

## Euroroundup

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- **Ascertainment of meningococcal disease in Europe**

## Rabies: a 'neglected disease'

## Surveillance report

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- **HTLV infection in England and Wales**

## Outbreak report

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- **Human-to-human transmission of avian influenza A/H7N7**
- **OUTBREAK DISPATCHES**  
**Malaria deaths in travellers**
- **SHORT REPORTS**  
**Congenital rubella syndrome in the Netherlands**





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**CONTENTS****EDITORIALS** 210

- **Avian and Pandemic Influenza - Five Questions for 2006** 210  
A Nicoll
- **Rabies remains a 'neglected disease'** 211  
AR Fooks

**ORIGINAL ARTICLES** 213**Topic: Rabies**

- **Rabies in Europe in 2005** 213  
H Bourhy, L Dacheux, C Strady, A Maïlles
- **Public health concerns in bat rabies across Europe** 217  
M Stantic-Pavlinic
- **Fox rabies in France** 220  
B Toma
- **An imported case of canine rabies in Aquitaine: Investigation and management of the contacts at risk, August 2004-March 2005** 222  
V Servas, A Maïlles, D Neau, C Castor, A Manetti, E Fouquet, J-M Ragnaud, H Bourhy, MC Paty, N Melik, J Astoul, F Cliquet, M-P Moiton, C François, M Coustillas, J-C Minet, P Parriaud, I Capek, L Filleul
- **A human case of travel-related rabies in Austria, September 2004** 225  
R Strauss, A Gränz, M Wassermann-Neuhold, R Krause, Z Bagó, S Revilla-Fernández, FS Simón-Soria, JE Echevarría, T Popow-Kraupp, F Allerberger, M Schönbauer, H Hrabčik
- **Rabies surveillance, trends in animal rabies and human post-exposure treatment in Poland, 1990 -2004** 226  
M Sadkowska-Todys, M Rosinska, M Smreczak, M Czerwinski, JF Zmudzinski
- **Fox rabies in Germany – an update** 229  
T Müller, T Selhorst, C Pöttsch

**Surveillance reports** 232

- **New diagnoses of HTLV infection in England and Wales: 2002-2004** 232  
S Dougan, R Smith, JC Tosswill, K Davison, M Zuckerman, GP Taylor
- **Disseminated and chronic Lyme borreliosis in Norway, 1995-2004** 235  
K Nygård, A Broch Brantsæter, R Mehl
- **Epidemiology of invasive meningococcal disease in France in 2003** 238  
A Perrocheau, MK Taha, D Levy-Bruhl

• <b>Did you have flu last week? A telephone survey to estimate a point prevalence of influenza in the Swedish population</b>	241	• <b>Rubella outbreak in an unvaccinated religious community in the Netherlands leads to cases of congenital rubella syndrome</b>	274
L Payne, S Kühlmann-Berenzon, K Ekdahl, J Giesecke, L Högberg, P Penttinen		Y van der Veen, S Hahné, H Ruijs, R van Binnendijk, A Timen, A van Loon, H de Melker	
• <b>Completeness of malaria notification in the Netherlands 1995-2003 assessed by capture-recapture method</b>	244	• <b>Transmission of HIV/AIDS in Europe continuing</b>	275
S Klein, A Bosman		A Nardone	
<b>Euroroundups</b>	<b>247</b>	<b>OTHER ONLINE-ONLY CONTENT</b>	<b>276</b>
• <b>Ascertainment of meningococcal disease in Europe</b>	247	<b>NATIONAL BULLETINS</b>	
C Trotter, S Samuelsson, A Perrocheau, S de Greeff, H de Melker, S Heuberger, M Ramsay			
• <b>Surveillance of Listeria infections in Europe</b>	251		
H de Valk, C Jacquet, V Goulet, V Vaillant, A Perna, F Simon, JC Desenclos, P Martin on behalf of the Listeria surveillance feasibility study participants			
• <b>Legionnaires' disease in Europe 2003-2004</b>	256		
KD Ricketts, CA Joseph on behalf of the European Working Group for Legionella Infections			
• <b>European recommendations for the management of healthcare workers occupationally exposed to hepatitis B virus and hepatitis C virus</b>	260		
V Puro, G De Carli, S Cicalini, F Soldani, U Balslev, J Begovac, L Boaventura, M Campins Martí, MJ Hernández Navarrete, R Kammerlander, C Larsen, F Lot, S Lundin, U Marcus, L Payne, AA Pereira, T Thomas, G Ippolito			
<b>Outbreak reports</b>	<b>264</b>		
• <b>Human to human transmission of avian influenza A/H7N7, The Netherlands, 2003</b>	264		
M. Du Ry van Beest Holle, A Meijer, M Koopmans, CM de Jager, EEHM van de Kamp, B Wilbrink, MAE Conyn-van Spaendonck, A Bosman			
• <b>Late detection of an outbreak of Shigellosis in a school in Madrid words ref table</b>	268		
J Jonsson, M del Carmen Álvarez-Castillo, JC Sanz, R Ramiro, E Ballester, M Fernández, MA Echeita, F Martínez Navarro			
<b>OUTBREAK DISPATCHES</b>	<b>271</b>		
• <b>Outbreak of verotoxin producing <i>E. coli</i> O157 infections involving over forty schools in south Wales, September 2005</b>	271		
R Salmon			
• <b>Cholera in Belgian tourists after travel to Turkey</b>	271		
K De Schrijver, H Boeckx, G Top, A Mertens, P De Mol			
• <b><i>Salmonella</i> Typhimurium DT104 outbreak linked to imported minced beef, Norway, October – November 2005</b>	272		
E Isakbaeva, B-A Lindstedt, B Schimmer, T Vardund, TL Stavnes, K Hauge, B Gondrosen, H Blystad, H Kløvstad, P Aavitsland, K Nygård, G Kapperud			
• <b>Malaria cases and deaths in UK travellers returning from The Gambia</b>	273		
CJ Williams, J Jones			
<b>SHORT REPORTS</b>	<b>274</b>		
• <b>First isolation of <i>Clostridium difficile</i> PCR ribotype 027, toxinotype III in Belgium</b>	274		
R Joseph, D Demeyer, D Vanrenterghem, R van den Berg, E Kuijper, M DeLmée			

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# AVIAN AND PANDEMIC INFLUENZA FIVE QUESTIONS FOR 2006

A Nicoll\*

European Centre for Disease Prevention and Control (ECDC)

In January this year it was observed that 2005 was going to be the Year of the Rooster in the Chinese calendar, and that perhaps was an ill omen for bird (avian) and pandemic influenza. Certainly, influenza was the infection that then dominated the popular press in 2005, and so in a certain way this was a very 'good' year for influenza and those who study it. The infection has been getting the attention it deserves as a human threat.

In this edition of *Eurosurveillance* there is an important report of one highly pathogenic avian influenza virus (HPAI type A/H7N7) that affected humans during the 2003 poultry epidemic in the Netherlands and Belgium [1]. The human infections were mostly among those working to control the infection, and their families. In response, ECDC, together with an expert group, has produced interim occupational guidance for Europe that will reduce the risk [2]. However, this experience also emphasises the variability in the influenza virus families. While H7N7 was quite infectious for humans and showed measurable person to person transmission, another better known avian influenza, A/H5N1, is quite different, as it currently seems to infect humans only rarely and human-to-human transmission seems to be even rarer [3].

The year's end is traditionally a time for reflection, and I would like to propose five fundamental questions about pandemic risk for the start of 2006.

## Has the risk from avian and pandemic influenza been exaggerated?

The answer to this question must be both 'Yes' and 'No'. In the autumn of 2005, when H5N1 appeared on the borders of Europe in Romania, Turkey and Croatia, there was suddenly massive public interest and gross confusion of three separate, although related, influenza types: *Seasonal Influenza*, *Avian Influenza* and *Pandemic Influenza*. [see ECDC website [http://www.ecdc.eu.int/influenza/factsheet\\_influenza.php](http://www.ecdc.eu.int/influenza/factsheet_influenza.php) for definitions] Even the serious media's presentations of the situation gave the strong impression that a human influenza pandemic was about to start, and that the pandemic virus would probably be brought to Europe by migrating birds. If there is no pandemic in 2006, members of the lay public may reasonably feel that some authorities have been 'crying wolf'. Although official statements have been mostly measured and accurate, the reporting of those statements tended to exaggerate the current threat from H5N1. The reality is thus far in its evolution, the family of H5N1 viruses available for study are avian viruses that are poorly adapted to humans, for whom they are not very infectious, but highly pathogenic in those few humans that they do infect [4,5]. That *low risk* (of becoming infected) - *high risk* (of severe disease if you are infected) message is a difficult one for risk communicators to convey. Occasionally, H5N1 transmits from one human to another, but none of the viruses at present seem to represent a pandemic strain, as their reproductive rate in humans ( $R_0$ ) is far below unity [3,6].

That is not to say that the H5N1 viruses are without social impact. In Thailand they have prejudiced that country's economically important export trade in poultry products to Europe and Japan. For societies like China and Vietnam where poultry are key to food security, the threat to the rural communities is considerably greater [7]. It is not surprising that both China and Vietnam are turning to the potentially risky measure of poultry immunisation as a measure to protect their huge flocks. This is a massive task. It is estimated that at any moment China's human population of 1.3 billion keeps around four billion domestic birds (point prevalence) and that each year they require fourteen billion domestic birds (period prevalence).

The main threat, however, is of a human pandemic. Any pandemic would represent a major risk to human health and a threat to social functioning worldwide. The two lesser pandemics of the 20th century (1957 and 1968) are each estimated to have killed between one and four million people worldwide. A pandemic on the scale of 1918-1919 (at least 20 million deaths) would be catastrophic [8]. Arguably, the interconnected industrialised world of today is more vulnerable to a pandemic than it was

even forty years ago. Not only is there much more international travel to spread infection, but societies are more dependent for daily existence on goods and services that are produced elsewhere. Efficient 'just in time' stockkeeping systems, e.g. for food, will be vulnerable to the sudden mass illness in production and distribution staff that would take place in a pandemic. It is estimated that for short periods at the height of a pandemic up to 20% of working adults might be unavailable for work, because they are ill with influenza, or caring for others who are ill, or simply out of fear of infection. Fortunately, these periods of intense illness will not occur everywhere at the same time, but the disruption could nevertheless be considerable.

## Will the next pandemic be due to H5N1?

We do not know. Pandemics occur through the emergence of a new strain of influenza virus which can infect and is pathogenic to humans, to which there is little pre-existing immunity and which can transmit readily from person to person. This is thought to happen by one of two mechanisms. Either through two pre-existing influenza virus types exchanging genetic material (recombination) or spontaneous genetic shift (mutation) from a single pre-existing influenza strain. Could H5N1 do either? It is certainly a candidate for a pandemic strain, as it can infect humans and is highly pathogenic. Some have argued that it only needs to make the final step of efficient person to person transmission, and WHO has set its global scale at Pandemic Alert Phase 3, the last phase before efficient human-to-human transmission. Others, however, consider that the next pandemic is equally if not more likely to come from a low pathogenicity avian influenza, such as H9N2 [5]. None of the three pandemics of the 20th century were based on a H5 strain, and H5N1 has been around at least since 1996 without a pandemic having resulted. It is also relatively uninfecious for humans, unlike the H7N7 strain observed by De Ry et al [1]. At the same time, H5N1 has spread massively, with the result that there are outbreaks in poultry in many East and South East Asian countries, including the huge bird populations of China. Although recombination involving H5N1 has not yet been detected, the possibility of it happening must have increased. H5N1 is not a uniform strain, but rather a large and complex family of viruses, and one of these may eventually mix and exchange genetic material with a transmissible human influenza [9]. However further risk assessments to determine whether or not H5N1 will cause a pandemic are of less value than making preparations for a pandemic due to H5N1 or any other influenza virus.

## How bad will the pandemic be and what will be its characteristics?

Again, we do not know. Pandemics are not standard. The three 20th century pandemics varied not only in their driving viruses and scale, but also in their characteristics. For example, the 1918-1919 pandemics affected young adults in particular, while the later epidemics more often affected the elderly. We cannot assume that the next pandemic will be driven by transmission in particular groups, and data that can only be derived during the actual pandemic must guide interventions. It could be that workplace transmission will be crucial or that transmission among school-age or younger children will predominate. When a pandemic happens, the two most important investigations will be isolating the virus (to develop tests and the pandemic vaccine) and carrying out early quick, focused epidemiological studies at the sites of first outbreaks, both in Europe and beyond (to determine basic parameters such as mode of transmission, age-specific attack rates, and case-fatality rates, to guide countermeasures) The analogy with the evidence-based approach to controlling SARS is clear [10].

## What role will antivirals play during a pandemic and how big a stockpile should countries have?

There is a danger that the availability of antivirals (especially oseltamivir) dominates thinking and preparations for a pandemic [11]. A detailed

and rational approach to the use of antivirals in a pandemic has yet to be determined. Hospital doctors will, quite reasonably, expect to have available antivirals to treat those requiring hospitalisation, although it will be impossible to know ahead of time whether they will be effective at later stages in a patient's illness. Some countries are planning to have national stockpiles. However, simply having a stockpile is not enough, and if one European country has a stockpile ten times larger than its neighbour, it cannot be therefore judged to be ten times better prepared. Since in order to be effective in treatment of influenza, antivirals must be delivered within 48 if not 12 hours of symptom onset, it can be seen that mass delivery to populations will be a major issue. A stockpile without a rapid delivery system will provide little protection. Some have proposed that there be a European Union stockpile of antivirals. A modest European stockpile could for example assist in protecting workers during poultry outbreaks close to Europe [1,2]. It would also be an asset in the unlikely event that the next pandemic started in or near Europe, so that WHO's stamping out tactic could at least be attempted, supposing the existence of a practical plan to do so [12]. However, rapid development and production of a pandemic vaccine will probably be more important for the second wave, with the more distant hope of more cross-protective vaccines that would protect against pandemic first waves (so-called universal vaccines) [13]. Equally important and more immediately accessible will be the simple public health measures (early self-isolation of those with symptoms, handwashing, respiratory hygiene, etc.) that are already available, and will save lives [14].

### Is Europe prepared for a pandemic?

Not as prepared as it could or should be. Six national assessments have been undertaken by countries using a standard assessment tool and working with teams from ECDC, the European Commission and WHO European Region. These assessments (which will continue in 2006) found that while all six countries were preparing rapidly, all also had considerable way yet to go. Major issues remain to be addressed, notably the need for preparations to extend outside the health sector alone and for plans to be made more operational [15].

In conclusion, the threat from a pandemic has not been exaggerated. It could happen in 2006 from H5N1, or, more likely, in the future, and with another strain. However, in 2005 most European authorities and politicians started to give the risks the serious attention they deserve, and to invest the necessary resources to develop countermeasures. It is to be hoped that as the media interest inevitably declines, those in authority will sustain the investment and the levels of preparatory activity. Certainly, the pandemic risk will not decline.

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## EDITORIAL

# RABIES REMAINS A 'NEGLECTED DISEASE'

### AR Fooks

Rabies and Wildlife Zoonoses Group, Veterinary Laboratories Agency, and WHO Collaborating Centre for the Characterisation of Rabies and Rabies-Related Viruses, UK

Europe continually encounters the serious threat posed from zoonotic diseases including ancient bacterial agents such as *Mycobacterium tuberculosis*. The largest threat, however, is from RNA viruses such as the SARS-CoV, the Henipah viruses, avian influenza viruses and emerging lyssaviruses. The ability of RNA viruses to expand their cell tropism in response to immune selection and to fill new ecological niches has demonstrated that this collection of viruses is extremely versatile with an enhanced capability for crossing the species barrier. One explanation that might account for this observation is that much higher nucleotide substitution rates for RNA viruses permit more rapid adaptation, greatly increasing the chances of successfully invading a new host population [1]. RNA viruses do not exist in a 'genetic stasis' and by mutation, crossing the species barrier, immune evasion and viral adaptation to a new animal host, further RNA viruses will emerge as human pathogens in the future and cause a threat to both animal welfare and human health in Europe.

The subsequent emergence of animal diseases that have the capability of crossing the 'species barrier' to humans ('zoonotic pathogens') will therefore continue to have a major impact on policy issues that relate to human healthcare. This has been witnessed with the re-emergence of rabies in some regions of Europe that were previously designated 'rabies-free', which

has demonstrated the need for continual vigilance and the adoption of strict control measures. Despite the significant advances that have been made during the 20<sup>th</sup> century in reducing the burden of rabies, especially in central and eastern Europe, the disease remains endemic in many countries, largely as a result of financial limitations and a poor medical / veterinary infrastructure. Rabies therefore, remains a 'neglected' disease.

Since 1939, the epizootic of terrestrial rabies in Europe had spread 1400 km westward from Poland. It had been reported that the front of the epizootic advanced 20 km - 60 km per year [2]. Although other susceptible species, both wild and domestic, were involved in the epizootic, the red fox (*Vulpes vulpes*) was the principal reservoir, playing a key role in the maintenance and transmission of the virus. However, maintaining a rabies-free status, as reported by Servas and colleagues, incurs considerable costs and there is a continual risk of re-importation [3]. In France, Pr. Toma reports the effective reduction of rabies in the red fox [4]; however, the risk from rabies in imported dogs has since become a principal concern [3].

Since 1989, the increased use of oral rabies vaccines (ORV) has been instrumental in successfully eliminating sylvatic rabies from large areas within Europe. From 1990 onwards, we have witnessed the elimination of rabies from terrestrial mammals (principally the red fox) in many Western

European countries: the Netherlands (1991), Switzerland (1999), France (2000), Belgium and Luxembourg (2001) and the Czech Republic (2004) resulting in these countries being declared 'rabies-free'. Oral rabies vaccination (ORV) field trials were first reported in Switzerland in 1978 using a live-attenuated rabies virus strain (Street Alabama Dufferin, SAD). The use of a genetically modified vaccine (vaccinia recombinant expressing the rabies virus glycoprotein; VRG) has also been widely used in recent years. A planned and managed rabies control protocol with the use of ORV in urban areas complemented with intensified rabies surveillance has been proposed by Mueller and colleagues to tackle a residual focus of rabies in parts of Germany in the border triangle of Hessen, Baden-Württemberg and Rhineland Palatinate [5]. The results from the German study are very encouraging, with an obvious decrease in rabies incidence in the infected areas leading to the overall goal that Germany will be free of terrestrial rabies in due course. It is good to hear that the 'lessons learned' in reducing the incidence of rabies in western Europe can be applied to other rabies-endemic countries.

Moreover, elimination of rabies from the animal reservoir constitutes an investment in preventing rabies in humans. More recently, the Pan American Health Organisation has demonstrated that a reduction of canine rabies has correlated with a substantial decrease in human rabies cases. If rabies, as in the majority of Europe, is eliminated from domestic animals and wildlife, the incidence of rabies in man will also be controlled [6]. While the success of ORV in wildlife in Poland has resulted in a decrease in reported animal rabies cases, Sadkowska-Todys [7] and colleagues have not observed the expected reduction in the use of post-exposure prophylaxis (PEP) for rabies in humans. One possible explanation is that while rabies still circulates in animal reservoirs in Poland, any exposure, especially a biting incident is treated as a 'suspect' exposure, particularly if the animal carcass is not available for diagnostic testing. As rabies continues to remain a 'neglected' disease, an increased awareness of human infection is required, especially among the medical community, to ensure that PEP is administered in a timely and correct manner. This lesson was exemplified in the United Kingdom when a thirty seven year old woman died of rabies three and a half months after returning from a holiday in Goa, India, where she had bitten by a dog [8]. In this case, PEP was not administered. In 2004, the case of rabies in a 23 year old Austrian man after being bitten by a dog in Morocco as reported by Strauss and colleagues [9] further confirms the need to maintain awareness of the risks of rabies during foreign travel and to re-emphasise the public health challenge of 'neglected' diseases [10].

Another case of human rabies was reported in 2004, although at the time of death, rabies was not considered as the cause [11]. Following the death of the patient, various organs were transplanted into six recipients. Within six weeks of transplantation, three of the organ recipients developed encephalitis and died. Rabies was confirmed by laboratory diagnosis as the cause of death. The patient who received the liver was given immediate PEP and survived. The two recipients of the corneas were also treated and the grafts removed. Retrospectively, rabies was diagnosed in the donor from fixed brain samples and a history of a dog bite confirmed during a visit to India in October 2004. This incident followed a similar case in the United States earlier in 2004 [12]. The rabies transplant cases remind us to suspect rabies in unusual presentations of the disease. In addition, individuals with neurological sequelae and a history of travel to rabies-endemic countries should not be considered as suitable candidates for organ donation.

While the threat in Europe from rabies in foxes has diminished in western Europe as reported by Bourhy and colleagues [13], dog rabies in some eastern European countries, fox rabies in central and eastern Europe and racoon dog rabies in northeastern Europe continue to pose a risk. Moreover, Stantic-Pavlinic [14] reports that bat variants of rabies virus are an increasing threat throughout Europe, which has led to international organisations adopting the legislation that rabies variants in bats are now considered a statutory notifiable disease. European variants of rabies virus include the European Bat Lyssaviruses (EBLVs) types-1 and -2 (genotypes 5 and 6 respectively) [15,16]. Due to the protected status of bats in Europe, our knowledge of EBLV prevalence and epidemiology is limited. It is possible that EBLV is under-reported and that the recorded cases of EBLV represent only a very small proportion of the actual number of infected bats. Four additional lyssaviruses have also been isolated from bats in Eurasia (Aravan virus, Khujand virus, Irkut virus and West Caucasian Bat Virus) and have been proposed as new members of the *Lyssavirus* genus. Concerns exist that conventional biologicals will be ineffective against these newly emerging lyssaviruses and they will therefore have considerable public health implications [17]. Research is still required to further understand the role that insectivorous

bats play in the virus-host relationship and subsequent transmission of EBLVs [18]. It is possible that insectivorous bats may harbour EBLVs for extended periods of time while the bat shows no obvious clinical signs ('silent infection'). Although it is feasible that EBLVs remain in the host in a 'latent' (dormant) state for long periods of time with potential 'asymptomatic carriage', strains of rabies virus are not, in general, considered to be 'persistent' viruses.

