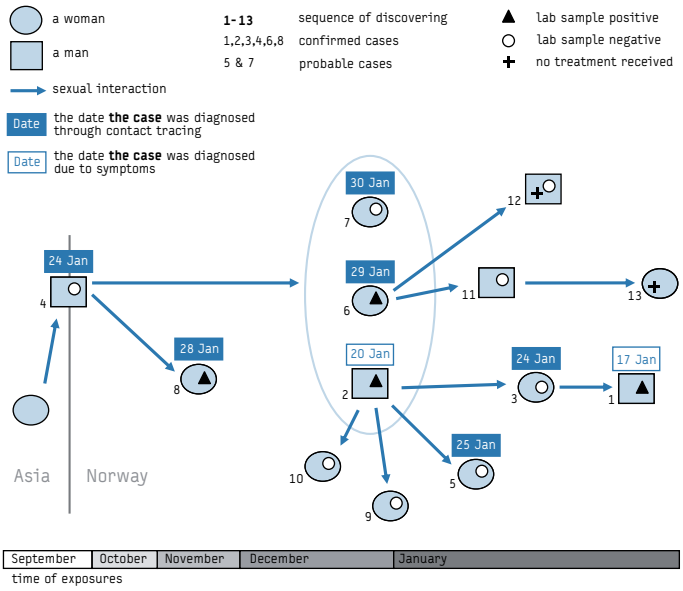
Microbiological data

Samples for culturing were obtained from all the cases and were positive in four cases (Figure). Among the swabs that tested positive, two were from cervix, two from urethra, one from the anus and one from the pharynx (Table).

Of the positive cultures, one strain of *N. gonorrhoeae* died in the laboratory and was not available for further resistance testing. The rest of the isolates did not grow on Mueller Hinton agar, so MTM

FIGURE

Sexual network of an outbreak of gonorrhoea in Norway, January 2008



agar had to be used instead. The strains exhibited chromosomally mediated increases in minimal inhibitory concentration of penicillin (2) and additional intermediate resistance to erythromycin and azitromycin. They were resistant to ciprofloxacin, doxycyclin and trimethoprim and sulfamethoxazole and sensitive to ceftriaxone, which was used for treatment of the cases (Table). Phadebact Monoclonal GC test revealed the samples to be positive in the WI serogroup (serogroup WII/III negative).

Discussion

We have described a localised outbreak of gonorrhoea in a very low incidence country. Although all of the eight cases experienced symptoms and most of them visited a doctor, six were diagnosed only after they had been linked to the outbreak through contact tracing.

Contact tracing in STI is particularly difficult as those infected may be reluctant to reveal the information about their sexual partners and/or may not wish their partners to be contacted by health officials. It is important that the contact tracing is done thoroughly to prevent the spread of the disease.

In the outbreak described here, we were not able to obtain a positive culture of *N. gonorrhoeae* from all the patients whom we regarded as cases due to their symptoms and epidemiological links. The reason some samples could not be cultured may be the lower sensitivity of culturing, partial sensitivity to the antimicrobials administered in the previous treatment or transportation problems. In the two probable cases, the symptoms might have had other etiological causes than gonorrhoea, such as chlamydia infection. However, chlamydia was also not proven, the onset of symptoms corresponded to the recent exposure to a gonorrhoea-positive case and the nature of the symptoms was more likely to arise from gonorrhoeal infection (Table, cases 5 and 7).

While the benefit from screening for gonorrhoea with culture might be low [6] in low prevalence countries, gonorrhoea should be an important differential diagnosis option in symptomatic patients. Our investigation revealed that the delay in recognising the disease in several patients led to a further spread of infection, health complications and even one unnecessary surgical procedure.

With increased travelling and migration, a resistant strain from a country with different gonorrhoea epidemiology can be introduced into a low prevalence country. Some authors suggest to change the recommended first choice treatment if the infection originated from abroad [9,10]. As the links to a foreign country might not be recognised in sexual contacts of the index patient, it is important to obtain a culture of *N. gonorrhoeae* for sensitivity testing. Regardless of the previous travel history, immigrants are a high risk population for STI's and "being a person from Africa or Asia" has been previously recognised as a potential predictor of penicillinase-producing *N. gonorrhoeae* (PPNG) in Norway, [5,10].

Quinolone-resistant strains have become increasingly represented in several European countries [12,13] and a third generation cephalosporin is now recommended for empirical treatment in many countries [4,14]. Although the national treatment guidelines are currently under revision in Norway, the first drug of choice is still quinolone [11].

Conclusion

This outbreak should serve as a reminder that effective contact tracing is crucial in preventing the spread of gonorrhoea. Gonorrhoea has become a rare disease, but should remain a differential diagnosis option, especially due to its high infectivity and the potential to spread. Clinicians should consider taking a sample from several anatomical sites, which is a simple, non-invasive procedure. Due to increasing antimicrobial resistance of *N. gonorrhoeae* and the potential of the infection being imported from abroad, national treatment guidelines should be followed cautiously. We recommend culturing, which enables routine antimicrobial resistance testing. We also believe that Norwegian national guidelines need to be updated promptly so that empirical treatment for gonorrhoea would be a third generation cephalosporin.

Table

Confirmed and probable cases in the outbreak of gonorrhoea in Norway, January 2008, by date of illness onset, anatomical location of positive sample and symptoms

Case	Case classification	Sex	Illness onset	Anatomical location of positive sample	Similar resistance pattern of *N. gonorrhoeae*	Phadebact serogroup	Experienced symptoms
1	confirmed	M	13 Jan 2008	urethra	yes	WI	dysuria, urethral discharge
2	confirmed	M	17 Jan 2008	urethra	yes	WI	dysuria, urethral discharge
3	confirmed	F	6 Jan 2008	no positive sample			pain, vaginal discharge
4	confirmed	M	Sept 2007	no positive sample			dysuria, urethral discharge
5	probable	F	17 Jan 2008	no positive sample			dysuria, vaginal discharge, salpingitis, abdominal pain
6	confirmed	F	Dec 2007	cervix, anus, pharynx	yes	WI	pharyngeal infection, fever, vaginal discharge, pelvic pain
7	probable	F	3 Jan 2008	no positive sample			pharyngeal infection, dysuria, fever
8	confirmed	F	Nov 2007	cervix	unknown		dysuria, vaginal discharge

Note: Case numbers correspond to numbers in Figure.

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Validation of a syndromic surveillance system using a general practitioner house calls network, Bordeaux, France

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A new syndromic surveillance system has been developed in Bordeaux City, South West France, using a general practitioners' house calls network. Routinely collected, sociodemographic data, patients' complaints and medical diagnoses made at the end of the visit were monitored using syndrome groups such as influenza syndromes, bronchiolitis, gastrointestinal, respiratory syndromes and others, based on International Classification of Primary Care (ICPC)-2 codes. A process control chart was implemented in order to distinguish signals of interest from "background noise". In 2005 and 2006, a total of 303,936 visits were recorded. Seasonal epidemics of influenza-like illness, bronchiolitis or gastrointestinal were identified. The automated and real time nature of the system also allowed the early detection of unusual events such as an acute increase in the number of heat syndromes during the heat-wave that occurred in France in July 2006. This new system complements existing surveillance programs by assessing a large part of episodes of illness that do not require hospital admissions or the identification of an etiologic agent. Attributes and advantages of the system, such as timeliness and diagnostic specificity, demonstrated its utility and validity in term of syndromic surveillance purposes, and its extension at the national level is in process.

Introduction

Recent health events in France, such as the dramatic excess of mortality occurred during the heat-wave in 2003 [1] showed the need for a better provision of information to health authorities to help them with the decision-making process [2]. Enhancing public health surveillance to include electronic syndromic surveillance [3] has received increased attention in recent years [4-9]. In July 2004, the French institute for public health surveillance (Institut de Veille Sanitaire, InVS) initiated a pilot network, based on different sources of data available in real time from hospital emergency departments and mortality registry offices [9]. These daily collected data can be used for early detection of abnormal health-related events or to quantify the health impact of major events. However, hospital emergency and mortality data reflect the most severe forms of the diseases and some disease outbreaks could escape detection, if not associated with significant hospital admissions or excess mortality. It seems therefore necessary to gather multiple sources of data on various health problems to improve the monitoring of population health, notably through general practitioners (GPs) who might be particularly useful information providers. In this context, an information system based on a computer network of physicians (the Sentinel network) has been developed in France since 1984 [10]. This continuous and ongoing national surveillance network is constituted of voluntary sentinel practitioners all over the country and allows the monitoring of 14 communicable diseases or health events (acute diarrhea, asthma attack, chickenpox, hepatitis A, B and C, herpes zoster, hospitalization, influenza-like illness, male urethritis, measles, mumps, hepatitis C serologies , suicidal attempts), with weekly data analysis [10, 11]. However, in order to detect various outbreaks and to identify sanitary alert, surveillance systems must be conduced both nationally and locally and a wide range of specific health outcomes must be monitored. In particular, the emergence of new infectious hazards [12] such as Severe acute respiratory syndrome (SARS), potential bioterrorist-initiated [13] outbreaks or avian influenza, makes it necessary to increase public health surveillance systems which can identify these types of risks on an urban area scale.

The Aquitaine regional epidemiology unit (Cellule Interrégionale d'Epidémiologie, Cire), located in Bordeaux, which is the regional office of the InVS is in charge of coordinating public health surveillance in the Aquitaine area, the south-western region of France. In collaboration with SOS Médecins Bordeaux, an organization of general practitioners, the Cire developed a new syndromic surveillance system based on GP's house visits in the Bordeaux area.

The aim of this paper is to describe the functioning of such a surveillance system and to give some examples of application.

Methods

General description of the network

Founded in 1966, SOS Médecins is the most important GP emergency and healthcare network in France. It consists of 60 local organisations spread across the country, responding to private houses calls 24 hours a day, seven days a week. Patients in need of a home medical visit can request it from the organisation by telephone when their usual general practitioner is not available.

In the urban area of Bordeaux, a city located in southwestern France, SOS Médecins comprises 60 GPs making more than 400 interventions a day. SOS Médecins Bordeaux operates in an area of approximately 800,000 inhabitants.

Telephone calls are handled by a two-person call centre and logged in a local database. This database is linked via internet to electronic notebooks held by GPs who can update the database with pertinent information following a patient visit. All complaints reported by the patients are coded and recorded according to the International Classification of Primary care (ICPC-2) [14], as well as the final diagnosis.

Data collection and processing

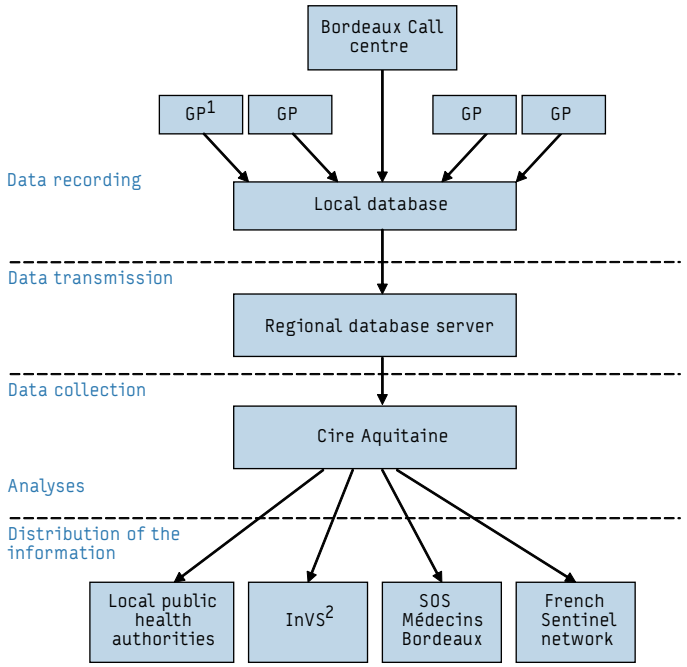
Daily data are recorded on the secure regional database server. The data collected includes: the date of the visit, postal code, age, sex, the health complaints of the patient and the medical diagnosis. Each morning, the data including all the visits logged during the previous 24-hour period (midnight to midnight) are downloaded from the Cire Aquitaine according to the flow-chart outlined in Figure 1.

Data analysis

Data have been monitored and analyzed daily everyday from 1 January 2005 to 31 December 2006. The first step is based on the global activity of SOS Médecins Bordeaux with a description of the total number of visits. The second step is a specific analysis based on syndromes groups or particular subgroups of the population (under two years and over 75 years), based on diagnoses made by the doctors. In collaboration with the GPs, ICPC-2 codes were grouped into 16 syndrome groups including influenza, bronchiolitis, gastrointestinal and respiratory syndromes, as well as syndromes linked to high temperature and others (Table 1).

FIGURE 1

SOS Médecins Bordeaux - Cire Aquitaine Syndromic Surveillance flow chart



[1] General practitioner
[2] Institut de Veille Sanitaire

TABLE 1

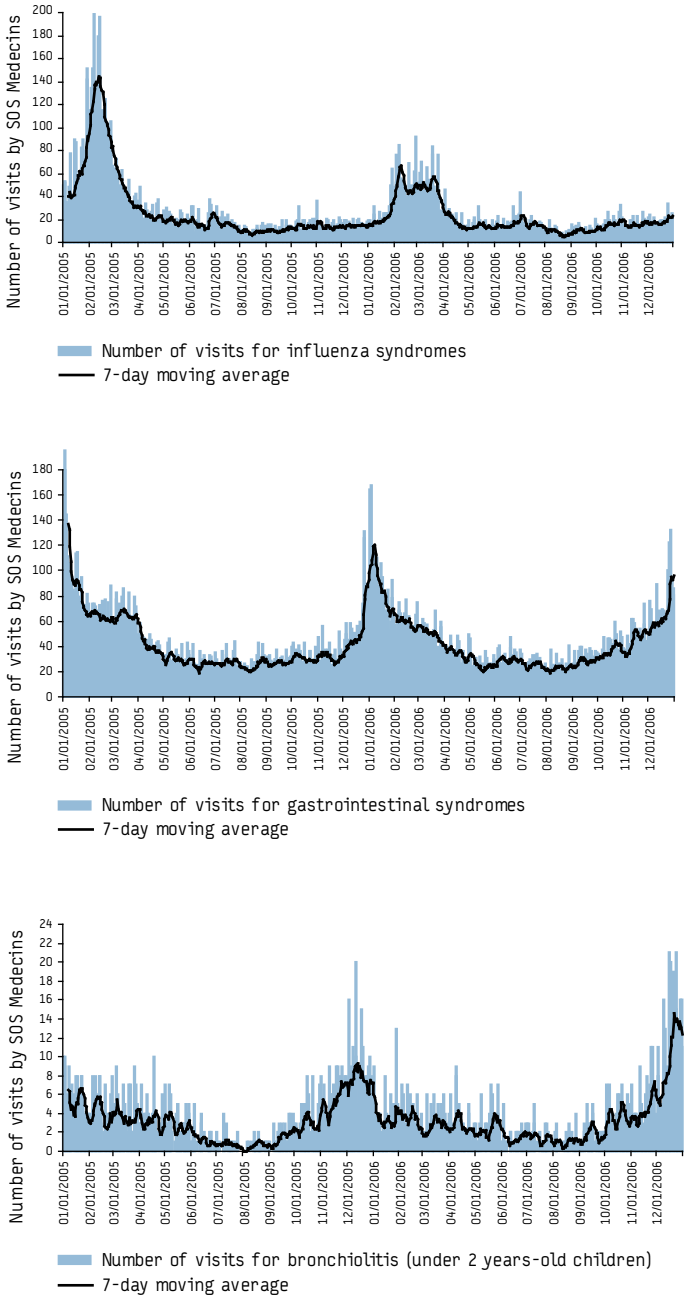
Syndrome groups under daily surveillance , SOS Médecins Bordeaux - Cire Aquitaine, 1 January 2005 – 31 December 2006

Syndrome groups	International Classification of Primary Care-2-codes	General description
Allergy	S98.01	Urticaria
	R97	Allergic rhinitis
	A92.01	Allergy/ allergic reaction not otherwise specified
	F71	Conjunctivitis allergic
General imparing	A04	Weakness/tiredness general
	A29.02	General symptom
	P29.08	Psychological symptom
Bronchiolitis (in children under two years old)	R78.01	Acute lower respiratory infection
	R03.02	Inspiratory wheeze/Asthma
	R78.02	Bronchitis
	R02.03	Dyspnoea
Heat syndromes	A88.01	Heat burn /Heatstroke
	T11	Dehydratation
Conjunctivitis infectious	F70	Bacterial/viral conjunctivis
Death	A96	Death
	Z62.02	Administrative procedure for death
Gastrointestinal	D11	Diarrhoea
	D10	Vomiting
	D73.01	Gastroenteritis presumed infection
Coronary thrombosis	K74.02	Ischaemic heart disease with angina
	K75.02	Acute myocardial infarction
Fainting	A06	Fainting / Syncope
	K88	Postural hypotension
	N17	Vertigo/Dizziness
Heart failure	K77	Heart failure / pulmonary oedema
	K29	Cardiovascular symptom/Heart trouble
Other respiratory infection	R83	Rhinitis
Influenza	A77	Viral disease other
	A03.01	Fever
	R80	Influenza / Influenza-like illness
Viral exanthem other	A76	Viral exanthem other
Suicide/Suicide attempt	P77	Suicide/Suicide attempt
Urinary infection	U02	Urinary frequency/urgency
	U71	Cystitis
	U05.01	Urination problems other
	U01	Dysuria
	U95	Urinary calculus
	U70	Pyelonephritis
Chickenpox	A72	Chickenpox

An analysis system using the Shewhart Control Chart for individual measurements based on moving ranges (MR) [15,16] was implemented allowing a continuous real-time assessment in order to immediately detect unusual variations in each of the 16 syndrome groups. This analysis is based on a comparison between the number of reported cases and a control limit calculated on the basis of the average of observations recorded during previous weeks and standard deviation estimated by the moving ranges of size 2.

FIGURE 2

Daily number of visits for seasonal syndromes (influenza, gastrointestinal and bronchiolitis among children under two years old) – SOS Médecins Bordeaux, 1 January 2005 – 31 December 2006 (n=303,936 visits)



The 2σ control limit (CL) expressed as a multiple of the process standard deviation is given by:

$$CL = \bar{x} + 2\frac{\overline{MR}}{d_2}$$

where $\bar{x}$ is the average of observations in previous weeks, $\overline{MR}$ is the average of all the moving ranges of size 2 included in previous weeks and d_2=1.128 . The moving range is defined as:

$$MR_i = |x_i - x_{i-1}|$$

which is the absolute value of first difference (e.g. the difference between two consecutive data points) of the data. The day of the week, public holidays and special events were taken into account in the process, comparing the counts for the current day with those for the comparable days and excluding special events from the average.

Results

Global approach

All visits made at home were collected and recorded in the database during the monitoring period from the beginning of 2005 to the end of 2006. For 15% of the records, the database was not updated by the doctor at the end of the visit; with the result that the diagnosis was missing. Over the study period, 303,936 visits were recorded, with an average of 417 visits per day (varying from 198 to 818) including 10% of visits to children under two years of age and 11% to people of 75 years and older. More than an half (56%) of patients were female. Global activity was influenced by important day-of-the-week and seasonal variations. The number of visits increased during the weekends and the winter.

Syndromic approach

Surveillance of seasonal outbreaks

The monitoring of the syndrome groups enables the surveillance of seasonal outbreaks such as influenza-like illness, gastrointestinal or bronchiolitis among young children (Figure 2). Epidemic periods were clearly identified on the curves reaching high peaks in winter seasons.

Figure 3 shows the weekly number of GP's visits for influenza-like illness and the same data collected by the sentinel network on two different scales [10]. The scales are different, as the SOS data only refer to the Bordeaux area, whereas the sentinel network data refer to the whole region of Aquitaine. Furthermore, the definition of influenza-like illness is not precisely the same: in the sentinel system, influenza-like illness is defined by a sudden fever (>39°C or >102°F) accompanied with myalgia and respiratory signs; whereas in the SOS Médecins system, it includes three diagnoses, gathered with the accordance of GP from the organization (influenza / influenza-like illness, fever and febrile symptoms, and viral disease other). Despite these differences, both sources of influenza syndrome data were strongly linked with a coefficient of correlation of 0.92.

Detecting unusual events: the example of the heat-wave of July 2006

In July 2006, a significant heat-wave occurred in France and all public health services were placed on alert. In the Bordeaux area, the level of « warning and actions » of the Heat Health Watch Warning system [17] was activated from 16 to 27 July while the biometeorogical indicators reached the alert thresholds (Figure 4).

At that time, the daily monitoring showed an acute increase in the number of GP visits for heat syndromes. This indicator was very sensitive to daily temperatures and the coefficients of correlation between both data sets were significant (0.72; $p<10\text{-}4$ for maximal temperature and 0.60; $p<10\text{-}4$ for minimal temperature). According to the statistical control chart analysis, threshold limits were exceeded from 14 July on, while the warning action level was activated from 16 to 27 July in the Bordeaux area.

Discussion

A new syndromic surveillance system based on GP's house visits was developed in the Bordeaux area and allowed to follow seasonal outbreaks and to detect unusual events.

Attributes of the system

This system has several important attributes [18] and advantages which demonstrate its validity and its performance for syndromic surveillance purposes [3].

Among the most important advantages is its capacity for the monitoring and of a wide range of specific health problems using the diagnosis made by the doctor at the end of the visit. While a number of syndromic surveillance systems based on emergency data are being developed and evaluated in different countries to improve early detection of outbreaks, most of them are based on a real-time transmission of chief complaints. Studies have shown that diagnosis data results in higher sensitivity and better agreement with expert reviewers than chief complaints for syndromic surveillance [19,20].

Other advantages include the simplicity and the acceptability of the system which does not depend on additional voluntary reporting since all the GPs collect data on electronic notebooks for administrative reasons.

In terms of timeliness, the automated and real-time nature of the system allows the downloading of all visit information during the following day, making the data available for analysis within 24 hours of the GP's visit. Regarding flexibility, the system can adapt to changing information needs and can easily accommodate new health-related events or new diseases in the syndromes groups under surveillance. Another positive attribute is the quality of data: the use of ICPC-2-coded diagnosis ensures uniformity in the database. Differences in coding practices between the different GPs are possible but the use of syndrome groups should reduce the bias induced and increase sensitivity of the indicators.

Due to a lack of elementary data on the characteristics of the population who have access to SOS Medecins, the representativeness of the system could not be evaluated. it is therefore difficult to know how representative this population seen by SOS Medecins is. However, the observed trends of diseases and dynamics of outbreaks were coherent with the knowledge of the different diseases monitored and the high correlation in seasonal variation between our influenza-like illness episodes and the ones reported by the sentinel network provides one measure of assurance that our system identified relevant events.

Contribution of the system in regional surveillance

This new system complements existing surveillance programs by assessing a large part of episodes of illness which do not require hospital admissions, or identification of an etiologic agent. Until now, only hospital morbidity and mortality data have been used to monitor the health of populations in order to detect an outbreak in the Bordeaux area; the use of such data has limitations since, in addition to delays in reporting, there can be a delay between the detection of an outbreak from the number of cases reported by our system and the increase in the frequency of hospital morbidity or mortality data, which only reflects the most severe forms of the diseases. On the contrary, an increase of GP activity can be or more sensitive indicator since it can allow detecting an unusual health event as soon as it happens.

This surveillance system enables the monitoring of a large number of syndromes on a daily basis, which was not possible with the pre-existing Sentinel surveillance system. Furthermore, it includes enough GPs to obtain reliable data at the local level, whereas the sentinel system is mainly used for surveillance at the national level.

Figure 3

Weekly number of visits for influenza-like illness made by SOS Médecins Bordeaux and declared by the sentinel network, 1 January 2005 - 31 December 2007

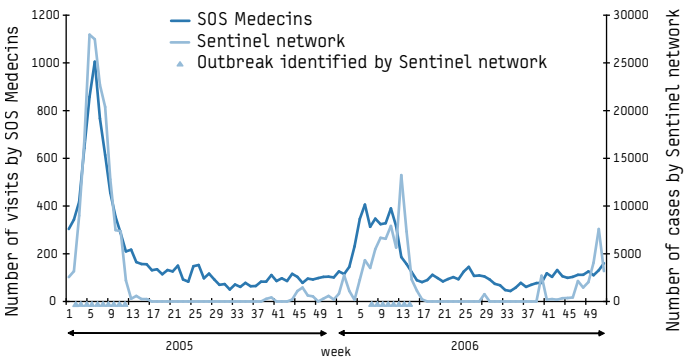
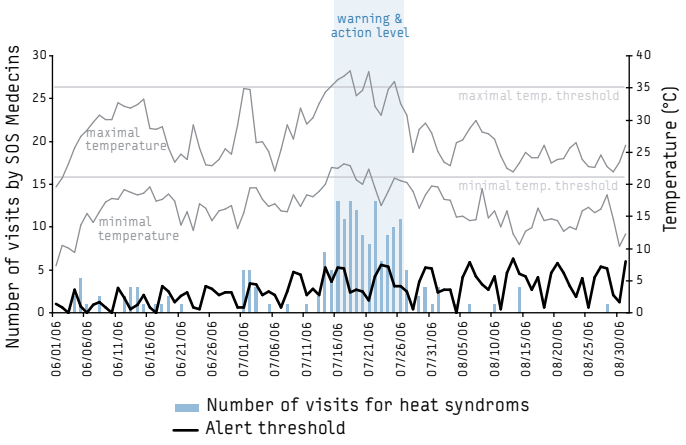


Figure 4

Daily number of visits for heat syndromes made by SOS Médecins Bordeaux and temperatures, 1 June 2006 – 31 August 2006



The availability of the postal code of the patient's residence is another benefit because the distribution of postal codes might allow spatial analysis and help in identifying an outbreak.

Another key point is that this syndromic surveillance system has the potential to show the importance of an early signal, increasing GPs' awareness of the need to bring any unusual event to the surveillance analyst's attention. This reinforces the communication links between clinicians and institutions in charge of health security. For example, in the context of the heat-wave that occurred in 2006, this system allowed to enlarge the preventive messages to the whole population since we showed that young adults as well as elderly people could be affected, contrary to what people believed. It also enabled an estimation of the heat-wave's health impact in order to provide objective data to politicians and help them take decisions.

Furthermore, the system has also been used several times to reassure health authorities that an outbreak has not occurred following a public health alert, such as the consumption of potentially dangerous food in a large part of the population of the area.

In conclusion, SOS Médecins surveillance can serve several different purposes including, monitoring disease patterns in order to detect outbreaks, providing detailed and timely information to health authorities, informing clinicians of conditions that are prevalent in their communities and supplementing current infectious disease surveillance systems.

For all these reasons, the development of tools – currently in progress – will allow the use of this system on a national basis in order to fulfill the same purposes in any other major French urban area.

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Surveillance of air-travel-related tuberculosis incidents, England and Wales: 2007-2008

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The potential spread of tuberculosis (TB) from infectious passengers during air travel has recently received increasing attention in the media and from public health authorities. We reviewed all air travel-related tuberculosis incidents reported to the Health Protection Agency Centre for Infections between January 2007 and February 2008 in England and Wales and investigated the effectiveness of contact investigation. Incidents involving air travel were defined according to the World Health Organization's guidelines on TB and Air Travel. We collected data on the index case, the incident and the outcome of contact investigation where available. We identified 24 incidents involving 39 flights. The median flight duration was 8.9 hours (inter-quartile range (IQR) 8 to 11.7). Most flights (36) were from or to a high burden country and 19 of the 24 incidents reported had a smear-positive index case. Two index cases had multidrug-resistant tuberculosis. In 17 incidents, no further investigation could be undertaken due to the lack of passenger information. In the remaining seven incidents, the quality of contact information obtained was variable. No further cases of TB infection or disease were identified. This study suggests that the process of investigating passenger contacts of a TB infected individual travelling by air is complicated and usually unsuccessful without dedicated resources and availability of high-quality contact information from airlines. Further research into the effectiveness of contact investigation in this setting is needed.

Introduction

The risk of the spread of tuberculosis (TB) from an infectious passenger during air travel has achieved increasing attention in the media and the public health community due to recent events such as the publication of World Health Organization (WHO) guidelines [1,2], the emergence of extensively drug-resistant (XDR) TB [3] and an incident involving a passenger believed to have XDR TB who travelled between Europe and North America [4] in 2007. Despite these events, the evidence for transmission of TB and the effectiveness of contact investigation in this setting are lacking. We undertook a review of all incidents reported in England and Wales to describe our experience and to investigate the effectiveness of contact investigation.

Method

Incidents with the potential for the transmission of TB are usually reported to the Health Protection Agency Centre for Infections for information or advice. In response to the increasing number of such incidents reported in a range of institutional settings, and a lack of evidence to inform their public health management, a passive system of TB incident and outbreak surveillance (TBIOS) was established in 2004. TBIOS relies on information gathered through a variety of means and sources, such as requests for advice by telephone or email and non-TB-specific incident reporting databases. There is no obligation for public health officers or physicians to report to this system. Incidents reported include those involving a smear-positive or smear-negative culture confirmed index case with a history of air travel.

We reviewed all air travel-related TB incidents reported to the TBIOS system, or identified through active follow-up of additional reports, between January 2007 and February 2008. Incidents involving air travel were defined as all reported events in which the WHO guidelines [1] for initiating contact tracing were met and in which local or national public health officers took a decision to undertake an investigation. Data collected included characteristics of the index case, duration of flight, amount of contact information available from airlines and the outcome of screening, where available. Where incidents were not directly investigated by the national unit, relevant local public health offices were contacted to obtain information. We assessed the effectiveness of the process by evaluating contact information obtained and the proportion of contacts traced.

Results

We identified 24 incidents between January 2007 and February 2008 based on a combination of the passive TBIOS system and active follow-up of other reports. Before January 2007, 21 air travel-related incidents were reported to the TBIOS system between 2004 and 2006 (12 in 2004, seven in 2005, two in 2006).

The 24 index cases were known to have travelled on a total of 39 flights while considered infectious. The median approximate duration of flight was 8.9 hours (inter-quartile range (IQR) 8 to 11.7). Most flights (36) were either from or to a high burden country in Africa or Asia. Table 1 summarises the characteristics of air travel-related TB incidents reported. Nineteen of the 24 incidents reported involved a smear-positive index case. In three cases, the diagnosis was based on bronchoalveolar lavage samples rather than an electively coughed up sputum sample. Results from drug susceptibility tests were available for only six of the 24 index cases. Two incidents involved a passenger with multidrug–resistant (MDR) TB and one with evidence of rifampicin resistance, based on a rapid molecular probe (no other drug susceptibilities were available for this person).

