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Tuberculosis and vaccination

Euroroundup

- Meat inspection for *Trichinella*

Surveillance reports

- Tattooing and piercing in Amsterdam
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- OUTBREAK DISPATCHES
  Measles outbreak in Greece

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Tribute to Andrea Infuso

This issue of Eurosurveillance with a Topic on tuberculosis and vaccination (pp 6-33) is dedicated to the memory of Andrea Infuso, a dear and respected colleague and friend, who died suddenly on 20 September 2005 at the age of 44. Andrea was actively involved in the preparation of this special issue on vaccination and tuberculosis. As EuroTB coordinator since 2000, his knowledge of and contacts with all European experts involved in tuberculosis surveillance in Europe were very valuable in conceiving this thematic issue. The Euroroundup, *European survey of BCG vaccination policies and surveillance in children, 2005* (pp 6-11), written by Andrea as first author, is a posthumous publication.

The editorial team

Andrea Infuso, medical epidemiologist, and coordinator of the European tuberculosis surveillance network EuroTB, died suddenly on 20 September 2005, at the age of 44. He made outstanding contributions to the development of HIV and tuberculosis surveillance in Europe.

When he qualified as a doctor in Milan in the mid-1980s, at the height of the emergence of AIDS, his first job was as a clinician, caring for AIDS patients in one of the major infectious disease hospitals in Milan. He later joined Médecins sans Frontières to work at a refugee camp in northern Thailand, where he was in charge of a small hospital and trained community health workers. When he returned to Italy, he worked at the Istituto Superiore di Sanità in Rome for several years, where he was known for his intelligence, his ability and his commitment to public health. In 1995, he was selected by the Italian government to be part of the first cohort of the European Programme for Intervention Epidemiology Training (EPIET). The director of the Italian Centre for Epidemiology and Surveillance said that Andrea was considered to be the best investment that they could make.

His European career began with his EPIET assignment at the Institut de Veille Sanitaire (InVS) in France. He was so much appreciated there that, after completing the two year EPIET programme, he was recruited to lead major European surveillance activities and remained in France, first with the European Centre for the Epidemiological Monitoring of AIDS (CESES) and later with InVS. He played an essential role in developing the surveillance of HIV infection at the European level. In 2000, he took over the scientific coordination of EuroTB, which is funded by the European Commission and is a World Health Organization collaborating centre. He continued to make substantial and valuable contributions, harmonising data from 52 countries and introducing programmatic aspects into tuberculosis surveillance to monitor drug resistance and treatment outcomes. He was very concerned about the rising incidence of HIV and tuberculosis in eastern Europe and never stopped drawing attention to this urgent public health issue.

Andrea Infuso, coordinator of EuroTB, pioneer in European tuberculosis and HIV surveillance

Andrea was respected not only for his scientific acuity but also for his commitment to his colleagues. He was always there to help and defend others, and he had an incredible force and energy to fight for good causes. He asked the most incisive, often provocative, questions, always stimulating constructive discussions. He was both direct and respectful. He was devoted to his wife, Monica, and their children, Milo and Gae, whose drawings papered the walls of his office. He was a fine musician and a good singer. Above all, he was fun. Andrea will be sorely missed by his many friends and colleagues.

Françoise Hamers, Institut de Veille Sanitaire, France

Note: This tribute was previously published online on 29 September 2005 in the Eurosurveillance weekly release http://www.eurosurveillance.org/ew/2005/050929.asp#4

EDITORIAL

TUBERCULOSIS AND BCG IN EUROPE

John M Watson
Health Protection Agency, Centre for Infections, London, UK

BCG (Bacillus Calmette-Guerin) vaccine was developed from an attenuated strain of *Mycobacterium bovis* at the beginning of the twentieth century. Its widespread use as a vaccine against tuberculosis spread in Europe, and subsequently globally, over the next 50 years. It remains one of the most frequently administered vaccines in the world. It has also been one of the most controversial. Widely differing estimates of the effectiveness of BCG at protecting against different forms of tuberculosis in different population subgroups in different settings have been published [1]. Some countries, with a low incidence of tuberculosis, did not adopt the use of BCG vaccine at all and some others abandoned its use at a later stage. In addition, great variation developed in national programmes for the administration of BCG including the age(s) at which it should be given, whether or not its administration should be preceded by tuberculin sensitivity testing, and whether repeat vaccinations with BCG should be given.

Policies for the use of BCG vaccine are under review in 12 European countries. The most common proposal is a shift from universal vaccination to selective vaccination of children at risk.

In recent decades, some consensus has been reached about the role of BCG vaccination in populations where it appears to offer some protection. Protection appears to be greatest in infants and children and against the early primary progressive forms of disease (including disseminated disease and meningitis) [2,3]. Protection against disease resulting from secondary reactivation, particularly pulmonary disease in adults, appears to be much more limited. As this is the group of cases responsible for most transmission of infection, BCG vaccination probably has very limited impact on controlling the incidence of new infections in the community. In addition, the evidence that repeat vaccination offers additional protection is very limited.

It is therefore timely that, on World TB Day, this edition of Eurosurveillance brings together a series of articles on the use of BCG vaccination in Europe demonstrating not only the continued variation in policies for the use of BCG, sometimes in otherwise very similar epidemiological settings, but also the growing number of countries reviewing and revising their national policies in the light of the growing consensus on its role and the local pattern of occurrence of TB.

Andrea Infuso and Dennis Falzon, on behalf of the EuroTB network (www.eurotb.org), have surveyed national policies on BCG vaccination in Europe [4]. Most (83%) countries responded to reveal policies that varied from no use of BCG vaccine at all, through use of vaccine in neonates and infants in population groups assessed to be at high risk of infection, to vaccination of all children at birth, in infancy, at school entry or in later school years. Routine revaccination, with or without prior tuberculin sensitivity testing, is recommended in four countries – in one instance, for all children at four separate ages. In 12 countries, the current policy was reported to be under review with a shift from universal vaccination to selective vaccination of children at risk being the most common proposal.

Limited data on BCG vaccine uptake levels or information on the occurrence of adverse effects was available and the authors conclude by calling for more systematic collection of comparable data between countries, as well as the discontinuation of routine revaccination. The availability of comparable data on the occurrence of TB in different countries and an understanding of current policies for BCG vaccine use and its uptake, contribute usefully to discussions within individual countries about future policy.

France is one such country that is currently reviewing its approach to the use of BCG vaccine. Daniel Levy-Bruhl reports that revaccination with BCG has ceased from 2004 in France [5]. Moreover, the Conseil Supérieur d'Hygiène Publique de France (the national high committee of public hygiene) has recommended the discontinuation of routine vaccination of all schoolchildren, in favour of a more targeted approach, but only when other measures to strengthen control measures to decrease the risk of infection in children have been implemented. In Finland too, where all newborns have routinely been offered BCG vaccination with an uptake rate of 98%, Eeva Salo reports that the national policy has recently been revised so as to offer BCG only to risk groups [6]. A similar review and revision of BCG policy in the United Kingdom has also taken place in July 2005, with the implementation of selective vaccination and abandonment of the universal schools BCG programme in place since the 1950s [7].

Sweden, by contrast, abandoned its policy of universal BCG vaccination in 1975 while retaining selective vaccination for high risk groups [8]. Victoria Romanus reports that the incidence in indigenous Swedish born children, which was already very low in the 1970s, has remained low. High uptake of BCG vaccination, however, has been achieved in the high risk groups. Despite the low incidence in Sweden, outbreaks occasionally occur in vulnerable groups such as young children in association with delayed diagnosis, providing a reminder of the need to identify and institute treatment in active cases early as well as to screen contacts who may have been exposed.

Another benefit of the collaboration of all European countries in the EuroTB surveillance network has been the opportunity to collate information on the outcome of treatment in patients with tuberculosis. This is not without difficulty as assessment of treatment outcome in individuals within countries involves decisions about which cases to include, how to classify various categories of failure to complete standard treatment and how to deal with cases on which there is only partial or complete absence of information on outcome. To collate these data from different countries and provide information that can usefully be compared between countries is an even greater challenge. Dennis Falzon and colleagues [9], on behalf of EuroTB, have gone along to achieving this through the development of standardised outcome categories, and definitions of disease type and population subgroups to be included (all confirmed pulmonary cases with or without previous treatment). Forty-two of 51 eligible European countries submitted results and completeness of reporting was reported to be very high in most countries (at least 98% of originally notified cases in 35 countries). Despite generally high levels of reported successful treatment completion, problems with the interpretation of outcome categories such as 'defaulted', 'transferred' and 'unknown' continue to complicate the interpretation of the outcome in those in whom treatment has probably not been successful. The authors conclude that further simplification of outcome categories combined with standardisation of the application of the definitions will lead to more robust and comparable data.

Finally two reports from TB trouble spots, Latvia and London, illustrate the different tuberculosis problems in those widely different settings and the challenges to achieving effective control of tuberculosis. Vaira Lemaine from Latvia [10] describes the high incidence of disease, including high prevalence of multi-drug resistance (MDR), that has emerged since the early 1990s with the socio-economic disruption and health system reform that followed the political changes of that period. The implementation of a new national tuberculosis programme in 1996 with adoption of the WHO Directly Observed Therapy Short-course (DOTS) strategy for all new cases and, in 1999, the addition of the WHO DOTS-Plus strategy for individualised management of MDR tuberculosis, has led to great progress in reducing case numbers. Much remains to be done, however, and progress to date is threatened by a developing HIV epidemic. In London, as Delphine Antoine and colleagues report [11],

tuberculosis is not under control and case numbers continue to increase, though not at the levels reported from Latvia. Particular problems are identified with tuberculosis in the homeless, drug users and alcoholics. The authors call for greater adaptation of treatment and care services in London to cater for the special needs of those at greatest risk of tuberculosis in the capital including greater use of DOT (especially in the intensive phase) and greater support for patients during treatment.

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EDITORIAL

TATTOOING AND PIERCING – THE NEED FOR GUIDELINES IN EU

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As in Amsterdam [1], the impetus for UK guidelines for hygienic tattooing came from an outbreak of hepatitis B caused in 1978 by a tattooist. The outbreak resulted in 30 primary and 3 secondary cases [2]. Guidelines for hygienic tattooing followed soon after, and were taken up, fairly enthusiastically on the whole, by the tattooists. These were expanded in 1982 to include acupuncture, ear-piercing and hair electrolysis. Laws to control the hygiene of these practitioners were introduced at the same time {Local Government Miscellaneous Provisions Act 1982 [amended 2003] and the Greater London Council [General Powers] Act 1982}. Body piercing was hardly heard of at the time: although it was undoubtedly and somewhat furtively practised, it was not as popular or as open as it is now. Guidelines for beauty therapy, hygienic hairdressing and micropigmentation followed.

The main, and most urgent, problem with non-medical skin penetration is hygiene – in particular the transmission of bloodborne viruses, and especially hepatitis B. This virus is arguably the most infectious organism known to man and can survive for long periods in the environment. Fortunately, the guidelines formulated in 1978 and 1982 in the UK were for hepatitis B, so that when the other two main bloodborne viruses, hepatitis C and HIV, became known a little later, being much less resistant, they were adequately covered by the guidelines.

HCV may be asymptomatic for years, and HIV may also be asymptomatic, though usually for a shorter period. HBV infection in adults is less commonly asymptomatic, but all three infections eventually cause serious symptoms. The incubation periods for these three infections can be long, which can make outbreaks difficult to recognise. Bacterial infection must also be considered – in my experience, these usually arise from poor aftercare or poor aftercare advice. Infection introduced at the time of the piercing may lead to septicaemia and even to endocarditis in susceptible persons, and also, of course, to wound infections. Infection arising after piercing the cartilage of the ear is a particular and urgent problem, brought about as frequently by poor aftercare as by an unhygienic piercing.

Besides the hygiene of non-medical skin piercing, other factors need to be addressed such as training and accreditation of practitioners

The hygiene of non-medical skin piercing needs to be addressed urgently in the EU, so that uniform and effective guidelines can be applied throughout the Community. Otherwise, with different guidelines, standards of practice will vary from country to country.

Other factors that need to be addressed urgently (not all to do with hygiene) are

- Age of consent for each type of piercing, as well as competence to give consent;
- The use of disinfectants, including alcohol for skin disinfection and work surfaces, chlorine-based solutions for surfaces and blood spills, etc
- The training and accreditation of practitioners, which follows from the above;
- The use of anaesthetics, including ethyl chloride which is more painful than the piercing and may cause freezer burns, and local anaesthetic creams;
- Pre-piercing advice, including warning of the possibility of complications (for ear-cartilage piercing in particular);
- Aftercare advice given to customers;
- Record keeping;
- Ethical issues, such as forming an accredited association of competent practitioners who will ensure high standards so that members of the public know they will receive a guaranteed service of competence and safety, as well as those (alcohol and drugs) referred to by Worp and colleagues. There should be one national association for each type of practitioner, so that uniform standards are followed.
- Epidemiological studies of the rate and incidence of complications following the different types of piercing. A study is currently being conducted by the Health Protection Agency Centre for Infections in England and Wales.

The use of non-sterile or chemically toxic pigments, as specified by Worp and colleagues, undoubtedly also needs attention but I am not aware of infection caused by pre-contaminated pigment and the problems of toxicity and allergy need more research before making recommendations. Guidelines for hygiene and the other factors mentioned should not have to wait for these.

The authors are to be congratulated for their fine work in controlling non-medical skin piercing in Amsterdam, and in particular for their work in monitoring the performance of skin piercing establishments.

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EDITORIAL

TRICHINELLOSIS: STILL A CONCERN FOR EUROPE

Jean Dupouy-Camet
President of the International Commission on Trichinellosis, French National Reference Centre for *Trichinella*, Hôpital Cochin, René Descartes University, Paris, France

Trichinellosis is a zoonotic disease caused by the ingestion of raw meat containing larvae of the nematode *Trichinella*. Four species of *Trichinella* are found in Europe : *Trichinella spiralis* (cosmopolitan), *T. britovi* (in wildlife from mountainous areas), *T. nativa* (in wildlife from colder and northern regions) and *T. pseudospiralis* (a cosmopolitan nonencapsulating species). Human trichinellosis causes high fever, facial oedema, myositis and eosinophilia. It can be a serious disease, particularly in elderly patients in whom neurological or cardiovascular complications can lead to death.

In this issue of Eurosurveillance , Webster et al list the pros and cons of EU approved methods for current and future use for the detection of *Trichinella* larvae in meats intended for human consumption. The authors point out that several methods recommended so far may be unreliable and that others could be improved by technical modifications. These methods are used to provide "*Trichinella*-free" certification for meat exports, and are also very useful for testing meat for the EU markets, particularly in the case of horses, organic pigs and wild boars slaughtered or hunted locally.

Trichinellosis is still present in Europe. In the past 30 years, horse meat has been identified as the main source of human trichinellosis in the EU with more than 3350 cases reported in 14 outbreaks [1,2]. However, the classical porcine vehicle remains. Small outbreaks due to wild boar meat are still reported in hunters and their families in France, Spain, Poland [3, 4]. Outbreaks due to infected pork have been reported in Spain and Germany and are still reported in Latvia and Lithuania [5,6,7,8]. Until recently, *Trichinella* was considered to be absent from the Mediterranean islands but ten infected pigs were found in Corsica in 2004 and, small outbreaks of pork-related trichinellosis involved patients in Sardinia in 2005 [7,8]. Infected foxes have also been found in Ireland, although this country was considered to be *Trichinella* free [8]. Is trichinellosis emerging in these islands or is the disease simply better recognised? These observations are good examples illustrating the difficulty to declare that some countries or areas are "*Trichinella* free". Pork-related trichinellosis is frequently reported in the potential future European Union states of Serbia, Croatia, Romania and Bulgaria where the disease has re-emerged in recent years [9]. A survey performed by the International Commission on Trichinellosis (http://www.med.unipi.it/ict/ICT%202004%20human%20survey.htm) identified more than 1100 trichinellosis cases in Europe for the year 2004, with 984 cases being reported from these four countries. Therefore, suitable and sensitive methods to detect parasitised animals are of crucial importance. Interestingly, the report by Webster et al shows that meat inspection methods used for porcine species may differ in the various countries of the EU and the authors conclude that the classical trichinoscopy method could not be longer recommended, as it has a low sensitivity and usually fails to detect non encapsulated species such as *T. pseudospiralis*. This last species was involved in a small wild boar meat outbreak in southern France [10]. Therefore, trichinoscopy should be replaced in every country by the magnetic stirrer digestion method.

The reliable use of sensitive methods requires adequate training, proficiency testing and performance in a recognised quality assurance system. Meat inspection for *Trichinella* in horsemeat was implemented in Europe in 1985 after huge outbreaks but it did not prevent the subsequent occurrence of ten additional outbreaks in France and Italy. Then, following the occurrence of two new outbreaks involving 550 cases in 1998 in the south of France, the meat inspection system was modified by implementing examination of larger samples and quality control. Consequently, two infected horses were detected, one in 1999, the other in 2001 [7]. However, these preventive measures cannot prevent the occurrence of trichinellosis from imported meat inspected in countries not belonging to the European Union and the risk still exists, as demonstrated by the occurrence of seven cases due to horse meat consumption reported in October 2005 in the north of Italy (E. Pozio, personal communication).

Travel is also a driver for some cases acquired in highly endemic regions (for example, Romania, the former Yugoslavia, Laos and Argentina) and others are due to persons returning from these countries and bringing back traditionally prepared sausages and delicatessen for consumption by their families and relatives. Such cases have been described in France, the United Kingdom, Denmark, Germany, Spain, Italy [11]. Recently, eight hunters contracted trichinellosis in Quebec, Canada with infected black bear meat; two of them brought this meat back to France, where it was the source of infection for nine additional persons [12]. Travellers should be informed of the risks of illegal importations of such meat products [13].

Training the technicians in charge of meat control and education of the consumers are also key preventive measures

Trichinellosis is a concern for public health authorities in Europe and efforts have been made to promote and fund European networks such as Trichiporse, TrichiNet and Trichimed. Key scientists in this field have been identified and meet or communicate regularly to improve the management and prevention of this potentially lethal disease (http://www.medvetnet.org/cms/templates/doc.php?id=53). Training the technicians in charge of meat control, and education of the consumers (to cook potentially infected meat thoroughly) are also key preventive measures.

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European survey of BCG vaccination policies and surveillance in children, 2005

A Infuso†, D Falzon on behalf of the EuroTB network*

Abstract

In 2005, all 25 EU countries, as well as Andorra, Bulgaria, Norway, Romania and Switzerland, participated in a survey on BCG vaccination in children. BCG was recommended nationally for children under 12 months in 12 countries, in older children in five countries and in children at risk (from origin, contact or travel) in 10 countries. Seven countries did not use BCG systematically. Revaccination was practised in four countries. In countries with universal vaccination, BCG coverage was high (83.0% to 99.8%). TB cases commonly occurred in vaccinated children (at least 30%-98% in five countries using universal or high-risk approach). Disseminated infection due to BCG was rarely reported in recent years (0-1/100 000 vaccinated). There is a wide variation among BCG recommendations in Europe, and nearly half the countries surveyed were considering revisions, at a time when the European Centre for Disease Prevention and Control is advocating for harmonised vaccine strategies. Data on monitoring of BCG coverage in target groups is important but often lacking in Europe. Information on BCG status and eligibility should be collected routinely through TB case notification. The incidence of severe adverse effects of BCG in children should be monitored. Given lack of evidence to its efficacy, revaccination should be discontinued.

Euro Surveill 2006;11(3): 6-11 Published online March 2006
Key words: BCG policies; children; tuberculosis; surveillance; Europe

Introduction

In most of the countries in the European Union (EU) and western Europe, tuberculosis (TB) notification rates are lower than 20 cases per 100 000 population [1]. In recent years, TB incidence has continued to decrease by around 4% yearly overall in the EU, to reach a mean notification rate of 13.8 per 100 000 in 2003. However most of the decrease has occurred among individuals originating from EU countries, while rates have remained stable, at much higher levels, in people of foreign origin, most of whom come from countries with high TB incidence. The proportion of cases of foreign origin has increased steadily to reach at least 31% of TB cases notified in 2003.

The decrease in overall incidence of TB, coupled with the increasing proportion of cases among patients originating from high incidence countries, has led to important modifications of BCG policies since the 1960s [2,3]. In a growing number of European countries, BCG vaccination has been discontinued or has been limited to children 'at risk', such as those born in or originating from countries with high prevalence. Additionally, BCG revaccination has been progressively abandoned.

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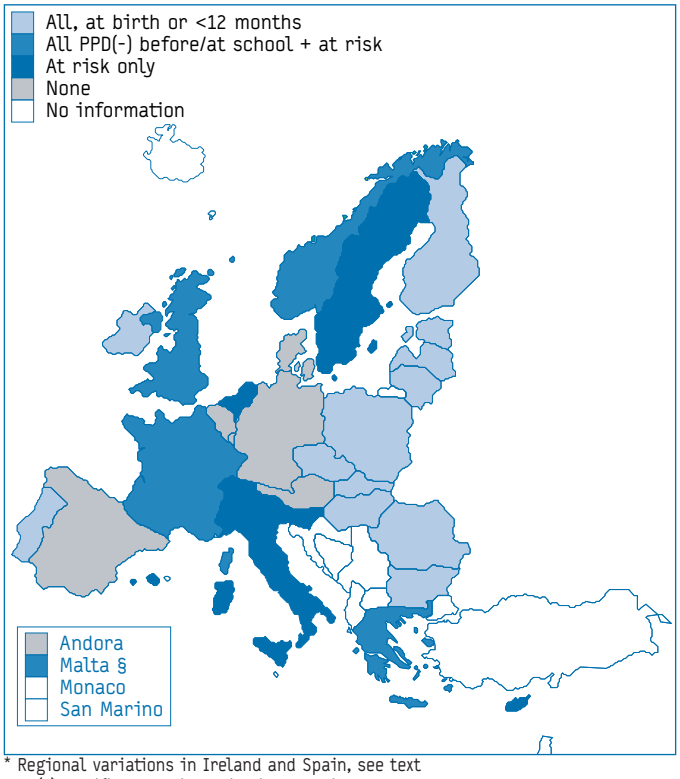
BCG vaccination has no sizeable impact on TB transmission dynamics as its effectiveness has been mainly demonstrated in childhood, when tuberculosis is rarely contagious. Studies in European countries have shown that discontinuing BCG vaccination in children or decreasing its coverage results in an increased incidence of TB [4-6] and other mycobacterial diseases in children [7,8]. In Sweden, when the BCG vaccination strategy was changed from one covering 95% or more of all newborns to one targeting only children at higher risk, there was a temporary increase in TB rates observed in Swedish-born under-5 year olds although rates remained very low since then [6,9]. The occurrence of serious TB since has been extremely low (0.2 per million person-years) but half the cases occurred in unvaccinated, at-risk individuals who might have benefited from BCG.

In 2005, EuroTB undertook a survey of BCG vaccination policies and vaccination-related surveillance in children in Europe. The aim of the survey was to update information useful for describing and comparing BCG policy and surveillance in Europe and to stimulate further European collaboration in this area.

Figure 1

Groups of children targeted for BCG in national recommendations*, Europe, 2005



* Regional variations in Ireland and Spain, see text
PPD (-): Purified protein derivative negative
§ Schoolchildren only

Methods

A questionnaire was developed, field tested by national EuroTB correspondents in three countries and distributed in March 2005 to national EuroTB correspondents in the 25 EU countries, seven other European countries with low TB incidence (Andorra, Iceland, Israel, Monaco, Norway, San Marino and Switzerland) and four EU applicant countries (Bulgaria, Croatia, Romania and Turkey). A reminder was sent one month later. All questionnaires received up to early July 2005 were validated through communication with responders. Countries defined children as individuals aged 0-14 years, except the Netherlands, where children were defined as being aged 0-12 years. Data on paediatric TB notification in 2003 were extracted from EuroTB databases. Responses were accepted up to September 2005.

Table 1

TB notification rates per 100 000 (2003), BCG recommendations in children (2005), and BCG coverage, Europe

	TB notification rates, 2003			Groups of children targeted for BCG vaccination, 2005							BCG coverage			Changes to BCG policy being considered?
Country	Overall	Children	Rate Ratio (adults: children)	All, at birth or <12 months	All, older age	Parents from / birth in high incidence areas	Travel to high incidence areas	Family history of / Contact with TB case	Other risk	No systematic use	%	Year		
Bulgaria	41.3	16.1	2.8	X*			-				n/a	-		No
Czech Republic	11.3	0.7	18.9	X*							98.8%	2003	*	Yes
Estonia	47.1	1.9	29.3	X							97.0%	2004		Yes
Finland	8.0	0.4	24.0	X							98.0%	2002		Yes
Hungary	27.8	0.6	55.0	X							99.8%	2003		No
Ireland	10.6	2.8	4.5	X	X (reg.)	X (reg.)	X (reg.)	X (reg.)			90.2%	2004	§	Yes
Latvia	74.8	30.3	2.7	X							99.7%	2004		No
Lithuania	81.9	20.5	4.7	X							98.9%	2004		No
Poland	26.2	1.5	20.9	X*							95.0%	2003	*	Yes
Portugal	41.1	5.0	8.0	X							83.0%	2003		No
Romania	141.6	43.5	3.7	X							98.6%	2003		Yes
Slovakia	18.2	2.1	10.3	X*							98.1%	2003	*	Yes
Malta	1.8	1.3	1.5		X						87.0%	2004		Yes
France	9.8	2.7	4.3		X				risk environment		95.0%	1997	†	Yes
Norway	7.5	2,0	4.4		X	X		X			>95.0%	2002	†	Yes
United Kingdom	12.3	3.4	4.2		X	X					75.0%	n/a	†	Yes
Greece	5.6	1.1	5.5		X			X			31.3%	2003	†	No
Sweden	4.6	1.1	4.9			X	X	X			88.0%	2004	‡	No
Netherlands	8.2	2.0	4.8			X	X				60-90%	2000-4	**	Yes
Slovenia	14.8	3.1	5.4			X			HIV+ mother		70-90%	2004	§§	No
Switzerland	8.7	2.1	4.7				X				n/a	-		No
Cyprus	4.4	0.0	-					X			n/a	-		No
Italy	7.9	2.2	3.9					X			n/a	-		No
Andorra	12.6	0.0	-							X	-	-		No
Austria	12.1	3.2	4.3							X	-	-		No
Belgium	10.9	4.0	3.1							X	-	-		No
Denmark	7.3	3.3	2.5							X	-	-		No
Germany	8.7	2.3	4.3							X	-	-		No
Luxembourg	11.9	1.2	12.0							X	-	-		No
Spain	18.2	8.2	2.4	X (reg.)						X	-	-		No

(reg.) = regional policy; n/a = not available; - = not applicable

* revaccination also recommended; BCG coverage only refers to newborns

§ coverage estimated in 4 regions + 1 unit

† coverage among older children

‡ coverage among all three target groups (at 2 years of age)

** coverage among children of parents from high incidence country (calculated for 4 areas)

§§ coverage among children of parents from high incidence country; 98% for children of mother with active TB or HIV

Results

Questionnaires were returned from 30 countries (all 25 EU countries, and Andorra, Bulgaria, Norway, Romania and Switzerland), a response rate of 83% [FIGURE].

National BCG recommendations and practices

BCG recommendations in children were applied nationwide in 28 countries but had notable regional variations in Ireland, where neonatal BCG was used in 6/8 regions, and in Spain, where national recommendations discourage routine BCG vaccination, while neonatal vaccination is only practised in one region. In this description of national policies, these two countries are classified according to their national recommendations [TABLE 1].

BCG vaccination was recommended nationally for:

- all children at birth or under 12 months of age in 12 countries;
- older children before starting kindergarten/school or at 6-14 years in five countries;
- selected groups of children at risk in 10 countries, including four of those where all older children were vaccinated.

In seven countries BCG was not used systematically in any group of children [TABLE 1]. In two of these countries, BCG was administered on an individual basis to children planning to have a long stay in a high TB incidence area (Denmark), or to live permanently in such an area (Belgium).

Revaccination of all or of PPD (purified protein derivative) negative older children was recommended in four of the countries where BCG was recommended at birth: Slovakia (PPD negative at 11-13 years), Czech Republic (PPD negative at 10 years), Poland (all at 7 years and PPD negative at 12 years) and Bulgaria (all at 7-10 months, 7 years, 11 years, 17 years).

Groups of children targeted for BCG vaccination

The definition of children at risk for whom BCG vaccination was recommended varied across countries [TABLE 1], and included one or more of the following reasons:

- born in, or with parents/family originating from, high incidence areas — 5 countries
- contact with or family history of active TB — 5 countries
- travel or planned residence in high incidence countries — 3 countries
- born to a HIV-infected mother — 1 country
- 'risk environment', not further specified — 1 country

Furthermore, the exact meaning of these groupings differed between countries. Likewise, the age range for vaccination and the recommended minimum age for PPD testing before BCG administration varied.

Date of issue or last update of recommendations and plans to change BCG recommendations

BCG recommendations were last updated before 2000 in 10 countries and in 2000 or later in 19 countries. In 12 countries there were ongoing discussions or plans to change or update national BCG recommendations, including 7 of the 21 countries that had already updated recommendations since 1999. Planned changes included:

- Shifting from universal vaccination to vaccination of children at risk — 4 countries
- Stopping school vaccination, strengthen vaccination of newborns at risk — 1 country
- Defining a policy for travellers — 1 country
- Defining a policy for children of HIV+ mother — 1 country
- Stopping vaccination of children at risk — 1 country
- Discontinuing neonatal BCG in selected areas — 1 country
- Stop revaccination — 1 country
- Decreasing number of revaccinations — 1 country
- Not specified — 1 country

Countries without systematic use of BCG were not currently considering changes to their policies.

BCG coverage

In 11 of 12 countries implementing universal BCG vaccination of newborns, BCG coverage ranged from 83.0% to 99.8% (no data for Bulgaria) [TABLE 1]. In countries where only older children were vaccinated, coverage of BCG vaccination was low in Greece (31%) and ranged from 75% to over 95% in the other four countries. Coverage data for children originating from a high TB incidence area was not available in the United Kingdom (UK); this data ranged from 60% in two rural areas to 90% in two urban areas in the Netherlands; coverage was estimated at between 70% and 90% in Slovenia and was considered to be 'high' in Norway. In Sweden, coverage was 88% overall for all three groups of children targeted for BCG vaccination.

No coverage information was reported for vaccination of children travelling to high TB incidence areas or contacts of TB cases. In Slovenia, coverage of the newly introduced recommendation to vaccinate newborns of HIV-infected mothers was estimated to be 98%.

Table 2

BCG eligibility and BCG status among paediatric tuberculosis cases*

Country	Criteria used to define BCG eligiblity	Childhood BCG coverage §	Paediatric tuberculosis cases							
			Years	Total notified	Eligible for BCG		Vaccinated with BCG		BCG status unknown	
					N	(%)	N	(%)	N	(%)
France	No information	80-95%	2003	311	n/a	-	193	(62.1)	64	(20.6)
Ireland (6/8 regions)	All newborns	90%	2000-2003	42	42	(100.0)	18	(42.9)	10	(23.8)
Latvia	All newborns	100%	2004	110	108	(98.2)	108	(98.2)	0	(0.0)
The Netherlands	Child / parent national of a high incidence country	60-90%	1993-2003	715	517	(72.3)	215	(30.1)	68	(9.5)
Sweden	Risk linked to origin, travel, or contact	88%	2000-2004	94	91	(96.8)	44	(46.8)	28	(29.8)
United Kingdom	Non-white child	75%	not stated	389	324	(83.3)	n/a	-	n/a	-

* 0-14 years, except The Netherlands (0-12 years)

§ among all children targeted (see also Table 1)

BCG coverage and eligibility among paediatric TB cases

Among children with tuberculosis, information on BCG status was collected through TB notifications in 15 of the 23 countries that used BCG systematically. At least five of 10 countries recommending BCG for children at risk collected information on whether paediatric TB cases had been eligible for BCG or not.

Data about the BCG vaccination status and/or eligibility for BCG among children with notified TB infections were provided by six countries [TABLE 2]. Information on BCG status was frequently incomplete. In Ireland and Latvia, where BCG was recommended for all newborns (coverage >90%), and in France (coverage >80% at 2 years and 95% at 6 years), the majority of notified paediatric TB cases for which information on BCG status was available occurred in vaccinated children.

Three of the countries with targeted BCG recommendations provided information on BCG eligibility for paediatric TB cases. The majority of paediatric TB cases reported were in children who had been eligible for BCG. In the UK, 83% of the cases were considered eligible when non-white ethnicity was taken as a proxy of origin from a high incidence country. In the Netherlands, 72% of cases notified between 1993 and 2003 were in children who had (or were born into a family with) foreign citizenship. In Sweden, 99% of the cases (2000-2004) belonged to one of the three groups targeted for BCG.

Among the four countries with information about both BCG status and eligibility, only Latvia reported 100% vaccination coverage among eligible cases, with the other three countries achieving less than 50% coverage.

Mycobacterial disease other than TB in children

The questionnaire addressed availability of data on the frequency of mycobacterial infections other than TB in children. Data on mycobacterial infections other than TB in children were available in eight countries. All mycobacterial isolates are notifiable by laboratories in Finland, Norway and Sweden. Data are available from the national reference laboratory in Denmark and from TB case notification in the Czech Republic and in Italy. Sentinel surveillance of these infections, based on hospitals and laboratories, exists in Germany and in certain parts of Spain. Specific studies are known to have been carried out in Spain [8], Sweden [7] and the UK [10].

Surveillance of disseminated BCGitis

A surveillance system or a source of data on disseminated infection due to BCG (BCGitis) was reported to exist in 13 countries, as part of surveillance of adverse effects following immunisation (AEFI) or of reporting systems for severe adverse effects of drugs and medical products [TABLE 3]. In Sweden a specific study has estimated the incidence of disseminated BCGitis at 4 per 100 000 infants born in Sweden and vaccinated at birth for the period 1979-1991 [11].

Discussion

While the response to this survey was high, information from six countries (Croatia, Iceland, Israel, Monaco, San Marino and Turkey) was not available. The interpretation of target groups differed between countries and the availability and the completeness of data requested also varied, rendering comparison problematic at times.

This survey confirms the wide variability and the continuing evolution of BCG recommendations in Europe that has been highlighted in previous surveys [2,3]. Nearly half the EU countries were considering changes to their policy. Universal vaccination of newborns remains recommended in all countries with higher notification rates (over 20 cases per 100 000). In countries with lower incidence, recommendations were very diverse, ranging from no systematic use of BCG in children in seven countries to universal use of BCG at birth in four countries with revaccination in older age groups in two of them. In five countries, all PPD negative children were vaccinated before starting or leaving school, including the UK, where the school vaccination programme has been discontinued since this survey was conducted.

Table 3

Data on disseminated BCG infections, Europe

Country	Data source	Years	Total vaccinated	Cases of disseminated BCG infections
Cyprus	TB case reporting	2001-2004	n/a	0
Denmark	Surveillance of AEFI*	-	-	-
Finland	Surveillance of AEFI, clinician reporting and laboratory reporting	2001-2004	220 860	4 (3 osteitis, 1 miliary)
Hungary	Routine reporting	1991-1994	n/a	0
Germany	Surveillance of AEFI	2000-2003	n/a	0
Ireland	Irish Medicine Board	1981-2004	n/a	0
Malta	Self report	-	23 843	0
Norway	Surveillance of AEFI	recent years	n/a	less than 1 case per year
Poland	Surveillance of AEFI	2000-2003	2 086 319	0
Portugal	Nat. Inst. of Pharmacy & Medicine	2000-2004	472 120	1
Slovakia	National reporting system	2001-2003	233 605	2
Sweden	Specific study#	1979-1991	101 000	4
	Medical Product Agency and laboratory reporting	1992-2004	n/a	0
United Kingdom	Not specified	-	-	-

* AEFI = Adverse events following immunisation

n/a = not available

Romanus et al [11]

Targeted vaccination of children considered to be at risk was the only policy recommended in six countries, two of which were considering changes to this policy, such as stopping BCG before travel and following cases with skin testing upon return. Four other countries were planning to shift to targeted vaccination. Children born in, or with family members from, a high TB incidence area were the most numerous and important risk group targeted for BCG, as they represented over 10% of birth cohorts in many countries. The data on eligibility available from TB notification show that most paediatric TB cases occurred in this group, indicating that it represented a suitable target in the current epidemiological situation in low incidence countries in Europe. However, data also indicate lower coverage in this group compared with coverage of universal neonatal BCG vaccination. Maintaining high coverage in this group may represent the most important challenge to render targeted BCG vaccination effective.

Among the other groups of children targeted for BCG, those travelling to areas with high TB incidence and those in contact with TB patients represented smaller groups, in which an individual risk assessment is often required before vaccination. Data on coverage in these groups were generally not available. Defining 'travellers at risk' presents difficulties linked to duration, destination and type of contact during the stay. Vaccination of children travelling from low incidence areas to high incidence areas is included in World Health Organization (WHO) recommendations for travellers [12]. Use of BCG in PPD negative children who are in prolonged contact with TB patients, or who have a family history of TB, was recommended in some countries, with indications being frequently very specific. The implementation of this policy could be monitored as part of routine feedback information on interventions following investigations of TB contacts.

In western Europe, an increasing proportion of HIV infections is diagnosed in persons from sub-Saharan Africa or from other high TB incidence countries. Many children originating from such regions are targeted in countries using a high risk approach to BCG. Vaccination of children born to HIV-infected mothers was recommended in only one country and is under consideration in another. In a number of low prevalence countries, including the Netherlands and the UK, HIV infection was a contra-indication to BCG vaccination [13,14]. Infants born to HIV-positive mothers may have their BCG vaccination withheld for a few months after birth until HIV infection can be excluded.

BCG at birth or in infancy significantly reduces the risk of TB by over one half [15]. Tuberculosis case surveillance would thus be expected to be useful in monitoring the efficacy of BCG policies. Unfortunately, it has several limitations. Laboratory confirmation of notified paediatric cases was not frequent in several countries. With the high BCG coverage achieved by many countries implementing universal BCG at birth, most TB cases occur in children who have been vaccinated. In countries with information on BCG status of paediatric TB cases, the proportion of vaccinated cases among paediatric TB cases was highly variable, reflecting mainly the wide range of BCG vaccination strategies and coverage in children. In certain countries using neonatal BCG, higher TB rates in adults compared to children [TABLE 1] may reflect the protective effect of BCG in childhood, although this may be compounded by other issues, such as the proportion of TB cases among recent immigrants.

Information on BCG status and eligibility of notified paediatric TB cases was available in a limited number of countries and is frequently incomplete. In countries with information on BCG eligibility, such as Sweden or the UK, the very high proportion of children eligible for BCG among paediatric TB cases suggests that children at risk are an appropriate target for BCG vaccination and such policies could be effective provided a high coverage is maintained in this group.

The utility of revaccination of children after a first dose in infancy is not confirmed [16]. Only four countries reported this practice, and two of the four were considering the elimination or restriction of revaccination.

Studies have already been undertaken in Europe to weigh the advantages and disadvantages of maintaining universal BCG vaccination against other alternatives [17,18]. One of the advantages of universal BCG is the reduction of disease due to mycobacteria other than *M.tuberculosis* complex. The European experience has shown a marked increase in the incidence of mycobacterial disease other than TB after stopping BCG or targeting BCG to children at risk [7]. However, the size of this effect is hard to quantify as these infections are rarely notifiable in Europe, because most are relatively benign. The frequency of severe adverse effects of BCG vaccination is also important to consider when evaluating the risks and benefits. Serious adverse effects of BCG are rare but may be very severe in immunocompromised children. In Sweden, the recommended age for vaccination was shifted from birth to 6 months following a study showing appreciable occurrence of BCGitis in neonates [11], and the policy was retained despite an increase in the occurrence of atypical mycobacterial disease thereafter [7]. In several European countries, information on disseminated BCGitis is not available, or not readily accessible to TB surveillance teams, while surveillance of adverse effects following immunisation is recommended by WHO.

Conclusions and recommendations

Our study uses surveillance data to describe health policies in the context of a changing epidemiological situation. We trust that our findings will enhance collaboration between European countries and complement the initiatives of the European Centre for Disease Prevention and Control (ECDC) to harmonise vaccine strategies and schedules.