As the list of European countries that have eliminated terrestrial rabies continues to increase, the major issues will be on maintaining this situation. While the control of rabies in foxes is applauded, the vigilance and surveillance of rabies must continue especially in new reservoir species such as the racoon dog and in assessing the prevalence of new and emerging variants of rabies virus in European species of bats. This can be achieved through harmonisation of a laboratory network throughout Europe and in closer working between international organisations including the European Union, the Office International des Epizooties (World Organisation for Animal Health) and the World Health Organisation.

**Surveillance of rabies  
must continue especially  
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## ORIGINAL ARTICLES

## Euroroundup

## RABIES IN EUROPE IN 2005

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Rabies is still present in Europe in 2005. Its incidence in humans remains limited (fewer than 5 human cases per year) through the application of strict prophylactic measures (anti-rabies treatment) and by means of veterinary rabies control measures in the domesticated and wild animal populations. The main indigenous animal reservoirs are: the dog in eastern European countries and on the borders with the Middle East; the fox in central and eastern Europe; the racoon dog in northeastern Europe; and the insectivorous bat throughout the entire territory. Finally, each year, cases of animals with rabies imported from enzootic areas are reported, showing the permeability of borders and traveller's lack of consideration of the rabies risk. These importations constantly threaten the rabies-free status of terrestrial animals in western European countries and complicate the therapeutic decisions taken by physicians in the absence of information regarding the biting animal.

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**Key words:** Rabies, europe, epidemiology, reservoir, human, fox, raccoon dog, travel

### Rabies is still present in Europe

Rabies is a lethal form of encephalitis [1]. It is induced by neurotropic viruses of the *Lyssavirus* genus. Rabies prevention methods are known since Louis Pasteur and described in specialised reports from the World Health Organization (WHO) [2]. However, the estimated rabies morbidity in humans remains high worldwide: approximately 40 000 to 50 000 deaths per year. Finally, about 10 million anti-rabies treatments are still distributed annually. From a virologic point of view, 7 lyssavirus genotypes have been identified based on the comparison of their gene sequences.

Rabies is still present in Europe. Its incidence is low (fewer than 5 human cases per year) and stable. Three lyssavirus genotypes are endemic: genotype 1 or rabies virus (RABV), which infects terrestrial animals, and genotypes 5 and 6 or European bat lyssavirus type 1 (EBLV-1) and type 2 (EBLV-2) [3-4]. In addition, imported cases with viruses of other genotypes can appear in Europe. Europe has quality anti-rabies vaccines and immunoglobulins. This article describes the epidemiologic status of animal and human rabies in Europe.

### Animal rabies

#### Introduction

Rabies is a zoonosis with a complex epidemiology. Its description requires a clear definition of the terms used. The term 'reservoir' is

used to define a susceptible animal species, which by itself sustains the infection or the epidemiologic cycle in a given geographic area. The term 'vector' is used to define any susceptible animal species, reservoir or not, which can constitute an effective transmitter of the infection to another animal species or humans. Symptoms of rabies in infected animals correspond to those associated with encephalitis. Thus, they are not characteristic and the diagnosis of certainty is based exclusively on laboratory tests [2,5,6].

In Europe, several epidemiologic cycles of rabies coexist. These epidemiologic cycles are characterised by an animal species reservoir of a lyssavirus variant that is specifically adapted to it. However, these variants maintain the ability to infect other mammals. These mammals then become either an epidemiologic 'cul-de-sac' (e.g., humans) or a non-reservoir vector species, or secondary species in the epidemiologic cycle responsible for a limited chain of transmission (e.g., bovines infected by fox rabies).

During the last century, important modifications of the epidemiologic cycles of rabies in Europe were observed, and the establishment of new epidemiologic and biologic investigations revealed evidence of new epidemiologic cycles.

The remainder of this article will review the different epidemiologic cycles presenting a risk in Europe: rabies in domesticated carnivores, or canine rabies; rabies in the fox, or vulpine rabies; and rabies in bats (chiroptera).

### Canine rabies

#### Affected species

The dog constitutes the only reservoir and the main vector. However, numerous other species of domesticated mammal (cows, sheep, goats, pigs, cats and ferrets) can be infected and thus constitute efficient vectors between dogs and humans on one hand and other domesticated or wild animals on the other.

Although there have been exceptional cases, such as infection in the laboratory or contamination in captivity through infected wild animals, rodents and lagomorphs (rabbits, hares and pikas) do not constitute infection relays.

### History

The canine rabies which once affected all of Europe progressively disappeared in the majority of countries in central and western Europe during the first half of the twentieth century. This disappearance was probably linked more to the enforced circulation restriction of animals than to a policy of animal vaccination. Nevertheless, epidemiologic and genetic analysis of the isolates show that canine rabies remains in certain European countries, as well as on the borders of Europe. To the east of Europe, the canine type isolates are still responsible for enzootic rabies areas, for example in Turkey and the rest of the Middle East. In addition, isolates whose genetic characteristics make them part of the canine-type virus were identified sporadically in the 1990s in the former Yugoslavia and Hungary [3]. The epidemiologic and virologic data available for the more northern countries (Ukraine,

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Belarus and Russia) do not allow the exclusion or confirmation of a residual presence of canine-type isolates in these regions. To the south of Europe, canine rabies is endemic in all the North African countries of the Maghreb. All these viruses belong to lyssavirus genotype 1 and to the phylogenetic line common to the viruses circulating in Europe, the Middle East and North Africa [7].

#### Current situation

Today, canine rabies has disappeared from the countries of the European Union. The main risk, therefore, resides in the translocation of uncontrolled animals originating from neighbouring countries to the east and south of Europe. The risk can also originate from more distant areas of enzootic rabies by way of illegal importations from, for example, Asia, or sub-Saharan Africa. Many recent examples show that travellers are not aware of the sanitary risks they take and impose on their environment by travelling with their non-vaccinated dogs to an endemic region or by adopting animals from an endemic area to take back home with them at the end of their holiday.

#### Rabies in wild terrestrial animals

##### Affected species

The main epidemiologic cycle of rabies in wild animals in Europe is maintained by the red fox (*Vulpes vulpes*). Another epidemiologic cycle, maintained by the racoon dog (*Nyctereutes procyonides*) originally native to Asia, seems to be developing in the Baltic countries and in Poland [3].

The non-reservoir infection vectors are the same animal species as those described in the case of canine rabies.

##### History

The spontaneous mutation capability of the rabies virus allows it to generate mutants during its multiplication; some of these can randomly show a selective advantage for animal species other than the original reservoir species.

A mutant of the rabies virus once adapted to the dog seems to have changed vector in the 1930s to 1940s at the Russian-Polish border. A new virus adapted to the red fox appeared. The area of epizootic rabies then expanded rapidly in all directions, with an average progression of 20 km to 60 km per year, expanding into several countries in eastern, central and western Europe. The maximum north-south extension in western Europe was reached in the late 1970s, extending from the Netherlands to Italy. The maximum extension to the west was reached in 1989, covering a large portion of the northeastern quarter of France. Today this extension has been arrested and the front of enzootic vulpine rabies has been pushed back to central Europe thanks to the oral vaccination of foxes [8].

The initial efforts to distribute anti-rabies vaccine baits started in Switzerland in 1978. This strategy of oral vaccination of foxes then began in Germany in 1983, followed by Italy in 1984 and then by Belgium, France and Luxembourg in 1986. Despite these measures, the highest number of registered cases in wild animals in Europe was reached in 1989. In the same year, the European Commission subsidised the campaigns at 50%, on condition that the vaccination plans included coordination across borders. Thus, the Czech Republic in 1989, Hungary and the Slovak Republic in 1992, Poland in 1993, Slovenia in 1995, and then many other countries, began to undertake oral vaccination campaigns of larger or smaller scale.

##### The current situation

Numerous European countries are today free of rabies in terrestrial animals: Ireland, the United Kingdom, Sweden, Norway, Finland, Denmark, the Netherlands, Luxembourg, Belgium, France, Switzerland, the Czech Republic, Italy, Spain and Portugal.

#### Chiroptera rabies

Bat rabies has long been recognized in Europe. The first isolates were obtained in 1954. Beginning in 1985, important campaigns to capture and test bats were undertaken in Denmark and the Netherlands and revealed the importance of enzootic rabies areas. Since the end of these exploratory campaigns, approximately 50 cases per year have been diagnosed in numerous European countries. Another article in this issue discusses this topic specifically [9]. The number of human cases is limited (four human cases since 1977).

#### Human Rabies

##### Introduction

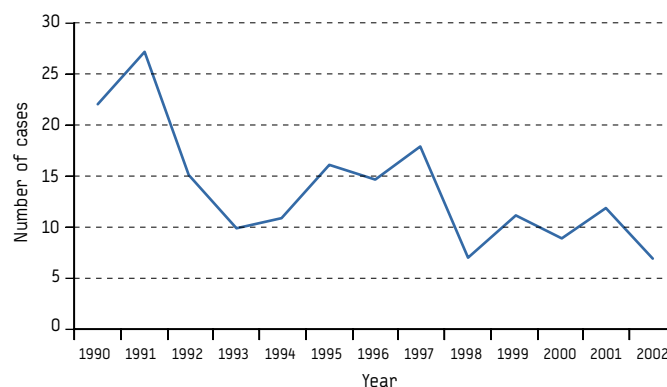
Rabies is a disease with known methods of prevention [2]. It results exclusively from animal contamination by bite wound, scratch wound, or licking of mucous membranes. The several cases per year in Europe result from inadequate or absent care of infected patients. The most frequent causes are the absence of administration of post-exposure treatment (PET) [10], the absence of administration of anti-rabies immunoglobulins and delayed care after contamination. There is no direct interhuman contamination. However, some cases of rabies transmission through organ transplant have been described worldwide, with three cases recently reported in Germany [11].

Human rabies cases in Europe arise in two epidemiologically distinct situations: indigenous cases from contact with an infected animal in a known enzootic areas, or imported cases resulting from a visit to an endemic region, usually in Africa and Asia. These two situations will be addressed separately.

##### Indigenous human rabies

The number of human cases of indigenous origin recorded in Europe diminished in parallel with the retreat of the vulpine rabies 'front' [FIGURE 1]. From 2000 to 2004, 45 cases of indigenous human rabies were reported, all in countries where the vulpine enzootic rabies continues (see below), in central and eastern Europe [TABLE 1], [FIGURE 2]. No cases were identified during this period in the regions where only canine rabies is present (Turkey for example). This difference is probably not related to a higher pathogenicity of the vulpine virus compared with the canine virus in humans but rather to a failure to implement human rabies prophylaxis procedures. As an illustration of this, the number of human cases that occurred in western European countries affected by vulpine rabies is low. In France for example, more than 49 000 cases of animal rabies have been recorded and no indigenous human case has ever been reported. However, a significant number of anti-rabies treatments (3000 to 10 000 per year) were administered in France when vulpine rabies was enzootic.

FIGURE 1  
Total number of human rabies cases notified in Europe, 1990-2002



Source: [12]



TABLE 1

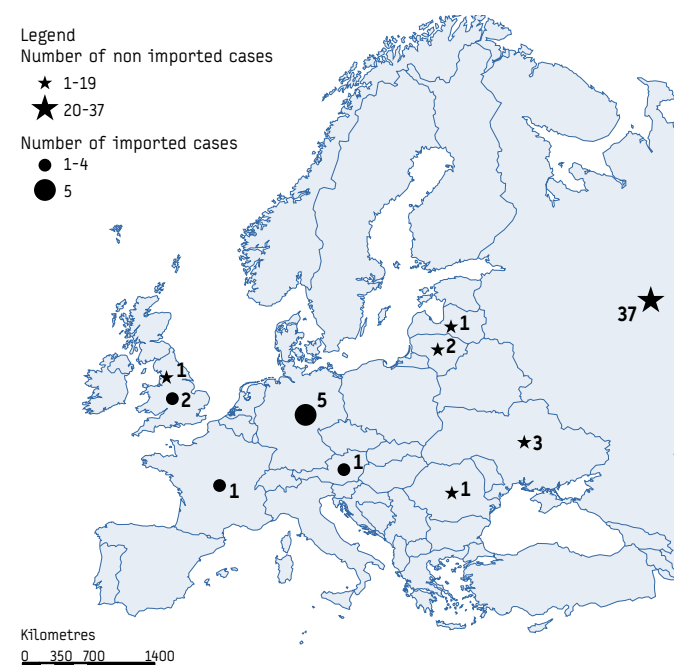
## European autochthonous human cases

Country	2000	2001	2002	2003	2004	Total
Latvia				1		1
Lithuania	1				1	2
Romania	1					1
Russia	7	10	5	3	12	37
Ukraine			1	2		3
UK			1*			1
<b>Total</b>	<b>9</b>	<b>10</b>	<b>7</b>	<b>6</b>	<b>13</b>	<b>45</b>

\* EBLV-2 rabies encephalitis in a bat handler, Scotland, UK  
Sources: [13-17]

FIGURE 2

## Cumulative numbers of human rabies cases in Europe by country, January 2000 to June 2005



The five human cases reported in Germany were two imported cases and three cases in recipients of organ donation from an imported case. The autochthonous case in the UK was infected with EBLV-2 in 2002

Sources: [11, 13-17]

With the exception of the patient from the United Kingdom in 2002, all of these cases were attributed to infections with genotype 1 lyssavirus (classic canine rabies).

TABLE 2

## Human rabies cases in Europe, 1 January 2000-1 July 2005

Year / Country	2000	2001	2002	2003	2004	2005
Germany					1 (India)	1 <sup>§</sup> (India) + 3 (grafts)
Austria					1 (Morocco)	
France				1 (Gabon)*		
UK		2 (Philippines, Nigeria)				

\* No bite or scratch reported

§ Case giving rise to a case following graft

Sources: [11, 13-17]

Infectious contact with a wild or a domesticated carnivore was reported for any of these human cases excepted the case from the United Kingdom in 2002 and Lithuanian case in 2004.

The origin of the infection of the Lithuanian case diagnosed in 2004 could not be determined; it concerned a 5 year old boy living in a rural region where cases of vulpine rabies are regularly recorded [18]. The patient from Scotland in the United Kingdom diagnosed in 2002 died of an encephalitis due to EBLV-2 virus for which bats are the reservoirs (see specific article in this issue) [19]. This patient, a professional bat handler, endured several dozens of bites during the course of each capture season. He had not been vaccinated prophylactically against rabies and he did not wear gloves while handling bats. The last known bite before appearance of symptoms had been inflicted by a Daubenton's bat (*Myotis daubentonii*) approximately 2 months before the onset of rabies symptoms [20]. The patient had not received PET after any of his bites. This was the fourth case of rabies due to EBLV described worldwide and the second attributable to EBLV-2. The first case concerned a Finnish bat handler who captured and handled bats in Switzerland and Finland, and who died of rabies in 1985 [21-22]. A case of human rabies caused by EBLV-1 was described in the former Soviet Union in 1985 in an 11 year old child, [23]. An earlier case had been suspected in 1977 in the Soviet Union in a 15 year old child, but could not be confirmed due to the lack of characterisation of the viral strain [21]. The recent case in Scotland has resulted in vaccination recommendations for bat handlers in most western European countries [24-25].

## Human rabies by importation

The imported cases of human rabies, although rare, reflect travellers' lack of awareness of the rabies risk [26]. From 2000 to July 2005, 6 imported cases have been reported in Europe [TABLE 2], [FIGURE 2]. Among them, 3 cases of infection occurred on the African continent (Morocco, Niger, Gabon), 2 infections occurred on the Indian subcontinent and one infection occurred in Asia (Philippines). In the case imported from Gabon to France in 2003, the patient had not been bitten or scratched and the contamination was attributed to licking of the mucous membranes while playing with an asymptomatic dog in an urban area [27]. Imported human rabies cases can escape diagnosis in the absence of reported exposure to the virus (unconscious patient) or notification by the patient (nonaggressive excreting animal, contact with a species not known by the patient as a rabies vector, ignorance of the situation in the country visited). Human rabies can also present in a nonspecific form. Recently, this weak clinical specificity and the absence of a witness account of exposure to rabies led to the acceptance of a young German woman as an organ donor [28]. The organs of this patient, who had originally been admitted to the psychiatric ward of a hospital, were transplanted to six recipients (two corneal transplants, one liver transplant, one pancreas transplant and two kidney transplant recipients). The recipients of the two kidneys and the

pancreas developed rabies encephalitis in the 3 weeks following the transplant. The two recipients of the corneas underwent an excision of the grafts and received PET. The recipient of the liver had been vaccinated prophylactically several years before and he received PET. This unusual but dramatic event underlines the necessity to consider rabies when evaluating encephalitis of unknown cause, particularly in a patient who has travelled abroad. A meticulous examination of medical records before removal of organs for donation should also be recommended for patients presenting with nonspecific neurological signs of undetermined origin [29]. This review of the record has to take into consideration the available epidemiologic elements to identify exposure to exotic infectious agents or agents not elicited at the time of the diagnosis.

### Conclusion

Rabies remains present in Europe. The decline of vulpine and canine rabies highlights the emerging risks related to the increase in travel to regions where rabies is enzootic and the increase in contacts between humans and bats. These risks should not overshadow the importance of vulpine rabies, which is still responsible for the majority of European cases and still far from elimination.

Many patients ignore the indigenous or imported rabies risk and the existence of pre-symptomatic excretion in carnivores with rabies. Finally, countries recently declared free of rabies are vulnerable to the threat of the illegal importation of infected animals. This risk is increased by the freedom to travel within the European Union, and it is therefore mandatory for these countries to educate their populations regarding anti-rabies measures so that they can react rapidly to an importation incident. In view of the complexity of rabies epidemiology in Europe, it is important to keep health professionals, particularly physicians and veterinarians, regularly informed and updated in order to maintain vigilance. Recommendations to improve control measurements of animal rabies in Europe and in the rest of the world like preventing human transmission or infection were recently published in the WHO Expert Consultation on Rabies [2].

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## ORIGINAL ARTICLES

## Euroroundup

## PUBLIC HEALTH CONCERNS IN BAT RABIES ACROSS EUROPE

M Stantic-Pavlinic

Rabies due to two independent and different genotypes of lyssaviruses - European bat lyssaviruses (EBLV) type 1 and type 2 - is present in many European countries. Infection is usually seen in bats, the primary reservoirs of the viruses but a few spillover infections have been seen in three other species: stone martens, sheep and humans. Spillover infections (with the exception of the two human cases) were EBLV-1 only. No EBLV-2 spillover cases have been reported in terrestrial animals.

The disease is fatal in humans and has been described in Europe following a bat bite. We have studied in the available literature EBLV rabies cases across Europe in bats and humans, and have also carried out an analysis of recommendations for rabies prevention and treatments in humans. Rabies pre-exposure vaccination and post-exposure treatment is recommended for occupationally exposed persons. Some European countries have already adopted recommendations through specific protocols. Treatment of international travellers after bat bites is also recommended. The promoting of research programmes on bat rabies in Europe is underway. Bats are listed as protected species across Europe.

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**Key words:** bats, health education, lyssaviruses, mandatory testing, public health practice, rabies, vaccination

### Introduction

Over one thousand species of bats are known worldwide. In recent years, evidence has suggested that they are like most animals reservoirs or biological and accidental vectors for different kinds of micro-organisms including lyssaviruses, West Nile virus, Venezuelan equine encephalomyelitis virus, Hendra virus, Menangle virus, and *Histoplasma capsulatum* [1,2]. Nipah, Menangle and Hendra viruses have all been isolated from bats. Rabies is a notifiable disease in European countries both within and outside the European Union.

Bat rabies has been laboratory confirmed in different parts of the world, and is a public health concern [3]. Much literature has been published on this subject, mostly in the Americas. In Europe, over 30 species of bats have been recognised [4]. All are protected under the *Agreement on the Conservation of Population of European bats* [5]. It has been demonstrated that some but not all bat species carry the viruses. EBLVs are host-specific to specific bat species. Although the common serotine bat (*Eptesicus serotinus*) is mainly affected by EBLV1, different mouse-eared bats (*Myotis spp.*) are more affected by EBLV2.

Most human cases worldwide result from a dog bite or other contact with terrestrial mammals. Bat rabies in humans in Europe is very rare, but in some other parts of the world e.g. USA and Brazil is more frequently recognized. Bat bites may go unrecognised, while bites from terrestrial carnivores are usually noticed. Large outbreaks of bat rabies have been observed in South America in humans and in livestock, associated with bites of the vampire bat (*Desmodus rotundus*), a species only seen in Central and South America [6].

The *Lyssavirus* genus, within the *Rhabdoviridae* family, is subdivided into seven genotypes based on RNA sequencing [7-9]:

- genotype 1 - classical rabies virus, worldwide
- genotype 2 - Lagos bat virus, Africa
- genotype 3 - Mokola virus, Africa
- genotype 4 - Duvenhage virus, Africa
- genotype 5 - European bat lyssavirus 1 (EBLV-1), Europe
- genotype 6 - European bat lyssavirus 2 (EBLV-2), Europe
- genotype 7 - Australian bat lyssavirus, Australia.

Rabies in bats in Europe are caused by two independent lyssavirus infections, distinct from rabies infections in foxes, dogs, cats, cattle and other terrestrial animals. Classic rabies virus strains associated with terrestrial animals are from genotype 1.

This paper deals with bat rabies across Europe, and rabies pre-exposure vaccination and post-exposure treatment in humans.