Table 1

Characteristics of air travel related tuberculosis incidents reported in England and Wales, January 2007 to February 2008

			n or Median (IQR*)
Flights N=39	Duration	Hours	8.9 (8 - 11.7)
	High incidence country	Yes	36
	Flight to notification delay	Days	41 (21 - 61)
Index cases N=24	Smear positive case	Yes	19
		No	1
		Unknown	4
	Drug-resistance	MDR**	2
		Rifampicin- resistant	1
		None	3
		Unknown	18
Contact investigation N=24	Availability of contact information from airlines	No further information	13
		Further information available	5
		Airline unwilling to share data	2
		Passenger details deleted by airline	2
		Passenger lists available but no contact details	2

* IQR – inter-quartile range,
** MDR – multidrug-resistant tuberculosis: resistance to at least isoniazid and rifampicin

Table 2

Characteristics and outcomes of air travel related tuberculosis incidents with information on contacts, England and Wales, January 2007-February 2008

Date Reported	Flight origin and destination	Approximate duration	Smear status	Drug-resistance	Contact information
25/06/2007	1. London to Bangalore 2. Bangalore to London	10hr 35 each way	Positive	None	1. 28 contacts: 3 UK, 1 with address 2. 28 contacts: 3 UK, 2 with address
26/07/2007	1. London to Hong Kong 2. Hong Kong to London	11hr 40min each way	Positive	Unknown	1. 22 contacts: 7 UK with personal/travel agent phone numbers 2. 32 contacts: 4 UK with personal/travel agent phone numbers
30/08/2007	1. Japan*** to London 2. London to Japan***	1. 12hr 15min 2. 11hr 30min	Positive	Unknown	1. 4 UK contacts with travel agent phone numbers 2. 2 UK contacts with address and phone numbers (both had a negative Mantoux test)
28/12/2007	1. London to Miami*** 2. Delhi to London 3. Miami*** to London 4. London to Delhi	1. 9hr 45min 2. 9hr 30min 3. 8hr 10min 4. 8hr 10min	Negative	MDR**	1. Followed up by CDC* 2. 41 contacts: 9 UK, 4 with address, 3 with phone, 1 with travel agent details 3. 43 contacts: 15 UK, 1 with address and phone, 1 with address, 4 with phone and e-mail, 9 with travel agent details 4. 47 contacts: 9 UK, 7 with phone numbers
06/02/2008	Vietnam to London	Over 8 hours	Unknown	Unknown	Passenger lists obtained, no further response.

* CDC – US Centers for Disease Control and Prevention, Atlanta
** MDR – multidrug-resistant tuberculosis: resistance to at least isoniazid and rifampicin
*** Non high incidence area

In 17 of the 24 incidents, no further investigation could be undertaken due to lack of passenger information. In two of those incidents, the airline was unwilling to provide data and for an additional two incidents data had been deleted by the airline. In the remaining 13 incidents, no further information could be obtained despite repeated contact with the airlines. In seven of the incidents, some information was available. In two of these, the airlines provided a list of passenger names, but no further information. In the remaining five of the 24 incidents, the airlines provided the passenger names plus variable amounts of contact information (Table 2). Among these five incidents, the results of screening for TB infection were only available on four individuals, including two household contacts, all of whom had a negative Mantoux test.

It has been suggested that longer delays between the date of travel and initiation of contact investigation may decrease the ability to obtain information from airlines. The median duration between the date of flight and notification to a public health authority was 41 days (IQR 21 to 61) with no association between this duration and the availability of information from airlines (k-test for equality of medians, p=0.23).

Discussion and conclusion

This analysis of surveillance data suggests that the process of tracing and investigating contacts of air passengers infected with TB is usually unsuccessful without the availability of appropriate contact information from airlines. Previous studies reported transmission of TB from smear-positive pulmonary TB cases during air travel (5-7). The majority of published investigations, however, did not identify evidence of transmission [1] and the cost of such investigations is reported to be very high [8,9]. This suggests that current recommendations may not be cost effective. McFarland et al. published estimates of costs of $25,000 (over 600 hours of personnel time) [8], and Vassiloyanakopoulos et al. of $4,000 (over 300 hours' personnel time with poor response) per incident [9].

A key limitation of our study is the lack of availability of contact tracing outcome information. Nevertheless, it shows the futility of the process. Furthermore, it is possible that not all air travel-related TB incidents were captured by the surveillance system.

It is occasionally possible to obtain a list of passengers and their contact details. Where this happens, a letter is sent to those passengers identified as contacts; the proportion of contacts who respond is variable. In the few studies where, with substantial resources, it has been possible to achieve good response rates, the proportion with evidence of recent infection of Mycobacterium tuberculosis is invariably negligible [5-7]. Furthermore, the interpretation of tuberculin skin tests in many countries is complicated by previous BCG vaccination and exposure to non-tuberculous mycobacteria. The development of interferon gamma release assays may improve this situation. Evidence for compliance with preventative therapy in this setting is lacking.

The majority of flights (36) involved passengers originating from or travelling to a high TB burden country. This, in part, reflects the prevalence of disease in such countries as well as the nature of air traffic to the United Kingdom due to historical links with African and Indian sub-continent nations.

There are no reliable data on the extent of transmission of TB on aircrafts. The WHO estimates that there are currently over nine million new cases of active TB diagnosed annually worldwide, of which four million are estimated to be potentially infectious [10]. Some of these will travel by air and several will do so for eight hours or more. Many will also travel by train, bus or car [12,13]. The cases identified following recent air travel are likely to represent a very small proportion of potentially infections cases undertaking travel. How likely is transmission of TB infection among air passengers? Byrne estimated that the incidence of TB among air passengers is 0.05 per 100,000 using data from one airline [11]. As only a small proportion of potentially infectious cases travelling by air will ever be identified, and as the rate of transmission of infection is very low, it is reasonable to ask whether contact investigation of air passengers is an effective method in the control of TB or cost-efficient method for identifying cases. Further research is needed into the contribution of air travel-related TB transmission to the burden of this disease and the cost effectiveness of contact investigation.

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Multiple exposures during a norovirus outbreak on a river-cruise sailing through Europe, 2006

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In the summer of 2006, several cruise-related viral gastroenteritis outbreaks were reported in Europe. One report came from a river-cruise, belonging to a ship-owner who had two other ships with outbreaks. This situation warranted onsite investigation in order to identify a potential common source of infection. A retrospective cohort study was performed among 137 people on board. Epidemiological questionnaire data were analysed using logistic regression. Stool, food, water and surface samples were collected for norovirus detection. Norovirus GGII.4-2006b was responsible for 48 gastroenteritis cases on this ship as confirmed in six patients. Identical norovirus sequences were detected in stool samples, on surfaces and in tap water. Epidemiological and microbiological data indicated multiple exposures contributing to the outbreak. Microbiological results demonstrated person-to-person transmission to be clearly present. Epidemiological results indicated that consuming tap water was a risk factor; however, this could not be concluded definitively on the basis of the available data. A common source for all cruise-related outbreaks was unlikely. The ongoing outbreaks on this ship demonstrated that evidence based guidelines on effective disinfection strategies are needed.

Introduction

Noroviruses are a well known viral cause of acute gastroenteritis (GE) on cruise ships [1,2]. Most norovirus outbreaks on cruise ships are described as being caused by person-to-person transmission. The virus is persistent and eradication is complicated in such closed settings [3]. On 3 July 2006, the National Institute for Public Health and the Environment (RIVM) in the Netherlands was notified of an outbreak of GE with characteristics indicating a viral agent. The outbreak occurred during successive voyages of a river-cruise ship sailing through several European countries. The outbreak was one of a large cluster of cruise-ship-related outbreaks reported in Europe at that time [4-6], all of which had ascribed norovirus as the causative agent. Moreover, it was the third ship from one company reporting ships with outbreaks and one of four ships that was dealing with GE while sailing through the Netherlands. In addition, this notified outbreak had endured consecutive voyages from 11 June 2006, despite sanitation measures, triggering questions about a possible and persisting common cruise-ship-related source of infection other than person-to-person transmission. An investigation by an outbreak investigation team was initiated to identify a possible source of infection. The ship docked in Nijmegen in the Netherlands on 6 July 2006, and provided the opportunity to undertake an onsite investigation.

Methods

A retrospective cohort study was performed among passengers and crew joining the second of three successive voyages, being further referred to as the current voyage, of this ship affected by outbreaks of GE. The outbreak investigation team included two epidemiologists from the National Institute for Public Health and the Environment (RIVM) and an inspector from the Food and Consumer Product Safety Authority (VWA). This team interviewed the ship's captain and hotel manager, following a structured questionnaire that focussed on the origin of viral GE outbreaks. Information concerning cleaning procedures was collected. Passengers and crew, joining the ship's current voyage affected by GE, were provided with a questionnaire that they completed individually. Stool, food and drinking water samples together with surface swabs were collected.

Epidemiological data-collection

The starting date, the menu cycle and information of facilities on board during the current voyage were used to prepare a questionnaire. The questionnaire is available from the authors by request. All food items from the menu served between boarding time on 25 June 2006 and breakfast on 27 June 2006 were included, considering an incubation period of 12-72 hours of the first reported symptomatic person. The following additional risk factors were addressed: water use, public toilet use and contact with infected people. To assess the potential introduction of the virus by a person, history of GE during the week preceding the cruise trip was asked. To allow the grouping of respondents with respect to biological plausible risk from food consumption according to the incubation period, the exact starting and ending time of symptoms were collected.

To determine the potential initial introduction of the causative agent through a person, the person who was the first to report symptoms was contacted. This occurred during the previous and first voyage of this ship affected by GE. This person – the index case – was interviewed by telephone using a questionnaire adjusted to the menu during his voyage.

Virological data collection

Stool samples

Twenty packages for the collection of stool samples, together with a detailed instruction form, were left on board the ship with the people responsible for passenger health. Stool samples were sent to the RIVM by overnight mail and then stored at 4°C. This is a commonly accepted procedure for the stable norovirus; furthermore, it increases the response rate for stool sample collection [7]. Crew members were instructed to approach at least five symptomatic and five asymptomatic people for stool sampling. Stool samples were tested for the presence of norovirus, as this virus was the suspected causative agent causing cruise-related outbreaks of GE in Europe at that time [4-6]. For confirmation of a norovirus outbreak, at least two of five case-originating samples need to be tested positive [8]. Stool samples were analysed as described by Svraka et al. [9]. Genotyping was done by sequence analysis of a fragment of the ribonucleic acid (RNA) dependent RNA polymerase gene, as described previously [10].

Potential source samples

The VWA collected food, water and surface samples according to a protocol designed to avoid cross-contamination of samples. Before sampling tap water, taps were cleaned with alcohol and contact between tap and sample bottle was avoided. Environmental swabs were analysed using a method which will be described elsewhere (Boxman et al., submitted 2008). Food samples were analysed for the presence of norovirus according to in-house protocols using (nested) real time polymerase chain reaction (PCR) assays [11,12]. One of the food samples – raspberries – was also analysed in three other specialised food laboratories in France, Finland and the Netherlands, according to local protocols Water samples of one litre were filtered through a positively charged membrane and detected according to Van den Berg et al [13].

Data analyses

As in most European countries, in the Netherlands microbiological diagnosis of norovirus is outbreak-based [8] instead of case-based. To identify norovirus patients, we used the following definition for acute GE: at least two episodes of diarrhoea and/or at least two times of vomiting within 24 hours. Discrimination was made between early cases and late cases, to determine biological plausible exposure from food addressed in the questionnaire. Early or late cases were characterised as people in whom illness occurred within or after, respectively, 72 hours after the last breakfast included in the questionnaire, i.e. before or after, respectively, 30 June 2006 10 a.m. To determine biological plausible risk from specific food items, the exact onset of disease was compared to the serving moment of the food item while assuming an incubation period of 12 to 72 hours.

Relative risk was calculated for all questionnaire items. Significant and biological plausible risk factors were analysed using a multiple logistic regression model to determine relevant factors after adjustment for potential confounders. Proportions were compared calculating p-values according to χ^2 if numbers were sufficient; Fisher's exact test was applied if cells in cross tables contained five or fewer records. All results are presented including 95% confidence intervals (95% CI). Data were analysed using SAS 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

The voyage started on 25 June 2006, and ended on 9 July 2006, while docking in 12 cities in Switzerland, France, Germany, the Netherlands and Belgium (Figure 1).

Epidemiological results

During the outbreak 33 crew members from Romania (n=8), Slovakia (n=7), Hungary (n=3), Bulgaria (n=3), Croatia (n=3), the Netherlands (n=3), Poland (n=2), Serbia (n=2) and Germany (n=2), and 104 passengers from the United States of America (n=102) and the United Kingdom (n=2) were on board. Of these 137 people at risk, 48 (35%) met the case definition of acute GE. Questionnaires from 29 (88%) crew members and 98 (94%) passengers were returned (Table 1). Of these, 2 (7%) crew and 46 (47%) passengers met our case definition for acute GE, with crew having a significantly lower attack rate (p<0.001). The epidemic curve for the cases showed a clear peak in the number of reported cases on day 4. The somewhat tailed distribution suggested a

Figure 1

Epidemic curve during a second outbreak of norovirus on a cruise ship with the locations of stops, 25 June–9 July 2006

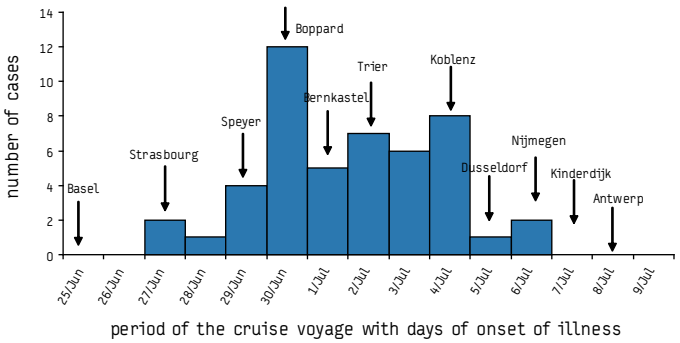


Table 1

Characteristics and case-definitions of the population at risk during an outbreak of gastroenteritis during a river-cruise

Characteristic	Crew (n=31)*	Passengers (n=98)*	Total (n=129)*
Mean age (range)	29.4 (20-43)	69.3 (14-87)	59.7 (14-87)
Sex male / female	19 / 12	47 / 50	66/62
Symptomatic / asymptomatic people based on			
Case definition for acute gastroenteritis (AGE) †	2 / 27	46 / 45	48 / 72
Case definition AGE and plausibility food risk‡	1 / 27	10 / 45	11 / 72

* Questionnaire-data of two crew members and six passengers are missing.
† At least two episodes of diarrhoea and/or at least two episodes of vomiting within 24 hours.
‡ Food items addressed in the questionnaire a time-span from boarding time through breakfast at 27 June, 2006 If the requested food item was consumed within 12-72 hours before onset of illness, risk from this food item was considered biological plausible.

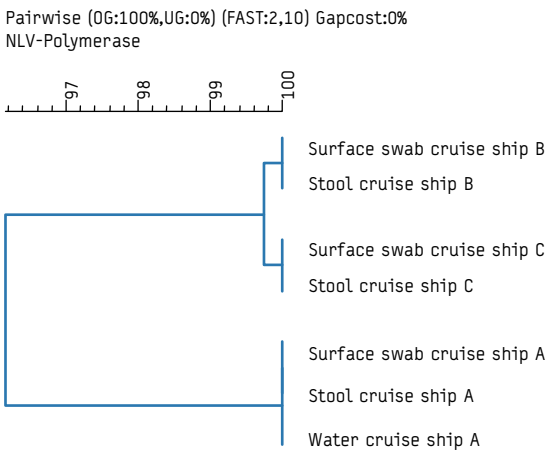
secondary wave of cases (Figure 1). Two Romanian crew members who had recently entered the ship during the current voyage reported symptoms of GE the previous week when at home.

Over 100 food items and five behavioural risk factors were addressed in the questionnaire. Of these, possible risk factors for cases in univariate analyses were: contact with a sick room-mate, and consumption of egg, carrot pie, tap water and whipped cream (Table 2). The number of early cases was too low for univariate analysis; however, results indicated tap water, ice cubes, egg consumption and a sick room-mate as possible risk factors. When restricting the plausible exposure from these factors to illness within 72 hours after consumption, the risk from egg, carrot pie and whipped cream consumption was considered unlikely: only eight of 38 ill egg consumers, three of 15 ill carrot pie consumers and two of nine ill whipped cream consumers became ill within 72 hours of consumption of the food item. Raspberries were not a significant risk factor when served as 'raspberry yoghurt'. Raspberries were also used as garnish, but this was not mentioned on the menu and thus not requested in the menu-based questionnaire. Use of public toilets on board could not be a risk factor, since public toilets had been closed a few hours after boarding time. This measure was introduced based on the outbreak during the ship's preceding voyage.

For juice and ice cubes, tap water was needed for preparation. Therefore, juice-drinkers and ice cube users were added to the water consumers in order to account for misclassification. Relative risk from water consumption became 3.2 (1.3-7.8) when combined with ice cube users and 4.2 (1.3-13.5) when combined with juice drinkers, suggesting a potential dose-response relationship. Adding both ice cube users and juice drinkers to the water consumers resulted in a relative risk of 3.3 (0.9-12.3). In a multiple logistic regression model, the consumption of tap water, ice cubes, orange juice and whipped cream were corrected for person-to-person transmission through the variable 'sick room-mate'. In this model, water - either with or without accounting for misclassification - remained a statistically significant risk.

Figure 2

Norovirus strains causing outbreaks of gastroenteritis in Europe in the summer of 2006



Strains were detected in stool, water, food and surface swabs on cruise ships which sailed through the Netherlands. Cruise ship A is the cruise ship investigated in this study. Ship A and B belonged to the same ship-owner.

In the outbreak during the previous voyage, 47 of 147 (32%) people on board presented with symptoms of gastroenteritis. These illness reports were poorly recorded with consequent missing dates of onset, and no attack rates specified for passengers and crew. Reportedly, none of the patients had vomited in a public area on board. A telephone interview with the index case took place at 27 July 2006, which was 6 weeks after the voyage. Since the index patient had noted the details of his illness, he was able to answer the questions quite accurately. The passenger became ill 26 hours after boarding 10 June 2006, which is within the 12-72 hour incubation period. The index patient did not have contact with ill people during the week before boarding the ship. He described having consumed ice cubes, but no tap water or raspberries. This interview was performed before analysis of questionnaire data, but after microbiological testing of collected food and environmental samples.

Virological results

Stool samples

Seventeen stool samples were received and analysed at the RIVM (Table 3). Six of seven stool samples belonging to symptomatic and none of the 10 asymptomatic person stools tested positive for norovirus genotype GGII.4, convincingly assigning this outbreak to norovirus. Sequence analysis confirmed that the outbreak strain was a 2006b variant, which was not the same as 2006a variant strains detected during the other cruise-ship outbreak from the same company and one other ship sailing through the Netherlands at that time and for which samples were collected for testing by VWA and RIVM (Figure 2) (https://hypocrates.rivm.nl/bnwww/Divine-Event/index.html) [5].

Potential source samples

Eleven environmental samples were collected during the onsite investigation. Two tap water samples as well as a swab from a door handle and the toilet were taken from a cabin that belonged to a symptomatic crew member. Three swabs were taken from the handle of an alcohol-based hand-disinfection container, the restaurant door and an alcohol-disinfected elevator button. The following food samples were taken: frozen raspberries, frozen mussels, ready-to-eat tomato and cucumber salad. In five out of eleven environmental samples GGII norovirus could be detected: one of the tap waters; the toilet; the handle from a disinfection container; the restaurant door; and the raspberries. Except for the raspberries, for which no further typing was possible, in each sample the norovirus was identified as a GGII.4-2006b strain identical in an overlapping sequence of 249 nucleotides to the sequence generated from stool (Figure 2). Three weeks later tap water was re-sampled, in which norovirus could not be detected. The ship's water supply tank included 192.10 m3. The water quality of the drinking water at docking time in Nijmegen did not exceed the Escherichia coli count based European legislative standards for drinking water.

Measures taken

No specific guidelines for control of (noro)virus outbreaks were available on board during the initial outbreak. During the previous and initial outbreak (11-25 June 2006) a set of hygiene instructions was acquired from a cleaning company at 15 June 2006. Since then, measures according to this hygiene protocol were taken accurately: public toilets were closed, patients were isolated during their illness, ill crew members disembarked, and hand washing, hygiene and disinfection measures were taken.

Discussion

Our combined epidemiological and microbiological results illustrate the difficulties of unravelling sources of infection in cruise ship norovirus outbreaks, and indicated that multiple exposures to norovirus played a role during the outbreak. Contaminated food, water, surfaces and having a sick room-mate may all have contributed to this outbreak. Proof for introduction of the virus via food or water could not be disentangled from the easily and rapidly taking over person-to-person transmission. This is a common problem during ongoing outbreaks in closed settings and may be an important reason why cruise-related outbreaks are mostly assigned to person-to-person transmission. In order to determine whether or not a food-borne source or water-borne source is the cause of an outbreak, the initial and not a successive outbreak should be thoroughly investigated.

Since this ship was one of three ships affected by GE outbreaks and belonging to one owner, a common water- or food-borne source of infection was considered possible. This possibility was strengthened by the fact that the ships partially have the same route, menu cycle and food supplier. Our epidemiological results were based on a high response rate (93%) and indicated that contaminated tap water

Table 2

Relative risk (95%CI) and biological plausibility for having acquired a norovirus infection on board of a river-cruise ship within the time-span addressed in the questionnaire. Significant risks are presented in bold (n=120)

Risk factor	All cases RR(95%CI)	Early case* RR(95%CI)	Late case† RR(95%CI)	Plausibility‡
Tap water	**2.8 (1.4-5.6)**	2.6 (0.7-7.3)	**2.8 (1.3-6.0)**	**Yes**
Ice cube use	1.7 (0.9-3.1)	3.8 (0.6-25.4)	1.4 (0.7-2.6)	Yes
Fresh juice	1.4 (0.9-2.1)	2.0 (0.7-5.3)	1.1 (0.8-1.8)	Yes
Sick room-mate	**2.2 (1.3-3.6)**	3.3 (0.9-11.7)	**1.9 (1.1-3.1)**	**Yes**
Egg	**2.9 (1.5-5.8)**	4.6 (0.7-29.5)	**2.5 (1.3-5.2)**	**No**
Carrot pie	**1.3 (1.0-1.6)**	1.2 (0.8-1.7)	1.3 (1.0-1.7)	No
Whipped cream	**1.2 (1.0-1.4)**	1.2 (0.9-1.5)	1.2 (1.0-1.4)	No

* Early cases were characterised as people in whom illness occurred within 72 hours after the last breakfast included in the questionnaire, i.e. before 30 June 2006 10 a.m.
† Late cases were characterised as people in whom illness occurred after 72 hours after the last breakfast included in the questionnaire, i.e. after 30 June 2006 10 a.m.
‡ Food items addressed in the questionnaire a time-span from boarding time through breakfast on 27 June, 2006 If the requested food item was consumed within 12-72 hours before onset of illness, risk from this food item was considered biological plausible.

Table 3

Characteristics of the people on board and taking stool samples during a norovirus outbreak on a river-cruise sailing through Europe, 2006

Case	Crew/passenger	Origin	NLV PCR	Onset of illness	Sample date	History of illness
Yes	P	USA	+	30-06-2006	07-07-2006	No
Yes	P	USA	+	30-06-2006	06-06-2006	No
Yes	P	USA	+	30-06-2006	06-06-2006	No
Yes	P	USA	-	03-07-2006	07-07-2006	No
Yes	P	USA	+	03-07-2006	07-07-2006	No
Yes	C	Hungary	+	03-07-2006	07-07-2006	No
Yes	P	USA	+	04-07-2006	06-06-2006	No
No	C	Romania	-	n.a.	06-06-2006	No
No	C	Poland	-	n.a.	06-06-2006	No
No	C	Hungary	-	n.a.	06-06-2006	No
No	P	USA	-	n.a.	06-06-2006	No
No	C	Servia	-	n.a.	07-07-2006	No
No	C	Romania	-	n.a.	06-06-2006	No
No	C	Germany	-	n.a.	06-06-2006	No
No	C	Germany	-	n.a.	06-06-2006	No
No	P	USA	-	n.a.	07-07-2006	No
No	P	USA	-	n.a.	06-06-2006	No

may have contributed to this and previous norovirus outbreaks on this river-cruise ship. The relative risk from water consumption became higher when combined with those who used ice cubes and drank juice, suggesting a potential dose-response relationship. The risk from water remained after correction for having a sick roommate. Moreover, the index case mentioned having consumed ice cubes during his incubation period on board the ship. Given that freezing is an excellent way to preserve viruses [14], and that the ice cubes were made with tap water, the consumption of water was a potential risk factor.

Food, water and environmental samples taken during the outbreak investigation tested positive. Unfortunately, however, these data could not be considered definitive proof due to the potential of cross-contamination. The positive water sample was taken from a tap in a room which was used by a symptomatic person. Consequently, contamination of the tap surface may have caused the contamination. To identify water as a cause of infection, water samples should be taken from the supply tank or a tap used by people free of symptoms. Similarly, the raspberries that tested positive were derived from an opened bag, since closed bags were not available for sampling. As crew members reported history of GE and the transmission through contaminated surfaces was clearly present, this may have resulted in contamination of the raspberries. Environmental swabs taken in public places on the ship tested positive. The norovirus positive handle of the ethanol-based hand sanitation bottle demonstrated that person-to-person transmission played a role despite – or even because of – prevention measures taken. This bottle was used for hand rubs just before having a meal at the buffet. Ethanol-based hands rubs may be effective in reducing bacterial infectivity, however, they may not be able to significantly reduce viral infectivity [15]. This situation illustrated the need for practical (noro)virus specific guidelines for both primary and secondary prevention of outbreaks on cruise ships.

However, for several reasons initial introduction via from water or food cannot be ruled out, and are points of concern for primary prevention measures. First, the tap water samples left a brownish colour after filtering, suggesting suboptimal quality of the water system. Water-borne outbreaks and contamination of tap water are more often described after unusual heavy rainfall [16], which also occurred in Europe at the time of the outbreaks [17]. The cruise ship had a water tank which was filled each time the ship was docked, while using the local water system (Figure 1). The tank supply was used for consumption during sailing time. It remained unclear if disinfection of the water tank was a current procedure on this ship. In general, water tanks may be a risk for infections at cruise ships [18-20], including norovirus. Second, raspberries are a well-described source of infection [21]. Unfortunately, the risk from consumption as garnish was not addressed in the questionnaire. Despite insufficient epidemiological evidence, the finding of norovirus-positive raspberries triggered a message in the European Rapid Alert System for Food and Feed (alert 2006.0546). There were no other illness reports associated with the product.

Attack rates for crew and passengers differed, with a significantly lower attack rate for crew, as has been described by others: four of five described outbreaks of GE on cruise ships in the United States in 2002 showed higher attack rates for passengers. A prospective survey on one of these ships showed 41% of the passengers suffering from GE, while 8% of passengers and 2% of crew sought medical attention [1]. Although an explanation was not given, the difference may be due to short-term immunity, which may have been acquired during successive outbreaks [22]. However, reporting bias could also play a role; underreporting by crew is imaginable in order not to worry the passengers or consequential loss of income, but was not addressed during our outbreak investigation. Although ill crew members were disembarked as a prevention measure during the previous outbreak, two new crew members were allowed on board shortly after their recovery of GE without the need for reporting their history of illness. This is a point of concern for the cruise ship industry, since person-to-person spread – directly or indirectly through food handling – is common in norovirus transmission. When returning to work, recovered employees need to be identified and thoroughly instructed to ensure personal hygiene, including food handling hygiene [14,23].

Molecular analysis of viruses identified on board showed that one of the other two ships with outbreaks was contaminated with a different norovirus strain (ship B, Figure 2). On the third ship, no microbiological tests were performed for the detection of norovirus. As Figure 2 shows, strains detected on another cruise-ship (ship C) sailing through the Netherlands at that time were also distinct, although the difference was small. Interpretation of data from molecular typing needs to be undertaken with caution when no data are available about the source: in food-borne contamination events, the source of contamination is an important determinant. In food-handler associated outbreaks, typically a single strain is found and finding dissimilar sequences is supportive evidence. However, when contamination occurs higher in the food chain, e.g. during irrigation, multiple strains may be present and finding dissimilar sequences does not necessarily disprove a causal link. Only thorough outbreak investigations that include product tracing can provide definitive evidence, but this is often considered to be too complicated [24,25].

Cruise ships are highly susceptible to norovirus outbreaks [2,26]. Once the virus is introduced in this closed setting, person-to-person transmission plays an important role [27]. If the virus is not eliminated – either through identification of a point source, disinfection of the environment or disembarkation of shedding crew – a successive outbreak at a cruise ship is likely to occur as a consequence of a group of new and susceptible people entering the ship [28]. Therefore, the detection of point sources and the immediate implementation of accurate cleaning measures during the initial outbreak are necessary for the prevention of new outbreaks on successive trips. As cruise ships usually sail through several countries, international guidelines for reporting, investigating and controlling norovirus outbreaks on cruise ships are needed [29]. Such guidelines need to be practicable for cruise staff, since an outbreak investigation team will mostly be present when person-to-person transmission cannot be separated from a potential point source introduction [4]. Since July, 2007, guidance for the management of cruise ships in the United Kingdom has been available online, which is a first step towards European outbreak control: http://www.hpa.org.uk/publications/2007/cruiseliners/cruiseliners.pdf.

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Ethnic differences in HSV1 and HSV2 seroprevalence in Amsterdam, the Netherlands

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Herpes simplex virus type 1 (HSV1) and 2 (HSV2) infection can lead to significant morbidity, and HSV2 is considered a risk factor for HIV transmission. The majority of HSV-infected people are asymptomatic and unaware of their infection. We aimed to determine the HSV1 and HSV2 prevalence among various ethnic groups in a large urban area in the Netherlands. In 2004, serum samples from a population-based serum repository of 1,325 people over 18 years living in Amsterdam were tested for HSV1 and HSV2 antibodies in order to determine high-risk groups. Prevalence ratios were estimated and all analyses were weighted by sex, age, and ethnicity. In the general population of Amsterdam, 67% had HSV1 antibodies, 22% had HSV2 antibodies, 15% had HSV1 and HSV2 antibodies, and 26% had no indication of HSV infection. In multivariate analyses, HSV1 seroprevalence increased with age, and was higher among people of Turkish and Moroccan origin, homosexual men, and individuals with low educational level. HSV2 seroprevalence was associated with increasing age, Surinamese/Antillean background, and having a history of sexually transmitted infections (STI). These differences between ethnic groups in Amsterdam regarding the distribution of HSV1 and HSV2 infection emphasise the importance of an ethnic-specific approach of serological testing as well as campaigns aimed at behavioural change and counselling to raise awareness of the risk of HSV transmission.

Introduction

Herpes simplex virus (HSV) causes oral-facial, genital and cutaneous infections. Both people with symptomatic lesions and asymptomatic individuals can shed virus particles particles and transmit HSV. When transmitted vertically, HSV causes neonatal herpes, which can lead to neurological damage or death [1]. In addition, the increase in genital transmission of herpes simplex virus type 1 (HSV1) and the evolving evidence that genital HSV infection is a potent facilitator of the sexual transmission of human immunodeficiency virus (HIV) are a considerable public health concern [2-5].

The majority of HSV-infected individuals are asymptomatic and unaware of their infection. Sero-epidemiological studies suggest that serologic testing for genital herpes identifies more infected individuals than are recognised clinically [1,6]. Therefore, control strategies at the population level will not be fully effective if limited to symptom management.

Two types of HSV can be distinguished, type 1 (HSV1) and 2 (HSV2). HSV1 is a common childhood infection, with prevalence ranging from 52-84% in Europe [7]. HSV2 is mostly sexually transmitted and is more restricted to subgroups of the population, such as men who have sex with men (MSM), with prevalence ranging from 4-80% [8]. Population-based studies on HSV in the Netherlands are scarce and studies have been conducted primarily in high-risk groups, such as attendees of sexually transmitted infections (STI) clinics and MSM [9,10]. Two studies conducted in the general population found HSV1 seroprevalences of 60% and 70% and HSV2 seroprevalences of 8% and 35% [7,11]. In the first study, non-native Dutch individuals were underrepresented and the second study excluded men.

HSV vaccine studies have reached phase II; phase III efficacy trials are in progress. Since vaccine studies on HSV2 are progressing, the epidemiology of HSV has received increasing attention [12]. By testing samples from the first population-based serum repository in Amsterdam, we aimed to obtain a representative picture of the HSV1 and HSV2 prevalence among men and women of different origin and background in a large urban area. Almost half the residents of Amsterdam are non-Dutch and originate mainly from Suriname and the Antilles (22%), Morocco (18%), and Turkey (11%) [13].