In order to enable monitoring of the effects of any newly introduced policy, such as targeted BCG, surveillance of TB in children should first be strengthened. Monitoring BCG coverage in target groups is important and may necessitate new measures to capture the denominator for certain risk groups (such as travellers to high incidence regions or child contacts of open TB cases). Information on BCG status and eligibility should be routinely collected through TB case notification and regularly analysed.

Operational research, taking into account cost considerations, should be used to augment the knowledge base on the subject and to help decision making.

While HIV infection is a contra-indication to BCG vaccination in a number of low-prevalence countries, the decision to give BCG at birth to the asymptomatic child of a HIV-positive mother should be based on a careful assessment of benefits versus potential adverse effects in a setting at increased risk of tuberculosis transmission .

Given the lack of evidence to its efficacy, revaccination should be discouraged, regardless of TB incidence.

The incidence of severe adverse effects of BCG in children should be monitored as part of the surveillance of adverse events following immunisation and by introducing laboratory reporting. Data on isolates of *M. bovis* BCG or *Mycobacteria* other than *M. tuberculosis* complex in children could be obtained by introducing laboratory reporting of all human isolates of *Mycobacteria*, as already exists in Scandinavian countries.

† Andrea Infuso, EuroTB scientific coordinator, died suddenly on September 20, 2005. This Eurorounddup is a posthumous publication.

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ORIGINAL ARTICLES

Surveillance report

PROSPECTS FOR THE BCG VACCINATION PROGRAMME IN FRANCE

D Lévy-Bruhl

Until recently, the French BCG vaccination programme consisted of a mandatory BCG vaccination before children started at daycare centres, and of re-vaccination of tuberculin-negative children. A re-assessment of this programme has been undertaken in recent years. It has led to the discontinuation of all revaccinations and post-vaccination tuberculin tests except those post-vaccination tuberculin tests performed as part of a diagnosis of tuberculosis infection or disease or of the follow-up of health or social workers for whom BCG vaccination remains mandatory. Based on an estimate of the epidemiological impact of either selective vaccination of high risk children or discontinuation of BCG vaccination, and taking into account the risk-benefit balance that can be made of the two options, the Conseil Supérieur d'Hygiène Publique de France (CSHPF, national high council of public hygiene) has recommended a change to selective vaccination. However, the committee has proposed the strengthening of other control measures aimed at decreasing the risk of infection for children, as a pre-requisite to the implementation of this strategy. This position is made more complex by the withdrawal of the multipuncture technique in early 2006, previously used in France in more than 90% of BCG primary vaccinations.

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Key words: BCG, vaccination, France, vaccination programme

Introduction

In France, primary BCG immunisation is mandatory for children before they can enter daycare centres or the care of childminders, and must be given by the age of six years at the latest, when school entry is compulsory. BCG is also recommended in the first month of life for high risk children. Until June 2004, a tuberculin test was required between 3 and 12 months after vaccination and at 11-13 years of age, followed in both cases by revaccination, if negative. Following an evaluation initiated by the publication of a report by the national institute for public health surveillance, the Institut de Veille Sanitaire (InVS), routine tuberculin testing in children and revaccination were discontinued in July 2004, as was revaccination for exposed professionals [1]. Tuberculin testing remains indicated as a diagnosis tool for tuberculosis infection or disease and for the follow up of health or social workers for whom BCG vaccination is still mandatory.

The InVS report also questioned the need for universal BCG immunisation of children. For the period 2000-2002, the incidence of positive sputum smear tuberculosis cases was 4.6 per 100 000 (5.7 when correcting for the lack of exhaustiveness of the notification). For the 1998-2002 period, the incidence of meningitis in children less than five years old was 0.4 per 10 millions. This epidemiological situation was thus very close to the threshold values proposed by the International Union Against Tuberculosis and Lung Diseases for possible discontinuation of BCG vaccination [2]. An overview of tuberculosis control strategies, and an epidemiological assessment of the consequences of reducing BCG vaccination activities was conducted in the context of a multi-disciplinary evaluation by the national institute for health and medical research (Inserm), at the request of the health authorities.

In this context, InVS assessed the epidemiological impact of discontinuing universal children BCG immunisation. Several arguments were in favour of also studying the impact of a strategy targeted on children at risk. The data from mandatory notification of tuberculosis cases in France show that the risk of tuberculosis is highly heterogenous, according to nationality or country of birth. In 2003, the incidence of the disease was 10.2 per 100 000 but was tenfold higher in non-French nationals than in nationals (respectively 72.1 versus 8.1 per 100 000, all ages together, and 18.7 versus 1.8 per 100 000, in children under 15 years old) [3]. In 2003, eight out of the then 15 European Union (EU) countries had chosen to target children at high risk of tuberculosis for immunisation [4]. By 2005, nine of the 25 member states of the EU had applied such targeted strategies [5].

Two scenarios for changes in BCG immunisation programme in France were therefore assessed: the total discontinuation of any vaccination and targeted vaccination for children living in a risk environment.

Methods

Assessment of the impact of total discontinuation of immunisation

The number of excess tuberculosis cases that would be observed if immunisation were completely discontinued is equivalent to the number of cases of tuberculosis avoided each year by the current immunisation programme. This figure was estimated from BCG effectiveness estimates, immunisation coverage and tuberculosis notification data [6]. Based on published data, we considered the hypothesis of a protection provided by BCG lasting until the age of 15 years, and concerning only vaccinated persons (no indirect protection for unvaccinated subjects due to the absence of reduction of the circulation of the tuberculosis bacillus, as childhood tuberculosis is rarely contagious). Two hypothesis on vaccine effectiveness were considered. In the basic hypothesis, BCG effectiveness was considered to be 75% for tuberculous meningitis and miliary, the most severe localisations of the disease, and 50% for other sites, mainly pulmonary. In the hypothesis most favourable to immunisation, considered in order to avoid underestimating the number of additional tuberculosis cases that would follow the reduction in BCG immunisation activities, the effectiveness of BCG was considered 85% on tuberculous meningitis and miliary and 75% on other sites.

The numbers of observed cases were estimated from mandatory notification data between 1997 and 2002, corrected for lack of exhaustiveness, on the basis of a notification rate of 75% for childhood tuberculosis [6]. The data on immunisation coverage are available through the analysis at national level of health certificates completed at 24 months of age for each child and from a national survey carried out in schools in 1997, in children 5 to 6 years old [7,8].

Assessment of the impact of immunisation targeted on children at risk

The definition used was based on the Swedish experience and matched the French epidemiology of tuberculosis. It included children meeting at least one of the following criteria:

- A child coming from a country with high tuberculosis prevalence;
- A child born into a family coming from a country with high tuberculosis prevalence;
- A child of any origin with a history of tuberculosis in his/her family.

Africa, Asia (except Japan), Central and South America, the Russian Federation and Baltic countries were considered as areas or countries with high tuberculosis prevalence.

Among total childhood TB cases, the proportion of those occurring in at-risk children was estimated at 75%, based on a study carried out in 1997 in the Parisian area [9].

Two levels of immunisation coverage of at-risk children were considered: 95% and 50%. Interrupting the universal immunisation of children could lead to a decrease in the current immunisation coverage among targeted populations, as such a decision would de facto imply the discontinuation of mandatory vaccination.

Based on data from a survey carried out by the National Institute for Demographic Studies (INED) [10], the number of children at risk was estimated at 14% of each yearly birth cohort (that is about 100 000 children out of a birth cohort of about 750 000).

Assessment of adverse effects of BCG immunisation

Frequency of clinically significant adverse effects was studied in the evaluation carried out by Inserm [4]. BCG immunisation was estimated to result each year in about 300 lymphadenitis (corresponding to a rate of about 40 per 100 000 vaccinated children) and about 12 disseminated BCG infections (corresponding to a rate of about 1.6 per 100 000 vaccinated children), the latter occurring in children with severe immunodeficiency. These data have been used to calculate the decrease of the expected number of side effects for the different options of reduction of immunisation activities.

Results

The epidemiological consequences of the different immunisation options that were considered, for children under 15 years old, are summarised in the table. If immunisation is restricted to children at risk, there might be 80 to 200 additional cases per year in the non vaccinated low risk population, corresponding to an incidence rate between 0.9 and 2.3 per 100 000 non vaccinated children. In case of a decreased coverage in the targeted population, additional cases would also occur in children at risk. For a vaccination coverage of 50%, annual additional cases could range from around 200 to almost 500,

corresponding to an incidence rate in non vaccinated children between 2,1 and 5,2 per 100 000. If vaccination were discontinued, 320 to 800 additional cases might occur every year, depending on the hypothesis for vaccine effectiveness, corresponding to an estimated incidence of additional tuberculosis cases between 3,2 and 8,0 per 100 000.

The projected increase to the current incidence in children 0-14 years, and the number of additional cases and incidence in non-vaccinated children, broken down for pre-school (0-5 years) and school-age children (6 to 14 years) are also presented in the table.

As about 15% of the children can be considered to be at risk, at least 85% of side effects due to BCG would be avoided through targeting immunisation to those children.

Discussion

The first option analysed the total discontinuation of BCG vaccination. Our study shows that such a choice could lead to several hundreds of additional tuberculosis cases in children each year. These results are in accordance with observations from other European countries, particularly Sweden, when immunisation was first completely discontinued [11], and are in favour of maintaining the current programme. In another hand, such an option would induce several disseminated BCGitis cases each year.

The alternative option analysed was the targeting of BCG vaccination on children living in a risk environment. Based on our assessment, this programme would avoid approximately three quarters of tuberculosis cases that are currently avoided by the universal vaccination, while requiring the vaccination of only about 15% of children. The real impact of this option will depend on the ability in maintaining a high vaccine coverage among children at risk. Such an option would also facilitate the interpretation of tuberculin tests performed in non-vaccinated children exposed to tuberculosis cases.

To analyse the epidemiological impact of immunisation, we relied on hypotheses or point estimates, particularly those concerning the exhaustiveness of tuberculosis notifications in France, the vaccine effectiveness, the proportion of tuberculosis cases occurring among children with a risk factor, and the size of this latter population. The resulting estimates should be considered as orders of magnitude of the current or future impact of different immunisation options. Nevertheless, the conclusions on the relevance of the different options can be considered as fairly reliable. It is worth mentioning that in this analysis, we did not consider the increase of incidence of non-tuberculosis mycobacterial diseases that would follow the decrease in BCG immunisation coverage, and that only mainland France was considered.

These results were presented in 2005 to the Comité Technique des Vaccinations (CTV, national advisory board on vaccination) and to the Conseil Supérieur d'Hygiène Publique de France (CSHPF, national high council of public hygiene). Both recommended that the Ministry should adopt the BCG vaccination strategy targeted at children at high risk of tuberculosis. They also recommend, as a prerequisite before actually switching to such a strategy, the strengthening of other tuberculosis control measures aimed at reducing the risk of infection for children (such as early identification of cases, tracing of secondary cases and of the source of contamination, and supervision of treatment of cases), in the context of a national tuberculosis control plan. Following this recommendation, the Ministry of Health has, in early 2006, set up an ad hoc national committee that has began to formulate such a document.

The schedule for implementation of a targeted strategy will have to take into account a new situation that could influence the BCG vaccination coverage and the acceptability of maintaining the current programme. Since early 2006, the multipuncture device used in France for more than 90% of BCG primary vaccinations, is no more available. Administrating the vaccine intradermally in young infants is a difficult technique for untrained vaccinators. Currently, more than 80% of children are vaccinated in their first year of life. A survey of over 800 general practitioners carried out in 2005 found that fewer than 30% felt ready to routinely immunise very young infants intradermally [12]. To avoid the problems that would arise from mandatory vaccination before entering school or daycare centre, when only intradermal inoculation would be possible, a strategy targeting the most exposed children, who are mainly those from families of foreign origin, should perhaps be considered rapidly. The feasibility and social acceptability of this option would have to be ascertained beforehand.

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Table

Estimates of the epidemiological impact of various BCG vaccination strategies or level of coverage according to BCG effectiveness assumptions, France

		Estimated additional tuberculosis cases (incidence rate per 100 000 in non vaccinated)			Estimated avoided BCG side effects
		0-5 years old	6-14 years old	Total 0-14 years old % increase/universal vaccination	
Targeted BCG – Vaccine coverage 95%	Low BCG effectiveness scenario	31 (1.0)	49 (0.9)	80 (0.9) 20%	10 disseminated BCG infections 260 lymphadenitis
	High BCG effectiveness scenario	68 (2.3)	132 (2.4)	200 (2.3) 51%	
Targeted BCG – Vaccine coverage 50%	Low BCG effectiveness scenario	75 (2.3)	117 (1.9)	193 (2.1) 49%	11 disseminated BCG infections 280 lymphadenitis
	High BCG effectiveness scenario	166 (5.1)	320 (5.3)	486 (5.2) 124%	
Discontinuation of BCG	Low BCG effectiveness scenario	124 (3.5)	194 (3.0)	318 (3.2) 81%	12 disseminated BCG infections 300 lymphadenitis
	High BCG effectiveness scenario	274 (7.8)	528 (8.1)	800 (8.0) 204%	

→→→

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ORIGINAL ARTICLES

Surveillance report

SELECTIVE BCG VACCINATION IN A COUNTRY WITH LOW INCIDENCE OF TUBERCULOSIS

V Romanus*

In 1975 the BCG vaccination policy in Sweden changed from routine vaccination of all newborn infants to selective vaccination of groups at higher risk. This report aims to evaluate the present BCG policy, with focus on the tuberculosis situation in Sweden during the period from 1989 to 2005. The population structure in Sweden has changed, with increasing numbers and proportions of people who were born outside Sweden, especially in countries with high prevalence of tuberculosis. BCG vaccination coverage fell from more than 95% before 1975 to less than 2% in 1976 to 1980, and then again increased to around 16 % (corresponding to about 88% of the risk group recommended for vaccination). The increasing proportion of foreign born tuberculosis patients among all tuberculosis cases of illness in Sweden, and the high age-specific incidence of tuberculosis in the childbearing age groups in the foreign-born population, indicate the need to continue selective vaccination of children in families originating from countries with high tuberculosis incidence. The cumulative incidence of tuberculosis in the 30 cohorts born in Sweden after 1974 and observed to the end of 2004 was estimated at 0.5 cases per 100 000 person-years.

Sweden still has one of the lowest incidences of tuberculosis in the world, which means a minimal average risk of infection for the majority of children born to Swedish parents. The observed increase of tuberculosis in 2005, partly attributed to an outbreak at a day nursery, is a reminder of the serious consequences of delayed diagnosis.

Intensified active case finding is the most important action to prevent childhood tuberculosis, by means of eliminating the sources of infection to prevent transmission to the child population. Early detection and treatment of infected children is necessary to prevent development of serious disseminated tuberculosis.

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Key words: selective BCG vaccination, tuberculosis in children, tuberculosis in Sweden

Introduction

In 1975 the BCG vaccination policy in Sweden changed from routine vaccination of all newborns to selective vaccination. The impact of the changed BCG policy on tuberculosis among children born in Sweden has previously been analysed and reported [1].

This report aims to evaluate the selective vaccination program in relation to the epidemiological tuberculosis situation in Sweden, with focus on the period from 1989 to 2005. It is based on impact studies conducted following the change towards selective BCG vaccination. The analysis is based mainly on routine surveillance of BCG vaccination coverage, as reported once a year for two year old children, and on information from the statutory notifications of tuberculosis [2].

BCG vaccination policy in Sweden

Starting in the 1940s, vaccination against tuberculosis was offered to almost all newborns and also to school children who were nonreactive to the tuberculin skin test at seven and 15 years of age. General neonatal vaccination was ended in 1975. Tuberculin skin testing and revaccination of nonreactive schoolchildren was ended in 1965 for seven year olds and in 1986 for 15 year olds [3].

The main reason for the changed BCG policy in 1975 was an increased frequency of BCG vaccine induced osteomylitis (BCG osteitis), with 29 cases per 100 000 vaccinated infants during the period from 1972 to 1974 [1,4]. In view of the declining incidence of tuberculosis in Sweden, the risk of infection and disease was estimated to be much lower in the Swedish child population than the risk of serious vaccine adverse reactions. However, it was still recommended that vaccination be offered to children who had higher risk of exposure to tuberculosis than the general population [5].

After 1975, the risk groups targeted for BCG vaccination in childhood included children and young people fulfilling at least one of the following criteria:

- A family history of tuberculosis (present or previous, even if long time ago) or close contact with other persons with tuberculosis
- Origin from continents or regions with high prevalence of tuberculosis, including children born in these regions, and children born in Sweden to parents who were born in these regions.
- Planned travel to high prevalence continents or regions involving close contact with the local population.

Continents or regions with high incidence of tuberculosis or considerable higher incidence than Sweden are defined as follows: Africa, Asia, Latin America, eastern Europe, central Europe, Spain and Portugal.

Up to 1993 children born to parents from Finland were also offered BCG vaccination.

From 1975 to 1993, it was recommended that vaccination be given during the neonatal period. In 1994 the recommended age for vaccination was postponed until 6 months or older. The reason for postponing vaccination to six months was to avoid accidental vaccination of infants suffering from severe combined immunodeficiency syndrome [6].

However, in cases of overwhelming risk of infection, it is still recommended to give vaccination soon after birth. In these cases, vaccination must be preceded by a careful assessment of family history regarding any occurrence of immune deficiencies or infant deaths in any close family members, in cousins or in siblings to the parents.

Methods

The analysis presented in this paper is mainly based on surveillance available data - routine surveillance of BCG-vaccination coverage and TB statutory notifications - and on previous studies on the impact of the BCG vaccination policy change.

Vaccination coverage

The BCG vaccine used in Sweden, from the introduction of vaccination in 1926 until 1978, was based on the Swedish BCG strain, named Gothenburg. Since 1979 the SSI vaccine, based on the Danish BCG strain Copenhagen 1331, and produced at Statens Serum Institut in Copenhagen, has been used in Sweden.

Estimates of the BCG vaccination coverage are based on nationwide annual reports given since 1981 to the Swedish Institute for Infectious Disease Control from all child health centres in Sweden. During the period from 1981 to 1983, vaccination status was reported for all children aged 0-6 years, and for two year old children only from 1984. The reports for the period 1981 to 1997 cover information on BCG vaccination status for at least 92% of preschool children born during the period from 1974 to 1994 (information missing from two of 24 counties) and from 1998 the reports cover 99% of two year old children belonging to cohorts born in 1995 to 2002. For the most recent period, information was obtained regarding vaccination coverage related to the magnitude of the defined risk group to be vaccinated.

Adverse vaccine reactions must be reported to the Medical Product Agency [4, 6].

Target population for BCG vaccination

Among cohorts born in Sweden between 1975 and 1985, about 12% were born to foreign born parents (one or both parents). The risk group targeted for BCG vaccination was calculated to comprise approximately 17 000 children (17%) per birth cohort. (These estimates are based on the annual statistical reports from the child health centres; the reported figures are in agreement with population statistics related to country of birth and parental origin, as reported in 2002 for age group 0-17 years).

TB notification

Tuberculosis is a notifiable disease according to the Communicable Disease Act. Incidence figures related to national origin for the period from 1984 to 1988 were based on the TB patients' citizenship (previous or current) and therefore approximated (Swedish National Association against Heart- and Lung Diseases). Comparable figures related to country of birth (for population born in Sweden and born abroad, respectively) are available from 1989 onwards [2].

Population statistics

Population figures are based on data from population statistics, Statistics Sweden. The population of Sweden increased from 8.2 million inhabitants in 1975 to 9.0 million in 2004 and the number of foreign born inhabitants almost doubled from 550 000 (6.7%) to 1.1 million (12%). The proportion of immigrants from Africa and Asia increased from 0.3% to 3.7%. The annual number of live born infants varied during the same period between 90 000 and 124 000. For cohorts born in Sweden in 1969 or later, population figures related to country of birth and to national origin of the parents were specifically requested from Statistics Sweden for calculations of the incidence figures during the first study periods from 1969 to 1993.

Results

Vaccination coverage

Among cohorts born during the first five year period (1976 to 1981) following the changed BCG policy, vaccination coverage of newborns fell from at least 95% (before 1975) to below 2%. This level was too low to cover the risk group. Nurses at the child health centres were given more information and education about the reasons for the change to selective vaccination, and in particular, about the case definition for risk groups to be vaccinated. There was a gradual increase of vaccination coverage from 1982 onwards, reaching levels above 15%, among cohorts born in 1998 and later. The BCG coverage of children in the defined risk groups was estimated at about 88% among children born during the period 1998 to 2002. On average, these figures correspond to 15 000 BCG vaccinated children per birth cohort (annual reports on vaccination statistics from child health centres, Swedish Institute for Infectious Disease Control).

Serious vaccine adverse reactions

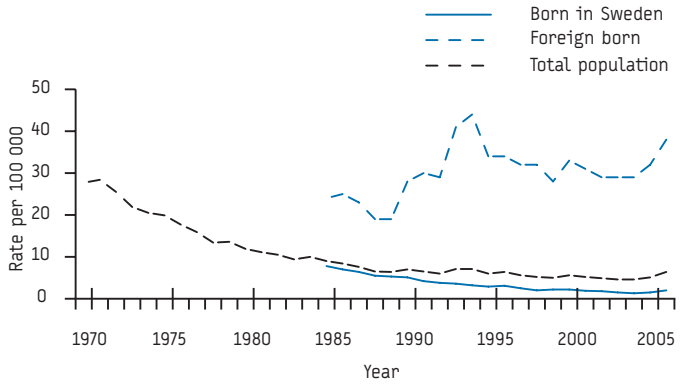
Three cases of BCG osteitis were reported among 3500 infants born and vaccinated neonatally with the vaccine based on the Gothenburg strain during the period from 1975 to 1978 [1]. After 1979, a few cases of clinically suspected BCG osteitis have been reported, but none have had bacteriologically confirmed diagnosis of BCG infection. During the period from 1979 to 1991, four cases of serious disseminated BCG infection occurred among 101 000 neonatally vaccinated infants [6]. Three of the infants suffered from severe combined immunodeficiency (SCID) and two of them died because of the BCG infection. These incidents were the impetus for the decision to postpone the 'routine' vaccination of risk groups to the age of six months or later. By that age, it was considered that any infant with severe combined immune deficiency would have been diagnosed and thus excluded from vaccination [5,6]. No case of fatal neonatal disseminated BCG infection has been reported since 1991.

Epidemiology of tuberculosis

In 1984, Sweden became a low incidence country, with fewer than 10 cases (all forms) of tuberculosis per 100 000 population [7]. During the period from 1989 to 2005, the previous declining trend [FIGURE 1] slowed down and then increased in 2004, and the incidence in 2005 was 6.4 per 100 000 population. The incidence of highly infectious (that is, sputum smear positive) pulmonary tuberculosis varied during the same period between 1.8 and 1.1 per 100 000, with 1.5/100 000 in 2005.

FIGURE 1

Annual incidence of tuberculosis per 100 000 population in Sweden during the period 1969 to 2005, and related to national origin of the population during the period from 1984 to 2005



Source: [2]

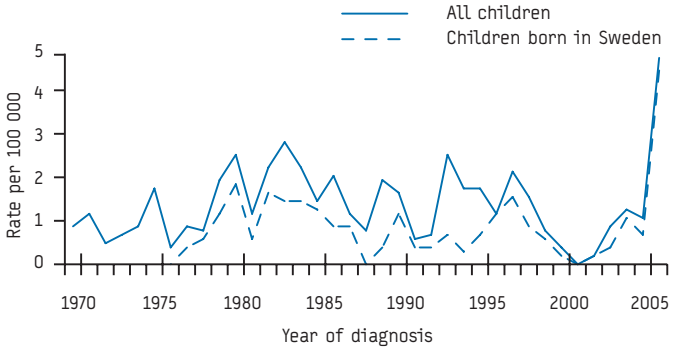
In the Swedish born population, the incidence of tuberculosis per 100 000 declined from 5.1 in 1989 to 1.5 during 2004, but then increased to 2.0 in 2005. In parallel, the proportion of foreign born tuberculosis patients increased from 34% in 1989 to more than 70% during the last four years. The estimated incidence in the foreign born population has remained on an average level of about 30 cases per 100 000 population per year, but increased to 38 in 2005. In different subgroups of the population, such as the African born population, incidence was more than 200 per 100 000 population. The average age specific incidence were highest in age groups 18-44 years in the foreign born population, at 58 per 100 000 during 2005 compared with 0.6 in the same age group in the Swedish born population.

The proportion of tuberculosis cases in age groups below 15 years of age amounted, on average, to 4% during the period from 1989 to 2004, but increased to 7% in 2005. The majority of children were born abroad (66% of all paediatric cases) or born in Sweden to foreign parents (20%), and were therefore in the risk groups targeted for BCG vaccination. In age group 0-14 years the average annual incidence per 100 000 population during the period 1989 to 2005 varied during different years from 0.5 to 2.6, *in children born in Sweden* variations from 0.1 to 2.0 and *in foreign born children* variations from 6.9 to 41.7.

It was expected that the immediate impact of the changed BCG policy in 1975 would be observed mainly in the youngest age group under five years of age, among children born in Sweden who were no longer vaccinated. Despite a temporarily increased level during the period 1979 to 1983 [1], the annual incidence of tuberculosis in children remained low, varying between 0 and 1.9 per 100 000 during the period 1975 to 2004. The corresponding incidence in children born abroad varied between 0 and 90 per 100 000. During 2005 tuberculosis incidence increased dramatically among children born in Sweden, up to 4.6 per 100 000 [FIGURE 2]. This increase was related to an outbreak at a day nursery, where 20 small children were diagnosed with active tuberculosis in connection with contact tracing around a person who had worked several months at the nursery, despite cough and other symptoms of illness, before the diagnosis of infectious tuberculosis [9].

FIGURE 2

Annual incidence of tuberculosis per 100 000 children aged 0-4 years in Sweden: all children from 1969 to 2005, and Swedish-born children only from 1975 to 2005



Sources: [1,2]

Cumulative incidence of tuberculosis in cohorts born in Sweden after 1974 and observed to the end of 2004.

Today thirty birth cohorts have been born in Sweden after the changed BCG policy. The oldest cohort (born in 1975) was observed during 29 years and the observation period for the youngest one (born in 2004) was on average six months. Up to the end of 2004 the cumulative number of reported cases of active tuberculosis in these birth cohorts amounted to 227, which corresponds to 0.5 per 100 000 person years i.e. on average less than one case per birth cohort per year of observation. The cumulative number of children developing tuberculosis before five years of age was 121 corresponding to 0.8 cases per 100 000 person years. Tuberculosis was diagnosed before 12 months of age in 26 infants i.e. 0.9 per 100 000 live born children. Fifty-seven per cent (129/227) of all cases belonged to the main risk group targeted for BCG vaccination, i.e. born in Sweden to foreign parents. A history of previous BCG was reported in 45% of this risk group (58/129) including 27% (7/26) of infants younger than 12 months of age.

According to information in the notifications of sources of infection, most children were infected by their parents or by other household contacts. In several occasions the source of infection was identified after the diagnosis of tuberculosis in the child. In some cases infection might have occurred during travel abroad [8]. Genetic typing of isolated strains of Mycobacterium tuberculosis has also confirmed transmission from occasional contacts in the community.

The main benefits of BCG vaccination is protection against serious disease, meningeal and/or miliary tuberculosis, therefore increased awareness was directed to the occurrence of these manifestations in the cohorts born in Sweden in 1975 or later [1,10,11]. In total seven children developed serious illness, which corresponds to 0.016 per 100 000 person years. Three of them died. Four of the seven children belonged to the risk group in which vaccination is recommended. Only two of them have been BCG vaccinated, but as shown later, they had been exposed before the vaccination. One infant was diagnosed with tuberculosis at seven weeks of age and died. His mother developed tuberculous meningitis after delivery. This case of perinatal infection could not have been prevented by BCG vaccination [11].

Discussion

Previous evaluations of the impact of the changed BCG policy in Sweden, during six years and during 14 years, respectively, demonstrated an increased incidence of tuberculosis in the mainly non-BCG vaccinated birth cohorts born in Sweden after 1975 compared to those born during period of general vaccination in 1969 to 1974.

Cumulative incidence rate before 5 years of age increased from 0.8 to 3.9 per 100 00 children born to Swedish parents and from 2.6 to 39.4 per 100 000 children born in Sweden to foreign parents. In the non-BCG vaccinated child population the incidence of tuberculosis was on average ten times higher among children born in Sweden to foreign parents than in those born to parents of Swedish origin. However, in parallel with improved BCG coverage of the risk group population, the incidence of tuberculosis declined in children born in Sweden to foreign parents [8].

The observed increase of tuberculosis in children after 1975 indicated a protective efficacy of about 85% for the vaccine used in 1969 to 1974. The observed decrease of tuberculosis in parallel with increasing BCG coverage of the risk group population indicated an effectiveness of the selective vaccination program at 82%. However, there are several limitations to be considered, especially the small number of cases, the wide confidence intervals and the retrospective analysis of the period from 1969 to 1974, which implies uncertainties in the calculations [8].

The tuberculosis trend during the past fifteen years, with increasing proportion of new cases of tuberculosis in the foreign born population and especially high incidence of tuberculosis in the childbearing age groups of the foreign population, means an increased risk of exposure for children in these families and the continuous need for them to receive BCG vaccination. However, the optimal age for vaccination to be performed is still a matter of discussion. A small number of children in risk group have been exposed to tuberculosis before receiving BCG vaccination at six months of age or later.

Despite the observed increase in 2004 and 2005, Sweden still has one of lowest incidences of tuberculosis in the world and the incidence of sputum smear positive tuberculosis in the population born in Sweden is very low, 0.5 per 100 000 in 2005. This means a minimal risk of infection for the majority of Swedish born children, which still supports the decision to restrict vaccination to high risk groups [8].

One advantage of the restricted BCG policy is that when non-BCG vaccinated children are unexpectedly exposed to tuberculosis, it will be easier to disclose latent tuberculosis infection by means of the tuberculin skin test than it would be among BCG vaccinated children [12]. However, new methodology with in vitro test of specific cell mediated immunity to *M. tuberculosis* will make it possible to also diagnose latent infection in BCG vaccinated individuals [13].

The recent outbreak in a day nursery shows that the favourable situation reported in Sweden is subject to change, and serves as a reminder of the serious consequences of delayed diagnosis [11]. Intensified active case finding to identify and treat the sources of infection and therefore avoid infecting children is the most important action to prevent childhood tuberculosis. Early diagnosis and treatment of infected children is crucial to prevent development of serious disseminated tuberculosis. The greatest danger in a country with low incidence of tuberculosis is that the diagnosis might be neglected.

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BCG IN FINLAND: CHANGING FROM A UNIVERSAL TO A SELECTED PROGRAMME

EPI Salo

In Finland, all newborns are currently offered BCG vaccination, and the national coverage is over 98%. The annual incidence of tuberculosis is low, at 6.6/100 000 in 2004 and has been steadily declining in recent years. Finland differs from the other Nordic countries in that the majority of cases are detected in people aged 65 and over in the indigenous population and only a smaller proportion (12%) detected in immigrants. The high incidence of TB and MDR-TB in neighbouring countries has raised concern, but no increase in TB detected in Finnish-born citizens has been seen. A decision has been made to change from mass BCG vaccination to targeting risk groups.

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Key words: BCG, Bacille Calmette-Guérin, tuberculosis, vaccination, vaccination policy

Finland is one of the few European countries where neonatal BCG (Bacille Calmette-Guérin) vaccination is still universally implemented. Sweden, which is culturally and geographically our nearest neighbour, moved to a selective programme in the 1970s [1]. Finland has a low incidence of tuberculosis (TB), and has met the International Union Against Tuberculosis and Lung Disease (IATLD) criteria for discontinuing a universal BCG programme in countries with a low prevalence of TB [2]. Following a change in vaccine strain, an increase of vaccination complications has been seen. The National Vaccination Advisory Board has recently recommended changing the policy to targeting risk groups, and it is planned that the new programme will begin in January 2008. New official recommendations are being prepared but are not yet available.

Background

The newborn BCG vaccination programme was begun in Finland in the 1940s. It is administered by physicians (mostly paediatricians) in maternity hospitals and uptake of the vaccine is high, with over 98% of newborns being vaccinated. Tuberculin testing and revaccination of tuberculin-negative schoolchildren was practised until 1990. In 2001, the newborn vaccination programme was evaluated by Tala-Heikkilä et al [3]. This evaluation concluded that a selective BCG vaccination strategy would be a safe and cost-effective approach in preventing tuberculosis in Finland, if the identification of high-risk groups were successful. A transition period was recommended to identify the risk groups and to prepare for the change.

From 1971 to 1978, when Finland used the Gothenburg BCG strain, the frequency of BCG osteitis was very high, at 36.9/100 000 vaccinated. It decreased to 6.4/100 000 after changing the vaccine to the Glaxo-Evans strain and decreasing the dose to 0.05 ml [4]. In August 2002 the vaccine strain had to be changed at short notice. Due to concerns about reduced potency of the Evans vaccine, it was withdrawn by the manufacturer. Since August 2002, the vaccine produced by Denmark's Statens Serum Institut (SSI) has been used in Finland.

Following the change of the vaccine strain to BCG SSI, a sharp rise in the incidence of inguinal lymphadenitis was noted, from about 8/100 000 with the Evans strain to 285/100 000 in the months immediately following the change [5]. An increase in the rate of BCG lymphadenitis was also noted in London (Royal London Hospital) after the same change in vaccine strain, although the application method was also changed at the same time from percutaneous to intradermal route [6]. The initial increase of reported lymphadenitis has settled in Finland to 140/100000 (Marko Luhtala, National Public Health Institute, KTL, personal communication). Milstein et al noted clusters of increased reported adverse reactions to BCG vaccine following a change in the vaccine strain in different populations or settings [7]. Until 2002, only one to two cases of BCG osteitis per year were notified in Finland [5]. Six cases of BCG osteitis have been notified in children vaccinated in 2003, [8, Marko Luhtala, KTL, personal communication]. The increase in adverse reactions to BCG SSI is also a factor influencing the view of both the medical faculty and the public about universal neonatal BCG vaccination. As the incidence of TB has decreased, the complications are no longer considered acceptable.

Factors considered during the preparation of the new programme

Demographics of TB patients

In the Finnish BCG debate, Finland has been repeatedly compared with Sweden, where mass BCG vaccination was stopped in 1975, when TB incidence in Sweden was 18/100 000 [3]. In comparison, the annual incidence of TB in Finland is currently lower at 6.6/100 000 in 2004, and has continued to decline steadily [9].

The difference between Finland and the other Nordic countries is the population in which new cases are detected. In Denmark, Norway and Sweden the majority (60 to 80%) of TB cases are detected in individuals born abroad [10], whereas in Finland the proportion of TB cases in foreign-born people was only 12% in 2004, although this proportion has been increasing on an annual basis, (5.6% in 1995 and 8.4% in 2000) [9].

In 1960 the incidence of TB in Finland was high at 172/100 000 [3]. As a consequence, many of those aged 65 years and older had contracted TB infection in their youth. The incidence of TB is highest in the oldest age group, those over 75 years [9] [FIGURE]. However, the most significant decline in the number of cases has also been seen in this group, possibly due to a reduction of the exposed people in the age group. Childhood TB is very rare in Finland, with an annual average of four cases registered in children in the whole country [9].

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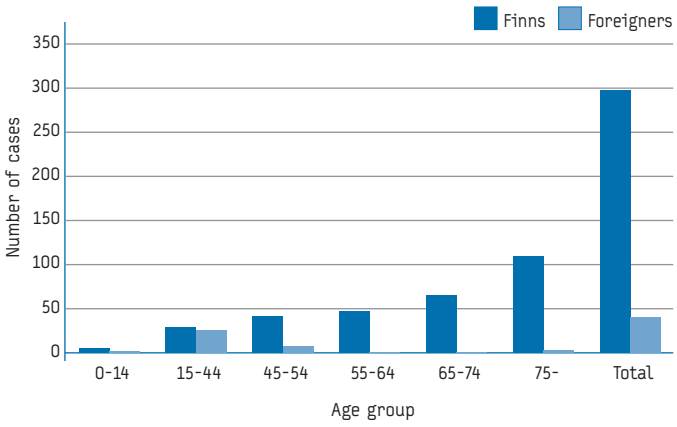
Figure

TB Infections in Finns and persons of foreign origin by age group in 2004



Source: [9]

Geography

Finland shares a large border with Russia, where the notification rate for TB was 106/100 000 in 2003, and the proportion of multidrug resistant (MDR) TB is high, 6.7% in new cases in 1999 [9], compared with Finland where no MDR cases were notified in 2004. In addition, the Russian Federation has one of the highest rates of HIV infection in all of Europe, with St. Petersburg and the Leningrad Oblast being heavily affected [11]. In recent years, there has been an increase in migration from Russia to Finland. Communication across the border is frequent, and trade and commercial cooperation is increasing. Despite this, no increase in the incidence of TB among Finnish-born people living near the Russian border has been noted to date, but the situation will continue to be monitored.

Finland has also frequent interactions with Estonia, with several boats making the journey between Helsinki and Tallinn daily. In Estonia, the proportion of MDR-TB is high, 12% [10]. The HIV epidemic in Estonia also continues to expand. The possibility that MDR-TB may spread to Finland has been a cause of concern, although one which has so far not been realised. There have been a few separate cases but no outbreaks detected.

Inoculation site

BCG in Finland is administered intradermally in the left thigh, as originally described by Wallgren [12]. Among active parent groups in particular, concern has been raised about the possible contribution of the vaccine site to the frequency of complications. In Sweden, the thigh was also used until the 1970s. However, when the mass BCG vaccination changed to a selective immunisation programme, it was decided that the inoculation site should be changed from the thigh to the left upper arm (Victoria Romanus, personal communication). The manufacturer of the current vaccine, SSI, recommends the left thigh as the inoculation site. The only article found comparing these two sites was published by Gaisford and Giffiths in 1954 [13]. The study is not randomised but observational and describes the decreasing frequency of regional lymphadenitis as the authors decreased the dose and changed the site to the upper arm. The authors recommend inoculation in the arm, but their results may have been influenced by the different dosages of the vaccine, different strains used and the growing skill of the vaccinators.

When asked about their BCG scars, English children found them unsightly and showed a preference for other sites than the outer arm [14]. These children were vaccinated at age 11 to 13, and their reaction might have been different if they had grown up with an old scar acquired as infants. WHO recommends vaccinations in the upper arm, and by convention BCG scars are looked for over the left arm everywhere else in the world but Finland. As it is better to have an internationally recognised token of a successful vaccination, it is recommended that the vaccination site be changed to the upper arm when the vaccination programme changes in 2008.

Age at vaccination

In Finland, there has been public discussion about the age of BCG administration, with parents expressing their concern for the young age of the vaccinees, and demanding the vaccination to be postponed to several weeks or months of age. BCG is most effective in preventing cases of severe TB, such as meningitis and miliary TB, in small children [15]. For maximum benefit children should be vaccinated soon after birth. On the other hand, severe immune deficiencies such as severe combined immune deficiency (SCID) may not be evident at birth, exposing the children to severe complications of BCG, a reason why Sweden defers BCG vaccine until six months of age. Although the incidence of SCID is unknown, a recent review estimated that it is at least 1/100 000 [16]. If this figure is correct, with targeted BCG vaccination a newborn child with SCID would receive BCG in Finland once in 30 years. HIV screening is offered to all pregnant mothers in Finland, with coverage of over 99%. Children of HIV positive mothers are offered BCG only after they have been found not to have contracted the virus, so the risk of vaccinating an HIV positive child is low.

Vaccination centres

The rate of BCG complications has been observed to be influenced by the training and skills of the vaccinator [7].

With fewer children being vaccinated, vaccinating expertise will gradually decline. To ensure adequate skills the number of vaccinating centres needs to be limited. Almost all children in Finland are born in hospitals and it is recommended that the paediatricians will continue the vaccination of newborns. However, there is controversy about who should vaccinate older children, and the discussion is ongoing.

Recommendations

Target groups

Newborns to be vaccinated are those corresponding to the following definitions:

1. Children of immigrant families, with parents or grandparents originating from countries with a high incidence of TB, or with a member of the household from a high incidence country
2. Children of Finnish-born parents with a first or second-degree relative (parent, grandparent, sibling or parent's sibling) who has or has had TB
3. Children of families planning to stay for a prolonged period in a high-incidence country
4. Children of families requesting BCG for their child.

Using these target groups, the estimated annual number of newborns eligible for BCG is between around 3000 and 3500, or 5%-6% of this age cohort.