### Lyssaviruses and rabies in European bat species

In Europe, bats are infected by two different lyssavirus genotypes, genotype 5 (EBLV-type 1) and genotype 6 (EBLV type-2). Both are related to the classical rabies virus, although EBLV2 is closer to genotype 1 than EBLV1 [3,10]. EBLV-1 and EBLV-2 have been subdivided into two phylogenetic lineages, EBLV-1a and EBLV-1b and EBLV-2a and EBLV-2b.

A different bat lyssavirus, named Aravan was recently isolated from a lesser mouse-eared bat, *Myotis blythii* [11] and a new lyssavirus, *West Caucasian bat virus*, was isolated in *Miniopterus schreibersii* in 2002 [12]. Their position within *Lyssavirus* genus is still being studied. Modern methods based on phylogenetic relationships were used, comparing nucleotide sequences of the nucleoprotein gene and the amino acid sequence to find the phylogenetic tree showing genetic relationships between different lyssaviruses.

Infection with EBLV has occurred in Europe in several bat species [13-16]. Rabies in bats has been reported from the Netherlands, Germany, France, Spain, Switzerland, Hungary, Poland, Denmark, Lithuania, the Russian Federation, Ukraine, Slovakia, Finland, and the United Kingdom.

In France, 14 cases of bats rabies caused by EBLV-1 have been diagnosed from 1989 to 2002, all in serotine bats (*Eptesicus serotinus*) [13]. EBLV-1a strains have been distributed in northeastern France and EBLV-1b strains in the northwest. European bat lyssavirus type 1, EBLV-1 (genotype 5), is enzootic in the insectivorous bat populations in Germany. In 2001, a single stone marten (*Martes foina*) was infected with EBLV-1a [16]. No clinical signs were observed as the animal was found dead. EBLV-1 has been identified in Spain [17]. The results came from serology and RT-PCR. EBLV-2a has been isolated in the United Kingdom [14]. The geographic distribution of infected bat species across other European countries according to laboratory determined genotypes of lyssaviruses has been described by different authors [18-21]. EBLV-1 has been found in *E. serotinus* in Denmark, the Netherlands, Poland, and Switzerland.

### Host restriction of EBLV

Bats are the primary reservoir of EBLV viruses, but natural infections have occurred in at least three other species. In very rare

circumstances, infections with the same lyssaviruses have been identified in a stone marten (1 case), sheep (2 cases) and humans [22]. To date, only three cases of rabies in humans have been reported and confirmed: one case was infected with EBLV-1 and two with EBLV-2 [14] [TABLE 1].

TABLE 1

Human rabies of bat origin – Europe

Year	Infected by	Country	Age of patients	Patient	Site of bite
1985	EBLV-1	Ukraine	11	Girl	Lower lip
1985	EBLV-2	Finland*	30	Bat researcher	Multiple bites
2002	EBLV-2	Scotland	56	Wildlife biologist	Probably on the fingers

\* This bat researcher had been mainly working on bats in Finland and Switzerland, but had also been working in Asia

Protection of humans

According to recommendations from the World Health Organization (WHO) and other institutions [3,21,23], post-exposure treatment after a bat bite is advised. Anyone exposed to bats should be vaccinated preventively against rabies. Post-exposure vaccination and treatment are recommended after a bite or after exposure to bats [TABLES 2 and 3].

TABLE 2

Bats and recommendations for rabies protection in Europe

Pre-exposure rabies vaccination	Post-exposure rabies treatment
All bat handlers and people who work with bats should receive pre-exposure rabies vaccination	After a bite of EBLV positive bat
Persons who frequently come in contact with bats in their spare time (for instance, cavers or amateur bat handlers)	Post-exposure prophylaxis should be considered when contact between a human and bat has occurred unless the exposed person can rule out a bite, scratch or exposure to a mucous membrane  Travellers bitten by a bat: <ul style="list-style-type: none"> <li>Arrived from bat rabies infected countries that report bat bites</li> <li>Arrived from countries where epidemiological data on bat rabies are missing</li> </ul>

Sources:

- WHO. Introduction of an information leaflet on bat rabies and bat conservation. Rabies Bulletin Europe 2003; 27(4): 5-7
- CDC. International Notes Bat Rabies - Europe. MMWR 1986; 35(26): 430-2

TABLE 3

WHO recommendations for treatment according to category-I to category-III exposures

Nature of exposure	Status of biting animals		Recommended treatment
	Exposure	15 <sup>th</sup> day following exposure	
I. Contact but no lesions	Rabid		None
II. Skin licked by bat; scratches or abrasions; minor bites covered	Suspected to be rabid	Healthy	None
	Rabid; wild animals or animals unavailable for observations	Rabid	Vaccination and administration of rabies immunoglobulins  Vaccine and rabies immunoglobulins immediately according to country by country risk and previous vaccination status
III. Mucosa licked by bat; major bites (multiple or on face, head, finger or neck)	Suspected or rabid domestic or wild animal or animal unavailable for observation		Vaccine and rabies immunoglobulines

Source: From the Eighth Report of the WHO Expert Committee on Rabies. Geneva: World Health Organisation; 1992. WHO Technical Report No.824

Humans bitten by a bat suspected to be infected with lyssavirus receive post-exposure prophylaxis. In previously unvaccinated persons this consists of an immediate injection of vaccine (days 0, 3, 7, 14, and 28) with additional anti-rabies immunoglobulin (20 IU/kg of body weight). Unvaccinated persons should receive an immediate dose of rabies immunoglobulin and the first dose of vaccine, and then complete the series by receiving four additional doses of vaccine on days 3, 7, 14, and 28 after the first dose. Commercially available rabies vaccines are prepared in cell cultures from the inactivated classical rabies virus, i.e. genotype 1. In central Europe, post-exposure treatment is usually given on days 0, 7 and 21; two doses are given on day 0 in the deltoids of both arms and additional doses are given on days 7 and 21. This is one of the WHO validated vaccination schedule [24]. In the United Kingdom, pre-exposure vaccination of all bat handlers, as well as post-exposure vaccination of anyone bitten or in other close contacts with bats, are recommended [24].

Some European countries already have immunisation programmes against bat rabies to protect bat handlers, as well as the general population. Pre-exposure vaccination consists of four doses of modern rabies vaccines given at 0, 7 and 21 days [24,25]. Post-exposure prophylaxis should always be considered, no matter how trivial seeming the exposure.

Current tissue cell rabies vaccines and specific immunoglobulins are used against all genotypes of lyssavirus genus. Rabies researchers generally agree that current vaccines confer a protective immune response against different genotypes of lyssaviruses, with the notable exception of West Caucasian bat virus. Antibody response of  $\geq 0.5$  IU/ml in sera, measuring neutralising antibodies of vaccinated subjects, is admitted as a sufficient antibody level for protection [25].

Underreporting of cases?

European bat lyssaviruses are recognised in Europe in a limited number of countries, and in under one third of native bat species. In many countries, there is no research, monitoring or surveillance in this field. Data is limited to accurately mapping the geographical distribution of lyssaviruses in the different bat species across Europe. Over the past fifty years, only about 800 cases of rabid bats have been notified in Europe, and more than 90% of these were in the Netherlands, Denmark, Germany, Poland, Spain and France. Serological examination of carriers of lyssaviruses in living bat populations is interesting for bat researchers and public health officers. Bats may be seropositive for antibodies against lyssaviruses and yet not be carriers of the virus. Further research on EBLV viruses occurring in bat infections and different animal species across Europe will be welcomed. At the same time laboratory confirmation of viral encephalitis in humans in Europe should include examination on

lyssaviruses to find out the real risk for domestic human rabies infections. Underreporting of viral encephalitis cases and reporting without the association of an aetiological agent for the disease is well known [26].

Infection with EBLV has been naturally identified in only two other species apart from bats and humans; stone marten and sheep. Most recently Vos et al. [27] reported successful laboratory induced infections of ferrets and mice by EBLV-1 and EBLV-2.

According to the results of studies performed on different bat species in Europe, laboratory testing on the European bat lyssavirus 1 (EBLV-1) was positive in *Tadarida teniotis*, *Myotis myotis* (EBLV-1b), *Myotis nattereri* (EBLV-1b), *Pipistrellus nathusii*, *Vespertilio murinus* (EBLV-1a), *Nyctalus noctula*, *Miniopterus schreibersii* (EBLV-1b) and *Rhinolophus ferrumequinum* (EBLV-1b). However, no virus strain was isolated in this study, and only positive serology and PCR tests were obtained. Infection is not usually lethal for bats [28].

### Successful treatment

Rabies pre-exposure vaccination and post-exposure treatment with modern rabies vaccines is safe and protective and should be extended. Although vaccination schedules are well adapted for genotype 1 classical rabies virus, this is not the case for the other genotypes. Despite a lack of evidence, vaccination schedules are still strongly recommended for the other lyssavirus genotypes. In persons occupationally exposed to bats, pre-exposure vaccination is necessary, but for the general population, only post-exposure treatments after bat bites is recommended. Different schedules with different modern generations of rabies cell culture vaccines are approved in Europe, most of all prepared on human diploid cell (HDCV) and chick embryo cell cultures (PCEP).

There have been infrequently deaths reported following bat bites of bat handlers in Europe where EBLV-1 infected bats reside. Nevertheless, even one case that carries a risk deserves attention of public health. Most bat bites are superficial and do not break through the skin to reach the nerves. Bat researchers use protective plasters and gloves to protect their fingers and hands, or perform disinfection of the wound immediately after bat bites.

### Conclusion

Rabies in bats is often considered not to be a serious risk to public health when compared with other threats [29] that may cause higher numbers of human infections per year or are more easily transmissible. No one should handle diseased or dead bats without protection, such as gloves or sticking plaster. Pre-exposure vaccination is also necessary in this context. It is vital to obtain laboratory confirmation of rabies in bat after human exposure through biting incidents. Rabies post-exposure treatment is recommended after bat bites in patients, if previous pre-exposure vaccination was (as usually) not performed.

Significant evidence of positive cases of rabies in European bats in almost all the countries where laboratory confirmation of bat rabies is implemented, and the fact that bats migrate long distances across Europe [30] deserve attention. Health education and information on bat rabies for health workers in various fields and for the public in Europe should be promoted.

According to our experience with travellers, dogs represent a more serious threat in many countries, yet the risk of bat bites also exist. Education and recommendations should be given to travellers in order to reduce their risk of infection [31]. Post-exposure rabies treatment should be recommended to travellers reporting bat bites after returning from countries where bat rabies is confirmed, or where epidemiological data on bat rabies is missing. Experiences worldwide show that modern rabies vaccines are extremely efficient for pre-exposure vaccination and post-exposure treatment of rabies. Vaccines are highly immunogenic, safe and protective [32].

Of 1727 bats examined in Europe in 2003, there were 33 cases of rabies: 0/1204 in England, 2/153 in France, 7/125 in Netherlands, 3/40 in Denmark, 13/73 in Germany, 0/6 in Check Republic, 0/1 in Austria, 0/24 in Switzerland, 0/3 in Hungary, 0/5 in Slovakia, 6/6 in Poland, 1/12 in Ukraine, 1/1 in Russian Federation and 0/74 in Albania [33]. Great caution is needed in interpreting this data, because species should be properly identified, the reason for data submission known, and the virus strains typed. It is certainly not possible to deduce any prevalence figure from this data.

Some countries do not report cases of rabies in bats to the WHO because they do not carry out research in that field. The risk of rabies infection after human contact with bats or bat bites in Europe is obviously present. Pre-exposure rabies treatment is recommended for all those who are occupationally exposed to bats anywhere in the world and in Europe.

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## ORIGINAL ARTICLES

### Surveillance report

# FOX RABIES IN FRANCE

B Toma

Fox rabies was first recorded in France in March 1968, and remained a problem until 1998. In the course of the first two decades and despite the control measures applied, rabies expanded both in terms of the enzootic surface area and number of cases.

The measures applied consisted of actions aimed at reducing fox population density, the mandatory vaccination of domestic carnivores in the officially infected areas, and use of human prophylaxis.

Following the large scale implementation of oral vaccination of foxes, starting 1989-1990, the rabies front was pushed back and yearly incidence decreased until rabies was eliminated at the end of 1998. The comparison of results obtained during both periods of applying various strategies is spectacular. France remains exposed to the risk from bat rabies on one hand, and from accidental cases of canine rabies imported from enzootic countries, on the other.

*Euro Surveill* 2005;10(11): 220-2

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**Key Words:** fox, France, rabies, vaccination

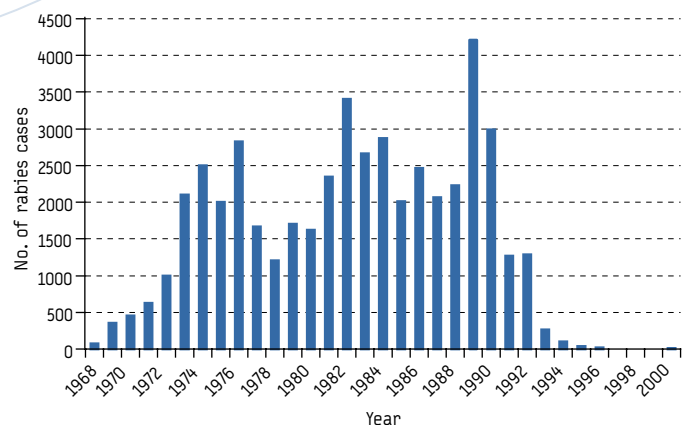
The period between March 1968 and December 1998 represented three decades of fox rabies in France. Looking back over several years, it is possible to evoke the characteristics of the descriptive epidemiology (evolution in time and space) of this fox rabies 'invasion', and the measures applied to control it. After two decades of semi-failures, those measures eventually were successful thanks to the prophylactic 'revolution' represented by oral vaccination of foxes against rabies [1].

## Descriptive epidemiology of fox rabies in France (1968-1998)

The evolution of the yearly incidence of fox rabies in France is shown in figure 1.

FIGURE 1

### Evolution of yearly incidence of fox rabies in France, 1968-1998

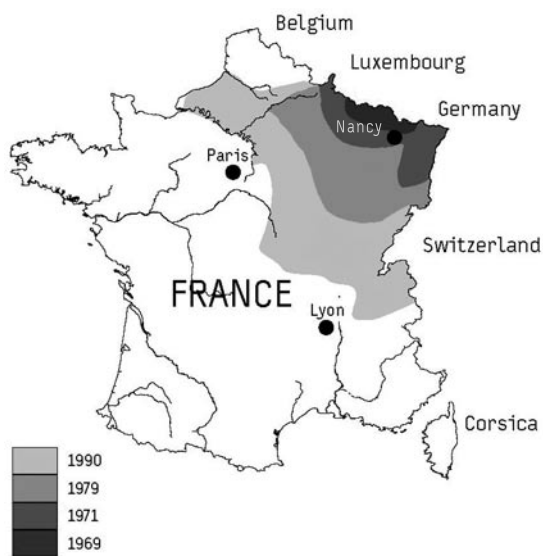


Source: Bulletin épidémiologique mensuel de La rage en France, 1968-1998 [2]

The evolution of the fox rabies front during the years when the enzootics progressed (1968-1990) is shown in figure 2 [3].

FIGURE 2

Situation of the enzootic front of fox rabies in France, 1969-1990



From 1968 to 1975, the progression of the fox rabies front was uninterrupted and the increase of incidence was exponential. From 1975, the progression of the front slowed down. Epidemic waves were observed every 3-6 years in the infected area.

Until 1990, the control efforts, which were mainly based on limiting fox populations and vaccination of domestic animals, were unable to control the disease. A retrospective study on 10 years [4] of the efficacy of sanitary control measures on rabies incidence did not show any constant efficacy.

From 1990, the yearly incidence decreased until the complete disappearance of rabies in 1999. The enzootic area progressively shrank northwestwards until it disappeared.

The success of the eradication programme was due to the change in policy against rabies implemented in 1989.

### The fight against fox rabies in France

For two decades, rabies prophylactic measures applied to foxes were mainly based on attempts to reduce fox populations using various available means, strongly opposed by ecologists, such as poisoning, rifle shooting, gassing fox dens with chloropicrine, etc.

In France, the first actions 'on-site' oral vaccination of foxes were carried out in 1986 along the borders with Belgium and Luxembourg. The results were disappointing, unlike the more satisfying results obtained in Switzerland [5].

In December 1998, the Scientific Commission of the National Federation of Cattle Sanitary groups dedicated its annual meeting to rabies, gathering together specialists from the National Rabies Laboratory (Nancy) and Pasteur Institute (Paris). Vaccination of foxes against rabies was clearly a topic of interest, and proposals were made to implement it on a large scale in France. In 1989, the decision was made at the highest level (by the prime minister) to adopt a strategy to surround the enzootic area by a vaccination belt, followed by an action of forcing back infection towards the north east.

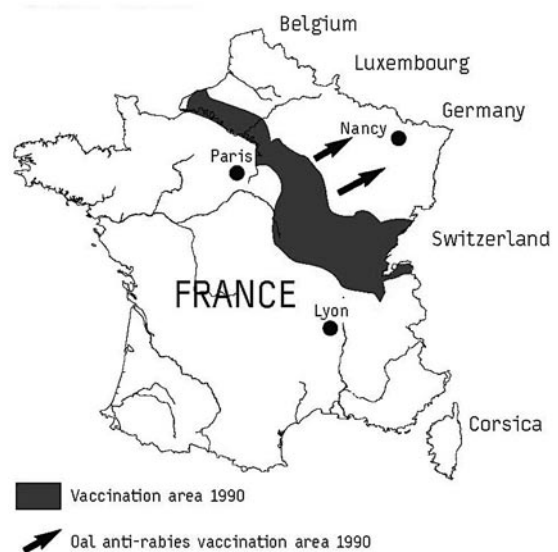
The strategy was defined by the National Rabies Laboratory and the "Entente Interdépartementale de la rage" (ERZ), which also organised and implemented all the campaigns.

The immunity barrier to block the advance of the rabies front was set up in 1989 and 1990, and ran from the Swiss border to the North Sea, covering 54 792 km<sup>2</sup>, nearly 41% of the enzootic area [6].

Vaccination areas were then progressively extended, moving up to the northeastern borders [FIGURE 3]. The whole enzootic area was covered by the autumn 1992 (192 418 km<sup>2</sup> treated in the year).

FIGURE 3

Oral anti-rabies vaccination strategy in foxes in France, Spring 1989-Autumn 1990



This systematic vaccination policy over the whole enzootic area achieved the elimination of fox rabies within a few years, with the last case being recorded at the end of December 1998.

The rules set up were:

- Vaccination in spring and in autumn in enzootic areas;
- Implementation of three successive vaccination campaigns in free areas after the last recorded case;
- Application on extended areas all in one block with a sanitary cordon representing a rabies-free territory of at least 30 km wide;
- Maintenance of increased alertness (continuous surveillance of rabies by sampling, then analysing suspect animals) in areas considered rabies-free in order to quickly react in case a cluster appears.

The efficacy of oral fox vaccination campaigns was increased thanks to various procedures such as [7]:

- Extra vaccination by distributing baits in front of dens;
- Increase of bait density distributed (number by surface).

The intensive efforts carried out between 1989 and 1998 by the National Rabies Laboratory and the ERZ yielded dramatic results. Every year that followed 1998, safety measures were implemented along the German border. From 1999 to 2003, nine oral vaccination campaigns (with only one campaign in autumn 2003) were performed along the German border in order to avoid recontamination of France.

France, along with other western European countries (such as Belgium, Switzerland and Luxembourg), succeeded in eliminating fox rabies from its territory, thanks to the methodical use of anti-rabies vaccination of foxes [8]. Since 2000, France has been listed as rabies-free according to the OIE criteria. France is faced with two potential rabies risks: on one hand, the risk from bats, although the yearly incidence in recent years (since 1989, year of the first bat rabies diagnosis, 20 bat rabies cases all due to EBLV-1 virus on *Eptesicus serotinus* have been recorded in France [9]) suggests that the situation has stabilised; and on the other hand, the risk from imported dog rabies, as recently experienced in Southern of France [10]. With the recent tightening of European regulations [11] that now require anti-rabies vaccination for any transport of pets between rabies-free countries, the fear is that illegal importation of young cats and dogs acquired by travellers to rabies enzootic countries (mainly in North Africa) will continue.





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## ORIGINAL ARTICLES

### Outbreak report

# AN IMPORTED CASE OF CANINE RABIES IN AQUITAINE: INVESTIGATION AND MANAGEMENT OF THE CONTACTS AT RISK, AUGUST 2004-MARCH 2005

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In August 2004, a case of rabies was diagnosed in a puppy that had been illegally imported from Morocco to Bordeaux (France). Because a great number of people and animals were thought to have come into contact with the puppy, extensive tracing measures were implemented, and an international alert was launched to trace and treat the contacts at risk. One hundred and eighty seven people received post-exposure treatment, eight of whom also received serovaccination, and 57 animals known to have been exposed to the puppy were tested. Six months after the death of the rabid animal, none of the people treated showed any signs of rabies, nor was any secondary animal case reported. The management of this crisis highlights the importance of the role of a rapid alert system at European level. Strict application of sanitary control regulations is essential for animals introduced into EU countries, and all

necessary information must be made available to EU residents travelling to rabies enzootic areas.

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**Key Words:** dog rabies, investigation, control, treatment

## Introduction

On 26 August 2004, the CNNR (National Reference Centre for Rabies - Pasteur Institute) reported a case of rabies in a 4-month old puppy illegally imported from Morocco to Bordeaux in France to the French public health institute, the Institut de Veille Sanitaire (InVS). The animal, which was neither officially registered nor vaccinated, was acquired in the Moroccan region of Agadir and brought to France by car, via Spain, on 11 July 2004. After becoming aggressive on 17 August, the dog's condition rapidly deteriorated and it died on 21 August.