Methods

Study population and sampling procedure

The population-based serum repository is a result of the Amsterdam Health Monitor (AHM) which was carried out from April until June 2004 [14]. With approval of the Medical Ethical Committee of the Amsterdam Medical Centre, the AHM collected information about the health of the general population in Amsterdam to gain more insight into the determinants for public health in Amsterdam. The study sample was drawn from the Amsterdam municipal registers in five city districts. These districts comprised a population representative to the Amsterdam general population in terms of ethnic mix, sex, and age. The sample was stratified by ethnic origin and five age groups (18-34, 35-44, 45-54, 55-64 and 65 years or older). Within each stratum a random sample was drawn with an oversampling of Turkish and Moroccan people who are relatively underrepresented in the total population and had a lower participation rate in previous national and local surveys in the Netherlands. Ethnic origin was classified by the country of birth of the participant and/or the country of birth of the parents. Ethnicity was determined as foreign if the participant or one of their parents was born outside the Netherlands.

The total study sample consisted of 4,042 residents aged 18 years and older. The participants were invited by mail to a face-to-face interview based on a structured questionnaire regarding issues such as socio-demographics, chronic and infectious diseases, drug use, and living environment. For questions on sexual behaviour, participants could choose between interview-administration and self-administration of the answers.

The final response rate on the AHM was 44% [14]. After written informed consent, 79% of the participants (n=1,376) donated blood for the serum repository. There was a relation between whether a person responded or not and their age, sex and ethnicity. Among those who did respond, there were no significant differences in age and sex between participants who gave blood and participants who only participated in the survey, but those who did not give blood were more often of Turkish origin.

When comparing the participants who agreed to have a blood sample taken and the control group of those who did not respond to the survey at all, certain subgroups were more willing than others to give blood: Those who gave blood were more often 45-64 years-old (45% versus 36%) and of Dutch ethnic origin (33% versus 23%), whereas the youngest and oldest age groups (16% versus 24% of the 18-34 year-olds, and 17% versus 20% of those 65 years-old and older), the male participants (46% versus 51%), and those of Moroccan ethnic origin (21% versus 26%) were less likely to agree to give blood.

Serological testing

Of the 1,376 blood samples, 1,362 were tested for HSV1 and HSV2 using HSV1 and HSV2 antibody assays (HerpesSelect, Focus Technologies, USA). According to the manufacturer instructions, test results below a cut-off value of 0.9 were defined as HSV1- or HSV2-negative, values between 0.9 and 1.1 as equivocal, and test results over 1.1 as HSV1- or HSV2-positive. Samples with an equivocal HSV test result (n=29; 1.6% for HSV1 and 0.5% for HSV2,), and samples for which data on age or country of birth (n=8) was not available were excluded, resulting in a final dataset of 1,325 participants for statistical analysis.

Variables and statistical analysis

For respondents of Turkish and Moroccan ethnic origin (age 18-34 years) we defined their generation as: 1) first generation: participant and one or both parents born in a foreign country; 2) second generation: participant born in the Netherlands and one or both parents born in a foreign country. For males, attraction to mainly the same sex was defined as homosexual preference.

Relative risks were estimated instead of odds ratios, because the rare event assumption was not reached. Prevalence ratios were estimated using a modified Poisson regression model [15]. To correctly estimate the standard error for the estimated relative risk, a robust standard error was obtained by implementing a repeated statement in the SAS GENMOD procedure. Variables with a $p<0.10$ in univariate analyses were entered into the multivariate model into which ethnicity, age and sexual preference were forced. Interaction between risk factors and gender was explored, but no significant interaction was found to be present.

The questionnaire also included detailed questions on sexual behaviour. In total, 976 (74%) of the 1,325 respondents who gave blood answered these questions. People of Turkish and Moroccan origin and those with a low educational level were more likely to decline answering questions on their sexual behaviour. Univariate analyses were carried out to examine the association between seropositivity for HSV1 or HSV2 and sexual behaviour in the past year (e.g. sexual contact or not, number of partners, anal sex).

Defining results above a cut-off value of 1.1 as positive for HSV2 in populations with multiple infections (e.g. African populations) has yielded a high rate of false positive results in earlier studies [16,17]. In those studies, false positives were less frequently detected in sera with HSV index values of over 3.5 compared to values in the low positive range (1.1-3.5). As suggested in one of the studies [16], we conducted sensitivity analyses using a cut-off value of 3.5 (excluding those with an index value between 0.9 and 3.5). The risk factors for HSV infection that were found in these analyses were comparable to those obtained in analyses with a cut-off value of 1.1 (data not shown).

All the analyses were weighted according to the cell weighting method [18] by sex in two groups, age in five groups, and ethnicity in six groups, to account for oversampling and deviations of the sample distribution in sex, age, and ethnicity from the general population aged 18 years and older in Amsterdam in 2004. In this way results were representative for the adult population in Amsterdam [14].

Results

Characteristics of the study sample

The study population (those who participated in the survey and gave a blood sample) consisted of 611 men and 714 women. The median age for men was 51 years (interquartile range (IQR) 41-62 years) and for women 47 years (IQR 37-58 years). The majority of men (80%) and women (76%) in the sample had a Dutch, Turkish, or Moroccan ethnic background, and 40% of the participants had a medium educational level (lower vocational school or secondary school). More women (20%) than men (17%) had had an HIV test, but more men (11%) than women (8%) reported a history of one or more STIs.

Prevalence of HSV infection

Overall, 67% (95% confidence interval (CI): 63.5-71.0) of the population had HSV1 antibodies, 22% (95% CI: 18.9-24.9) were positive for HSV2, and 15% (95% CI: 12.1-17.2) were co-infected with HSV1 and HSV2.

Twenty-six percent (95% CI: 21.9-29.2) of the population had no serological evidence of HSV infection. Most of those were of Dutch (33%) or other Western (26%) ethnic origin. As shown in Figure 1, the proportion of people with no HSV infection decreased with age, from 37% in the group of 18-34 year-olds to 11% in the 55-64 year-olds. This age effect was not visible in people of Turkish, Moroccan and other non-Western origin. The proportion of seronegative people in these populations was very low (around 5%) across all the age groups.

Determinants and predictors of HSV1 infection

Over 80% of the people with Turkish, Moroccan, and other non-Western ethnicity were HSV1 seropositive across all the age groups (Figure 2). In contrast, the HSV1 seroprevalence of those originating from the Netherlands and other Western countries increased with age: from 40% in the age group 18-34 years to 80% in the age group 65 years and older. Ethnic background therefore had the largest influence in the youngest age group of the 18-34 year-olds who were twice as likely to be infected if they were of Turkish, Moroccan, and other non-Western origin. Responsible for

the high seroprevalence among people from Morocco and Turkey were primarily immigrants of the first generation. In the youngest age group (18-34 years), we observed a non-significant tendency (exact chi-square test, p=0.07) towards higher seroprevalence in immigrants of the first generation among whom 98% (78/80) were HSV1 seropositive compared to 87% (20/23) of the second generation.

In multivariate analyses, HSV1 seropositivity was associated with increasing age, being of Turkish or Moroccan ethnicity, and low educational level (Table). After controlling for ethnicity, age and education, homosexual men were more likely to be seropositive for HSV1 than women and heterosexual men. No association was found between HSV1 seroprevalence and sexual behaviour in the past year.

Determinants and predictors of HSV2 infection

People of Surinamese, Antillean, and other non-Western ethnicity had the highest seroprevalence of HSV2 (26% and 32%) compared to people of indigenous Dutch ethnicity (20%). No significant differences were found between generations of migrants, but older individuals and those who had ever had an STI were more likely to be HSV2 seropositive (Figure 3 and Table). None of the estimated risks for HSV2 seropositivity was significantly different for males and females, but HSV2 seroprevalence was (not significantly) higher in females and in homosexual men compared to heterosexual men.

Additional analyses on the association between sexual behaviour and HSV2 infection were done for the part of the study population which had responded to those questions (n=976). These analyses showed that individuals with more than one sexual partner in the past year had a 1.56 higher risk of HSV2 infection (95% CI 1.13-2.16) compared to those with one or no sexual partner in the past year.

Discussion and conclusion

Our study demonstrates clear differences in HSV distribution among ethnic groups in Amsterdam, the Netherlands. The HSV1 seroprevalence among migrants born outside the Netherlands reflects the prevalence reported in their country of origin, because most HSV1 acquisition occurs during childhood or young adulthood [8,19,20]. As a corollary, a lower HSV1 seroprevalence was found among the second generation of migrants, who were born in the Netherlands. This could partly be explained by improved socio-economic conditions and adaptation to certain western cultural habits. The HSV1 seroprevalence among indigenous Dutch persons in Amsterdam (59%) supports the results of a European serological survey in 1994, in which 57% of the Dutch samples were found to be HSV1-positive [7]. Consistent with population-based studies worldwide, we found an association between HSV1 infection and age as well as socio-economic factors such as low education [7,8,20,21].

HSV2 prevalence likewise varied with geographic origin and this might explain the higher HSV2 seroprevalence in Amsterdam in 2004 (22%) compared to the prevalence in the general population in the Netherlands in 1994 (9%), since our study included non-indigenous individuals. In addition, a higher concentration of high risk profiles in urban areas, and an increase in sexual risk behaviour over time might explain the discrepancy.

In line with other studies, HSV2 prevalence in our study was highest among people originating from Suriname, the Antilles and other non-Western countries (excluding Morocco and Turkey) [6,8,11,21,22]. High HSV2 seroprevalence in these populations living in Amsterdam reflects parameters of sexual behaviour such as a higher number of sexual partners and concurrent partnerships among men originating from Suriname, the Netherlands Antilles, and Africa [22,23].

As HSV2 infection facilitates HIV transmission, it is worth noting that the largest non-Dutch group of HIV-infected individuals in the Netherlands are sub-Saharan Africans (44%), followed by people

Figure 1

Weighted prevalence of HSV seronegativity by age and ethnicity among the general population of Amsterdam in 2004

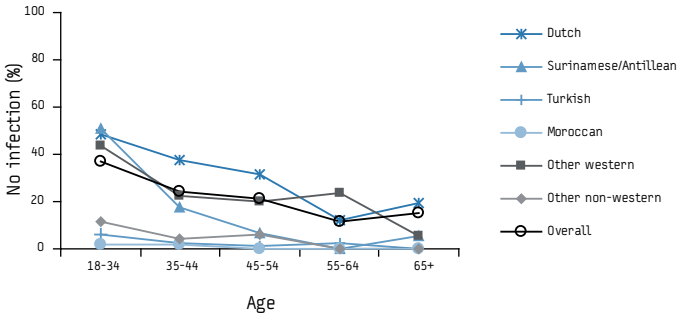


Figure 2

Weighted HSV1 prevalence by age and ethnicity among the general adult population of Amsterdam in 2004

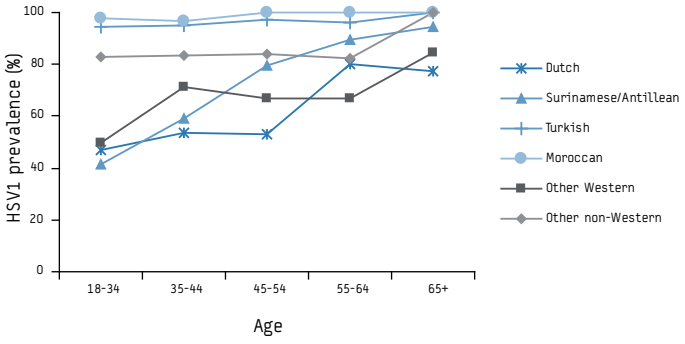
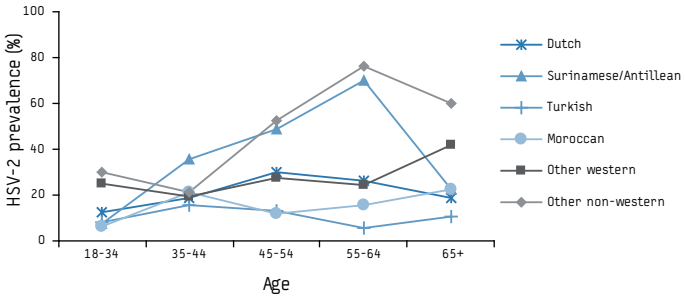


Figure 3

Weighted HSV2 prevalence by age and ethnicity among the general adult population of Amsterdam in 2004



Table

Multivariate model of associations with HSV1 infection among the general population of Amsterdam, 2004 (n=1,325)

		HSV1		HSV2	
	N	Rate±SE (95% CI)	PRR (95% CI)	Rate±SE (95% CI)	PRR (95% CI)
Age (per 10 years)	1,325		1.09(1.06-1.15)***		1.26(1.14-1.39)***
Ethnicity					
Dutch	435	58.9±2.7 (53.6-64.2)	1.00***	19.9±2.1 (15.9-23.9)	1.00**
Surinamese/Antillean	88	63.1±7.6 (48.1-78.2)	1.15(0.90-1.47)	25.7±5.3 (17.1-34.3)	1.60(1.03-2.51)
Turkish	314	95.2±1.7 (91.9-98.5)	1.73(1.51-1.98)	11.1±2.3 (6.6-15.5)	0.80(0.49-1.31)
Moroccan	276	98.3±1.1 (96.2-99.9)	1.78(1.56-2.03)	12.4±2.3 (7.8-16.9)	0.81(0.51-1.29)
Other Western[a]	136	64.2±6.0 (52.3-76.0)	1.10(0.91-1.33)	27.2±5.3 (16.6-37.7)	1.42(0.93-2.18)
Other non-Western[a]	76	85.1±4.6 (75.9-94.4)	1.59(1.36-1.87)	32.0±5.6 (20.8-43.2)	2.01(1.34-3.02)
Educational level[b]					
High	268	55.4±3.9 (47.8-62.9)	1.00**	22.0±2.9 (16.4-27.7)	
Medium	530	71.5±2.8 (66.0-77.0)	1.22(1.05-1.41)	20.9±2.1 (16.8-25.0)	
Low	308	88.1±2.1 (83.9-92.3)	1.19(1.01-1.39)	24.2±3.5 (17.4-31.1)	
History of STI	125	71.9±5.2 (61.6-82.4)		42.6±5.5 (31.6-53.6)	1.82(1.30-2.56)**
Sexual preference					
Men-Homosexual	59	82.1±6.8 (68.3-95.8)	1.36(1.12-1.64)	29.5±6.5 (16.4-42.6)	1.48(0.74-2.94)
Men-Heterosexual	536	63.5±3.2 (57.1-69.9)	1.00*	18.2±2.2 (13.9-22.6)	1.00
Women	691	68.1±2.5 (63.1-73.0)	1.08(0.96-1.22)	24.4±2.1 (20.3-28.4)	1.27(0.95-1.72)

SE = standard error; PRR = prevalence rate ratio
[a] other Western (Europe, North America, Oceania), other non-Western (Asia, Africa, South America)
[b] low (primary school), medium (lower vocational school, secondary school), high (higher vocational school, university)
*$p < 0.10$; **$p < 0.01$; ***$p < 0.001$

from the Caribbean and Latin America (14%), predominantly Suriname and the Netherlands Antilles [24]. The HSV2 prevalence we found among people of Moroccan origin corresponds to the prevalence rate (12%) found in a national HIV sentinel surveillance conducted in Morocco [20]. In contrast, the HSV2 seroprevalence among the Turkish residents of Amsterdam (11%) differed considerably from the prevalence (42%) found among pregnant women attending an antenatal clinic in Turkey [19]. It has to be noted, however, that the two groups do not necessarily compare and HSV2 prevalence reported in women are usually higher than in men [6-8].

Consistent with other studies, we observed an increased risk of HSV2 with increasing age across all ethnic groups [6,7,8,20], but also a peak in HSV2 seroprevalence in the age group of 55-64 years old. This probably reflects the increasing number of years of sexual activity. Across geographic areas, attendees of STI clinic consistently had higher prevalence of HSV2 infection [25]. Our study showed that a history of STI and the number of sexual partners were markers of higher risk of HSV2 infection.

Unlike other studies conducted in the US, Africa and Europe, we found no association between gender and HSV seropositivity [6-8]. However, we did find evidence of a higher HSV1 prevalence in homosexual men compared to heterosexual men and women, and the data may suggest that HSV2 prevalence was higher in both women and homosexual men compared to heterosexual men.

Several studies have shown discrepant results as to the interaction between HSV1 and HSV2 [25,26], and it has been proposed that prior HSV1 infection may protect against acquiring HSV2. However, we observed no association between being positive for HSV1 and being negative for HSV2.

The results of the study could have been biased due to the low response rate of 44%. Although this response rate is comparable with several national surveys in the Netherlands (50%), it is nevertheless a cause for concern. Response rates in Dutch survey research generally tend to be lower compared to similar American and European studies (60-80%) [27,28]. Two reasons are often mentioned. Firstly, the Netherlands is a highly urbanised country and response rates tend to be lower in urban areas. Secondly, lower response rates could in part be due to higher mobility of the population, especially in Amsterdam. It should also be noted, however, that HSV does not in itself 'cause' non-response. The association between HSV and response is indirect and will have had a relatively modest influence.

For estimation of the prevalences, the data were weighted by sex, age, and ethnicity, both overall and within the subgroups where relevant. The effects of differences in response between groups are addressed in this way and we believe that prevalence from this perspective can be considered representative for the whole adult population of Amsterdam.

Limitations of the HerpesSelect antibody assay are well known. Discrepant results are mainly obtained in populations with multiple infections. Use of a higher cut-off value (>3.5) instead of a cut-off value of >1.1 have been recommended by other studies. A higher positive index value resulted in increased specificity (98%), but has shown to reduce sensitivity (90%) [16,29]. In our study, risk factors identified with a cut-off value of 3.5 were comparable to those identified when using 1.1 as cut-off value.

Current HSV control strategies include behavioural intervention and symptom management. However, a combined approach of behavioural change, suppressive therapy and serological testing for genital herpes simplex for those with current or recent STI or high-risk behaviour, is more likely to have a substantial impact on the prevention of HSV acquisition and transmission. Serological testing gives the opportunity to counsel patients. Patients who have been counselled on the natural history of HSV and the correlation between HSV transmission and HIV infection may be more aware of the fact that they have an increased risk of acquiring HIV or other STIs and of what they can do to limit this risk [30].

It is possible to limit the spread of HSV1, as shown by the somewhat lower prevalence of HSV1 in the second generation compared to the first generation of Turkish and Moroccan migrants. However, since HSV1 infections are primarily acquired during childhood and first generation immigrants are more likely to become infected before taking up residence in the Netherlands, a further decline in HSV1 transmission also depends on the prevention efforts in their countries of origin.

A decrease in HSV1 seroprevalence among migrants of the first generation would lead to a larger group of young people susceptible to HSV1 primary infection, for example genital infection. On the other hand, a decrease in seroprevalence would at the same time mean more people who could potentially benefit from an HSV2 vaccine, which currently has been shown to be effective only in HSV1-negative women [3].

Our results provided useful insight into the distribution of HSV in a large urban area with a high proportion of residents of non-Western origin. Our study showed that migrant groups have different patterns and epidemiology for infectious diseases and these patterns could differ between generations. These findings emphasise the importance of an ethnic-specific approach to raise awareness for the prevention of HSV transmission.

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Survey of European programmes for the epidemiological surveillance of congenital toxoplasmosis

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The objective of this investigation was to describe systems for the epidemiological surveillance of congenital toxoplasmosis implemented in European countries. In September 2004, a questionnaire, adapted from the evaluation criteria published by the United States Centers for Disease Control and Prevention, was sent to a panel of national correspondents in 35 countries in the European geographical area with knowledge of the epidemiological surveillance systems implemented in their countries. Where necessary, we updated the information until July 2007. Responses were received from 28 countries. Some 16 countries reported routine surveillance for toxoplasmosis. In 12 countries (Bulgaria, Cyprus, Czech Republic, England and Wales, Estonia, Ireland, Latvia, Lithuania, Malta, Poland, Scotland and Slovakia), surveillance was designed to detect only symptomatic toxoplasmosis, whether congenital or not. Four countries reported surveillance of congenital toxoplasmosis, on a regional basis in Italy and on a national basis in Denmark, France and Germany. In conclusion, epidemiological surveillance of congenital toxoplasmosis needs to be improved in order to determine the true burden of disease and to assess the effectiveness of and the need for existing prevention programmes.

Introduction

Toxoplasmosis is caused by a protozoan parasite (*Toxoplasma gondii*). While toxoplasmosis infection is often benign, congenital toxoplasmosis (transmission to the foetus when a pregnant woman acquires toxoplasma infection for the first time during pregnancy) can lead to severe sequelae for the foetus and the newborn with visual or neurological impairment or death.

It is important to evaluate the burden of toxoplasma infection in the general population, as well as in pregnant women, foetuses, newborns and children, because this contributes to the rationale behind the different screening programmes currently performed (none, prenatal or postnatal) [1-3]. Frequency and severity of a disease are the basic measurements used to assess its burden, and data on this can be collected in specific studies or surveillance systems. The value of epidemiological surveillance is that it can be used to monitor trends over time. Public health strategies to prevent congenital toxoplasmosis differ between European countries. It is still being debated which are the best methods for controlling congenital toxoplasmosis, and the debate is not always based on accurate information.

The EUROTOXO project (http://eurotoxo.isped.u-bordeaux2.fr) is a European consensus initiative aimed at defining the implications of current scientific knowledge for a research agenda and for policy decisions on how best to prevent congenital toxoplasmosis and its consequences. The project has reviewed the state of the knowledge concerning the burden of toxoplasma infection in Europe. This article presents a systematic review of the systems implemented in European countries for the epidemiological surveillance of toxoplasmosis.

Methods

Source of information

We identified contacts for national surveillance programmes in 30 European countries (Table 1) from the following sources:

- the members of the Eurosurveillance Editorial Board listed on the Eurosurveillance website at the time;
- the Inventory of Resources for Infectious Diseases in Europe (IRIDE) (http://iride.cineca.org/public/invcountries.html);
- the European Programme for Intervention Epidemiology Training (EPIET) network (http://www.epiet.org/).

Contacts for six other European countries (Albania, Bosnia-Herzegovina, Bulgaria, Croatia, Macedonia, and Serbia-Montenegro) were identified by Google search.

We did not find correspondents for Andorra, Monaco or Northern Ireland. The list of correspondents is shown in Table 1. All contacts were sent emails in September 2004 and those who did not respond were sent three further emails in January/February, April, and July 2005. We maintained contact with our correspondents in each participating countries until July 2007 and updated the data when a change in the surveillance systems was signalled. This was the case for France (implementation of a new surveillance system) and Denmark (surveillance system stopped).

Data collection and interpretation

We developed a comprehensive questionnaire, based on the criteria published by the United States' (US) Centers for Disease Control and Prevention (CDC) for the evaluation of epidemiological surveillance systems [4]. Epidemiological surveillance was defined as ongoing and systematic collection, analysis, and interpretation of health data in the process of describing and monitoring a health

Table 1

European correspondents contacted to participate in the survey on the epidemiological surveillance of toxoplasmosis

Countries that participated in the survey	
Austria	Reinhild Strauss, Federal Ministry for Health, Family and Youth, General Directorate of Public Health, Vienna
Belgium	Germaine Hanquet, Scientific Institute for Public Health, Unit of Epidemiology, Ministry of Social Affairs, Public Health and Environment, Brussels
Bosnia and Herzegovina	Semra Cavaljuga, Institute for Epidemiology and Biostatistics, School of Medicine, University of Sarajevo, Sarajevo
Bulgaria	Mira Kojuharova, National Centre of Infectious and Parasitic Diseases, Department of Epidemiology, Sofia
Cyprus	Olga Kalakouta, on behalf of Dr. Chrystalla Hadjianastassiou, Chief medical Officer, Medical and Public Health Services, Ministry of Health, Nicosia
Czech Republic	Petr Kodym, National Reference Laboratory for Toxoplasmosis, National Institute of Public Health, Prague
Denmark	Henrik Vedel Nielsen, Unit for Mycology and Parasitology, Statens Serum Institut, Copenhagen
England and Wales	Robert Smith, Public Health Laboratory, Service of Communicable Disease, Surveillance Centre Wales, Cardiff
Estonia	Kuulo Kutsar, Department of Communicable Diseases, Health Protectorate Inspectorate, Tallinn
Finland	Maija Lappalainen, Department of Virology, Hospital District of Helsinki and Uusimaa, Helsinki
France	Isabelle Villena, National Reference centre for toxoplasmosis, Reims; Véronique Goulet, Department of Infectious Diseases, Institut de Veille Sanitaire, Saint-Maurice
Germany	Katharina Alpers, Department for Infectious Disease Epidemiology, Gastrointestinal Infections, Zoonoses and Tropical Infections, Robert Koch Institute, Berlin
Greece	Yanis Tselentis, Laboratory of Clinical Bacteriology, Parasitology, Zoonoses and Geographical Medicine, University of Crete, Faculty of Medicine, Heraklion
Ireland	Darina O'Flanagan, HSE-Health Protection Surveillance Centre, Dublin
Italy	Wilma Buffolano, Perinatal Infection Unit, Department of Paediatrics, Federico II University of Naples; Maria Grazia Pompa, Communicable Disease Unit, DG Health Prevention, Ministry of Health, Rome
Latvia	Irina Lucenko, Division of Epidemiology of Infectious Diseases, State Public Health Agency, Riga
Lithuania	Bronius Morkunas, Centre for Communicable Disease Prevention and Control, Vilnius
Malta	Tanya Melillo Fenech, Disease Surveillance Unit, Department of Public Health, Ministry of Health, Msida
Netherlands	Laetitia M. Kortbeek, Diagnostic Laboratory for Infectious Diseases and Perinatal Screening (LIS), National Institute of Public Health and the Environment, Bilthoven
Norway	Hans Blystad, Department of Infectious Disease Epidemiology, Norwegian Institute of Public Health, Oslo
Poland	Malgorzata Sadkowska-Todys, Laboratory of Zoonoses, Department of Epidemiology, National Institute of Hygiene, Warsaw
Portugal	Judite Catarino, General Health Directorate, Lisbon
Romania	Adriana Pistol, General Department of Public Health, Service of Prevention and Control of Communicable Diseases, Ministry of Health and Family, Bucharest
Scotland	Lynda Browning, Zoonoses Section, Health Protection Scotland, Glasgow
Slovakia	Maria Avdicova, Department of Epidemiology, Regional Institute of Public Health, Baska Bystrica
Slovenia	Jernej Logar, Institute of Microbiology, Medical Faculty, Ljubljana
Sweden	Johan Lindh, Department of Parasitology, Mycology and Water, Swedish Institute for Infectious Disease Control, Solna
Switzerland	Karim Boubaker, Infectious Diseases Section, Division of Communicable Diseases, Swiss Federal Office of Public Health, Public Health Direction, Bern
Countries that were asked but did not participate in the survey	
Albania	Eduard Kakarriqi, Department of Epidemiology, Institute of Public Health, Rruga
Croatia	Ira Gjenero-Margan, Croatian Public Health Institute, Department of Epidemiology of Infectious Diseases, Zagreb
Hungary	Márta Melles, 'Johan Béla' National Centre for Epidemiology, Budapest
Luxembourg	Robert Hemmer, National Service of Infectious Diseases, Centre Hospitalier de Luxembourg, Luxembourg
Macedonia	Kristin Vasilevska, Medical Faculty Skopje, University 'Sv. Kiril i Metodij' Institute of Epidemiology, Biostatistics and Medical Informatics, Skopje
Spain	Luiza Sanchez Serrano, Sección de Sistema de Información Microbiológica, Vigilancia de Salud Pública, National Centre of Edpidemiology, Hospital Carlos III, Madrid
Serbia-Montenegro	Danica Masanovic, Sanitary Inspection of the Ministry of Health of Montenegro, Podgorica

event. The survey included questions about the objective of the surveillance system, the description of the health event under surveillance (case definition), the population under surveillance, the period of data collection, who was responsible for case reporting (sources of information) and a flow chart describing the system. We also asked how often the data were analysed and fed back to the reporting sources, and for the estimated costs of the toxoplasmosis surveillance system.

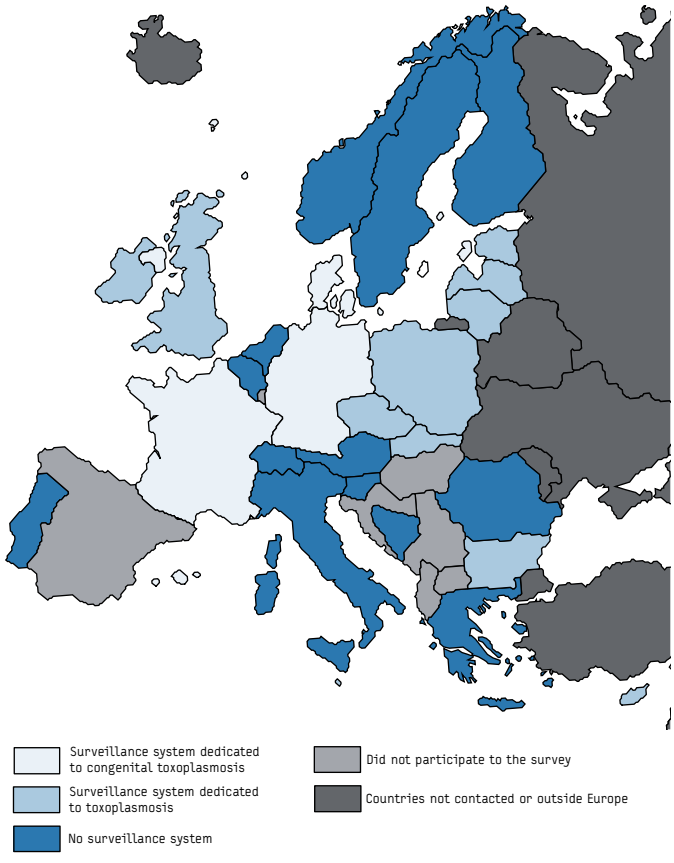
The usefulness of a given surveillance system was evaluated according to the following criteria:

- simplicity (ease of operation) , flexibility (adaptability to changing information needs or operating conditions) and acceptability (cooperation of people on whom the system depends) based on the number and qualification of the reporting sources;
- sensitivity (proportion of cases detected by the system) and representativeness (the ability to describe the distribution of cases over time and in the population) based on the qualification of the reporting sources and on the figures available from the surveillance systems;
- timeliness (delay between steps in the system) based on the frequency of analysis and reports distribution.

These criteria are described in the US CDC's guidelines (http://www.cdc.gov/mmwr/preview/mmwrhtml/00001769.htm) [4,5].

Figure

Different surveillance systems for toxoplasmosis in Europe. Eurotoxo, 2007



Results

We received responses from 28 of 35 countries. Seven countries (Albania, Luxembourg, Croatia, Hungary, the Former Yugoslav Republic of Macedonia, Serbia-Montenegro and Spain) did not send a response at all. Information on Denmark and France was updated in July 2007.

Of the 28 countries that responded, 12 did not have a surveillance system for toxoplasmosis (congenital or not). The 16 countries that did report to have a system for the epidemiological surveillance of toxoplasmosis in place, are almost all situated in central or eastern Europe (Table 2; Figure). Poland has the oldest surveillance system (dating from 1966), while the most recent systems are in Cyprus, Ireland and Malta (dating from 2004).

Only four countries operate surveillance specifically for congenital toxoplasmosis: Denmark, France, Italy and Germany.