Older children

Older immigrant children from high-incidence countries who have not yet started school should be offered BCG if they have not been previously vaccinated and are tuberculin negative. Another group of older children to be vaccinated is unvaccinated contacts of detected cases of infectious TB who are healthy and tuberculin negative. The annual number of these children needing vaccination is calculated to be between 200 and 500.

Identifying newborns who need to be vaccinated

The need for BCG in a newborn should be ascertained before delivery. Finland has a well-functioning system of public maternity clinics with almost universal attendance by pregnant mothers. A questionnaire to be used by midwives at maternity clinics is currently being tested with the guidance of the National Public Health Institute (Kansanterveyslaitos, KTL). When the questionnaire has been evaluated, training will take place to prepare for its implementation in all maternity clinics.

Training and education

As childhood TB is very rare in Finland [9], physicians' ability to suspect and diagnose it has declined. Very few paediatricians have ever seen a child with miliary TB or tuberculous meningitis. During the last 10 years, there has been only one case of paediatric tuberculous meningitis in Finland detected in an immigrant child [17]. With universal BCG, the risk of an infected child developing serious disease has been small. The medical community must be alerted to the real risk of TB in exposed unvaccinated children and the need for vigorous contact tracing.

Implementation of the new programme

The Ministry of Social Affairs and Health (Sosiaali-ja terveysministeriö) and KTL have agreed that KTL will take the lead in the preparation for the change to the targeted BCG programme. New official recommendations are being prepared but are not yet available.

A committee organised by the Finnish Lung Health Association (Filha ry), cooperating with the KTL and supported by the Ministry for Social Affairs and Health, has been preparing a new tuberculosis control programme for Finland. Several parts of the guideline have already been published in the national medical journal Suomen Lääkärilehti and are also available online [18]. The guidelines will be completed in 2006. While enhancing awareness and knowledge of TB the guidelines will support the preparation for the change to the new BCG programme.

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Original Articles

Euroroundup

Tuberculosis outcome monitoring – is it time to update European recommendations?

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We discuss tuberculosis treatment outcome monitoring and the adherence of countries in the WHO European Region to modifications introduced in 2001 to enhance inter-country comparability.
Outcomes for definite pulmonary tuberculosis cases were compared for cases reported in 2001 and 2000. Reporting was considered complete if 98% or more of cases originally notified had outcome reported. In both years, maximal period of observation was 12 months from start of treatment. In 2000, countries reported outcome as 'cured', 'completed', 'died', 'failed', 'defaulted', 'transferred' and 'other, not evaluated' for cohorts of new and retreated cases. In 2001, following changes, countries were also requested to monitor cases with unknown treatment history and two outcome categories were added – 'still on treatment' and 'unknown'.
Of 42 countries reporting outcomes in 2001, 74% (31) had

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nationwide, complete data, up from 50% (19/38) in 2000. Twelve of 21 countries that reported on observation period complied with that recommended. 'Defaulted' and 'transferred' were applied interchangeably with 'unknown'. Among new cases, 'still on treatment' was used by 15/31 countries (range: 1%-15%). 'Failed' was rarely recorded in western European countries (<1%).
European tuberculosis outcome monitoring should include all definite pulmonary cases, applying the standard period of observation and revised categories, and preferably reported using individual data.

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Key words: definitions, Europe, treatment outcome, tuberculosis surveillance

Introduction

In 1991 the World Health Assembly established targets for the detection and treatment of infectious tuberculosis cases, following the worldwide resurgence of tuberculosis [1]. Efforts by the World Health Organization (WHO) to monitor the progress of countries towards achieving these targets have necessitated the standardisation of surveillance definitions across countries [2,3]. A number of issues surfaced in the application of these definitions in national programmes, limiting the comparability of data between different countries and over time, and prompting modifications [4,5].

In the countries of the WHO European Region [6] (henceforth referred to as Europe), the key document on treatment outcome monitoring was published in 1998 by WHO and the International Union Against Tuberculosis and Lung Disease with a working group representing 37 European countries [7]. EuroTB, a network of national tuberculosis surveillance institutions in Europe, has been working with WHO since 2000 to improve completeness of reporting and standardisation of national treatment outcome monitoring data in Europe. Each year, EuroTB and WHO jointly collect data on tuberculosis cases notified in the previous calendar year, as well as outcome reports for cases notified the year before the last. Revisions to the definitions and parameters of cohort analysis were discussed between EuroTB and WHO and piloted during the annual collection of tuberculosis notification data for 2001 in an effort to improve inter-country comparability. We identify unsolved issues in outcome monitoring in Europe and recommend an update to its methodology based on the results of this analysis.

Methods

Classification of outcomes and cohorts

For the collection of data on tuberculosis cases notified in 2000, all 51 European countries were requested to classify their outcomes using the six standard categories ('cured', 'completed', 'died', 'failed', 'defaulted' and 'transferred') [TABLE 1] [7]. The first outcome observed within 12 months from start of treatment or diagnosis would be considered definitive. If treatment lasted beyond 12 months for any reason, a case would be classified as 'other, not evaluated'. Cases lost to follow up were to be classified as 'defaulted' (unless fulfilling the conditions for 'transferred'), and cases diagnosed post mortem were to be classified as 'died'. Those found to have been wrongly diagnosed as tuberculosis or notified more than once in the same calendar year, as well as those notified from areas not participating in outcome monitoring, were to be excluded from the cohort. Monitoring was limited to new and retreated cohorts of definite pulmonary cases that were culture positive, or smear positive if culture was not available. Data were to be submitted in aggregate form on paper or electronically.

Changes were introduced, beginning with the cohorts of cases reported to European surveillance for the year 2001. Countries were to report outcomes on all the definite cases that had been notified to EuroTB for 2001, including those with unknown previous treatment history. Two additional outcome categories were introduced: 'still on treatment' (at 12 months) and 'unknown' [TABLE 1]. The 'still on treatment' category had already been contemplated in the European recommendations as a way of dealing with previously treated cases failing a full re-treatment course [7]. Instructions on data submission and definitions were developed in English and Russian [8]. Countries were requested to report outcomes in individual format where possible. Participants were invited to give feedback on compatibility between national and recommended definitions.

TABLE 1

Tuberculosis treatment outcome categories, 2000 and 2001

Cured	Treatment completion and: • culture becoming negative on samples taken at the end of treatment and on at least one previous occasion or • sputum microscopy becoming negative for acid-fast bacilli at the end of treatment and on at least one previous occasion
Completed	Treatment completion, not meeting the criteria to be classified as cure or treatment failure
Died*	Death before starting treatment or during treatment, irrespective of cause
Failed	Culture or sputum microscopy remaining positive or becoming positive again at 5 months or later during treatment
Defaulted†	Treatment interrupted for 2 consecutive months or more
Transferred	Patient referral to another clinical unit for treatment and information on outcome not available / not obtained
Still on treatment§	Patient still on treatment at 12 months and who did not meet any other outcome during treatment. It includes patients with: • treatment prolonged because of side effects / complications, initial regimen planned for > 12 months • initial treatment changed due to polyresistance (ie resistance to at least two first line drugs) on the isolate taken at the start of treatment • information on the reasons for being still on treatment not available
Unknown§	Information on outcome not available

* Includes cases diagnosed post mortem
† Includes cases not starting treatment following diagnosis
§ Categories introduced from 2001
Adapted from [7]

Other definitions

For the purpose of this article, a new case is defined as a patient with no history of curative, combination antituberculosis treatment or one who has had such treatment for less than four weeks. A retreated case is a patient who had at least one treatment episode lasting four weeks or more before the current notification but not in the same calendar year; a relapse is a retreated case, previously declared cured, and notified again with definite tuberculosis. Multidrug resistance (MDR) refers to resistance to at least isoniazid and rifampicin. 'Success' refers to the sum of 'cured' and 'completed'. Countries are grouped in three geographic areas: EU & West (countries of the European Union post-May 2004, plus Andorra, Iceland, Israel, Norway and San Marino), East (countries of the former Soviet Union excluding the Baltic states) and Centre (other countries in the Balkans and Turkey).

Analysis

Outcomes are expressed as the percentage of cases in the respective outcome category divided by all cases included in the cohort. The most recent cohorts reported were used for both numerator and denominator. Data used are those received up to 28 February 2005. For 2000 cohorts, cases classified under 'other, not evaluated' were retained in the denominator. Unless stated otherwise, the median of outcomes is used for inter-country comparison. Arithmetic means are used where statistical significance is tested on cases pooled from different countries (P value limit for significance = 0.001). Smear positive cohorts are used for both years in countries where culture positive cohorts were not available.

Completeness of cohorts is calculated as the percentage of definite cases included in outcome monitoring cohorts divided by the number of definite cases previously notified [TABLE 2]. It could exceed 100% if outcome reports included additional cases identified subsequent to initial notification. This commonly occurs after reclassification of cases based on belated retrieval of culture results. Outcome results are discussed for new, definite cases from nationwide cohorts reported in 2001 with 98% completeness or more [TABLE 3]. As completeness tended to be lower in 2000, changes in outcome coding between 2000 and 2001 are discussed solely for countries with >90% completeness in 2000 and reporting more than 10 cases [TABLE 3, countries in bold].

Results

Completeness of cohorts

Whereas 38 of 51 countries submitted outcome data for definite pulmonary cases notified in 2000, the number of countries increased to 42 in 2001. Ten countries did not report outcome information in 2000 or 2001 (Belarus, Croatia, Finland, France, Greece, Luxembourg, Monaco, Spain, Switzerland, Ukraine). In 2000, 19/38 reporting countries had nationwide cohorts with at least 98% completeness, increasing to 31/42 in 2001 [TABLE 2]. The total number of cases included in complete cohorts increased from 25 735 in 2000 to 57 692 in 2001. In 2001, seven countries reported outcome for cases with unknown treatment history, which represented between 1% and 26% of cases reported (1206 cases in total). The number of countries reporting nationwide, complete cohorts increased in all geographic areas. Eleven countries, all from the EU & West, sent individual outcome data.

Compatibility of period of observation and outcome categories

Romania and 20 countries from the EU & West submitted feedback on their coding experience in 2001. Twelve countries (57%) stated that they applied a 12 month maximal observation period, while in the others this was longer (three countries) or not defined. Fourteen countries (67%) reported no incompatibilities between outcome categories proposed and those in national use. Three countries (14%) noted differences with one category while four countries differed in more than one category. 'Cured' was not always differentiated from 'completed' (four countries), 'failed' was sometimes defined differently, or was not available as a category (three countries), and 'defaulted' was sometimes applied in a different way (three countries). A number of countries could distinguish between death from tuberculosis or from other causes. One country reported that an outcome could be changed within the 12-month period if, for example, a defaulter resumed treatment after an interruption.

Classification of outcomes in 2001 and changes from 2000

Among nationwide, complete cohorts of new cases in 2001 [TABLE 3], 'success' ranged from 54% to 100% (median: 76%). 'Died' was more frequent in the EU & West compared with the Centre and East (means: 9% versus 4%, P<10-6). In general, the number of 'unknown' was inversely proportional to the total of 'defaulted' and 'transferred'. In 20 countries that reported fewer than 2% of cases as 'unknown', cases overall were classified more often as 'transferred' or 'defaulted' than in the 12 countries with a higher proportion of 'unknown' (means: 8% versus 5%; P<10-6). 'Failed' was rarely reported in the EU & West (<1%) in contrast to the Centre (3%) and East (8%). Conversely, 'still on treatment' was more commonly reported in the EU & West (1%; country range: 0%-15%) than in the Centre and East (0%; 0%-9%).

In 2001, 15 of 31 countries reporting outcomes had cases classified as 'still on treatment' (1%-15%) and 15 as 'unknown' (1-30%), with higher proportions in both categories amongst retreated cases (data not shown). Three types of shifts in outcome coding could be discerned in 2001 cohorts when compared to 2000 [TABLE 3]

a) 'other, not evaluated' shifted to 'still on treatment' in Estonia, Latvia and Portugal;

b) 'other, not evaluated' shifted to 'unknown' in Austria, and possibly in Sweden where this shift was accompanied by an increase in 'still on treatment' and a drop in 'success';

c) 'defaulted' shifted to 'unknown' in Ireland.

Discussion

Changes to the outcome monitoring methodology introduced in 2001 were meant to enhance inter-country comparability and ensure that all definite pulmonary cases would be monitored and assigned an outcome. Cases with unknown previous treatment history, or who were still on treatment at 12 months, would be retained in the calculation of cohort completeness. Ensuring completeness would reduce the likelihood of selection bias when reporting outcomes. In countries reporting nationwide outcome data, cases notified in areas or units not participating in monitoring would be classified as 'unknown' and kept in the denominator for the calculation of outcome percentages. Reducing the proportion of 'unknown' would then become an intermediate goal to improve coverage.

The increase in the proportion of countries submitting nationwide cohorts from 37% to 60%, which more than doubled the size of complete cohorts, is an important achievement in European tuberculosis surveillance. However, sustaining or improving upon this achievement in future is not assured, especially in certain Eastern countries where reporting systems are not yet stable. The definition of a retreated case is not harmonised, particularly in countries of the former Soviet Union, and has at times changed in the interim [9]. This precludes conclusive discussion of outcomes among retreated cases. For many countries, the compatibility between recommended and national outcome monitoring parameters is not known. In countries providing information, the period of observation was not standardised, and this limits inter-country comparison, since chances of success may vary with the duration of evaluation. Another possible source of bias when comparing national programmes is the absence of a lower time limit for defining treatment completion, which may therefore be expected to vary substantially if drug regimens are not standardised. Likewise, 'success' may improve if outcome is changed after the case first satisfies the definition of another outcome category (eg, reclassification of defaulters). There is evidence that 'defaulted', 'transferred' and 'unknown' tend to be used interchangeably, thus reducing the possibility of meaningful comparison of these categories at European level. Having a sub-category of 'died' for cases dying directly from tuberculosis rather than a concurrent cause could be useful in programme monitoring [7] but this would require a harmonised definition of which cases to include.

The shift observed from 'other, not evaluated' to the 'still on treatment' category was anticipated, since the former category was reserved for cases on prolonged treatment. In Portugal, where drug resistance is low, this shift has largely been caused by the continued use of long term chemotherapy regimens for non-MDR tuberculosis (A Fonseca Antunes, personal communication, 11 May 2005).

TABLE 2

Size and completeness of treatment outcome cohorts, definite pulmonary tuberculosis cases*, Europe, 2000 and 2001

Geographic area	Tuberculosis notifications, 2000			Tuberculosis notifications, 2001		
Country	Total notified (A)	Total with outcomes (B)	Completeness† (B/A, %)	Total notified (C)	Total with outcomes (D)	Completeness† (D/C, %)
EU & West						
Andorra	5	7	>100%	3	3	100%
Austria	666	621	93%	590	590‡	100%
Belgium	758	660	87%	739	724	98%
Cyprus	-	-	-	26	26	100%
Czech Republic	815	720	88%	729	729‡	100%
Denmark	313	129	41%	254	213	84%
Estonia	516	516 r	100%	557	557‡	100%
Germany	-	1155	-	3943	3943‡	100%
Hungary	896	961	107%	917	917‡	100%
Iceland	7	7	100%	7	7‡	100%
Ireland	182	186	>100%	122	181	>100%
Israel	248	346	>100%	249	313	>100%
Italy	-	338 s	-	1212	315 s	26%
Latvia	1278	1278	100%	1275	1335	>100%
Lithuania	1490	1490 r	100%	1698	1698	100%
Malta	9	9	100%	10	10‡	100%
Netherlands	591	584	99%	627	627‡	100%
Norway	111	111	100%	156	156‡	100%
Poland	-	270 s	-	3699	3636	98%
Portugal	2042	2104	>100%	2097	2241	>100%
San Marino	1	1	100%	0	0	-
Slovakia	528	528	100%	517	517‡	100%
Slovenia	285	285	100%	273	273‡	100%
Sweden	128	121	95%	111	113	>100%
United Kingdom	-	-	-	2477	1874	76%
Centre						
Albania	-	-	-	191	191	100%
Bosnia & Herzegovina	1508	1294	86%	1618	1551	96%
Bulgaria	-	-	-	-	429 s	-
Macedonia	183	168	92%	190	190	100%
Romania	13 431	15 042	>100%	13 536	14 863	>100%
Serbia & Montenegro	-	280 s	-	372	372 s	100%
Turkey	4315	3461	80%	4444	4359	98%
East						
Armenia	686	501 s	73%	330	330 s,r	100%
Azerbaijan	964	964 r	100%	1689	1689	100%
Georgia	1451	1277	88%	1691	1691	100%
Kazakhstan	12 926	11 682 r	90%	12 095	11 794 r	98%
Kyrgyzstan	1726	1511 r	88%	1774	1754 r	99%
Moldova, Rep of	651	651 n	100%	1250	1109 r	89%
Russian Federation	-	5310 s	-	4933	4912 s,r	100%
Tajikistan	434	665 n	>100%	781	768 r	98%
Turkmenistan	-	1512	-	1797	1797	100%
Uzbekistan	-	1794 s	-	854	854 s,n	100%

n = new cases only; r = retreated cases only include relapses; s = selected areas (non-nationwide)

* Pulmonary culture positive cases, except for countries underlined (smear positive)

† Values >100% indicate complete cohorts with additional reporting of outcome on cases included in monitoring after the initial notification. 2001 cohorts also include cases with unknown treatment history if present

‡ Individual outcome data

In Estonia, however, 'still on treatment' cases were mostly MDR (data not shown), and a similar explanation would be likely for Latvia, another Baltic state with a high MDR burden [10]. In Lithuania, the proportion of 'still on treatment' in 2001 was more modest than in neighbouring Baltic states despite similar MDR levels [11]. This shift was not observed in other former Soviet countries probably because MDR cases were mostly classified as 'failed' both in 2000 and 2001. Such differences may represent variability in patient access to drug-susceptibility testing and appropriate chemotherapy.

Where access to laboratory testing is good, MDR cases are commonly identified ahead of the fifth month of treatment and embarked on long term medication, making it more likely that they are classified as 'still on treatment' at 12 months rather than 'failed'. In much of western Europe, 'failed' is rarely used, because the follow-up bacteriological information required to define this category is often not captured by surveillance systems. In the new definitions for outcome monitoring in MDR cases, 'failed' is reserved for cases who are bacteriologically positive at a much later stage in the course of their second line treatment [12]. Until such time as second line treatment becomes widely available in all European countries, the category 'failed' will have to be retained. As more countries develop the capacity to rapidly diagnose drug resistance and to change over to second line regimens, the 'still on treatment' option will have a wider utility, and the 'failed' category will become less important.

Table 3

Tuberculosis treatment outcomes, new definite pulmonary cases, Europe, 2000 and 2001*

Geographic area	Total number		Success %		Died %		Failed %		Defaulted %		Transferred %		Other / not evaluated %		Still on treatment %		Unknown %	
Country	2000	2001	2000	2001	2000	2001	2000	2001	2000	2001	2000	2001	2000	2001†	2000†	2001†	2000†	2001
EU & West																		
Andorra	7	2	86	100	0	0	0	0	14	0	0	0	0	-	-	0	-	0
Austria	**607**	**545**	**71**	**76**	**12**	**9**	**0**	**0**	**6**	**6**	**0**	**0**	**12**	**-**	**-**	**0**	**-**	**8**
Belgium	577	534	65	63	12	9	1	0	18	1	2	2	3	-	-	1	-	24
Cyprus	-	25	-	92	-	0	-	0	-	0	-	8	-	-	-	0	-	0
Czech Republic	645	704	69	69	18	5	1	0	2	1	2	0	8	-	-	0	-	24
Estonia	**401**	**351**	**73**	**68**	**8**	**9**	**1**	**2**	**6**	**11**	**0**	**0**	**12**	**-**	**-**	**10**	**-**	**0**
Germany	1003	2589	77	66	16	12	0	0	2	2	4	0	0	-	-	5	-	15
Hungary	**778**	**732**	**61**	**54**	**14**	**10**	**3**	**10**	**12**	**7**	**6**	**3**	**4**	**-**	**-**	**15**	**-**	**1**
Iceland	6	7	83	86	17	0	0	0	0	14	0	0	0	-	-	0	-	0
Ireland	**160**	**129**	**53**	**59**	**10**	**7**	**0**	**1**	**37**	**3**	**0**	**0**	**0**	**-**	**-**	**0**	**-**	**30**
Israel	**320**	**288**	**78**	**79**	**11**	**9**	**1**	**1**	**3**	**6**	**7**	**3**	**1**	**-**	**-**	**0**	**-**	**3**
Latvia	**957**	**1004**	**76**	**77**	**9**	**7**	**2**	**1**	**6**	**7**	**0**	**0**	**6**	**-**	**-**	**9**	**-**	**0**
Lithuania	**1067**	**1142**	**76**	**74**	**7**	**10**	**3**	**2**	**12**	**11**	**1**	**0**	**1**	**-**	**-**	**2**	**-**	**0**
Malta	8	9	100	89	0	11	0	0	0	0	0	0	0	-	-	0	-	0
Netherlands	**543**	**601**	**87**	**86**	**6**	**4**	**0**	**0**	**5**	**7**	**1**	**0**	**0**	**-**	**-**	**2**	**-**	**0**
Norway	**105**	**145**	**78**	**86**	**10**	**6**	**3**	**0**	**1**	**3**	**9**	**6**	**0**	**-**	**-**	**1**	**-**	**0**
Poland	214	3155	72	76	11	6	6	1	6	6	5	1	0	-	-	0	-	11
Portugal	**1893**	**2024**	**82**	**80**	**5**	**5**	**0**	**0**	**4**	**5**	**2**	**3**	**6**	**-**	**-**	**6**	**-**	**0**
Slovakia	**421**	**413**	**83**	**86**	**14**	**11**	**1**	**0**	**2**	**1**	**0**	**0**	**1**	**-**	**-**	**1**	**-**	**0**
Slovenia	**247**	**250**	**84**	**79**	**10**	**14**	**0**	**0**	**3**	**4**	**3**	**1**	**0**	**-**	**-**	**2**	**-**	**0**
Sweden	**112**	**106**	**79**	**62**	**11**	**12**	**0**	**1**	**2**	**3**	**0**	**3**	**8**	**-**	**-**	**7**	**-**	**12**
Centre																		
Albania	-	177	-	81	-	5	-	3	-	3	-	0	-	-	-	0	-	8
Macedonia	**152**	**164**	**86**	**89**	**4**	**0**	**2**	**2**	**7**	**8**	**1**	**0**	**0**	**-**	**-**	**0**	**-**	**1**
Romania	**12 071**	**10 960**	**77**	**71**	**4**	**4**	**8**	**6**	**8**	**6**	**0**	**1**	**4**	**-**	**-**	**1**	**-**	**11**
Turkey	3461	4359	73	72	3	2	0	0	6	5	6	5	12	-	-	9	-	7
East																		
Azerbaijan	**890**	**1421**	**90**	**77**	**1**	**4**	**2**	**8**	**3**	**7**	**4**	**2**	**0**	**-**	**-**	**0**	**-**	**1**
Georgia	807	1014	63	67	3	2	9	7	25	14	0	8	0	-	-	0	-	1
Kazakhstan	**8781**	**8894**	**79**	**78**	**5**	**5**	**10**	**12**	**3**	**4**	**3**	**2**	**0**	**-**	**-**	**0**	**-**	**0**
Kyrgyzstan	1233	1458	82	81	3	5	4	6	5	6	6	2	0	-	-	0	-	0
Tajikistan	665	670	77	72	15	14	8	12	0	0	0	2	0	-	-	0	-	0
Turkmenistan	1017	1243	81	64	9	9	6	12	3	14	1	0	0	-	-	1	-	0

* The two columns under Total number show total new cases in outcome cohorts by year; value in other columns are percentage outcomes. Excluding countries with incomplete (<98%) and/or non-nationwide cohorts, and San Marino (0 cases) in 2001. Countries **in bold** had >10 cases and > 90% completeness in 2000 (see Methods)

† 'Other/not evaluated' discontinued from 2001; 'still on treatment' and 'unknown' introduced in 2001

In conclusion, outcome should be reported for all definite pulmonary cases notified, regardless of treatment history. The 12-month maximum period of observation should be applied for the classification of all outcomes. Cases treated beyond 12 months and having MDR tuberculosis (identified at start or during the current treatment episode) would form the subject of continued monitoring with a longer period of observation (24-36 months).

The eight outcome categories proposed can be used for national outcome monitoring. Owing to the incomplete differentiation of 'cured' from 'completed', and to the non-uniform use of 'defaulted', 'transferred' and 'unknown' in classifying cases lost to follow up, analysis of outcome monitoring at European level and inter-country comparison should be based on five categories: 'success', 'death', 'failed', 'still on treatment' and 'others'. European countries should further standardise their parameters for tuberculosis outcome monitoring in order to enable a more meaningful comparison of programme performance between countries and over time. In the West, where tuberculosis patients are older and deaths are thus expected to be higher, it is all the more imperative to bolster patient follow up if countries are to approach the 85% success target.

The WHO and EuroTB should continue working together to harmonise monitoring methodology, promote the evaluation of control programmes and support countries to provide nationwide, complete data. In order to better understand the determinants of outcome, collection of tuberculosis notification data on an individual case basis should be promoted.

† Andrea Infuso, EuroTB scientific coordinator, died suddenly on September 20, 2005. This Euroroundup is a posthumous publication.

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ORIGINAL ARTICLES

Surveillance report

EPIDEMIOLOGY AND RESPONSE TO THE GROWING PROBLEM OF TUBERCULOSIS IN LONDON

D Antoine[1], H Maguire[2], A Story[1]

As in other countries with low tuberculosis incidence, tuberculosis in England and Wales tends to be concentrated in some subgroups of the population, and is mainly a problem in large cities. In 2003, almost half of all tuberculosis cases reported in England and Wales were from London, where the incidence was almost five times higher than in the rest of England and Wales. While the highest proportion of cases occur in foreign born patients, evidence from a large outbreak of drug resistant tuberculosis points to ongoing active transmission among marginalised groups including homeless people, hard drug users, and prisoners. Increasing rates of disease and levels of drug resistance, combined with a concentration of disease in hard-to-reach risk groups now present a major challenge to tuberculosis control in the city. To respond to the changing epidemiology observed in recent years, treatment and control services are being reconfigured,

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surveillance has been improved with the implementation of the London TB register, and the utility of mobile digital x ray screening for at risk populations such as homeless people and prisoners is being evaluated. However, tuberculosis in London is not yet under control and more needs to be done. Services must adapt to the needs of those groups now most affected. This will require continued improvements to surveillance and monitoring, combined with improved access to care, better case detection, rapid diagnosis and active social support for people undergoing treatment.

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Key words: control, epidemiology, London, England and Wales, tuberculosis

Introduction

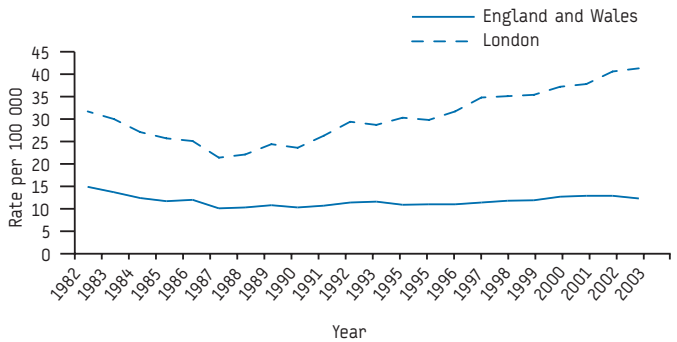
As in other countries with low tuberculosis incidence, tuberculosis in western European countries tends to be concentrated in subgroups of population and is mainly a problem in large cities [1]. London, with around 7.4 million habitants in 2003, represents 14% of the total population in England and Wales (52.8 million) and shares with other large cities marked contrasts in economic wealth with high levels of deprivation and social exclusion. Population groups most at risk of tuberculosis, such as the homeless, recent immigrants from high tuberculosis incidence countries and people with HIV infection, are more common in London than in other large cities.

Following a decline over more than two centuries, the incidence of tuberculosis cases has increased since 1988 in England and Wales. This changing epidemiology has been accompanied by a concentration of the disease in major urban centres, particularly London. The proportion of tuberculosis cases reported in London has increased from 28% in 1987 to 45% in 2003 of all tuberculosis cases reported in England and Wales. In the last decade, the tuberculosis notification rate in London has continued to increase, while it has remained stable or declined in the rest of the country [FIGURE 1].

This paper describes the epidemiological pattern and trends in tuberculosis in London and outlines the efforts to control tuberculosis that have been made to date.

FIGURE 1

Tuberculosis rate, London and England and Wales, 1982 - 2003



From: Statutory Notifications (NOIDs) and London 2000-2003: Enhanced Tuberculosis Surveillance

Methods

London is defined as the Greater London region, including inner London and outer London.

Epidemiological data presented in this article are mainly based on case reports from the statutory notification of suspected tuberculosis (NOIDs), collected since 1913, and from the Enhanced Tuberculosis Surveillance (ETS) system implemented in 1999 in England and Wales and in 2000 in Northern Ireland. The ETS provides more detailed information on each case and allows more accurate notification since cases can be better checked and duplicates identified and removed. Surveillance of treatment outcome at one year following start of treatment has been implemented since 2002 on tuberculosis cases reported in 2001. Outcome is considered to be successful if the treatment has been completed and if the patient is considered cured and discharged by a clinician.

In London, ETS information on tuberculosis cases is collected through a web-based register, the Health Protection Agency London Tuberculosis Register (HPA LTBR), which was implemented in 2002 in each of the 33 tuberculosis clinics across the city.

Cases to be reported include culture confirmed cases with *Mycobacterium tuberculosis* complex (*Mycobacterium tuberculosis*, *M. bovis* or *M. africanum*) and non-culture confirmed cases treated with a full course of antituberculosis treatment on the basis of other clinical, radiological or histopathological evidence.

Information on culture, drug susceptibility testing and species is collected through a national network of Mycobacterium reference laboratories by the MycobNet system. Laboratory information is then linked with tuberculosis case reports. Drug resistance at the start of treatment is reported as a proportion of case reports, using as the denominator cases with drug susceptibility results. Multidrug resistance (MDR) is defined as resistance to at least isoniazid and rifampicin.

The proportion of HIV infection among tuberculosis cases reported has been estimated by linking HIV reports with tuberculosis cases reported between 1998 and 2000 in persons aged 15 to 64 years.

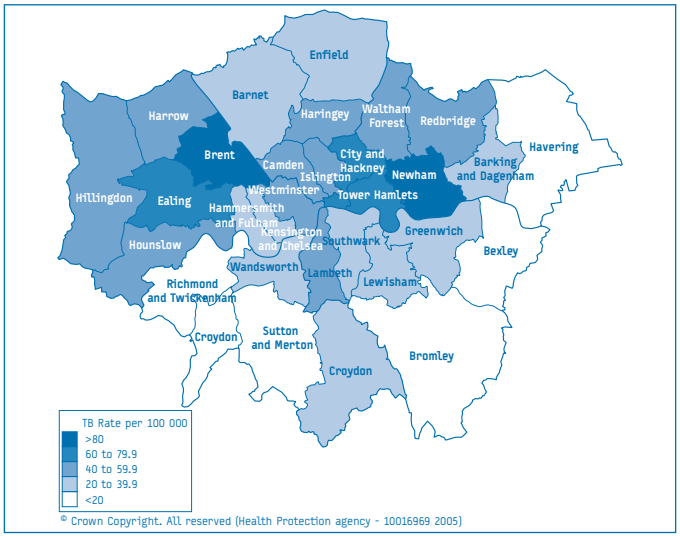
In addition to information on tuberculosis cases reported, in London a cross sectional survey was performed by the London tuberculosis nurses on tuberculosis cases who were or should have been taking tuberculosis treatment on 1 July 2003.

Tuberculosis epidemiological situation

6780 tuberculosis cases were reported in England and Wales in 2003, of which 3049 (45%) were in London. The tuberculosis incidence in London is almost five times higher than in the rest of England and Wales (respectively 41.3 and 8.2/100 000 in 2003). Local prevention and control of tuberculosis in England and Wales rests with the local Primary Care Trust (PCT), which is part of the National Health Service (NHS). London is composed of 31 Primary Care Trusts (PCTs. In 2003, in 16 PCTs the tuberculosis incidence was below 40 per 100 000 and reached 40 per 100 000 population or more in 15 PCTs [FIGURE 2].

FIGURE 2

Tuberculosis rate per 100 000 by Primary Care Trust, London, 2003



Note: Tuberculosis rate for England and Wales was 12.8 in 2003
From: Enhanced Tuberculosis Surveillance

In London incidence peaks in young adults for both sexes and rises again in old age in males. In 2003 tuberculosis rates were 71.3 per 100 000 population in men aged 20 to 39 years, 40/100 000 in men aged 40 to 59 years, and 44/100 000 in men aged 60 years and over.

In 2003, tuberculosis incidence in London was 11 times higher in people born abroad, who represented 83% of cases reported, than in those born in the United Kingdom (respectively 111 versus 10 per 100 000). The tuberculosis incidence between 1998 and 2003 has increased in young adults (20 to 39 years) both in persons born in the UK and in those born abroad [FIGURE 3].

In 2003, 59% of all cases reported in London were culture confirmed. The proportion of isoniazid resistant cases at start of treatment among all cases reported with drug susceptibility testing results was 9.7% (162/1671) in London and the MDR cases represented 1.8% (30/1671). The level of MDR at start of treatment has remained stable in London until 2002 but has increased in 2003. The proportion of isoniazid resistant cases has steadily increased between 1998 and 2003 (5.8% versus 9.7%). This increase is mainly linked to an outbreak of isoniazid resistant tuberculosis first recognised in 1999-2000. A unique genetic fingerprint on restriction fragment length polymorphism (RFLP) typing, has allowed tracking of the strain. As of January 2006 this strain has been recovered from 261 cases, of which 222 were diagnosed in London. Many of the cases are from groups at high risk of tuberculosis, including the homeless, users of heroin and crack cocaine and prisoners [2,3].

In London, the proportion of HIV infection among tuberculosis cases aged 15 to 64 years reported between 1998 and 2000 has been estimated to be 5.3% (307/5781) (D Antoine, personal communication, February 2006).

The proportion of tuberculosis cases reported in London in 2002, having treatment completed by 12 months after the start of treatment was 82% (78% in England and Wales). The proportion of patients who died was 6% of which 40% were cases in which tuberculosis caused or contributed to death. Patients who were lost to follow up represent 5.6% of cases and those still on treatment 2.8%. For 1% of the cases the treatment was stopped, for 2.2% patients were transferred out to other clinics in the country or abroad and for 0.4% outcome was not reported [4].

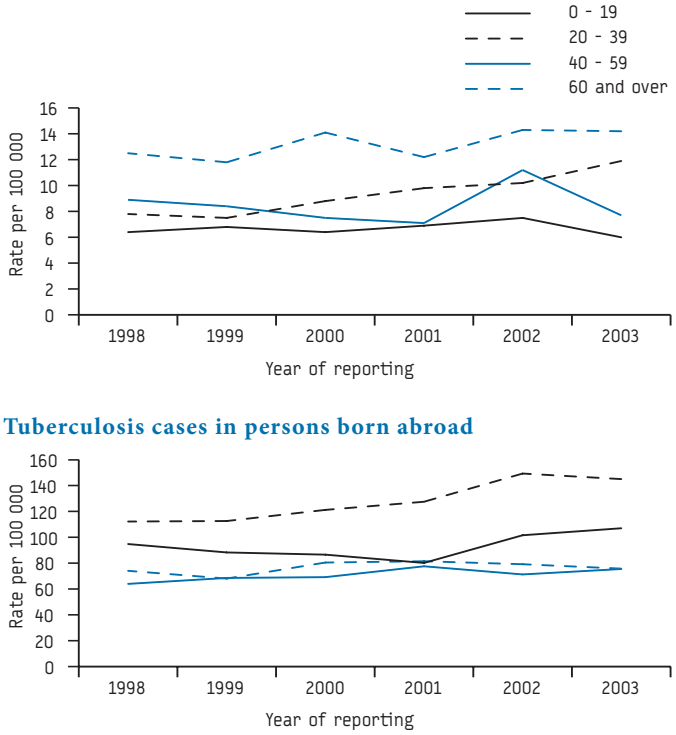
From the cross sectional prevalence survey performed in London, results were available for 2010 of 2080 patients with tuberculosis on 1 July 2003 (97%). The overall prevalence of disease in London was 27 per 100 000, but reached 788 in homeless people, 550 in prisoners, 354 in drug users and 878 in patients diagnosed HIV positive. This survey demonstrated a prevalence of disease in recent migrants of 149/100 000 and among refugees and asylum seekers of 92/100 000 [5].

Discussion

Tuberculosis incidence in London has continued to increase since 1987. Changes in the surveillance systems with the implementation of Enhanced Tuberculosis Surveillance in 1999 and the London TB register in 2002 may have contributed to improve case reporting. However a previous study has demonstrated that the increase observed in tuberculosis cases reported was corroborated by other sources [6]. Other indicators such as the consistent increase in incidence in young adults and of proportion of isoniazid resistant tuberculosis at start of treatment up to 2003 indicate a deterioration of the tuberculosis situation in the city. The proportion of HIV infection among tuberculosis cases of 5.3% in London between 1998 and 2000 represents a minimum estimate due to limitations in the linkage process and possible under reporting of tuberculosis cases among people with HIV infection. Two studies conducted in London during the same period have estimated a higher proportion of co-infection (11.4% and 13%) [7,8].

FIGURE 3

Tuberculosis rate by age group and by place of birth, London, 1998-2003



From: Enhanced Tuberculosis Surveillance

The proportion of cases with treatment completed was higher in London compared with the rest of the country. This is despite a higher incidence of tuberculosis and higher proportions of patients with complex needs that may complicate treatment, such as being homeless, being a recent immigrant, or having an HIV co-infection. Differences in the age structure and case characteristics of the tuberculosis cases as well as in methods used for data collection could explain this result, but from the information currently available it is not possible to give clear explanation for this difference [9].

The epidemiological situation observed in London in 2003 is similar to that in other large cities in western Europe. Results of a study performed on epidemiology and control of tuberculosis in western European countries showed that in 1999 the tuberculosis rates in Brussels (Belgium), Copenhagen (Denmark), Milan (Italy), Thessalonica (Greece), Amsterdam and The Hague (the Netherlands) were more than twice the national rates in those countries [1]. In most cities, isoniazid resistant cases represented less than 10% of cases and MDR less than 2%, but HIV co-infection was estimated to be over 10% in Rome (Italy), Amsterdam (the Netherlands), Lisbon (Portugal) and Milan (Italy). In London, tuberculosis incidence continues to increase while in most other western European cities it seems to have stabilised or declined in recent years. The increase in cases is likely to be multifactorial, with increased risk associated with HIV co-infection, changing patterns of immigration, increased opportunities for international travel, homelessness, and alcohol and other substance misuse.

Local prevention and control of tuberculosis in England and Wales rests with the local PCT, which is part of the National Health Service. The local Consultant in Communicable Disease Control (CCDC) employed by the Health Protection Agency (HPA) works with and supports the PCT in this role. All tuberculosis cases should be under

the care of physicians and specialist nurses with full training in the disease. Specialist tuberculosis nurses are recognised as key to the prevention and control of tuberculosis [10].

Treatment for tuberculosis in London is currently provided from more than thirty centres across the city mainly located in acute hospitals. These centres offer a diverse range of approaches to service delivery. Routes of access to treatment vary: a few centres offer walk in appointments, while the majority require a referral from either a general practitioner or consultant physician. Most centres are currently working towards providing a named case manager responsible for each patient's care. Efforts to implement this approach across the city have been limited by a shortage of qualified nursing and allied professional staff and problems in accessing local funding.

The European framework for tuberculosis control in low incidence countries recommends Directly Observed Therapy (DOT) to those groups known at increased risk of poor treatment adherence and for all patients during the intensive phase of treatment [11]. In the UK, DOT is recommended for patients 'who are unlikely to comply with treatment'. These include homeless people, alcohol and drug abusers and people with previous history of poor adherence to treatment [12].

Despite these recommendations, the use of DOT is not yet common or standardised in London as in other European cities [1]. The cross sectional survey performed in London in July 2003 has demonstrated high prevalence of tuberculosis in subgroups of the population who are underserved by health and social services. This survey has prompted recent calls for an increased emphasis on outreach, the use of DOT and active case finding to strengthen control among higher risk groups of tuberculosis. While DOT can improve medication adherence it is unlikely to lead to improved treatment outcomes unless initiated in conjunction with a package of supportive care tailored to patients' needs [13].