Rabies is a zoonosis caused by a rhabdovirus of the genus *Lyssavirus*. The disease can be transmitted to humans via biting, scratching, or licking of excoriated skin or mucosa; the incubation period typically ranges from 1 to 3 months. If untreated during this phase, rabies infection leads to fatal encephalomyelitis. France has been free of rabies in terrestrial mammals since 2001. Fox rabies, which was first recorded in France in 1968, was eliminated following an oral vaccination programme for foxes combined with increased control of stray animals [1].

An investigation was initiated by the DDASS (Departmental Health and Social Services Division) and the DDSV (Departmental Veterinary Services Division) of the relevant French districts and the CIRE (Inter-Regional Epidemiology Centre-) of the Aquitaine region, in conjunction with the health and food industry authorities, the CNNR and the InVS. The purpose of the investigation was to

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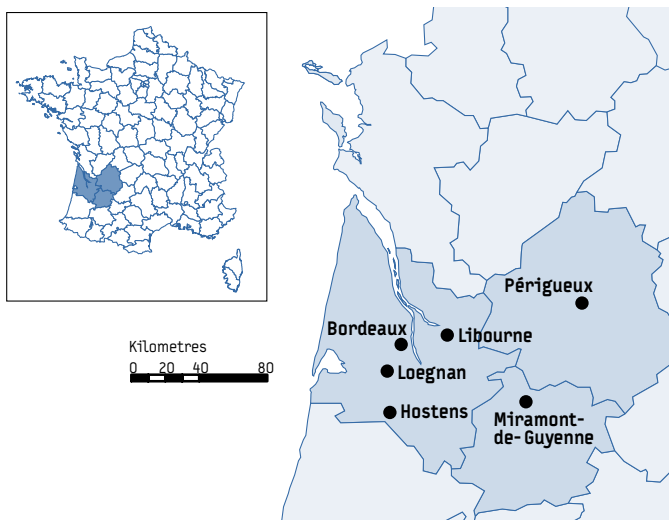


identify all humans who had been in contact with the puppy during the communicable risk period and to refer them to a CAR (anti-rabies centre), the only structures in France empowered to diagnose rabies and administer the post-exposure vaccination. The investigation also aimed to locate all animals that had been exposed to the virus, in order to prevent rabies from being reintroduced in France.

The salivary excretion phase starts, at the earliest, 15 days before the appearance of clinical signs and lasts until death. The puppy could therefore potentially have transmitted the virus at any time between 2 and 21 August. During this period, the animal and its owner had travelled to various locations in Gironde, Dordogne and Lot-et-Garonne, and spent much time attending arts festivals. These events attract thousands of visitors from France and other European countries (FIGURE). The puppy was not constantly kept on a lead.

#### FIGURE

**Itinerary of the rabid animal from 2 to 21 August 2004 (Imported case of canine rabies in Aquitaine, August 2004–March 2005)**



#### Methods

Because of the great number of humans and animals possibly in contact with the puppy during the communicable risk period, the Gironde Prefect set up a crisis centre in Bordeaux from 27 August to 22 September 2004. An inter-ministerial crisis centre was also set up at the national level. These centres expedited contacts between stakeholders, helping to coordinate investigations and action plans. The centres included all parties involved at the local and the national levels.

#### Investigation of contacts

The owner of the puppy was questioned and his trip to Aquitaine was retraced in order to establish a list of potentially exposed humans and animals during his travels between 2–21 August 2004.

An extensive media campaign was launched in order to encourage anyone who had had contact with the puppy to get in touch with a 'Centre 15' (medical emergency service hotline) or the health authorities; and to encourage owners of pets that had come into contact with the puppy to consult a veterinarian or the local DDSV (veterinary organisation). Pictures of the puppy and the description of the possible contacts based on indications provided by the owner were regularly broadcast by the media. Posters were sent to all of the DDASS for display in public places, emergency services, Centre 15s, and the CAR.

An alert was sent to European Union (EU) member states' health authorities via the HSSDC-EWRS network, and to third countries

via the World Health Organization (WHO), to find potential contacts among citizens of other countries. The dog's description and the places visited by the dog and owner were issued. Additional information was sent to any country that requested it, and the 'decision model form' used in France to define 'contacts presenting a risk' was sent to the European Commission's Directorate-General of Health and Consumer Protection (DG-SANCO) and to the national health authorities that requested it [2]. The European health authorities and the WHO were duly notified in order to locate possible contacts living abroad [2].

A 24 hour hotline was set up in the Gironde prefecture every days until 22 September 2004, and the service then operated daily between 0800 and 1800 until 15 October 2004. Based on the initial assessment lists, individuals for whom contact was either ascertained or suspected (through biting, scratching, or licking of excoriated skin or mucosa) with any puppy that matched the description of the rabid puppy, or was compatible in time and place) were directed to a CAR. After 8 September 2004 this procedure was extended to include contacts with any carnivore that had come into contact with the puppy and then disappeared, since these animals could possibly be vectors.

Police handled questioning of witnesses and investigations to locate possibly infected humans or animals.

A national hotline was made available between 10–22 September 2004.

All medical emergency services in France reported any cases of dog bites in the Aquitaine region in August 2004 to the InVS. The CIRE and the InVS then contacted the people who had been bitten to determine whether the rabid puppy was involved.

#### Management of contacts

At the CAR, a risk assessment was made of all humans referred, to ascertain whether post-exposure treatment was appropriate and, if so, to determine what treatment should be prescribed (vaccine with or without rabies immunoglobulin (RIG)) in accordance with WHO recommendations [3].

The DDSV and veterinary authorities identified animals that had been in contact with the carrier.

Samples were analysed by the CNRR in cases of possible human exposure and by the LNR (National Reference Laboratory for animal rabies) in cases of possible animal exposure.

#### Results

##### Investigation of possibly infected subjects

In addition to the seven humans and two dogs within the immediate environment of the puppy, a search was initiated to locate and additional 13 people and 17 dogs, based on information provided by the owner and additional accounts by witnesses. Of these, eight people and five dogs were found.

The hotline in the Gironde prefecture received 3500 calls in 50 days; the DDASS and the DDSV in the Dordogne and Lot-et-Garonne regions received 29 and 61 calls respectively, and the national hotline received 483 calls. In all, 429 people were advised to contact a CAR. Of the people referred, 40% had no connection with the rabid animal. One hundred and sixty two calls were followed up with a veterinary investigation.

Feedback from emergency wards yielded only one person, which had already been identified by a crisis centre.

##### Post-exposure treatments

Post-exposure treatment for rabies was prescribed to 187 subjects, 147 (79%) of which were treated in the Bordeaux CAR. Fifty four per cent of subjects were male (the male to female ratio was 1.15).

The mean age, as derived from data available on 176 subjects, was 17 years. Ages ranged between 1 and 83 years with a median of 9 years.

The puppy was clearly identified by 29 of the treated subjects (16%). In four cases, an animal had been in contact with the puppy during the exposure risk period. Half of those treated had attended the Festival de Libourne (TABLE 1). The type of contact was undetermined in 58 cases, especially for young children (TABLE 2). In total, 8 people were bitten, 5 by the identified animal.

TABLE 1

Distribution of persons receiving post-exposure treatment according to location of contact at risk (Imported case of canine rabies in Aquitaine, August 2004-March 2005)

Place	No. of persons	%
Hostens	3	1.6
Périgueux	12	6.4
Miramont de Guyenne	34	18.2
Libourne	94	50.3
Bordeaux	39	20.8
ALL	2	1.1
Not documented	3	1.6
<b>Total</b>	<b>187</b>	<b>100.0</b>

TABLE 2

Distribution of persons receiving post-exposure treatment according to type of contact at risk (Imported case of canine rabies in Aquitaine, August 2004-March 2005)

Type of contact	No. of persons	%
Bite	8	4.3
Scratch	12	6.4
Licking of excoriating skin	49	26.2
Licking of mucosa	1	0.5
Licking of excoriating skin and of mucosa	5	2.7
Undetermined contact	109	58.3
Not documented	3	1.6
<b>Total</b>	<b>187</b>	<b>100.0</b>

A four-injection course of treatment was used for 94% of cases. One person was treated by a series of five injections followed by injection of immunoglobulin. In total, eight people were treated by serovaccination.

#### Veterinary laboratory

Over a period of six months more than 1200 animals, the majority of which had been found dead, were analysed in the three relevant departments in the Aquitaine region of France.

A total of 57 animals that were confirmed as having had contact with the puppy (including six from outside the Aquitaine region) were identified and analysed.

Testing found no evidence of rabies virus.

In addition, 759 stray animals that had been impounded by authorities, and that could not be identified as having escaped from their owners, or that had no evidence of having had a rabies vaccine, were monitored for a period of one year, in compliance with applicable legislation in the region.

#### Discussion

The last case of imported human rabies are rare with only 20 cases recorded between 1970 and 2003 [4]. At present, rabies in France is considered to be a traveller's disease, as it is in many other European countries [5]. A few human cases are regularly reported in EU rabies-free countries [6]

However, there is a risk of contracting the disease in France due to illegal importation of animals from enzootic rabies areas [7,8]. Two other cases of rabies were diagnosed in Lorient and Bordeaux in 2004, in dogs that had been illegally brought to France from Morocco, via Spain. These two cases led to the vaccination of 24 and 11 people, respectively [9,10]. A total of 22 cases of imported canine rabies have been reported in France since 1968.

In the case described here, the level of risk was thought to be significant because of the large number of humans (attendance at the festivals was estimated at 80 000) and animals potentially exposed, and due to extensive geographical scattering.

Identification of contacts at risk, in order to insure that they received appropriate care, relied on the timely transmission of information, because of the large number of non-French citizens present at the locations visited by the dog. The management of this crisis at the international level highlights the essential role of a European level rapid alert system and the need for complete transparency in the case of a threat involving member states.

At the national level, the situation was managed through close cooperation between the various organisations involved, which made it possible for a large number of potentially infected humans to be treated. Furthermore, as a consequence of this episode, a substantial increase in activity at the CAR was noted due to increased awareness regarding the risk of rabies on the part of the medical community and the general public.

In parallel with efforts to locate exposed humans and animals, control measures concerning the circulation of the domestic carnivores and stray animals were reinforced locally in the Aquitaine region for a period of six months [11-12].

Six months after the death of the rabid animal, none of the subjects treated showed any signs of rabies infection and no cases of secondary animal rabies had been declared.

The five people who were sought but not found had been described by eyewitness testimonies, and we cannot be sure either of that these people were exposed, or that they were described accurately.

The recurrence of this type of alert, underlines the necessity to control the importation of domesticated and wild animals. Health inspection regulations for animals brought into the European Union must be strictly applied [13]. Importers of domesticated carnivores originating in countries where rabies has not been eradicated must provide animal identification and proof of vaccination; animals must also test positive for rabies antibodies.

Travellers to rabies enzootic areas should be informed of the risk to public and animal health that illegal importation of animals can engender. The list of the countries at risk must be made widely available to physicians and the public.

#### Acknowledgements

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Lot et Garonne departments; the liberal and hospital practitioners and the surveillance network of the French veterinary services; the Regional Union of liberal practitioners of the Aquitaine department. Teams of National Reference Laboratory for animal rabies and National Reference Centre for Rabies.

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## ORIGINAL ARTICLES

### Outbreak report

# A HUMAN CASE OF TRAVEL-RELATED RABIES IN AUSTRIA, SEPTEMBER 2004

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A young male Austrian tourist, aged 23 years and unvaccinated against rabies, was bitten by a dog in Morocco in July 2004. One month later he was hospitalised in Ceuta with symptoms compatible with rabies. He died on 23 September in an Austrian hospital after a diagnosis of rabies was confirmed by FAT, IHC and RT-PCR (including sequencing) of the neck skin and the RT-PCR (including sequencing) of the pharyngeal swab. This Austrian case of laboratory confirmed rabies highlights the urgent need for reinforcement of the international recommendations for travel vaccinations.

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**Keywords:** Austria, outbreak, rabies

### Introduction: case report

Two Austrian citizens, a man aged 23 and a woman aged 21, travelled to Morocco in July 2004. The couple encountered a young dog near Agadir and continued to travel around Morocco with the dog. Soon after, the dog showed a strange and aggressive behaviour. In late July the dog attacked the woman and bit her on the right hand. The man tried to help her and was bitten on the right hand

and foot. The dog died soon afterwards and was buried without being tested for rabies. On 1 September 2004, almost one month after the dog attack, the man was admitted to hospital in Ceuta (a Spanish city situated in the north coast of Africa) after presenting with a clinical picture of excitability and confusion. The patient and his girlfriend were given anti-rabies vaccine and anti-rabies gammaglobulins. On 2 September, the patient was transferred to the intensive care unit in a coma after showing symptoms of acute encephalitis and hydrophobia. The patient's hospital records have not been made available to the medical staff who later treated the patient in Austria, and no further details about his clinical presentation are known. A message was sent via the European Union's Early Warning and Response System by the Spanish Ministry of Health after consultation with the Austrian Ministry of Health, in order to fulfil the requirements as laid down in Commission Decision 2000/57/EC [1]. The patient was evacuated to Austria by air transport and admitted to the intensive care unit of the Abt. für Infektiologie, Medizinische Universitätsklinik Graz, in Steiermark. Psychological counselling was offered to the patient's girlfriend and the family. The patient died on 23 September. His girlfriend, who was admitted to the same hospital together with the patient, did not show clinical signs of rabies and was released from hospital on Sept 17<sup>th</sup>. She completed the course of rabies vaccination on 28 October, having received vaccination on days 0, 3, 7, 14 and 28.

### Methods

Fluorescent antibody testing (FAT), immunohistochemical investigation (IHC) and RT-PCR (including sequencing) were performed from punch biopsy samples of the neck skin. RT-PCR (including sequencing) was also performed from pharyngeal and

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nasal swab, blood, serum and CSF. Rabies tissue culture infection testing was performed from CSF, skin, nasal, conjunctival and pharyngeal swabs. Rabies virus specific neutralising antibody testing was performed from serum samples.

### Results

On 8 September a first positive result for lyssavirus RNA by RT-PCR on a punch biopsy of the neck skin was reported by the Centro Nacional de Microbiología, Instituto de Salud Carlos III (Madrid, Spain). On 9 September, rabies infection was confirmed by FAT and IHC of punch biopsy of the neck skin by the National Reference Laboratory for Rabies (Österreichische Agentur für Gesundheit und Ernährungssicherheit, Institut für Veterinärmedizinische Untersuchungen, Mödling). On 23 September the Austrian Ministry of Health was informed by the Centro Nacional de Microbiología, Instituto de Salud Carlos III that a rabies virus genotype 1 of North African origin had been found by sequencing of a 400 bp fragment of the nucleoprotein gene. Thus, FAT, IHC and RT-PCR (including sequencing) of the neck skin, and the RT-PCR (including sequencing) of the pharyngeal swab all gave positive results. In contrast, RT-PCR of other samples (blood, serum, CSF, nasal swab), and rabies tissue culture infection test (CSF, skin, nasal, conjunctival and pharyngeal swabs) did not provide positive results. Rabies virus-specific neutralising antibodies were undetectable in the first serum sample collected during the first week of September and were present in a concentration of 52 IU/ml in the second serum drawn on 21 September. Since the patient had also received several shots of anti-rabies vaccine at that time, interpretation of these data is difficult.

### Discussion

Rabies infection usually is confirmed by post-mortem diagnosis of the suspected animal [2]. However, in vivo diagnosis in humans is also possible nowadays [3,4].

In Austria, the last human rabies case was reported in 1979. Animal rabies, oral vaccination campaigns for foxes are taking place in the areas of Burgenland, southern Carinthia and Styria, as well as several parts of Lower Austria, in order to prevent rabies outbreaks due to foxes crossing the borders from neighbouring countries. The last rabies infection to be detected in a fox was reported in

May 2004 in Carinthia, and was found to be vaccine related [5]. In contrast to information reported in ProMED mail on from 3 September 2004, the rabies-infected dog in the case reported here was not brought from Austria to Morocco [6]. Rabies is endemic in Morocco, and cases in that country are regularly to the World Health Organization. The latest available data are from 1999 and report 599 animals positive for rabies infection [7].

Since 1990 the number of human rabies cases reported in Europe declined from 22 to 7 [8]. Rare reports of travel-related human cases are occasionally reported from rabies-free countries [9]. This Austrian case of laboratory confirmed rabies highlights the urgent need for reinforcement of the international recommendations for travel vaccinations and post exposure treatment. The case was communicated through the EU's Early Warning and Response System to the EU member states by the ministries of health in both Spain and Austria. Additionally, rabies information sheets were distributed in Austrian airports warning travellers of the danger of illegally importing animals, and informing them of the need for immediate medical care for unvaccinated persons who have been bitten by animals in rabies-endemic countries.

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## ORIGINAL ARTICLES

### Surveillance report

# RABIES SURVEILLANCE, TRENDS IN ANIMAL RABIES AND HUMAN POST-EXPOSURE TREATMENT IN POLAND, 1990 - 2004

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This paper describes recent changes in the epizootical and epidemiological situation of rabies in Poland. Analysis of routine surveillance data on animal cases and human post-exposure treatment was performed in order to examine the impact of introduction of cell culture vaccine for human use and the implementation of the fox immunisation programme. The success of the immunisation programme for wild animals has become evident during the past 3 years, as a 9-fold decrease in animal

rabies cases has been observed. To date, however, the downward trend in animal rabies cases has had no effect on the frequency of administration of the post-exposure treatment for humans. Moreover, two cases of locally acquired human rabies have occurred in patients who did not receive post-exposure vaccination. These cases prove that rabies should be still considered a public health concern in Poland.

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**Introduction**

Rabies is a notifiable disease within both the public health and veterinary surveillance systems in Poland. Terrestrial rabies posed a serious problem in Poland in the 20th century, but within the past decade the epidemiological situation has started to change [1]. Three key factors in the strategy for the elimination of rabies have exerted a major influence both on the pattern of animal rabies and on the risk of human rabies. These include the introduction of mass vaccination of dogs in 1950, introduction of safe and immunogenic cell culture based vaccine in 1984 and the introduction of mass oral immunisation of foxes in 1993. The immunisation programme for foxes was implemented in 1993 on the western border and was then successively expanded eastward to cover the entire territory of Poland in 2002 [2].

Following the implementation of oral immunisation programmes of foxes in various European countries, rabies in terrestrial animals was eliminated in some countries and dramatically reduced in others [3]. The problem of and interest in bat rabies has become more significant.

Two genotypes of rabies virus have been isolated in Polish territory: genotype 1 (classical rabies virus) from terrestrial animals and genotype 5 (European Bat Lyssavirus type 1, EBLV1) from bats. Moreover, diversity within the genotype 1 cluster has been observed. Polish strains belong to four different phylogenetic groups of genotype 1 rabies virus present in Europe. Strains from two of the phylogenetic groups are dominant in Polish territory and their geographic spread is strictly dependent on the geographical barrier of the Vistula River. The north-eastern European (NEE) group is limited to the eastern side of the Vistula river, and the central European (CE) cluster has been isolated mainly in the west and south of Poland - on the west side of the Vistula river [4].

The purpose of this article is to highlight the recent changes in the epizootiology and epidemiology of rabies in Poland.

**Methods**

Data used in this study came from two sources. Cumulative data on annual number of animal rabies from the Veterinary Inspectorate were used to evaluate the epizootiological situation of rabies. In Poland, only laboratory confirmed animal rabies cases are reported. Fluorescent antibody test (FAT) is routinely used for diagnosis of rabies. Assessment of the public health hazard and human exposure to rabies were based on information derived from the routine infectious disease surveillance system. Surveillance data on human rabies and administration of post exposure treatment against rabies, collected by the National Institute of Hygiene, consist of annual cumulative numbers from 1964 to 2004 and individual detailed reports on persons vaccinated against rabies from 1990 to 2003.

**Results**

**Animal rabies**

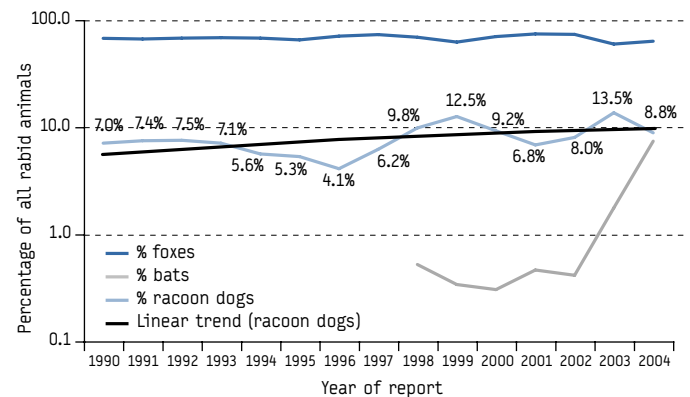
Between 1990-2003, foxes (*Vulpes vulpes*) were the main reservoir and source of rabies in Poland, as they were during the preceding two decades. They represented between 60% of all infected animals in 2003 (233/390), 69% in 2002 (822/1188), and 74% in 2001 (2241/3037) [FIGURE 1]. The second most important host species were racoon dogs (*Nyctereutes procyonoides*). In recent years the percentage of racoon dogs among all infected animals appears to be increasing, although substantial fluctuations are present. The influence of oral immunisation programme of foxes introduced in 1993 became clear from 2002 [FIGURE 1]. The number of cases in 2004 (136 cases) was nine fold lower compared with 2002 (1188) and 17-fold lower than the median annual number of cases during 1990-2001 (2294.5).

The proportion of infections occurring in domestic animals varied between 17% and 23% of the total number of cases of animal rabies. Rabies in domestic animals is closely related to rabies in foxes and racoon dogs. Between 1990-2003, no cases in domestic animals were reported in territories where no cases of rabies in wild animals occurred in the same year.