In **Denmark**, a nationwide neonatal screening programme based on neonatal Guthrie card testing for toxoplasma-specific IgM was implemented in 1999 but discontinued on 31 July, 2007 (Petersen E; personal communication). The Danish National Health Board found insufficient evidence that treatment for toxoplasmosis was effective, neither in preventing later attacks of ocular toxoplasmosis in children born without ocular lesions nor in preventing further attacks in children born with ocular lesions [6]. In case of a positive Guthrie result, peripheral blood samples were taken from the newborn and the mother and analysed for IgM, IgA and IgG profiles. The epidemiological surveillance system was based on this screening programme and therefore included all infants with congenital toxoplasmosis, whether or not they had clinical manifestations. Surveillance and all laboratory analyses were coordinated by Statens Serum Institut in Copenhagen.

In **France**, a surveillance system for congenital toxoplasmosis was initiated in May 2007 which lies in the area of responsibility of the French National Institute of Public Health (Institut national de Veille Sanitaire; InVS) and the National Reference Centre for Toxoplasmosis (CNR toxoplasmose). The surveillance includes foetuses, newborns and children until the age of one year. Congenital toxoplasmosis cases are notifiable and defined as:

- Detection of *T. gondii* in body tissues or fluids by polymerase chain reaction (PCR), inoculation of mice, cell culture or immunocytochemistry;
- Detection of specific IgM or IgA antibodies;
- Neosynthesis of specific IgG, IgM or IgA antibodies;
- Stable specific IgG titres until after the age of one month;
- Persistently stable specific IgG titres until the age of one year.

Cases are notified by laboratories qualified for antenatal or postnatal diagnosis.

In **Germany**, congenital toxoplasmosis cases have been notifiable since 2001, when a nationwide surveillance system was implemented under the Protection Against Infection Act. The case definition of congenital toxoplasmosis is based on at least one of the following criteria:

- Demonstration of *T. gondii* in body tissues or fluids;
- Detection of specific IgM or IgA antibodies;
- Persistently stable specific IgG titres or a single elevated specific IgG-titre.

TABLE 2

Characteristics of European epidemiological surveillance programmes for toxoplasmosis. Eurotoxo, 2007

Country	Year started	Population under surveillance	Case definition	Reporting sources	Frequency of analysis	Frequency of surveillance reports	Surveillance report distribution
Surveillance systems specifically dedicated to congenital toxoplasmosis							
Denmark	1999	Live newborns	Detection of IgM on blood filter sample confirmed by IgA, IgM and IgG profile in newborn and mother	Statens Serum Institut	NA	Annually	Healthcare authorities
France	2007	Foetuses, newborns and infants	PCR, mouse inoculation, cell culture or immunocytochemistry on body tissues or fluids; detection of specific IgM or IgA antibodies; neosynthesis of specific IgG, IgM or IgA antibodies,;persistence of IgG until one year of age	Laboratories qualified for antenatal or postnatal diagnosis	NA	NA	Healthcare authorities
Germany	NA	Live newborns and infants	Detection of *Toxoplasma gondii* in body tissues or fluids; detection of specific IgM or IgA antibodies; persistently stable specific IgG titres or a single elevated specific IgG titre	Laboratories	Continuous	Quarterly and annually	Free access on the Website of the Robert Koch Institute
Italy*	1997	Live newborns	Persistence of IgG until one year of age	Social workers Paediatricians Neonatalogists	Annually	Annually	National Health Institute, physicians, Regional Public Health Surveillance on Infectious Diseases
Surveillance systems dedicated to toxoplasmosis (congenital or not)							
Bulgaria	NA	All	EU⮝ (notifiable disease)	Physicians Laboratories Epidemiologists	Annually	Monthly and annually	Ministry of Health National Centre of Health Information National Centre of Infectious and Parasitic Diseases
Cyprus	2004	All	EU⮝ (notifiable disease)	All registered medical practitioners	Weekly	Twice a year	Physicians
Czech Republic	1970	All	EU⮝ (notifiable disease)	Epidemiologists	Monthly	Monthly and annually	Epidemiologists, Physicians Laboratories
England and Wales	1975	All	EU⮝ (notifiable disease)	Toxoplasma Reference Unit Swansea	Monthly	Quarterly and annually	Electronic distribution (http://www.hpa.org.uk/hpr)
Estonia	1997	All	EU⮝ (notifiable disease)	General practitioners Laboratories	Monthly	Monthly and annually	Health protection Inspectorate and Ministry of Social Affairs
Ireland	2004	All	EU⮝ (notifiable disease)	All registered medical practitioners Laboratories	Weekly and annually	Weekly and annually	Physicians, Public health departments and population (Website)
Latvia	1995	All	EU⮝ (notifiable disease)	Physicians Epidemiologists	Annually	Monthly and annually	Ministry of Health, Physicians
Lithuania	1992✦	All	EU⮝ (notifiable disease)	All registered medical practitioners	Monthly and annually	Monthly and annually	Territorial healthcare institutions, Ministry of Health, European surveillance networks, WHO
Malta	2004	All	EU⮝ (notifiable disease)	Physicians Laboratories	Continuous	Weekly, monthly and annually	Physicians, Ministry of Health, WHO
Poland	1966♦	All	EU⮝ (notifiable disease)	Physicians	Occasionally	Quarterly and annually	Public administrations, research institutions, sanitary stations
Scotland	1988	All	EU⮝ (notifiable disease)	Laboratories	Continuous	Available on Website	Free access for all (on demand)
Slovakia	1975	All	EU⮝ (notifiable disease)	Physicians	Monthly and annually	Monthly and annually	Physicians, Ministry of Health

NA: Not available; WHO: World Health Organization;
⮝ as defined by the European Union
* Regional surveillance system (Campania county)
✦ Distinction between acquired and congenital toxoplasmosis since 1999
♦ Distinction between acquired and congenital toxoplasmosis since 1997.

Laboratories report anonymised cases to the Robert Koch institute in Berlin. Part of the data can be accessed at http://www3.rki.de/SurvStat/QueryForm.aspx. Quarterly summaries and yearly reports are also published [7].

In **Italy**, surveillance is confined to a regional programme in the Campania region, which has been running since 1997. The population under surveillance are living newborn babies. A case of congenital toxoplasmosis in defined as the persistence of specific IgG antibodies until the age of one year. Cases are reported by social workers, paediatricians and neonatalogists. Information about toxoplasmosis primary infection among pregnant women is collected retrospectively on medical records, and information about congenital toxoplasmosis and complications among congenitally infected children are collected prospectively. The creation of a nationwide surveillance system is still being debated.

In the 12 other countries (Bulgaria, Cyprus, Czech Republic, England and Wales, Estonia, Ireland, Latvia, Lithuania, Malta, Poland, Scotland, and Slovakia, see Table 2), the health event under surveillance is toxoplasmosis (congenital or not), as defined by the European Union (symptomatic toxoplasmosis cases serologically confirmed) [8]. It is considered a notifiable disease and subject to continuous data collection (Table 2). Cases are reported by physicians, epidemiologists, or laboratories. Several sources of reporting contribute to the systems, except in Cyprus, Lithuania, Poland and Slovakia, where the physicians are the only health professionals to report cases, and in the Czech Republic and Scotland, where cases are declared only by epidemiologists and laboratories, respectively.

All 16 surveillance systems analyse the data regularly (from daily to annually). The reports are sent to the health authorities weekly to annually.

Only two countries were able to provide data about the costs of the system. In Italy, the global cost of the regional pilot programme is estimated to be 68,000 Euros a year for 67,000 to 70,000 live births. In Denmark, the cost of the nationwide surveillance system was estimated to be 600,000 Euros a year.

Discussion

Our study provides detailed, up-to-date information on systems implemented for the surveillance of toxoplasmosis (congenital or not) in 28 European countries. We have identified a high degree of heterogeneity.

12 countries do not have any surveillance system for toxoplasmosis in place. In 12 countries, the event under surveillance was symptomatic toxoplasmosis. Five of those countries did not provide details about the qualification of the physicians who reported the information. In the field of toxoplasmosis, gynaecologists, ophthalmologists, paediatricians or neurologists are able to diagnose toxoplasmosis at different stages of the disease. Therefore, it is important that all those specialists take part in the surveillance process. However, toxoplasmosis is a notifiable disease in all those countries, and we assume that all registered medical practitioners are involved in the surveillance system.

Denmark, France, Germany, and Italy (the latter only at regional level), are the only participating European countries who have implemented a surveillance system that is specifically dedicated to congenital toxoplasmosis and that is able to detect symptomatic as well as asymptomatic cases. Systems which survey symptomatic toxoplasmosis in the general population are of least interest because it is impossible to distinguish congenital from acquired toxoplasmosis without data on the serological status during pregnancy or at birth [9]. Furthermore, the vast majority of acquired toxoplasmosis infections in healthy individuals are benign and the proportion of asymptomatic cases is estimated to be 70% [10-13].

Differences in the structure of these four specific surveillance systems may be responsible for differences in their usefulness. We consider the surveillance system in Denmark to be simpler than those in Italy, Germany, and France. Centralised analysis like in Denmark and France also increases the acceptability as the system relies on professionals specifically dedicated to the system, contrary to the systems in Italy and Germany where the tasks are divided between health professionals and laboratories. The Danish surveillance system could also be considered the most flexible, because of its centralised approach, which allows for changes to be implemented in only one place, should they become necessary.

In Denmark, the surveillance system was linked to a nationwide systematic neonatal screening [14]. The sensitivity and the representativeness of this system could thus be considered higher than in Germany where the surveillance system is suffering from an underestimation of the number of congenital toxoplasmosis cases. Data on the number of congenital toxoplasmosis cases detected by the two surveillance systems were available for 2001 and 2002. In Germany, 38 cases were reported 2001 and 18 in 2002 (http://www3.rki.de/SurvStat/QueryForm.aspx) among a population of 82 million inhabitants, compared to 19 cases in 2001 and 13 in 2002 in Denmark (5.4 million inhabitants) [14]. According to these data, the estimated frequency of congenital toxoplasmosis is ten-fold lower in Germany than in Denmark. Based on what is known about the geographical variation of the burden of congenital toxoplasmosis, this is unlikely.

In Italy, congenital toxoplasmosis cases are declared by social workers, paediatricians and neonatalogists. It is well known that passive reporting by physicians only captures a fraction of cases, most often only the most serious ones [15,16].

Overall, we consider the epidemiological surveillance system that was implemented in Denmark be the most useful. However, it was discontinued in July 2007.

A European survey was conducted within the EUROTOXO initiative to describe the national public health policies and routine programmes to prevent congenital Toxoplasmosis [17]. One of the fundamental criteria to evaluate the efficiency of such programmes is the frequency of the prevented disease. Some countries did not define congenital toxoplasmosis as a public health issue and consequently have not implemented a prevention programme or surveillance system.

Several countries that do not have a congenital toxoplasmosis prevention policy have nevertheless defined congenital toxoplasmosis as a public health issue and implemented a surveillance system. But of these countries only Germany has implemented a system specifically dedicated to congenital toxoplasmosis.

Austria, Denmark, France, Italy, Lithuania and Slovenia have defined congenital toxoplasmosis as a public health issue and implemented a national systematic prevention programme [17]. Among these six countries, Denmark and France are the only

countries where a specific and exhaustive surveillance system of congenital toxoplasmosis was implemented. However, screening and surveillance in Denmark were stopped in July 2007 and in France has only existed since May 2007, 29 years after the implementation of the national screening programme.

In the absence of a dedicated surveillance system, data on the burden of a disease can be obtained only through ad hoc epidemiological surveys. A systematic review of the published data on the burden of congenital toxoplasmosis was conducted by the EUROTOXO study group in 2005 [18]. The main results of this review were the following: Firstly, the prevalence of toxoplasmosis among pregnant women (the reservoir of congenital toxoplasmosis) decreases over the years, as previously reported. Due to limited available data, other epidemiological parameters such as incidence of seroconversion in susceptible pregnant women or incidence of complications among congenitally infected children cannot be analysed in detail. Such accurate data on the trends of diseases can only be obtained through continuous data collection such as surveillance systems.

Secondly, published data on the burden of congenital toxoplasmosis in Europe are limited, in terms of both quantity and quality. In fact, the vast majority of surveys evaluated by the group were not representative, in particular with respect to rare events such as the incidence of complications among congenitally infected children. For these estimates to be sufficiently precise, children were recruited in specialised centres. Such representative estimates could be improved by systematic data collection, for example as part of a surveillance system.

Nevertheless, periodic snapshot surveys based on consistent reporting definitions can also be an effective way of determining the burden of congenital toxoplasmosis. This is the approach used in the United Kingdom for symptomatic toxoplasmosis in children through the British Paediatric Surveillance Unit and the British Ophthalmic Surveillance Unit [9].

Few countries in Europe have implemented specific surveillance systems in accordance with their prevention policies regarding congenital toxoplasmosis. The epidemiological surveillance of congenital toxoplasmosis needs to be improved in order to determine the true burden of disease and assess the need for and effectiveness of existing prevention programmes.

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Salmonella infections associated with reptiles: the current situation in Europe

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Salmonella infections are caused by consumption of contaminated food, person-to-person transmission, waterborne transmission and numerous environmental and animal exposures. Specifically, reptiles and other cold blooded animals (often referred to as "exotic pets") can act as reservoirs of *Salmonella*, and cases of infection have been associated with direct or indirect contact with these animals. Approximately 1.4 million human cases of *Salmonella* infection occur each year in the United States and it has been estimated that 74,000 are a result of exposure to reptiles and amphibians [1]. Regular case reports of reptile-associated salmonellosis in the US are available for the period 1994-2002 [2-4]. Cases of *Salmonella* infection attributed to direct or indirect contact with reptiles or other exotic pets have been described in a number of European countries, too [5-16] but a more comprehensive overview of the magnitude of this problem in Europe is lacking. In total, 160,649 human cases of salmonellosis were reported in 2006 in the then 25 European Union Member States, Bulgaria, Romania, Iceland, Liechtenstein and Norway [17].

Methods

Following the publication in Eurosurveillance of a recent report on reptile-associated salmonellosis in residents in the south east of Ireland 2005–2007 [16], a quick survey was circulated among our journal's editorial advisors to collect data on the occurrence of such cases in other European countries. We asked whether there have been reported cases of salmonellosis attributed to exposure to reptiles or other exotic pets in their country in the past three years and, if yes, to provide data on the age of cases, animals involved and *Salmonella* serovars associated. The results of our inquiry do not aspire to being exhaustive. Rather, we hope to inspire further investigations and receive more comments and reports on this topic from other European countries.

Results

Belgium

Since 2005, approximately 3,000 to 5,000 human *Salmonella* infections have been detected annually in Belgium [18]. The majority of these infections are food-borne, but sporadic cases acquired by contact with animals have also been reported.

A case of a four-month-old girl who suffered of septicaemia due to *Salmonella enterica* serovar Pomona was described in 2007. The source of infection was established to be the family's pet turtle [14].

In April 2008, three cases of infection with *S. enterica* subspecies arizonae (*S. enterica* subspecies IIIa 41:z4,z23:-), all three associated with exposure to snakes were reported. Two infants, both females, aged one month and two months, and a 57-year-old woman, receiving renal dialysis, were infected. The Belgian Heath Inspectorate investigated the cases and conducted interviews with the adult patient and the parents of the affected children. The three cases were not geographically linked. All patients had only indirect contact with snakes. The snakes had been family pets for three weeks to approximately five years before illness onset. The three isolates were not clonally related as determined by pulsed-field gel electrophoresis and were susceptible to all antibiotics tested.

The two infants recovered without antibiotic treatment. However, the 57-year-old woman was hospitalised and the use of antibiotics was necessary.

Finland

Annually, from 2,300 to 3,000 cases of salmonellosis are reported to the National Infectious Disease Registry (NIDR) in Finland [19]. Less than 20% of the cases are considered domestically acquired. During 2005–2008, three cases of salmonellosis (S. enterica serovar Paratyphi B biovar Java 4,5,12:b:1,2, *S. enterica* serovar Morehead 30:i:1,5 and *S. enterica* subspecies diarizonae 47:-:-) associated with pet snake were reported: a 50-year-old female, a seven-month-old girl and a 10-month-old boy. None of the cases had previous travel history. The findings above were based on additional information available from laboratory notifications since the suspected source of *Salmonella* infection is not reportable to NIDR. The *Salmonella* status of the animals is not known.

In 2005, a family outbreak of *S. enterica* serovar Braenderup 6,7:e,h:e,n,z15 associated with a pet turtle was detected. Six cases were identified: four males aged from 11 months to 39 years and

two females aged six years and 56 years. All cases and the turtle were tested positive for S. Braenderup.

France

In France, three reptile-associated cases of *Salmonella* infection were identified in the past three years: two cases in 2005 and one, imported from China, in 2006. The patients were all young children, aged eight months, three years and four years, respectively. They were infected with a multi-resistant strain of *S. enterica* serovar Typhimurium. The first two cases had contact with, respectively, a snake and an iguana; in the third case an indirect link to turtle (consumption of turtle soup) was found. In France, information about exposures at risk of infection is not systematically available through the surveillance system. Exposure information is obtained when an investigation is carried out usually because of the occurrence of a cluster. Therefore, it is likely that the occurrence of reptile-associated cases in France is underestimated.

Germany

An increasing number of human cases of *Salmonella* infection associated with reptiles have been reported in Germany in the past three years [20]. The majority of cases were detected retrospectively, after serotyping of the *Salmonella* strains. According to the standard procedures, in case of an infant infected by *S. enterica* subspecies II-IV the National Reference Laboratory informs the local health authorities about the possibility of transmission of an exotic *Salmonella* strain from reptile to child. In many such cases subsequent telephone interviews conducted by the local health authorities with the parents of the infected children have revealed direct or indirect contact to reptiles living in the same household.

Although infections in adults with contact to reptiles have been reported, in most cases infants less than one year old were affected. Some children had to be hospitalised. The age of cases and the serovars with antigen formula are shown in Table 1.

The youngest child affected was an eight-week-old female baby with acute haemorrhagic diarrhoea and fever. With symptomatic treatment and breastfeeding, her condition improved without antibiotic therapy. Microbiological analysis and subtyping identified infection with *S. enterica* serovar Pomona. The source of the infection was found to be a bearded dragon (Pogona species) living in a neighbourhood household. Monitoring of the child showed shedding of the bacterium over a nine month period [21].

An investigation of *Salmonella* infection in five-month-old triplets living with two reptiles in the household revealed that the animals harboured a population of concurrent *Salmonella* serovars. In the children, *S. enterica* subspecies I, serovar Apapa was identified. From the reptiles, S. Apapa was isolated along with three other serovars: *S. enterica* subspecies II 58:c:z6, *S. enterica* subspecies II 47:d:z39 and *S. enterica* serovar Tennessee [Robert Koch Institute, Wernigerode Branch, unpublished]. All these serovars are pathogenic to humans.

Ireland

At least 14 cases of salmonellosis associated with reptile contact have been identified in Ireland over the last three years (Table 2). Six cases in south east Ireland have been described previously [16], information on the remaining cases was obtained by writing to the Directors of Public Health in the eight regions (replies received from two), from searching the national infectious disease system database (Computerised Infectious Disease Reporting - CIDR), and from the National *Salmonella* Reference Laboratory. It cannot be considered comprehensive but is an indicator that the problem of salmonellosis transmission from pet reptiles is present in Ireland.

Latvia

In Latvia, there have been no cases of salmonellosis associated with direct or indirect exposure to reptiles during the past three years, except a single case of *S. enterica* serovar Stanley reported earlier this year in a two-year-old child. The source of infection was established to be pet food used for reptiles which the child had often put in his mouth. S. Stanley was isolated from food sample. Other countries were notified about the possibility of pet food contamination through the early warning response system (EWRS). In Latvia, exposure to pet food is now considered to be an additional risk factor of infection in small children and it has to be taken into account during investigation of salmonellosis cases.

The Netherlands

Salmonellosis is not a notifiable disease in the Netherlands and no information is recorded routinely with regard to the (probable) source of infection. However, the National and European Reference Laboratory (CRL) for *Salmonella* at the Dutch National Institute for Public Health and the Environment (RIVM) identifies all the isolates sent in from humans (mostly from regional public health laboratories - PHLs) and farm animals, from food, animal food, pet animals and from the environment [22]. Since 1984, this has covered typing results for over 200,000 isolates of 1,143 serovars and phagetypes (of Enteritidis and Typhimurium only). Over 2,200 isolates have been derived from reptiles and amphibians typically sent in by zoos (Table 3). The majority of these isolates were found to belong to the subspecies II (salamae), IIIa (arizonae), IIIb (diarizonae), VI (houtenae) and a few to S. bongori (before 1987, S. subsp. V, now own species) or VI (indica) but a sizable number of specific serovars from subspecies enterica (subspecies I) were identified as well.

Attribution techniques comparable to those used in Denmark [23,24] were used to estimate the fraction of isolates derived from humans that could be accounted for by exposure to reptiles or amphibians, broilers, layers/eggs, pigs, cattle, large explosions, travel or miscellaneous sources. Of 15,146 cases of laboratory-confirmed salmonellosis sent in by the PHLs (64% coverage of the Dutch population) between 2000 and 2007, an estimate of 103 could be associated with reptiles or amphibians, presumably by direct or indirect contact (Figure). While laboratory-confirmed salmonellosis from humans dropped dramatically in the eighties of the past century and gradually decreased afterwards, the absolute number of isolates attributed to exposure to reptiles and amphibians clearly increased in the new millennium although was still <1% of all human cases of salmonellosis in 2007. It can be concluded that the importance of *Salmonella* infections related to reptiles and amphibians in the Netherlands is minor but has increased in recent years.

Other

We received also responses from Austria, Bulgaria, Estonia, Luxembourg, Malta, Norway, Portugal, Romania and Spain reporting no known human cases of salmonellosis associated with reptiles and other exotic pets. However, often information on this kind of exposure is not available in the notification data. In addition, it is worth noting that in Norway it is forbidden to have reptiles as pets except with a special permit.

Table 1

***Salmonella* infections with known exposure to reptiles in Germany from 2006 to date (as of 24 May 2008)**

Year of notification	Gender	Age	*Salmonella* subspecies, serovar, antigen formula	Associated reptile contact
2006	F	2 months	*Salmonella enterica* subspecies IV, 45:g,z_{51}:-	Bearded dragon
2006	F	6 months	*Salmonella enterica* subspecies IV, 48:g,z_{51}:- (former *S.* Marina)	Gecko
2006	F	2 years	*Salmonella enterica* subspecies II, 50:z:z_{23}	Iguana
2006	M	2 months	*Salmonella enterica* subspecies IV, 50:g,z_{51}:-	Snake
2006	M	1 year	*Salmonella enterica* subspecies II, 58:c:z_{6}	Reptile
2006	M	42 years	*Salmonella enterica* subspecies IV, 44:-:-	Reptile
2006	M	25 years	*Salmonella enterica* subspecies IIIb, 47:i:z_{53}	Snake
2006	F	25 years	*Salmonella enterica* subspecies IIIb, 50:z:z_{23}	Snake
2006	M	3 months	*Salmonella enterica* subspecies IV, 44:z_{4},z_{23}:-	Snake
2006	F	8 weeks	*Salmonella enterica* subspecies I, serovar Pomona 28:y:1,7	Bearded dragon
2006	F	8 months	*Salmonella enterica* subspecies IIIa, 41:z_{4},z_{23}:-	Snake
2006		3x5 months (triplets)	*Salmonella enterica* subspecies I, serovar Apapa, 45:m,t:-	Bearded dragon
2007	F	8 months	*Salmonella enterica* subspecies II, 47:d:z_{39}	Bearded dragon
2007	F	24 years	*Salmonella enterica* subspecies IIIa, 41:z_{4},z_{23}:-	Snake
2007	F	20 years	*Salmonella enterica* subspecies IV, 45:g,z_{51}:-	Gecko
2007	F	29 years	*Salmonella enterica* subspecies II, 58:-:1,6	Bearded dragon
2007	M	4 months	*Salmonella enterica* subspecies IV, 44:z_{4},z_{23}:-	Snake
2008	M	7 months	*Salmonella enterica* subspecies IIIb, 53:z_{10}:-	Snake
2008	M	8 months	*Salmonella enterica* subspecies II, 58:lz_{13},z_{28}:z_{6}	Bearded dragon
2008	F	16 months	*Salmonella enterica* subspecies IIIb, 61:l,v:1,5,7	Snake
2008	F	42 years	*Salmonella enterica* subspecies I, serovar Ago 30:z_{38}:-	Bearded dragon
2008	F	47 years	*Salmonella enterica* subspecies IV, 44:z_{4},z_{23}:-	Bearded dragon
2008	M	29 years	*Salmonella enterica* subspecies IV, 50:r:z_{35}	Snake
2008	F	47 years	*Salmonella enterica* subspecies IIIb, 61:z_{52}:z_{53}	Snake
2008	M	7 months	*Salmonella enterica* subspecies I, serovar Poona, 13,22:z:1,6	Snake
2008	F	11 months	*Salmonella enterica* subspecies I, serovar Gaminara, 16:d:1,7	Bearded dragon
2008	M	3 years and 9 months	*Salmonella enterica* subspecies I, serovar Jangwani, 17:a:1,5	Reptile
2008	F	8 months	*Salmonella enterica* subspecies IV, 18:$z_{36}$$z_{38}$:-	Iguana
2008	F	17 months	*Salmonella enterica* subspecies I, 28:y:1,7	Turtle
2008	M	8 weeks	*Salmonella enterica* subspecies II, 35:g,m,s:-	Bearded dragon or chamaeleon
2008	F	2 months	*Salmonella enterica* subspecies IV, 44:z_{4},z_{23}:-	Snake or bearded dragon

Data source: National Reference Centre of Salmonella and other Enterics, Wernigerode, Germany

Table 2

***Salmonella* infections with known exposure to reptiles and other exotic pets in Ireland from 2005 to date (as of 16 May 2008)**

Year of notification	Gender	Age	Organism Description	Associated reptile contact
2005	M	11 years	*Salmonella enterica* subspecies I, serovar Minnesota	Pet iguana
2006	M	12 years	*Salmonella enterica* subspecies I, serovar Monschaui	Pet iguana
2006	F	15 years	*Salmonella enterica* subspecies I, serovar Enteritidis PT21	Pet terrapin
2006	M	6 months	*Salmonella enterica* subspecies IIIb (*diarizonae*)	Parents have pet snakes
2007	M	4 months	*Salmonella enterica* subspecies I, serovar Pomona	Contact with Terrapins
2007	M	4 weeks	*Salmonella enterica* subspecies IIIa (*arizonae*)	Parent has pet snake. Child visited reptile farm with parent
2006	F	8 months	*Salmonella enterica* subspecies I, serovar Florida	Reptile owner
2007	M	36 years	*Salmonella enterica* subspecies I, serovar Paratyphi B biovar Java	Contact with birds and tropical fish
2007	M	1 month	*Salmonella enterica* subspecies I, serovar Stanley	Lizard
2008	F	3 months	*Salmonella enterica* subspecies I, serovar Infantis	Turtles in house
2008	F	9 months	*Salmonella enterica* subspecies I, serovar Thompson	Terrapins. Swabs from terrapin tank also positive for Salmonella Thompson
2008	F	1 month	*Salmonella enterica* subspecies I, serovar Pomona	Terrapins
2008	M	50 years	*Salmonella enterica* subspecies I, serovar Infantis	Contact with turtles, terrapins, lizards, other reptiles
2008	F	23 years	*Salmonella* species	Keeps reptiles and exotic rodents as pets

Note: The first six cases were already described in another paper [16]

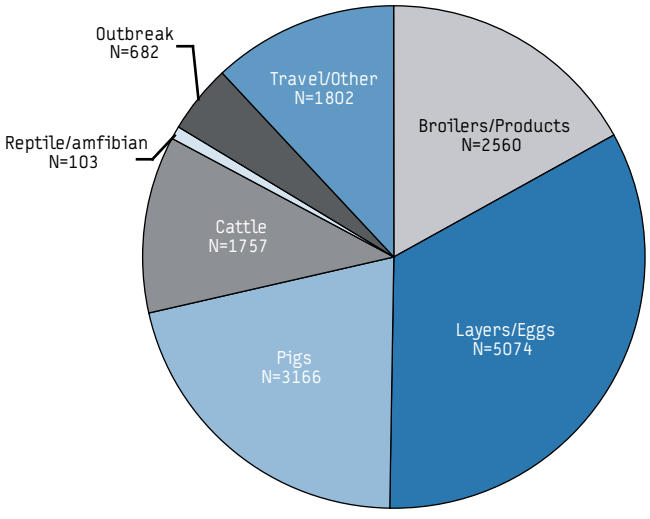
Table 3

Isolates received and typed at the Netherlands' National Institute for public health and the environment (RIVM) between 1984 and 2007, human cases and reptiles and amphibians

S. enterica subspecies	serovar	human	reptile/ amphibian
***enterica* (I)**	Typhimurium	31,602	61
	Enteridis	20,543	22
	Typhi	1,086	--
	Paratyphi A/B/C	379	--
	Other serovars	22,705	848
***salamae* (II)**		32	274
***arizonae* (IIIa)**		16	196
***diarizonae* (IIIb)**		33	569
***houtenae* (IV)**		16	289
***bongori/indica* (V/VI)**		3	3

Figure

Estimated source origin of human cases of salmonellosis in the Netherlands between 2000 and 2007, using attribution analysis of typing data (n=15,146 isolates)



2000-2007
(15,146 isolates from human cases)

Discussion

Data presented in this paper is far from complete and uniform. Due to differences in surveillance systems, the information on the probable source of *Salmonella* infection varies greatly across countries, and this is reflected in the above contributions from various countries. For example, in the Netherlands where salmonellosis is not subject to mandatory notification, the estimate of the proportion of cases due to contact with reptiles and amphibians was based on typing results from the national reference laboratory. In most countries, although cases of salmonellosis are reported within the national surveillance system, the source of infection is not routinely given, and the possible exposure to reptiles is usually revealed in the course of additional epidemiological investigation following the results of laboratory testing. The true number of cases due to direct or indirect contact with these animals is thus likely to be underestimated.

The prevalence of infants below one year of age among cases associated with exotic pets may be partly due to the bias in investigating these cases of salmonellosis more thoroughly. Nevertheless, small children should be considered to be at an increased risk of infection, and targeted specifically by recommendations. All the more so, considering evidence of the serious complications including sepsis and meningitis in children who acquired salmonellosis from reptiles [2-5,14].

An important subject not tackled by this paper is the problem of antibiotic resistance. It would be interesting to collect and analyse available data on antibiotic resistance of strains associated with this kind of transmission but such investigation would have surpassed the scope of the present article.

Conclusion

The present article and earlier publications [5-16] indicate that although known cases attributed to exposure to reptiles and other exotic pets may constitute a small proportion of all human cases of salmonellosis, it is likely to be an underestimated but growing problem that merits more attention. The number of pet reptiles is steadily increasing in some European countries. For example, in Germany in 2007, more than 500,000 reptiles were imported through the airport in Frankfurt am Main [18]. Reptiles are known to shed *Salmonella* frequently. They are pathogenic to humans and reptile-associated salmonellosis is being recognised as an emerging zoonosis.

Import restrictions and public information campaigns were shown to be effective public health measures against reptile-associated salmonellosis in Sweden [10]. In the US, the Association of Reptilian and Amphibian Veterinarians (ARAV) produced guidelines for reducing the risk of transmission of *Salmonella* from reptiles to humans, including a client education handout distributed at the points of sale of these animals [25]. Also, the US Centers for Disease Control and Prevention (CDC) published recommendations which include washing hands with soap and water after handling reptiles or their cages and keeping reptiles out of food preparation areas. The CDC also advises that pregnant women and young children should not have reptiles as pets [4].

In Europe recommendations related to the handling of reptiles and other exotic pets exist in the veterinary sector but it appears that agreed guidelines on prevention of salmonellosis transmission from reptiles to humans should be extended to the field of public health, and target health professionals as well as the general public. The public needs to be made aware of the possibility of acquiring infection from exotic pets, and it is important that physicians and public health experts consider this way of transmission when investigating cases.