In October 2004 the Chief Medical Officer published the action plan Stopping Tuberculosis in England [14]. This plan has initiated the formation of a national tuberculosis programme and recognises that public health efforts need to be better organised and targeted where they are most needed and that the capability to detect tuberculosis at the earliest opportunity needs to be strengthened. A mobile screening project using targeted digital radiography is being piloted within London to evaluate how this approach could strengthen screening defined populations, including, for example, prisoners or hostel dwellers.

Tuberculosis in London is not at present under control and tuberculosis services in the city seem to have difficulties adapting to changing needs of those groups most affected by tuberculosis. Treatment and control services need to be tailored to the specific needs of the capital and its at risk groups in order to ensure control and improve the tuberculosis situation in London.

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Surveillance data are available on the web site of the Health Protection Agency: http://www.hpa.org.uk/infections/topics_az/tb/menu.htm for England and Wales and on http://www.hpa.org.uk/london/ for London.

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ORIGINAL ARTICLES

Surveillance report

TUBERCULOSIS CONTROL IN LATVIA: INTEGRATED DOTS AND DOTS-PLUS PROGRAMMES

V Leimane, J Leimans

From 1991 until the end of 1998, the number of patients with tuberculosis in Latvia increased 2.5 times with a simultaneous increase of drug resistant and multidrug resistant tuberculosis (MDR-TB).

Descriptive analysis of different TB programme services, activities and strategies including Directly Observed Therapy Short-course (DOTS) for tuberculosis and treatment of MDR-TB, were performed. Data from the state tuberculosis registry, drug resistance surveillance, and the national MDR-TB database were used. The state-funded national tuberculosis control programme (NTAP, Nacionala Tuberkulozes Apkarosanas Programma), based on WHO recommended DOTS strategy, was introduced in Latvia in 1996. The NTAP includes TB control in prisons. Treatment of MDR-TB using second line drugs was started in 1997. Cure rates for TB patients increased from 59.5% in 1996 to 77.5% in 2003. Between 1996 and 2003, more than 200 patients began MDR-TB treatment each year, and the cure rate was between 66% and 73%. Numbers of MDR-TB patients were reduced by more than half during this period. Treatment results including MDR-TB reached the WHO target, with cure rates 85% of newly diagnosed patients. These results demonstrate that MDR-TB treatment and management using the individualised treatment approach can be effectively provided within the overall TB programme on a national scale, to successfully treat a large number of MDR-TB patients.

Rapid diagnostic methods combined with early intensified case finding, isolation and infection control measures could decrease transmission of TB and MDR-TB in hospitals and in the community. Highly important that MDR-TB management follows WHO recommendations in order to stop creating drug resistance to first and to second line drugs.

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Key words: DOTS, Latvia, MDR-TB, tuberculosis

Introduction

Latvia has a population of 2.4 million people. Since independence from the former Soviet Union in 1991, Latvia has experienced an increase in tuberculosis (TB) morbidity and mortality together with the appearance of drug resistant and multidrug resistant tuberculosis (MDR-TB). Socioeconomic disruption, increasing poverty, unemployment, homelessness, substance abuse, increasing alcoholism and more recently, intravenous drug use have been the main factors.

In 1991, incidence of TB was 29 cases per 100 000 population [1], increasing to 74 cases per 100 000 in 1998 and then declining to reach 59 per 100 000 in 2004.

State Agency for Tuberculosis and Lung Diseases, Latvia

In 1998, the incidence of TB in prisons was alarmingly high, at 37 times higher than the national incidence, with outbreaks in several prisons leading to incidence 100 times higher than national incidence. Following the implementation of a strong TB control policy in the prison system, TB incidence declined rapidly.

Lack of first line antiTB drugs, and low quality and misuse of these drugs in the early 1990s are the most important factors for the development of TB drug resistance and MDR. Overcrowded hospitals, prisons and other mass gathering settings with bad environmental conditions, and lack of ventilation and other infection control measures have all contributed to the ongoing transmission of MDR Mycobacterium tuberculosis strains to healthcare workers, other patients and prisoners [2].

Health system reform including TB control services started in early nineties. Government support received for development and implementation of International standards in TB control.

The first global antiTB drug resistance survey performed by the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Diseases (IUATLD) from 1994 to 1996 [3] surveyed 35 countries, and found that Latvia had the highest level of MDR-TB, with 14.4% (1 in 7) newly diagnosed infectious TB cases without prior history of TB treatment being diagnosed as MDR-TB [4-6].

Technical and financial assistance were given by several organizations (WHO for development and implementation of new international standards; the Nordic countries within the project No-TB Baltic for development of Directly Observed Therapy (DOT) as a standard of ambulatory care integrated with general services; CDC (Centre for Disease Control and Prevention, Atlanta), / United States Agency of International Development (USAID) supported two fold projects: 1/ to develop a Centre of Excellence for MDR-TB treatment and management, 2/ to establish self-sustainable International Training Centre.

The aim of the study is to demonstrate the implementation and effectiveness of the National Tuberculosis Control Programme in Latvia.

Methods

Descriptive analysis of different TB programme services, activities and strategies including Directly Observed Therapy Short-course (DOTS) for TB and treatment of MDR-TB, were performed. Data from the state tuberculosis registry, drug resistance surveillance, and the MDR-TB database were used. MDR-TB is defined as in vitro resistance to at least isoniazid and rifampin- the two most potent antiTB drugs used for TB treatment.

TB control in Latvia

The National Tuberculosis Control Programme (NTAP) of Latvia is operated by the Ministry of Health. The State Agency for Tuberculosis and Lung Diseases (TPSVA, Tuberkulozes un Plausu slimibu Valsts Agentura) has primary responsibility for prevention and control

TB through development and implementation of the TB control programme core components activities throughout the country (http://www.tuberculosis.lv). The first NTAP was implemented in 1996. It was based on WHO guidelines for TB control of DOT short course and DOTS strategy - combining the five following elements: sustained political commitment; case detection through quality assured bacteriology laboratory; standardised short-course chemotherapy to all cases of TB under proper case-management conditions including DOT and patient support; uninterrupted supply of quality certified TB drugs; and a reporting and recording system allowing assessment of TB treatment and programme performance (http://www.who.int/gtb/dots/whatisdots.htm).

All five DOTS programme components were introduced and adopted nationwide to address the increasing TB epidemic. Penitentiary system TB control began in 1996 and was fully integrated into the NTAP in 1997. All TB control activities were applied simultaneously to the prison and civil sectors.

MDR TB was already a problem in Latvia and the number of diagnosed patients increased dramatically since 1994. Although DOT short course can cure almost 90% of new smear positive cases sensitive to antiTB drugs, the treatment success of MDR-TB cases is much lower. Untreated, these patients contribute to the spread of MDR-TB in hospitals, in the community and in prisons, to healthcare workers and to other patients.

NTAP initiated MDR-TB patients' treatment, based on individualised case management, in 1997 and implemented it in prisons a year later. MDR-TB management was built into the existing DOTS programme. Existing recourses for TB control were reallocated, facilities for MDR-TB treatment and management established, and staff trained.

In 1999 WHO and its partners launched a strategy for managing MDR-TB called DOTS-Plus, allowing access to second line drugs for countries with MDR-TB and well implemented DOTS strategy. Latvia was one of the pilot projects to evaluate a feasibility of using second line drugs in limited resource settings.

Results

Government commitment

The NTAP is state-funded. All patients diagnosed with TB or MDR-TB are treated free of charge.

Inpatient treatment is provided by nine TB hospitals in Latvia, including one TB ward within the penal system. The total number of beds was 2010 in 1991, 1380 in 1998 and 1150 in 2004. Specialised facilities are established to treat MDR-TB patients including facilities for prisoners and psychiatric patients.

Table 1

Social background of TB patients in 2002 (n=1540) and 2003 (n=1481), Latvia

	2002		2003	
	Number	%	Number	%
TB in prisons	162	10.52	95	6.41
Born in other country	98	6.36	75	5.06
Unemployed	742	48.18	693	46.79
Alcoholics	466	30.26	445	30.05
Contact with TB	321	20.84	350	23.63
Drug users	13	0.84	39	2.63
HIV infected	21	1.36	34	2.30
Ex-prisoners	111	7.21	117	7.90
Homeless	92	5.97	87	5.87

State health reform is continuing with a transition to more ambulatory-based health care, including for TB. In all 26 districts, TB control is under the general health services. On district level, TB specialists are responsible for TB control including MDR-TB and closely collaborate with the primary healthcare services, sharing responsibility for case finding and for providing treatment under direct observation during the ambulatory phase of treatment.

TB case detection

TB case detection is based on bacteriological examination of symptomatic patients who attend primary healthcare services. Active case finding is performed to detect secondary cases during contact investigation and active screening of high risk populations (such as prison inmates, homeless people, soup kitchen attendants, harm reduction programme participants) [TABLE 1].

In all patients, TB diagnosis is based on bacteriological examination. Three consecutive sputum smears, two cultures and one drug susceptibility test to first line drugs are performed before the initiation of TB treatment. For all mycobacterium strains confirmed as MDR-TB, a drug susceptibility testing for second-line antiTB drugs is performed.

Laboratory diagnostic services

Laboratory network with three levels provide diagnostic services for country (smears, cultures and DST). The central bacteriology laboratory (CBAK LAB, Centrala Bakteriologiska Laboratorija) is part of the TPSVA. It provides all diagnostic services and, serves as the national reference laboratory for TB and collaborates with the Swedish Institute for Infectious Disease Control (Smittskyddsinstitutet, SMI) on external quality control. The Central Bacteriological Laboratory is the only laboratory performing DST in Latvia.

Drug resistance surveillance was established in 1997 and reports are published yearly. The laboratory reports all DST results weekly to the TB registry. The third WHO/IUTLD drug resistance surveillance data shows improvement in drug resistance trends in Latvia [7].

The rapid diagnostic method BACTEC-MGIT is used for patients suspected to have MDR-TB. Early diagnosis and treatment initiation with proper isolation of MDR-TB patients facilitates infection control within healthcare facilities and decreases transmission. New rapid diagnostic methods are studied in Latvia for implementation in the future for routine use [8].

Treatment

The treatment of TB was changed to short course chemotherapy according to the WHO guidelines in 1995. Patients routinely receive treatment in hospitals, for a minimum of two weeks, until smear conversion to negative. After smear conversion, patients are discharged for ambulatory treatment using daily DOT. To help patients complete treatment and to improve treatment adherence, patients receive social aid provided by districts social departments of Ministry of Welfare during the ambulatory phase. Treatment outcomes have improved from a 59.6% treatment success rate in 1996 to 77.5% in 2003. MDR-TB treatment is centralised. As soon as MDR-TB is confirmed, the patient is directed to the expert group of physicians to confirm diagnosis and to design treatment regimen with second line drugs and follow-up treatment effectiveness. Individually tailored treatment regimens are used based on the results of in vitro susceptibility tests of M. tuberculosis obtained from patients before the initiation of treatment. Treatment of MDR-TB usually starts with an empiric regimen of 5 to 7 drugs. It takes approximately 3 - 8 weeks to adjust the treatment regimen according to DST results. Injectable drugs are used daily until culture conversion, and then continued 5 times per week for an additional 2 to 3 months, and 3 times per week depending on the clinical status of the each patient.

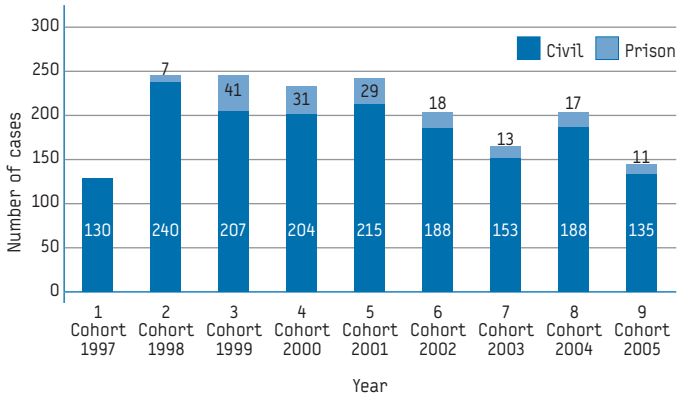
MDR-TB patients receive treatment at four specialised treatment centres that rely on inpatient care, followed by outpatient DOT when possible. Duration of hospital admission depends on sputum culture conversion to negative. During ambulatory phase treatment for all TB patients is provided in one case management system.

Every year from year 1998 to 2004 n addition to newly detected cases of TB and re-treatment cases, more than 200 patients from both civilian and penal sectors have begun treatment under the DOTS-plus programme in Latvia, decreasing to 146 in 2005 reflecting the trend of newly diagnosed MDR-TB patients [FIGURE 1].

Latvia applied to the WHO Green Light Committee (GLC) and got approval to treat 350 MDR-TB patients with inexpensive second-line antiTB drugs which ensured treatment for all diagnosed MDR-TB patients.

FIGURE 1

Annual number of MDR-TB patients, Latvia, 1997 to 2005



All registered MDR-TB patients who start treatment during the year are included in cohort analysis. For patients who began MDR-TB treatment in the years 2000 and 2002, treatment outcomes show treatment success from 66% to 73%.

Under DOTS plus conditions, treatment efficacy (treatment outcome excluding default) has improved over time. Positive outcome (treatment completed and patient cured) increased from 70% in 2000 to 83% in 2002, and negative outcome (treatment failure and patient death) decreased from 30% to 17% [9]. For treatment outcome analysis, internationally accepted outcome definitions are used [10].

The WHO goal to cure 85% of patients under DOTS programme conditions in settings with high levels of MDR-TB is difficult to achieve without treatment for MDR-TB. To estimate the impact of MDR-TB on treatment outcome we use the additional outcome: MDR-TB patients who continued treatment. Cohort analysis of the DOTS programme in Latvia shows that the cure rate for new bacteriological confirmed patients during the 1998 -2002 period increased from 74% (747/1010) in 1998 to 78% in 2002 (729/934). In addition, between 8% MDR-TB cases were counted as still under treatment in the treatment outcome in 2002. After completing MDR-TB treatment for these patients the overall cure rate increased from 76% to 82% in 2002 [11] [TABLE 2].

Surveillance of TB in Latvia

The national tuberculosis registry was established in 1996 when the old registration system was replaced by new international standards. Standardised forms and registries recommended for effective TB control are used at district and national level. TB notification is mandatory for both physicians and laboratory on district and national levels.

TABLE 2

Treatment outcomes of TB new cases in 2002 (n=934), Latvia

Treatment outcomes	After 12 months	After 24 months	After 24 months
	All cases	MDR-TB cases	All cases
Cured	709 (75.9%)	53 (70.7%)	762 (81.6%)
Completed	20 (2.1%)	2 (2.7%)	22 (2.4%)
Failure	10 (1.1%)	1 (1.3%)	11 (1.2%)
Default	51 (5.5%)	12 (16%)	63 (6.7%)
Transferred out	3 (0.3%)	-	3 (0.3%)
Died*	66 (7.1%)	4 (5.3%)	70 (7.5%)
Still on treatment (DOTS-Plus)	75 (8%)	3 (4%)	3 (0.3%)

*Includes 11 MDR-TB patients: 5 died before MDR-TB diagnosis, 4 died under DOTS-Plus treatment, 2 were not enrolled in DOTS-Plus treatment

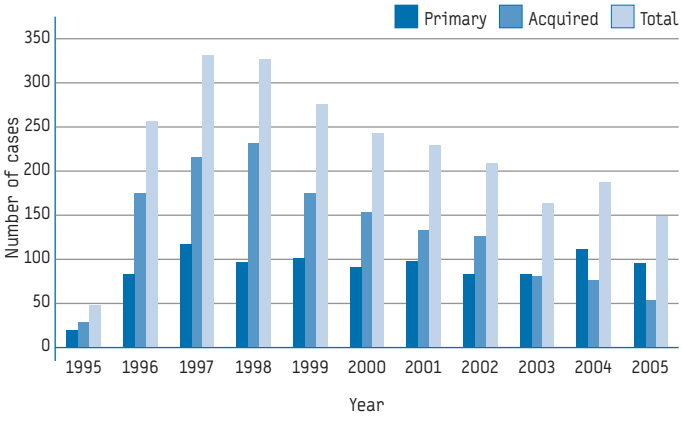
Cohort analysis of treatment outcomes was introduced in 1996, using international definitions. Database for MDR-TB registration and outcome analysis were developed in 1999 and implemented in 2002. Data of cohort 2000 have been entered and analysed [12].

All MDR-TB cases detected in laboratory are registered in the national tuberculosis registry. In 1997, 332 new MDR-TB cases were registered; data from previous years are incomplete and not comparable. After the peak of diagnosed MDR-TB cases in 1997, the number began to decline, with to 163 cases diagnosed in 2003, followed by a slight increase in 2004 to 187 cases, and a decline thereafter to 148 diagnosed cases in 2005 [FIGURE 2].

The total number of annually registered MDR-TB cases has decreased by 51% since 1997.

FIGURE 2

Number of patients with primary and acquired MDR-TB in Latvia, 1994-2005



The annual report on TB and MDR-TB surveillance is prepared by TB registry staff. The report is presented at the meeting of the society of tuberculosis and lung physicians, and submitted to the responsible department at the Ministry of Health. NTAP TB registry participates in voluntary reporting of individual data to the EuroTB network [13].

The problem of TB/HIV coinfection

Since the first patient was registered with TB/HIV co-infection in 1994, the number of patients diagnosed with both infections continues to increase each year [TABLE 3].

Screening for HIV-1 was introduced in Latvia in 1989, and is volunatary in the general population, except for blood donors. TB infection is a one of the risk groups for HIV-1 screening. All TB

patients are counselled and offered tested for HIV; the coverage is about 90% of all TB patients. Data from testing is collected nationally by the National AIDS Prevention Programme. Information exchange is established between the TB and HIV programmes.

The NTAP of Latvia and HIV/AIDS Centres of Latvia have, under the umbrella of the Ministry of Health, established a coordination board to address emerging issues in TB/HIV since 2005. Links between the TB and HIV registries have been established, and intensified case finding in high risk groups of HIV, and consultation and screening on TB in harm reduction programmes have been implemented. The initial results of the intensified case finding are encouraging, with 5% TB case detection among those tested.

Table 3

HIV prevalence among TB patients, Latvia, 1998-2003

Year	Among TB patients		Among MDR-TB patients	
	Number tested TB	Number HIV positive (%)	Number tested MDR-TB	Number HIV positive (%)
1998	1945	1 (0.1)	327	0 (0)
1999	1758	9 (0.5)	276	1 (0.4)
2000	1893	14 (0.7)	243	2 (0.8)
2001	1882	27 (1.4)	234	13 (5.6)
2002	1840	25 (1.6)	209	3 (1.4)
2003	1755	40 (2.3)	163	7 (4.2)
Total	11 073	116	1452	22

Between 1994 and 2004, 158 cases of TB/HIV coinfection were notified. HIV seroprevalence increased from 0.1% of TB patients tested [14] in 1998 to 2.3% in 2003 [15]. Similar trends have been observed for MDR-TB patients. HIV seroprevalence in MDR-TB patients increased from 0.4% in 1999 to 5.6% in 2001. In 2001, an outbreak, 13 primary MDR-TB cases with HIV co-infection was registered. Only three cases were registered in 2002, and seven cases in 2003. The average number of cases registered since 2002 is seven, and 4% of our newly diagnosed MDR-TB cases are co-infected.

Discussion

The DOTS strategy, endorsed by WHO, is the world's most effective tool to combat TB. The DOTS-Plus programme is developed by WHO and partners to manage MDR-TB using second-line antiTB drugs.

MDR-TB requires longer duration of treatment (up to 2 years) to achieve cure, in comparison with 6 months treatment for drug susceptible TB. MDR-TB has much higher level of mortality than drug susceptible TB, lower cure rates and even higher default rates. Infection control of MDR-TB are more difficult to implement in hospitals due long time until DST results available,and start adequate treatment as well worse response to treatment with second line antiTB drugs. The cost of drugs to treat a MDR-TB case can be up to 100 times more than the cost of treating a drug susceptible TB case.

If drug sensitive TB is not treated properly develops drug resistance to I line antiTB drugs and I line drugs will no longer be effective. The first measure of TB program is to stop create new MDR-TB cases.

The establishment of sound TB control strategies in Latvia has led to a 65% reduction in acquired MDR-TB cases over 10 years. However, primary MDR-TB rates remained stable during this period. Unless it was possible to reduce MDR-TB with good DOTS programme only, our data demonstrates that reduction of MDR-TB was not achieved in settings with high levels of drug resistance. If MDR-TB patients are untreated, or treated with first line drugs, they continue to spread deadly disease, and become increasingly resistant to drugs. Therefore, the DOTS-Plus programme to treat and cure the existing reservoir of MDR-TB should be built on a well functioning DOTS programme to stop the development of drug resistance and interrupt the chain of transmission.

DOTS and MDR-TB treatment and case management in Latvia have been implemented as integral parts of NTAP. All five components with MDR-TB related elements were included: MDR-TB case detection strategy; individualised treatment regimens using second line drugs; individualised approach to case management; recording and reporting and treatment outcome analysis; drug supply and distribution without interruptions in treatment for patients.

By addressing drug sensitive and drug resistant TB, the Latvian National TB programme achieved a decrease of TB incidence by 21%, an improvement of cure rates for all bacteriologically confirmed TB cases, reaching the WHO target for 85% cure. Most important is that development of drug resistance was prevented through proper treatment and management of newly diagnosed TB cases (improving cure rates, decreasing number of re-treatment cases, decreasing default rate). As a result, the number of patients with acquired MDR-TB decreased by 65%. Every year, two thirds of patients who began treatment for MDR-TB were cured.

In cooperation with CDC, the Nordic countries within the No-TB Baltic project, and University of Arkansas of Medical Sciences (UAMS), the Centre of Excellence for MDR-TB treatment and management and self sustained International Training Centre in Latvia (TPSVA/SIZN) were established. They use state-of-the-art equipment, world-class diagnostic and treatment methods, and operational research. In 2004, ITC has been recognised as a WHO Collaborating Centre for Research and Training in Management of MDR-TB. ITC and National TB programme receives full government support. Over the past five years, the demand for training has increased dramatically. Training programmes are based on evidence gained through scientific and operational research, as well as field experience in DOTS and DOTS-Plus implementation, and aim to develop the competences and skills of trainees.

Prioritising TB control activities, coordinating at local, national and international level, following international recommendations for TB and MDR-TB treatment and management have all improved TB programme effectiveness in controlling the TB and MDR-TB epidemic.

Some remaining areas of concern for MDR-TB management in Latvia include treatment interruptions and the country's growing HIV epidemic.

Treatment interruptions and default are closely linked with the development of extensive drug resistance (resistance to 8 or more antiTB drugs) which in most cases becomes incurable. Although patients receive therapy under direct observation, on average 5% of new patients and 13% of MDR-TB patients have defaulted each year. Individual case management approach and patient trace back are used to promote patients' adherence. To improve patients' adherence to the regimen during ambulatory treatment, the NTAP, with the support of district social service departments and the Ministry of Welfare, provides daily food coupons and transport reimbursement for people who attend medical facilities for directly observed treatment. Improving treatment adherence, especially among those previously treated, should improve overall treatment success.

Strengthening case management of new case, rapid MDR-TB diagnosis, contact investigation and genotyping to detect chain of transmission are the next steps to improve MDR-TB control in Latvia.

An emerging HIV epidemic also threatens recent progress in TB control. Although the number of cases with TB/HIV or MDR-TB/HIV coinfections is low, they require prompt interventions to reduce HIV-related TB morbidity and mortality.

Conclusion

These results demonstrate that a MDR-TB treatment and management using the individualised treatment approach can be effectively provided within the overall TB programme on a national scale, and can successfully treat a large number of MDR-TB patients.

Rapid diagnostic methods combined with early intensified case finding, isolation and infection control measures could decrease transmission of TB and MDR-TB in hospitals and in the community.

It is highly important that MDR-TB management follows WHO recommendations in order to stop creating drug resistance to first and to second line drugs.

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TATTOOING, PERMANENT MAKEUP AND PIERCING IN AMSTERDAM; GUIDELINES, LEGISLATION AND MONITORING

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Tattooing, body piercing and permanent makeup are increasing in popularity. Here, we describe the procedures involved in these practices, their risks, the content of guidelines developed by the Municipal Health Service in Amsterdam (the Netherlands) to reduce infection risks, the legislation in the city of Amsterdam, and results of monitoring in tattoo and piercing studios.

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Key words: infection prevention, piercing, tattooing

Introduction

In 1982, an American physician notified the Municipal Health Service (MHS) in Amsterdam that eight American soldiers had contracted hepatitis B during their stay in Amsterdam. All these soldiers had visited the same tattoo studio. A public health nurse from the MHS department of infectious diseases made a site visit, where he noticed that the tattooist used extremely unhygienic procedures. He had a bucket filled with bloody water and a sponge, which were used to 'clean' the skin where the tattoo was to be applied. He used the same needles for all clients, without any cleaning in between. To test whether the needles were still sharp, he touched them on the back of his hand before he started tattooing clients [1].

In the same year, a survey carried out among all tattoo studios in Amsterdam indicated that hygienic conditions were universally bad. This finding, together with the hepatitis B outbreak , supplied the impetus to urgently set up local regulations for the tattoo studios, working with one of the tattooists. This gave us the possibility of enforcement. The first guidelines consisted of ten 'golden rules' for infection prevention in tattoo studios, but more elaborate guidelines were established in 1987. In 1990 the guidelines were expanded to include piercing and permanent makeup studios [2,3]. Based on these regulations a nationwide law is now being prepared for skin procedures performed by non-medical persons (expected in January 2006). Here, we describe the procedures involved in tattooing and piercing, their risks, the content of our guidelines, the developed legislation and the results of monitoring in tattoo and piercing studios. We realise that other cities and countries have set up regulations - for example, after a large outbreak of hepatitis B, United Kingdom brought in legislation for tattoo studios (and other piercing establishments) as early as 1982 [4,5] - but by publishing ours in this journal we hope to promote discussion and further implementation.

Tattooing and Piercing

The English word 'tattoo' originates from the Tahitian word 'tatu', which means 'to mark'. In tattooing, ink is applied below the surface of the skin with a needle (often electrically driven). Traditional tattoos, which are purely decorative, may be applied to all parts of the body, but a tattoo is usually not applied to parts of the body that are not usually covered by clothing, such as the face or hands. Tattooists generally work without medical supervision, and techniques are often passed from one tattooist to another.

Tattoos for cosmetic, rather than decorative purposes, were first reported in 1984 [6]. Categorised as 'permanent makeup' they include lip outlines, eyeliner and eyebrows, and camouflage for scars and other skin imperfections. Although cosmetic tattoos have different purpose and are applied in different settings from traditional tattoos, the techniques used are the same.

Piercing involves making holes in the body with a needle so that rings or bars can be inserted. Piercing can be applied to many parts of the body, including ears, nose, lips, nipples and genitals. Piercing is not limited to the skin, and many include cartilage.

Infection risks and other complications

The use of unsterilised needles, needle bars and tubes, forceps, jewellery and contaminated pigments can result in bloodborne infections, such as hepatitis B , hepatitis C and HIV infection [7-11]. These infections may be asymptomatic in the early phases and are therefore rarely noted.

As healing time may vary from one week (tattoo) to 9 months (navel piercing), there is a risk for infection after the initial application of a tattoo or piercing. The most common causal agents of these later infections are Staphylococcus aureus, group A streptococcus and Pseudomonas spp [9,11]. Typical symptoms of a local bacterial infection are redness, swelling, warmth and pain. Such infections may cause chronic infections.

Other complications include the formation of cysts and keloid scars. Local infection or bleeding of piercing cases is reported in 10%-30% [12]. Allergic reaction to nickel is another common complication [13]. Sometimes piercing may result in irreversible tissue damage. Piercing of the tongue may result in extreme swelling and/or bleeding. It may also cause dental problems, including chipping, cracking and breaking of teeth, as well as abrasion of teeth. Navel piercing is often complicated by bacterial infections [14], and urinary tract infections have been reported after genital piercings [15]. Other problems with genital piercing, in both men and women, are ruptures of the skin and bleeding during or after sexual intercourse.

Less common complications are allergic reactions to inks, pigments, or to the gloves used by the tattooist or piercer [16]. A study conducted by the MHS department of infectious diseases, in collaboration with the Inspectorate for Health Protection has shown that inks and pigments are often not sterile. Also, these substances often contain heavy metals such as lead, cadmium, cobalt, nickel and zinc. One in five inks contained azopigment, from which carcinogenic aromatic amines can be formed [6].

Our experience is that knowledge about complications is insufficient among both tattooists and piercers and their clients. The industry is largely unregulated and serves uninformed clients who have difficulty knowing whether the tattooists or piercer is using proper procedures and equipment. However, most professional tattooists and piercers wish to promote good practice (the cleaner their work, the better their results and reputation) and look forward to the development of guidelines and legislation.

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General rules for a well-equipped studio and preparation

The studio must have a treatment room, where one can concentrate and work hygienically, and a separate waiting room. Walls and floors of the treatment room must be of a smooth and easily cleanable material. The chair or table for treating clients must be upholstered with a non-absorbent fabric that can be thoroughly cleaned. The room must be equipped with a basin with a no-touch hot and cold water tap, a disposable paper towel holder, and a soap dispenser. A waste bin with a pedal operated lid must be present.

Information leaflets for studio clients must be available, with information concerning age restrictions for these procedures, possible complications, and instructions for aftercare. In the Netherlands, the age at which persons may decide for themselves to have a tattoo and piercing is 16 years. This age limit is suspended for earlobe piercing but pertains to all other areas, because children younger than 16 are still growing and thus at risk for displacements of tattoos and piercing.

Informed consent forms, with information concerning health (including allergies) must be available and must be signed by the client. In the case of children under 16 years, a parent or guardian must sign. If they have signed but are not present with the client, the tattooist or piercer must verify their consent by telephone. Signed consent forms must be kept by the studio in a locked file for ten years.

Personal hygiene among studio staff is very important, including clean hands and proper clothes. Single use gloves should be used during tattooing or piercing. These gloves do not have to be sterile, and must be disposed of after use. Before starting with tattooing or with piercing, all pertinent materials should be within easy reach. When the skin to be tattooed or pierced is covered with hair, it should be shaved and disinfected.

The use of injectable anaesthetics by the tattooist or the piercer is under no circumstance permitted. The use of analgesic creams is allowed, but only if the client's physician has prescribed the cream. The name of the client must be present on the tube or pot of cream, which can be used only for the client in question. The cream must be allowed 20 minutes to take effect. The skin, after removal of the cream, must be disinfected with alcohol 70%-80% (ethyl alcohol, ethanol, isopropyl alcohol or isopropanol). Ethyl chloride spray may be used, but has superficial and negligible effect and its use is discouraged.

The use of the right equipment and materials and procedures

Only disposable sterile single-use needles are permitted for tattooing and piercing. These needles must always be disposed of after one use. They must not be thrown into a waste bin but collected in a puncture-resistant container (sharps container) for proper disposal.

Tattooing

Complete sets of disposable needles, needle bars and tubes for tattooing, all sterile wrapped, are currently available on the market. If using such sets, an autoclave is not necessary (see end of this section). Ink must be sterile and must not endanger a person's health or safety (ie, not engender the formation of aromatic amines, nor contain any prohibited dyes or preservatives). Only single-use ink cups should be used and they must not be refilled, except for same customer at the same attendance.

Piercing

Piercing requires the use of a sterile disposable infusion needle covered with a plastic canule. Push-through instruments for ears and nostrils are permitted. They must be hygienic, and fitted with entirely disposable, sterile cartridges. Skin may be marked with a toothpick dipped in a gentian violet 70% alcohol solution or in Betadine®. A marker pen, if used, should be used once only.

Jewellery, forceps, scissors and other equipment used in piercing must be sterilised before application.

An ultrasonic cleaner is needed to remove ink and coagulated blood from instruments. Special ultrasonic disinfectants are needed, and after use the instruments must be rinsed with demineralised water. Sterilisation must be performed using an autoclave with preliminary air elimination and drying programme, in order to sterilise the inside of instruments when all air has been evacuated.

Aftercare

After a tattoo is performed, gloves should be removed and discarded.

Disinfectants must not be used routinely after piercing or tattooing. The tattooist should inform the client that some tenderness, swelling, and pain are normal after these procedures and that, if infection does occur, only 70% alcohol should be used and early medical advice should be sought.

The materials used to make a piercing or a tattoo must be immediately and properly discarded (needles in a sharps container, other disposable materials in the waste bin, and re-usable instruments in special cleaning fluid).

Clients must be given verbal and standardised written instructions regarding aftercare of the tattooed area or piercing. These must include the instruction to contact their general practitioner if any complications arise such as redness, swelling, pus or other fluid secretions, jewellery migration or rejection.

Needlestick accident protocol

Vaccination of tattooist and piercers against hepatitis B is recommended. The MHS protocol for response to needle-stick accidents or other 'blood-blood' contacts must be present in the studio. According to this protocol, in case of such an accident, the MHS department of infectious diseases must be contacted immediately, where there is a physician on call 24 hours a day. The protocol emphasises that although one may be protected against HBV by vaccination, the risk of infection with HCV and HIV and other (unknown) bloodborne infections remains.

Monitoring and law enforcement

The City of Amsterdam Health Regulations define the Municipal Health Services' duty to monitor compliance with its hygiene guidelines [17]. These regulations have been in effect since November 1987. The authorised health official must at all times be allowed access to any tattoo and piercing studios for inspection of the premises, instruments and materials or for observation of a tattoo or piercing to gain insight into the method of operation. The tattoo and/or piercing studios are visited without any prior notification.

According to the City of Amsterdam Health Regulations [17], the following sanctions may be applied if a tattoo or piercing studio does not meet the hygiene guidelines:

- A verbal warning will be issued after observing a condition qualified as unacceptable.
- In case of a condition that constitutes a serious threat to the health of the clients visiting the tattoo studio, a follow-up check will be carried out after the verbal warning.
- If the situation has not been rectified, the studio will be closed for the period of time necessary to implement hygienically acceptable operations.
- The closure will be rescinded once the business operator has provided sufficient guarantees (as judged by the Amsterdam Municipal Health Service executive) that the business will comply. The term of closure depends in principle on the time taken to implement the necessary improvements and will thus vary from case to case.
- A second closure will be cause for permanent closure.

In September 2003 the Dutch government legislated against the use of harmful tattoo inks. Strict regulations compel manufacturers to comply with quality requirements. The Inspectorate for Health Protection and Veterinary Public Health will therefore collect ink samples at both the factories and the studios for tattoo and permanent make up.

Results of monitoring tatoo- and piercing studios

In Amsterdam, inspection of the studios has taken place since the regulations were set up, but these were unfortunately not standardised until 2002. For each item included in the checklist the studio could score between zero (to be changed immediately) and three points (good). The maximum score is the number of items times 3 and this total number is equivalent to 100%.

In 2002, there were 15 studios in Amsterdam, all of which were inspected: 9 tattoo and piercing studios and 6 tattoo studios. The mean score was 89.5% (range 63.9% - 97.4%). Seven studios scored less than 90%. In 2004 Amsterdam had 22 tattoo and piercing studios, all of which were inspected: 10 tattoo- and piercing studios, 8 tattoo studios and 4 piercing studios. The mean score was 96.6% (range 88% - 100%). Six studios scored less than 90% and 6 scored 100%.

The main finding of the inspections over the years [18] is that written guidelines alone are not sufficient to improve safety. Regular inspection visits, with verbal instruction, are needed. It appears to be difficult for non-medical persons to understand what it means to 'work aseptic'. For example they open drawers with disinfected gloves, put sterile jewellery on an unsterile table or smoke while tattooing. Also, they tend to mix up detergents and disinfectants: a disinfectant for the skin was used for cleaning the floor. In aftercare instructions composed by the tattooist or piercer, we found the instruction to take 5 showers a day during the healing period of a nipple piercing. On the other hand, true risks were not always mentioned to the potential client, for example, that healing for a nipple piercing may take 6-9 months. In general, there were problems with the opening and dating of sterilisation bags. And last but not least: the informed consent form is sometimes used as a safeguard more for the tattooist/piercer than for the client.

Discussion

In 1987 the MHS published the first version of its guidelines for tattooing, followed in 1990 by guidelines for piercing. Since the relevant techniques and materials change very fast, these guidelines are updated very regularly. The number of studios in Amsterdam has increased over the years. As of 2004, there were 39 studios in Amsterdam, including 17 permanent makeup salons.

According to Dutch infectious disease control law, a patient with acute or chronic hepatitis B must be reported to the MHS department of infectious diseases, so that source and contact tracing can be carried out. This department has not received any notifications of hepatitis B infections due to tattooing or piercing during the past 10 years. We realise, however, that hepatitis B virus infections may be asymptomatic and therefore not diagnosed, or not always reported when diagnosed.

Recently, two cases of acute hepatitis B were reported to the MHS. In both the most probable source was the same nail studio in Amsterdam. A site visit to this studio showed clear risks for infections, and we advocate that nail studios must also be informed about hygiene and the prevention of infections.

So far, enforcement for tattoo, permanent makeup and piercing studios affects only Amsterdam. However, a nationwide law, based on the MHS guidelines [2,3], is now being prepared for skin procedures performed by non-medical persons (expected in June 2006). Curricula have been developed for hygienists working at Municipal Health Services who will do the inspections and training has started in October 2005

Recently, discussions also have started within the EU for a pan-European legislation, which will be modelled on existing (national) guidelines, including ours [19]. We look forward to the standardisation of guidelines throughout the EU, including guidelines for age, use of anaesthetic, record keeping, ethical standards (eg, not tattooing or body piercing anyone who is intoxicated or under influence of drugs), and licensing after approved training. The exchange between the member states of the name of tattoo and piercing studios that may be possible sources for bloodborne infections should also be encouraged.

In conclusion, public health professionals have to stay alert for new fashions that may include infection risks. In order to detect new sources of infections, a close collaboration is needed between departments of infectious diseases and departments of hygiene and prevention. Standardising guidelines throughout the EU and cross-border notification are recommended.

Addendum: In the national regulations, on which the nation wide law (expected in June 2006) is based, it is advised not to set a tattoo in a person less than 16 years old and not to pierce somebody less than 12 years old. Each person younger than 18 years old has to be accompanied by a parent or guardian who has to give written consent.

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HEPATITIS A VACCINATION POLICY FOR TRAVELLERS TO EGYPT IN EIGHT EUROPEAN COUNTRIES, 2004

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In 2004, an outbreak of hepatitis A occurred in European tourists returning from Egypt. The reported hepatitis A attack rates varied considerably between tourists from different European countries. To determine the reason for this divergence in attack rates, a survey was undertaken with the following objectives: (a) documentation of national hepatitis A prevention policies for people travelling to Egypt and (b) documentation of hepatitis A reporting practices in these countries. A questionnaire was compiled and distributed to 13 European countries. All eight of the countries that responded had produced guidelines for the prevention of travel-associated hepatitis A. Between 2001-2003, 40% (range 4-51) of hepatitis A cases reported annually were associated with travel abroad. This occurred despite the fact that all countries recommended active vaccination with hepatitis A vaccine for people travelling to Egypt for holidays. There was no standard case definition for reporting confirmed cases in the countries that reported hepatitis A cases. As it is likely that travel-associated infections will increase as more people take overseas holidays, innovative ways to increase the number of travellers who seek and adhere to appropriate medical advice prior to travel must be explored. In addition, we recommend the use of the European Commission case definition for notification of confirmed cases of hepatitis A.

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Introduction

Hepatitis A virus (HAV) has worldwide distribution and causes a systemic infection that attacks the liver. In children under 6 years most infections are asymptomatic but in older children and adults, infection is usually symptomatic and jaundice occurs in up to 70% of cases [1,2]. In older and vulnerable people (including people with pre-existing liver disease, the immunocompromised and injecting drug users) hepatitis A can cause serious morbidity and mortality [3]. In Europe, there are three main patterns of infection with HAV: sporadic infection in travellers to countries of high endemicity, common source outbreaks, and large community outbreaks associated with faecal-oral transmission [4].

Travel-associated hepatitis A is the most frequent vaccine preventable infection in non-immune travellers to countries of high endemicity [5]. Passive immunisation with immunoglobulins can be used, close to departure date, to protect travellers during their period of stay in an endemic area. However, this option has a number of shortcomings: the antibody titre that must be achieved for one to be protected is undetermined, the protection is of limited duration, and there is also concern about the safety of blood products [6]. Consequently, this option has been superseded by active vaccination with hepatitis A vaccine since it became available in 1992.