Until 1998 only 4 cases of bat rabies had been reported in Poland. However, in recent years, several cases have occurred every year. The annual number of rabid bats reported in 1998-2004 varied between 4 in 1999 to 14 in 2001 and 10 in 2004. Although the numbers are not high, their relative importance is increasing [FIGURE 2].

**FIGURE 2**

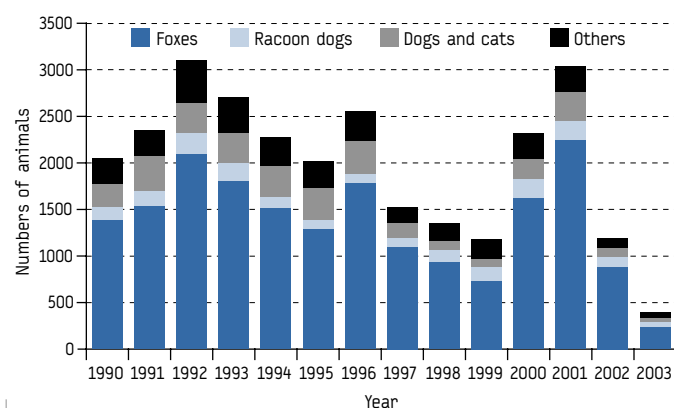
**Percentage of foxes, racoon-dogs and bats among animal rabies cases in Poland, 1990-2004**



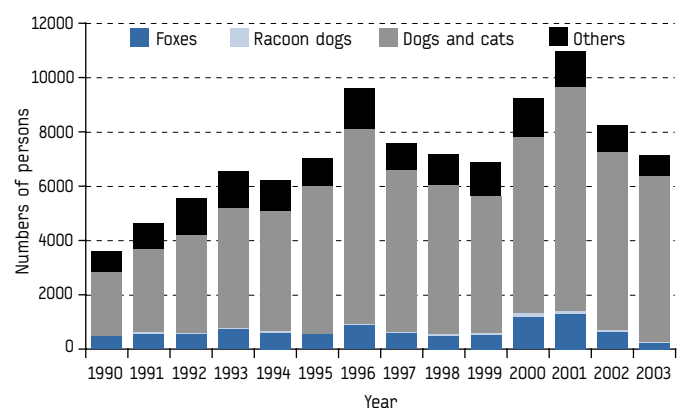
**FIGURE 1**

**Animal rabies in different species and human exposures leading to vaccination, in Poland, 1990-2003**

**A. Number of animal rabies cases, by species**



**B. Number of persons vaccinated against rabies after exposure to different animal species**



### Human rabies

No human cases occurred between 1985 and 2000 in Poland. Then two deaths were reported - in 2000 and 2002. Both infections were acquired in Polish territory. The first case occurred in a 59 year old woman in northeast Poland who was bitten on the finger by her cat in 2000. The second case occurred in a 28 year old man in southern Poland in 2002, who was most probably exposed to a wild animal. The strains of rabies virus isolated from both cases belonged to genotype 1. The first one represented the phylogenetic group north-eastern Europe (NEE) and the second one the central European (CE) group. Neither patient received either pre- or post-exposure prophylaxis.

### Human post-exposure treatment against rabies

In Poland, a country of approximately 38 millions inhabitants, post-exposure treatment is administered to approximately 7000 persons annually. The individual reports sent to the National Institute of Hygiene from 1990 to 2003 cover approximately 90% of all persons vaccinated against rabies. Of the 100 395 persons vaccinated against rabies in this time period, only 26% were immunised following exposure to animals definitively confirmed to be rabid; 64% were immunised following exposure to animals in which rabies could neither be ruled out nor confirmed.

The proportion of different animal species to which humans are exposed is unrelated to their distribution among all reported rabid animals in Poland. Rabid dogs and cats, constituting about 12% of all infected animals, were the reason for vaccination for 74% of the total number of vaccinees [FIGURE 1].

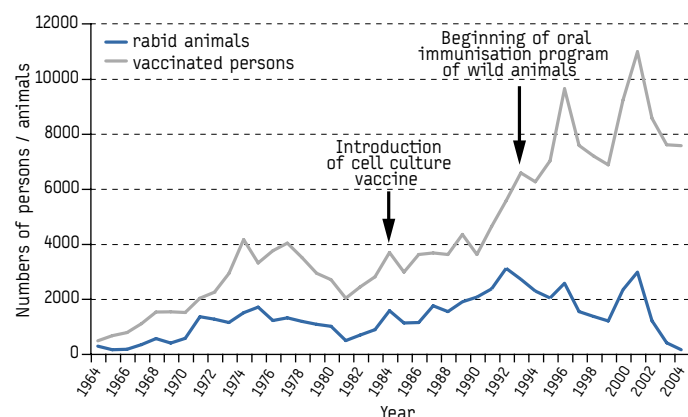
Contact with rabid foxes, which represent 68% of rabid animals, were the reason for vaccination for only 9% of the total number of vaccinees. Moreover, in the case of red foxes, indirect contact (e.g. contact with a dog bitten by a fox), touching and contact with saliva were the most common types of exposure (88%), leading to human vaccination. Exposures among vaccinees to dogs and cats were most often associated with bites (83%).

### Impact on post-exposure treatment

Figure 3 shows time trends in the numbers of vaccinated people, compared with the number of cases of animal rabies. The impact of two important events on the number of post-exposure treatments administered was considered. Firstly, in 1984, a highly immunogenic and safe cell-culture vaccine against rabies was introduced for human use. Secondly, in 1993, mass oral rabies vaccination of foxes was implemented. From the introduction of the cell culture vaccine the number of vaccinated people increased. This trend has continued in recent years, although a considerable decrease in animal rabies cases was already apparent.

FIGURE 3

### Trends in number of animal rabies cases and number of post-exposure treatments administered in Poland, 1964-2004



### Discussion and conclusion

Routine surveillance data confirm a decreasing trend in animal rabies, which is a consequence of the implementation of the fox immunisation programme. At the same time, an increase of rabies reservoirs other than fox host species has been observed, which merits further attention and is currently being investigated. One important example is the increasing importance of bat rabies, while terrestrial rabies incidence is falling. At the present time it is difficult to determine whether there is a real increase of rabies infection in bats, or whether this observation results from greater attention given by the public health authorities.

Public attention and fears currently seem to be most focused on foxes as the source of rabies. This is supported by the fact that the majority of human post-exposure treatments are administered following low risk contact such as being licked by a fox, or even having indirect contact with foxes.

In contrast, dogs and cats either known or suspected to be rabid were responsible for most of the bites and abrasions. This underlines the importance of preventive vaccination of these animals against rabies and their potential influence on the human hazard. Immunised dogs and cats create a protective barrier between wild animals and humans. This was once again confirmed by the recent case of human rabies in a person exposed to a cat.

Recent human cases show that the risk of becoming infected on the Polish territory is still present. Additionally, new risk factors have emerged, such as travel to rabies endemic areas. Based on the situation in France, the United Kingdom and Germany, where animal rabies is eliminated or well controlled, we may expect that in the near future cases of human rabies will be imported rather than acquired in Poland [5,6,7]. In conclusion, rabies should still be considered a public health concern in Poland. Moreover, there is a need to fill the existing gaps in public awareness about rabies.

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## ORIGINAL ARTICLES

## Surveillance report

## FOX RABIES IN GERMANY – AN UPDATE

T Müller, T Selhorst, C Pötzsch

In comparison with conventional methods of wildlife rabies control, oral rabies vaccination of foxes (ORV) is without doubt the most (cost-) effective method in wildlife rabies control. As a result of ORV, several European countries have become rabies-free. Although rabies had been eliminated from much of Germany, there still exists a residual rabies focus in the border triangle of Hesse, Baden-Württemberg and Rhineland Palatinate. Corrective actions have been initiated to eliminate this last remaining rabies hotspot in Germany.

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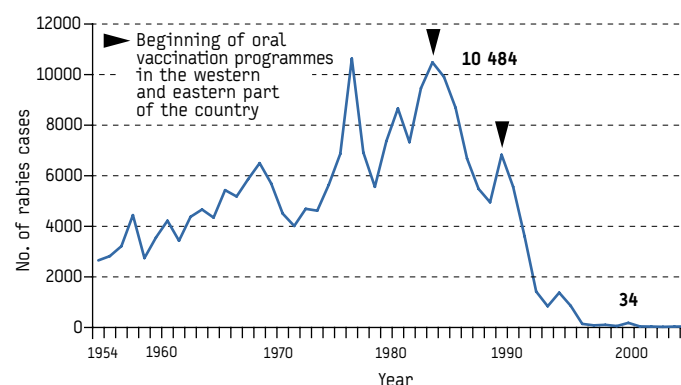
**Keywords:** corrective actions, epidemiology, Germany, oral vaccination, rabies, setbacks

## Introduction

Fox rabies arrived in northeast Germany in 1947 from the other side of the Odra River in Poland, and the disease rapidly moved westwards into West Germany. In 1951, the infection spread to foxes in southeastern Bavaria bordering Austria and what was then Czechoslovakia. In subsequent years there was dramatic progression of the disease in many parts of Europe, and rabies spread all over Germany [1]. Consequently, from 1953, the number of reported rabies cases steadily increased until 1968 [FIGURE 1]. As did other European countries, Germany attempted to solve the rabies problem using conventional methods of fox rabies control aimed at the disruption of the natural route of infection by reducing the fox density below a certain threshold. These included attempts to hormonally sterilize foxes, distribution of poison baits, trapping, digging and destroying fox cubs in dens, den gassing and intensive culling. None of these methods were successful in reducing and maintaining the fox population below this endemic threshold [2]. In fact, rabies incidence drastically increased nationwide in the late 1970s and early 1980s resulting in peaks of 10 634 and 10 484 reported rabies cases in wildlife and domestic animals in 1977 and 1983, respectively [FIGURE 1].

FIGURE 1

## Development of sylvatic rabies (fox mediated rabies) in Germany, 1954-2005



Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health, WHO Collaborating Centre for Rabies Surveillance and Research, Wusterhausen, Germany

## Oral vaccination of foxes against rabies

Oral rabies vaccination (ORV) of foxes using modified live virus vaccines offered a new method of rabies control in wildlife. In Germany, the first field trial using chickenhead bait was conducted in the federal states of Hesse and Bavaria in 1983 [3]. Soon afterwards, ORV was markedly enhanced by the development of a new machine-made bait known as the Tübingen bait [4] that met the requirements for a large-scale vaccination program, which was launched in West Germany in 1985. In East Germany, ORV started in 1989 [5]. With the enlargement of vaccination areas reaching a maximum size of about 215 000 km<sup>2</sup> in 1995, the policy of using ORV became increasingly successful and rabies incidence decreased drastically in subsequent years [FIGURE 1]. However, achieving complete elimination of rabies using ORV was more complicated than originally predicted.

In Germany, the federal states are responsible for all animal disease control, including rabies control. Rabies incidence in certain areas of Germany clearly reflected these differences in vaccination strategies between the different federal states. Whereas in West Germany vaccination areas were frequently adapted to the current rabies situation resulting in a patchy pattern permanently changing with each vaccination campaign, in East Germany large-scale vaccination was used. The federal states in the east rapidly enlarged their vaccination areas and were able to continuously vaccinate the entire territory for several consecutive vaccination campaigns [6]. As a consequence, in the eastern parts of Germany, a rapid decrease in the number of rabies cases was observed in the early 1990s after the implementation of ORV. These eastern regions have been free of rabies for more than 10 years. In contrast, some areas in the west were declared 'rabies-free' too early: the status frequently proved to be unsustainable, and severe set-backs occurred [7]. Once large-scale vaccination was applied in the western regions, rabies was quickly eliminated. During the past 10 years, as in other European countries, the efficacy of oral fox vaccination campaigns has been increased by a permanent adaptation and optimisation of the vaccination strategy based on analysis of the prevailing conditions and recent scientific perceptions. These measures have included (i) den baiting, (ii) double baiting (repeated aerial distribution of baits 14 days after the first vaccination campaign in the same area using perpendicular flight lines with a distance of 1000 metres), (iii) summer vaccination, (iv) an increase of bait density and (v) a reduction of flight lines.

## Recent and current rabies situation

As a result of ORV, the rabies incidence drastically decreased during the past 20 years from 10 484 rabies cases in 1983 to 56 in 1999; the lowest number of rabies cases ever reported in Germany. In 2000 a local increase in rabies incidence was observed with 182 rabies cases were reported, exceeding the level reached in 1998 [FIGURE 1]. For example, the rabies situation in Saxony reflected a classical cross-border problem at this time [FIGURE 2]. Here, an increasing rabies incidence in the neighbouring regions of the Czech Republic and Poland resulted in permanent re-infection along the common borders. This situation forced the veterinary authorities to safeguard the territory by maintaining a vaccination belt in those border areas [8]. The breakthrough in rabies control in the Saxony region came when continuous annual trilateral meetings with the countries involved were initiated which led to a considerable improvement of the vaccination strategies in the adjacent areas to Saxony. For more than three and a half years no rabies case has been reported from this region.

However, in 2000, the main problem was two separated endemic rabies foci comprising 3 western federal states [FIGURE 2]. Whereas the rabies incidence in North Rhine Westphalia was unaltered, the increase in rabies incidence was due mainly to a deterioration of the rabies situation in the border area of Bavaria and Hesse. North Rhine Westphalia had to face the problem of rabies in suburban and urban areas of the Ruhr, one of the most densely populated areas in Europe, during the final phase of rabies eradication. Due to improvement and adaptation of vaccination strategies that took into consideration the peculiar topographical features of a fragmented landscape and the high fox densities, the number of rabies cases decreased in 2001. The last observed rabies case due to sylvatic terrestrial rabies has been observed in Bavaria and North Rhine Westphalia were reported in March and June 2001 respectively, although rabies continued to be endemic in Hesse at a low level in subsequent years [TABLE]. Here, rabies has been endemic in a very limited area in the southernmost parts of the federal state, reflecting similar topographical and geographical features of a fragmented landscape to North Rhine Westphalia. Although large scale vaccination using aerial distribution has been applied for several years, rabies cases in the past five years have been frequently associated with suburban and urban areas. While the rabies cases were initially limited to a 65 km<sup>2</sup> region affecting two adjacent communities close to the city of Offenbach, due to inconsistent hand baiting the disease spread northwards into the suburbs of Frankfurt/Main in 2002 and in the following year also spread southwards into urban areas of adjacent districts. In 2004, rabies cases were mainly concentrated in the southernmost part of Hesse, the border triangle with Baden-Württemberg and Rhineland Palatinate [FIGURE 2]. Though Bavaria and Baden-Württemberg have maintained a preventive vaccination belt along the border with Hesse for over three years, an adjacent area in Baden-Württemberg became re-infected in December 2004. In order to reduce the infection pressure in the core area, emergency vaccination was carried out in the respective federal states in the same month. One month earlier, in November 2004, the rabies situation in Hesse had forced veterinary authorities to establish a 25 km deep preventive vaccination cordon in Rhineland Palatinate along the Rhine River. Unfortunately, rabies crossed the river and the first rabid foxes were found after 6 years of absence in January 2005, near the

border with Hesse. In fact, the vaccination coverage in the fox population after this first vaccination campaign continued to be suboptimal, and up to April 2005 a total of 18 rabies cases were confirmed in that area. Up to the end of September 2005, a total of 30 rabies cases have been reported from Rhineland Palatinate [FIGURE 3].

TABLE

Rabies situation in German federal states ('Bundesländer'), 2000-2005 (bat rabies cases not included)

Federal State	Year					
	2000	2001	2002	2003	2004	2005*
Schleswig Holstein	0	0	0	0	0	0
Lower Saxony	0	0	0	0	1*	0
Bremen	0	0	0	0	0	0
Hamburg	0	0	0	0	0	0
North Rhine Westphalia	35	9	0	0	0	0
Hesse	83	24	34	24	28	4
Rhineland-Palatinate	0	0	0	0		33
Baden-Württemberg	0	0	0	0	5	5
Bavaria	57	3	1*	0	1*	0
Saarland	1	0	0	0	0	0
Berlin	0	0	0	0	0	0
Brandenburg	0	0	0	0	0	0
Mecklenburg Western Pomeranian	0	0	0	0	0	0
Saxony	6	4	0	0	0	0
Saxony-Anhalt	0	0	0	0	0	0
Thuringia	0	0	0	0	0	0
<b>Total</b>	<b>182</b>	<b>41</b>	<b>35</b>	<b>24</b>	<b>35</b>	<b>42</b>

\* Situation at 19 November 2005

# Imported rabies case of dog origin

# Imported human rabies cases

FIGURE 2

Rabies in Germany in 2000 and 2004

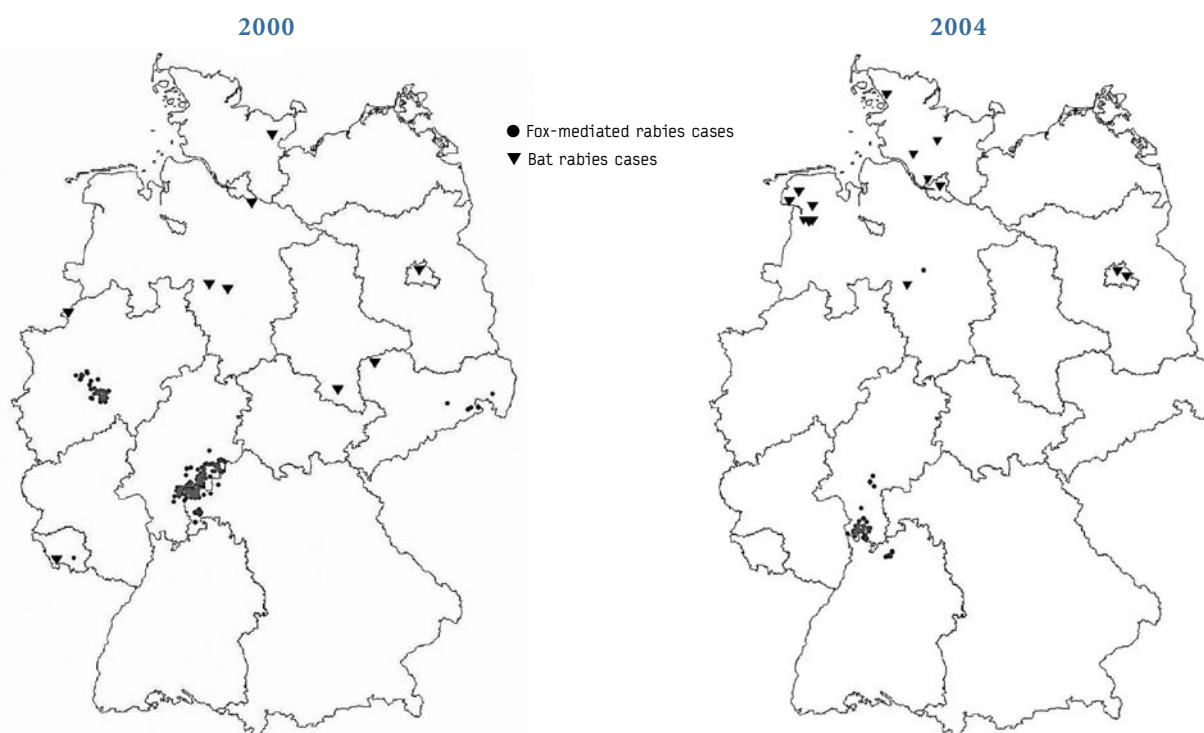




FIGURE 3

Rabies in Germany in 2005, situation at 22 September 2005



### Conclusions and corrective actions

The local increase in the number of rabies cases and the resulting spread of rabies in Germany in recent years are mainly due to (i) increased fox densities (ii) the persistence of rabies in areas with a extremely high density of settlements in which ORV is severely hindered (a phenomenon that no other country in Europe has been confronted with), (iii) inconsistent vaccination, e.g. missing complementary distribution of baits per hand in non-flying zones and (iv) insufficient prioritisation being given to rabies control in the final phase of its elimination. Because animal disease control, e.g. rabies control and ORV, is the responsibility of each federal state, insufficient cooperation in the planning of vaccination campaigns between neighbouring federal states has also been an important shortcoming.

As national and international concerns increased, several corrective actions have been implemented in 2005, aimed at improving vaccination protocols and a consistent vaccination strategy in the respective federal states aiming to eliminate the residual focus this year.

In addition to strict application of EU recommendations [9], the measures comprise:

- central planning and management of vaccination campaigns under the auspices of the national reference laboratory for rabies,
- drastic enlargement of vaccination areas in particular in Rhineland Palatinate, Baden-Württemberg and Bavaria to avoid further spreading of the disease,
- increased frequency of vaccination campaigns in hot spots (6 week intervals),

- strict complementary and intensified hand distribution in urban and suburban areas,
- intensified rabies surveillance beyond the recommended sample size of 8 foxes/100 km<sup>2</sup>/year, as well as consequent follow-up investigations.

Furthermore, to overcome possible cross-border problems and to improve ORV programmes between neighbouring federal states, regular half-year consultations including all stakeholders have been implemented, at which the success of past vaccination campaigns is thoroughly evaluated, problems discussed and common planning of subsequent vaccination campaigns carried out. A completely new approach far beyond the EU recommendations is the documentation of the precise location of bait drops during aerial distribution using a satellite navigated and computer-supported fully automatic system (SURVIS) for distributing oral rabies vaccine baits [10]. This documentation allows real-time analysis of the quality of aerial distribution by calculating the resulting bait density on the ground after each vaccination campaign to identify areas with suboptimal bait densities where complementary hand distribution needs to be applied at a local level [11].

So far, the corrective actions taken in 2005 have resulted in halting rabies spread in the respective areas. Recent epidemiological analysis showed that rabies incidence has significantly decreased, and attainment of rabies elimination can be expected in due course [unpublished data]. Nevertheless, the implemented vaccination strategy must be continued for two more years after the last confirmed rabies case in order to achieve the rabies-free status [9].