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Tick-borne encephalitis in Europe and beyond – the epidemiological situation as of 2007

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This review presents an overview of the developments in the epidemiology of tick-borne encephalitis (TBE) during 2007 in Europe, the Far East and Asia, as well as some comments interpreting the various developments. The recent TBE situation in 29 European and four non-European countries is shown and discussed. The number of registered TBE cases from 1976 to 2007 in 19 European countries with endemic TBE is presented.
Although criteria for TBE reporting vary from one country to another and it is necessary to account for unreported cases, an overall increase of TBE incidence during the last 30 years can clearly be established. Besides changes in climate and weather, a number of additional factors are probably responsible for this rise: increased exposition, partly due to socio-economical and political changes, and other factors that are for the most part unknown. In addition, the immunisation coverage in the population of some of the countries is discussed.

Introduction

In this article, we provide an overview on the epidemiology of tick-borne encephalitis (TBE) in Europe, the Far East, and Asia as of 2007, and comment briefly on the situation. We refer to the extensive overview on this subject compiled in 2003 [1], which includes all available data up to 2001, and the overview of 2005 [2], which summarises the epidemiology of TBE up to 2004.

The epidemiology of TBE in Europe

Over the last 30 years, a continuous increase in TBE morbidity – 400% from 1974 to 2003 – was observed in Europe [3]. From 2004 to 2006, another considerable increase was seen in a series of TBE-endemic countries, such as the Czech Republic, Germany, Slovenia, Sweden and Switzerland. In addition to social, political, ecological, economic, and demographic factors, changing climate conditions may have created more favourable living conditions for ticks and thus led to a further spread of tick-borne diseases [4-8]. A continuous increase of the average temperatures and of the precipitations leads to increased humidity and improves the living conditions of ticks. For example in Germany there was an increase in the average temperatures of over 0.6 to 1.5°C from 1951 to 2000 (prognosis 2001 to 2055 >1.8°C) and rainfall has increased annually by 9%, = 90 mm [9]. Data show that the winter activity of ticks increases [10,11], that their life cycle accelerates [12,13], that they are found at higher and higher altitudes above sea level [14,15] and that they can be found in more northern regions [16-19, Jeskelainen pers. comm.].

TBE is a notifiable disease in 16 European countries, including 13 European Union (EU) Member States (Austria, the Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Latvia, Lithuania, Poland, Slovak Republic, Slovenia, Sweden) and three non-EU Member States (Norway, Russia and Switzerland) [20].

At present, TBE is not notifiable in Belgium, France, Italy, Portugal, Spain, Denmark, and the Netherlands. In Belgium, Portugal, Spain, Denmark (cases on Bornholm only) and the Netherlands, no authochthonous TBE cases were reported; the reasons are largely unknown.

Figure 1 lists the number of TBE cases for 19 European countries in which TBE is endemic and which report reliable data from 1976 to 2007. We have tried to assess the situation as a whole, despite being aware of the fact that the registration procedure for TBE cases is different in the individual countries, that in some countries the disease is not notifiable and that different case definitions for TBE are applied, In countries without notification of TBE cases some research groups register the TBE cases. We also know that there are significant differences in the quality and quantity of the diagnostics in individual countries. In some countries, a high number of under-reporting/ under-diagnosing must be expected. In highly endemic areas where the majority of the population is vaccinated against TBE, as is the case in Austria, the number of reported cases of TBE does not adequately reflect the real risk of infection.

In these countries, between 1990 and 2007 a total of 157,584 TBE cases were documented; in Europe without Russia a total of 50,486 cases. This is an average of 8,755 cases per year in Europe within this 18-year period, or 2,805 cases in Europe excluding Russia. Between 1976 and 1989, a total of 38,572 cases in Europe and of 20,328 cases in Europe excluding Russia were registered, an average of 2,755 per year including Russia and 1,452 in Europe excluding Russia. A comparison of the two time periods shows an increase in registered TBE cases to 317.8% in Europe and to 193.2% in Europe excluding Russia. This clearly demonstrates the importance of this disease for the individual as well as for the healthcare systems of these countries and shows a significant increase in the number of registered TBE cases since 1990.

In 2006, 3,914 cases were reported in Europe (7,424 if Russia is included). This was the highest value since 1995. In 2007,

the number of registered cases in Europe fell to 2,364 (5,462 if Russia is included). This is a reduction of 60.4 %. This decrease was observed in nearly all European countries (Croatia, Czech Republic, Estonia, Germany, Lithuania, Poland, Russia, Slovak Republic, Slovenia and Switzerland), with the exception of Sweden, Norway, and Hungary, where a further increase of incidence was observed, and Latvia, where the numbers stabilised at the low level of 2006. It should be noted, however, that more attention to the disease may have led to a higher number of registered cases in these countries.

Possible factors influencing the epidemiology

The reasons for the increase of TBE cases over a period of 30 years throughout Europe and their decrease in most of the countries in 2007 are unknown. However, there may be an association with the exceptional weather conditions in 2007 (in Central Europe). After the extremely warm winter 2006/07, the ticks were active very early in the year (February/early March) and had certainly lost some of their energy due to their constant activity. The urgently required search for a host for a blood meal, however, was hampered in April by the extremely warm and dry weather conditions. As a rule, the ticks had to retreat to the leaf litter as a humidity reservoir. In the summer of 2007, strong precipitations led to a reduced exposure of humans due to a reduced rate of outdoor activities. It is also supposed that the development cycle (larva-nymph) of *Ixodes ricinus* was changed in a so far unknown way by the mild winter and the weather conditions that followed [13].

These extreme fluctuations in the morbidity of TBE within two years which were observed in most European countries can neither be explained by weather phenomena only nor by the very sophisticated models published by the working group of S.E. Randolph [5-7,21]. At present, an explanation for this almost uniform trend in geographically distant countries with different climatic, microclimatic and weather conditions and with completely different political and socioeconomic structures remains to be found.

Even if we regard the epidemiology of TBE from 1976 to 2007 in general, most questions remain to be answered. Thus, the political turnaround and the resulting socioeconomic changes and changes in the behavioural pattern of the exposed population in the former Eastern Bloc at the beginning of the 1990s [5] certainly are a significant influence factor. However, this does not explain the similar development, the strong increase in the number of TBE cases since the 1990s, in Sweden, Italy, Hungary, Finland and Germany. As a result, the TBE incidence in the German risk areas shows the same trend as in the Baltic States; the political turnaround, however, only took place in the eastern part of the country, where TBE incidence is very low compared to southern Germany and the influence on the total number of registered cases consequently is very low. The strong reduction of the incidence in Russia since 1999 cannot be interpreted either.

Clinical presentation of TBE

TBE usually takes one of three clinical courses: complete recovery within two months, occurring in approximately one quarter of patients; protracted, mainly cognitive dysfunction; or persisting spinal nerve paralysis with or without other post-encephalitic symptoms. Up to 46% of patients are left with permanent sequelae at long-time follow-up, the most commonly reported residuals being various cognitive or neuropsychiatric complaints, balance disorders, headache, dysphasia, hearing defects, and spinal paralysis [22].

Long-lasting or lifelong damage and a mortality rate of 1 to 2% in Europe [22,23] in patients whose central nervous system is affected by the virus, can be prevented by relatively simple means of vaccination. Human infection with the Far Eastern subtype (previously Russian Spring Summer Encephalitis virus, RSSEV) results in the most severe form of CNS disorder with a tendency for focal meningoencephalitis or polyencephalitis to develop, accompanied by loss of consciousness and prolonged feelings of fatigue during recovery. Case-fatality rates of 20-40% have been recorded following outbreaks of RSSEV in some years [24]. According to data collected in Western Siberia over the past 20 years, TBE becomes chronic in 1.7% of patients. In the acute period, the disease in such cases usually progresses in the form of meningoencephalitis [25]. Human infections with the Siberian subtype virus in the Western Siberian region of Russia are associated with a milder acute period and a high prevalence of the non-paralytic febrile form of encephalitis. Case fatality rates rarely exceed 6-8% [24].

Prevention through vaccination

TBE can be prevented by vaccination and the quality of the vaccines and their effectivity are excellent. New reliable statistics show that with a field effectiveness of 99% (2000 to 2006) with no statistically significant difference between age groups [26] TBE vaccines have one of the highest effectiveness rates of all inactivated vaccines. The data of Heinz et al. [26] confirm the excellent performance of TBE vaccine under field conditions and provide evidence that, in Austria, about 2,800 TBE cases were prevented by vaccination in the years 2000 to 2006. These statistics clearly show the tasks of the health care systems concerned.

However, as there have repeatedly been reports of clinical TBE in vaccinated individuals over the age of 50 years, it seems increasingly important to focus future investigations not only on long-term protection after TBE booster vaccination, particularly in older-age groups, but also on low responsiveness to vaccination and T-cell immunity [27].

In addition, the economic consequences of this disease should not remain unmentioned.

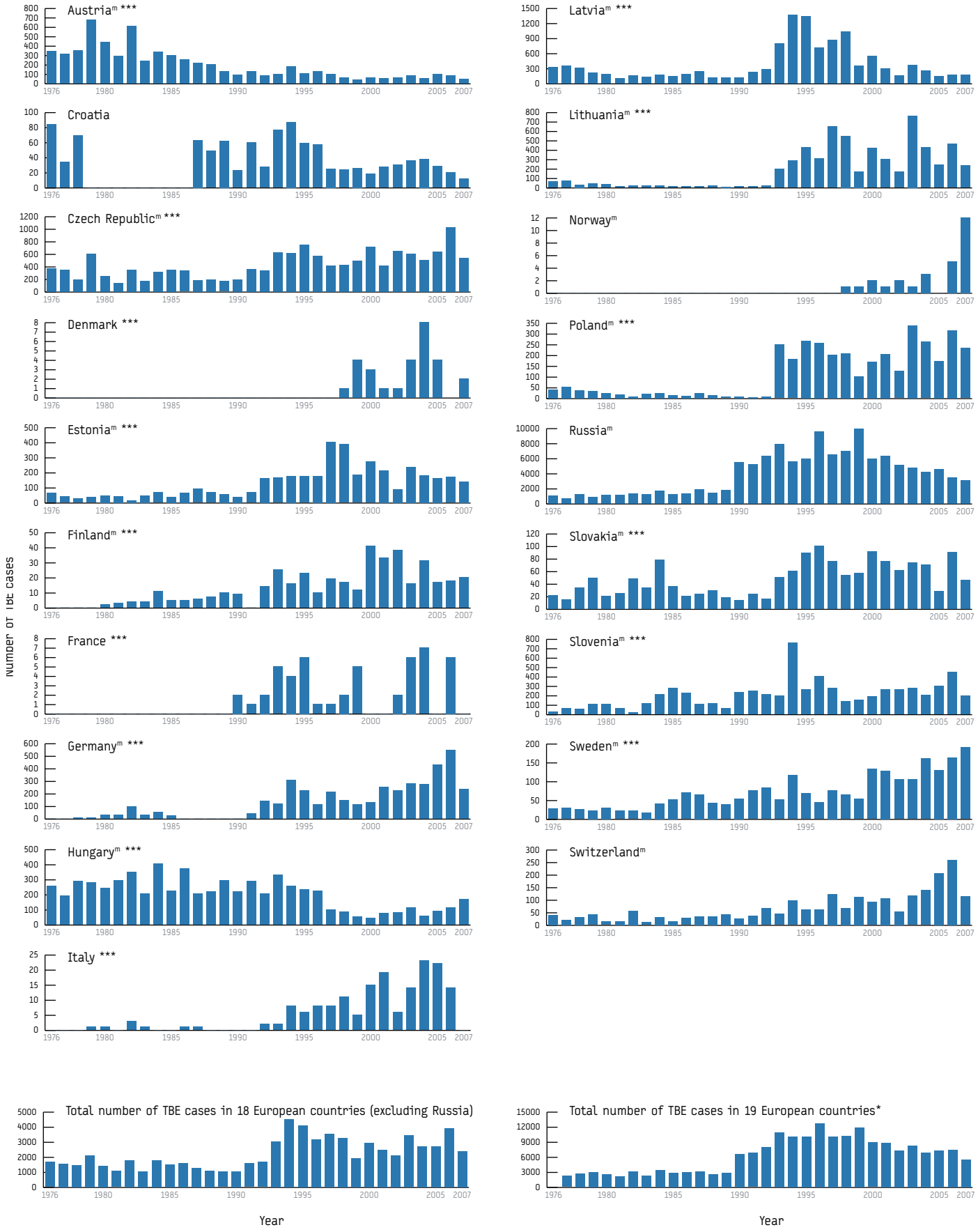
With the exception of Austria, the low TBE vaccination rate in the other countries is either not responsible at all for this lower incidence, or only marginally so. Today, 88% of Austrians have had at least one TBE vaccination, and 58% are within the officially recommended vaccination schedule [26]. With this vaccination rate, however, a massive influence on the number of cases can be seen. In the pre-vaccination era, 600 to 700 cases were registered per year, within the past 10 years the annual number has decreased to 64 [26] (Figure 1).

Vaccination coverage in the other TBE-endemic countries is low, but statistics show an increase in the number of vaccinees over the past few years.

The average vaccination rate is 38% in Latvia; between 1997 and 2006 the annual number of third-primary vaccinations (complete vaccination course) was ca. 30,000 [6]. The rate is 14% in Estonia with around 15,000 third-primary vaccinations annually between 1997 and 2006, in Lithuania 6% (around 7,500 fully

FIGURE 1

Tick-borne Encephalitis (TBE) cases in Europe 1976 – 2007, 19 TBE endemic countries* and total number of TBE cases in Europe**



* Austria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Norway, Poland, Russia, Slovakia, Slovenia, Sweden, Switzerland

** The numbers represent reported individual cases of TBE and not incidence, as in most countries the risk for TBE is restricted to some areas or regions and therefore a calculation of the incidence for the entire country might lead to false interpretations.

*** European Union Member State

m= mandatory notification

protected vaccinees annually) [6]. In Slovenia, the annual number of vaccinees who received ≥ 1 vaccine dose between 1997 and 2006 was around 15,000 [6]. The vaccination rate in Switzerland was 17% in 2007 (13% 2006), in the Czech Republic 16 % in 2007 and in Sweden 12% in 2006 and 2007 [28,29]. In Germany, 24% of the population in risk areas, not of the whole population of the country, are vaccinated [28, 29]. It should be pointed out, that in Latvia, Estonia, Lithuania, Slovenia and the Czech Republic, more or less the whole country is characterized as a risk area. These vaccine coverage data are highly preliminary and have been collected under different conditions.

These vaccination rates provide a safe protection for the vaccinated individuals, however, they hardly have any influence on the incidence. In addition, the virus circulation in the risk habitats cannot be influenced.

Recently, the knowledge on TBE in Asia has increased considerably. This is shown by reports from China, Mongolia, Japan and Korea.

The TBE situation in individual European countries

Austria

Before the annual TBE vaccination campaign was introduced in 1981, Austria had the highest recorded morbidity of TBE in Europe, with up to 700 hospitalized cases annually. The increase in vaccination coverage since 1981 has led to a steady decline in TBE. In 2007, 88% of Austrians have had at least one TBE vaccination, and 58% are within the officially recommended vaccination schedule. In the 5-year period between 2003 and 2007, an annual average of 73 cases were reported, equaling an incidence rate of 0.82 per 100,000 inhabitants. According to recent statistics, 2,800 TBE cases were prevented in Austria by vaccination between 2000 and 2006 [26].In 2003, new endemic areas were described in the region around Mattsee, Wallersee, and Thalgau north of the city of Salzburg.

New risk areas have recently been identified upstream the valleys of Inn and Isel during 2005-2006 [30] and in Ziller valley and Vorarlberg, e.g. near Feldkirch.

For an unvaccinated tourist staying in a highly endemic province of southern Austria, such as Styria, the risk of acquiring TBE has been estimated at 1 to 10,000 person-months of exposure. Based on the number of tourist overnight stays in Austria during the summer, around 60 travel-associated cases of clinical TBE can be expected to occur among visitors of Austria.

Croatia

Only one natural focus in the northern part of the country is described, i.e. between the rivers Sava and Drava. Between 1998 and 2007, the annual number of cases ranged from 12 to 38. In the five-year period between 2003 and 2007, a mean of 27 cases were reported annually.

The Czech Republic

TBE is present in all parts of the country. Between 2003 and 2007, an average of 666 TBE cases were reported annually. In 2006, there was an exceptionally sudden increase, with 1,029 registered TBE cases, i.e., the national incidence was 10/100,000, the highest level recorded so far. It is documented that this situation was significantly influenced by exceptional weather in 2006 [31]. It is remarkable that almost 500 cases were acquired during the last third of 2006. Thus, the Czech Republic is second only to Russia in terms of TBE incidence in Europe. The incidence is higher in regions south of Prague near the city of Ceske Budejovice. The incidence has constantly been high near the town of Pilsen in the western part of the country. Recently [2004, 32], TBE foci have been identified in the northern part of the province of Bohemia. In the eastern part of the country, there has been a high incidence near Olomouc.

The number of TBE cases in 2007 dropped to 542, i.e. 52.7% of the number registered in 2006.

I. ricinus and TBE virus were detected in the Bohemian Mountains at an altitude of over 1,100 metres above sea level [14]. Warm winters have led to an increased number of cases during the last third of the year.

Denmark

In Denmark only the the island of Bornholm has since long been considered a risk area for TBE. Between 2003 and 2007, 18 cases of TBE were reported on Bornholm. Four cases were notified in 2003, and eight in 2005. The minimum level of prevalence of TBEV in ticks on Bornholm is similar to that found in other European countries where TBEV is endemic.

Estonia

Between 2003 and 2007, 179 cases were reported in Estonia on average annually. The highest TBE distribution rates are seen in western Estonia (Pärnumaa, Läänemaa), eastern Estonia (Ida-Virumaa), on Saaremaa (island in the west), and in south-eastern Estonia (Polvamaa, Tartumaa). Between 2004 and 2007, the TBE incidence ranged between 10.4 (2007) and 13.5 (2004).

Finland

Between 2003 and 2007, an average of 20 cases were reported annually in Finland, with a record number of 41 cases in 2000. The known endemic areas are situated mainly on the Åland archipelago (66% of 125 cases reported between 1987 to 1997, 80 per 100,000 inhabitants in 2000), the archipelago of Turku (10%), and in the Kokkola (6%) and Lappeenranta regions (5%). In 2001 [33], nine cases were identified on an island close to the city of Helsinki. Finland has the northernmost occurrence of the TBE virus.

France

Single cases have been reported from the Alsace region, and from the region Nancy, Lorraine. In 2002, cases were reported from Faverges and Grenoble.

Germany

The map of TBE risk areas is updated periodically by the Robert Koch Institute (Epi. Bull.). Since 1992, between 100 and 300 autochthonous clinical TBE cases were recorded annually. An all-time high was reached in 2005, when 431 cases were reported – an increase by 58% compared to 2004. This was overshadowed by an additional increase in 2006, with 546 cases. These occurred mainly in southern Germany, i.e., in the federal states of Baden-Wuerttemberg and Bavaria, but also in Thuringia and Hesse. In 2007, only 236 TBE cases were reported.

There are risk areas in Bavaria and Baden-Wuerttemberg and newly identified risk areas in Hesse and Thuringia. One small risk area is located in Rhineland-Palatinate. Between 1994 and 2007, more than 55 single cases were reported from areas previously not defined as risk areas, i.e. in Saxony, Lower Saxony, Mecklenburg-Western Pomerania, Saxony-Anhalt, and Brandenburg. In such a

"non-risk area" a TBE case with lethal end was reported in 2007 (unpublished).

Whereas the incidence of TBE in Bavaria and Baden-Wuerttemberg has remained stable on a high level for years, increasing incidences have been reported in other areas of Germany. 132 of the 440 German counties are currently classified as TBE risk areas. In 2006, 35.6% of the cases occurred in Bavaria, 52.6% in Baden-Wuerttemberg, 10.8% in Hesse, 0.4% in Thuringia, 0.6% in Rhineland-Palatinate, 0.6% in Brandenburg, 0.2% in Mecklenburg-Western Pomerania, and 0.6% in Saxony. In 2007, the Robert Koch Institute modified the definition of risk areas (Epi. Bull. 15/2007).

Greece

For several years, there have been publications indicating a very low incidence of TBE virus in northern Greece in the province Thessaloniki. However, no cases of TBE have been registered for many years.

A new study by Pavlidou et al. [34] provides seroprevalence data in healthy blood donors from northern Greece (ELISA, IgG). According to this study, in the provinces Chalkidiki 5.8%, Evros 3.6%, Imathia 2.7%, Kastoria 2.4%, Kavala 1.6%, Pella 5.4% and Xanthi 2.9% of the test persons were TBEV-IgG-positive. Results from neutralisation tests are not available, which would exclude IgG-antibody cross-reactivity due to other flavivirus contacts (e.g. vaccination against yellow fever or Japanese encephalitis or infection with dengue viruses).

Hungary

The average yearly incidence rate between 1977 and 1996 was 2.5 per 100,000 inhabitants (range 1.3 to 3.8), with the highest incidences between 1981 and 1990. From 1997 to 2000, a significant decrease in the number of registered TBE cases was observed, with an incidence rate of 0.5 per 100,000 in 2000. Since 2001, the incidence has increased again. Between 2003 and 2007, an average of 106 cases were reported annually. Extended areas of high risk are located in western Hungary and along the Danube river, i.e., the counties of Zala, Somogy, and Vas (western Hungary), Nógrád (northern Hungary), and around Lake Balaton.

Unconfirmed reports indicate that the reduction of the TBE incidence at the end of the 1990s was due to reduced diagnostic efforts.

Italy

A few clinical cases have been recorded in Northern Italy in the area of Florence, Trento, and Belluno. In 2006, first cases were reported in Friuli Venezia Giulia. Anti-TBEV antibodies were found in about 1% of potential risk persons, such as foresters, hunters, woodcutters, and gamekeepers. Since the early 1990s, between 2 and 19 cases were reported annually, 23 cases in 2004. In 2006, 14 cases were registered, one reported TBE case took a lethal course.

Kazakhstan [Pavel N. Deryabin, pers. comm., 29]

As supposed, there are endemic areas for TBE in Kazakhstan. These are located in the east of the country and in the Almaty region. In the east, 34 cases were reported in 2004, 28 in 2005 and 18 in 2006; in the Almaty region, 10 cases were reported in 2004, 9 in 2005 and 6 in 2006. However, the real incidence is expected to be much higher. In Almaty itself, 6 cases were registered in 2004, 12 in 2005 and 8 in 2006. In Kazakhstan, a Russian vaccine is used (e.g. 60,630 doses in 2006). A kind of mandatory passive immunisation with immunoglobulin is applied nationwide up to 3 days after a tick bite.

Latvia

The TBE risk areas are spread over the entire country, although there are differences in the virus load.

Latvia was considered the country with the highest TBE incidence rates in the world between 1990 and 2000, since then the number of cases has decreased considerably. Between 1990 and 1994, an average of 558 cases were reported per year, between 2003 and 2007, the average number of cases was 220 per year. TBE cases were even reported in and around the city park of Riga. Ticks in Latvia carry a higher TBEV load than those in other risk countries. Food-borne outbreaks (caused by dairy products, mainly goat milk) accounted for up to 5% of the total number of cases per year.

Between 2004 and 2007, the TBE incidence ranged from 6.2 (2005) to 10.8 (2004).

Lithuania

TBE is present in all districts of Lithuania. In 2003, the epidemiology of TBE in Lithuania was very unusual. The incidence rate (763 cases, 22 per 100,000 inhabitants) was twice the average incidence over the last ten years, and the highest annual rate recorded since notification was observed at the end of the 1960s. This rate was also the highest of all Baltic countries in 2003. Four lethal cases of TBE were notified in 2003. Between 2003 and 2007, 425 hospitalized cases were reported annually. Even though normally transmitted through a tick bite, 22 cases of TBE in 2003 (four clusters) were acquired by the consumption of unpasteurized goat milk – a well-known transmission route. The highest annual incidences of TBE, about 80% of all notified cases, are recorded in the northern and central parts of the country, i.e., mainly in the counties Kaunas, Panevezys, and Siauliai. In 2003, the incidence rates in these areas remained unchanged. However, they were much higher in many other counties. Eight of 44 districts reported an incidence rate two to five times higher than the average incidence in Lithuania. The highest incidence rate was recorded in Panevezys, with about 100 per 100,000 inhabitants.

Between 2004 and 2007, the TBE incidence ranged from 6.9 (2007) to 13.5 (2006).

Norway

Norway is an example for the occurrence of new TBE risk areas. TBE was first reported in 1997. All 28 cases between 1997 and 2007 were acquired within a limited area along the southern coast and in the municipality of Tromøy [35]. The TBE virus RNA was detected in the serum of TBE patients in Norway [36].

Poland

Since 1993, the number of reported cases at country level has ranged from 100 to 350 cases per year. In 2003, the number of reported cases was 339 (0.89 per 100,000). In 2006, 316 cases were reported. Between 2003 and 2007, 265 cases annually were reported. The north-east of the country around Bialystok is the main area of endemicity. 80% of cases occurred in the two north-eastern provinces adjacent to Lithuania and Belarus. Another important focus of the disease is in the south-western part of Poland, in districts adjacent to the Czech Republic. A present serosurveillance study (human and goat samples) indicates the possible existence of endemic foci in north-western provinces of Poland, in which barely any cases were reported during 1070 – 2005 [37].

Romania

Risk of tick-borne encephalitis is reported for the Tulcea district and in Transylvania at the base of the Carpathian Mountains and the Transylvanian Alps. However, details about the annual numbers of TBE cases have not been published.

Russia

Russia is the country with by far the highest number of registered TBE cases.

Approx. 58 million people who are potentially at risk of acquiring TBE live in a broad TBE corridor ranging from St. Petersburg over Chelyabinsk, Kazan, Tyumen, Novosibirsk, Irkutsk to the Far East as far as Khabarovsk and Vladivostok.

In Russia, a total of 54,526 cases of TBE were registered over the past 10 years (1998 to 2007), in addition the real incidence is expected to be much higher. 8,725 of these cases were reported in children < 14 years.

Western Siberia is the region with the highest known incidence of TBE in the world, with 40 to >80 cases/100,000 population [38]. In this region the Aina strain of the Siberian virus subtype could be isolated.

The highest numbers were registered in 1996 (10,298 cases) and 1999 (9,955 cases). Since then, the numbers have decreased continually and have reached the lowest level in 2007 with 3,098 cases. The strongest decrease in morbidity was registered in the Ural Mountains and in Western Siberia. However, the majority of TBE infections is acquired in Siberia (e.g. 2003 – 2007: 11,440) and in the Ural Mountains (e.g. 2003-2007: 4,181). These are 56.7% and 20.7% of the total morbidity in Russia (20,164 cases from 2003 to 2007).

The reasons for this reduction are unclear, an influence of the vaccination rate can be excluded.

As there are records on the incidence of TBE in Russia since 1950, a certain dynamic of the frequency can be observed. Thus, the total incidence reached a peak of approx. 4/100,000 inhabitants between 1955 and 1965 and, after a period with a lower incidence (between 1-2/100,000 inhabitants) between 1993 and 1998, a further peak occurred with approx. 6-7/100,000 inhabitants, followed by a reduction up to the year 2007 [39].

Serbia

A few cases have been reported in the area near Belgrade, including food-borne outbreaks near the coastal regions of the Adria, but there is no published information available on these cases.

Slovakia

Between 1998 and 2007, the average annual number of reported cases was 67, ranging from 46 to 92. In 2006, 91 cases of TBE were reported compared to 46 in 2007. Between 2003 and 2007, 66 cases annually were reported. Some of the reported cases were caused by the consumption of homemade raw goat and sheep milk. New foci have recently been identified in areas of eastern Slovakia traditionally thought to be free of the virus.

Slovenia

Endemic foci of TBE are spread all over the country. Between 2001 and 2005, the 5-year average was 261 cases. The highest number of TBE cases had been reported in 1994, with a total of 492 cases. In 2006, 445 cases were reported. Between 2003 and 2007, 283 cases annually were reported.

Sweden

In the five-year period between 2003 and 2007, the average was 150 annual cases. Occurrence has been highest in 2007, with 190 reported cases. Except for Hungary, this makes Sweden the only country, where no significant reduction in the number of cases is observed from 2006 to 2007. Most of the infections were acquired in the counties of Stockholm (62%), Södermanland (13%), and Uppsala (8%). In the county of Västra Götaland, south of Lake Vänern, 5 to 10 cases are notified annually. Sporadic cases occur in the rest of Sweden every year.

A recent study of Brinkley et al. [40] (virus prevalence data in ticks, sequence data) show a distinct migration of the virus (Western subtype) to the western parts (Västra Götaland).

Also, data of Eisen [19] provided tantalizing hints that climate warming allowed *I. ricinus* to expand its distribution toward the north and become more abundant in Central Sweden from the early 1980s to the early 1990s.

Switzerland and Liechtenstein

In the five-year period between 2003 and 2007, a mean of 165 cases were reported annually. In 2006, 259 cases were reported, the highest number in recorded history in Switzerland. There are two high-risk regions, the larger one covering the midland, with the exception of the far-western part, and the smaller one located in the upper Rhine valley, including the principality of Liechtenstein. A focus of ticks infected with the TBE virus (TBEV) is located on a much-used forest path near Vaduz, the capital of the principality. The canton Zürich has become the most dangerous region for TBE in Switzerland, followed by Thurgau, St. Gallen, Aargau, and Bern. The TBE risk areas in the northeast of Switzerland remain stable, however, new risk areas in the western part of the country (Neuchâtel) have been identified.

Turkey

TBEV has not been detected in Turkey, there are no safely confirmed cases of disease. The serosurveillance data published by Esen et al. [41] (ELISA, 7 TBEV-IgG-Ab positive sera, 1 TBEV-IgM-Ab) have not been confirmed by neutralisation tests and presumably are due to cross-reactivity. It is known that the presumably false-positive sera were collected in areas endemic for Crimean Congo Haemorrhagic Fever, in addition other flaviviruses not belonging to the TBEV complex persist in Turkey.

Belarus, Bosnia, Moldavia, and Albania

Belarus, Bosnia, Moldavia, and Albania are believed to be countries with risk areas and a high TBEV prevalence in ticks, information on clinical cases is scarce.

The TBE situation outside Europe

Outside Europe, only data from China, Japan, Mongolia, and more recently from South Korea have become available, which indicate that there are TBE risk areas in these countries:

First data from China [Guo-Dong Liang, pers. comm., 29,42]:

TBE is endemic in China, but the disease is not notifiable so data are only sporadic. The disease is mainly reported in the northeastern forest areas of Changbai Mountains in Jilin Province, Daxingán Mountain in Inner Mongolia Province, and Xiaoxingán Mountain in Hei Longjiang Province. Moreover, TBE is intermittently reported in the forest regions in the northern slope of Tianshan Mountain and the southern slope of the Altai Mountains in Xinjiang Uygur Autonomous Region (north-western China). There are also some

reports related to TBEV in Yunnan (south-western China) as well as in Tibet (western China).

The main endemic areas are located in the province Heilongjiang in the far northeast of the peoples' republic. In this area, 2,202 cases were reported between 1980 and 1998, although a much higher number must be expected, as the disease is not notifiable. Between 1995 and 1998, 420 cases were diagnosed, most cases were reported in May (44 cases) and June (210 cases). The first case was registered in 1943, in 1953 TBE virus was first isolated from a patient and from ticks. The main vector is *I. persulcatus*.