In August 2004, an outbreak of hepatitis A occurred in tourists from Germany and eight other European countries who had stayed in a hotel in the Red Sea area of Egypt. A total of 351 cases including 271 primary and 7 secondary infections were reported in Germany, and 73 cases (60 primary and 13 secondary infections) were reported from other European countries. The subsequent case-control investigation implicated fruit juice as the likely vehicle of infection in the outbreak [7].

The attack rate, based on the proportion of HAV infected hotel guests notified nationally from the total number of guests per country as recorded by the hotel staff, during June and July, varied between countries from 4.6% in Germany to 10.5% and 14.6% in the Netherlands and Austria, respectively. Among the hypotheses for this divergence in attack rate were differences in risk behaviour, variations in national vaccination policy and practice, and variations in the sensitivity of hepatitis A reporting in the various countries. In order to explore these hypotheses further, a survey was undertaken with the following objectives: (a) assessment of the policies for hepatitis A prevention for people travelling to Egypt in a selection of European countries and (b) documentation of hepatitis A reporting practices in these countries in order to identify reasons for divergence in attack rates.

Methods

This survey targeted countries with hepatitis A cases staying in the hotel linked to the hepatitis A outbreak during June and July 2004. A questionnaire was developed in collaboration with epidemiologists from Sweden, Denmark, the Netherlands and Germany. The questionnaire covered the following areas:

1. Current vaccination recommendations for travel to Egypt, agencies producing and implementing the recommendations, cost of vaccine, health insurance cover for vaccination and the role of travel agents in hepatitis A prevention.
2. Description of hepatitis A reporting within the countries, reporting category of hepatitis A (ie, whether mandatory or not), case definition used, reporting personnel, burden of travel-associated hepatitis A with particular reference to travel-associated with Egypt between 2001-2003, and sensitivity of reporting system.

The questionnaire was sent by email in September 2004 to lead epidemiologists in the targeted countries. Two follow-up reminders were sent to improve the response rate. Results were returned to all participants for validation and feedback.

Results

Eight of the13 targeted countries responded to the questionnaire [TABLE 1]. All eight countries had guidelines for prevention of travel-associated HAV. These guidelines were produced by various institutes working either alone or in collaboration: national institutes for infectious disease surveillance (N=4), Ministry of Health (N=3), institutes of tropical medicine (N=1) national vaccination committees (N=2) Federal Office of Public Health (N=1) and travel clinics/ networks (N=3).

Municipal Public Health Department, specialised travel clinics, occupational health services and general practitioners were involved in the implementation of these guidelines [TABLE 2].

1. National Institute for Public Health and the Environment, Bilthoven, the Netherlands
2. Statens Serum Institut, Copenhagen, Denmark
3. Robert Koch-Institut, Berlin, Germany
4. European Programme for Intervention Epidemiology Training (EPIET)

All eight countries recommended active vaccination against HAV for travel to regions where HAV was endemic, including Egypt. In addition, some countries recommended immunoglobulin in specific circumstances (children < two years, immunocompromised persons and pregnant women). Only in the Netherlands were travel company representatives obligated to inform travellers of risk of hepatitis A associated with travel to Egypt. The median estimated lowest cost for one adult HAV vaccine administration was €37 per dose (range €18-55) [TABLE 2]. In none of the eight countries was the cost of travel-associated HAV vaccination reimbursable by the medical insurance, used by the majority of residents. However, in England & Wales administration of vaccine was free of charge in the National Health Service.

There was no information available on the percentage of travellers to Egypt vaccinated against hepatitis A. In all responding countries except France, hepatitis A was a statutorily notifiable disease. Six countries reported confirmed cases of hepatitis A on the basis of clinical symptoms and laboratory confirmation of infection [TABLE 3]. Between 2001-2003, the average proportion of HAV infection that were travel-associated varied considerably between the five countries that provided information, England & Wales (4%), Germany (32%), Switzerland (40%), the Netherlands (45%) and Denmark (51%). In the latter four countries 2% of travel-associated HAV infection was reported as being related with travel specific to Egypt. No country had undertaken a national assessment of completeness of hepatitis A reporting.

Discussion

These results highlight many similarities in policy for travel-associated hepatitis A infection in Denmark, England & Wales, France, Germany, Ireland, the Netherlands, Spain and Switzerland. Hepatitis A vaccine is incorporated into vaccination recommendations for travellers in all these countries. In addition to hygiene measures, these countries recommend HAV vaccine for holiday travel to areas where hepatitis A is endemic, including Egypt, which is in line with recommendations of most expert bodies including the World Health Organization (WHO), the United States Centers for Disease Control and Prevention, and Viral Hepatitis Prevention Board (www.vhpb.org) [6]. However, despite this consistency in recommendations the burden of travel-associated HAV infection in five of the respondent countries was considerable.

The cost implications of appropriate vaccination may have acted as a financial disincentive jeopardising optimal vaccine uptake. The reported incidence of hepatitis A infections in respondent countries is uniformly below the average of 10/100 000 reported in the WHO European region [8]. Consequently, most of the adult population remain susceptible to acquiring hepatitis A when travelling to highly endemic areas, including those staying in luxury hotels [9].

While currently HAV infection is not notifiable in France, an evaluation of the French surveillance system for hepatitis A in 1998-2000 recommended mandatory notification based primarily on laboratory surveillance [10]. Among the seven countries where hepatitis A was statutorily notifiable, the case definition for reporting confirmed cases was not uniform. In addition, the personnel who reported were not consistent between countries. Thus, direct comparison of hepatitis A incidence between countries may not be valid. In order to improve the comparability of data from different member states, the European Commission (EC) produced a decision (2002/253/EC) in 2002, stipulating case definitions for reporting infectious diseases. The recommended case definition for confirmed hepatitis A is a combination of clinical symptoms and laboratory confirmation.

Table 1

Organisations producing guidelines for travel associated infectious diseases, in eight European countries, 2004

Country	National institutes disease surveillance	Ministry of health	Institutes of tropical medicine	National vaccination committees	Federal office of public heath	Travel clinics/ Travel health network
Denmark	x					
England & Wales	x	x				x
France		x				
Germany			x	x		x
Ireland	x			x		x
The Netherlands	x					
Spain		x				
Switzerland					x	

Table 2

Organisations administering hepatitis A vaccine, preventive measures for two weeks travel to Egypt and cost of hepatitis A vaccine in eight European countries, 2004

	Vaccine administration personnel*				Hepatitis A preventive measures		
Country	MPHD	STC	OHC	GP	Hepatitis A vaccination	Immunoglobulin	Cost (€)^ of vaccine
Denmark	x	x		x	Yes	Special risk groups	55
England & Wales	x	x	x	x	Yes		36
France		x	x	x	Yes		18
Germany	(x)§	x	x	x	Yes	Special risk groups	54
Ireland	x	x	x	x	Yes		27
The Netherlands	x	x	x	x	Yes	Special risk groups	25
Spain		x	x		Yes	< 2 years	31
Switzerland		x		x	Yes		47

* MPHD: municipal public health department, STC: specialist travel clinics, OHC: occupational health services, GP: general practitioners

§ only in some MPHDs

^ Cheapest option for one adult dose

Table 3

Notification category, case definition and notification personnel for hepatitis A in eight European countries, 2004

		Notified cases HAV/100 000	Case definition*			Notification personnel	
Country	Mandatory notification	Averaged 2001-2003	A	B	C	Medical/ nursing	Laboratory
Denmark	Yes	1.36	x x	x	 x	yes	no
England & Wales	Yes	1.96	x			yes	no
France	No	N/A	-	-	-	-	-
Germany	Yes	2.06	x x	x	 x	yes	yes
Ireland	Yes	1.40	x	x		yes	yes
The Netherlands	Yes	1.60	x x	x	 x	yes	yes
Spain	Yes	1.92	x	x		yes	no
Switzerland	Yes	2.30	 x x	x x	 x 	yes	yes

* Confirmed case: A: clinical symptoms, B: laboratory confirmation, C: epidemiological link to serologically confirmed case. The number of lines per country corresponds to various combinations of clinical, laboratory and epidemiological criteria used for notification of hepatitis A nationally

Uniform use of such a case definition for confirmed cases of hepatitis A would facilitate more accurate comparison between countries. As a result of a feasibility study, EUROHEP.NET (www.eurohep.net) has made a similar observation. However, as with all notifiable infectious diseases, country-specific factors, such as the tendency of people to seek medical care, different diagnostic methods in use, and the percentage of physicians sending in notifications, will probably continue to have an impact on reported incidence [11].

Although all eight countries recommended active vaccination against hepatitis A for travel to endemic areas, a considerable proportion of reported hepatitis A was travel-associated, indicating that a large number of travellers continue to set out on their journeys inadequately protected against hepatitis A. Appropriate medical advice and efficacious vaccines against hepatitis A virus are readily available, and so the risk of hepatitis A should be avoidable, but our survey supports similar reported findings of a general reluctance by travellers to seek and adhere to timely medical advice [11,12,13,14,15,16]. Such reluctance may be partly explained by the low risk of hepatitis A associated with travel that seems to be generally perceived by holidaymakers. While travel agents should be encouraged to take a more active role in informing travellers of travel-associated health risks, this policy is potentially limited by the increasing number of travellers who use the internet to plan and book their holidays. An automated reminder of appropriate vaccination recommendations linked to internet travel ticket bookings to hepatitis A endemic destinations would be a beneficial adjunct to such increased involvement by travel agencts.

There is consistency in hepatitis A vaccine recommendations for travellers to HAV endemic areas from the European countries that responded to this questionnaire. Despite this, the burden of travel-associated infection is considerable. Consequently, innovative ways to increase the number of travellers who seek and adhere to appropriate medical advice prior to travel must be explored. In addition, there remain differences in reporting practices from HAV infection between countries. In order to minimise this variation we also recommend use of the EC case definition for notification of HAV infection. Active steps must be taken by public health authorities to improve their utilization of health services and prevent the accrued health risk for these travelers.

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ABSENCE OF INFECTION IN ASYMPTOMATIC CONTACTS OF INDEX SARS CASE IN FRANCE

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The first case of severe acute respiratory syndrome (SARS) in France was diagnosed in March 2003. We conducted a serological survey to assess whether or not asymptomatic persons who had been in contact with this patient during his infectious stage had been infected. They were interviewed and asked to provide a blood sample for SARS coronavirus immunoglobulin G antibody testing. Despite the likely high infectivity of the SARS patient, no asymptomatic SARS infection was found in any of the 37 contacts included. These findings support a SARS case definition that is essentially based on clinical and epidemiological assessment, should SARS re-emerge.

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Introduction

Soon after the severe acute respiratory syndrome (SARS) international alert was issued by the World Health Organization (WHO) on 12 March 2003, surveillance of SARS was set up in France to detect and isolate possible and probable SARS cases as early as possible. Contacts of SARS cases were identified, quarantined and followed up on a daily basis for ten days. By the end of the outbreak in July 2003, seven probable SARS cases had been identified, of which four were confirmed by serology or polymerase chain reaction (PCR). All cases had been infected outside France and no secondary SARS transmission occurred in France. We report the results of a serological survey conducted among the asymptomatic contacts of the index SARS case introduced in France on 23 March 2003.

Methods

The index patient had been infected in Hanoi, Vietnam, where he worked as a physician in a hospital where an outbreak of SARS had been reported [1]. He developed clinical symptoms on 20 March 2003 and travelled by plane to France on 22 March. Upon arrival in Paris, he presented to an infectious diseases hospital close to his home, and reported that he had been exposed to SARS patients in Hanoi hospital. He was admitted to a specific isolation unit and SARS coronavirus (SARS-CoV) infection was confirmed by PCR on nasopharyngeal aspirates. Viral RNA was detected in endotracheal aspirates and stool samples for 66 days after onset of symptoms (Dr Yazdanpanah, personal communication).

Active case finding among close contacts allowed the identification of four secondary SARS probable cases (of which three were confirmed), infected before their arrival in France: one case had had previous contact with the index patient in Hanoi and three had been infected during the flight [1].

The study population included all persons who had contact with the index patient during his infectious stage and who remained asymptomatic. The patient's infectious stage started from the date of travel on 23 March (while symptomatic) until the date when his biological samples tested negative for SARS-CoV on 26 May 2003. Contacts, as defined by WHO criteria [2], included the AF171 flight passengers seated in the same row, one row in front and one behind the patient, the crew members, the medical personnel responsible for passengers screening upon arrival at the airport, the taxi drivers who transported the patient from the airport to his home and from his home to the hospital, and the healthcare workers (HCWs) who cared for the patient in the hospital where he was admitted. The four symptomatic secondary probable cases of SARS, infected in Hanoi or during the flight, were excluded from the study.

After informed consent, contacts who agreed to participate responded to a standardised questionnaire administered by a physician. Data collected included demographic information, the nature, duration and type of contacts with the index patient, the use of personal protective equipment and the occurrence of any clinical symptom compatible with SARS. A blood specimen was then collected, frozen and sent to the National Reference Centre for Influenza, Institut Pasteur, Paris.

This retrospective serosurvey was conducted on a voluntary basis and received approval from our corresponding ethical committee.

Sera were tested for SARS-CoV immunoglobulin G antibodies using an indirect immunofluorescence assay.

Results

We identified 65 eligible contacts, of whom 37 (57%) agreed to participate : five of the six airline passengers, one taxi driver who drove the patient on a thirty minute journey from his home to the hospital, and 31 (61%) of 51 HCWs who cared for the patient (11 nurses, 7 auxiliary nurses, 6 radiographers, 5 kinesitherapists and 2 physicians). Aircraft crew members and airport attendants could not be included because their respective companies refused to provide staff lists. Interviews and blood sampling took place from 24 May to 24 June 2003.

Among the 37 contacts, the male to female ratio was 0.65 and median age was 33 years (range 24-64 years). The median time interval between first exposure to the index case and blood collection was 70 days (range 30-91 days), and the median time interval between last exposure and blood collection was 33 days (range 10 - 87 days).

None of the participants reported fever or other symptoms related to SARS within 10 days after first exposure. However, three contacts reported a non-febrile rhinitis, myalgia that lasted for two days and a cough that lasted for three days. For these three persons, clinical examination, blood counts and chest radiographs were normal.

Of the 31 HCWs, thirty (97%) reported having always worn at least one protective respirator (N95 type), gloves and goggles when caring for the patient. One HCW reported contacts with the patient during two days: he did not wear any protective equipment during the first day but did do so on the second day. The taxi driver did not wear any protective device, but the patient himself wore a surgical mask during the taxi journey. The flight passengers seated close to the patient did not wear any protective equipment.

All 37 serologic samples (100%) tested negative for SARS-CoV immunoglobulin G antibodies.

Discussion

Our study did not show any SARS-CoV infection among asymptomatic contacts of a confirmed case of SARS. Healthcare

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workers in the hospital where the patient was admitted had made preparations to admit the index patient and were warned of his potential SARS diagnosis. As a consequence, they were able to adopt adequate protective behaviours as reported during their interviews. The transmission risk for HCWs was high, since the patient was severely ill and the exposure period included his peak contagious period, that is, in the course of the second and third weeks after the onset of the disease. Furthermore, the risk of secondary transmission from this patient was ascertained a couple of days after the illness onset, when three secondary cases were found to have occurred during the flight [1]. In addition, potentially aerosol-generating invasive procedures had been carried out during the patient's care. They consisted of endotracheal intubation and aspiration and could have fostered transmission, despite the use of personal protective equipment, as reported by Ofner et al [3].

The absence of asymptomatic or subclinical SARS-CoV transmission among HCWs in our study is consistent with reports from other countries that did not show any evidence for asymptomatic SARS infections [4,5,6,7,8] or reported it as uncommon (1.4 to 2.3%)[9,10,11], despite larger series and greater exposure (from 87 persons in Singapore to 1147 in Guangzhou, China).

Available studies on SARS transmission indicate that inflight transmission is rare but can occur, especially in 'superspreading events' [12,13,14]. In a previous article, we showed that SARS transmission occurred from the French index patient during his flight from Hanoi to Paris [1]. In the study reported here, we explored further the serological status of asymptomatic passengers, crew members and airport personnel who had been in contact with the patient during his flight and upon arrival. Unfortunately, this study in the aircraft was limited to five passengers, because airline company internal management considerations prevailed. Like Breugelmans et al [12], we deplore the lack of collaboration with the travel industry, regarding it as a major public health risk that is directly amplified by international travels.

Our study had some limitations. First, refusal to participate for some HCWs may have biased our results. In particular, the HCWs who refused to participate may have adopted protective measures less strictly and felt more at risk of having been infected. For those who participated, recall bias was probably not present, since interviews took place soon after events. However, some HCWs may have reported appropriate protective practices that they felt they should have adopted, rather than their own behaviours during patient care. Secondly, for some participants, blood collection took place at week 2 after contact with the patient; this delay may have been too short to allow detectable seronconversion rates. A second sample collected at least 30 days after last day of exposure would have allowed to confirm the absence of seroconversion among asymptomatic contacts.

In conclusion, like other studies, we showed no asymptomatic or subclinical SARS infection among close contacts of an index patient, despite his severe clinical condition. These findings support the WHO SARS case definition that is essentially based on clinical and epidemiologial assessment, should SARS re-emerge.

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Contributors

The authors contributed as follows: Stéphane Le Vu contributed to the design, planning, implementation and analysis of the study and drafted the manuscript. Yazdan Yazdanpanah contributed to the data collection and made comments on the manuscript. Julien Emmanuelli and Isabelle Bonmarin contributed to the study design and planning. Dounia Bitar contributed to the manuscript drafting. Jean-Claude Desenclos contributed to the study conception, implementation and reviewed the manuscript.

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COMMUNITY-ACQUIRED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN SWITZERLAND: FIRST SURVEILLANCE REPORT

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is an emerging community pathogen. Community-acquired MRSA (CA-MRSA) has been associated with virulent strains producing Panton-Valentine leukocidin (PVL) and a variety of other exotoxins. In Geneva, PVL-producing CA-MRSA was first reported in 2002 and a surveillance system based on voluntary reporting was set up.

Each MRSA-positive culture result with an antibiotic resistance profile different from the endemic strain prevailing in the Geneva healthcare setting diagnosed in a patient without a history of hospital admission in the previous 12 months was notified to the local health department. A questionnaire was completed by the attending physician with demographic, clinical and exposure information.

From January 2002 until December 2004, data on 58 cases were reported, including 26 cases grouped in 13 distinct transmission clusters. Most were family related and for two of them, colonisation persisted over a 12 month period despite treatment. Thirty three patients (57%) were male. Median age was 32 years, 22% being younger than 10 years. Forty one cases (71%) were infected and 17 (29%) colonised. Symptomatic skin lesions such as furunculosis, impetigo or abscess were present in 40 (97%) of the 41 infected cases. Most cases had no underlying disease. Thirty eight cases (65%) had travelled abroad. Forty (69%) of 58 isolates carried the PVL toxin.

CA-MRSA infections in Geneva appear to be an emerging problem in the canton. Surveillance should continue and should possibly be extended to other parts of the country to better describe transmission patterns and the spread of this pathogen. Prevention and control of CA-MRSA infections represent a challenge for the future, requiring contact tracing, education and treatment of infected and colonised contacts.

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Key words: community, methicillin resistance, Leukocidin, Panton-Valentine, Staphylococcal infection, Switzerland

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an emerging community pathogen. It was first reported in the early 1990s among closed communities of Aborigines in Western Australia [1]. Outbreaks of community-acquired MRSA (CA-MRSA) infections in healthy children and adults have been described worldwide [2]. CA-MRSA infections tend to occur in younger persons than do hospital-acquired MRSA (HA-MRSA) infections. They often cause sporadic cases of skin and soft tissue infections but cases of necrotising pneumonia have also been reported [3]. CA-MRSA has been associated with virulent strains producing Panton-Valentine leukocidin (PVL) and a variety of other exotoxins [4]. It shows resistance to methicillin, which is encoded by the *mecA* gene, mostly found on the type IV staphylococcal cassette chromosome (SCC) [2]. The spread of these strains does not seem to be limited to the community and may also concern the hospital setting [5], although in Geneva, low prevalence of CA-MRSA on admission to the main hospital has been reported [6].

Voluntary laboratory-based CA-MRSA surveillance was set up in Geneva in 2003, to ensure adequate case investigation and contact tracing, estimate incidence and transmission patterns, and develop prevention strategies. We report the first results of this surveillance system.

Methods

Four laboratories (the Geneva University Hospital (Hôpitaux Universitaires de Genève, HUG), clinical microbiology laboratory and three private ones) participated on a voluntary basis in the surveillance system. Physicians from public hospitals and private clinics also provided information on cases. The population of the Canton of Geneva is estimated to be around 427 400 persons (2004).

For surveillance purposes, a laboratory reportable CA-MRSA was defined as any MRSA isolate with an antibiotic resistance profile different from the endemic strain prevailing in the Geneva healthcare setting, diagnosed in a patient without history of hospitalisation in the previous 12 months.

All CA-MRSA cases reported by the laboratories since 2002 and fitting this case definition were included in our database.

Presence of PVL or other exotoxins was determined with PCR-based assays [2,8].

For each laboratory reported case, a questionnaire was sent to the clinician in charge requesting demographic, clinical and epidemiological data information. Data on the type of infection and other specific clinical features were collected (questionnaire in French available on request).

For each infected CA-MRSA case, active contact tracing was done within one week of identification of the index case. The case's family members or close contacts were offered screening and treatment (or decolonisation) if required. This active search increased the number of infected or colonised cases included in the surveillance database and allowed the identification of several clusters.

Results

From January 2002 to December 2004, 58 CA-MRSA cases were reported; 41 cases (71%) had a clinical infection and 17 (29%) were colonised. Thirty three patients (57%) were male. Median age was 32 years (inter-quartile range: 11-49) and 22% of cases were younger than 10 years. Symptomatic skin lesions such as furunculosis, impetigo or abscess were present in 40 (97%) of the 41 infected cases. Abscesses and furunculosis were the most common clinical presentation. Sixteen cases (28%) had a close contact person with similar skin lesions.

Thirty one cases (75%) were in patients who presented with their first episode and 10 (25%) with a relapsing infection. The majority of infected cases (34/41, 83%) had no comorbidity. No deaths or severe infection were reported. Seven cases were in temporary residents who lived abroad and 38 had travelled abroad in the preceding 12 months (Africa, 6; Europe, 11; Asia, 4 and North America, 2; not known, 15). The epidemic curve is shown in the figure.

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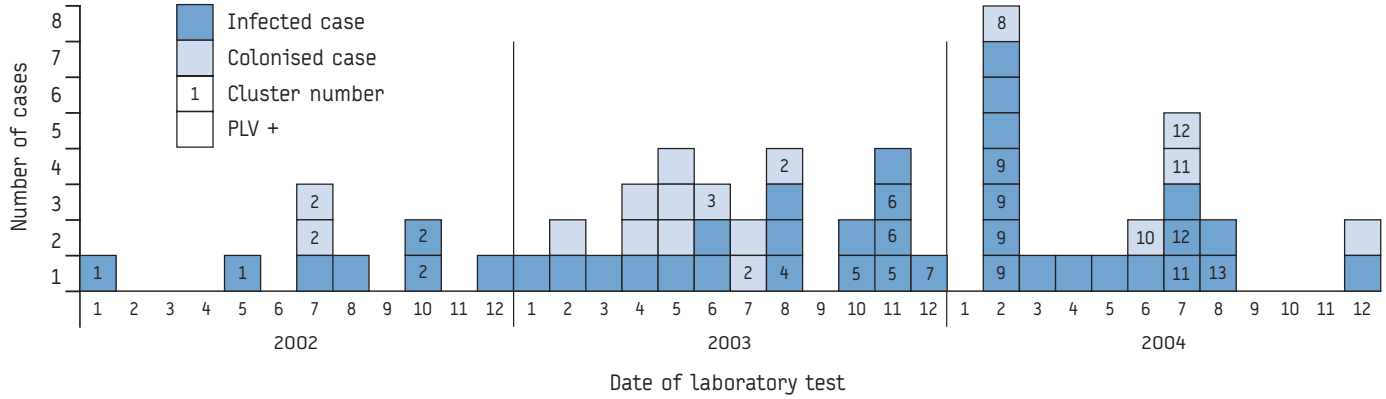
FIGURE

Cases of community-acquired MRSA reported to the Geneva surveillance database, 2002-2004



Forty of 58 isolates carried the PVL toxin. Twenty seven (66%) of these isolates were recovered from infected cases and 13 (76%) from colonised cases.

A total of 26 cases could be grouped in 13 distinct transmission clusters. Of them, 9 clusters were family-related (size: 2-7 persons); 3 were heterosexual couples and 1 occurred within an ambulatory health setting (private practice) (size: 3). In two of the familial clusters, colonisation persisted over a 12-month period despite several treatment attempts administered simultaneously to all family members.

Discussion

It is essential to differentiate healthcare-associated MRSA infections occurring in the community among patients at risk of HA-MRSA (such as a previous history of hospital admission) from true CA-MRSA infections due to strains which are present in the community only [3,6]. The possibility that strains first identified in the community will disseminate further within the hospital population is of great concern [7]. It should be noted that, to our knowledge, Geneva is currently the only canton in Switzerland where such specific surveillance (a systematic, patient-based surveillance of CA-MRSA infections detected in both outpatients and inpatients) exists.

In Geneva, PVL-producing CA-MRSA was first reported in 2002 [4]. Within weeks of the alert, the Direction Générale de la Santé (DGS), with the assistance of a CA-MRSA epidemiology working group (see appendix), set up a voluntary CA-MRSA surveillance system. The medical community and microbiology laboratories were informed and as a result, participate actively and voluntary in the surveillance system.

The case definition of our surveillance system was based on microbiological criteria (antibiotic resistance profile) together with epidemiological criteria (no hospital contact within the previous 12 months). However, more specific microbiological characteristics such as the SCC *mec* type or the presence of PVL were also investigated in all cases. Because case definitions may vary between surveillance systems, caution should be applied when comparing CA-MRSA prevalence in different settings.

Skin and soft tissue infections caused by CA-MRSA may be an emerging problem in Geneva and, probably, other parts of Switzerland. Continued and expansion of surveillance is critical to asses the spread of this new pathogen.

The majority of isolates (69%) carried the PVL toxin. Further studies should be conducted to determine the role of PVL as a marker of community acquisition and its importance to distinguish from healthcare-associated acquisition.

The existence of more than a dozen clusters demonstrates the importance of local transmission. More data are needed to clarify the risk profile for infection and the relative contribution of imported cases versus local transmission. Our population-based surveillance network will help to better understand the extent of the spread of CA-MRSA not only in the community but also to the healthcare setting. Specific epidemiological studies are planned to better understand these potential risk factors and transmission patterns.

Prevention and control of CA-MRSA infections represents a challenge for the future, requiring better surveillance, contact tracing, education and treatment of infected cases and colonised contacts.

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Appendix

The Geneva CA-MRSA epidemiology working group is composed of Dr P Sudre, M Girard, Dr C Aramburu (EPIET)/ DGS Geneva; Dr S Harbarth, Dr S Hugonnet, Pr Didier Pittet/ SPCI, HUG Geneva ; Pr J Schrenzel, G Renzi/ DMI, HUG Geneva ; Dr A Gervaix, Paediatric department/ HUG Geneva, Dr Na Liassine, Bioanalytique-Riotton UNILABS, Geneva ; Dr L Gauthey, Dr M Pechère, Association of Physicians in Geneva ; Dr CA Wyler/ Youth Health Service, Geneva

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EMERGENCE OF MRSA INFECTIONS IN HORSES IN A VETERINARY HOSPITAL: STRAIN CHARACTERISATION AND COMPARISON WITH MRSA FROM HUMANS

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has become an emerging public health problem worldwide, no longer only associated with healthcare-associated infections. With the exception of some recent reports concerning infections in cats, dogs and horses, infections with MRSA in companion animals have been infrequently reported. Here we submit findings for MRSA infections in horses in a central European university veterinary hospital.

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Key words: animal to human transmission, horse MRSA, molecular typing, *Staphylococcus aureus*

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a worldwide public health problem [1,2]. Increasing prevalence of healthcare-associated MRSA infections is usually associated with a wide dissemination of particular epidemic clonal lineages of the *S. aureus* population [3]. Since the late 1990s, MRSA has emerged in many countries as a cause of invasive skin infections in the community, independently from the healthcare setting [4-8]. In this context, colonisation and infections with MRSA in domestic animals are of particular interest with regard to a mutual dissemination between humans and animals. The first communication on MRSA infections in domestic animals concerned mastitis cases in dairy cows in Belgium in 1972 [9]. Since that time there have been reports of sporadic cases of infection with MRSA in a variety of other domestic animal species such as horses, chickens, dogs and cats [10-13]. MRSA infections in horses associated with wide dissemination of a particular clonal lineage have been recently documented in Canada [14,15].

Here we report on emergence of MRSA in a university veterinary hospital and on an assessment of the relation of human and animal MRSA isolates by means of molecular typing. This includes *Sma*I macrorestriction patterns, multilocus sequence typing (MLST) for assessing the core genome of *S. aureus* and characterisation of SCC*mec* elements of which at least 5 different groups have so far been described [16]. SCC*mec* (staphylococcal cassette chromosome *mec*) elements contain the *mec*A gene that codes for methicillin resistance [17].

Materials and methods

Description of the setting:

The Veterinary University of Vienna [Veterinärmedizinische Universität Wien, (VUW)] consists of a large hospital with separate departments for small animals, horses, farm animals, reproduction and diagnostic imaging/laboratory diagnostics. On average, 23 000-24 000 domestic animals including horses, ruminants, pigs, dogs, cats and rodents are admitted to hospital for a variety of diseases each year. Within the equine department there are separate clinic buildings for orthopaedics, soft tissue surgery and internal medicine. When necessary for diagnostics and/or specialised treatment, animals are moved between different clinics. Furthermore, veterinarians undertaking postgraduate education are on duty in different departments, and move freely between the various clinic buildings.

Origin of MRSA from infections and nasal colonisation in horses

Clinical isolates (from 24 cases) were obtained from specimens for bacteriological diagnostics that were routinely submitted in cases of wound infections, infected joints and suspected infections of various organ systems from summer 2003 until spring 2005.

In order to investigate nasal colonisation, the both nostrils of 24 horses (4 with an MRSA infection, 20 without) that were treated by the orthopaedics department during the same time period in 2004 and 2005 were screened for MRSA by taking nasal swabs. Colonisation was found in only 1 of these animals.

MRSA from nasal colonisation of VUW staff and veterinarians:

Specimens originated from direct cultures of swabs taken from both nostril.

Reference strains for healthcare-associated epidemic MRSA

These strains represent multilocus sequence types (ST) of the major clonal lineages of epidemic MRSA from Europe (ST22: 1678/96; ST05: 3391/02; ST247: 134/93; ST45: 1150/93, ST254: 993/93 and 1000/93).

The strains were initially isolated from outbreaks of healthcare-associated infections and were established by representative *Sma*I macrorestriction patterns and multilocus sequence types (MLST). These strains were included in the HARMONY collection of epidemic MRSA from Europe [18] and in the first MLST-based population study of MRSA from sources worldwide [3].

In the study described here, these reference strains were used for comparison of *Sma*I macrorestriction patterns.

Reference strains for community-acquired MRSA (CA-MRSA)

ST80: 3925/02; ST01: 2773/03; ST30: 1880/04.

These strains represent multilocus sequence types of community-acquired MRSA that are frequently isolated in central Europe [(6-8] and have been used in this study for comparison of *Sma*I macrorestriction patterns. They originate from deep-seated skin infections in the community without hospital association, and are positive for the Panton-Valentineleukocidin determinants (*luk*S-*luk*F).

Methodology of specimen processing

MRSA from infections in horses were obtained from direct cultures of swabs onto blood agar-plates. Colonies typical for *S. aureus* were subjected to species identification according to standard procedures [19] and were also evaluated for antimicrobial susceptibility [20]. Nasal colonisation swabs from the anterior of horses and of veterinary personnel were streaked onto blood agar plates and in parallel onto CHROM agar for MRSA from Becton-Dickinson. After incubation for 48 hours, at least five colonies that were suspected to be *S. aureus* were further subjected to species identification and antimicrobial susceptibility testing.

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Susceptibility testing

First line testing in veterinary clinical microbiology was performed by disk diffusion assay [20]. All isolates exhibiting oxacillin resistance were subjected to microbroth assay for MIC determination [20] and to polymerase chain reaction (PCR) for the *mec*A gene.

Molecular typing

*Sma*I macrorestriction patterns were obtained by use of the standardised HARMONY protocol [18] with subsequent cluster analysis based on the soft ware described by Claus et al [21]. For comparison of *Sma*I patterns, cluster analysis was performed by comparing gel images.

For multilocus sequence typing (MLST) primers used and conditions of the PCR reaction corresponded to those described by Enright et al [3]. Sequences were analysed by use of the MLST databank (http://www.mlst.net).

Characterisation of SCCmec elements by PCR

PCR for *ccr*-complexes, detection of type II and type III specific sequences and discrimination of type IV was performed as described by Witte et al [6].

Demonstration of antibiotic resistance and virulence associated genes by PCR

PCR for *luk*S-*luk*F was performed as described by Witte et al 2005 [5]. For PCR detection of genes conferring resistance to methicillin (*mec*A), oxytetracycline (*tet*K, *tet*M), macrolides (*erm*A, *erm*B, *erm*C) and gentamicin (*aac*6'-*aph*2"), primers used and conditions were as in previous studies (Braulke et al [22] and Werner et al [23]). For PCR for superantigen determinants (*tst*, *eta*, *etb*, etc) primers and conditions were used as described by Mehrotra et al 2000 [24].

Results

Emergence of MRSA infections in horses:

In 2003 there were 344 equine cases from which clinical specimens were submitted for bacteriological, diagnostics. *S.aureus* was isolated in 47 (14%) of these cases including 19 infections with MRSA. In 2004 samples from each of 29 among 259 cases were positive for S.aureus (11%) with 3 of them confirmed as MRSA infection. From January 2005 until April 2005 there were 21 S.aureus infections among 165 equine cases (13%), 2 of them were MRSA infections.

The time course, type of infection with MRSA and clinical department affected are shown in Figure 1. The index case occurred in surgery in mid 2003. Investigation into the introduction of MRSA from the community into the hospital via this patient was unsuccessful.

Currently, we have no information regarding cases of MRSA infections from other veterinary institutions in Austria. In this country the frequency of MRSA among *S. aureus* from healthcare-associated infections in humans is approximately 10%. This represents a relatively low incidence of infections when compared to the situation in other European countries [1]. Overall, the incidence of infections at the VUW with MRSA appears low considering the number of about 5000 horses admitted in 2004 and 2005, that means about 4.8 cases with an MRSA infection MRSA per 1000 admissions.

Typing and comparative characterisation to MRSA from humans:

All 24 isolates from infections horses exhibited similar *Sma*I macrorestriction patterns with only minor variations that are still in the range of variability during the course of an epidemic (25). This pattern is consistent with intrahospital spread of one particular MRSA clone. These fragment patterns were different from those exhibited by healthcare-associated epidemic MRSA disseminated in Europe and from those of community-acquired MRSA [FIGURE 2].

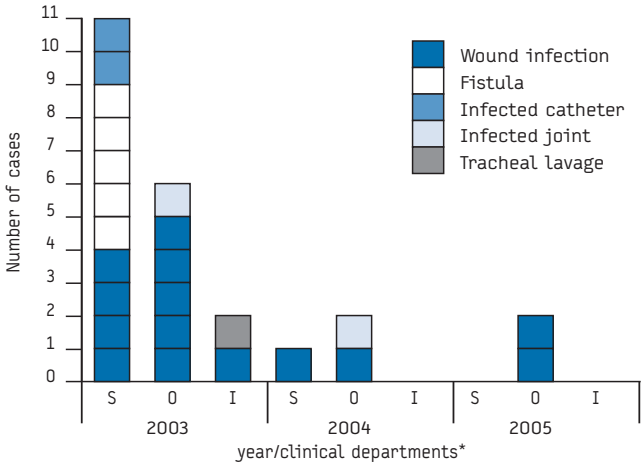
Furthermore, there was no congruence when *Sma*I-patterns of MRSA from horses were compared to patterns of 3680 MRSA isolates from healthcare-associated and community-acquired infections that were sent for typing to the author's laboratory as the German National Reference Center for Staphylococci at the Robert Koch Institute between 2001 and 2004.

Five horse MRSA isolates that were subjected to MLST were identified as ST254.

PCR for typing of SCC*mec* elements that was performed on 5 isolates from horses revealed type IVd whereas IVc was found for MRSA of ST254 from humans [TABLE]. None of the investigated horse MRSA contained lukS-lukF, tst1, eta, etb or etc.

FIGURE 1

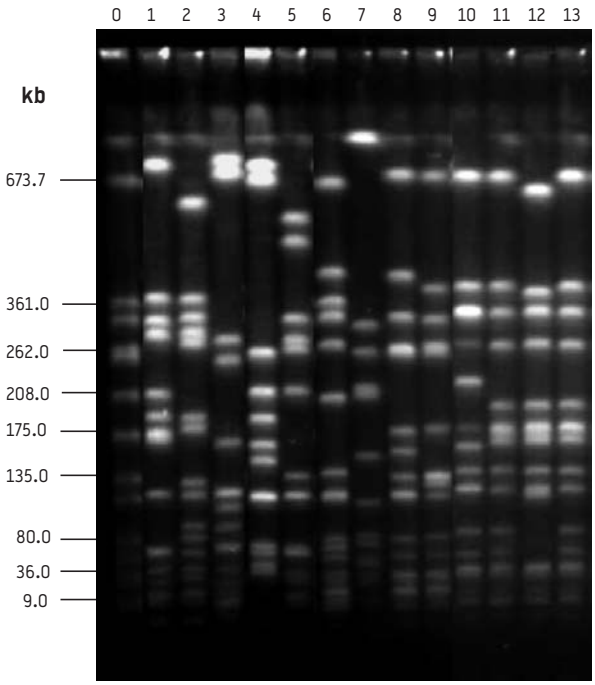
Emergence of 24 infections with MRSA in horses in different clinical departments from 2003 to 2005



* Clinical departments: S = surgery; O = orthopaedics; I = internal medecine

FIGURE 2

S*ma*I macrorestriction patterns of MRSA from infections in horses, shown together with S*ma*I macrorestriction patterns of epidemic MRSA from healthcare-associated infections and of community-associated MRSA from central Europe



Reference strains for epidemic nosocomial MRSA and for community MRSA are indicated by code numbers and MLST types (STs in brackets)

Reference isolates as molecular mass standard S. *aureus* 8325: lane 0

Community-associated MRSA: lane 1: 3925/02 (ST80); lane 2: 2773/03 (ST01); lane 3: 1880/04 (ST30)

Epidemic healthcare-associated MRSA: lane 4: 1678/96 (ST22); lane 5: 3391/02 (ST05); lane 6: 134/93 (ST247); lane 7: 1150/93 (ST45); lane 8: 1000/93 (ST254); lane 9: 994/93 (ST254)

Horse isolates: lane: 10: 1831/03 (ST254); lane 11: 762/04 (ST254); lane 12: 1457/03 (ST254); lane 13: 2576/03 (ST254)

Table

Characterisation of MRSA of MLST ST254 from infections in horses in VUW compared with healthcare-associated MRSA of MLST ST254 from humans and to MRSA from infections in horses, Canada

Origin	MLST	No. of isolates investigated	Resistance phenotypes	Resistance genes	PCR characterisation of SCC*mec*-elements
Horses, VUW	254	5	PEN, OXA, TET, GEN, TMP	mecA, tetM, aac6'-aph2"	IVd
Humans	254	5	PEN, OXA, ERY, CLI, TMP	mecA, ermA	IVc
Horses, Canada	8	1	PEN, OXA, ERY, CLI, GEN, OTE	mecA, ermC, aac6'-aph2", tetM	IV

Transmission to human nasal colonisation of personnel and veterinarians:

During the time periods of emergence of MRSA infections in horses in the surgery and orthopaedic clinics in 2004 and 2005, nasal swabs from 43 people that were directly involved in treatment of animals (veterinarians, veterinary assistants, animal keepers) were investigated. Two veterinarians were revealed as long term carriers (massive colonisation demonstrated in both a first investigation and follow-up sample 3 weeks later). The MRSA isolates exhibited the same *Sma*I macrorestriction patterns as isolates from infections in horses and contained SCC*mec* IVd elements.