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# NEW DIAGNOSES OF HTLV INFECTION IN ENGLAND AND WALES: 2002-2004

S Dougan<sup>1</sup>, R Smith<sup>1</sup>, JC Tosswill<sup>2</sup>, K Davison<sup>3,4</sup>, M Zuckerman<sup>5</sup>, GP Taylor<sup>6</sup>

Human T cell lymphotropic viruses (HTLV) are retroviruses transmitted through breast-feeding, sexual contact, blood transfusion and injecting drug use. HTLV is endemic in the Caribbean, and parts of Africa, Japan and South America, with isolated foci in other areas. Infection is life-long. Less than 5% of those infected progress to one of the HTLV-related diseases, but these are debilitating and often fatal.

In England and Wales, laboratory and clinical reports of new HTLV diagnoses are routinely collected, including infections identified by the blood service since the introduction of anti-HTLV testing in August 2002.

Between 2002-2004, 273 individuals were diagnosed with HTLV: 102 (37%) were male and 169 female (gender was not reported for two). Median ages at diagnosis were 54 and 50 years respectively. Clinical reports were received for 78% (212/273) individuals. Where reported, 58% (116/199) of individuals were of black Caribbean ethnicity and 29% (57/199) white; 87% (128/147) were probably infected heterosexually or through mother-to-child transmission; 45% (66/146) were probably infected in the Caribbean and 40% (59/146) in the UK.

An appreciable number of HTLV infections continue to be diagnosed within England and Wales, with increases in 2002-2003 because of anti-HTLV testing of blood donations. While most infections diagnosed are directly associated with the Caribbean, transmission of HTLV infection is occurring within England and Wales. Specialist care services for HTLV-infected individuals and their families have improved in recent years, but prevention remains limited.

Euro Surveill 2005;10(10): 232-5

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**Key words:** Caribbean, England and Wales, epidemiology, HTLV-I, HTLV-II

## Background

The Health Protection Agency undertakes surveillance of new diagnoses of human T cell lymphotropic viruses (HTLV) in England and Wales (E&W). HTLV types I and II can be transmitted through breast feeding, sexual contact, and blood transfusion, with HTLV-II particularly associated with injecting drug use. HTLV-I is endemic in the Caribbean, Japan, South America, and parts of Africa, with HTLV-II found among some native American groups. If infected, the lifetime risk of developing disease is low (less than 5%). Clinically, HTLV-I infection may cause adult T cell leukaemia/lymphoma (ATLL) and/or HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [1]. It is also associated with other inflammatory conditions

[1]. There is some evidence that HTLV-II infection is associated with neurological and lympho-proliferative disorders [2].

## Methods

Surveillance of new laboratory diagnoses of HTLV infection in E&W began in the late 1980s [3]. In 2002, surveillance was enhanced by the collection of further epidemiological information through a clinical reporting scheme, described in full elsewhere [4]. This coincided with the introduction of the national, routine testing of all blood donations for anti-HTLV by the UK Blood Services in August 2002 [4]. Reports of any HTLV infections diagnosed by the blood service in E&W are included in the routine surveillance scheme.

Probable route and country of infection are collected on clinical HTLV reports. The clinician indicates through which route the patient is most likely to have been infected through, and in which country. Where it is not clear, more than one route or country can be indicated. For those infected through heterosexual intercourse, information on their sexual partner is sought (e.g. had the partner injected drugs or has the partner had heterosexual intercourse in the Caribbean).

Surveillance findings from 2002 have previously been published [4]. Here, we present data from the surveillance system for 2002, 2003 and 2004; based on reports made to the scheme by the end of May 2005. The surveillance system coverage is likely to be near complete for laboratory-confirmed HTLV diagnoses made in E&W as most confirmatory testing for HTLV is undertaken at either at the Health Protection Agency Centre for Infections or the Health Protection Agency laboratory at King's College hospital, from which routine laboratory reports are sent. In 2004, the laboratory at the Centre for Infections performed approximately 1,500 HTLV tests. Clinical reports are sent out for completion for every HTLV positive laboratory report received.

## Results

Between 2002 and 2004, 273 reports of new HTLV diagnoses were made in E&W; 88 in 2002, 101 in 2003 and 84 in 2004. Two hundred and fifty one (93%) were HTLV-I infections, 13 HTLV-II, one a HTLV-I&II co-infection and for eight HTLV type was as yet undetermined. Of the 273 people diagnosed with HTLV between 2002 and 2004, 102 (37%) were men (four HTLV-II), 169 (62%) women (nine HTLV-II) and gender was not reported for the remaining two (one HTLV-II). The proportion of diagnoses among women increased over time: in 2002 57% of HTLV diagnoses were among women, by 2004, 69% [TABLE]. Median age at diagnosis was 54 years for men and 50 years for women.

The majority (67%) of reports were about individuals diagnosed or receiving care in London [FIGURE 1]. Elsewhere in E&W, the largest numbers of reports were about HTLV-infected individuals diagnosed/cared for in the West Midlands region of England.

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2. Sexually Transmitted & Bloodborne Viruses Laboratory, Health Protection Agency Centre for Infections, London, UK

3. Immunisation Department, Health Protection Agency Centre for Infections, London, UK

4. National Blood Service, London, UK

5. Virology Department, King's College Hospital, Health Protection Agency, London

6. Imperial College School of Medicine, St Mary's Hospital, London, UK

TABLE

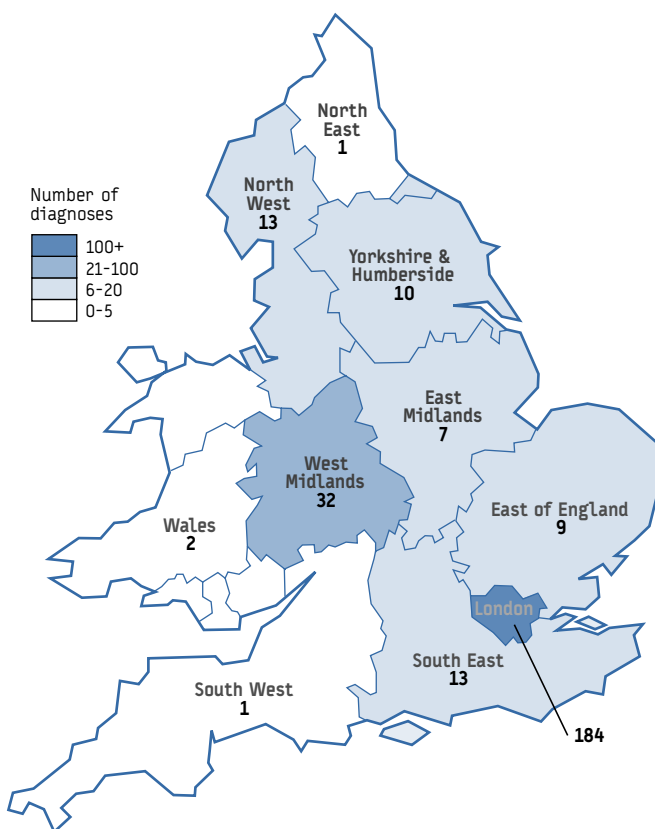
Sex and age distribution of individuals diagnosed with HTLV by year of diagnosis, England and Wales, 2002-2004

Age group (years)	2002			2003			2004			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
<35	2	4	6	9	5	14	5	4	9	16	13	29
35-44	9	12	21	6	11	17	3	13	16	18	36	54
45-54	7	14	21	9	21	30	5	14	19	21	49	70
55-64	7	8	15	7	13	20	3	9	12	17	30	47
65-74	10	10	20	7	8	15	4	13	17	21	31	52
75+	3	2	5	2	2	4	4	4	8	9	8	17
<b>Total*</b>	<b>38</b>	<b>50</b>	<b>88</b>	<b>40</b>	<b>60</b>	<b>100</b>	<b>24</b>	<b>57</b>	<b>81</b>	<b>102</b>	<b>167</b>	<b>269</b>

\* Total excludes one female diagnosed in 2003 and one female diagnosed in 2004 with no reported DOB and two individuals diagnosed in 2004 with no reported sex as yet

FIGURE 1

Latest reported region/country of HTLV diagnosis/care, England and Wales



Note: One individual known to have left England and Wales and so not included in figures

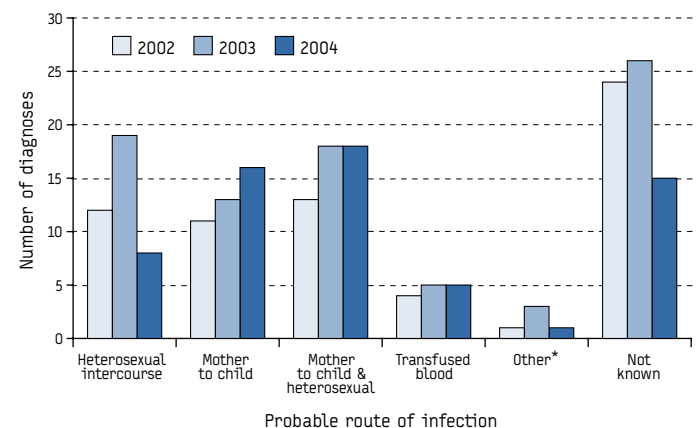
At the time of writing, a clinical report (collecting more detailed epidemiological information), had been made for 212 (78%) individuals. The proportion of clinical reports made for individuals by year of diagnosis is as follows: in 2004 (75% [63/84]), in 2003 (83% [84/101]) and in 2002 (74% [65/88]). Further clinical reports for diagnoses made in 2004 are expected during 2005.

Where ethnicity was reported (199), 116 (58%) individuals were black Caribbean, 57 (29%) white (10 HTLV-II), 15 black African (one HTLV-II) and 11 of other ethnicity. The rate of HTLV diagnosis was therefore 20.5 per 100,000 among black Caribbeans living in E&W between 2002 and 2004, compared to 3.1 per 100,000 among black Africans and 0.1 per 100,000 among the white population [5]. The probable route of infection was reported for 147 individuals: 39 (27%) were probably infected through heterosexual intercourse

(four HTLV-II), 40 (27%) through mother to infant transmission, 49 (33%) through either route, 14 through blood transfusion (two HTLV-II) and five through other routes (two HTLV-II) [FIGURE 2]. Where the probable country of infection was reported (146), 66 (45%) individuals were probably infected in the Caribbean (35 in Jamaica), 59 (40%) in the UK (four HTLV-II), 12 in Africa (seven in West Africa) (one HTLV-II), four in the Middle East, two in Asia and three elsewhere (one HTLV-II).

FIGURE 2

Probable route of HTLV infection by year of HTLV diagnosis, England and Wales, 2002-2004



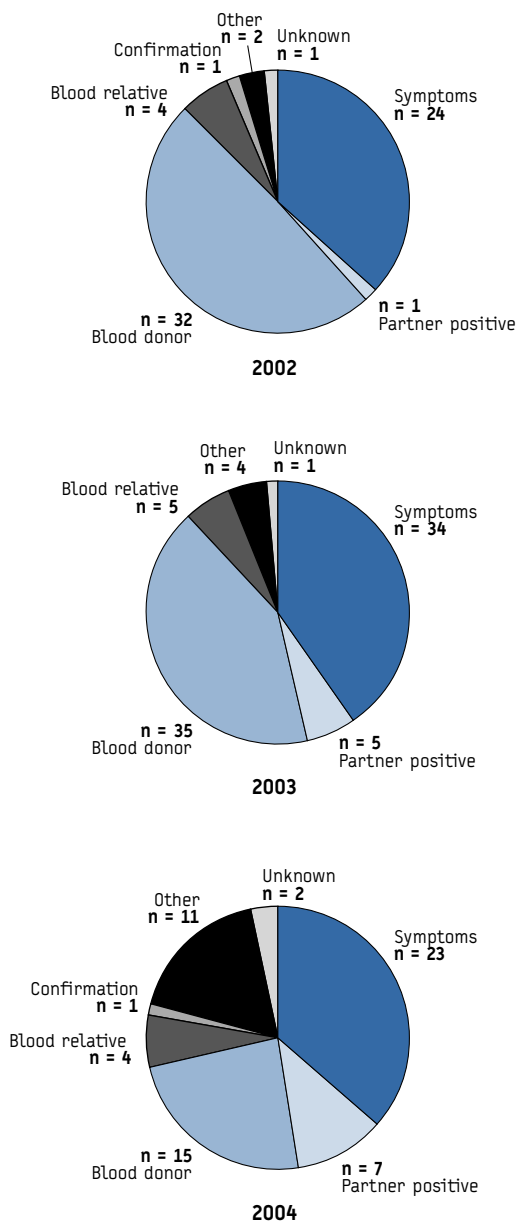
\* Includes two men infected through sex between men; two people infected through injecting drug use; and one through a needlestick injury (undocumented)

There were 42 individuals infected through either heterosexual intercourse or mother to child transmission within the UK, of whom four were known to have had a 'high risk' sexual partner (e.g. injecting drug user); 19 a partner or parent infected in the Caribbean, two a partner or parent infected in the UK and one, a partner or parent infected in Africa.

Where reason for testing was reported (208), 81 (39%) individuals had been tested because of symptoms (one HTLV-II), 82 (39%) as blood donors (eight HTLV-II), 13 (6%) had a HTLV-infected positive sexual partner, 13 (6%) had a HTLV-infected blood relative and 19 (9%) for other reasons (two HTLV-II). The reason stated changed over time [FIGURE 3]. There were larger numbers of individuals diagnosed through the screening of blood donors during 2002 (n=32) and 2003 (n=35) than in 2004 (n=15).

FIGURE 3

Reason for HTLV diagnosis by year of HTLV diagnosis, England and Wales, 2002-2004



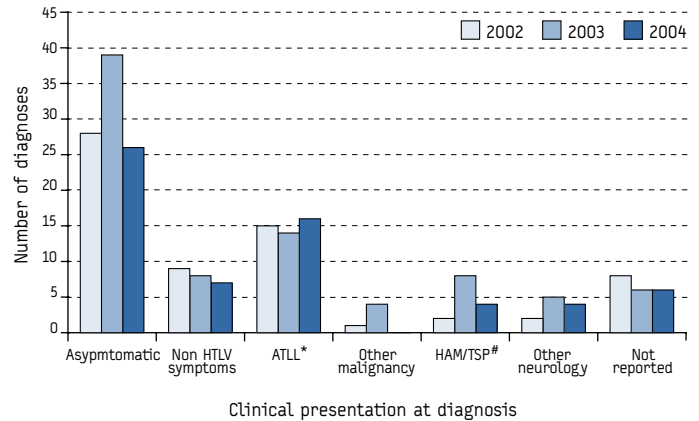
Clinical presentation at diagnosis was reported for 192 individuals, of whom 93 (48%) were asymptomatic (seven HTLV-II), 45 (23%) had ATLL, 14 (7%) had HAM/TSP and 40 (21%) had other symptoms (three HTLV-II) [FIGURE 4]. Where ATLL type was reported (n=36), 19 (53%) had a lymphoma, 11 (31%) acute ATLL, four chronic ATLL and two smouldering ATLL. Of all the individuals diagnosed between 2002 and 2004 in E&W, 14 are known to have died (one HTLV-II).

**Discussion**

An appreciable number of HTLV infections continue to be diagnosed within E&W each year. The introduction of anti-HTLV testing of blood donations increased the number of new HTLV diagnoses in 2002 and 2003. However, by 2004 low numbers of infected blood donors were identified - most donors had already been tested, with those found positive excluded from further donation and referred to specialist centres for appropriate care. Overall, the rate of HTLV infection in blood donations E&W between August 2002 and December 2004 for new donors was 5.1 per 100,000 donations and for repeat donors, 0.9 per 100,000 donations [6].

FIGURE 4

Clinical presentation at HTLV diagnosis by year of diagnosis, England and Wales, 2002-2004



\* ATLL: adult T cell leukaemia/Lymphoma  
 #HAM/TSP: HTLV-I-associated myelopathy/tropical spastic paraparesis

The majority of HTLV diagnoses were among those of black Caribbean ethnicity, with HTLV diagnoses rates highlighting that in E&W, the black Caribbean population is disproportionately affected by HTLV infection. Infections were thought to have been mainly acquired through heterosexual intercourse and/or mother to child transmission, both within the Caribbean and the UK. In the main, those infected in the UK had a partner or parent from an endemic area. Data illustrate therefore, that while HTLV infection in E&W is mainly found among those originating from endemic areas there is also transmission of the infection in E&W itself. The geographical distribution of diagnosed HTLV infection in E&W reflects both the distribution of the black Caribbean population, which is focussed in London (60%) and the West Midlands (14%) [7], and also the location of specialist HTLV centres in London and Birmingham.

A clinical report containing more detailed epidemiological and clinical information had not yet been received for 21 (25%) individuals diagnosed in 2004. More outstanding clinical reports are expected over the coming months. It is important to bear this in mind when interpreting trends. For a relatively large proportion of individuals for whom a clinical report was made, the probable route and country of was not known (~30%), highlighting difficulties in assigning these variables for infections acquired many years previously, particularly in clinical settings where sexual histories are not collected routinely (as they would be for example, in GU medicine). In addition, probable route of infection was not known for those with only a laboratory report. Such data incompleteness may bias conclusions from routine surveillance data. In this case, proportionally more of those diagnosed with symptoms or with no reason for test did not have a probable route of infection reported compared to those diagnosed as blood donors, a blood relative or because of a positive partner, as well as older individuals and those with no reported ethnicity. Finally, it is important to remember that not all of those living with HTLV infection in E&W will be diagnosed and there will be biases in ascertaining HTLV infections within the population. For example, all blood donations are tested for HTLV, and people with HTLV-associated symptoms or HTLV-infected relatives or partners are more likely to be tested than those with no symptoms or contacts.

In conclusion, while HTLV infections continue to be diagnosed in E&W, the number of diagnoses in any given year seems to have peaked in 2003 with the identification of HTLV-infected blood donors, when considering trends since 1987 [3]. While there are now three designated sites across E&W (London, Birmingham and Manchester) providing specialist investigation, therapy and contact screening services for those infected and their families, the prevention of HTLV transmission, for example through screening of pregnant women for HTLV infection and contact tracing, is limited.

## Acknowledgements

We gratefully acknowledge the contribution of all of those who have reported to the HTLV surveillance system over the years, and support of Dr Barry Evans (Health Protection Agency Centre for Infections).

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## ORIGINAL ARTICLES

### Surveillance report

# DISSEMINATED AND CHRONIC LYME BORRELIOSIS IN NORWAY, 1995 – 2004

K Nygård, A Broch Brantsæter, R Mehl

Lyme borreliosis is the most common tickborne infection in Norway. All clinical manifestations of Lyme borreliosis other than erythema migrans are notifiable to Folkehelseinstituttet, the Norwegian Institute of Public Health. During the period 1995-2004 a total of 1506 cases of disseminated and chronic Lyme borreliosis were reported. Serological tests were the basis for laboratory diagnosis in almost all cases. The annual numbers of cases showed no clear trend over the period, but varied each year between 120 and 253 cases, with the highest number of cases reported in 2004. Seventy five per cent of cases with information on time of onset were in patients who fell ill during the months of June to October. There was marked geographical variation in reported incidence rates, with the highest rates reported from coastal counties in southern and central Norway. Fifty six per cent of the cases were in males and 44% in females. The highest incidence rate was found in children aged between 5 and 9 years. Neuroborreliosis was the most common clinical manifestation (71%), followed by arthritis/arthralgia (22%) and acrodermatitis chronica atrophicans (5%). Forty six per cent of patients were admitted to hospital. Prevention of borreliosis in Norway relies on measures to prevent tick bites, such as use of protective clothing and insect repellents, and early detection and removal of ticks. Antibiotics are generally not recommended for prophylaxis after tick bites in Norway.

Euro Surveill 2005;10(10): 235-8

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**Key words:** Lyme disease, borreliosis, tickborne, Norway

## Introduction

The incidence of Lyme borreliosis in different areas of Norway reflects the distribution of the tick vector, *Ixodes ricinus*. The prevalence of *Borrelia* sp. in *I. ricinus* has been investigated by phase contrast microscopy in many tick-infested locations along the Norwegian coast. Generally, the prevalence has been found to be 20%-30% in nymphs and 40%-60% in adult ticks [1]. No larvae examined were infected. Small rodents and birds are considered to be the main reservoir hosts in Europe [2].

The first description of erythema migrans with meningopolyradiculitis after tick-bite in Norway was published in

1955[3]. Cases of Lyme borreliosis were notified sporadically to the MSIS (Norwegian surveillance system for communicable diseases) from 1983, under the category 'other infectious diseases'. Since 1991 it has been a specified notifiable disease. In the early years of notification, all manifestations of Lyme borreliosis were notifiable, including erythema migrans. The case definition was revised with the implementation of the Infectious Disease Control Act in 1995, after which only disseminated and chronic manifestations remained notifiable, (that is, cases of erythema migrans were excluded).

In this article, we review surveillance data for disseminated and chronic Lyme borreliosis in Norway during the ten year period 1995-2004 in order to examine trends over time, geographical distribution, characteristics of patients and their clinical presentation.

## Materials and methods

The MSIS (Norwegian surveillance system for communicable diseases) is administered by the Department of Infectious Disease Epidemiology at Folkehelseinstituttet (the Norwegian Institute of Public Health, NIPH) in Oslo. Laboratories of clinical microbiology and clinicians are required by law to notify cases of certain infectious diseases to the MSIS central unit at NIPH. The reports from the laboratory and clinician are combined and registered as one case at NIPH.

We reviewed cases of disseminated and chronic Lyme borreliosis notified in Norway during the ten year period 1995 to 2004. The case definition for laboratory confirmed Lyme borreliosis was clinically suspected disseminated or chronic disease, like acrodermatitis chronica atrophicans (ACA), arthritis or neurological disease and demonstration of the bacteria *Borrelia burgdorferi* or definite antibody titres. Population data from Statistics Norway ([www.ssb.no](http://www.ssb.no)) were used to calculate annual incidence rates.