Japan [Ikuo Takashima, pers. com., 29]

The unusual TBE situation in Japan remains unchanged. The autochthonous case of a 37-year-old woman from the city of Kamiiso on Hokkaido described in 1993 has remained unique. However, the virus has been isolated several times from sentinel dogs and ticks (*I. ovatus*) and a serosurvey of sera from domestic animals suggested the presence of TBE foci in Hokkaido [43,44]. The Oshima 5-10 virus is a far eastern strain. Animal studies have shown that the vaccine produced based on the central European prototype completely covers this Oshima strain as well as other far eastern and Siberian strains. The Japanese have become more interested in protective vaccination since a Japanese tourist acquired the infection in Salzburg and died after his return to Japan.

Mongolia

In 2004, some endemic areas were described close to the Russian border in the north of the country (provinces of Selenga and Bulgan) and around the capital city Ulan-Bataar [45].

South Korea – new among TBE-endemic countries

TBEV was isolated recently from ticks (*Haemaphysalis longicornis*; *Ixodes nipponensis*) and mice (*Apodemus agrarius*) [46]. Surprisingly, the virus belonged to the western European subtype. Virus isolation was successful in the regions Dongducheon, Geyonggi-do; Jeongseon, Gangwon-do; Hapcheon, Gyeongsangnam-do; and Gurye, Jeonrabuk-do. TBE cases have not been registered yet, but a series of diseases of unknown origin affecting the central nervous system recently [46] have been reported. Further investigations have been initiated.

Note:

The author invites more detailed and additional information regarding the epidemiology of TBE in individual countries. Please email jochen.suess@fli.bund.de.

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The measles situation in Austria: a rapid risk assessment by an ECDC team and the outcome of an international meeting in Vienna, Austria

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Background

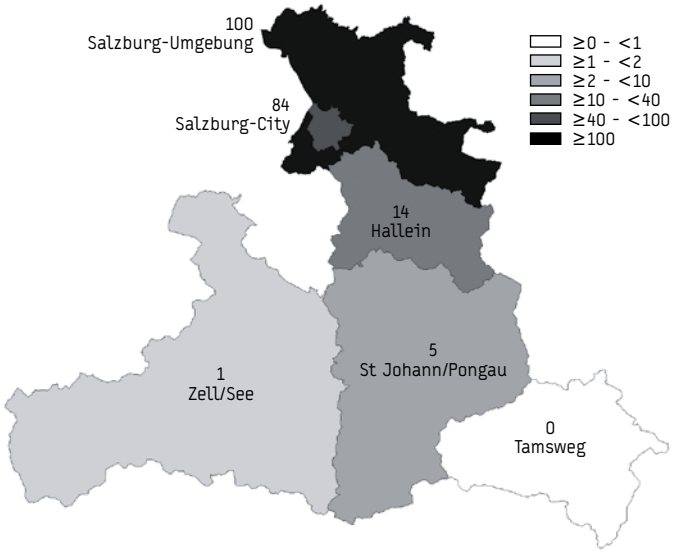
For the last three years, Austria has been considered a low-moderate incidence country (< 1/100,000/year) for measles [1] and the last significant measles outbreak occurred in 2003 involving 64 cases [2].

However, around Easter in March 2008, the health authorities identified a measles outbreak in the Austrian province of Salzburg in an anthroposophic school and day-care centre. By mid-April, 207 cases had been reported. Most of them (182 cases) were from Salzburg. The other cases included Salzburg citizens that fell ill in two other provinces and small clusters in Upper Austria and Tyrol with possible epidemiological link to the Salzburg outbreak (Figures 1,2).

In addition, about 50 cases with direct link to the anthroposophic school were reported in the same period from Bavaria, Germany, two from Baden-Württemberg, Germany and four from Norway. Further details on the outbreak have been reported earlier [3]. In line with the current European Union (EU) legislation, Austria informed the

Figure 1

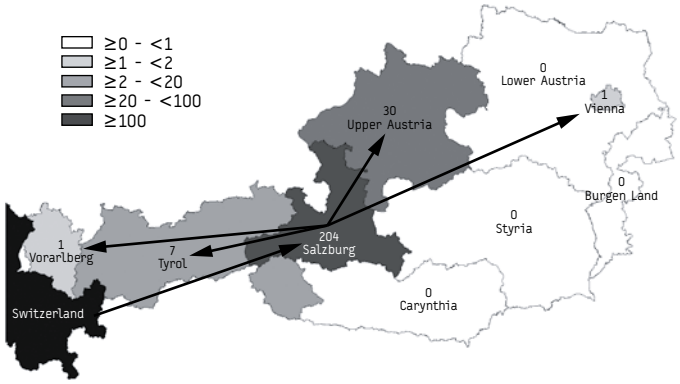
Geographical distribution of cases in the Austrian region of Salzburg



Source: regional Health Board Salzburg, update 21st April 2008

Figure 2

Geographical distribution of cases in Austria: import and export of cases



Source: Regional Health Boards, update 21st April 2008

Vorarlberg: 1 exported case (pupil fron Salzburg with indirect connection to Rudolf-Steiner-School)

Salzburg: inclusive one case with presently doubtful "vaccination measles"

Upper Austria: therefrom 7 cases obviously without connection with Salzburg

Vienna: 1 exported case (resident from Salzburg who was diagnosed in Lower Austria and hospitalised in Vienna - pneumonia, meanwhile released)

European Commission and the EU Member States about the event and the development of the outbreak [4]. At the same time, the measles outbreak in Switzerland is still ongoing [5,6].

The threat of the development of a major multi-state outbreak just about two months ahead of the upcoming European Football Championship (EURO 2008, June 6-29, 2008; jointly hosted by Switzerland and Austria) gave rise to considerable concerns leading the Austrian Ministry of Health (MoH) to invite a team from the European Centre for Disease Prevention and Control (ECDC) for a rapid assessment of the situation. Furthermore, an international meeting was convened at the Austrian Ministry of Health to discuss the direct implications on the EURO 2008.

Results of the rapid risk assessment and proposed options for the Austrian Ministry of Health

From 14-16 April the ECDC team consisting of an expert each from the ECDC Preparedness and Response Unit and the EU Surveillance network for vaccine-preventable diseases (EUVAC.NET) met with health authorities of all involved administrative levels, the National Measles Reference Centre and the Austrian Vaccination Board to discuss in depth the current measles outbreak. Additionally, outbeak-related data were provided by the health authorities to be re-analysed by the expert team.

The objectives of the visit were:

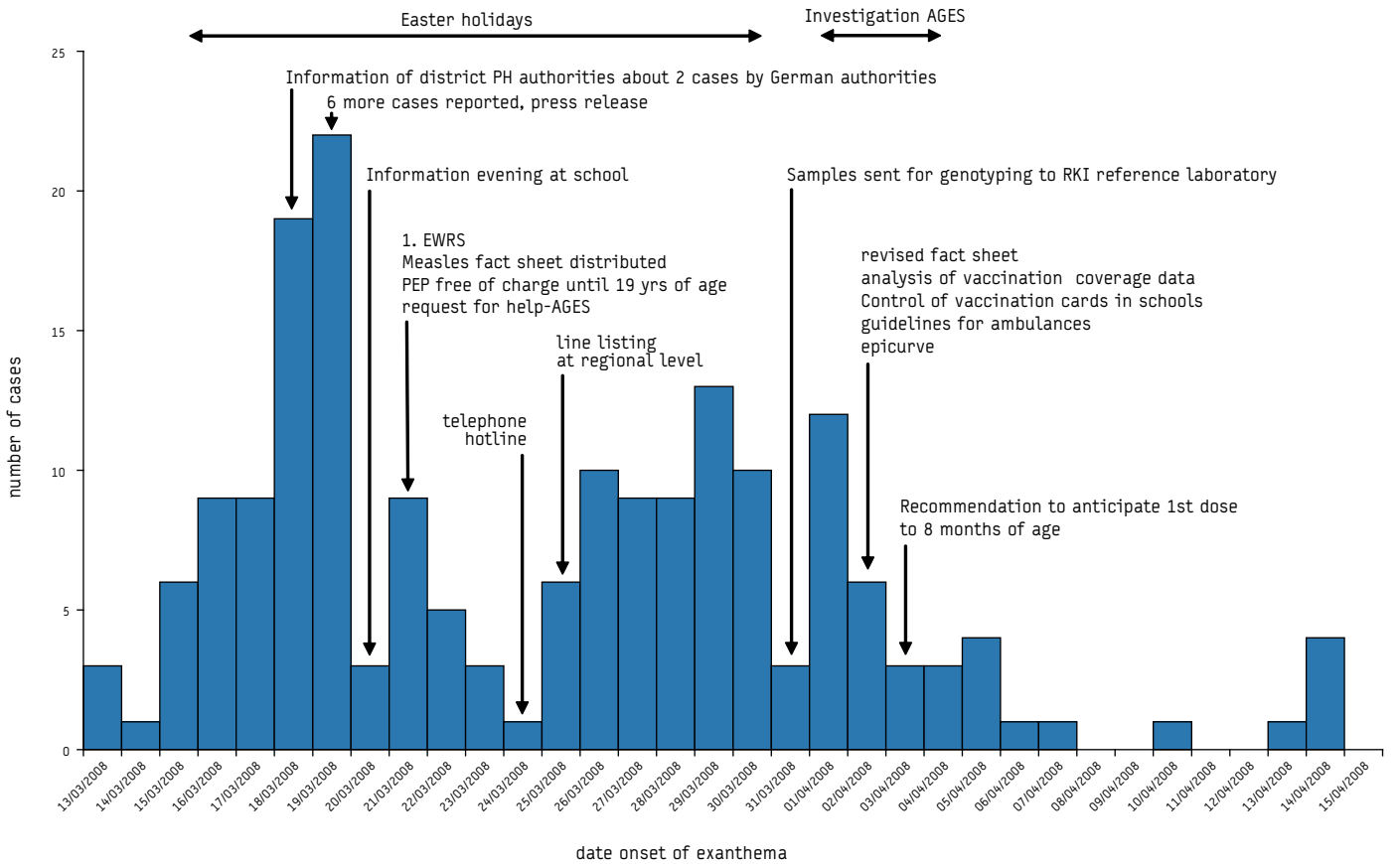
- To assess the situation in Austria and elaborate short, medium and long-term options for improvement of the measles situation;
- To provide evidence for planning a coordinated response, particularly in relation to the upcoming EURO 2008 football championship.

The following findings were presented by the ECDC-team:

- The outbreak was most probably imported by Swiss nationals who visited the anthroposophic school in Salzburg as the laboratory investigation of the D5 strain available showed a 100% sequence compatibility and identity with the genotype D5 measles virus from Switzerland;
- The outbreak that has primarily affected the anthroposophic community and their direct contacts has to date apparently been contained;
- Despite sub-optimal vaccination coverage of about 90 percent in the Austrian population transmission of the infection beyond the anthroposophic community and their immediate contacts was limited;
- Both the excellent cooperation between the health authorities at the different levels and the rapid introduction of measures (swift information campaigns, general offer of vaccination free of charge to people up to the age of 19 years, ring vaccination free

Figure 3

Epidemic curve and overview of control measures taken (CAVE: cases were reported later than they occured!)



of charge for all ages, positive immune status as a pre-requisite for visiting community facilities) allowed for fast containment of the outbreak (Figure 3) – although a few cases still occurred and are expected to occur in the near future.

On the basis of these findings, the following options for improvement were proposed to the Austrian MoH:

- To improve the quality and timeliness of epidemiological and vaccination data by the introduction of the electronical reporting system that was already planned for 2009,
- To ensure optimal management and flow of epidemiological data between district, regional and national levels for rapid outbreak response by continuation of the ongoing training initiative for health authorities at regional and district level, and
- To perform a nationwide sero-epidemiological study in order to identify unvaccinated risk groups and reasons for low uptake in order to tailor information campaigns for these groups and to allow planning of targeted vaccination campaigns to improve vaccine uptake.

Outcomes of the International Meeting on Measles

In addition to the rapid assessment of the specific Austrian situation an international meeting was convened on 17 April at the Ministry of Health. The meeting involved key persons from Austrian Ministry of Health, the surveillance unit, and the National Measles Reference laboratory along with representatives from Switzerland, the affected provinces of Germany (Bavaria, Baden-Württemberg), the ECDC Preparedness and Response as well as Scientific Advice Unit, the WHO European Office, EUVAC.NET and the EU Commission. The objective of the meeting was to discuss possible coordinated action in preparation of and during the EURO 2008.

The main outcomes of this meeting were:

- Information to stress the importance of measles vaccination to all European citizens with a special emphasis on participants of the EURO 2008 is planned to be published on the ECDC website. EU Member States will be encouraged to distribute this information. Similar information was already released by Switzerland and Austria and should also be released by all EURO 2008 participating countries (EU + Croatia, Turkey and Russia) (7,8).
- Closer cooperation between the health authorities of Switzerland and Austria in the preparation and during the EURO 2008.
- As a long-term strategy to improve the vaccination coverage, a well-prepared and evidence-based vaccination campaign ("catch-up campaign") for specific risk groups imbedded into a general action programme to reach the goals of the WHO Measles Elimination Programme by 2010 should be implemented [9].

Further perspectives

Most of the proposed options are already covered by ongoing projects within Austrian MoH:

- A web-based electronical reporting system that is planned to be operational in 2008 will facilitate real-time surveillance;
- A specific outbreak module as part of the electronical reporting system will provide substantial support for the responsible health authorities on district regional and national level;
- The electronical vaccination registration system planned for 2009 will both increase quality and timeliness of data on vaccine coverage and identification of geographic and demographic vaccination gaps;
- Due to Austria's federal political structure with decentalised responsibilities, outbreak management capacities fall within the district and regional levels. Therefore the intensive and successful cooperation between the Austrian Ministry of Health and the ECDC concerning training in epidemiological methods and outbreak management will benefit the country at sub-national level. So far about twenty Austrian public health officers have participated in such training [10];
- A EURO 2008 workshop will take place at the Ministry of Health with support of the ECDC and the German Robert-Koch-Institute (RKI). The objective is to optimise the preparatory work of the Austrian public health system concerning infectious diseases surveillance and response to health crises. Furthermore, the principles of collaboration and information exchange during the EURO 2008 will be laid down together with the participating Swiss colleagues [11,12].

A comprehensive assessment report as well as a detailed meeting report are currently under preparation and will be published soon. In conclusion, the ECDC assessment and the International Measles Meeting represent impressive examples for the close cooperation of member states and international organisations such as WHO, ECDC and European Commission and EU-projects such as EUVAC.NET in health crises.

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An approach to monitoring influenza vaccination uptake across Europe

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Currently, the monitoring of influenza vaccination uptake is mainly a national issue. As influenza infection easily crosses international borders, it is in the interest of all countries to have a high vaccine uptake in people who may be vulnerable when influenza spreads. A Europe-wide monitoring system can provide insight into the strengths and weaknesses of uptake rates in countries and, once sufficient levels are achieved, can safeguard the continuation of the achieved levels. This paper aims to address the following issues: a) How is influenza vaccination uptake monitored in Europe? b) What methods to monitor vaccination uptake are available and what are their limitations? c) What steps should be taken to implement a European-wide influenza vaccination uptake monitoring system?
Based on existing literature and experiences in monitoring influenza vaccination uptake, an approach to set up a European-wide monitoring system is proposed.
The following issues were identified as relevant for influenza vaccination uptake monitoring: a) Agreement on the population groups in which vaccination uptake should be monitored; b) The frequency of data collection; c) The importance of sharing experiences regarding existing influenza vaccination campaigns in order to learn from each other, and develop 'best practices'; d) The need to publish uptake data in close relation with influenza surveillance data and other European efforts on dissemination of vaccination knowledge.
To stimulate the discussion on implementing a pan-European influenza uptake monitoring scheme the following recommendations were suggested : a) Develop a common set of variables; b) Build on experience from individual countries; c) Create a coordinating body; d) Create or identify a platform to publish the data; e) Start small and expand rapidly.

Introduction

Monitoring influenza vaccination uptake in the population is important for several reasons. Firstly, influenza vaccination has an effect on the health of the population: it is generally assumed to prevent premature deaths and reduce the burden of disease [1-9]. However, some critical studies have been published recently concerning selection bias, which may have led to more favourable outcomes for vaccine effectiveness in community-dwelling elderly people [10-12]. Secondly, as a public health intervention associated with considerable resources and costs, influenza vaccination campaigns need to be monitored and evaluated. Finally, information on influenza vaccination uptake is needed because of the current pandemic threat: countries should have an existing and well functioning distribution channel for influenza vaccinations in the inter-pandemic period in order to be able (potentially) to use part of this infrastructure to distribute vaccines in a pandemic situation.

Currently, monitoring influenza vaccination uptake is mainly a national issue. Although almost all European countries have national recommendations for influenza vaccination [13], not all countries are able to provide data on uptake of all the groups for whom the vaccination is recommended [14]. Attempts to provide international overviews of uptake rates have so far been on an ad hoc basis: Van Essen et al. used sales figures to calculate vaccination uptake in the population [13-15]. This is the only European-wide attempt to monitor trends in vaccination uptake, but it does not provide insight into the uptake rates for high-risk persons. In some countries, comparative population surveys have been carried out, either on an ad hoc basis (Netherlands, Germany, Poland, Sweden and Spain [16]) or annually (Belgium, France, Italy, Germany, Spain and United Kingdom [17]).

As influenza infection easily crosses international borders, it is in the interest of all countries to have high vaccine uptake in people who may be vulnerable when influenza spreads. A European-wide monitoring system can provide insight into the strengths and weaknesses of the vaccination campaigns of each country. Once sufficient levels are achieved, the monitoring system contributes to safeguarding the continuation of the achieved levels and provides complementary information to already existing European public health monitoring efforts such as the European Influenza Surveillance Scheme (EISS, http://www.eiss.org/index.cgi) [18] and the Vaccine European New Integrated Collaboration Effort (VENICE, http://venice.cineca.org/) [19].

This paper addresses the following issues:
- How is influenza vaccination uptake monitored in Europe?
- What methods to monitor vaccination uptake are available and what are their limitations?
- What steps should be taken to implement a European-wide influenza vaccination uptake monitoring system?

The aim of this paper is not to provide straightforward answers, but to stimulate discussion by proposing one possible approach to the development of a European influenza vaccination monitoring system.

Existing monitoring efforts in Europe

Most countries in Europe have some form of influenza vaccination monitoring system. In 2001, 70% of 27 European countries (EU-25 Member States, Norway and Switzerland) had such a system [14]. This may range from ad hoc surveys to advanced information systems involving general practitioners (GPs) who provide detailed monthly data. In some countries the monitoring systems may also vary by region. For instance in the United Kingdom (UK), annual data are available from the GP-registration forms in paper copies only in Northern Ireland [20,21], whereas in England there is a web-based system that provides monthly data and is even capable of daily reports [22,23]. In some other countries, different methods may coexist, as in the Netherlands, where both ad hoc population surveys and data from the GP information networks are available [24,25].

The level of detail of monitoring also differs across countries. Almost 70% of those that have a monitoring system are able to provide uptake rates for the elderly. The percentage of countries that can provide uptake rates for those suffering from chronic conditions who are younger than 65 years is much lower [14]. However, for most countries in Europe there is currently no internationally available information about the monitoring systems used, the frequency of collecting the data and the responsible institutions.

Strengths and weaknesses of different methods used to monitor influenza uptake

Several methodologies are available for collecting data on influenza vaccine uptake. Their appropriateness depends on the existing health care and vaccine distribution systems. Information may be collected by means of population surveys, physician information networks, information networks of other health care workers or vaccine sales data.

Population surveys

Method: Population surveys are based on questionnaires that are conducted among a representative sample of the total population. This can be done either by telephone, by mail or face-to-face. Population surveys are independent of the way the health care system is organised.

Limitations: The data on both influenza vaccination uptake and belonging to a high-risk group depend on self-reported data, which cannot be verified by medical records. Previous research revealed that for both vaccination uptake and chronic conditions, self-reported data appear to be sufficiently reliable [26-30]. A significant problem with population surveys is that large numbers of respondents are needed to obtain data on specific high-risk groups. Other limitations, which often make comparisons between countries difficult, include different sampling methods used and different timing and frequency of health surveys in different countries. In addition, population surveys often a priori exclude institutionalised populations, such as residents of nursing homes, who are among risk groups often targeted by influenza vaccination recommendations.

Physician information networks

Method: Physician information networks can also be used to collect vaccination uptake data [26]. In this case, GPs and/or specialists register each vaccine they administer.

Limitations: This approach depends on the following conditions: the vaccine is administered mainly by physicians; vaccination uptake is registered and chronic conditions are accurately coded according to an internationally recognised system (like the International Classification of Primary Care - ICPC); Besides this, physicians included in the network should act as gatekeepers in the existing health system, that is the patient population has to be registered with individual GPs or practices and the GPs should manage the medical records of their patients. This latter condition is necessary to obtain a population denominator. Furthermore, a system to collate and process these data needs to be established. Other limitations of physician information networks include possible miscoding of vaccinations and potential problems with obtaining access to such data by third parties for confidentiality reasons. Currently, many European Union (EU) countries are piloting electronic patient record systems, which have great potential for monitoring of vaccination coverage. However, again, there are substantial differences in the structure and functioning of these recording systems between regions and countries. Different systems within a country may hinder the merging and analysing of data at national level; different systems between countries may complicate international comparisons. Furthermore, the GP registration networks do not monitor influenza vaccination outside the traditional health care setting, such as employee vaccination campaigns organised by large companies or shopping centres.

Vaccine sales data

Method: Vaccine sales data can be used to estimate the overall population vaccination rates [13].

Limitations: This method requires the implementation of careful procedures to ensure the cooperation of vaccine manufactures to provide confidential sales figures. Besides this, the sales figures do not give insight into the vaccine coverage rates of the respective risk groups.

Information networks of other health care workers

Method: Information networks of other health care workers may also be able to provide uptake data, such as vaccination sales by pharmacists.

Limitations: It is not clear to what extent health care workers other than physicians are able to provide data on, for instance, chronic conditions and to what extent a reliable population denominator can be established.

Which method is best?

It should be stressed that not all methods are appropriate for all countries because of differences in the health care systems. In addition, it may be difficult for countries to change their existing monitoring systems, should such need arise for the sake of international comparisons, because the existing systems probably fit best in the health care system and/or because changing the monitoring system may have financial consequences. Presently, an answer to the question 'Which method is best?' cannot be given. It is possible to use different data collection methods, choosing the most suitable one for each country. However, in this case one needs to know the bias resulting from each system. An ad hoc comparison between the GP information system data and postal survey data in the Netherlands revealed that the GP information network provided a 10% higher uptake rate estimate than the postal survey [31].

Another relevant issue is the costs of the data collection. It is currently not clear which method is the most cost-effective. This may differ per country and depend on the health care system, existing monitoring systems, etc.

Furthermore, it is important to realise that all methods appear to, a priori, exclude parts of the population.

Relevant issues and conditions for a European monitoring system

For the development of a European-wide influenza vaccination monitoring system, several basic questions need to be addressed:

In what population groups should vaccination uptake be monitored?

Problem: In order to be able to know to what extent the high-risk population is vaccinated, it is important to define the high-risk groups and to explore the feasibility of gathering data on these groups. A basic question is whether the information at a European level should be uniform, with comparable groups for all countries, or could be country-specific, adjusted to the national recommendations. With the first type of information, cross-country comparisons would be possible, with the second type of information the countries' ability to fulfil their own policy recommendations would be monitored and could result in getting more reliable figures for the overall uptake in the recommended groups.

Possible solution: There should be an agreement about the minimal set of information and level of detail that needs to be collected in each country for proper monitoring. Preferably, the aim should be to achieve a monitoring system that satisfies both international and country-level information needs on vaccine uptake. The issues to consider here may be for instance whether the age limit for the elderly should be 55 or 65 years, or whether to include children, when the groups for whom vaccination is recommended differ among countries. These issues may lead to a discrepancy between an international agreed dataset to be collected and the national available dataset. Preferably this discrepancy should be as small as possible.

Who should be involved in registering?

Problem: Different health professionals and organisations may be involved in influenza vaccination administering. Several influenza vaccination campaigns may run simultaneously, targeting partly overlapping populations, e.g. vaccinating employees by large companies and vaccinating high-risk persons by GPs.

Possible solution: for each possible administrator an inventory should be made from the information they are able to provide on vaccinated individuals and clear procedures need to be developed on how this information should be registered. However, this does not solve the denominator problem, which remains a serious one.

Furthermore, it is important to ensure completeness of the data collection, in order to avoid underestimation of the influenza vaccination uptake.

Frequency of data collection

Problem: It currently seems logical to collect influenza uptake data on a yearly basis, since the vaccination is a yearly event. However, a higher frequency can be advocated, especially during the vaccination season, in order to be able to intervene when it seems that a pre-set target may not be reached that season. On the other hand, for countries with satisfactory and stable uptake levels (e.g. countries that already meet the WHO recommendation of attaining vaccination coverage of the elderly population of at least 75% by 2010 [32]), a two-yearly monitoring might be sufficient. There may also be differences between national frequencies of data collection and the frequency needed for data at a European level.

Possible solution: A minimum level of frequency should be defined, which should eventually expand towards a more detailed monitoring.

Insight into existing influenza vaccination campaigns

Problem: Differences in uptake rates do not provide insight into why some countries have higher vaccine coverage compared to others. In order to learn from each other, countries should share experiences, to be able to develop best practices.

Possible solution: This can be done by collecting information for each country on the ways the vaccine is distributed and administered, and the means of informing the public. This information, in combination with the influenza vaccination uptake data, can reveal the practical barriers that hinder vaccination in different countries.

Publication of the data

Problem: It would seem sensible to present all influenza-related data in one place. However, this raises the question of who should provide the data and what quality checks would be necessary, before data may be published.

Possible solution: The uptake data may be published in close relation with influenza surveillance data (e.g. by EISS and the European Centre for Disease Prevention and Control (ECDC)) and the output of other European efforts on dissemination of vaccination knowledge, such as the VENICE project [19]. However, a formal agreement would be needed for each country regarding the persons/institutions responsible for submitting and validating data before publication.

Recommendations for implementing a monitoring scheme for influenza vaccination uptake

The following are the steps we think need to be taken to successfully implement a European-wide monitoring system:

1. Develop a common set of variables

Questions about the level of detail and the frequency of data collection should be addressed. A set of targets should be defined to give direction to the way the scheme should develop, including variables for defining the risk groups to be included and methods of data collection. These targets should describe the final desired situation for the monitoring scheme. A minimum set of requirements for the monitoring system that is both useful at a European level and feasible for countries that will join the scheme should be established. We propose that a group of national experts from across Europe should deal with these questions.

2. Build on experience from individual countries

Many countries collect at least some information on influenza vaccination uptake. For each country, the organisation that is responsible for monitoring influenza vaccination uptake and the contact persons within these organisations should be involved in the scheme. Building on existing efforts is likely to be cheaper and more effective and will have a better chance of becoming a stable and continuous way of providing data compared to introducing a complete new system that may need new ways of data collection. At a later stage, harmonisation of the monitoring methods can be targeted. Various methods of data collection can be used, as long as they are properly described and their limitations known. Allowing different methods increases the possibility of using existing national data collection methods, which may be adjusted to the desired data format in an incremental way, instead of having to develop and institutionalise new methods of data collection.

3. Create a coordinating body

At a European level, a coordinating body is necessary to collect and disseminate the data. This body should preferably work closely

with existing efforts in influenza surveillance. It can also carry out research on vaccination uptake in Europe and work on vaccination recommendations.

4. Create or identify a platform to publish the data

To make the data available for a wide public a platform to publish the data should be available. This platform should be easily accessible and highly visible. It could be, for instance, a website linked with existing influenza surveillance data (e.g. ECDC, EISS).

5. Start small and expand rapidly

When the harmonised set of data is agreed, we suggest the monitoring system be tested in a few countries with a limited data set (e.g. collecting only data for uptake among the elderly). These countries should preferably have different types and quality of their national monitoring systems in order to be able to identify and tackle all kinds of problems at this early stage. With the lessons learned from these countries, the next step would be to extend the network in a stepwise manner so that eventually influenza vaccination uptake data will be available for all countries in Europe, and a European monitoring system will be put in place.

Conclusions

Influenza vaccination uptake monitoring is a 'forgotten' subject in the EU, which is strange in the light of the costs that come with the vaccination programmes and the discussion of expanding of the recommendations for this vaccination. This paper does not provide ready answers in the sense of a fully developed proposal for such a monitoring system, but rather highlights the problems likely to be encountered when developing such a system, and describes a possible route towards a uniform monitoring system. It aims to increase the awareness of this important albeit neglected subject and inspire discussions on this issue.

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Prevention of the spread of infection – the need for a family-centred approach to hygiene promotion

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Infectious diseases circulating in the home and community are a continuing and significant burden on the health and prosperity of the European community. They could, however, be significantly reduced by better standards of hygiene. Across Europe, public health is currently structured such that the separate aspects of hygiene in different settings (food hygiene, personal hygiene, handwashing, pandemic flu preparedness, patient empowerment etc.) are dealt with by separate agencies. If efforts to promote hygiene at community level are to be successful in changing behaviour, we need a concerted family-centred approach to ensure that a basic understanding of infectious disease agents and their mechanisms of spread, together with an understanding of a risk-based approach to hygiene, are promoted as part of the school curriculum and as part of public health campaigns. Alongside this, we also need unambiguous communication with the public on issues such as the hygiene hypothesis and environmental issues.

Introduction

The last two decades have seen infectious diseases moving steadily back up the health agenda, prompting new emphasis on strategies for prevention and control. Increasingly, this includes strategies to reduce the spread of infection within the family at home, and in their social and work lives outside the home.

In the event of a flu pandemic, it is likely that hygiene will be a first line of defence during the early critical period before mass vaccination becomes available. 'Global Preparedness' means that respiratory hygiene needs to become part of our daily lives already before such an event; the evidence suggests that not just protection from coughs and sneezes, but also hand and surface hygiene play a part in reducing the spread of respiratory infections such as colds and also influenza [1,2]. Whereas at one time there was a feeling that it was only a matter of time before we could 'close the book' on infectious diseases, experience now shows that, as soon as we begin to get one pathogen under control, another emerges. Indications are that poor hygiene is a contributory factor in the spread of pathogens such as norovirus, *Helicobacter pylori*, *Legionella* and *Campylobacter*, pathogens which were largely unheard of before the 1980s.

Across Europe, healthcare-associated infections (HCAIs) are no longer seen as a nuisance, but as a major barrier to delivering health. In addition, there is acceptance that controlling infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* and norovirus is a community as well as a hospital problem [3]. Hospital managers now realise that managing HCAI is hampered by people (new patients, visitors and healthcare workers) walking into their facilities who are silent carriers of these organisms, and that one of the key aims is containing these infections at the source in the community. Hygiene is also recognised as key to tackling antibiotic resistance. Good hygiene means fewer infections, fewer patients demanding antibiotics from their general practitioner, and thus fewer resistant strains developing and circulating in the community. Reducing the reservoir of carriers in the community reduces the risk of these strains being carried into healthcare facilities by new patients.

Across Europe, governments are under pressure to fund the level of healthcare that people expect. Although shorter hospital stays mean reduced hospital costs, the gains are likely to be undermined by inadequate infection control associated with care at home. Across Europe, up to one in five people living at home have impaired immunity to infection and need special care [1]. Those at risk include the growing elderly population, patients discharged earlier from hospital as a result of shorter hospital stays, and patients undergoing outpatient treatments such as chemotherapy, or patients with indwelling catheters.