Nasal colonisation of horses:

Data from human medicine indicates that nasal colonisation is an important reservoir with regard to infections of the primary carrier and to further dissemination [26,27]. A temporary colonisation (negative in a second investigation) was detected in only one among 24 horses. The MRSA isolate exhibited the same *Sma*I macrorestriction pattern as the isolates from infections and also contained a SCC*mec* IVd element.

Discussion

MRSA from infections in horses in a central European veterinary hospital exhibit MLST ST254. This type has also been identified in healthcare-associated epidemic MRSA. This strain was frequent in the 1990s but has subsequently decreased in prevalence [28]. Reference isolate 994/93 is a representative of ST254 that was disseminated in the hospitals of the Order of Holy Elisabeth in the south-west of Germany and west of Austria [28]. A direct relationship between human MRSA of ST254 to those from horses is however unlikely,as both exhibit different *Sma*I-macrorestriction patterns and contain different subtypes of SCC*mec* IV elements. Subtypes of SCC*mec* elements of type IV differ by various DNA sequences in the region downstream from *mec*A. At the present time, no acquisition or loss of these sequences has been observed during the time course of dissemination of epidemic MRSA. PCR typing based on subtype specific DNA sequences appears to be a reliable tool for discrimination of subtypes. Demonstration of different subtypes of SCC*mec* elements in the genomic background of ST254 does however, not exclude an exchange of MRSA between humans and horses in the past. Another possibility is that methicillin-susceptible *S. aureus* of ST254 that was already widely disseminated among humans [29] was transferred to horses and later acquired a SCC*mec* element that is different from those acquired by human MRSA of ST254.

Until now MRSA exhibiting typing patterns like those of ST254 from horses have not been detected among MRSA isolates from infections in humans. Furthermore, the human ST254 strain has so far only been associated with healthcare-associated infections and has not emerged in the community.

However, the finding of stable nasal colonisation of two veterinarians who had been in contact with animals affected by MRSA infections demands further investigation of potential animal to human transmission.

This is underlined by findings of MRSA among horses that were reported from Canada. In this report a single well-recognised MRSA clone exhibiting the so called CA-MRSA-05 typing pattern that previously had been identified in healthcare-associated settings from 5 different geographical sites in Canada was demonstrated to have the ability to colonise the nose of horses. This clone spread among both horses and humans on farms and among personnel in veterinary hospitals (14,15). When representative isolates of these MRSA strains were subjected to MLST, we found it to be ST 8 [TABLE]. MRSA strains exhibiting ST8 are widely disseminated in US hospitals and may also become more frequent in Canada since a population dynamics of *S. aureus* and in particular of MRSA is well known [30]. Furthermore, MRSA of this clonal lineage containing the *luk*S-*luk*F gene that confers enhanced virulence became prevalent as community-acquired MRSA in the US [31], and sporadic cases of infections in the community have also been reported from Norway [32].

Conclusion

Infections in horses with MRSA of MLST ST254 emerged independently of MRSA infections in humans. Although MRSA in horses may presently not represent a substantial reservoir for infections in humans in central Europe, further surveillance is needed with respect to human transmission and to emergence of new clonal lineages.

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ORIGINAL ARTICLES

Surveillance report

SURVEILLANCE OF ANTIMICROBIAL RESISTANCE OF INVASIVE PATHOGENS: THE ESTONIAN EXPERIENCES

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The aim of the present study was to evaluate the needs for surveillance of invasive Gram-negative pathogens in Estonia. The antimicrobial susceptibility data of invasive isolates of *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella spp, Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae* and *enterococci* were collected in accordance with EARSS (European Antimicrobial Resistance Surveillance System) protocols. Despite the higher rate of Gram positive pathogens, their resistance was low in contrast to the elevated resistance established for Gram negative pathogens. The higher resistance to antimicrobials was particularly associated with *A. baumannii* and *P. aeruginosa*. Also, the proportion of extended-spectrum beta-lactamases (ESBL)-producing strains was 23% among *Klebsiella spp.* and 3.6% among *E. coli*. The inclusion of invasive Gram negative pathogens in antimicrobial resistance surveillance provides useful information concerning local pathogen susceptibility, as well as for the empirical treatment of suspected infections.

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Introduction

The epidemiology of invasive bloodstream pathogens has changed dramatically over the years [1-3]. The change in the incidence and epidemiology of infecting organisms has also brought about an increase in resistance to many antibiotic compounds [2,4,5]. Despite numerous publications on antimicrobial resistance, the comparison and evaluation of data is difficult, as the patient groups, sampling sites and infections involved in each study were different.

In order to overcome these problems, the European Antimicrobial Resistance Surveillance System (EARSS) began the collection of standardised data about the resistance of invasive isolates, focusing especially on Gram positive pathogens. Until 2005, information about Gram negative bacteria was available only in case of *E. coli* [6]. In addition, from the summer of 2005 onwards, data are being collected on *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* [6]. Infections with Gram negative bacteria still constitute a topical problem in patients with invasive infections, which are quite frequent in Europe [7-13].

The high degree of cultural, economic and social diversity, as well as the habits of antibiotic usage in European countries, probably influence the spectrum and susceptibility pattern of invasive pathogens, for example, the variation in the number of antibiotic prescriptions per 1000 population as well as the choice/preference of different antibiotic groups between the northern, central and eastern European countries was found [14,15,16,17]. Treatment and infection control guidelines also vary between countries [17]. Hence the usefulness of the resistance markers traditionally used in surveillance (such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and penicillin-nonsusceptible *Streptococcus pneumonia*) may have limited value for empirical antibiotic therapy and the evaluation of resistance trends in some regions. The aim of this study was to use the EARSS protocols and network to introduce surveillance of the resistance of invasive Gram negative pathogens and to evaluate their resistance and importance, in addition to studying the pathogens traditionally dealt with by EARSS.

Methods

The antimicrobial susceptibility data of invasive (blood and cerebrospinal fluid) non-duplicated isolates of *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella spp., Escherichia coli, S. aureus, S. pneumoniae* and *enterococci* were collected between March and December 2004 at ten Estonian hospitals participating in EARSS. Since these hospitals include all hospitals performing blood cultures, the catchment population is almost all of Estonia's 1.4 million population. Two culture systems were used: Bactec (Becton Dickinson, USA, six hospitals) and Signal System (Oxoid, UK, four hospitals). For background data about the hospitals, number of samples and percentage of positive cultures and their nomenclature (non-duplicated analyses only) was collected from January to December 2004.

Gram negative pathogens were tested for meropenem, ceftazidime, cefepime, ampicillin/sulbactam, piperacillin/tazobactam, amikacin and ciprofloxacin by E-test (AB Biodisk, Solna, Sweden), according to the manufacturer's instructions. In order to determine extended spectrum betalactamase (ESBL) producers, an E test with ceftazidime and ceftazidime combined with clavulanic acid was used. The susceptibility of Gram positive bacteria was established on the basis of EARSS protocols [6].

The study protocol was approved by the ethics committee of the Estonian Institute of Experimental and Clinical Medicine (2004).

Table 1

Spectrum of invasive pathogens isolated in Estonia, January-December 2004

Pathogens (n=1315)	Total	Percentage
Gram negative pathogens	433	33%
E. coli	174	13.2
Enterobacteriaceae	87	6.6
Klebsiella spp.	61	4.6
Gram negative nonfermenters	48	3.7
P. aeruginosa	36	2.7
A. baumannii	27	2
Gram positive pathogens	824	62.7%
CONS	470	35.7
S. aureus	113	8.6
Streptococci	88	6.7
Enterococci	76	6
S. pneumoniae	49	3.7
Gram positive aerobic rods	28	2
Anaerobes	19	1.5
Pathogenic fungi	39	3

Results

Ten hospitals with between 160 and 942 beds (mean 487) and a total of between 48 291 and 272 169 patient days (total 1 297 246) per year participated in the prospective study. The number of collected samples (blood bottles) per 100 patient days varied from 0.1 to 3.2 (median 1.6 per 100 patient days). In total, 19 648 invasive samples were examined and 1315 non-duplicate invasive isolates were isolated from blood and cerebrospinal fluid in 2004 [TABLE 1]. The median proportion of positive samples was 12% (ranges 4.6-16.4%).

The majority were coagulase-negative staphylococci (CONS, 35.7%) followed by E. coli (13.2%) and *S. aureus* (8.6%). Among the Gram negatives, other Enterobacteriaceae accounted for 6.6%, *Klebsiella spp.* 4.6%, other Gram negative non-fermenters 3.7%, *P. aeruginosa* 2.7% and *A. baumannii* 2%. Among the Gram positives, the share of *S. pneumoniae* was 3.7%, the share of enterococci 6% and the share of other streptococci 6.7%.

A subset of 216 Gram negative pathogens were collected during the study period, including 117 *E.coli*, 56 *Klebsiella spp.*, 29 *P. aeruginosa*, and 14 *A. baumannii* strains [TABLE 2]. The isolates of E.coli and Klebsiella spp were susceptible to meropenem and amikacin, resistance to ciprofloxacin was 3% and 11% respectively. The higher resistance to antimicrobials was associated particularly with *A. baumannii* and *P. aeruginosa*. Also, the proportion of ESBL-producing strains was 23% among *Klebsiella spp.* and 3.6% among *E. coli*.

Table 2

$MIC_{50/90}$ values and percentage of susceptibility of *A. baumannii, P. aeruginosa, Klebsiella* spp, and *E.coli* invasive strains isolated in Estonian hospitals, March-December 2004

Antibiotic	Pathogen $MIC_{50/90}$ (% of susceptibility)			
	A. baumannii N=14	*P. aeruginosa* N=29	*Klebsiella* spp. N=56	*E. coli* N=117
Ampicillin sulbactam	4/16 (64)	ND	ND	ND
Piperacillin tazobactam	ND	6/64 (89)	ND	ND
Cefepime	6/16 (71.4)	ND	ND	ND
Ceftazidime	ND	1.5/8 (91.4)	ND	ND
Meropenem	1.5/4 (100)	1/6 (86)	0.032/0.064 (100)	0.023/0.032 (100)
Amikacin	3/256 (78.6)	3/12 (96.6)	2/3 (98)	2/3 (100)
Ciprofloxacin	ND	0.19/6 (83)	0.032/1 (89)	0.016/0.047 (96.7)

Overall antimicrobial resistance among major bloodstream pathogens in Estonia was relatively low in the case of Gram positive indicator pathogens. No penicillin non-susceptible S. pneumoniae were found. The proportion of methicillin-resistant *S. aureus* was 4%, and the proportion of vancomycin non-susceptible enterococci was 1.6% (one strain with MIC value 6 mL).

Discussion

The most frequent invasive pathogens were coagulase-negative staphylococci, *E. coli* and *S. aureus*. Similarly, the five most common pathogens in other European studies were also *E. coli*, *S. aureus*, CONS, enterococci and *Klebsiella spp.* [8,10,11]. In our study, the ratio of Gram positive to Gram negative pathogens was 1.9. According to the data from the literature, Gram negative bacilli were the predominant pathogens in the 1970s; in recent decades, Gram positive cocci, especially CONS, have emerged as a more frequent cause of invasive infections [1-3,18]. The increase in CONS could be attributed to the increasing proportion of neonatal and haematological patients. However, the quantity of

true infections and contamination is impossible to evaluate, since harmonised exclusion algorithms for common skin contaminants are not used in our study or other published studies.

Antimicrobial resistance among Estonian invasive pathogens was relatively low, more closely resembling northern European than southern and eastern European regions [19]. This is especially true in the case of Gram positive pathogens [6-8,10,20]. However, the isolation of the first strains of VRE and the recent increase of MRSA cases in some Estonian hospitals may predict an emergence of resistance [6].

Despite the relatively lower frequency of *A. baumannii* and *P.aeruginosa*, the higher resistance to antimicrobials was particularly associated with these pathogens, and this is similar to the experience of other authors [7-10,12,21]. A comparison of the data from the SENTRY and MYSTIC study with those from Estonia shows some differences in antibiotic choice and study criteria and the limitations of pooling those data. In general, Gram negative invasive isolates from Estonian hospitals were at least as sensitive as the European average [6,8].

The use of invasive strains in resistance surveillance has some advantages. The inclusion criteria are clear, and since colonisation and contamination are excluded (except CONS), these strains are real pathogens, making the data more comparable. Since the number of strains is relatively small, more expensive but also more informative methods, such as MIC detection and typing, can be used. However, different sampling habits between different hospitals and countries may influence the quality of the data [6]. It is also not clear how the resistance of invasive strains represents the overall situation of proportions and trends. Today, few studies with controversial results [13,19,22] are available offering comparative information about the aetiology and susceptibility of both invasive as well as non-invasive pathogens.

It is a common view that resistance surveillance should focus mainly on MRSA and other Gram positive organisms. In our situation, however, where high resistance and therapy failures are frequently associated with Gram negative bacteria (such as Klebsiella, Acinetobacter and Pseudomonas), the inclusion of these pathogens for antimicrobial resistance surveillance provides useful information [6,23].

Thus we can conclude that due to interstate and regional (for example, eastern, central and northern Europe) differences in pathogens' profile and susceptibility pattern, international conventional surveillance systems should be modified according to local situations, and additional diagnostic methods should be included if necessary.

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MEAT INSPECTION FOR *TRICHINELLA* IN PORK, HORSEMEAT AND GAME WITHIN THE EU: AVAILABLE TECHNOLOGY AND ITS PRESENT IMPLEMENTATION

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A new EU directive relating to meat inspection for *Trichinella*, expected to come into force in 2006, imposes important modifications to current legislation. Nevertheless, several issues need more attention. Optimisation of methods, especially concerning sensitivity and digestibility of the meat to be inspected, along with further simplification of the legislation with regard to the number of techniques accepted, is recommended to guarantee that all member states of the EU will be given tools to perform inspection of consumer meat at the same high level. Additionally, there is a need for guidelines and protocols regarding optimal proficiency testing procedures.

This paper presents an overview of the current methods for *Trichinella* meat inspection and their implementation in the EU, listing advantages and disadvantages for each method, including some suggestions for specific points of improvement.

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Introduction

Pork, horsemeat and game may be infected with muscle larvae of the zoonotic nematode *Trichinella*, which can cause severe disease in humans. Consequently, all countries in the EU perform mandatory official inspection of slaughtered animals intended for export to prevent distribution of infected meat to consumers. *Trichinella* infections have worldwide socioeconomic significance, and are of medical and veterinary concern in France, Germany, Italy, and Spain, but foremost in the east and central European countries [1, 2] where human trichinellosis is reported to be a very important zoonosis. Some of the new EU member states (Latvia, Lithuania and Estonia) as well as some candidate countries (Bulgaria, Romania, Turkey and Croatia) have outbreaks every year (reported by the International Commission on Trichinellosis (ICT) [3]. The costs for inspection of pork in the EU is estimated to €570 million annually [1, 4].

All procedures for *Trichinella* inspection are based on direct detection of the parasite larval stages in muscle tissue, initially (from around 1860s) by direct microscopy of compressed muscle tissue, termed trichinoscopy [5.6.7.8.9,10], later (in the 1970s) by pooled digestion of 1 g muscle tissue from up to 100 pigs, which allowed for significant improvements in sensitivity of the inspection test and were less labour intensive, hence allowing larger numbers of animals to be examined.

In the present EU legislation (Directive 77/96/EEC), seven methods are accepted [TABLE 1]: six digestion methods and trichinoscopy. In the anticipated future EU legislation (SANCO/1900/2002 Rev. 8 draft, in force 01-2006), the number of inspection methods has been reduced to four with magnetic stirrer digestion as the reference method to be preferred before three alternative (termed 'equivalent') methods. Trichinoscopy is only allowed as a transitional measure, and meat inspected by this method should be clearly marked. Furthermore, such meat is limited to be sold on the national market and is not acceptable for products where the production process does not kill *Trichinella*. The digestion methods have a theoretical detection limit of down to 1 larva per gram muscle tissue (lpg). However, there are several critical steps, which may compromise the sensitivity of the techniques [11, 12] and many of these are not adequately addressed in the new EU legislation.

Trichinella inspection methods after the present legislation

Below are brief descriptions of the methods allowed for meat inspection according to directive 77/96/EEC, Annex 1, (amended by Council Regulation (EC) No. 807/2003) [TABLE 1], along with some critical points and suggestions for improvements.

Method I: Trichinoscopy

The classical method for detection of *Trichinella* in pork is trichinoscopy (also termed the compressorium technique). Muscle samples from each of the two diaphragm pillars are cut into 7 very small (oat kernel sized) pieces, which are subsequently squeezed between two glass plates and examined under a microscope at 30-40 X magnification for the presence of capsules containing *Trichinella* larvae. The microscopic examination must last at least 3 minutes to ensure adequate time for the finding of larvae. For routine inspection, trichinoscopy is labour intensive, it is not as sensitive as the digestion methods (examines less tissue, 14 oat kernel sized pieces ~0.5 g) and finally does not detect larvae of *T. pseudospiralis* as this species lacks the physical structure (a surrounding collagen capsule) that is detected for other *Trichinella* species 2-4 weeks after infection. Due to the inherent errors of trichinoscopy, this method should no longer be used, hence there are no suggestions for improvements.

Methods II and III: Digestion of single or pooled samples with either no mechanical intervention or manual shaking of digestion fluid

These manual methods allow for artificial digestion of pools of minced meat samples (10 grams from each of 10 pigs (method II) and 1 gram from each of 100 pigs (method III). Any *Trichinella* larvae present in the pooled sample are released into the artificial digestion fluid and settle at the bottom of the beaker. For method II, the digestion fluid is left undisturbed for 18-20 h, whereas for method III the fluid must be shaken twice per hour for 4 h. The sediment from the digest is examined for larvae under a stereomicroscope at 20-40 X magnification. Although the methods work on a pool of samples, they are too time consuming and with the inbuilt risk of dead or young larvae being digested along with the muscle tissue resulting in a false

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negative outcome. Since other pooled digestion methods are superior, methods II and III have been omitted from future legislation.

Methods IV and V: Mechanical digestion (with a stomacher blender) of pooled samples followed by either sedimentation or filtration

The pooled sample (100 x 1 g pieces) and the digestion fluid are mixed in a plastic bag placed in the stomacher chamber where it is mechanically agitated for 25 min at 41°C. The fluid is then passed into a sedimentation funnel through a 177 mm sieve with addition of ice and either left to sediment under 1 minute vibration cycles every second minute for 30 min total (method IV), or poured through a 35 mm filter, which will hold back larvae (method V). Larvae have a tendency to adhere to the plastic bag causing a risk for false negative readings. Thus, the sensitivity of this method is less than the theoretical 1 lpg. Because the pooled sample consists of 1 g pieces, there is a risk of undigested residue after digestion for the recommended time (authors' own observations). For the improvement of these methods, the pooled sample may be subjected to blending or mincing prior to digestion, the initial filtration to retain undigested particles could be done with a larger mesh size (355µm) that allows all larvae to pass (see Method VI below), and finally, the adhesion of larvae to the plastic bag could be lessened by flushing the plastic bag twice.

Method VI: Mechanical digestion of pooled samples with magnetic stirrer

Minced or blended meat samples are placed in the digestion fluid for 30 min at 46-48 C° under constant stirring by the use of a magnetic stirrer, and subsequently poured through a sieve into a sedimentation funnel. After a sedimentation period of 30 min, the sediment is removed from below the funnel, and the volume further reduced through more sedimentation steps. The digestion is more complete with this method because the 1 g meat samples are minced. Improved larval recovery can be obtained by changing the filter size from 177µm (180µm) to 355µm (11; authors' own observations).

Method VII: Mechanical digestion with the Trichomatic35

The Trichomatic35 apparatus blends, digests and filters a maximum of 35 pooled 1 g samples in one short process (5-8 min). Digested material is filtered under high pressure and the resulting filter is examined under a stereomicroscope as above. This method is fast with a high sensitivity [13] but a disadvantage might be that the filter requires extra washing procedures to prevent cross contamination between samples [14]. It is therefore recommended to use a new filter for every sample tested. The Trichomatic35 is no longer on the market and once the existing spare parts have been distributed, no more will be available from the manufacturer.

Future legislation and performance of the future recommended techniques

In the future EU legislation (SANCO/1900/2002 Rev. 8 draft, in force 01-2006), the magnetic stirrer method is identified as the reference method and the two versions of the stomacher method and the Trichomatic35 method may be considered equivalent methods if the magnetic stirrer method is not accessible. For routine inspection, trichinoscopy will only be allowed as a national transitional measure, as it does not detect the non-encapsulating species, *T. pseudospiralis*, or young larvae of encapsulated species with incomplete capsule development. Thus, meat inspected by trichinoscopy cannot be sold to other EU countries or exported out of the EU.

Related to the four digestion methods, which remain in the future legislation, there are inherent critical aspects that compromise the sensitivity of the methods and therefore need to be dealt with. These aspects are, for example, related to washing and sieving procedures, the nature of employed materials (plastic versus glass), incubation times, contamination problems, and the condition of the meat to be inspected [11, 15, 16]. Other problems are related, for example, to the technical equipment failure, enzyme failure, and human errors, which all lead to a lack of compliance with protocols [17], reducing the efficiency of the methods.

Table 1

Methods used for meat inspection for *Trichinella* in pork, horsemeat and wild boar in EU (according to current Directive 77/96/EEC)

Method number according to Directive 77/96EEC - Annex 1	Method	Detection limits according to the Directive (larvae/ g)	Disadvantages	Advantages and practical considerations	PIG Grams of meat to be examined (diaphragm)	HORSE Grams of meat to be examined (tongue or masseter)	WILD BOAR Grams of meat to be examined (diaphragm)
I	Trichinoscopy/ compressorium	3-5	Laborious, low sensitivity Does not detect T. *pseudospiralis*	Rapid method if only few samples	0.5	Not allowed	0.5
II	Digestion (no mechanical intervention)	0.1-0.3	Long digestion time (18-20h). Risk of digestion of dead larvae	Pooled samples Large sample size (10g) increases sensitivity	10	10	10
III	Digestion (twice hourly manual shaking)	1-3	Long digestion time (4h) small sample size (1g)	Pooled samples	1	5	1
IV	Stomacher (constant mechanical treatment) and sedimentation	1-3	Larvae may adhere to plastic bag	Short digestion time (25min)	1	5	1
V	Stomacher (constant mechanical treatment) and filtration	1-3	Larvae may adhere to 2 x plastic bags Lower sensitivity than stated in the EU directive	Short digestion (25min)	1	5	1
VI	Magnetic stirrer (constant mechanical treatment)	1-3	Filter size needs adjustment Lower sensitivity than listed in the EU directive	Short digestion time (30min/100g)	1	5	1
VII	Trichomatic 35 blender	1-3	The device is out of production Maximum 35 samples	Pooled samples, easy manageable, Very short digestion time (5-8min)	1	5	1

At least two published studies have demonstrated that the sensitivity of the recommended methods is lower than stated [11, 12]. Forbes and Gajadhar [18] documented a higher sensitivity of the magnetic stirrer method when compared with trichinoscopy. In early studies forming the basis for recommendation of the stomacher method, larval recovery as low as 79% was reported [9]. A recent comparative testing at the Danish Institute for Food and Veterinary Research (Maddox-Hyttel et al, unpublished data) indicates that the sensitivity of the magnetic stirrer is lower than required by the legislation, and importantly, both the sensitivity and reproducibility of the stomacher methods are considerably lower as compared to the magnetic stirrer method. Thus in the test, the recovery of larvae spiked into ground meat, varied from as little as 34-40% using the stomacher method (V) to an average of 63% (range 18-86%) or 85% (range 74-100%) using the magnetic stirrer method with filter mesh size of 177µm (recommended in the present and future EU legislation) or 355µm (recommended by Gamble [11]), respectively. *Trichinella* larvae from the meat were obviously lost at various steps of the procedures and these steps need to be identified and corrected through optimisation measures to ensure reliable detection methods.

The sensitivity is also related both to the amount of meat and the type of muscle tissue used for inspection [12,19,20,21], and increasing the sample size would improve any detection method [12,18,22]. The detection limit for the artificial digestion is reported to be approximately 1 lpg, if at least 5g of muscle sample per animal is digested [23]. However, according to the legislation, the recommended amount of tissue for pork allows sampling of down to 1g/pig and, as a consequence, the detection may be only 3-5 lpg rather than 1 lpg as stated. The inspection methods are intended to have a detection limit to prevent clinical trichinellosis. There are, however, only estimates [24] and no reliable data on the actual margins of such a limit. Consequently, the detection limit should be as low as possible.

The efficacy of the above digestion tests when used on meat from horses, wild boar, and other animals, is relatively unexplored although important because digestibility varies considerably both between muscle types and animal species. Some muscle groups from horses are readily digested within 30 min (diaphragm, tenderloin, fillet, and rump), whereas others need up to 2-3 times as long (masseter, tongue and leg muscles) [25].

Table 2

Available information on meat inspection (pork) for *Trichinella* in EU: No. of national / local laboratories using the different direct detection methods

Country	*Trichinella* meat inspection level in the country	Approximate number of pigs inspected	I	II	III	IV / V	VI	VII
Austria		5.3 million	1885	37	5	3	56	
Belgium	Majority of meat produced	10.4 million					+	
Czech Republic				2	5	16	20	
Cyprus		357 633	1				4	
Denmark	All for export	23 million (99% of total slaughtered)				10	21	
Estonia	100%	430 509	78			1	5	
Finland	100%	2.2 million	67		2		30	
France	1.1%*	271 100					+	+
Germany	100%	43.3 million	+				+	+
Greece	25%	431 000	93	2	4			
Hungary			+		+		+	
Ireland	All for export	1.3 million (~50% of total slaughtered)					9	
Italy	50%	11 million	+				+	+
Latvia	100%	419 105	65				12	
Lithuania	100%	1.0 million	+				+	
Luxembourg		390						
Malta								
Poland		13 million	+				+	
Portugal	100%		9				12	
Slovakia	100%	1.1 million	+				+	
Slovenia	100%	440 385	11				18	
Spain		33.5 million	1122		1	18	268	10
Sweden	100%	3.4 million	14			1	21	1
The Netherlands	100%	13.9 million					7	
United Kingdom	13%	1.2 million				5	9	

Official numbers and information primarily provided via DG SANCO (R Dwinger) from 2002, 2003 or 2004. Additional information has been provided by participants in the TrichiNet network. For countries with only blank fields under methods and/or blank fields in the first two columns; information has not been provided

I: Trichinoscopy (compressorium)

II: Digestion (single samples)

III: Digestion (pooled samples)

IV or V: Stomacher (sedimentation or filtration)

VI: Magnetic stirrer

VII: Trichomatic35

+: the sign + is employed where the method is in use in the country concerned but the number of laboratories is not available

* Due to demands from import countries, France has begun annually routine examination of several millions of pigs

These requirements for longer digestion time according to muscle type of different hosts have not been addressed in the new legislation and hence, the recommended digestion times may lead to an incomplete digestion of several grams of tissue, depending on the choice of muscle. Consequently, it is imperative that the sensitivity of each method should be listed in detail for different muscle types and animal species.

Thorough comparison of the efficiency of the recommended detection methods (excluding the Trichomatic35, which is no longer produced) is therefore required and the future legislation should include a revised description with correct sensitivity and reproducibility of each muscle type from target animal species. Furthermore, guidelines for proficiency testing are urgently needed to ensure optimal test accuracy and quality of inspection. A recent ring trial among 33 laboratories in Germany [16] only emphasises this need; half the laboratories participating detected false negative or false positive results in between one and six of 10 examined samples. Meat samples for the trial, were prepared as duplicate samples containing between 8 and 71 *T. spiralis* larvae per gram of meat (that is,. a high infection level), or without any larvae (negative controls), and were examined using the magnetic stirrer method. The draft of the future legislation (SANCO/1900/2002 Rev. 8 draft, in force 01-2006) states that the competent authority should ensure that all personnel, who are involved in the examination of samples to detect *Trichinella*, are properly trained, participating in proficiency testing programs and in a regular assessment of the sensitivity and the specificity of the test involved. However, hitherto no protocols or guidelines have been formulated for uniform proficiency testing and quality assurance systems in the EU.

Level of implementation of direct detection techniques in EU

Tables 2, 3 and 4 aim to provide an overview of the rather heterogeneous implementation levels of *Trichinella* inspection in the EU member states. Especially for horsemeat and wild boar meat, data are scarce due to the lack of registration within several countries. Although meat inspection for *Trichinella* is mandatory in the EU, registration and reporting of the number of animals inspected and the methods by which inspection was performed is not required. Comparing the available data on the present inspection methods for a range of EU countries, it is evident that many countries do not have optimal *Trichinella* control. Most countries and laboratories have implemented the magnetic stirrer method at the large slaughterhouses, however all seven methods are reported to be in function in several EU countries and according to the personal experience of the authors, even at the national level, there can be as many variations of the techniques as there are laboratories.

Table 3

Available information on horsemeat inspection for *Trichinella* in EU: No. of national / local laboratories using the different direct detection methods

Country	*Trichinella* meat inspection level in the country	Approximate number of horses inspected	I	II	III	IV / V	VI	VII
Austria		1106						
Belgium		15 628					+	
Czech Republic			1		2	8	9	
Cyprus			1					
Denmark	All for export	1278				1	3	
Estonia		11	+			+	+	
Finland		1323					10	
France	100%	23 623					71	1
Germany	100%	11 295					+	+
Greece								
Hungary			+				+	
Ireland	100%						9	
Italy	100%	50 000					+	+
Latvia	100%							
Lithuania	100%					+	+	
Luxembourg		22						
Malta								
Poland								
Portugal	100%						+	
Slovakia	100%	0-50	+				+	
Slovenia		1415	9				13	
Spain			17	1		6	35	
Sweden	100%	5032					~10	
The Netherlands	100%	2395					7	
United Kingdom						2	2	

Official numbers and information primarily provided via DG SANCO (R Dwinger) from 2002, 2003 or 2004. Additional information has been provided by participants in the TrichiNet network. For countries with only blank fields under methods and/or blank fields in the first two columns; information has not been provided

I: Trichinoscopy (compressorium)

II: Digestion (single samples)

III: Digestion (pooled samples)

IV or V: Stomacher (sedimentation or filtration)

VI: Magnetic stirrer

VII: Trichomatic35

+: The + sign is employed where the method is in use in the country concerned but the number of laboratories is not available

Table 4

Available information on wild boar meat inspection for *Trichinella* in EU: No. of national / local laboratories using the different direct detection methods

Country	*Trichinella* meat inspection level in the country	Approximate number of wild boars inspected	I	II	III	IV / V	VI	VII
Austria								
Belgium		8834					+	
Czech Republic			2		3	4	7	
Cyprus			1					
Denmark	All for export	1141				2	1	
Estonia			+			+	+	
Finland		1221	12				5	
France	1.4%	5000	+				+	+
Germany	100%	370 187	+				+	+
Greece								
Hungary			+				+	
Ireland	-	None	-	-	-	-	-	-
Italy		35 000	+				+	+
Latvia			+				+	
Lithuania	100%	9000	+			+	+	
Luxembourg		1185						
Malta								
Poland	100%	68 000	+				+	
Portugal		2					+	
Slovakia	100%	15 063					+	
Slovenia		2598-3960	11				4	
Spain			567		1		73	4
Sweden	All for the market	6000-7000 (50% of total)	(+)				+	
The Netherlands		1013					7	
United Kingdom								

Official numbers and information primarily provided via DG SANCO (R Dwinger) from 2002, 2003 or 2004. Additional information has been provided by participants in the TrichiNet network. For countries with only blank fields under methods and/or blank fields in the first two columns; information has not been provided

I: Trichinoscopy (compressorium)

II: Digestion (single samples)

III: Digestion (pooled samples)

IV or V: Stomacher (sedimentation or filtration)

VI: Magnetic stirrer

VII: Trichomatic35

+: The + sign is employed where the method is in use in the country concerned but the number of laboratories is not available

Furthermore, a surprisingly large number of countries still use trichinoscopy and although it is likely that the method is primarily applied to detect *Trichinella* larvae in muscles from wildlife or from a limited number of domestic pigs (single animal examination), the use of this technique represents a major problem. Because of the low sensitivity and inability to detect of *T. pseudospiralis*, this method should be abolished as soon as possible.

Conclusions

In conclusion, there are several indications that the sensitivity of the recommended methods - used in their present form - is effectively lower and more variable than stated in the present legislation and accordingly also in the new EU Commission legislation draft for the future meat inspection procedures. Despite the fact that the new legislation draft requires quality control on the actual procedures, and calls for proficiency testing of *Trichinella* control laboratories, there are presently no guidelines for proper and uniform proficiency testing of the recommended direct detection methods. Thus, the future challenge is to develop and implement a meat inspection system, which is more complete, comprising a fully optimised gold standard method for *Trichinella* detection with reliable sensitivity and in addition provide guidelines for a quality assurance system to ensure uniform meat inspection within the EU. This will ensure a high quality of food and food safety for the consumers, and reinforce export opportunities.

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ORIGINAL ARTICLES

Outbreak report

FIRST GENERAL OUTBREAK OF VEROCYTOTOXIN-PRODUCING *ESCHERICHIA COLI* O157 IN DENMARK

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This report describes the first general outbreak of verocytotoxin-producing *E. coli* (VTEC) in Denmark. Twenty five patients, 18 children and seven adults, with culture-confirmed VTEC O157:H- infection and indistinguishable pulsed-field gel electrophoresis DNA profiles, were identified during a six month period from September 2003 to March 2004. The outbreak strain possessed the virulence genes: *eae*, *vtx*1 and *vtx*2c. All patients but one presented with diarrhoea; none developed haemolytic uraemic syndrome. The outbreak was restricted to Copenhagen and surrounding areas. A case-control study including 11 cases and 55 matched controls revealed an association between VTEC O157:H- infection and shopping in a specific supermarket chain in Copenhagen and surrounding area, matched odds ratio (OR): 8.7 (95% confidence interval (CI): 1.1-71). After exclusion of three assumed secondary cases, only consumption of a particular kind of organic milk from a small dairy was associated with disease OR: 8.7 (95% CI 1.6-48). Environmental and microbiological investigations at the suspected dairy did not confirm the presence of the outbreak strain, but the outbreak stopped once the dairy was closed and thoroughly cleaned.

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Key words: *Escherichia coli* O157; VTEC; outbreak; milk; diarrhoea; Denmark

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Introduction

Verocytotoxin-producing *Escherichia coli* (VTEC) is an important cause of gastroenteritis, in particular in industrialised countries [1,2]. In recent decades, VTEC has caused a number of outbreaks affecting large numbers of people [3,8], including outbreaks associated with both pasteurised and unpasteurised milk [9,12].

VTEC is mandatorily reportable in Denmark both through laboratory based surveillance and clinical notifications from the treating physician. Based on laboratory reports, the incidence has increased from 1.0 per 100 000 population in 1999 (53 cases), to 3.1 per 100 000 in 2004 (168 cases) [13,15]. This trend is most likely due to an increased number of stool specimens examined for diarrhoeagenic *E. coli*, including VTEC. General outbreaks of VTEC gastroenteritis have not previously been seen in Denmark; only sporadic cases or small family clusters of infection have been detected [13].

In late 2003, the Danish VTEC reference laboratory at Statens Serum Institut observed that seven isolates of VTEC O157:H- had identical patterns as judged by pulsed-field gel electrophoresis. The samples were received over a period of four months. In January and February 2004, seven additional isolates were detected, and we initiated an investigation of this first general outbreak of VTEC infection in Denmark. The objectives of the investigation were to characterise the outbreak and, if possible, determine the vehicle.

Methods

Diagnostics and surveillance

Diagnostics for VTEC infection are carried out either at the Unit of Gastrointestinal Infections (UGI), Statens Serum Institut (SSI), or at regional clinical microbiology laboratories (CMLs). UGI receives stool samples for diagnostics of VTEC and other bacterial enteropathogens as well as VTEC strains isolated at CMLs. Examination for diarrhoeagenic *E. coli* at UGI was performed by plating on SSI enteric medium [16] followed by a multiplex PCR determining the presence of the following virulence genes: Genes encoding for verocytotoxin (*vtx*1 and *vtx*2), the toxins of enterotoxigenic *E. coli* (*elt*, *estA*), intimin (*eae*), a marker of enteroinvasive *E. coli* (*ipaH*), and with 16S rDNA serving as a positive control. All VTEC isolates were thoroughly characterised with determination of virulence factors [17,18] and DNA-profiles by pulsed-field gel electrophoresis (PFGE) typing [19]. O:H serotyping was performed according to the methods described by Ørskov and Ørskov, using SSI diagnostic antisera [20]. Selected strains were phage typed at the Laboratory of Enteric Pathogens at the Health Protection Agency Centre for Infections, United Kingdom (21).

Case-control study

We conducted a case-control study from 17 to 25 March 2004. Cases were defined as patients with a laboratory confirmed VTEC O157:H- infection of the PFGE outbreak-type, diagnosed after 15 January 2004. Based on hypothesis-generating interviews, a six page case-control questionnaire was prepared. It included questions on clinical and demographic data as well as exposure variables, e.g., contact with animals, shopping preferences, consumption of organic foods, meat and meat products (including sausages), juice, fresh produce, dried fruits, and dairy products. Controls selected from the Danish population registry were matched to patients by date of birth, sex, and post code of residence but were otherwise randomly chosen. Participants were interviewed by telephone. The period under study was the week before symptom onset for cases and the week before interview for controls. Controls were excluded if they had experienced diarrhoea during the study period. Six controls per case were interviewed. Data were analysed by conditional logistic regression using Statistical Analysis System (SAS) version 8.2; matched odds ratio (OR) and 95% confidence intervals were calculated.

Environmental investigations

Regional food control officers carried out environmental investigations at a dairy where a suspected food item had been processed. The investigations included inspection of the production site, review of all log books, and collection of samples (raw milk, pasteurisation unit, processing system, packed milk and sewage drains). All samples were examined for VTEC O157 by the standard methods recommended by the Nordisk Metodikkomité for Næringsmidler (Nordic Committee on Food Analysis, http://www.nmkl.org).

Results

Characterisation of the outbreak strain

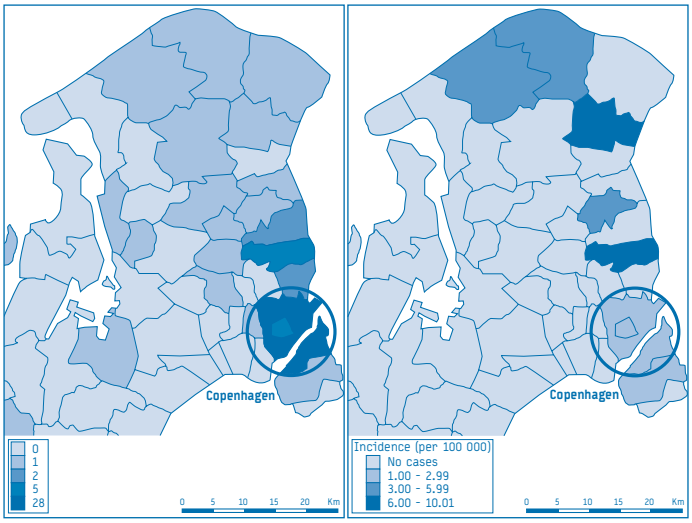
Between September 2003 to March 2004, 25 strains of VTEC O157:H- were isolated. All strains had a unique PFGE type and the virulence profile: *eae*, *vtx*1 and *vtx*2c. Three strains were selected for phage typing and found to be phage type 8.

Descriptive epidemiology

Geographically, patients were restricted to Copenhagen and its northern suburbs [FIGURE 1]. Among the 25 patients [FIGURE 2], the sex ratio (female/male) was 19/6. In total, 18 were children aged 1-7 years and seven were adults aged 36-60 years. Person-to-person transmission could not be excluded in some patients; three families had two patients each and two daycare institutions had two and three patients, respectively. All patients experienced relatively mild illness; the predominant symptoms were diarrhoea and abdominal cramps, and at least five had bloody diarrhoea. Two patients were admitted to hospital, but none developed haemolytic uraemic syndrome.