In order to study the geographical distribution of cases over time, we mapped the cases in the two years with the highest incidence rates. The maps were created as dot-density maps in ArcGIS 9, where one case was presented as one dot randomly placed within the border of the municipality of residence.

Based on information on clinical signs and symptoms as described by clinicians on the notification forms, patients were put into the following main categories: neuroborreliosis (including meningitis, facial paralysis and meningopolyradiculitis), arthritis, acrodermatitis chronica atrophicans (ACA), unknown and other. Cases with diagnosis based on analysis of cerebrospinal fluid (with or without confirmatory

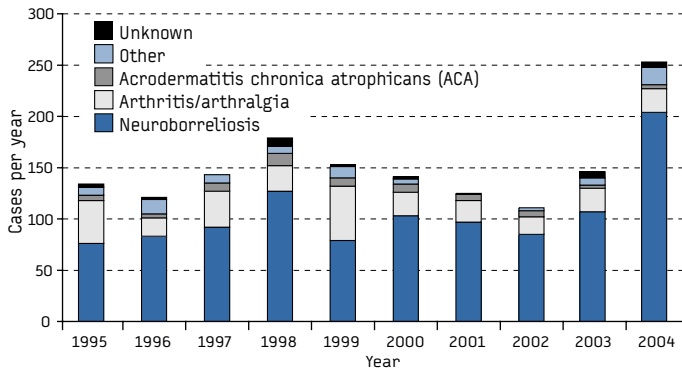
results from serum) were classified as neuroborreliosis regardless of information of other concomitant clinical manifestations.

**Results**

During the 10-year period 1995 to 2004, a total of 1506 cases of disseminated and chronic Lyme borreliosis were notified to NIPH. The number of cases varied between 120 and 253 annually, with the highest number of cases in 2004 [FIGURE 1].

**FIGURE 1**

**Number of cases of disseminated and chronic Lyme borreliosis notified in Norway by year of onset and main clinical symptoms, 1995-2004**

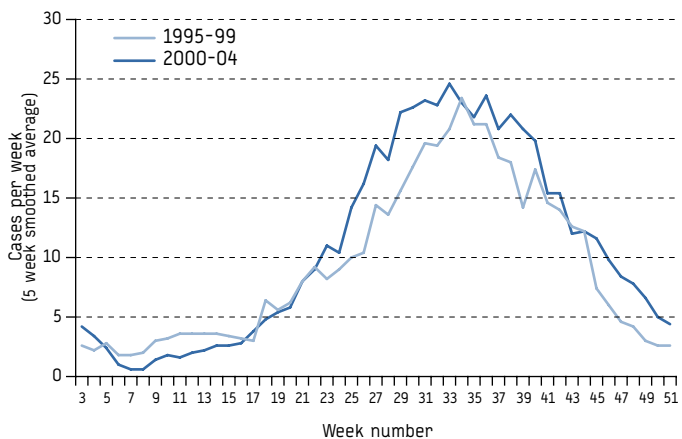


**Seasonality**

Date of symptom onset was available for 1014 cases. There was a clear seasonal pattern, with the number of cases starting to increase in week 20 (mid-May) and peaking in week 35 (August) [FIGURE 2]. Seventy five per cent (759/1014) of cases with information on time of onset fell ill during the months of June to October. The seasonal distribution of cases by onset remained similar during the ten year period [FIGURE 2].

**FIGURE 2**

**Seasonal distribution of disseminated and chronic Lyme borreliosis notified in Norway by week of onset by five-year period ; 5 week smoothed average**



**Geographical distribution**

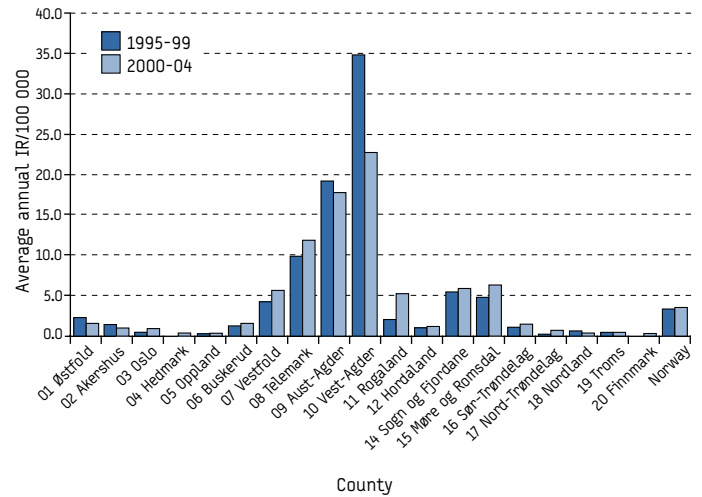
Of the 1506 cases reported, 1200 (79.7%) were reported as having been infected in Norway, 23 (1.5%) during travel abroad, and for 283 (18.8%) this information was missing.

There was marked geographical variation in reported incidence rates, with the highest incidence reported from coastal counties in southern and central parts of Norway [FIGURE 3]. Six counties in these areas accounted for 75% of the cases (these counties account for only 28% of the population in Norway). The highest annual

number of cases were reported in 1998 (n=179) and 2004 (n=253). The geographical distribution of cases was not markedly different in these years [FIGURE 4].

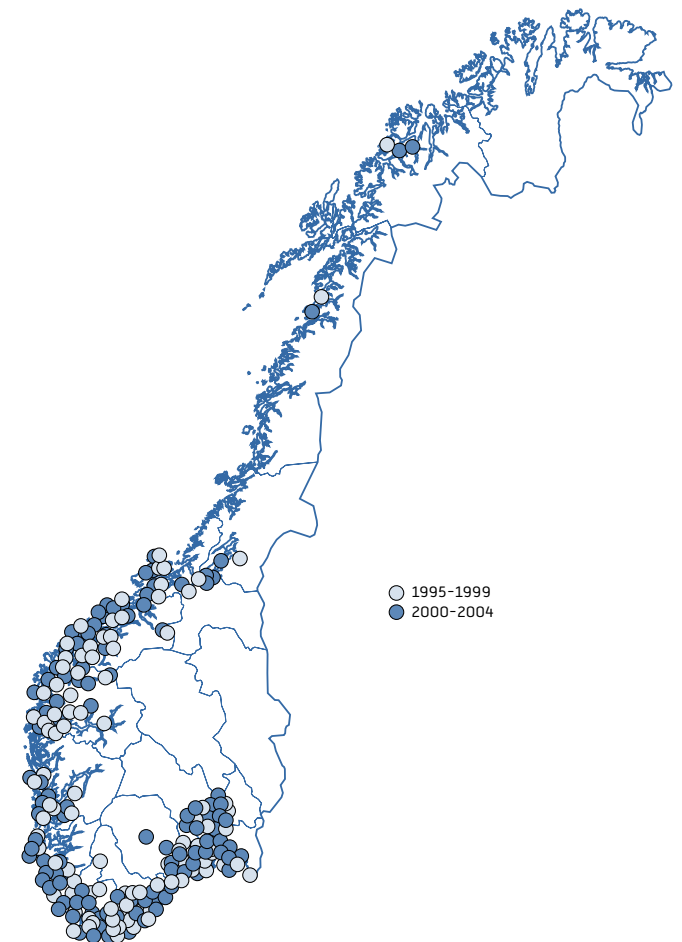
**FIGURE 3**

**Average annual incidence rate (IR) of disseminated and chronic Lyme borreliosis per 100 000 person-years by county, Norway 1995-2004**



**FIGURE 4**

**Distribution of cases of disseminated and chronic Lyme borreliosis notified in Norway 1995-2004**

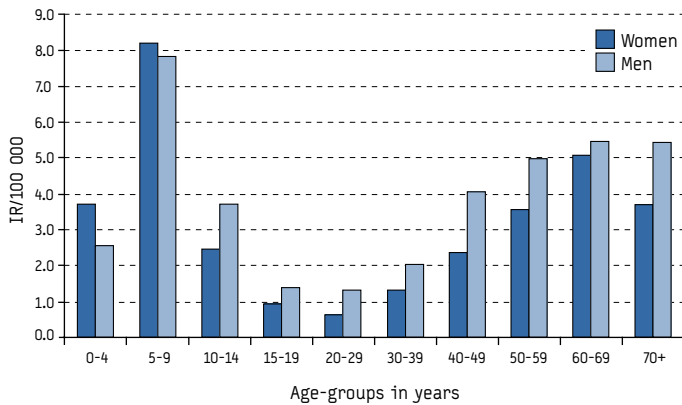


### Age and sex distribution

Fifty six per cent of the cases were in males and 44% in females. The highest incidence rate was found in children aged between 5 and 9 years (average annual IR 8.0/100 000) [FIGURE 5].

FIGURE 5

Age and sex specific average annual incidence rate (IR) per 100 000 disseminated and chronic Lyme borreliosis cases notified in Norway, 1995-2004



### Clinical symptoms and diagnosis

The most common clinical presentation in this study was neuroborreliosis, reported in 1070 of the patients (71.0%), with facial palsy as the most common reported presentation of neuroborreliosis (403 cases). Arthritis or athralgia was reported in 329 patients (21.8%), and acrodermatitis chronica atrophicans (ACA) in 75 patients (5.0%). For 65 patients (4.3%) more unspecific clinical symptoms were reported (e.g. fever, headache, myalgia, rash), and for 28 (1.9%) no clinical information was available. Ten cases (0.7%) had cardiac manifestations as a main or concomitant finding. For some cases, a combination of clinical manifestations were reported.

Forty six per cent of patients were admitted to hospital. The hospitalisation rate was highest for patients with neurological symptoms (81%). The high proportion of neurological disease in children below 10 years of age with disseminated and chronic Lyme borreliosis (92.8%) explains the high rate of admission to hospital in children under ten years of age (79%).

Demonstration of Borrelia-specific antibodies was the basis of diagnosis in 1491 cases, microscopy in 2 cases, nucleic acid detection in 2 cases and unknown in 11 cases. Diagnosis was based on analysis of serum in 730 cases, cerebrospinal fluid (CSF) in 429 cases, blood and spinal fluid in 328 cases, synovial fluid in 5 cases, skin biopsy in one case and unknown in 12 cases. According to the notification forms, neuroborreliosis was laboratory confirmed by demonstration of antibodies in CSF in 429 cases, serum and CSF in 326 cases, only serum in 304 cases and was not reported for 7 cases.

### Discussion

Borrelia infection is the most common notifiable tickborne disease in Norway, and the annual number of cases of disseminated and chronic Lyme borreliosis in Norway has been fairly stable during the study period 1995 to 2004. However, in 2004 we observed an almost twofold increase of cases compared to mean annual cases during the last ten years. It is not yet known if this reflects a true increase in incidence or increased rates of detection or reporting. We have, however, no data that indicate any changes in diagnostic methods or reporting practices that could have caused the increase in number of notified cases we observed in 2004.

Erythema migrans is the most common clinical manifestation of Lyme disease. However, it is also the least severe presentation and the diagnosis cannot easily be confirmed by laboratory testing, as most patients do not demonstrate an antibody response at the time of diagnosis. For these reasons, Lyme disease with erythema migrans as the only manifestation has not been notifiable in Norway during

the study period 1995-2004. However, in 1993 and 1994, all clinical manifestations of Lyme borreliosis were notifiable, and at that time erythema migrans represented 43%-59% of notified cases where clinical information was available[4,5]. This is in accordance with routine passive surveillance data from other countries [6,7], but lower than reported in enhanced clinical surveillance[8] or community-based cohort studies[9]. In general there is probably a higher degree of underreporting when diagnosis is based on clinical symptoms alone, as is often the case with erythema migrans lesions.

Antibiotic treatment is recommended for erythema migrans and is generally believed to protect against disseminated and chronic manifestations. However, Norwegian surveillance data do not contain reliable information on the frequency of prior erythema migrans or noticed tick bites in patients with manifestations of disseminated and chronic disease. It is, however, well known that many, if not most, tick bites go unnoticed and that disseminated and chronic disease can develop without history of tick bite or erythema migrans.

Although Lyme borreliosis is most commonly diagnosed during the summer season, cases are reported throughout the year, probably because unspecific symptoms cause both doctor and patient delay, and also because of the long incubation period of some clinical manifestations. Clinicians should therefore consider disseminated or chronic Lyme borreliosis in their differential diagnosis during all months of the year in patients who live in or have travelled to endemic areas along the coast in southern and middle parts of Norway [FIGURE 4], particularly in patients with neurologic, rheumatic and dermatological signs and symptoms compatible with late onset Lyme disease.

Several tick species have been found in Norway. However the main vector for transmission of Lyme borreliosis to humans is the hard tick *I. ricinus*. The tick can be found in coastal areas with relatively mild winters in the southern and middle part of Norway [10], and this is also reflected in the geographical distribution of Lyme borreliosis cases [FIGURES 3,4].

In 1943 Tambs-Lyche published an extensive survey of the distribution of *I. ricinus* in Norway based on collections of ticks from domestic animals and information concerning the distribution of the tickborne disease babesiosis in cattle[11]. The survey found *I. ricinus* distributed in a narrow zone along the southern coast between the Oslofjord and Jæren, and along the western coast in a relatively wide zone including the innermost regions of most of the fjords and neighbouring valleys. Both ticks and babesiosis were absent from the treeless Jæren. Tambs-Lyche pointed out the importance of vegetation for tick distribution, since it has a modifying effect on the humidity of a habitat. Later, *I. ricinus* became established in those areas where trees had been planted or where bushes and trees had been established. In the periphery of its normal range in Norway, *I. ricinus* is found in scattered, suitable localities.

Recent studies from Sweden have concluded that one of the main reasons for the observed increase in the density and geographical ranges of *I. ricinus* is relatively mild winters, and that this is a possible explanation for the increase in both TBE and Lyme borreliosis cases[12,13]. Other factors such as human behaviour and host animal populations may also have played a part, and these may also be partly related to climate. However, the effect of climate has been disputed by others [14,15]. If climate affects the density and geographic distribution of ticks, it would be expected to also affect the incidence of both Lyme borreliosis and TBE.

More recent studies of ticks in Norway [1,16] do not show any expansion of the range of *I. ricinus* since 1940. On the other hand, there is a marked rise in the density of the tick population in many parts of its range, especially on islands, due to changes in animal husbandry practices, in vegetation, and in the distribution and population densities of host animals such as the roe deer and the European elk.

Increased tick populations may lead to an increased annual spreading of ticks by birds within a country. More than 4000 migratory birds have been investigated for ticks, and the transport of ticks on migrating birds to Norway is well documented [17]. Climatic and

environmental factors may explain why tick populations have not so far become established outside their previous endemic areas.

There is no available vaccine for Lyme borreliosis. Prevention relies on measures to prevent tick bites, such as use of protective clothing and insect repellents, and early detection and removal of ticks. Antibiotics are generally not recommended for prophylaxis after tick bites in Norway.

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## ORIGINAL ARTICLES

### Surveillance report

# EPIDEMIOLOGY OF INVASIVE MENINGOCOCCAL DISEASE IN FRANCE IN 2003

A Perrocheau<sup>1</sup>, MK Taha<sup>2</sup>, D Levy-Bruhl<sup>1</sup>

National surveillance of invasive meningococcal disease (IMD) is based on mandatory reporting. The case definition for surveillance notification was changed in mid-2002 to include cases without microbiological confirmation. The IMD alert detection system was enhanced in 2003 with daily reporting and weekly analysis by district, serogroup, and age. Evaluation of the exhaustivity of the surveillance with capture-recapture analysis allowed correcting for underreporting.

In 2003, 803 cases were reported. After correction for underreporting, the estimated incidence was 1.78 / 100 000. After excluding 'new' cases reported with new definition criteria, the 2002-2003 increase was 4%. Incidence decreased with age, with the highest values in infants less than 1 year (20/100 000), children aged between 1 and 2 years (11/100 000) and in teenagers of 17 years old (7/100 000). The overall case fatality rate was 12%. Fifty nine per cent of cases were due to serogroup B, 32% to C, 5% to W135, and 4% to Y and non-groupable meningococci. Patients with *purpura fulminans* treated with intravenous antibiotics before admission to hospital were shown to have lower fatality rates than those not treated.

In 2001-2003, 5 situations required particular attention: two clusters of serogroup B IMD had set off mass prophylaxis, one outbreak due to a specific B IMD clonal complex with high case fatality rate, and two districts crossed the alert threshold for serogroup C IMD, 2/100 000, and mass vaccination was recommended.

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**Key Words:** meningococcal disease, surveillance, exhaustivity, France

#### Introduction

Invasive meningococcal disease (IMD) is a rare but serious infectious disease responsible for high case fatality and sequela rates, that affects mainly children and young adults. France, with an incidence below 2/ 100 000 inhabitants, is among those European countries with low incidence [1]. This article presents the characteristics of the IMD surveillance in France in 2003, and the recent epidemiological trends.

#### Methods

In France, IMD is a mandatory notifiable disease. When a new case is reported to the district health authorities, the patient's close contacts in the household and in the community during the 10 previous days of admission are traced, in accordance with the national recommendations [2]. All close contacts are requested to intake chemoprophylaxis and vaccination if appropriate. The notifying clinician or microbiologist fills in a notification form which is sent to the district health authorities, and then to the Institut de Veille Sanitaire (InVS) for national surveillance. Serogrouping of the strains is done at the hospital either after isolation of the strain or using polymerase chain reaction (PCR). Pathogen strains are sent to the National Reference Centre for Meningococci (CNRM) for phenotyping and genotyping analysis. The case definition used for national surveillance was expanded in mid-July 2002 from laboratory confirmed cases with *N. meningitidis* culture or positive antigen

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2. Centre national de référence des méningocoques, Institut Pasteur, Paris  
Epidemiology of invasive meningococcal disease in France in 2003



detection in blood, urine or cerebrospinal fluid (CSF) samples, to the new case definition defined by one of the four following criteria: 1) isolation of *N. meningitidis* from a sterile site or from necrotising skin lesions; 2) detection of Gram negative diplococci in CSF; 3) *Purpura fulminans*; 4) CSF revealing purulent bacterial meningitis associated with the skin petechial rash and/or positive antigen detection in CSF, blood or urine, and/or positive PCR from CSF or serum.

Data collected for each case are age, sex, clinical symptoms, serogroup, diseases outcome, number of persons targeted for prophylaxis and occurrence of a secondary case (form available on [www.invs.sante.fr/surveillance/](http://www.invs.sante.fr/surveillance/)). Reports are sent to the InVS on a daily basis for monitoring of district incidence (available at [www.invs.sante.fr/surveillance/](http://www.invs.sante.fr/surveillance/)) and detection of clusters. Yearly surveillance reports are published in the *Bulletin Épidémiologique Hebdomadaire* (weekly epidemiological bulletin).

The exhaustivity (number of reported cases divided by total number of cases reported and not reported) of the IMD surveillance is monitored through regular capture-recapture analysis [3, 4, 2000 analysis available on request] and is used to adjust annual incidence. Capture-recapture analysis allows to estimate the real number of cases occurring in a geographical unit by comparing several sources of data. The number of cases captured by several sources is used to estimate the number of cases not captured in any sources [5]. The exhaustivity of the surveillance in France increased from 50% in 1989-1990 to 75% in 2000-2003.

A cluster of cases was defined as the occurrence of more than one case among persons presenting an epidemiological link. Within a cluster, a co-primary case is a case that occurs within 24 hours after of another one; a secondary case is a case that occurs at least 24 hours after another one.

The population data used for the calculation of incidence were the 1999 census projections from the Institut National de la Statistique et des Etudes Economiques (national institute of statistics and economical studies, INSEE) for 2003.

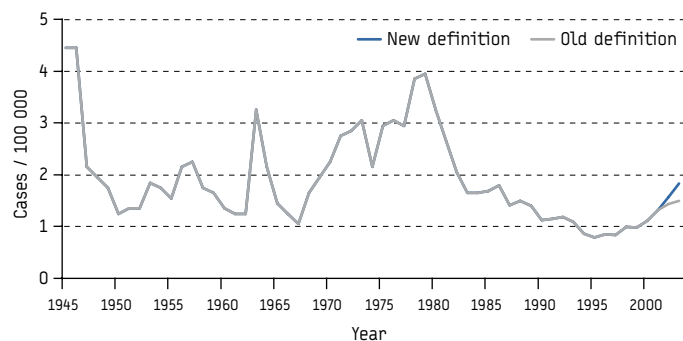
## Results

### Incidence

In 2003, 803 IMD cases were reported, 796 cases from France mainland and 7 from the overseas departments. From 2002 to 2003, the number of cases increased by 18%. The observed incidence in metropolitan France was 1.3 case /100 000 inhabitants and 1.8/100 000 after adjusting for the under-reporting. The new case definition criteria gave an additional 59 cases in 2002 (9%), and 153 cases in 2003 (19%) in addition of the cases fulfilling the former case definition. After excluding these 'new' cases the 2002-2003 increase was 4%. The incidence of IMD declined from 1980 to 1995 and increased steadily since 1996 [FIGURE 1].

FIGURE 1

### IMD incidence\* from 1945 to 2003, France



\* Corrected for under-reporting from 1985 to 2003

### National distribution

In 2003, 15 of the 99 french districts presented an incidence greater or equal to 2/100 000 [6]. The highest incidence was observed in the

Seine Maritime district (3/100 000). For serogroup C IMD, 5 districts had incidence higher than 1/100 000, with a maximum of 1.5/100 000 in the district l'Ariège; 28 districts reported no serogroup C IMD cases.