The 1990s saw rapid increases in the incidence of food poisoning, and finally a call to action to reverse this trend. Although this has been achieved in many European countries, levels of food-borne disease remain unacceptably high. 'The Zoonoses Report', published by the European Food Safety Authority (EFSA) and the European Centre for Disease Control and Prevention (ECDC) in 2007, estimated that one third of populations in developed countries are affected by food-borne diseases every year [4]. The 2003 World Health Organization (WHO) report concluded that about 40% of reported food-borne outbreaks in the WHO European Region occur in private homes [5]. The potential for food poisoning at home is indicated by the prevalence of food-related pathogens in products purchased from retail premises. The ECDC review estimated that campylobacter were most commonly detected in fresh poultry meat, with an average of 35% positive samples. *Salmonella* was most commonly found in fresh poultry and pork meat, with 5.6% and 1.0% positive samples. Chapman *et al.* showed that 0.4-0.8% of meat products purchased from butchers in the United Kingdom (UK) were positive for *Escherichia coli* O157 [6].

Obtaining a true picture of the burden of gastrointestinal infections circulating in the community is difficult. Surveillance systems mostly focus on food-borne disease, the data coming mainly from large outbreaks in restaurants, hospitals etc, whilst sporadic cases, particularly milder infections in the home go largely unreported. Community-based studies carried out in the UK [7] and the Netherlands [8] suggest that food-borne infections represent only a fraction of the total burden of gastrointestinal infections. The 2003 WHO report stated that, of the total outbreaks reported in Europe during 1999 and 2000, 60 and 69%, respectively, were due to person-to-person rather than food-borne transmission [5]. The UK community-based study, carried out between 1993 and 1996, estimated that only one in 136 cases of gastrointestinal illness is detected by surveillance and that, for every one reported case of campylobacter, salmonella, rotavirus and norovirus, another 7.6, 3.2, 35 and 1,562 cases, respectively, occur in the community. The incidence of non-food-borne infections in the UK is estimated at around 4.5 million cases per year, the largest proportion of which are norovirus infections, which are transmitted easily from person-to-person within community groups [9].

It is often assumed that milder respiratory and gastrointestinal infections are relatively trivial, but pathogens are increasingly being implicated as contributory factors in the development of cancers and other chronic conditions which can manifest at a later date [1]; examples include *Helicobacter pylori* (peptic ulcer disease) and *Campylobacter jejuni* (Guillain Barré syndrome). Food-borne illness is estimated to result in chronic sequelae in 2-3% of cases. A European Commission report [10] cites evidence of chronic disease, such as reactive arthritis, following 5% of salmonella infections, and 5% of *E. coli* O157 infections progressing to serious, sometimes fatal, complications.

Developing a risk-based approach to home hygiene

The International Scientific Forum on Home Hygiene (IFH) (www.ifh-homehygiene.org) was established in 1997 with the aim of developing an evidence-based approach to home hygiene, and promoting this approach to scientists, opinion-formers, policy-makers and community health professionals. As part of our work, IFH has developed an approach to home hygiene based on risk management [1,11]. This involves identifying the critical control points for preventing the spread of infectious diseases in the home. Risk management is the standard approach for controlling microbial risks in food and other manufacturing environments, and is becoming accepted as the optimum means to prevent such risks in home and hospital settings [12]. A risk-based approach has also been adopted in developing the WHO Global Patient Safety Challenge to promote hand hygiene in healthcare facilities. The central concept 'My five moments for hand hygiene' focuses, not just on getting people to wash their hands, but on getting them to do it at the right time and in conjunction with other critical control measures [13].

Applied to the home, the risk-based approach has come to be known as 'targeted hygiene'. Targeted hygiene starts from the principle that pathogens are introduced continually into the home, by people (who may have an infection or may be asymptomatic), contaminated food and domestic animals, but also sometimes in water, or via the air. Additionally, sites where stagnant water accumulates such as sinks, toilets, waste pipes, or items such as cleaning or face cloths readily support microbial growth and can become primary reservoirs of infection, although those are mostly bacterial species which only represent a risk to vulnerable groups [14]. In many homes, there will also be at least one family member who is more susceptible to infection for one reason or another.

Within the home, there is a chain of events, as described in Figure 1, which results in transmission of infection from its source to a new recipient. To an extent, we can limit the exit and entry of pathogens from and into the body, but the link that we have most control over is the 'spread of pathogens'.

Risk assessment is based on assessing the microbiological data related to each stage of the infection transmission cycle in order to identify the critical control points for preventing spread of infection. To identify these points, the frequency of occurrence of pathogenic contamination at individual sites and surfaces is assessed, together with the probability of transfer from that site such that family members may be exposed. This means that, even if a particular site or surface is highly contaminated, unless there is significant probability of transfer from that site, the risk of exposure is low. This approach allows us to rank sites and surfaces (Figure 2) according to the level of risk; this suggests that the critical points are the hands, together with hand and food contact surfaces, cleaning cloths and other cleaning utensils, which form the 'superhighways' for spreading pathogens around the home such that healthy family members or the food they eat become exposed.

Although this is a useful rule of thumb ranking, it is not constant. Toilets, baths, basins etc were invented for the purpose of dealing

Figure 1

The chain of infection transmission in the home

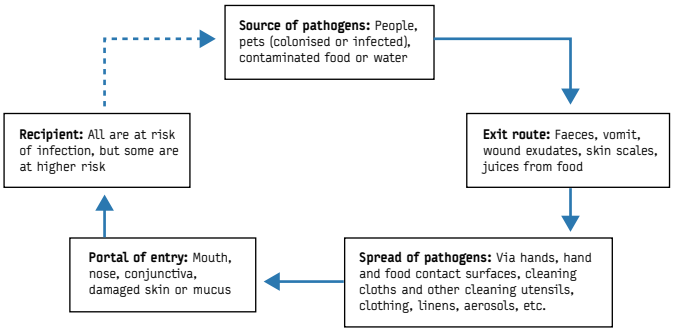
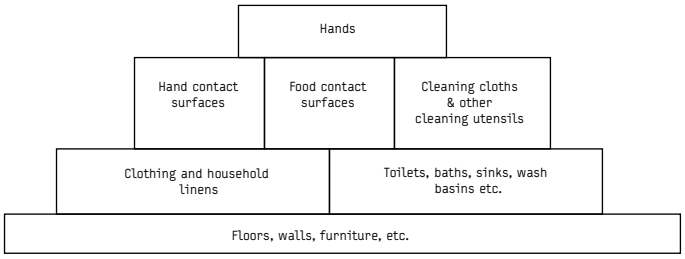


Figure 2

Ranking of sites and surfaces in the home based on risk of transmission of infections



with human waste, but this does not mean that they are zero risk areas, they still have risks associated with them, particularly when someone in the home has sickness, diarrhoea, or other contagious infections. Although floors, however dirty they may appear, are assessed as relatively low risk, the risks increase where a pet animal and a small child share a floor area, or where a floor surface is contaminated with vomit or faeces.

Targeted hygiene also means applying a suitable hygiene procedure at appropriate times to interrupt the chain of infection transmission. Since the infectious dose for many common pathogens such as campylobacter, norovirus and rhinovirus can be very small (1-500 particles or cells) [1], one must argue that, in situations where there is risk, a 'hygienic cleaning' procedure should be used which eliminates as many organisms as possible from critical surfaces [1]. Hygienic cleaning can be done in one of two ways, either by detergent-based cleaning with rinsing or by using a disinfectant/cleaner which inactivates the pathogens in situ. In many situations (e.g handwashing) a 'hygienically clean' surface can be achieved by soap and water alone, but recent studies suggest that this process is only effective if accompanied with thorough rinsing [15-17]. Wiping a surface with a cloth (or mop) will merely move organisms around the surface and onto the cloth and hands to be transferred to other surfaces. This means that in some situations we should not be afraid to recommend the use of a disinfectant. Waterless hand sanitizers should also be recommended for situations where access to soap and water is limited. To ensure elimination of most pathogens, clothing and household linens should be laundered either at 60ºC or at 40ºC using a bleach-containing laundry product [18].

The key to targeted hygiene is that it recognises that good hygiene is not a 'once weekly deep down clean', it needs to be an ongoing part of our daily lives where hygiene measures are targeted where and when necessary. Targeted hygiene also makes sense in that it offers the means to address issues such as the hygiene hypothesis because it maximises protection against infectious microbes whilst otherwise allowing normal exposure to non-harmful microbes.

As part of our work in promoting hygiene, the IFH has produced a set of 'Guidelines for Home Hygiene' together with 'Recommendations for selection of suitable hygiene procedures' [18,19]. These are based on the risk-based approach, and cover all aspects of home hygiene including food hygiene, general hygiene, personal hygiene, care of pets etc. IFH has also produced a teaching resource on home hygiene which presents home hygiene theory and practice in simple practical language which can be understood by community workers with relatively little infection control background [20].

Responding to the changing hygiene climate

The recent 'ECDC report on the state of infectious diseases' concluded that, although EU countries are generally doing well in the fight against infectious diseases, there is no room for complacency particularly in areas such as HCAIs, antibiotic resistant bacteria and the threat posed by influenza and pneumococcal infections [21]. Although international, regional and national authorities are now recognising that infectious disease prevention must be a responsibility which is shared by the family and community, and are beginning to invest in programmes to develop and promote hygiene, IFH believes that, if these programmes are to be successful in achieving behaviour change, a number of issues need to be addressed:

The need for a family-centred approach to hygiene

Across Europe, public health is currently structured such that the separate aspects of hygiene – food hygiene, personal hygiene, handwashing, pandemic flu preparedness, patient empowerment etc - are dealt with by separate agencies. This means that the information which the family receives is fragmented and largely rule-based. If things are to change we must recognise that fragmented, rule-based knowledge is not enough to meet the challenges we currently face. Hand hygiene, for example is a central component of all hygiene issues and it is only by adopting a holistic approach that the causal link between hands and infection transmission in the home can be properly addressed. There is a need for the various agencies to work in partnership in order to promote an approach to hygiene which is family-centred rather than issue-oriented. At the very least we need to ensure that the principles of infectious disease transmission and the role of hygiene are part of the school curriculum. In line with this the EU-funded e-Bug project is working to roll out education on antibiotic resistance and hygiene at primary and secondary school level across Europe [22]. In order to ensure continuity of information, we also need to work more closely with the private sector that invests considerably in communicating with consumers about hygiene and hygiene products.

Although we are seeing increasing emphasis on patient empowerment as part of strategy to reduce HCAIs, the evidence suggests that 'patient' empowerment is not enough, the need is for family empowerment. In response to the need for education on respiratory hygiene, ECDC has produced an 'Influenza Communication Toolkit' [23] for use by health communicators in devising campaigns to tackle seasonal influenza. In November 2007, the UK launched a winter communications campaign to encourage the public to practise correct respiratory and hand hygiene when coughing and sneezing [24]. .

The need to engage the family and change attitudes

In recent years hygiene has had a somewhat negative image and has come to be seen as old-fashioned and disciplinarian. We need to make hygiene more appealing to the public by realigning it with positive attributes of health and well-being. Persuading the public of the need to share responsibility without being accused of shifting blame may however be a significant challenge

The need for a risk-based approach to home hygiene

In the healthcare system, disease reduction is considered as the gold standard for assessing the effectiveness of clinical interventions. By contrast, in the industrial field, it is accepted that the cost-effective means to achieve quality (absence of microbial contamination) in products is by a risk management approach which ensures that critical control points within the process are 'under control'. Currently, there is a tendency to demand that data from intervention studies should take precedence over data from approaches such as risk assessment. Although there are those who still adhere to this, it is increasingly accepted that infection control policies and guidelines must be based on the totality of evidence including microbiological and other data, since transmission of pathogens is highly complex, involving many different pathogens, each with multiple routes of spread. This is particularly important for home hygiene, where little or no intervention data is available and the size and thus cost of intervention studies is prohibitive.

The need to balance risks against benefits of hygiene

In recent years, increasing attention has been given by the media to risks associated with hygiene. These include the perceived risk

of being too clean, concerns about toxic and environmental effects of cleaning and disinfectant products, and the possibility of links between disinfectant use and antibiotic resistance.

Media coverage of the hygiene hypothesis has declined, but a strong 'collective mindset' has become established that dirt is 'good' and hygiene somehow 'unnatural'. Although there is good evidence that microbial exposure in early childhood can protect against allergies, there is no evidence that we need exposure to harmful microbes or that we need to suffer a clinical infection [25,26]. Nor is there evidence that hygiene measures such as handwashing, food hygiene etc. are linked to increased susceptibility to atopic disease [25]. A consensus is now developing among experts that the answer lies in more fundamental changes in lifestyle that have led to decreased exposure to certain microbial or other species, such as helminths, that are important for development of immuno-regulatory mechanisms [27]. There is still much uncertainty as to which lifestyle factors are involved. There is also no evidence to suggest, as is often stated in the media, that we need to get regular infections to boost our general immunity to infection. Another key question is whether use of disinfectants is encouraging the emergence of so-called 'superbugs'. Although laboratory experiments demonstrate links between exposure to biocides and increased resistance to antimicrobials, there is currently no evidence that use of biocides in the community is linked to emergence and spread of antibiotic resistance [28].

It is vital that we continue to research these issues, but it is important to avoid overemphasising them at the expense of ensuring that the public understand the risks of not carrying out hygiene measures properly.

Conclusions

Infectious diseases circulating in the home and community are a continuing and significant burden on the health and prosperity of the European community, which could be significantly reduced by better standards of hygiene. It is now apparent that controlling infection needs to be addressed, not just in healthcare settings or in association with food hygiene, but across the community. If efforts to promote hygiene at community level are to be successful in changing behaviour, we need a concerted family-centred approach to ensure that a basic understanding of infectious disease agents and their mechanisms of spread, together with an understanding of a risk-based approach to hygiene are promoted, as part of the school curriculum and as part of public health campaigns. Alongside this, we also need unambiguous communication with the public on issues such as the hygiene hypothesis and environmental issues.

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The surveillance of communicable diseases in the European Union – a long-term strategy (2008-2013)

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This article presents the steps and considerations that led to the development of the European Centre for Disease Prevention and Control's (ECDC) long-term strategy for the surveillance of communicable diseases in the European Union (EU) for the years 2008 to 2013 [1]. Furthermore, it outlines the key features of the strategy that was approved by the ECDC's Management Board in December 2007.

Why is it necessary to carry out surveillance at the European level?

National surveillance systems and methods are very diverse and the quality of data collated varies across the EU and the three participating countries of the European Economic Association/ European Free Trade Association (EEA/EFTA). This diversity is not limited to different data collection and validation systems and different reporting systems but even to basic issues such as different interpretations of the same standard case definitions. There are also country- specific variations in the organisation of health-care systems and in the availability of facilities and equipment for diagnostics and case confirmation, all of which also contribute to this diversity. As a result, the data produced are often not comparable, as was recently demonstrated in the ECDC's first Annual Epidemiological Report on Communicable Diseases in Europe [2,3].

This diversity also applies to the 17 EU-wide Dedicated Surveillance Networks (DSNs) [4], some of which were established as early as the 1980s. They differ in scope and coverage, objectives, structure of organisation, and development phase. They have developed separate reporting rules and procedures, variable data validity checks and all have their own separate report layouts. Therefore, a more coordinated approach towards surveillance at the European regional level should lead to a better harmonisation of structures and improve the comparability of the data and hence provide an added value for all EU Member States (MS) and EEA/ EFTA countries (Table 1).

Types of surveillance

Several definitions of surveillance of health and disease have been published by a number of authors [5,6,7], with only slight variation between them. All these definitions incorporate the main elements of ongoing data collection, analysis to convert this data into statistics, interpretation of this analysis to produce information and then dissemination of this information to those who can take appropriate action.

In the context of the ECDC's work, surveillance is defined as the ongoing collection, validation, analysis and interpretation of that health and disease data that is needed to inform key stakeholders (in MS and elsewhere) to permit them to take action by planning and implementing more effective, evidence-based public health policies and strategies relevant to the prevention and control of disease or disease outbreaks. The prompt dissemination of the information to those who need to know is as essential as ensuring the quality, validity and comparability of the data.

Indicator-based surveillance

The traditional approach to the surveillance of communicable disease consists of routinely collecting data about the occurrence of predefined diseases, specific pathogens, syndromes or conditions from health-care providers. This notification process relies on standard case definitions for surveillance to ensure a uniform approach to reporting by all clinicians and laboratories and to improve the comparability of the data and reports across health-care services. The notifications are then routinely compiled and analysed to produce indicators that could suggest the existence of a threat or a problem that needs addressing. In some cases, a public health intervention would be required from the notification of a

Table 1

The main European Union added value of a more coordinated approach to surveillance

1. Improve inter-country comparability of data through a number of initiatives including by promoting the correct application of standard case definitions;
2. Reduce complexity in surveillance systems across Europe;
3. Avoid duplication of work through double reporting with various European organisations;
4. Provide more relevant and reliable data to produce higher quality public health evidence;
5. Strengthen the national surveillance systems by contributing to capacity building and standards setting in the countries;
6. Enhance the detection and monitoring of international outbreaks;
7. Be economically more efficient and sustainable in the long term than the disease-specific projects based system;
8. Allow easier access to and use of the data by all who may need it;
9. Better facilitate the inclusion of diseases into the surveillance and general research agenda according to the European priorities.

single case of the disease while in other situations, a threshold may be applied to an indicator to show up an unusual incidence rate of the disease in a given community. This "indicator-based" approach has proved to be very effective in monitoring threats related to known risks and then in ensuring the prompt implementation of public health measures.

While this traditional approach remains the backbone of public health surveillance for communicable diseases, it has proven to be less effective in ensuring prompt recognition of emerging problems. Several further approaches seek to complement traditional surveillance in order to enhance its ability to detect pubic health threats. Some of these, such as syndromic surveillance or activity monitoring, remain heavily reliant on the routine collection of structured data, again compiled as indicators. Inclusion of these approaches would only be done after discussion and agreement with MS.

Event-based surveillance

A novel approach takes advantage of the availability of advanced information technology by scanning such sources as the Internet and media continuously to detect information that may lead to the recognition of emerging threats. This "event-based" surveillance [8] approach has been introduced to complement effectively the indicator-based surveillance approach. It uses unstructured data, that then needs to be studied and verified and cannot be summarised as an indicator.

Together, both these approaches can conveniently be referred to as gathering strategic information on disease.

Steps towards a coordinated approach to surveillance in the EU

In 2005, a strategy for infectious disease surveillance in Europe was finalised to outline the transition phase from the existing project-based approach of the DSNs, mainly led by the Commission, to a more coordinated and sustainable one coordinated by the ECDC. Following this, the ECDC planned to develop a longer-term vision of the future surveillance of communicable diseases in the EU, to better ensure a common understanding of the direction and the decisions needed for the further development of the European wide surveillance systems. The drafting of this document took into account the ECDC's emergent strategy on how it will be developing the future work with laboratories, to ensure synergy across the organisation.

Goals of the ECDC's long-term surveillance strategy

The strategy defines the terms and scope of surveillance, broad goals and objectives, the organisational requirements, support needs for the MS and outlines a roadmap to implement the strategy. The overall goal of these surveillance activities is to contribute to reducing the incidence and prevalence of communicable diseases in Europe by providing relevant and accurate public health data, information and reports to decision makers and health-care professionals in an effort to promote actions that will result in the timely prevention and control of communicable diseases in Europe. Good comparability of surveillance data between MS and a high validity of communicable disease data is a key component dictating the success of this goal.

In order to achieve these goals, both the ECDC and MS have to work in close partnership to build up a strong surveillance system on the European level. MS need to strengthen, maintain or set up the structures which are required to provide the relevant data – in certain cases this may require support from the ECDC. At the same time, the ECDC will continue to develop the infrastructure and common framework, including quality assurance systems and training support, required at the EU level.

There are a number of areas where further work will be essential. These include revising the case definitions for surveillance on the EU level [9] and having a mechanism for occasional review; introducing clear principles of collaboration on data exchange, access and publication acceptable to all MS and the ECDC; ensuring a regular review of disease-specific surveillance objectives and priorities following wide consultation; developing links to other existing international databases; developing systems to critically review the diseases under EU-wide indicator based surveillance; planning for the greater integration of data from laboratories and developing ways of improving collaboration with them, in particular with the national reference level laboratories (NRL); developing more advanced data analysis methods and studying how best to communicate the results to ensure that this is information used for action.

Apart from these activities, several initiatives and systems will be essential to the success of this strategy.

The European Surveillance System

The ECDC has developed an information system for infectious disease indicator-based surveillance at the European level, The European Surveillance System (TESSy). TESSy will be a valuable tool to improve the collection, validation, storage and dissemination of surveillance data of the EU MS and EEA/EFTA countries. MS are already using it with the collection of a reduced set of common variables important for the routine surveillance of cases of all infectious diseases. TESSy will enable:

- Standardising data collection on infectious diseases surveillance;
- Providing a 'one-stop shop' for reporting and retrieving data for the MS;
- Standardising the basic reports based on surveillance data;
- Providing a consistent and easily available overview of the current situation in the EU.

Epidemic intelligence

Another system being developed focuses on developing event-based surveillance to better provide epidemic intelligence information [10]. The ECDC is working to ensure that all countries have standard procedures and tools in place to monitor and assess threats detected early. Similarly all countries will be able to use the ECDC developed 'Threat Tracking Tool' to perform joint risk assessments in the event of a threat potentially affecting more than one country. Finally the epidemic intelligence system will enable MS to continue to routinely report communicable disease threats through the Early Warning and Response System (EWRS) [11] once their assessment has confirmed the existence of a threat affecting the EU (as defined in the EWRS regulations).

Partnerships

Various collaborative agreements will be finalised with the other regional organisations also involved in the surveillance of disease, such as the World Health Organization (WHO) Regional Office for Europe and their global office in Geneva, the European Food Safety Authority (EFSA) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), in order to minimise duplication

and ensure that activities are complementary. Agreements on the principles of collaboration on data exchange between the ECDC and MS will be developed to define clearly the role of data providers and data users both in MS and the ECDC (and other parties, e.g. WHO) and the procedures for publishing the results of the analysis of data.

Collaboration with the Member States

The future collaboration with disease-specific experts in MS nominated by the ECDC's Competent Bodies, will be structured by a division of the diseases/pathogens into six main groups, namely respiratory tract infections; sexually transmitted infections, including HIV and blood-borne viruses; food- and water-borne diseases and zoonoses; emerging and vector-borne diseases; vaccine-preventable diseases; and antimicrobial-resistant pathogens and healthcare-associated infections. Where necessary, more focussed (disease-specific) subgroups can be established within any of these six groups. Annual meetings will be held for each of these six main groups to discuss issues pertinent to the surveillance of the whole disease group. If needed, specific 'parallel session' symposia can be held at the same time. For each of these six groups, a small Coordinating Group will be established and take over many of the functions carried out by the former DSN steering groups.

The ECDC plans to support the capacity development of MS to strengthen their surveillance by providing training, country visits to deal with MS-specific issues (including needs assessments and exploring ways to strengthen national systems), quality assurance (and EQA) and control processes, protocols, SOPs, guidelines, etc. Furthermore, the ECDC will work to strengthen the laboratory capacity in the EU and EEA/EFTA countries and the candidate countries in collaboration with the Commission, the ECDC Competent Bodies, and nominated National Microbiology Focal points, to ensure that every country should have the capacity of, or at least have the access to, Reference Level Laboratory (NRL) services enabling them to confirm the diagnosis, isolation of and further characterisation of all the important pathogens.

Implementation

The strategy will be implemented in two phases: a transition period until 2010, when the main focus will be on the integration of the coordination of the current DSNs to the ECDC while consolidating its own technical capacity; and the period between 2010 and 2013 when the ECDC will have taken over the full responsibility of surveillance and can then focus on developing and consolidating the highest quality and effective system possible for Europe. In order to keep this strategy and its objectives relevant, it will be revisited from time to time, with the Commission, MS and key stakeholders, so that it may be adjusted to incorporate emerging strategies or new evidence as required.

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Emergence of high-level azithromycin resistance in Neisseria gonorrhoeae in England and Wales

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The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) in England and Wales has monitored azithromycin resistance since 2001. In 2007, high-level azithromycin resistance (MICs >256 mg/L) was identified for the first time in six isolates, all of which were the same sequence type (ST 649).

High-level azithromycin resistance has also been reported in Scotland, but it is not known if this has wider geographical dissemination. It has been recommended that gonococcal resistance to azithromycin should be monitored in regions or countries where this drug is used to treat *Chlamydia trachomatis* infection. Furthermore, specific anti-gonococcal therapy should always be used to treat gonorrhoea. Azithromycin is not a recommended treatment for gonorrhoea in the United Kingdom [1]. Further information on this emerging resistance can be found at http://www.hpa.org.uk/hpr/archives/2008/hpr1408.pdf and http://www.dh.gov.uk/en/Publichealth/Patientsafety/Microbiologyandinfectioncontrol/DH_075723

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Local brucellosis outbreak on Thassos, Greece: a preliminary report

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Introduction

Brucellosis is a zoonosis resulting in reproductive failure in wild and domestic animals and febrile disease and occasionally severe infections of the central nervous system and endocarditis in humans. In animals and humans alike, it is found worldwide, including southeastern Europe, the Mediterranean basin (Portugal, Spain, southern France, Italy, Greece, Turkey, northern Africa), parts of Mexico, Central and Latin America, Asia, and Africa [1]. Human brucellosis represents a professional hazard, being acquired via ingestion, inhalation in laboratories or abattoirs, conjunctiva and skin trauma contamination with infected animal tissues and products [1,2]. Symptoms can appear as acute or insidious onset, after five to 60 days and last for days, months and occasionally as long as a year. Relapses can also occur. Treatment is effective with antibiotics. Untreated brucellosis can lead to death (case-fatality ratio around 2%), usually by heart complications.

Epidemiological situation in Greece

Between 2000 and 2007, the mean yearly incidence rate of brucellosis in Greece was 2.9/100.000 population. The annual incidence rate shows a decreasing tendency: 5 in 2000, 3.7 in 2001, 3 in 2002, 2.2 in 2003, 2.1 in 2004, 3.1 in 2005, 2.6 in 2006, and 1.38 in 2007. The data indicate that the disease mainly affects rural areas of the mainland, all cases either engaged in a high-risk occupation (shepherds, workers in animal husbandry, vets) or sharing unpasteurized milk or dairy products with friends and relatives [3,4,5]. Strict regulation in Greece only permits the circulation in the market of licensed producers' fully processed milk and its products (either pasteurized or cheese matured for at least three months before consumption) and Human Public Health and Veterinary Public Health authorities in all prefectures of the country ensure implementation by performing regular inspections in all restaurants, hotels, catering establishments and other settings. During the summer months, the Ministry of Health and Social Solidarity (MHSS) reinforces more frequent inspections for the prevention of all foodborne diseases, including brucellosis.

The majority of islands, including Thassos of Kavala mainland Prefecture, are free from human cases and herds are considered brucellosis-free, with serology conducted sporadically that prove this. The Ministry of Rural Development and Food (MRDF), regularly provides these results to the Hellenic Center for Disease Control and Prevention (HCDCP) and the MHSS, both of which it collaborates with closely. All animals are tested before importation to the islands, so no brucellosis vaccination is conducted thereafter. On the other hand, in mainland Greece the brucelfilosis control program includes vaccination of herds and regular testing for brucellosis.

Outbreak in Thassos

No cases of human brucellosis were reported in Thassos in 2007 or during the first quarter of 2008, until early May 2008, when a considerable number of cases were notified to the Department of Epidemiologic Surveillance and Intervention, of the HCDCP MHSS (Table 1). The onset of symptoms of the first case was 1 April 2008. As of 17 June 2008, 55 human cases have been reported: 53 had consumed unpasteurized milk and/or dairy products (Figure 1): eight had a high-risk profession (six herd owners and two butchers), and nine had had systematic contact with sheep and/or goats. A total of 50 cases and five cases were permanent residents of Thassos and Kavala respectively, the age ranging from eight to 88 years old, with a median of 46 years, sparing only 0-4 years old (Figure 2); 26 cases were male, 29 female.

Laboratory results

All cases reported tested positive for brucellosis (Standard Agglutination Test), except for one patient who met the clinical and epidemiological criteria while the laboratory result was pending when reported. Eight were asymptomatic while testing positive, six of whom reported consumption of non-pasteurized milk/dairy products, and two reported their husbands' illness and high-risk profession.

There is a widespread custom among local residents of Thassos of consuming unpasteurized milk and its products around Easter-time in their households. This does not affect tourists from Greece or abroad visiting the island.

Control measures

There is a a standard procedure of close cooperation between the Human Public Health (HPH) and Veterinary Public Health (VPH) officials at the local level in the Prefectures of Greece, under the constant supervision of the Unit for Zoonoses and Foodborne Diseases, of the HCDCP-MHSS, and the Ministry of Rural

Table 1

Number and percentage of brucellosis cases reported in an outbreak on Thassos, Greece, 2008

Health Unit	Number of cases (%)
Prinou's Primary Health Care Center	24 (43.7)
Thessaloniki's Hospital for Infectious Diseases	23 (41.8)
Kavala's General Hospital	1 (1.8)
Private Physicians	7 (12.7)

Development and Food. More specifically, once the HPH is informed by physicians of the National Health System (general practicioners, internists, pediatricians) of a single human brucellosis case, they define the animals or flock linked in any way with the patient and immediately provide this information to the Veterinary Public Health office so that brucellosis serology and/or testing of milk and its products are conducted in the veterinary reference laboratories. If indicated, the herd immediately undergoes all measures indicated by the brucellosis eradication and control programme operating in Greece. A spontaneous sharing of all data has been established across the country among local HPH, VPH authorities, HCDCP, and the General Veterinary Directorate, MRDF.

Soon after the first human case was notified early in May in Thassos, the above spontaneous usual procedure resulted in positive herds serology. The HPH officials, being aware of the local habit, distributed advice to all health authorities, and to all residents, door to door, suggesting the destruction of any improperly processed milk products in households.

Currently, the slaughter of seropositive animals and vaccination has been applied to all herds of the island, which is the control program already operating across mainland Greece [6], and this will continue until the island is again free of brucellosis.

Coordinated HPH and VPH inspections in all restaurants, groceries, hotels, and other settings proved that only licensed products were circulated in the market. A rapid telephone survey with a structured questionnaire was conducted by the Unit for Zoonoses and Foodborne Diseases, HCDCP, and all interviewed cases confirmed that these household products were not offered to any tourist in any setting.

Work on a case control study has been initiated and is scheduled to take place shortly.

Conclusions

Brucellosis is a disease of public health priority in Greece. The HPH and VPH authorities [7] at the central and local levels have a close collaboration and integration, aiming at the target of eradicating the disease which, judging by both reported cases and comments from leading hospitals' microbiologists, is thought to be in decline regarding annual incidence in the country. According to the information we have on this outbreak at the time of writing, it is unlikely that any tourists were exposed to brucellosis on Thassos. In addition, the public health measures applied after this local outbreak ensure that there is no future risk for tourists visiting the island.

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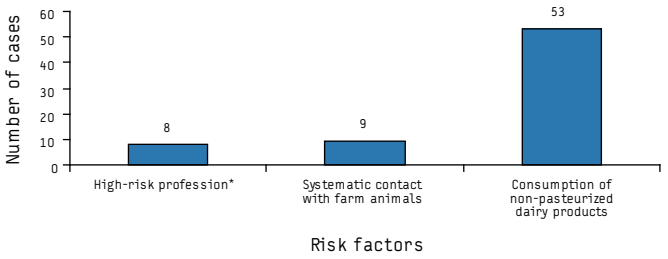
FIGURE 1

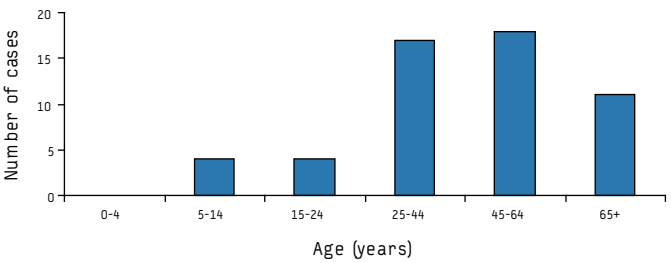
Distribution of brucellosis cases by risk factors, Thassos, Greece, 2008 (n=55)



*Shepherds, workers in animal husbandry and vets

FIGURE 2

Distribution of brucellosis cases by age group, Thassos, Greece, 2008 (n=55)



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Two cases of variant Creutzfeldt-Jakob disease reported in Spain in 2007 and 2008

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In 2005, the first case of variant Creutzfeldt-Jakob disease (vCJD) was reported in Spain, in a woman born in 1978 with clinical onset of symptoms in 2004 [1]. She subsequently died in 2005.