FIGURE 1

Distribution of VTEC O157:H- infections in Denmark, September 2003-March 2004



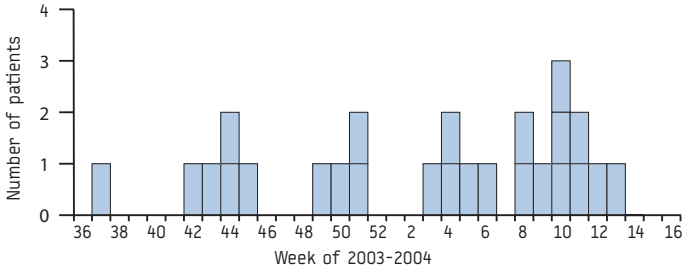
Supermarket chain A branches by municipality or county

VTEC O157 incidence by municipality or county*

* There were 13 patients in the municipality of Copenhagen (shown within the circle). In counties where cases occurred, there were between one and four patients.

FIGURE 2

Number of VTEC O157:H- cases with identical PFGE pattern per week of onset, n=25. Denmark, September 2003 to March 2004



Initial interviews and a descriptive epidemiological assessment showed that the infections were acquired domestically and that the patients shared no common exposures such as visits to restaurants, shops, recreational facilities or farms. Of 12 patients, 8 had bought food at supermarket chain A and 11 at chain B, although from different shops.

Case-control study

Eleven cases and 55 controls were included in the study. Ten patients reported buying food at supermarket A, matched odds ratio (OR): 8.7 (95% confidence intervals (CI): 1.1-71) and nine at supermarket B, OR: 0.99 (95% CI: 0.2-5.5). Organic milk from dairy X was the only food item found to be consistently associated with an increased risk. In an initial analysis including all case-control sets, the OR was 3.6 (95% CI: 0.9-14). However, three of the 11 cases were possible secondary cases (from kindergartens) and when these were excluded, five out of eight cases reported drinking milk from dairy X bought in supermarket A, in comparison with five of 39 control persons, OR: 8.7 (95% CI: 1.6-48). Initial hypotheses concerning beef sausage, other kinds of sausage, beef, green pepper and grapes could not be verified in the analysis. Consumption of beef sausage from a particular company was associated with an increased risk, OR: 8.5 (95% CI: 0.8-90), but only three patients had consumed sausage from this company, and they had each eaten a different type of sausage . Among seven cases and 14 controls who reported shopping exclusively at supermarket A, milk from dairy X was the only product that tended to be associated with an increased risk of illness OR: 6.6 (95% CI: 0.7-61). After completion of the case-control study, all patients were

interviewed about milk consumption and 13 of 22 patients reported drinking milk from dairy X. All of the patients during the outbreak period lived in municipalities served by supermarket chain A, which only operates in and around Copenhagen [FIGURE 1].

Environmental investigations and control measures

Dairy X is an independent dairy that produces approximately 80 000 litres of organic milk each week, and also produces a range of other organic dairy products. Based on the suspicion that milk from dairy X was a likely vehicle, the milk was recalled and dairy X temporarily closed on 25 March 2004. A careful inspection at the premises did not reveal any major deficiencies. According to the dairy's records, all alkaline phosphatase tests were negative. Finally, neither environmental investigations nor analyses of 42 samples of raw milk revealed any VTEC O157 strains.

Discussion

The case-control analysis clearly indicated that buying foodstuffs in supermarket A was associated with an increased risk of illness due to VTEC O157:H- infection, whereas other supermarkets and shops were not. Organic milk from dairy X was the only food item found to be associated with an increased risk.

Dairy X produces organic milk that is distributed to several parts of Denmark. One of the most popular products, however, is milk from Jersey cows, which was only distributed through supermarket A. Jersey milk is characterised by higher viscosity, protein and fat content than milk from red and black/white dairy cattle. The production of organic Jersey milk differs from the normal procedures for pasteurisation of milk, because the whole raw milk is pasteurised prior to fractioning. The Jersey milk from dairy X originated exclusively from about 15 herds of Jersey cows. From 1 September 2003 until 30 March 2004 a total of 1.25 million litre cartons of Jersey milk were sold from supermarket A, and 41% of these were sold in the Copenhagen municipality (central Copenhagen), where 52% of registered cases lived, equivalent to an attack-rate of 2 cases per 100 000 litres of milk. We therefore assume that the outbreak was caused by low-degree contaminated Jersey milk from dairy X distributed in a specific supermarket chain in Copenhagen and the municipalities north of Copenhagen.

The outbreak strain possessed the *vtx*1, *vtx*2c, and the *eae* genes. Though the PFGE profile of the outbreak-strain was rare, the specific combination of the *vtx*1 and *vtx*2c genes is common in *E. coli* O157 strains isolated from Danish cattle. Furthermore, phage type 8 is among the four most common phage types in bovine VTEC O157 isolates obtained in Denmark during the period 1994-2001 [17]. The presence of the variant *vtx*2c rather than the variant *vtx*2 could be the reason for the relatively mild symptoms experienced by most patients in this outbreak [22,23]. It has been suggested that *vtx*2c strains produce lower amounts of verocytotoxin than *vtx*2 strains [22].

Investigations at the dairy did not reveal faults in the production process that could explain the outbreak, and the results of alkaline phosphatase test (which demonstrates whether the mammalian phosphatase enzyme present in raw milk is inactivated by pasteurisation) were negative. No VTEC strains were recovered from pooled raw milk samples or from environmental samples taken at the dairy. However, sampling from individual cows in the herds, which was not carried out, might have yielded useful results. For example, in an outbreak of VTEC O157 phage type 21/28 associated with pasteurised milk, no positive samples were obtained from the milk at the time of the outbreak. However, several calf pen samples and samples from slurry were positive; these strains were indistinguishable from the outbreak strain [11]. In the outbreak reported here, it was decided that such extensive examinations were not necessary, and so microbiological confirmation of the source of the outbreak was not obtained. It is likely that the present outbreak was due to a limited environmental contamination of the Jersey milk after pasteurisation, or to intermittent inadequate heat treatment due to the specific properties of the milk, but these possible hypotheses remain speculative. The outbreak ended when interventions were carried out at the dairy.

The outbreak was detected through the national laboratory surveillance, thanks to the ongoing molecular typing of isolates. Descriptive and analytical epidemiological evidence indicated that the outbreak was caused by Jersey milk from a specific organic dairy, which was contaminated with VTEC O157 at a very low level and distributed through a specific supermarket chain, although this was not confirmed microbiologically. If feasible, we recommend that in future outbreaks, bacteriological examinations be extended to include dairy cattle, to improve the likelihood of microbiological confirmation of suspected milkborne outbreaks. The specific pasteurisation procedures of Jersey milk, or post-pasteurisation contamination, may have been critical factors for the outbreak.

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ORIGINAL ARTICLES

Outbreak report

AN OUTBREAK OF AIRBORNE TULARAEMIA IN FRANCE, AUGUST 2004

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Fifteen tularaemia cases were identified after a holiday spent at a converted mill in the Vendée region in France, between 9 and 12 August 2004.

The mill was visited, and descriptive, retrospective cohort and environmental investigations were conducted. The 39 people who had stayed at the mill between 24 July and 11 August were asked about symptoms, exposure to food and animals, and leisure activities.

A case was defined as a person with evidence of fever and a positive serology (seroconversion or significant rise in antibody titre, or a single titre) ≥ 40. Culture for *Francisella tularensis* and polymerase chain reaction (PCR) diagnosis was carried out for drinking water, firewood, and domestic animals at the mill.

Fifteen cases of tularaemia (38%) were confirmed. Twelve of the cases (80%) had the pulmonary form. None of the patients was admitted to hospital.

There was a strong association between infection and participation in a dinner at the mill on 4 August ($p<10^{-8}$). One of the three dogs present in the dining room was serologically positive for *F. tularensis*.

Results of analysis of environmental samples were negative.

These investigations confirmed the occurrence of a cluster of 15 tularaemia cases, in patients who were infected on the evening of 4 August, in a mill in Vendée, an endemic area for tularaemia. The investigations highlight the existence of nonspecific and benign pulmonary forms of the illness in France.

The pulmonary form of infection in the human cases and the positive serology of the dog suggest contamination by inhalation of contaminated particles from the dog's fur disseminated by the dog shaking itself.

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Key words: France, investigation, outbreak, pulmonary infection, tularaemia

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Introduction

Tularaemia is a bacterial zoonosis caused by *Francisella tularensis* [1]. Humans may become infected through bites from infected ticks or other insects, contact with infected animals or contaminated animal products, consumption of vegetables, water or earth contaminated by the faeces or corpses of infected animals, or inhalation of aerosolised bacteria. The median incubation period for the disease is 3 to 5 days (range: 1 to 14 days) [2]. The clinical form of tularaemia depends on the route of entry of the bacterium into the body: ulceroglandular tularaemia is involved if transmission is transcutaneous; pulmonary and typhoidal tularaemia if caused by inhalation; oropharyngeal tularaemia if by ingestion.

On 21 August 2004 a general practitioner informed the local Direction Départementale des Affaires Sanitaires et Sociales (Departmental Health and Social Services Division, Ddass) of 15 cases of flu-like infections in patients who had spent 4 August 2004 at a mill that had been converted into a home in Vendée, western France. On 8 September, blood tests confirmed the diagnosis of tularaemia for 3 of the 15 patients.

Because of the similarity of symptoms in the other 12 patients who had been at the same place on the same date, a diagnosis of tularaemia, and a common source of contamination were suspected for the whole group. Epidemiological and environmental investigations were performed to confirm the diagnosis and identify the source of contamination and the mode(s) of transmission with a view to taking appropriate outbreak control measures.

Methods

Epidemiological investigation

This investigation included a visit to the mill, a descriptive investigation of the cases and a retrospective cohort study of all the subjects who stayed at the mill from 24 July to 11 August 2004.

A site visit was conducted to describe the house and its surroundings, and to interview the owners in order to establish a list of animals and humans who were present during the period under study and retrace their activities during that time, particularly on 4 August.

A case was defined as any patient with fever and a positive blood test (agglutination): either a seroconversion, or a significant increase in antibody titres, or a single titer greater than or equal to 40. The blood tests for all the patients were performed by the national reference centre for tularaemia.

The clinical forms were classified as pulmonary tularaemia (minimum of one respiratory symptom or abnormalities on the chest x ray picture) and typhoidal tularaemia based on clinical and biological information collected from the physician.

The subjects included in the cohort were questioned using a standardised questionnaire about their symptoms and possible exposure to *F. tularensis* (contact with animals, water and soil, possible food exposure and leisure activities) during the 15 days before onset of symptoms for infected subjects and from 26 July to 10 August for uninfected subjects.

The strength of the association between the disease and the exposure was measured by calculating the odds ratio and the 95% confidence interval, using *Epi Info* 6fr.

A logistic regression including the variables significantly associated at a level of p=0.1 in a univariate analysis and those considered the most biologically plausible was performed using *Stata*.

Environmental investigation

The presence of *F. tularensis* was investigated by culture and PCR in suspected sources of the contamination, based on samples of the tank water, mud and fragments of bone from a small mammal collected from the bottom of the tank, and firewood piled close to the house.

Veterinary investigation

The presence of *F. tularensis* was investigated by culture and PCR of cloacal swabs from ducks at the mill and blood samples from the owners' dogs. The dogs' blood specimens were sampled for specific antibodies.

The SAGIR network, in charge of French national wildlife health monitoring, was questioned regarding the possible presence of animal corpses contaminated by tularaemia in Vendée.

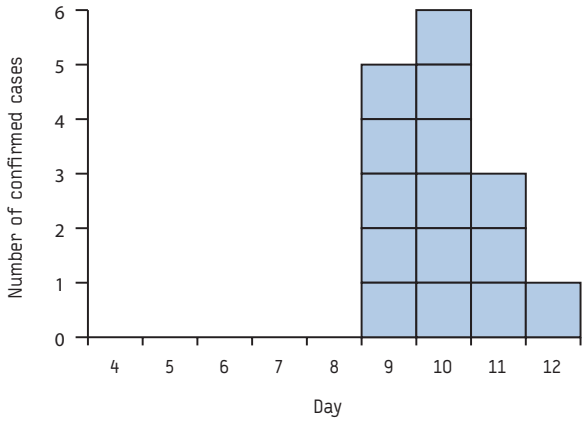
Results

Description of patients

The patients included 10 adults and 5 children, with a median age of 39 years [range: 6 to 49 years]; the male/female ratio was 1,1. The cases were grouped, and occurred between 9 and 12 August 2004, suggesting a single point of contamination [FIGURE 1].

FIGURE 1

Confirmed cases by date of symptom onset, tularemia outbreak, Vendée region, France, August 2004



Clinical presentation

The median duration of the symptoms was 6 days [range: 2 to 13 days]. All subjects experienced fever and headaches. Other signs were: asthenia (93%), myalgia (80%), arthralgia (73%) and respiratory symptoms (73%). Six of 11 chest x ray pictures were abnormal (four pneumonias, two pleural effusions). Twelve patients presented with pulmonary clinical symptoms, and three with typhoidal symptoms. None of the patients was admitted to hospital. The outcome for all patients was favourable, whether or not antibiotic treatment was prescribed. Seroconversion over a minimum of 10 days was documented in three cases, a significant elevation of antibody titre in 11 cases, and an elevated single titre in one case. The median duration of incubation was 7 days [range: 5 to 8 days].

Description on August 4, 2004

The mill had been renovated into a comfortable home and was supplied with water from a tank. On 4 August, 19 subjects, including the 15 patients, and domestic animals (five ducks, one donkey, one sheep, eight cats and three dogs) were present [FIGURE 2]. The four subjects who did not become ill had spent the day upstairs in the house and left before 7 pm. Four of the patients had handled firewood in the mill's woodpile, carrying it through the ground floor of the mill. Fifteen people attended dinner between 8 pm and midnight in a room on the ground floor where dogs were also present.

Cohort investigation

Thirty nine subjects, including 24 asymptomatic people, were included in the cohort. The incidence rate (IR) was 38%. Being at the mill during dinner on 4 August 2004 was strongly associated with contracting the disease (IR = 100%; $p < 10^{-8}$). Patients who developed disease were all exposed to bread or pizza cooked in the bread oven at the mill (IR = 60%; $p=4 \times 10^{-4}$) and to water from the tank at the mill (IR = 52% ; $p=6 \times 10^{-3}$).

Environmental and veterinary investigation

The analyses performed on environmental specimens and on domestic animals were negative for *F. tularensis*. One dog tested positive (titre 1:160). During the study, the SAGIR network did not identify any contaminated wild animal corpses.

Discussion

These investigations confirmed the occurrence of 15 grouped cases of tularaemia. It was shown that the contamination took place in a mill in Vendée on the evening of 4 August 2004 [3].

The pulmonary clinical form suggests contamination via aerosolised bacteria. This could be explained by dust particles suspended in the air while firewood was carried through the ground floor in the afternoon, or by contaminated particles present in dog fur. Dogs may carry bacteria in their fur after contact with an infected animal or contaminated environment [4,5,6]; bacteria are then disseminated when the dog shakes itself. The mill is located in an area where tularaemia is endemic [7]; one dog tested positive for previous contact with *F. tularensis*. This type of contamination has been described during a similar episode in the United States in 1978 [5,6].

All samples were analysed by PCR. The negative PCR test results can be explained by late performance of testing, since *F. tularensis* does not survive more than several days in animal bodies [8].

In France cases of tularaemia are notified sporadically, and modes of transmission include contact with wild game and tick bites [8]. Two thirds of the cases are ulceroglandular; the pulmonary form is unusual [1]. Additionally, the pulmonary form, as described in other countries, is usually severe [2,9,10].

This incident has demonstrated that a pulmonary form of tularaemia exists in France; given the uncharacteristically mild form of the disease, and in the absence of specific clinical symptoms, the diagnosis may often be missed.

Recommendations

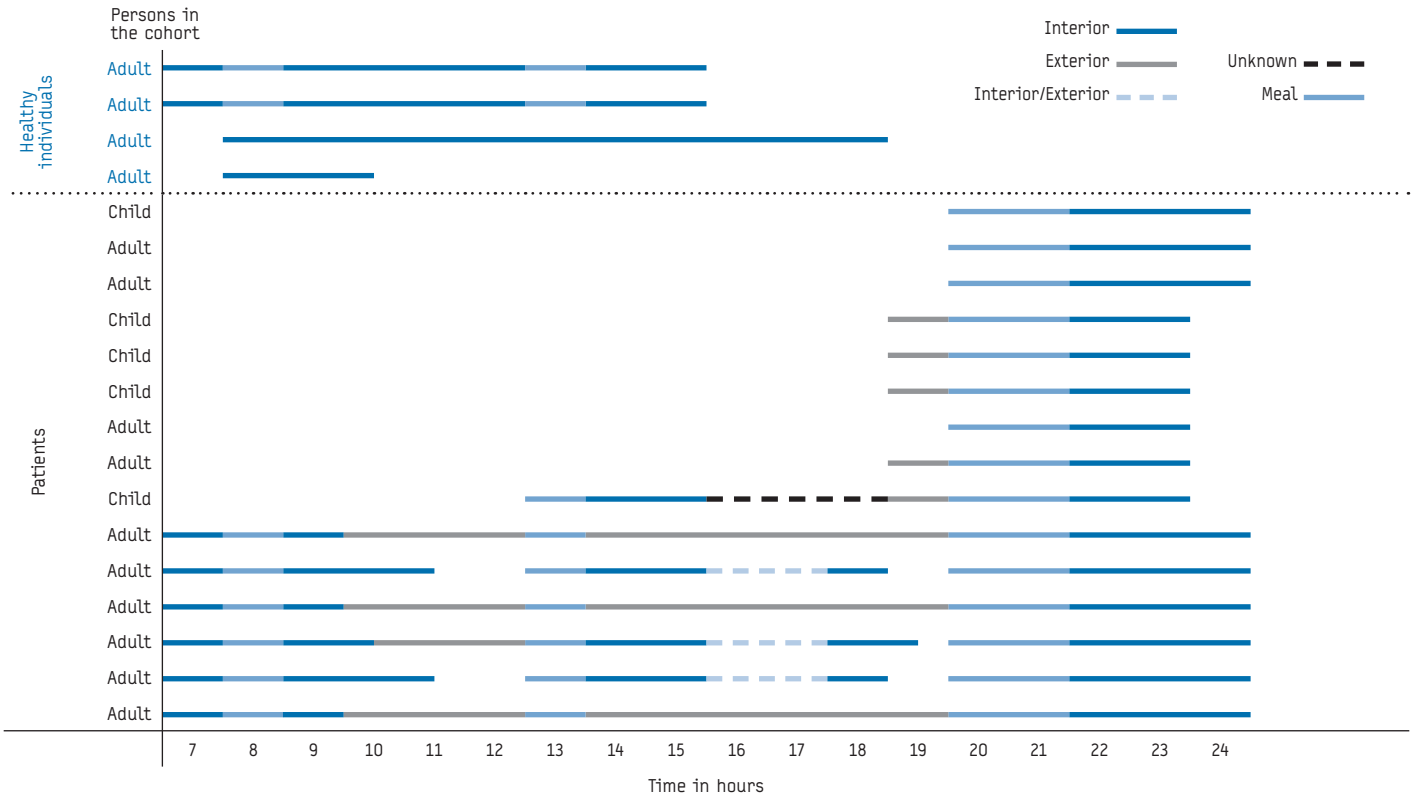
Tularaemia should be considered in cases of pneumonia of unexplained origin, especially if risk from exposure has been reported.

The mandatory reports required when a unusual phenomenon such as tularaemia cases is observed must be submitted to health authorities urgently to facilitate investigation and expedite rapid action. The transmission of *F. tularensis* by inhalation may be prevented by wearing protective equipment (goggles, gloves, masks), mainly used by professionals (gardener, farmer etc...).

Basic hygiene measures can help prevent transmission of the disease from pets, for example, washing pets (avoid splashing) before they enter the house if they have been rolling in mud or have been in contact with dead animals. Thorough handwashing is recommended for all people after contact with any animals, including pets.

FIGURE 2

Periods of meals and exposure inside and outside the mill for 19 subjects present at the mill on 4 August, tularaemia cluster, Vendée region, France, 2004



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EMERGING *SALMONELLA* ENTERITIDIS ANAEROGENIC PHAGE TYPE 14B: OUTBREAK IN NORWEGIAN, SWEDISH AND FINNISH TRAVELLERS RETURNING FROM GREECE

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In July 2001, the Norwegian Institute of Public Health (Folkehelseinstituttet, FHI) reported a cluster of *Salmonella* Enteritidis of phage type 14b infections in Norwegian travellers returning from Greece. An increase in the same uncommon phage type was also registered in Sweden and Finland at the same time. Cases of *S.* Enteritidis PT 14b in patients returning from Greece were reported in these three Nordic countries in 2001 (303 cases), 2002 (164 cases) and 2003 (199 cases). Case-control studies performed in 2001 in Norway and Sweden indicated that consumption of chicken was associated with illness. In 2002 and 2003, continuing case reports indicated that this uncommon phage type had probably become established in the Greek food chain. Tour operators were informed and contacts were made with Greek public health authorities. Because place of infection is not systematically included in most *Salmonella* notification systems, the *S.* Enteritidis phage type 14b outbreak reported here may represent only part of a larger outbreak among travellers visiting Greece. Infections are often reported only in the tourists' home countries and public health authorities in the tourist destinations may not be aware of the problem. Further collaboration between national institutes of public health in Europe is needed to detect outbreaks occurring among tourists.

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Introduction

Salmonellosis is a disease of considerable clinical and public health importance. In the 1980s, public health authorities in Europe and America noted a considerable increase in human foodborne illnesses caused by *Salmonella enterica* serovar Enteritidis [1,2]. This increase was caused predominantly by strains of phage type (PT) 4 in Europe, and PT 8 and 13 in the United States and Canada [3]. Epidemiological and environmental studies have most commonly implicated eggs and poultry products as risk factors for these infections [4-6].

In July 2001, the Norwegian Institute of Public Health (Folkehelseinstituttet, FHI) had received an unusually high number of notifications of *S.* Enteritidis infections in Norwegian travellers returning from Greece [7]. The national reference laboratory for enteropathogens at NIPH noticed a cluster of cases infected with atypical *S.* Enteritidis. Unusually, all the strains isolated from these patients were anaerogenic (*S.* Enteritidis PT 14b). The Swedish Institute for Infectious Disease Control (Smittskyddsinstitutet, SMI) and the National Institute of Public Health in Finland (Kansanterveyslaitos, KTL) also noticed an increase in the number of *S.* Enteritidis PT 14b infections in travellers returning from Greece in the same time period.

Here we describe the detection of an emerging *S.* Enteritidis subtype using surveillance data from travellers. To obtain an overview of the epidemiological setting, we calculated an annual risk per 100 000 travellers of *S.* Enteritidis reported in Norway, Sweden and Finland in travellers to Greece, from 1997 to 2003. During the outbreak in 2001, we performed two focused case-control studies among Norwegian and Swedish travellers to Crete, the most frequently visited tourist destination, to identify potential outbreak vehicles. Combined, these two approaches describe the impact and potential sources of infection of the largest outbreak of *S.* Enteritidis PT 14b reported in the literature.

Materials and methods

Surveillance system

Salmonella infection is mandatorily reportable to national communicable diseases surveillance systems in Norway, Sweden and Finland, and isolates from local laboratories are routinely forwarded to national reference laboratories (NRL). In Sweden and Finland, all *Salmonella* Enteritidis are phage typed, while in Norway, phage typing is performed on selected strains only when considered necessary for epidemiological reasons.

Analytical study design

Descriptive analysis 1997 – 2003

Surveillance data were compiled from Norway, Sweden and Finland of *Salmonella* infections reported to be acquired after travelling to Greece within the incubation period for *Salmonella* for the period January 1997 and December 2003.

We calculated an annual risk per 100 000 travellers of *S.* Enteritidis and *S.* Enteritidis PT 14b or anaerogenic *S.* Enteritidis infections associated with a travel to Greece and reported in Norway, Sweden and Finland, from 1997 to 2003. For the denominator, data on the number of travellers to Greece from Norway, Sweden and Finland were collected through the national civil aviation in Norway [8], Sweden [9] and Finland [10]. Numerator data consisted of all cases meeting the following case definition.

A case was defined as a human infection notified in Norway, Sweden or Finland with a microbiologically confirmed finding of *Salmonella* Enteritidis after travel to Greece within the incubation period for salmonellosis, with symptom date between 1 January 1997 and 31 December 2002.

Epidemiological investigation of the 2001 outbreak

The first contact with the Greek public health authorities took place on 13 September 2001. Regular contacts were maintained during the entire investigation.

- **Case definition of the studies from 2001:**

An outbreak-associated confirmed case was defined as a person notified in Norway, Sweden or Finland with a microbiologically confirmed finding of *S.* Enteritidis phage type 14b after travel to Greece within the incubation period for salmonellosis, with date of symptoms between 1 May and 31 December 2001. Since Norway did not phage type all *S.* Enteritidis isolates, an outbreak-associated probable case was defined as an infection notified in Norway with a positive finding of an anaerogenic *S.* Enteritidis, after travel to Greece

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within the incubation period for salmonellosis, occurring between 1 May and 31 December 2001.

Two case-control studies were conducted independently in Norway and Sweden to identify potential vehicles of the outbreak. To facilitate the epidemiological investigation, the case-control studies were limited to travellers who visited Greece, but who spent a part of their trip in Crete, the region with the greatest number of tourists from Norway and Sweden. Different methodological approaches are described below.

• **Pilot study**

Starting on 3 September 2001, a pilot study among 40 Norwegian travellers was performed by telephone interviews using a standardised questionnaire. Information was obtained on demographic details, place of stay, tour operators, airline companies, food consumed during the three days before onset of symptoms and names of restaurants visited. Results of the pilot study were shared between national institutes. As the pilot interviews did not give any hypothesis to test in a case-control study, we decided to focus our questionnaire on the most likely vehicles of *S.* Enteritidis, eggs and meat. Meals containing either eggs or meat that were likely to be available in Greece were listed. These included well-known main dishes served in restaurants in tourist areas (based on information given by local tour operators), and were included in the questionnaires for the case-control studies. Only outbreak associated cases were included in the case-control studies.

• **Case-control study in Norway**

Addresses and telephone numbers of the first 45 notified cases with anaerogenic *S.* Enteritidis were obtained. A standardised questionnaire was mailed to this group of cases (16 October 2001). The case-control study was limited to the group of cases, over 15 years of age, who stayed in Chania district, Crete, between 9 July and 2 September 2001. Three controls per case were matched among travellers who used the same tour operator to visit Greece in the same period of time (+/- one week).

• **Case-control study in Sweden**

The case-control study was limited to the group of patients who stayed in Crete and whose infections were notified to the Swedish infectious disease surveillance system between 1 September and 15 November 2001. Only people over 20 years of age were included. Controls were selected by tour operators from people who had travelled to the same destination during the same time period. Information from both cases and controls was collected by a postal questionnaire similar to the one used in the study in Norway. Additional questions regarding food served on the flights were also included. Due to the long time lapse between the outbreak and distribution of the questionnaires, and potential recall bias, it was not considered feasible to collect data on food consumed on the individual dates. Cases were therefore asked about food consumption in Crete before falling ill (three days before onset of symptoms), and controls were asked about food consumption during their stay abroad.

Laboratory investigations

Isolates from patients were characterised by standard biochemical and serological assays at the reference laboratories. The Norwegian reference laboratory routinely tested formation of gas during fermentation of D-glucose after overnight incubation of tubes at +35oC in ambient air. Strains that did not produce gas from D-glucose were called anaerogenic. The anaerogenic property was also tested on a random number of strains at SMI. The antimicrobial susceptibility was routinely tested on Norwegian and Finnish isolates. Phage typing was performed on all strains in Sweden and Finland, and for a selected number of strains in Norway.

Analysis

Data was analysed using *SPSS* version 10.0 (SPSS Inc, Chicago, IL, USA). Food specific odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for the consumption of food items. The _ 2 test was used to compare proportions between groups (5% significance level). Exposures significantly associated with infection by univariate analysis ($p<0.1$ or $OR > 3$) were included in a multivariable logistic regression model (*LogXact* statistical software; Cytel Statistics and Epidemiology Research Corporation, Seattle, WA, USA). The final model was obtained through stepwise deletion of variables on the basis of statistical and epidemiological criteria.

Results

Surveillance data from 1997 to 2003 of Salmonellosis after travelling to Greece

From 1997 to 2000, *S.* Enteritidis infections represented an average of 61% of all *Salmonella* infections associated with a travel to Greece (mean of 244 cases per year, standard deviation of 40). However, a sharp increase of *S.* Enteritidis infections was observed in 2001, with 569 cases [TABLE 1]. Since non-outbreak strains remained at a constant level, the outbreak strain appeared to be the cause of the increased number of cases of *S.* Enteritidis [FIGURE 1].

FIGURE 1

Compiled data of Salmonella Enteritidis infections associated with travel to Greece reported in Norway, Sweden and Finland, 1997-2003

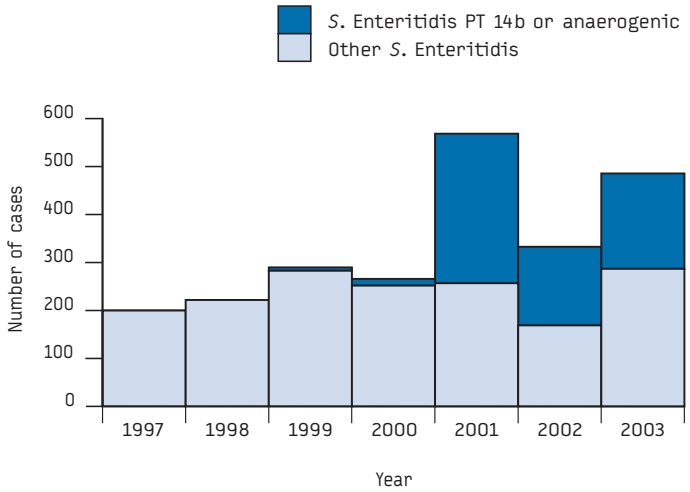


TABLE 1

Annual distribution of numbers of travellers to Greece and of *Salmonella* Enteritidis infections associated with travel to Greece reported in Norway, Sweden and Finland, 1997-2003

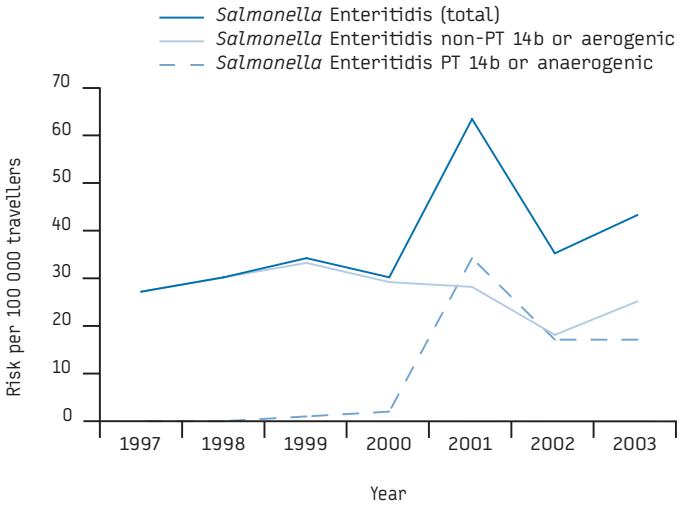
Years	1997	1998	1999	2000	2001	2002	2003
Total number of travellers to Greece*	740 870	731 597	844 901	875 010	909 966	955 996	1 138 155
All *Salmonella*	339	362	464	445	735	422	563
Proportion of *S.* Enteritidis/all *Salmonella*	59%	61%	63%	60%	77%	79%	86%
S. Enteritidis non-PT 14b or aerogenic	200	222	283	252	257	169	287
S. Enteritidis PT 14b or anaerogenic	0	0	7	14	303	164	199
Total *S.* Enteritidis	200	222	290	266	560	333	486

* Source: National civil aviation statistics bureaux of Norway, Sweden and Finland

The total number of travellers from Norway, Sweden and Finland visiting Greece increased from 740 000 in 1997 to 1 138 155 in 2003 [8,9,10]. Reported cases of *S.* Enteritidis in travellers increased dramatically in 2001, but was entirely due to the increased incidence of *S.* Enteritidis PT 14b [FIGURE 2].Compared with 2001, we observed a decreased number of *S.* Enteritidis PT 14b associated with travel to Greece in 2002 and 2003.

FIGURE 2

Risk of *S.* Enteritidis and *S.* Enteritidis PT 14b or anaerogenic infections per 100 000 travellers associated with travel to Greece and reported in Norway, Sweden and Finland, 1997-2003



Outbreak investigation in 2001

• **Descriptive findings**

The first case was a Swedish tourist who fell ill on 27 May 2001. By 31 December 2001, 303 cases had been reported in Norway, Sweden and Finland: 89 in Norway (49 confirmed cases and 40 probable cases); 149 in Sweden; and 65 in Finland. The median age was 35 years and the male:female sex ratio was 0.9.

The distribution of cases by week of symptom onset showed two peaks in each country [FIGURE 3]; the first in week 33 (from 13 to 19 August); and second in week 41 (from 8 to 14 October), corresponding to the summer and autumn school holidays.

Fifty one per cent of the patients (n=154) had only visited Crete and were suspected to have been infected there, but cases also occurred in various other tourist locations in Greece: 36 cases in Rhodes (12%), 17 cases in Kos (6%), 8 cases in Karpathos (3%), 4 cases in Samos, 3 cases in Corfu, 2 cases in Skiathos, 1 case in Athens and 1 case in Paros. For the remaining 77 cases (25%), the exact place in Greece was not specified.

• **Laboratory findings**

All cases had culture-confirmed finding of *S.* Enteritidis. All isolates (n=154) were sensitive to all antimicrobials tested (trimethoprim-sulfamethoxazole, chloramphenicol, tetracycline, ampicillin, nalidixic acid and ciprofloxacin). Ninety eight per cent of isolates (65/66) confirmed to be *S.* Enteritidis PT 14b in Norway and Sweden and related to travel to Greece were anaerogenic.

• **Results of the case-control studies**

There were some methodological differences between the Norwegian and Swedish studies, and so results are presented separately.

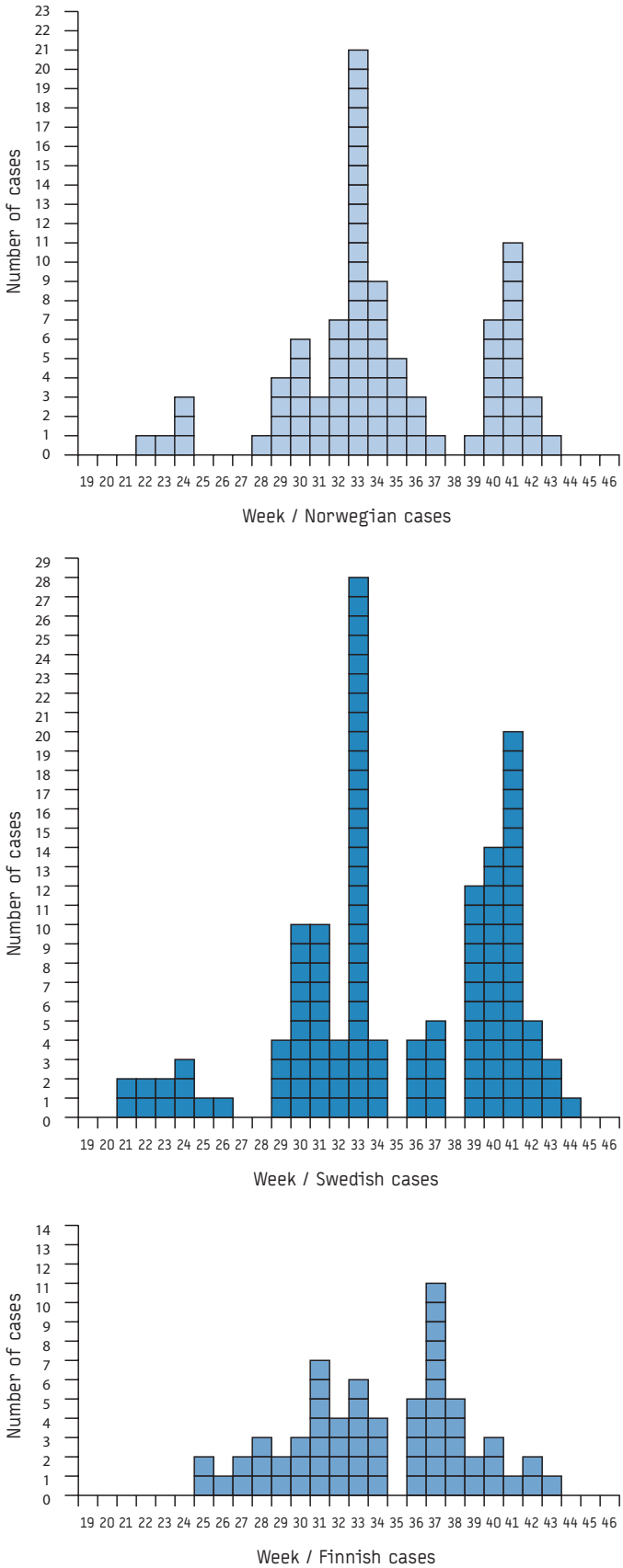
Study performed in Norway: 25 cases and 46 controls were enrolled in the study. In univariate analysis, two exposures were statistically associated with risk of illness [TABLE 2]. Sixty three per cent of the cases and 33% of the controls ate chicken in the three days before onset of symptoms (matched OR 3.4; 95% CI 1.2 to 9.7). Thirty three per cent of the cases and 13% of the controls ate hamburger (matched OR 3.3; 95% CI 1.0 to 11.1).

In a multivariable analysis using a model containing chicken and hamburger, only chicken remained significantly associated with illness (OR=3.3; 95% CI 1.0 to 11.3).

Study performed in Sweden: 24 cases and 33 controls were enrolled in the Swedish study. No significant associations were found for food items consumed during the stay in Crete. Chicken consumed during the stay in Greece was not associated with disease.

FIGURE 3

Distribution of cases of *S.* Enteritidis phage type 14b among Scandinavian travellers returning from Greece, by week of symptom onset and place of suspected infection, Norway, Sweden and Finland, May-December 2001



When food consumed on the flight (from Greece to Sweden) was analysed separately, chicken was found to be associated with infection (OR 3.4; 95% CI 0.7 to 18.8). When cases were divided into cases falling ill in Crete, and cases falling ill after returning to Sweden, chicken served on the return flight was associated with disease (OR 7.9; 95% CI 1.0 to 74.2) [TABLE 3].

Discussion

This is the largest outbreak of *S.* Enteritidis PT 14b reported in the literature. The emergence of this unusual phage type 14b in Greece has been detected through the communicable disease surveillance of travellers in three of the Nordic countries. Results of the case-control studies suggest that chicken was the probable vehicle of the 2001 outbreak. It is likely that other sources should be considered, because continued case reports in 2002 and 2003 suggest that this phage type might have become endemic in this region.

The results of the case-control studies conducted in 2001 suggested that chicken was the likely vehicle of transmission, as is very often reported for *S.* Enteritidis infection. There are several data and methodological limitations in the case-control studies which should be noted. Not all cases reported having consumed chicken, but this meat is sometimes used in salads, souvlaki, pizza or other meals, and there is also the risk of food contamination in the food chain. The delay between onset of symptoms and the investigation may have caused recall bias that may have weakened the significance of this finding. Environmental investigations could have strengthened our findings, but were not conducted. Further, the limited sample sizes available for the case-control studies in both Norway and Sweden limit our ability to draw strong conclusions.

In this outbreak, the first peak of cases was observed in mid-August, corresponding to the summer school holidays in Nordic countries, and a second peak in mid-October corresponding to the autumn school holidays. Greece is a popular holiday destination and the season is limited to the period between May and November. The high number of cases in people who had stayed in Crete may party reflect the higher proportion of tourists visiting the island.

The decrease in the number of cases observed in 2002 and 2003, for all *S.* Enteritidis infections, may be a consequence of the information given by Nordic public health institutes to travellers to Greece and/or measures taken by Greek authorities. Collaboration with tour operators has been an important channel of information. Additionally, reports of the 2001 outbreak in the media may have contributed to an increased awareness of travellers about raw or insufficiently cooked food.