Recently, two more laboratory-confirmed vCJD cases were reported to the Spanish CJD state registry. In February 2006, a woman born in 1957 developed progressive cognitive deterioration, and died in December 2007 with suspected sporadic CJD (typical EEG in October 2007) MM at codon 129 and no mutations in PRPN gene. A man born in 1967 had onset in May 2007 with psychiatric symptoms, and after several months developed progressive cognitive decline with dementia, typical MRI, MM at codon 129, no mutations in PRPN gene. He died in February 2008. Post-mortem, neuropathology with histochemistry confirmed vCJD in both cases. No clear specific dietary habits, blood donations or reception were recorded. Neither case appears to have visited the United Kingdom before 2004.

The latest two cases were resident in the same region of the country, Castilla y Leon, but no link between them was established.

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Increased mumps incidence in the Netherlands: Review on the possible role of vaccine strain and genotype

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As reported in a recent issue of Eurosurveillance, a mumps outbreak is ongoing in the Netherlands despite high vaccination coverage of 90-95% [1]. The reported mumps cases are restricted to geographic regions with a high percentage of residents who are members of a religious community that rejects vaccination. Consequently, two thirds of the mumps patients were not vaccinated. However, also vaccinated individuals in these regions were affected [1]. Since 1987, the measles-mumps-rubella (MMR) combination vaccine produced by the Netherlands Vaccine Institute (NVI) is part of the Dutch national immunisation programme and administered at the ages of 14 months and nine years.

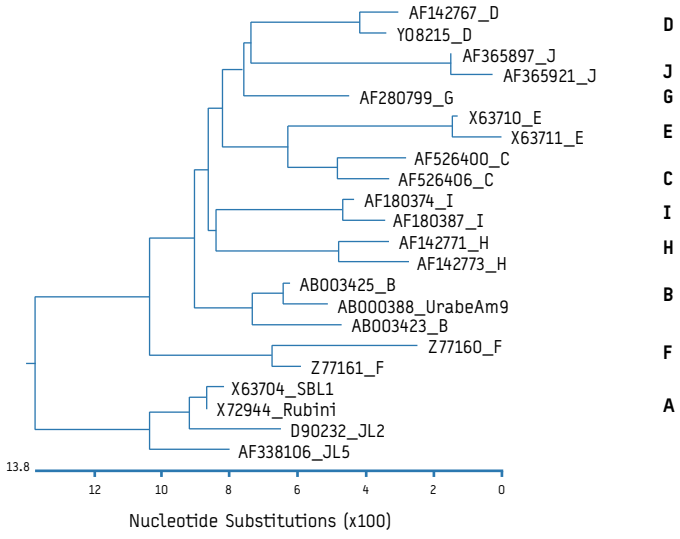
NVI's MMR vaccine contains the Jeryl Lynn mumps strain. The Jeryl Lynn strain consists of two distinct viral isolates (JL-2 and JL-5). Clinical studies have demonstrated 80-100% seroconversion after a single dose of the Jeryl Lynn mumps vaccine [2]. Outbreak-based studies have shown an effectiveness of the Jeryl Lynn mumps vaccine ranging between 63% and 96%, depending on the number of vaccinations given [2-4]. The Jeryl Lynn strain has consistently been shown to be very safe [4,5]. Table 1 shows an overview of available mumps vaccine strains.

The RIT 4385 mumps strain was derived from one of the two distinct virus populations of the Jeryl Lynn strain. Comparative studies of the RIT 4385 and Jeryl Lynn vaccines showed similar seroconversion rates, although the geometric mean titre was significantly higher among recipients of the Jeryl Lynn vaccine [2]. Several vaccines derived from the Urabe AM9 mumps strain were withdrawn from the market due to an excessive number of vaccine-associated aseptic meningitis [6]. The effectiveness of the Urabe vaccine ranges between 54 and 87% [3,5]. Another vaccine strain, Rubini, has shown to be less potent with respect to effectiveness [2,3,5]. For this reason, the WHO recommends that the Rubini strain should not be used in national immunisation programmes [2]. The Leningrad-3 strain was developed in former Soviet Union and its protective efficacy has been estimated to be 91-99% [2,4]. Unfortunately, aseptic meningitis is a particularly common event among recipients of this vaccine strain [4,7]. Furthermore, it has been reported that the Leningrad-3 strain can be transmitted horizontally, causing symptomatic disease [7]. Consequently, Leningrad-3 vaccine has not gained much attention outside former Soviet Union republics. The Leningrad-3 strain was further attenuated in Croatia and was renamed L-Zagreb, which showed equivalent good clinical protection [2]. Unfortunately, an association with aseptic meningitis has also been a matter of concern for the L-Zagreb strain as well as symptomatic transmission of the vaccine virus [4,8,9]. Several other strains have been used for mumps vaccination, but most of them on a limited scale. Therefore, little information is available on their safety and effectiveness. Based on the safety and efficacy data available for the vaccine strains, it can be concluded that the Jeryl Lynn strain has the most favourable benefit-risk profile.

A mismatch between the genotype of the circulating wild-type mumps virus and the vaccine strain may influence the efficacy of the vaccine. At present, the molecular epidemiology of mumps virus is characterised by the co-existence of 13 different genotypes named A–M [10]. Those genotypes are defined on the basis of the most variable part of the mumps virus genome, i.e. the gene encoding the small hydrophobic (SH) protein [10].

Figure

Phylogenetic tree of published sequences of 53 mumps virus strains, based on the nucleotide sequence of the small hydrophobic gene (SH)



Source: Figure obtained from Muhlemann, 2004 [11]

The designated genotypes A–J are indicated on the right.
JL2 and JL5 represent the two subpopulations of the Jeryl Lynn strain (genotype A).
Leningrad-3 and L-Zagreb vaccine strains constitute a distinct group, but no genotype has been ascribed to these strains. These strains are therefore not presented in the figure.

The currently available vaccine strains belong to a few different genotypes (see Table 1). Antigenic differences have been observed between different genotypes which result in incomplete cross-neutralisation [11]. The antigenic differences were largest between genotype A and genotypes B–D and G–I, which correlates well with the relative phylogenetic distance between these genotypes (see Figure 1) [10,11].

At present, there is no clinical evidence that a genotype mismatch leads to vaccine failure or may have epidemiological significance. For example, both the mumps virus in the outbreak in the United States (US) and Canada in 2005-2006 and the virus responsible for the mumps outbreak in the United Kingdom in 2004-2005 belonged to genotype G [4,12,13]. Nevertheless, the MMR vaccine based on genotype A (Jeryl Lynn) appeared to be effective during these outbreaks [12]. The mumps strains responsible for the current mumps outbreak in the Netherlands are of genotype D, and a previous outbreak in an international school in the Netherlands in 2004 [14] was caused by genotype G (R. van Binnendijk, personal communication), whereas the mumps vaccine strain (Jeryl Lynn) belongs to genotype A. Although cross-protection after vaccination with genotype A might not be as effective after infection with genotype G, no further transmission took place during the outbreak in 2004. This suggests that vaccine-induced (herd)

Table 1

Available mumps vaccine strains

Vaccine strain	Genotype	Manufacturer	Mumps or MMR vaccine	Main distibution area
Jeryl Lynn	A	Merck /Aventis Pasteur MSD	Mumpsvax® (mumps only) M-M-RVaxpro® (Europe) M-M-R II® (US)	United States and Europe
		Netherlands Vaccine Institute (NVI)	BMR vaccin®	Netherlands
		GSK (RIT 4385 strain obtained from Jeryl Lynn)	Priorix®	Worldwide
		Sevapharma Inc. Company	Pavivac (mumps only) Trivivac (MMR)	Czech Republic
Urabe AM9	B	Sanofi Pasteur	Trimovax®	Especially in developing countries, withdrawn in several European countries, United States and Canada
		GSK	Pluserix®	withdrawn by GSK
		Biken (Japan)		Japan
Rubini	A	Swiss Serum Institute		Not recommended by WHO due to low potency
Leningrad-3		Moscow Bacterial Medicine Institute		Russia
L-Zagreb		Institute Immunology Zagreb		Croatia, Slovenia
		Serum Institute India	Tresivac®	India
S79		Dalian Jinjang-Andi Bioproducts (China)		China
Sofia-6		Centre Inf Parasitic Dis (Bulgaria)		Bulgaria (suspended)
Hoshino	B	Kitasato Institute (Japan)		Japan, Korea
Miyahara	B	Chemo-Sero Ther Research Inst (Japan)		Japan
Torii		Takeda Chemicals (Japan)		Japan
NK M-46		Chiba (Japan)		Japan
S-12		Razi State Serum & Vaccine Inst (Iran)		Iran
		Berna Biotech (BBM-18 strain obtained from S-12)		Europe

Source: Netherlands Vaccine Institute (NVI), June 2008

Table 2

Recent mumps outbreaks with identified responsible wild-type virus (genotype)

Country	Year	Vaccine strain (genotype)	Responsible virus (genotype)	Reference
The Netherlands	2004	Jeryl Lynn (A)	(G*)	[14]
	2007-2008	Jeryl Lynn (A)	(D)	[1]
Canada/United States	2006-2007	Jeryl Lynn (A)	(G5)	[4,12]
United Kingdom	2004-2006	Jeryl Lynn (A)	(G5)	[13]
Russia	2002-2004	Leningrad-3	(C2) (H2)	[15]
Belarus	2001-2003	until 1996: Leningrad-3 since 1996: Urabe (B)	(H1)	[16]

* R. van Binnendijk (personal communication)
Source: Netherlands Vaccine Institute (NVI)

immunity was high enough to prevent further circulation of the mumps virus. On the other hand, it is striking that the viruses responsible for reported mumps outbreaks belong to genotypes of that are phylogenetically distinct from the vaccine strains used in the area of the outbreak (see Table 2). Therefore, the possibility that the mumps virus might evolve under selection pressure from the vaccine warrants surveillance of genotype distribution.

Finally, waning vaccine-induced immunity may contribute to a reduced effectiveness of the vaccine. Previously, it was assumed that mumps vaccination induces life-long immunity against mumps. However, increasing evidence shows that vaccinated individuals and possibly also naturally infected individuals, become more susceptible with time after the last exposure to the mumps virus [4,12,13]. Examples are two mumps outbreaks that occurred among vaccinated students in an international school in the Netherlands [14] and on college campuses in the US [12]. Therefore, stronger precautions should be taken to avoid an increase in susceptible adolescents and adults that are more at risk for mumps-related complications such as orchitis and meningitis. Catch-up immunisations should be considered for unvaccinated individuals and susceptible vaccinated people, especially for those living in groups in close contact.

In response to a mumps outbreak, several countries such as Ireland have decided to move the second MMR vaccination forward to the age of four or five years (instead of between nine and 14 years) to decrease the risk of waning immunity between the two vaccinations. However, other outbreaks show that waning immunity may also occur after the second vaccination. Moreover, by decreasing the age of the last MMR vaccination, the susceptibility of women for rubella during their fertile period may increase, which potentially leads to more cases of congenital rubella syndrome.

Conclusion

The first priority should be to avoid clustering of unvaccinated people by making an effort to convince people to get vaccinated. Although a number of mumps cases have occurred in vaccinated individuals, no other mumps vaccine strain is available at present with equivalent or better effectiveness and similar safety profile than the currently used Jeryl Lynn strain. However, the impact of a genotype mismatch between the wild-type virus and the vaccine virus on the mumps vaccine effectiveness as well as the possibility of waning vaccine-induced immunity should be further explored.

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An increase in reported cases of haemorrhagic fever with renal syndrome in Slovenia in early 2008

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Haemorrhagic fever with renal syndrome (HFRS) is an acute zoonotic viral disease, caused by hantaviruses. Hantaviruses infect rodents worldwide. They are transmitted to humans by aerosol from rodent excreta. Several hantaviruses are known to infect humans with varying severity.

In Europe, three hantaviruses pathogenic for humans are well documented. Puumala virus (PUUV) carried by *C. glareolus* (bank vole) and causing a milder form of HFRS (Nephropathia epidemica) is reported throughout Europe and western Russia [1]. Dobrava virus (DOBV) is carried by Apodemus flavicollis, the yellow-necked filed mouse, and is associated with a severe form of a disease with up to 12 % mortality in the Balkans [2,3]. Saaremaa virus (SAAV) is carried by Apodemus agrarius, the striped field mouse, and is found in the Baltic and Central Europe causing mild HFRS similar to PUUV infection [4,5,6].

The first hantavirus infection was diagnosed in Slovenia in 1952. Both severe and mild clinical courses of the disease have been observed, with an overall lethality rate of 4.5 percent [7]. We have demonstrated that DOBV and PUUV co-exist in a single endemic region of Slovenia and are capable of causing HFRS with significant differences in severity [2]. Earlier epidemiological surveys indicated that *A. flavicollis* and *C. glareolus*, which are common rodent species throughout central Europe, were most often infected with hantaviruses [8,9,10].

Notification of all hantavirus infections has been mandatory in Slovenia since 1978. They are reported to regional institutes of public health as HFRS (in the following text, all hantavirus infections caused by PUUV or DOBV will be addressed as HFRS). As of 16 April, 11 sporadic cases of HFRS have been reported in Slovenia (two in January, one in February, five in March, and three more until 16 April). This represents an early increase of reported HFRS cases (Figure 3). There were 14 cases of HFRS in the whole of 2007, and only two cases were reported in the same period last year (both in April).

All the cases reported this year have been from five of Slovenia's nine health regions: Ljubljana, Celje, Kranj, Maribor and Novo mesto (Figure 1). Two patients are women, nine are men . They are 34 to 75 years old.

Laboratory diagnosis (indirect immunofluorescent antibody (IFA) test for the detection of human serum IgG antibodies and ELISA for the detection of human serum IgM antibodies) of all HFRS cases was performed by the Institute of Microbiology and Immunology at the Medical Faculty in Ljubljana. In nine cases, the infectious agent was Puumala and in two Dobrava. The causative virus was indentified by using RT-PCR method in acute serum samples [11,12].

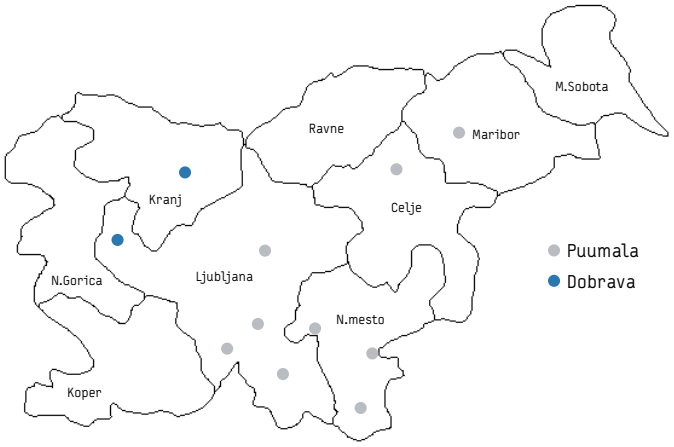
Some information about possible exposure is available for nine cases of HFRS (9/25 (25 = 14 from 2007 and 11 from 2008) =36%) reported in 2007 and 2008: three of them worked in the field, four had contact with rodent excreta or direct contact with rodents at home and two patients had direct contact with rodents at their workplace.

In the last 10 years, zero to 27 HFRS cases were reported annually. Figure 2 shows the number of reported HFRS cases between 1999 and 2008.

More cases than usual are expected this year due to an early increase of cases in the first three months of 2008 and because the usual season of HFRS in Slovenia has only just begun. In previous years, most cases were reported in late spring and summer (Figure 3). The increase of cases in early 2008 has probably been as a result of a mild winter and its impact on the rodent population [13,14].

Figure 1

Geographic distribution of reported hantavirus infections caused by Dobrava and Puumala, Slovenia, 1 January to 16 April 2008



Control measures

Information about this increased occurrence of HFRS cases has been sent to regional public health doctors, general practitioners, infectologists, nephrologists and pediatricians. Rodent control in and around the home remains the primary strategy in preventing hantavirus infection. Therefore, general precautions to limit exposure to rodents have been stressed in communications with the media.

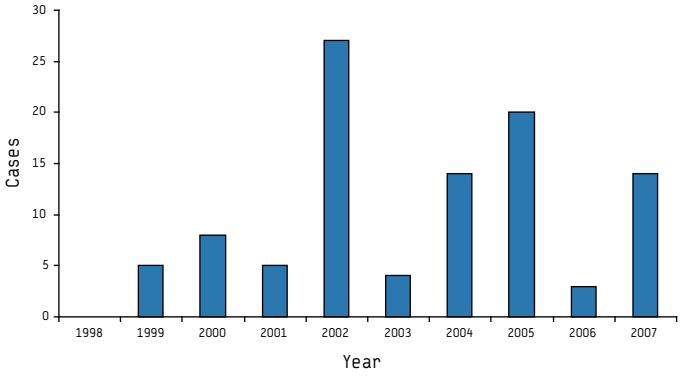
Precautions to limit exposure to rodents include:

- Interiors and exteriors of houses should be carefully inspected at least twice a year for any openings in which rodents could enter and for conditions that could support rodent activity [15], such as the possibility to store food or organic waste not kept in a rodent-proof manner;
- Inside the home, food, including pet food and water, should be kept in rodent-proof containers, while dishes and cooking utensils should be washed immediately after use.
- Leftover food should be cleaned up;
- Trash and garbage should be disposed on a frequent and regular basis;
- Safe methods to dispose of rodents' excreta and dead animals should be used.

If rodent infestation is severe or persistent, a pest control professional for rodent eradication should be called.

FIGURE 2

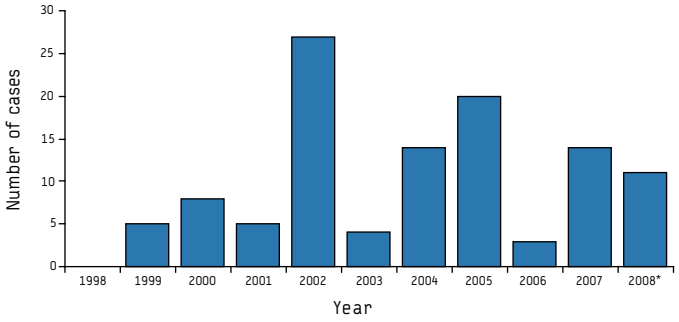
Monthly distribution of reported hantavirus infections caused by Dobrava and Puumala in Slovenia in 2008* (n=11), monthly distribution for 10 years (n=100) and 5 years (n=55) average and monthly distribution of average of two years with highest number of reported cases since the 1990s, when the electronic database was launched**



*1 January to 16 April 2008
** 2002 (n=20) and 2005 (n=27) reported cases

FIGURE 3

Number of reported hantavirus infections caused by Dobrava and Puumala in Slovenia (1999-2008*; n = 111)



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Imported rabies in a quarantine centre in the United Kingdom

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On the evening of 25 April 2008, the Health Protection Agency of the United Kingdom (UK) was informed that rabies had been confirmed through post-mortem examination of a dog that had died that same day in a quarantine centre in London. The dog, approximately 10 weeks old, had been imported from Sri Lanka, through Heathrow Airport in London, on 17 April by a charity that 'rescues' stray animals from that country and imports them into the UK. The public health response was undertaken through the coordinated activities of the authorities responsible for animal and human public health respectively.

Animal health investigations ascertained that the index dog had been imported on 17 April along with 4 other dogs, following capture in Sri Lanka on 12 April, and that following an overnight stay at the Animal Reception Centre in Heathrow, it had been transferred to a quarantine centre, were it had been kept in an isolation unit with 4 other dogs until the time of its death. The dog was reported to have first developed signs compatible with rabies on 23 April. The four dogs kept in isolation with the index dog were destroyed and post mortem tissues sent for examination for evidence of rabies; none had exhibited compatible signs at the time of death.

The immediate human health priority was to identify all individuals who may have had contact with the index dog during the period that it was potentially infectious, and to undertake individual risk assessment for each person and offer prophylaxis, using a specially developed risk assessment algorithm. All direct contact with the animal between its 'rescue' in Sri Lanka and its death was considered to pose a potential risk of exposure to rabies virus, in line with national policy that is based on infectiousness potentially extending for up to a maximum of 14 days before onset of signs in dogs or cats [1] .

A systematic approach to identifying potential human contacts, based on an analysis of each step in the dog's journey from Sri Lanka to the quarantine centre on London. The head of the importing charity was interviewed to ascertain who might have had contact during the capture in Sri Lanka and during the time between capture and departure from that country. This led to the identification of four British nationals who had been involved in the rescue mission, and a Sri Lankan veterinarian who had vaccinated the dog two days before departure. The dog was transported to the UK on a non-stop flight, during which there would have been no contact between the dog and flight crew. Interviews with ground staff at Heathrow Airport identified two groups of staff with potential contact, the ground crew unloading the dogs from the plane, and staff working at the Animal Reception Centre in the airport (where the dog was kept overnight, prior to transfer to a quarantine centre). All staff at the Quarantine Centre and any visitors during the period that the dog was there were also identified through interviews with the quarantine centre manager.

A total of 42 people were risk assessed to ascertain their degree of contact with the puppy, their previous rabies immunisation status and their need for rabies post exposure prophylaxis (rabies vaccine +/- Human Rabies Immunoglobulin (HRIG)).

A total of 12 persons were found to have had direct physical contact with the puppy (body fluid contact with skin or mucous membranes and/or bites) during the relevant time period: 11 resident in the UK, and one (the veterinarian) in Sri Lanka. Four of these people had had high-risk contact with the puppy, all within the quarantine kennels. Three of these people were bitten by the puppy in the latter stages of its illness, and one received faecal matter from the puppy into the eye. Of the 11 persons who had had direct contact with the puppy in the UK, five had previous complete vaccination against rabies, three had previous incomplete vaccination (primary course without adequate boosters) and three were unimmunised. All 11 received rabies post exposure prophylaxis, including vaccine and immunoglobulin (HRIG) where indicated. Information was passed on to the Sri Lankan authorities about the veterinarian who had had contact with the puppy in Sri Lanka.

Comment

This incident occurred shortly after two other rabies incidents associated with the importation of dogs into the European Union (EU) [3,4]. In those incidents, the imported dogs were not subject to statutory quarantine requirements, and in one incident this is known to have resulted in indigenous transmission between dogs within the EU. The incident in the UK described here, and the recent incidents that came to light in France and elsewhere, have highlighted the continued rabies threat associated with the importation of dogs, and emphasises the following key elements to the successful prevention and control of rabies:

- Effective quarantine measures, with minimal handling of animals and use of appropriate protective clothing during transfer and initial assessment, particularly if showing signs of ill health;

- The importance of ensuring that staff who may have contact with rabid animals are fully immunised, and that they maintain immunity through regular booster doses;
- The value of coordinated animal and human health responses, with regular and rapid communication.

This text is adapted from a news item originally published in the Health Protection Report of the Health Protection Agency on 2 May 2008 [2].

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Letter: Prevention of the spread of infection – the need for a family-centred approach to hygiene promotion

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To the editor: We read the article *'Prevention of the spread of infection – the need for a family-centred approach to hygiene promotion'* by Bloomfield *et al.* [1] with interest. While the authors raise valid points with regards to a more concerted approach to personal hygiene, there are two issues in the report which we wish to respond to.

Bloomfield *et al.* state that public health practitioners should be less ambiguous on issues such as the hygiene hypothesis which should be communicated to the public. Some studies suggest a role for the hygiene hypothesis in promotion of inflammatory bowel disease (IBD), whereby childhood exposure to infections confer protection against autoimmune disease [2,3]. However, an ecological study in a paediatric population demonstrated an association between cattle density and incidence of E. coli O157-mediated haemolytic uraemic syndrome (HUS) [4], and the importance of environmental transmission for this pathogen cannot be ignored [5]. Therefore, the concept of 'good dirt; bad dirt' remains a contentious area, especially in public health. Promulgating the hygiene hypothesis and related environmental issues to the public will serve only to confuse rather than to inform.

Bloomfield et al. also suggest that poor hygiene is a contributory factor in the spread of several pathogens including legionella without providing supporting references. In our experience, typical and atypical sources of legionella do not involve routes of transmission which can be exploited by improving hygiene and we are not aware of any references to support this. Indeed, it is current practice in Scotland for public health practitioners managing legionella outbreaks to ensure, within press statements, that the public are re-assured legionella cannot be spread through person-person contact or through poor hygiene.

We agree with Bloomfield *et al.* that promotion of personal hygiene should start from within the home as the simple task of hand washing has been shown to be one of the most effective means of controlling the transmission of infectious organisms from hands and beyond [6].

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Authors reply: Prevention of the spread of infection – the need for a family-centred approach to hygiene promotion

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We thank Kevin G. J. Pollock, Rod House and John M. Cowden for their response to our article *'Prevention of the spread of infection – the need for a family-centred approach to hygiene promotion'* [1].

We agree that promulgating the hygiene hypothesis and related environmental issues to the public can serve to confuse, rather than to inform. The reality is however that these issues have already received widespread coverage by the media, which tends to leave the public concerned and confused about the role of hygiene and cleanliness, particularly in relation to the functioning of the immune system. Although there is good evidence that microbial exposure in early childhood may help to protect against allergies, there is no evidence that we need exposure to harmful microbes or that we need to suffer a clinical infection [2]. There is also no evidence to show that reduced exposure to pathogens through hygiene measures such as handwashing, food hygiene etc. is linked to increased susceptibility to atopic disease [3]. To rectify the confusion, we need clearer communication with the public on these complex issues which includes emphasising the important role of 'hygiene' (the things we do to protect us from exposure to harmful microbes) and what hygiene means. In the risk perception of people, it is important that the 'hygiene hypothesis' is not used as an argument against implementing basic hygiene requirements in home, community and also in hospital settings.

As far as legionella is concerned there is some evidence that transmission can occur in the home as well as in public places, although we did not imply that this is through person-to-person contact, and we agree that it is important not to over-emphasise the risk in consumer advice communications. In August and September 2006, eight cases were reported to a local health authority in eastern England. No common source for this cluster could be established. Legionella was isolated from the home of two patients (two showerheads in one home and a hot tub in the other), although clinical isolates were not available for genetic typing. The investigators concluded that multiple sources (both domestic and environmental) may have caused the cluster [4]. In Germany, 47% of notified legionella Infections are estimated to be acquired at home [5]. The 'home hygiene' measure which the International Scientific Forum on Home Hygiene recommends to avoid the possibility of inhalation of pathogens such as legionella or pseudomonas which may become associated with showerheads, is to turn the hot water on full and allow it to flow for a while to create a flushing process before taking the first shower after an interval of no use [6]. This is particularly important in homes where there are family members who may be immuno-compromised.

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GERMANY

Epidemiologisches Bulletin
Robert Koch-Institut, Berlin
Weekly, print and online. In German.
http://www.rki.de/DE/Content/Infekt/EpidBull/epid__bull__node.html

HUNGARY

Epinfo (az Országos Epidemiológiai Központ epidemiológiai információs hetilapja)
National Center For Epidemiology, Budapest.
Weekly, online. In Hungarian.
http://www.oek.hu/oek.web?to=839&nid=41&pid=7&lang=hun

ICELAND

EPI-ICE
Landlæknisembættið
Directorate Of Health, Seltjarnarnes
Monthly, online. In Icelandic and English.
http://www.landlaeknir.is

IRELAND

EPI-INSIGHT
Health Protection Surveillance Centre, Dublin.
Monthly, print and online. In English.
http://www.ndsc.ie/hpsc/EPI-Insight

ITALY

Notiziario dell'Istituto Superiore di Sanità
Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome.
Monthly, online. In Italian.
http://www.iss.it/publ/noti/index.php?lang=1&tipo=4

Bolletino Epidemiologico Nazionale (BEN)
Istituto Superiore di Sanità, Reparto di Malattie Infettive, Rome.
Monthly, online. In Italian.
http://www.epicentro.iss.it/ben

LATVIA

Epidemiologijas Bileteni
Sabiedribas veselibas agentura
Public Health Agency, Riga.
Online. In Latvian.
http://www.sva.lv/epidemiologija/bileteni

LITHUANIA

Epidemiologijos žinios
Užkreciamuju ligu profilaktikos ir kontroles centras
Center for Communicable Disease Prevention and Control, Vilnius.
Online. In Lithuanian.
http://www.ulpkc.lt/ulpkc.laikrastis.php

NETHERLANDS

Infectieziekten Bulletin
Rijksinstituut voor Volksgezondheid en Milieu
National Institute of Public Health and the Environment, Bilthoven
Monthly, print and online. In Dutch.
http://www.rivm.nl/infectieziektenbulletin

NORWAY

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

POLAND

Meldunki o zachorowaniach na choroby zakazne i zatruciach w Polsce
Panstwowy Zaklad Higieny,
National Institute of Hygiene, Warsaw.
Fortnightly, online. In Polish and English.
http://www.pzh.gov.pl/epimeld/index_p.html#01

PORTUGAL

Saúde em Números
Ministério da Saúde,
Direcção-Geral da Saúde, Lisbon.
Sporadic, print only. In Portuguese.
http://www.dgsaude.pt

ROMANIA

Info Epidemiologia
Centrul pentru Prevenirea si Controlul Bolilor Transmisibile,
National Centre of Communicable Diseases Prevention and Control, Institute of Public Health, Bucharest.
Sporadic, print only. In Romanian.
http://www.cpcbt.ispb.ro

SLOVENIA

CNB Novice
Inštitut za varovanje zdravja, Center za nalezljive bolezni, Institute of Public Health, Center for Infectious Diseases, Ljubljana.
Monthly, online. In Slovene.
http://www.ivz.si

SPAIN

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

SWEDEN

EPI-aktuellt
Smittskyddsinstitutet, Stockholm.
Weekly, online. In Swedish.
htpp://www.smittskyddsinstitutet.se/publikationer/smis-nyhetsbrev/epi-aktuellt

A selection of report titles from the national epidemiological bulletins in the European Union and Norway is translated and published online once a month: http://www.eurosurveillance.org

UNITED KINGDOM

England and Wales
Health Protection Report
Health Protection Agency, London.
Weekly, online only. In English.
http://www.hpa.org.uk/hpr

Northern Ireland
Communicable Diseases Monthly Report
Communicable Disease Surveillance Centre, Northern Ireland, Belfast.
Monthly, print and online. In English.
http://www.cdscni.org.uk/publications

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

OTHER JOURNALS

EpiNorth journal
Norwegian Institute of Public Health, Folkehelseinstituttet, Oslo, Norway
Published four times a year in English and Russian.
http://www.epinorth.org

OTHER LINKS

European Union
"Europa" is the official portal of the European Union. It provides up-to-date coverage of main events and information on activities and institutions of the European Union.
http://europa.eu

European Commission - Public Health
The website of European Commission Directorate General for Health and Consumer Protection (DG SANCO).
http://ec.europa.eu/health/index_en.htm

Health-EU Portal
The Health-EU Portal (the official public health portal of the European Union) includes a wide range of information and data on health-related issues and activities at both European and international level.
http://ec.europa.eu/health-eu/index_en.htm

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