The Nordic surveillance systems have also recorded sporadic infections with anaerogenic *S.* Enteritidis PT 14b after travel to Italy, Bulgaria and Spain. However, the number of cases associated with travel to other European countries remains largely low when compared with the number of cases associated with travel to Greece. *S.* Enteritidis PT 14b was responsible for an outbreak in Spain in early 2001 [11] and for an outbreak in the United Kingdom (UK) in 2002 [12]. Because of homogeneity in *S.* Enteritidis of the same phage type, conventional PFGE using *Xba*I restriction enzyme was not able to differentiate these strains from the strains related to the outbreak in Greece. However, strains isolated in the UK were aerogenic [13],

TABLE 2

Frequency of selected exposures among cases and controls, S. Enteritidis phage type 14b infection in Norwegian travellers returning from Crete, July-September 2001

Food consumed*	Case patients			Control subjects			Odds ratio	95% CI
	No.	%	Total*	No.	%	Total*		
Egg products								
Soft boiled egg	0	0	24	7	15	46	Undefined	-∞ – 1.4
Hard boiled egg	2	8	24	2	4	46	2.0	0.3 – 15.2
Fried egg	3	13	24	8	17	46	0.7	0.2 – 2.8
Omelette	7	29	24	13	28	46	1.0	0.3 – 3.1
Scrambled egg	0	0	24	2	4	46	Undefined	-∞ – 8.1
Custard	0	0	24	2	4	46	Undefined	-∞ – 8.1
Cake with custard	0	0	24	1	2	46	Undefined	-∞ – 34.4
Béarnaise sauce	5	21	24	5	21	46	2.2	0.6 – 8.4
Rémoulade	0	0	24	2	4	46	Undefined	-∞ – 8.1
Other egg products	4	19	21	4	9	46	2.5	0.6 – 11.0
Meat products								
Chicken	**15**	**63**	**24**	**15**	**33**	**46**	**3.4**	**1.2 – 9.7**
Pork	5	21	24	17	37	46	0.4	0.1 – 1.4
Beef	6	25	24	21	46	46	0.4	0.1 – 1.2
Lamb	6	25	24	14	30	46	0.8	0.2 – 2.3
Souvlaki	6	25	24	16	35	46	0.6	0.2 – 1.9
Beef fillet	5	21	24	15	33	46	0.5	0.2 – 1.7
Meatballs	0	24	24	5	11	46	Undefined	-∞ – 2.5
Hamburger	**8**	**33**	**24**	**6**	**13**	**46**	**3.3**	**1.0 – 11.1**
Pizza	10	42	24	17	37	46	1.2	0.4 – 3.3
Pasta	5	21	24	5	11	46	2.2	0.6 – 8.3
Moussaka	4	17	24	10	22	46	0.7	0.2 – 2.6
Kebab	2	8	24	2	4	46	2.0	0.3 – 15.2
Sausage	3	13	24	8	17	46	0.7	0.2 – 2.8
Other meat dish	2	8	25	2	4	46	1.9	0.2 – 14.5

* Food items consumed by neither cases nor controls are not reported

while strains associated with Greece were predominantly anaerogenic. The testing of gas production of *S.* Enteritidis performed routinely at NIPH was a key element in identifying a cluster of cases in Norway. In Sweden and Finland, the cluster of cases was easily detected by phage typing all *S.* Enteritidis isolates.

Detecting emerging diseases through travellers surveillance systems:

The use of the term 'outbreak' in this context may be debatable as the increase in *S.* Enteritidis PT 14b infections in travellers returning from Greece may reflect the recent introduction of this unusual phage type into the Greek food chain. However, from the point of view of national surveillance systems in Norway, Sweden and Finland, the 2001 situation was a real outbreak in travellers. The Nordic surveillance systems had already noted a few cases of *S.* Enteritidis PT 14b infections in 1999 (7 cases) and 2000 (14 cases) [TABLE 1]. This may have been an early alert for the 'explosion' of cases observed in 2001. Identification of even these few cases in 1999 and 2000 could have been used as an opportunity for faster notification and exchange of information to our Greek colleagues, but this information was not transmitted until September 2001.

A key element in detecting the extension of the outbreak was the sharing of information among national public health institutes through Enter-net, the European network for surveillance of salmonellosis, campylobacteriosis, and infection with enterohaemorrhagic *E. coli*. This exchange allowed Norway, Sweden and Finland to pool their data and realise the scope of the problem. Today, increased collaboration between European countries regarding communicable diseases makes it possible to exchange this type of sensitive information. It must be noted that other European countries did not detect such events related to travel to Greece for several reasons: the number of travellers infected (absolute number and relative to their total population) might not have been sufficient to be visible; phage typing is not performed on *S.* Enteritidis strains in most European countries, and this unusual phage type might not have been noticed in numbers important enough at the country scale; probable place of infection is not part of the standard data collection of enteric diseases in most European countries, but is in Norway, Sweden and Finland. This last element explains why these three Nordic countries were able to quickly connect an unusual number of events to a probable place of origin. The sensitivity of the information lies in the fact that publicly disclosing information regarding an outbreak could have dramatic economic consequences for tourism and a country's public image.

TABLE 3

Frequency of selected exposures among cases and controls, *S.* Enteritidis phage type 14 infection among Swedish travellers returning from Crete, September-November 2001

Food consumed *	Case patients			Control subjects			Odds ratio	95% CI
	No.	%	Total*	No.	%	Total*		
Egg products								
Raw egg	0	0	16	1	3	29	Undefined	-∞ – 33.0
Soft boiled egg	3	19	16	5	17	30	1.1	0.1 – 7.1
Hard boiled egg	10	50	20	12	41	29	1.4	0.4 – 5.2
Fried egg	6	33	18	6	27	22	1.8	0.4 – 8.6
Omelette	8	47	17	9	32	28	1.8	0.5 – 7.9
Scramble egg	1	6	16	3	11	28	0.6	0.02 – 7.2
Chocolate mousse	2	13	16	4	14	28	0.9	0.1 – 6.7-
Ice cream	9	53	17	26	87	30	0.2	0.03 – 0.9
Doughnut	9	47	19	16	55	29	0.7	0.2 – 2.7
Cake with custard	3	19	16	6	26	23	0.9	0.1 – 5.1
Béarnaise sauce	6	35	17	13	48	27	0.6	0.1 – 2.4
Mayonnaise	3	21	13	5	19	24	1.9	0.2 – 15.2
Salad with mayonnaise	3	23	14	5	19	26	1.3	0.2 – 8.9
Meat products								
Chicken	14	70	20	23	82	28	0.5	0.1 – 2.4
Chicken - return flight	**12**	**70**	**17**	**7**	**41**	**17**	**3.4**	**0.7 – 18.8**
Pork	21	88	24	27	93	29	0.8	0.1 – 5.6
Beef	16	89	18	27	93	29	0.6	0.1 – 6.8
Lamb	6	38	16	14	52	27	0.6	0.1 – 2.3
Souvlaki	17	77	22	25	83	30	0.7	0.1 – 3.3
Beef fillet	6	46	13	15	56	27	0.7	0.2 – 3.2
Hamburger	7	44	16	10	34	29	1.5	0.4 – 6.3
Pizza	10	56	18	14	47	30	1.4	0.4 – 5.5
Pasta	13	72	18	15	56	27	2.1	0.5 – 9.3
Moussaka	11	58	19	25	78	32	0.4	0.1 – 1.6
Kebab	3	19	16	4	14	28	1.4	0.2 – 9.2
Sausage	5	29	17	8	29	28	1.0	0.2 – 4.8
Other meat dish	1	7	14	5	20	25	0.3	0.01 – 1.6
Cases falling ill after return								
Chicken - return flight	**11**	**85**	**13**	**7**	**41**	**17**	**7.9**	**1.0 – 74.2**

* Food items consumed by neither cases nor controls are not reported

These elements cannot be neglected and should strengthen the European policy to increase public health collaboration between states. In comparison, a similar situation in the United States, would probably have been easily handled between states, under the auspices of the Centers for Disease Control and Prevention (CDC). A mediating structure, the European Centre for Disease Prevention and Control (ECDC) was created in Europe in 2005 [14].

Detection of emerging organisms through infections in travellers returning from abroad has been previously described. These phenomena are especially likely to occur in tourist areas, particularly when the number of travellers is large (the number of Norwegian, Swedish and Finnish tourists visiting Greece was estimated to be about one million in 2001).

Because the place of infection is not included in *Salmonella* notification systems in most countries, it is likely that the *S.* Enteritidis PT 14b outbreak reported in Nordic countries represents only the tip of the iceberg of this outbreak among travellers visiting Greece.

Infections are often reported only in the travellers' home country, because patients often prefer to seek medical care after returning. Therefore public health authorities in the tourist destinations may not be aware of the problem, or not informed until later. Many cases of foodborne illnesses are not reported because patients do not seek medical care, healthcare providers do not obtain specimens for diagnosis, laboratories do not perform the necessary diagnostic tests or illnesses or laboratory findings are not communicated to public health officials. Therefore, to estimate the total number of illnesses caused by each pathogen, the degree of underreporting needs to be taken into account, that is, the difference between the number of reported cases and the number of cases that actually occur in the community. For *Salmonella*, a pathogen that typically causes non-bloody diarrhoea, the degree of underreporting has been estimated up to 38-fold [15-18]. However, it would probably be wrong to use this estimate for this outbreak since patients might choose seek medical care after travelling abroad more often than if infected in their home country. Even with a conservative approach, the number of European travellers infected in Greece may be substantial.

S. Enteritidis infections in humans showed a clear increase in several countries in Europe during the 1980s and early 1990s, and investigations showed that the increase was mainly related to consumption of eggs and poultry [19]. This spread of *S.* Enteritidis within the egg and poultry sector was probably largely facilitated by the intense breeding schemes used in egg producing units. Introduction of *S.* Enteritidis into breeding lines may therefore have contributed to the rapid and wide spread in the egg and poultry sector. A few phage types have dominated among the *S.* Enteritidis strains; mainly PT 4 in Europe and PT 8 and 13a in the US [3]. The detection and investigation of the present outbreak was facilitated by the presence of an atypical (anaerogenic) *S.* Enteritidis, subsequently demonstrated as belonging to a previously uncommon phage type, PT 14b. According to the literature, anaerogenicity is a rare property reported in only 3.9% of *S.* Enteritidis [20]. Our finding is in favour of the emergence of the unusual phage type, retrospectively shown to have started in 1999 and to have 'exploded' in 2001. Cases reported again in 2002 and 2003 further suggest that the phage type may have become established in the food chain, not necessarily only in poultry. This interpretation is supported by the study described by Nygard et al based on Swedish surveillance data [21,22]. In this study, infections in Swedish travellers correlate well with national studies conducted in the countries visited. In 2001 a change in phage type distribution in *S.* Enteritidis infections among Swedish travellers returning from some countries in southern Europe, including Greece was observed, and anaerogenic *S.* Enteritidis PT 14b became one of the most commonly diagnosed that year, continuing into 2002 and 2003.

Problems of food- and waterborne diseases in travellers are well identified. It is an important factor which, unless controlled, can have severe effects on local, national and international trade [23]. Further investigation must be performed to understand why this phage type has suddenly increased in this region, although it had already been present for some years without causing large outbreaks.

The *S.* Enteritidis phage type 14b outbreak reported in Nordic countries may only represent part of a larger outbreak among travellers to Greece. Notification of place of infection has been a key element to detect this outbreak reported among travellers. The Enter-net system has been crucial for sharing of information in Europe. Collaboration among public health institutions should be strengthened, particularly for outbreaks occurring in popular tourist destinations.

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SALMONELLA ENTERITIDIS PHAGE TYPE 21 OUTBREAK IN AUSTRIA, 2005

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We report an outbreak of gastroenteritis due to *Salmonella* Enteritidis PT 21 associated with attending an annual traditional fair in a small Austrian village on 4 May 2005. The outbreak lasted from 4 to 8 May. Descriptive and analytical epidemiological investigations were conducted in order to determine the extent of the outbreak and to identify outbreak risk factors. Of the 115 persons who visited the fair, 85 persons fulfilled the criteria of an outbreak case (attack rate = 73.9%). Stool specimens from 52 patients, including two kitchen staff, were tested for salmonella, and 20 specimens were positive for *Salmonella* Enteritidis PT 21. The cohort study revealed mixed salad (which included potatoes) as the likely cause of the outbreak (RR: 10.4, 95%CI 2.8 – 39.1; P=<0.001). The causative agent of the outbreak was cultured from the stock of eggs used at the fair and from all three drag swabs used for faecal samples and one barn dust sample collected from the responsible egg laying flock. Molecular subtyping by pulsed-field gel electrophoresis of genomic DNA after *Xba*I digestion showed that isolates from eggs, from the flock and from humans were indistinguishable. We hypothesise that cross contamination from eggs to boiled potatoes occurred in the kitchen area, where raw eggs were handled by village residents preparing a traditional Viennese egg dressing for the meat dishes. Unrefrigerated storage of peeled potatoes may have favoured bacterial growth. Eggs from small rural flocks of laying hens kept in a traditional 'natural' way should not be assumed to be salmonella-free.

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Key words: Austria, cross contamination, eggs, outbreak, potato salad, Salmonella

Introduction

Foodborne zoonoses may cause human suffering, as well as economic losses to food production and the food industry. The European zoonoses directive 2003/99/EC specifies that competent authorities should investigate foodborne outbreaks and that the investigation should provide data on the epidemiological profile, the potentially implicated foodstuffs and the potential causes of the outbreak [1]. According to the European Commission, thorough investigation of zoonotic foodborne outbreaks provides the opportunity to improve prevention and control of foodborne diseases. We describe the investigation of an outbreak of salmonellosis associated with attending a traditional annual village fair.

Materials and Methods

Outbreak background

A time-space cluster of approximately twenty cases of gastroenteritis due to *Salmonella* Enteritidis PT 21 was reported to the Österreichische Agentur für Gesundheit und Ernährungssicherheit (Austrian Agency for Health and Food Safety) by provincial health authorities on 12 May 2005. On 9 May, local general practitioners had alerted the local district health office to a cluster of gastroenteritis cases that started on 4 May and was restricted to a small district in southern Austria. On 11 May, a clinical microbiology laboratory reported a cluster of stool samples positive for *Salmonella* Enteritidis. The case series investigation revealed that was a relationship between the cases and visiting an annual fair in a small village on 4 May. An outbreak investigation team was set up by the provincial health authorities on 13 May, and it was decided that a full investigation should be carried out to determine the extent of the outbreak and to identify the outbreak cause by using a retrospective cohort design.

Outbreak case definitions

Probable case: A probable case was defined as a person who (1) visited the particular fair in village X on 4 May, (2) consumed dishes served at the fair, (3) subsequently fell ill with symptoms of diarrhoea and (4) had no bacteriologically confirmed infection with *S.* Enteritidis PT 21.

Confirmed case: A confirmed case was defined as a person who (1) visited the fair in village X on 4 May, (2) consumed dishes served at the fair, (3) subsequently fell ill with symptoms of diarrhoea and (4) had a bacteriologically confirmed infection with *S.* Enteritidis PT 21.

Recruitment of the cohort

The municipality provided a list of all residents of village X. Of 95 households , 87 (91.6%) were contacted and asked whether household members or relatives and friends not residing in village X had visited the fair. Of the 294 village residents contacted, 76 people (in 31 households) had taken part in the fair. An additional 39 people (village residents' relatives and friends who lived outside village X) were reported to have visited the fair. A total of 115 people were considered for the cohort analyses.

Exposure

An exposure was defined as consumption of a food item prepared and served by the staff of the inn where the fair was held.

The food items available at the fair included three different soups (garlic cream soup, liver dumpling soup, and soup with cut pancake pieces), frankfurter sausages, turkey fillets, boiled meat, roast pork, and a variety of food items prepared according to traditional Austrian recipes, breaded chicken, pork, Emmentaler cheese, goat meat (this is food dressed with a mixture of raw egg and white bread crumbs, and then fried),mixed salad (including potato salad, lettuce, green beans, haricot beans, and tomatoes), cooked rice and fried potatoes, and four different cakes.

Disease status

Patients who developed diarrhoea (with or without vomiting), abdominal pain or fever in the four days after visiting the fair were considered to have been ill with acute gastroenteritis.

Analysis

A standard questionnaire was developed at the Austrian Agency for Health and Food Safety using EpiInfo 3.3.2. Interviews were carried out by telephone, and included questions on basic demographic data, symptoms and clinical signs, date and time of clinical onset, duration of illness, admission to hospital, date of admission to hospital and food history, which included using the list of food items available at the fair.

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Epi Info 3.3.2 was used for data collection, and data were analysed with Epi Info v6.04d and the Statistical Analysis System (SAS). We compared the food-specific attack rates (AR) for each food item on the fair list among the exposed and the non-exposed cohort members in the univariate analysis using chi-square test or two-tailed Fisher's exact test. The measure of association was the relative risk (RR). In order to assess simultaneous effects of the exposure variables, a logistic regression model was applied. The variables age and sex, and the food items with a P value ≤0.1 in the univariate analyses were included in the regression model. Variables were removed one by one until only significant (P≤0.05) variables remained in the model.

Microbiology

The National Reference Laboratory for Salmonella at the Austrian Agency for Health and Food Safety receives the majority of all human and non-human salmonella strains isolated in Austria. All salmonella isolates received routinely undergo serotyping (Kauffmann-White method) and all *S.* Enteritidis isolates are phage typed as described elsewhere [2]. Pulsed-field gel electrophoresis of genomic DNA after *Xba*I (New England Biolabs, USA) digestion was performed as described elsewhere [3,4].

Results

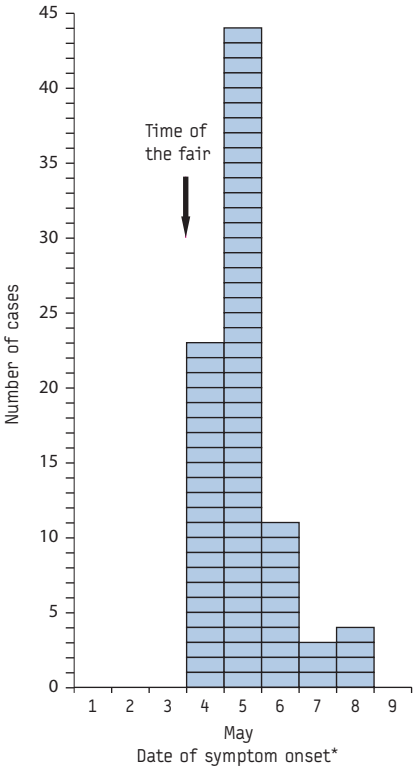
The questionnaires were completed for all cohort members (100% response). Only data on time of clinical onset were incomplete.

Women made up 53 (46.1%) of the 115 cohort members. The median age was 45 years (range 2–84).

The outbreak lasted from 4 to 8 May, peaked on May 5 and indicated a common point source outbreak [FIGURE].

FIGURE 1

Cases of *S.* Enteritidis infection by date of symptom onset (n= 85) after visiting a traditional fair in a small village in southern Austria on 4 May 2005.



*Data on time of onset were not available

Eighty five patients in the cohort fulfilled the case definition of an outbreak case (attack rate, AR=73.9%). Among these 85 cases, there were 39 women and 46 men (54.1%), the median age was 44 years (range 2 - 84). The case distribution by age group (0-9 years, 10-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, >70 years) and sex is illustrated in table 1.

TABLE 1

Outbreak cases by age group and sex, southern Austria, 2005

Age group years	Sex		Total
	Male (%)	Female (%)	
0-9	5 (10.9)	1 (2.6)	6
10-19	4 (8.7)	5 (12.8)	9
20-29	5 (10.9)	1 (2.6)	6
30-39	2 (4.3)	6 (15.4)	8
40-49	12 (26.1)	9 (23.1)	21
50-59	5 (10.9)	3 (7.7)	8
60-69	6 (13)	12 (30.8)	18
≥ 70	7 (15.2)	2 (5.1)	9
Total	**46**	**39**	**85**

Stool specimens from 52 patients, including two kitchen staff, were tested for salmonella, and 20 specimens (38%) were positive for *Salmonella* Enteritidis PT 21 and fulfilled the definition criteria of a confirmed outbreak case.

In addition to diarrhoea, 78 patients (91.8%) had nausea, 33 patients (38.8%) had vomiting, and 39 patients (45.9%) had fever. The mean duration of illness was 5 days (interquartile range 4 to 7 days). Fourteen patients (16.5%) were admitted to hospital. All 85 patients recovered.

On 12 May, food inspectors collected 10 table eggs from the inn's kitchen, where the meals for the fair had been prepared. No other food item served at the fair was available for microbiological examination at this point in time. The eggs came from a flock of 17 laying hens kept by the innkeeper. The flock had not been vaccinated against salmonella and was kept in a barn with access to a small fenced-in outside area. *Salmonella* Enteritidis PT21 was isolated from the pooled eggs and was cultured from all three drag swabs (pooled faecal samples) and one barn dust sample collected on 18 May.

It was not possible to ascertain the exact time when food exposure occurred, because food was available from 11.00 am until the late afternoon, and visitors were not able to recall the exact time of food consumption or the time of clinical onset.

Molecular subtyping by pulsed-field gel electrophoresis of genomic DNA after *Xba*I digestion revealed an isolate obtained from the eggs and four isolates from the flock to be indistinguishable from four human isolates.

The univariate analyses of food exposures revealed that consumption of soups, frankfurter sausages, fried potatoes, cakes, pork, boiled meat, fried chicken and fried Emmentaler cheese had no effect on the disease risk.

An association with disease risk at a 5% significance level was found for fried goat meat (RR: 1.4, 95%CI 1.3-1.6; P= 0.007), rice (RR: 1.4, 95%CI 1.0 -1.6; P=0.02), and for the mixed salad (RR: 10.4, 95%CI 2.8 – 39.1; P=<0.001). Consumption of turkey was found to have a protective effect on disease risk (RR 0.4; 95%CI: 0.19 – 1.2; P= 0.03) [TABLE 2]. No difference in the sex-specific attack rates was found.

The multivariate analysis found the mixed salad to be the only food exposure with a significant independent effect on the disease risk.

Discussion

In 2004, a total of 7320 laboratory confirmed salmonella infections in humans were documented in Austria. *S.* Enteritidis accounted for 83.0% of all human isolates, with 82.9% of all *S.* Enteritidis isolates belonging to three phage types: PT 4, PT 8 and PT 21 [5]. Berghold et al recently showed that Austrian chicken meat is nowadays only a minor source of human *S.* Enteritidis infections, regardless of phage type [6]. This applies to chicken meat as direct source of infection as well as infections from secondary contamination [6]. The main focus of preventive measures should be directed at reducing the risk of infection caused by table eggs [7-9]. The PT 21 outbreak described in this paper further underlines the importance of eggs as a vehicle for salmonella infection.

Table 2

Food-specific attack rates for *Salmonella* Enteritidis phagetype 21 infections associated with attending a fair, May 2005

	Exposure Yes			Exposure No				
Dishes available	Ill	Total	AR%	Ill	Total	AR%	RR (95% CI)	p
Soup with pancake pieces	6	7	85.7	79	108	73.1	1.2 (0.8 1.6)	0.4*
Liver dumpling soup	5	6	83.3	80	109	73.4	1.1 (0.8 1.7)	0.5*
Garlic cream soup	2	3	66.7	83	112	74.1	1.2 (0.8 1.6)	0.5*
Frankfurter sausages	0	0	0	85	115	73.9	Incalculable	-
Boiled meat soup	0	0	0	85	115	73.9	Incalculable	-
Fried chicken	21	29	72.2	64	86	74.4	1.0 (0.8 1.3)	0.9
Fried pork	32	46	69.6	53	69	76.8	0.9 (0.7 1.1)	0.5
Fried Emmentaler cheese	0	1	0	85	114	74.6	Incalculable	0.3*
Turkey fillet	3	8	37.5	82	107	76.6	0.4 (0.2 1.2)	0.03*
Goat meat	15	15	100	70	100	70	1.4 (1.3 1.6)	0.007*
Roast pork	11	12	91.7	74	103	71.8	1.3 (1.0 1.6)	0.1*
Cooked rice	26	28	92.9	59	87	67.8	1.4 (1.1 1.6)	0.02
Fried potatoes	29	41	70.7	56	74	75.7	0.9 (0.7 1.2)	0.7
Mixed salad°	83	92	90.2	2	23	8.7	10.4 (2.8 39.1)	< 0.001
Cake I	6	8	75	79	107	73.8	1.0 (0.6 1.5)	0.7*
Cake II	5	5	100	80	110	72.7	1.4 (1.2 1.5)	0.2*
Cake III	8	8	100	77	107	72	1.4 (1.2 1.6)	0.08*
Cake IV	2	2	100	83	113	73.5	1.4 (1.2 1.5)	0.5*

* Fisher's exact test was used

° Mixed salad including potato salad, lettuce, green beans, haricot beans, tomatoes

The epidemic curve indicated a common exposure of the cases at one point in time. The maximum and minimum incubation periods were traced back, using the clinical onset dates of the first and last cases, and 4 May was found to be the date of common exposure. A foodborne outbreak caused by dishes served at the fair was assumed, as there was no information about any other mass gathering as a potential common exposure prior to the fair. As this rural fair is usually visited exclusively by village residents and by their friends and relatives, a cohort study was chosen to elucidate the cause of the outbreak.

The likelihood that a selection bias was introduced is reasonably small, as contact was made with over 90% of the village households. The capture of outside visitors named by village community members appeared to be reliable, and all identified attendees responded to the questionnaire.

The analytical epidemiological investigation revealed the mixed salad as the highly likely cause of the outbreak. The causative agent of the outbreak could be cultured from the remainder of the stock of eggs used for the fair and taken from the kitchen. The preparation of the potato salad (part of the mixed salad) began during the night of 3-4 May, when the potatoes were boiled, peeled, and later stored, unrefrigerated for about 8 hours in another room. We hypothesise that cross contamination of the boiled potatoes occurred in a kitchen where raw eggs were used to prepare the traditional Viennese breading for the meat dishes. Storage of the peeled potatoes in inappropriate conditions may have favoured bacterial growth. Furthermore, meal preparation was carried out in the kitchen of an inn that had not been not used for commercial food preparation for several years. The yearly fair was the only occasion when large scale cooking and food serving was done in this location, and was carried out with the help of village residents. Lack of risk consciousness by untrained staff is a well- known risk factor for hygiene failure [10].

Bacteriological examination of the egg producing flock revealed that the innkeeper's hens were infected with PT 21. In rural Austria, many households still use eggs from their own hens. The fact that eggs are from a small flock of laying hens, kept in the traditional 'natural' way, is often misinterpreted as a guarantee against salmonella contamination. The flock owner had purchased his hens two years earlier from an industrial laying hen operation. We assume that the hens were already latently infected at this time.

The voluntary culling of the herd on 2 June led to the elimination of the reservoir of this circumscribed outbreak. This is an impressive example how a foodborne outbreak was traced from cases to the outbreak causative food item, the food-vehicle of contamination, and thence to the food producing animal that was the reservoir of the causative agent. Despite the fact that the causative phage type is widely distributed in Austrian chicken flocks, it was possible to elucidate and interrupt the chain of infection. Close cooperation between health authorities and the Austrian Agency for Health and Food Safety, bridging gaps between the fields of human medicine, food laboratories, and veterinary medicine and providing epidemiological expertise, are the essential bases for the success of such an endeavour.

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CURRENT MEASLES OUTBREAK IN GREECE

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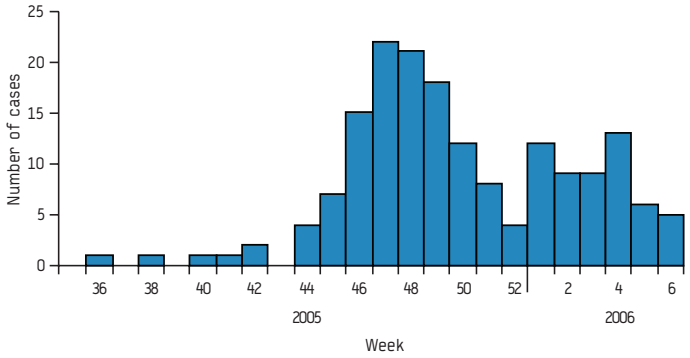
Since November 2005, there has been an outbreak of measles in Greece. Sporadic cases began to appear in September 2005.

Between 1 September 2005 and 12 February 2006, 171 cases of measles were reported, of which 53 (31%) have been laboratory confirmed (by detection of measles IgM), 99 (58%) are probable cases (clinical criteria according to case definition [1]), and 19 (11%) are still awaiting laboratory confirmation (figure 1).

FIGURE 1

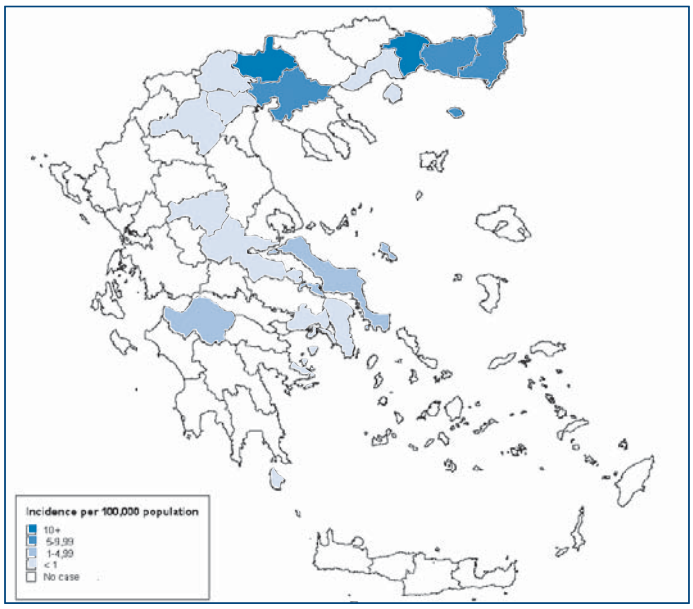
Notified cases of measles by week of symptom onset, Greece, 1 September 2005 - 12 February 2006



Cases were reported from 14 of the 52 districts of Greece (figure 2), and 159/171 patients (93%) are from northern Greece. Eighty eight cases (52%) are in males. About half (45%) of the patients are aged 0-4 years, 16% are aged 5-9 years, 15% are aged 10-19; and 25% are aged 20 or older, most of these being young adults.

FIGURE 2

Notified cases of measles by district, Greece, 1 September 2005 – 12 February 2006



Ninety four patients (55%) belong to Roma (gypsies) families and 25 (15%) to immigrant families; 52 cases (30%) belong to the non-minority general population, most of whom (71%) are 15 years old or more. Of 110 patients with known vaccination status, 98 (89%) were unvaccinated for measles and 12 (11%) had had one dose of measles-containing vaccine. Eight cases made up two hospital clusters (four cases in each). One hundred and three patients (60%) were admitted to hospital, and 27 (16%) had complications (mainly pneumonia and bronchiolitis), all of whom have recovered. Results of virus isolation and molecular typing, which are being carried out at the Hellenic Pasteur Institute, are pending.

Measles is a notifiable disease in Greece, and is under surveillance through a sentinel physician system with both private and public sector physicians. In both systems the EU case definition is used [1]. Laboratory surveillance of the disease is carried out through the national reference laboratory for measles in Greece (Medical Microbiology Laboratory, Hellenic Pasteur Institute).

Measures taken to control the outbreak include:

- campaigns to vaccinate children between 0-14 years old in Roma communities (estimated total population in Greece, 200 000)with MMR in affected districts as a priority (carried out since December 2005), and in the whole country subsequently
- recommendations to start vaccination of all infants at the age of 6 months in affected districts
- alerting physicians and the general public to the need for all children, adolescents and high-risk young adults to be vaccinated with two doses of measles containing vaccine
- asking health professionals to enhance surveillance, and be aware of vaccination requirements and prophylactic measures in healthcare settings.

Discussion

Measles vaccination was introduced in Greece in the early 1970s, when vaccines became commercially available, and vaccination at the age of 15 months was introduced in the national immunisation schedule in 1981; measles-mumps-rubella vaccine (MMR) was introduced in 1989. Vaccination with a second dose of MMR at the age of 11-12 years was introduced in the national immunisation schedule in 1991, and in 1999 this dose was shifted to 4-6 years.

According to several local studies carried out in 2003-2005 in different parts of Greece, vaccination coverage of preschool children, schoolchildren and adolescents with one dose of measles containing vaccine is >95% in the non-minority population, and 80%-90% in children of immigrant families. Vaccination coverage with two doses is about 60-80% for the general child population [2]. Older studies have shown that cohorts of young adults have much lower vaccination coverage, particularly with two doses of measles containing vaccine (86% and 37% of 14 year olds in a national study conducted in 1997 were vaccinated with one and two doses respectively) [3].

Vaccination coverage of Roma children has been found to be very low (2%-12% in studies of the period 2003-2005) [2], and although a number of vaccination campaigns have taken place in this group since these studies were made, vaccination coverage probably still remains very low.

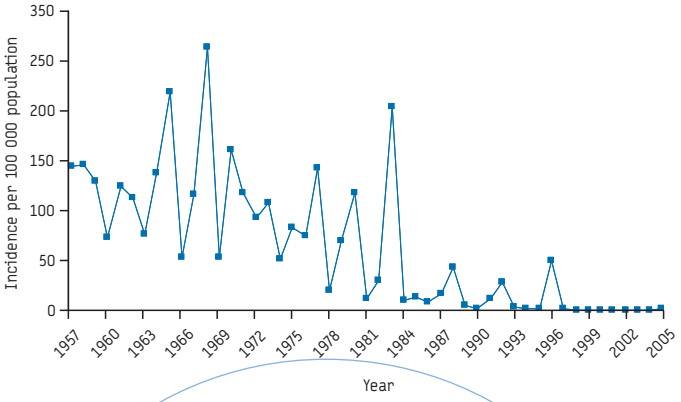
Overall, measles incidence has been steadily declining in Greece during the past 25 years. The current outbreak is the first observed in Greece since 1996. The 1996 outbreak was much smaller than previous outbreaks, and after it ended the 2-5 year epidemic cycles previously observed (Figure 3).

Conclusions

This is the first outbreak of measles in Greece since 1996. It has mainly affected three groups of the population: the majority of patients are unvaccinated Roma children aged 0-14 years, primarily of preschool age. The second group is older teenagers and young

Figure 3

Notified cases of measles per 100 000 population, Greece, 1957-2005



adults from the non-minority general population who were either unvaccinated or had had one dose of measles containing vaccine. Unvaccinated or incompletely vaccinated immigrants, without any particular age pattern, are the third group affected. The large majority of cases occurred in northern Greece.

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Short reports

Urgent action needed to stop spread of hepatitis B and C in Estonian drug users

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In 1996, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections began to spread rapidly in northeastern Estonia. Ninety per cent of all notified cases were in patients from the north and northeastern parts of the country, which are close to the Russian border and are the most urbanised and densely populated areas of Estonia.

Chronic hepatitis B, chronic hepatitis C and chronic hepatitis (unknown cause) have been notifiable since 1998 in Estonia. Hospitals and family doctors notify laboratory confirmed acute cases of hepatitis B and C to the Estonian Health Protection Inspectorate (http://www.tervisekaitse.ee/tkuus.php). Notification of HCV infection, based on HCV antibody detection was first implemented in Estonia in 1991, and notification of hepatitis B started in the early 1980's.

Trends in hepatitis B and C incidence

In Estonia, the average incidence of acute hepatitis B during the 1980s and early 1990s was 11.7 per 100 000 population (range 7.0-15.8) [1]. Incidence of HCV infection in the early and mid 1990s ranged from 0.4 to 4.4 per 100 000 population.

A large proportion of acute hepatitis infections are asymptomatic, and therefore the incidence is greatly underestimated [2]. There are no data on the proportion of asymptomatic cases in Estonia.

By 2001, the reported incidence of acute hepatitis B infection was 33 per 100 000 population: 2.9 times higher than in 1995. Acute hepatitis C affected 22 per 100 000 population in 2001, which was 4.7 times more than in 1995. However, 2002 and 2003 data showed a decline in incidences to 13 per 100 000 for acute hepatitis B, and 11 per 100 000 for acute hepatitis C.

Vulnerable populations

The incidence of HBV and HCV infections is highest among people aged 15-19 and 20-29 years, and higher among men than women. Injecting drug use is the most common risk factor for HBV and HCV in young people, accounting for more than half the new cases.

Several risk factors for HBV and HCV infection are well established.

Table

Acute hepatitis B and C incidence in Estonia, by age, 1996-2003

Age in years	Acute HBV incidence (per 100 000 population)			Acute HCV incidence (per 100 000 population)		
	1996	2000	2003	1996	2000	2003
0 - 14	3	2	3	1	3	0.4
15 - 19	71	175	37	26	162	36
20 - 29	53	89	35	19	69	31
30 - 39	19	22	18	8	19	16
40 - 59	6	8	5	1	5	6
60+	4	5	3	1	1	1

In Estonia, HBV and HCV transmission via blood transfusion and medical procedures has declined significantly during the last decade while risk factors other than transfusion were recognised as the most important. Currently, injecting drug use is the most common risk factor identified among youth, accounting for more than half of all new hepatitis cases for which there is data on likely transmission route. The route of transmission for approximately 40% of all cases remains unknown. It is often very difficult to determine the correct route of transmission, for example, sexual, through unhygienic tattooing or through unreported injecting of drugs - most often the latter.

Injecting drug users

Concurrent infections with multiple hepatitis viruses and other bloodborne pathogens such as HIV are common among injecting drug users (IDUs) in Estonia. Chronically infected IDUs are a major reservoir of HBV and HCV and may transmit the infections to the general population. A study of IDUs who visited anonymous HIV testing facilities found that 65% were seropositive for HBV and 95% for HCV. The co-infection rate was 65% [2].

In Estonia, the rapid increase in injecting drug use started in 1994-1995 and remains at a high prevalence which is now stable. There are an estimated 12 000-17 000 IDUs in the country who mostly use heroin. About 85% of them are Russian speaking and 75% are young men aged 15-25 years. As a result, the Russian speaking community is especially vulnerable to the spread of hepatitis B and C, as well as HIV infection [3]. The spread of viral hepatitis preceded the concentrated epidemic of HIV in 2000-2003 among IDUs in northeastern and northern Estonia [4,5]. The incidence rate of HIV infection remains the highest reported in Europe [6].

Prisoners

A large number of prisoners in Estonia are at risk of contracting hepatitis B and C infection as a result of sharing syringes while injecting drugs and unhygienic tattooing practices. It has been estimated that about 30% of Estonian prisoners are injecting drugs.

A study of 122 HIV positive IDUs at Tallinn Central Prison found that the prevalence of HBV antibodies was 89%, HCV antibodies 98% with both together at 89%. This was significantly higher than the prevalence in IDUs not in prison who visited anonymous HIV testing facilities.

A study of 237 HIV negative IDUs in prison indicated that the prevalence of antibodies to HBV and HCV in 1996-2000 was 82% and 94%, respectively. Eighty six per cent of HCV infected IDUs were found to have some marker of HBV infection. HBV and HCV infection was detected in 20% and 13% of self-declared non drug-dependent inmates (n=40) respectively [unpublished data, NIHD Virology Department].

Markers of current chronic HBV infection were detected among 8% of studied imprisoned IDUs, who were not clinically ill [7]. Data for chronic hepatitis C infection are not available.

Prevention and control measures

HBV vaccination is free of charge for some groups including healthcare workers (since 1997), adolescents aged 13 (since 1999) and newborns throughout the country (since 2003). Efforts to vaccinate adults (including IDUs and prisoners) have been limited, primarily due to the absence of sustainable programmes and the cost of the vaccine.

In 2002-2003, compliance to an accelerated schedule (at 0, 1 and 3 weeks), compared with the standard schedule (0, 1 and 6 months) for prophylactic hepatitis B vaccination among IDUs imprisoned in Tallinn Central Prison was investigated. The full vaccination course (three vaccinations) was administered to 457 IDUs (81%) of 566 inmates included in the study. The results revealed that a short hepatitis B vaccination schedule among imprisoned IDUs has a significantly higher compliance and seroprotection rate than the standard six month schedule, and should therefore be recommended for use in this population. Low seroprotection rate was correlated to concurrent hepatitis C infection [8]

Conclusion

Taking into account the current epidemiological situation for viral hepatitis in Estonia, there is an urgent need for preventive measures to be strengthened. Behavioural interventions to reduce the harm and risk of HBV/HCV infections, HBV vaccination, and appropriate medical management of chronically infected persons from the community at large and the IDU population could help to solve this serious public health problem in Estonia.

This article was adapted from reference 1 by the editorial team and Dr K Kutsar.

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