### Seasonal distribution

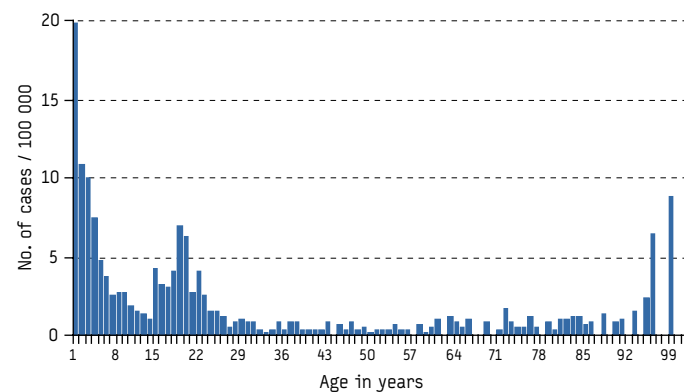
The number of cases increased in winter, starting in December or January, usually at the same time as the influenza epidemic wave. In 2003, the incidence peak was observed in February.

### Age and sex distribution

The male/female ratio was 1. The mean age of patients was 18 years, and the median age 13 years. Eighty per cent of cases were in patients under 25 years old. Age-specific incidence showed that infants (<1 year) were more affected than toddlers (1-2 years) [FIGURE 2]. Incidence decreased slowly up to 12 years of age, and then rose from 13 years of age, reaching a peak at 17 years of age. From 24 to 92 years of age, incidence was less than or equal to 1/100 000.

FIGURE 2

### Specific incidence\* by age in years, invasive meningococcal disease, France, 2003



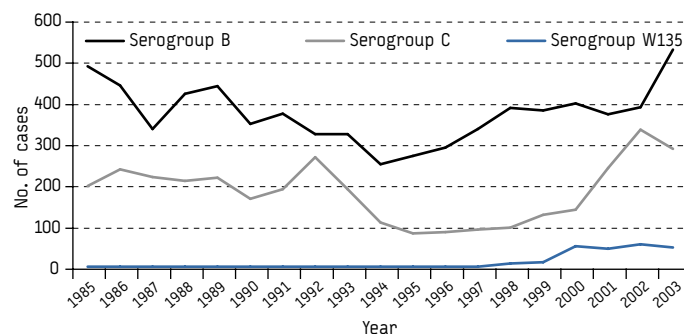
\* Corrected for under-reporting

### Serogroup distribution

In 2003, 668 cases (83%) were serogrouped. Among those, serogroup B represented 59% of cases; serogroup C, 32%; serogroup W135, 5%; and the other serogroups (A, 2 cases; Y, 19 cases; and non-groupable, 2 cases) represented 4% of cases. In 2002, the incidence of serogroup C IMD had reached a peak, with 250 cases representing 42% of all serogrouped cases. This was the highest value observed in France since 1985 (when the first serogrouped data became available) [FIGURE 3]. In 2003 the incidence of serogroup C IMD decreased to a more usual proportion and numbers. This trend continued in 2004.

FIGURE 3

### Number of IMD cases\* according to the main serogroups, France, 1985-2003



\* Corrected for under-reporting

### Clinical presentation

In 2003, 631 (79%) patients presented with meningitis, and 291 (36%) presented with septicaemia, of whom 172 also had meningitis. Eight patients presented with arthritis and one patient had meningococcal pericarditis. Of the cases for which data on clinical symptoms only is available, 73 (57%) were confirmed with *purpura fulminans* and 54 (43%) with purulent CSF associated with purpura or soluble antigens or positive PCR.

### Severity of the disease and outcome

The overall proportion of cases with *purpura fulminans* increased from 23% in 2001 to 30% in 2002 and 28% in 2003 ( $p=0.01$ ) [5]. The cases with *purpura fulminans* without laboratory confirmation were responsible for 16% and 34% of the increase of *purpura fulminans* in 2002 and 2003 respectively. The outcome of the disease was known for 94% of the cases. The 16% case fatality rate (CFR) observed in 2002 declined to 12% in 2003. The CFR was higher in the presence of *purpura fulminans* ( $p<0.001$ ) and varied according to age ( $p<0.001$ ) and serogroup ( $p=0.002$ ) (TABLE).

TABLE

Number of IMD cases and deaths depending on the presence or absence of *purpura fulminans*, France, 2001-2003

Age group in years	With <i>purpura fulminans</i>		Without <i>purpura fulminans</i>	
	Cases (n)	Case fatality rate (%)	Cases (n)	Case fatality rate (%)
<2	131	42.7	263	1.9
2-14	189	27.0	337	2.4
15-24	128	24.2	280	2.9
25-99	87	51.7	292	12.0
Total	535	34.2	1172	4.8
<b>Serogroup</b>				
B	219	33.8	580	2.8
C	183	37.2	358	8.1
W135	19	63.2	66	7.6
Other	14	35.7	42	9.5
<b>Total</b>	<b>435</b>	<b>36.6</b>	<b>1046</b>	<b>5.2</b>

However, the higher CFR in serogroup C and W135 cases may be due to a higher proportion of isolates belonging to the clonal complex ET-37/ST-11 among serogroup C and W135 isolates.

Between 2002 and 2004, of 507 patients with *purpura fulminans* and known evolution, 206 (41%) were given intravenous antibiotic treatment before admission to the hospital. The risk of death was lower in the group that had received antibiotic injection (24%) than in the group that did not receive it (35%) ( $p=0.01$ ) before admission.

### Clusters of IMD cases and specific prevention measures

In 2003, 14 clusters were documented: 8 with co-primary cases, 4 with secondary cases, and 2 with co-primary and secondary cases. The 12 secondary cases identified accounted for 1.4% of all IMD cases. This proportion has been stable for the past 10 years [7].

### Mass chemoprophylaxis campaign:

1. During spring 2003, chemoprophylaxis was recommended to 50 students after the occurrence of a cluster of four serogroup B IMD cases among teenagers attending a boarding school in Nantes and their close contacts. This measure was aimed at limiting the spread of the pathogenic strain into the general population when the students returned home for the school holidays.
2. During the summer of 2003, chemoprophylaxis was offered to 8000 people living in an urban neighbourhood of Metz, after the occurrence of seven cases of serogroup B belonging to the clonal complex ET5/ST32 within an 18 day period, among children within

an extended family and other children living in that the same neighbourhood. The attack rate for cases without direct contact was 17/100 000. More than 86% of residents presented to healthcare services to receive rifampicin, and no new case was reported after the measure was implemented.

### Awareness campaign

In a defined geographical area including the town of Dieppe and the surrounding area in the Seine Maritime district, the annual incidence was 12 cases/100 000 inhabitants in 2003 and 2004, with 40% of cases presenting *purpura fulminans*. *N. meningitidis* B14:P1.7,16, belonging to the clonal complex ET5/ST32, was isolated in 8 out of 10 cases in 2003. This clonal complex is characterised by high virulence and has been responsible for outbreaks in other European countries[8]. Information campaigns were launched, targeting clinicians and the general population, for prompt recognition of the cases to shorten the time between onset of illness and start of medical treatment. The number of fatal cases decreased from 8/32 cases to 4/28 cases between 2003 and 2004.

### Vaccination campaign against *C meningococci*

1. In January 2002, in the Puy-de-Dôme district, a vaccination campaign targeting around 100 000 children and young people aged between 2 months to 20 years old was carried out to stop the rapid increase of serogroup C IMD incidence (5 cases /100 000 inhabitants in Clermont-Ferrand) in that population. Many of these cases were presenting with *purpura fulminans* [9]. At the end of the campaign, vaccine coverage reached more than 80% of the target population.
2. At the end of 2002, a similar campaign targeting around 300 000 people was set up in three districts in southwest France, where the mean incidence for serogroup C IMD had reached 2.2/100 000 [10]. At the end of the campaign, vaccine coverage reached more than 85% of the target population.

In these two regions, the incidence of serogroup C IMD declined after the vaccination campaigns and has since remained low. No significant increase of serogroup B IMD incidence was observed in 2003 or 2004.

### Discussion

In France, the incidence of IMD has been steadily increasing since 1996. In 2003, the slope of the increase slowed down and in 2004 the incidence of IMD decreased for the first time for 10 years. The case definition adopted in 2002 allowed the inclusion of non-laboratory confirmed cases and increased the reporting sensitivity for the disease in France. The recommendations for the pre-admission antibiotic injection when a *purpura fulminans* was suspected were published in 2001 and we expected that the number of cases without laboratory confirmation would increase. Therefore the case definition was revised according to this recommendation and to new laboratory diagnosis practices. Some *purpura fulminans* may be due to *Streptococcus pneumoniae* but the main cause of *purpura fulminans* remains *N. meningitidis*. The administration of intravenous antibiotic treatments before admission to hospital for cases with *purpura fulminans* seems to be associated with a lower case fatality rate. However, surveillance data do not allow us to conclude that there is a causative association. Although a decrease in the CFR was observed in the Seine Maritime district after the public awareness campaign, we have no information on interval between onset of symptoms and start of medical treatment before and after this campaign.

In 2001 and 2002, a national increase of serogroup C IMD was observed in France and in several other European neighbouring countries. The alert threshold of C IMD (incidence > 2/100 000 with at least 5 cases occurring in 52 weeks in a district) [11] was crossed twice, and local vaccination campaigns implemented in response. The impact of the campaigns was excellent and high vaccine coverage were rapidly reached. In February 2003, the General Direction of Health decided not to recommend general vaccination for children and

teenagers in France [12]. This decision was based on the low incidence of C IMD cases in France, 0.4/100 000 in 2002, compared with the incidence in European countries that had introduced Men C routine childhood vaccination (ranging from 1.9 to 4 cases per 100 000), and took into account the theoretical risk of a capsular switch induced by vaccination. In 2003 and 2004, national incidence of C IMD decreased and the district incidences remained under the alert threshold for serogroup C IMD.

### Acknowledgements

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## ORIGINAL ARTICLES

### Surveillance report

# 'DID YOU HAVE FLU LAST WEEK?' A TELEPHONE SURVEY TO ESTIMATE A POINT PREVALENCE OF INFLUENZA IN THE SWEDISH POPULATION

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Sentinel surveillance usually underestimates the true burden of influenza in a population, as individuals must present to medical establishments to be included in the surveillance system. We carried out a telephone survey to estimate the national burden of influenza in the Swedish population for one week during the 2004/05 influenza season. Fixed-line telephone numbers were randomly sampled and households interviewed concerning influenza illness between 14-20 February 2005 (Week 7 of 2005). Questions regarding seasonal influenza vaccination status, symptoms and the impact of illness on daily life were also included. A self-defined influenza prevalence of 7.7% in week 7 of 2005 was estimated. On applying a case definition of 'cough and fever and muscle pain' for influenza like illness, the prevalence decreased to 3.6%. The survey provided insight into the burden of illness in the population further to that estimated through the sentinel surveillance system.

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**Key Words:** cross-sectional survey, influenza, prevalence, Sweden

### Introduction

Influenza A or B viruses circulate every winter in the northern hemisphere, approximately between the months of October and April. Though influenza disease is usually self-limiting, it causes a considerable impact on an individual's daily life, affects the demand

for health services and can create economic loss. The burden of influenza falls particularly on groups especially prone to complications or fatal outcome, such as the very young [1], the elderly [2] or the chronically ill.

Assessing the annual level of morbidity due specifically to influenza A or B viruses is however difficult, as the viruses lack pathognomonic features and co-circulate with other respiratory pathogens [3]. Consequently, many surveillance systems across Europe aim to identify a level of illness possibly caused by influenza viruses, i.e., influenza-like illness (ILI). A definitive set of symptoms for a clinical diagnosis of influenza has been difficult to achieve, and the ILI definition varies widely across Europe [4].

Reports of ILI are the basis of the influenza sentinel surveillance system in Sweden, where participating physicians from specific sites across the country report weekly number of ILI cases. No case definition for influenza or ILI is used. Together with laboratory reporting of influenza positive tests, the surveillance system allows a timely overview of the level and duration of influenza circulating in a season. However, the sentinel and laboratory surveillance systems depend on symptomatic individuals presenting to a physician for consultation. They thus underestimate the true burden of illness caused by influenza, since milder cases, clustered family cases, or severely affected individuals living alone, may not seek medical attention.

To understand the difference between measured (surveillance system) and the true burden of influenza illness in the Swedish population, we carried out a survey to estimate a point prevalence of self-reported influenza in the national population during one week

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of the influenza season. Secondary objectives included describing the symptoms experienced, calculating the influenza vaccination uptake during part of the 2004/2005 influenza season, measuring medical consultation, estimating the severity of illness as defined by absence from school or work, and time spent in bed. The survey was planned and realised within a 3 week period, testing a capacity to undertake real-time surveys of the national population and providing useful experience for surveillance in an event of an epidemic threat.

### Methods

A cross-sectional retrospective survey was undertaken of a random sample of the Swedish population. The sampling frame was a national register of landline household telephone numbers (SPAR) with the random sample being generated by the organisation holding the register. We contacted households by telephone and following oral consent, interviewed responders (aged 16 years and over) regarding each member of the household.

All questions regarding illness, symptoms and visits for medical attention were asked concerning the week prior to interview: Week 7, 14-20 February 2005. Data collected for each household member included: age, gender, vaccination against influenza that season, having influenza and any of the following: cough, fever, chills or muscle ache/pain. For individuals reporting symptoms, questions were asked about whether an individual had needed to stay in bed for a day or taken time off work or school because of their symptoms. No definition of influenza was provided to interviewees. To compare self-reported influenza status to a case definition for ILI, a closest match to the European Union influenza case definition [5] of 'cough and fever and muscle pain' was applied to the sampled population according to symptoms reported.

During an annual influenza epidemic, between 5% and 15% of a population suffer an upper respiratory tract infection [6]. By doubling the weekly average of 1% in an assumed 10 week epidemic, we required 1505 individuals (EPI6v.6.0.4). With a 95% CI, 4.2 million people accessible by telephone (SPAR), a lower acceptable limit of 1%, design effect of 2 and an average household size of 2.05 people [7], we needed to interview 734 households. Accounting for a higher response rate due to the national interest in influenza than experienced by recent SMI (Swedish Institute for Infectious Disease Control) telephone interviews [8], a list of 1500 telephone numbers was purchased.

Fifteen trained persons undertook the structured questionnaire interviews over evenings of 22-25 February 2005. Answers were entered directly onto computers using Epidata (v.3.02, Denmark). Three call attempts were made per household over at least two different evenings. Data were cleaned and proportions with confidence intervals calculated in EpiInfo using complex sampling statistics to allow for the design effect (Epi Info v.3.2.2).

### Results

Of the 1334 households to whom telephone calls were made, contact was established with 1070, and 872 agreed to participate in the survey. This resulted in a response proportion of 81% and a sample of 2119 individuals. Age was unknown for 15 individuals. Table 1 compares the sample and Swedish population by age group. The average household size was 2.43 persons (range 1-8).

TABLE 1

Sample (n = 2104) and population (9 011 392) age group distribution, Sweden

Age group (in years)	Sample %	Sample 95% CI	Population* %
0-4	5.9	4.9-7.0	5.4
5-14	14.2	12.4-15.9	12.2
15-29	15.8	14.0-17.7	18.2
30-44	21.6	19.8-23.4	20.9
45-64	26.5	24.1-28.9	26.1
65+	16.0	13.9-18.1	17.2

\* From: SCB statistics Sweden [9]

### Influenza status

Of people who had an opinion about their influenza status, 160 people of 2090 had influenza, giving a prevalence of 7.7% in Week 7 (95% CI 6.2-9.1, Design Effect= 1.7). Prevalence was highest in the lowest age groups [TABLE 2].

TABLE 2

Prevalence of self-reported influenza by age group, week 7, 2005, Sweden

Age group (in years)	Influenza	Total	Prevalence %	95% CI
0-4	19	122	15.6	8.3-22.8
5-14	38	292	13.0	8.5-17.5
15-64	84	1328	6.3	4.8-7.8
65+	19	333	5.7	2.8-8.7
<b>Total</b>	<b>160</b>	<b>2075</b>		

Note: Age was unknown for 15 individuals

### Vaccination uptake

Among the 2096 individuals who knew their vaccination status, 11.6% (95% CI 9.8-13.3) reported having been vaccinated. Seventy five per cent (184/ 243) of those reporting vaccination were aged 65 years or over, with a vaccination uptake among the 65+ age group of 55.1% (95% CI 49.0-61.2)

### Symptoms and severity of illness

Table 3 shows the symptoms and severity of illness in individuals reporting influenza versus those not reporting illness.

TABLE 3

Symptoms and effect of illness by self-reported influenza status, week 7, 2005, Sweden

	Influenza		No Influenza	
	Prevalence (sample size) % (n)	95% CI	Prevalence (sample size) % (n)	95% CI
<b>Symptoms</b>				
Fever	83% (155)	76-90	5% (1888)	4-6
Chills	73% (150)	64-82	4% (1882)	3-5
Cough	80% (159)	73-87	11% (1898)	10-13
Muscle pain	56% (145)	46-66	3% (1876)	2-4
<b>Severity of illness</b>				
Absent from school/work <sup>1</sup>	67% (121)	58-76	26% <sup>2</sup> (200)	19-32
At least one day in bed <sup>1</sup>	76% (122)	68-84	23% <sup>2</sup> (202)	16-29

1. 5-64 years only

2. Only individuals reporting one or more symptoms (fever, chills, cough or muscle pain) were asked for this information

### Applying a case definition for Influenza Like Illness (ILI)

When a case definition was applied to data collected, the ILI prevalence was 3.6% (74/2031, 95% CI 2.6-4.7, DE=1.7). Assuming ILI to be a true measure of influenza burden in the population, 41% of self-reported influenza cases had ILI (positive predictive value, 58/141). The sensitivity and specificity of self-defined influenza as a measure of ILI were 87% (58/67) and 96% (1858/1941) respectively [TABLE 4].

TABLE 4

### Influenza-like illness (ILI) status by self-reported influenza status, week 7, 2005, Sweden

	ILI	Not ILI	Total
Influenza	58	83	141
No influenza	9	1858	1867
<b>Total</b>	<b>67</b>	<b>1941</b>	

#### Survey logistics

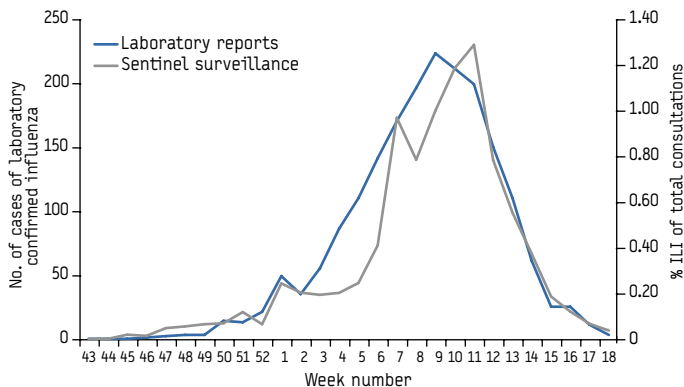
The time taken to complete the protocol, questionnaire, database, telephone number sourcing and recruitment of interviewers was approximately 125 working hours. The basic costs of the survey (telephone list, interviewers and telephone calls) amounted to approximately 3250€. To reach the 1334 households, 2084 call attempts were made, approximating 14 calls per hour per person.

#### Discussion

This is the first survey undertaken in Sweden to estimate the national burden of influenza during an influenza season. The telephone survey yielded a good response, with 81% of people contacted agreeing to be interviewed. The main survey finding was a point prevalence of 7.7% self-defined influenza in the Swedish population in week 7 of 2005. Due to the different denominator used in the sentinel surveillance (number of consultations), the survey prevalence estimate cannot directly be compared to the sentinel measure of 1.0% ILI activity in week 7 [FIGURE]. However, according to the surveillance system, Week 7 was 3-4 weeks prior to the peak of influenza activity of the 2004/2005 season.

FIGURE

### Sentinel surveillance for influenza-like illness (ILI) and laboratory confirmed cases, 2004-2005 season, Sweden



There are limitations to the survey method that may have underestimated the prevalence result. Firstly, a slight under-representation of individuals aged 15-29 years, likely to be due to the high level of mobile phone ownership and single households among this age group in Sweden. Secondly, due to the time proximity of the recall period and the survey, some households severely affected by influenza may have been omitted from the survey if household members were unable to answer the telephone.

The design effect of the prevalence measured was lower than expected, suggesting that reported influenza was not highly clustered by household. This could be an artefact due to the small size of households in Sweden. Conversely, it may be that many households in Sweden were concurrently affected by influenza, thus the ratio of between household variance and total variance is small. Results indicate that the burden of self-defined influenza was higher among younger age groups, consistent with reports from the European influenza surveillance system for 2004/2005 [10]. A higher burden of influenza on children would support a widespread distribution of influenza illness in the population.

The self-reported prevalence estimate of 7.7% influenza is likely to be an overestimate of the prevalence in Sweden in Week 7 of 2005. Reported symptoms show a relatively high prevalence of cough. With fever status also being self-defined, it is likely that other circulating respiratory infections were included as influenza. However, according to laboratory surveillance, respiratory syncytial virus activity during the 2004-05 season was relatively low [11] with 37 cases reported in week 7 [www.smittskyddsinstytutet.se]. Using the ILI case definition, the resulting prevalence was nearly half that of self-reported influenza. Clinical or laboratory confirmation of reported influenza would have allowed a comparison of these measures, but was not possible in this survey.

An indication of the national uptake of influenza vaccination in the 2004/2005 season was obtained. With the assumption that individuals are vaccinated within the first few months of the season, the vaccination uptake among the age group of those aged 65 years and over in Sweden was 55.1%. This was similar to the 51% identified in 2003 [12], much higher than the 30% identified within a representative sample of this age group in one region of Sweden between 1998-2000 [13], but lower than the national 62.7% vaccine coverage in the last season in the United States [14].

Influenza is considered to cause a high burden on society in terms of time, energy and economic impact [15]. This survey identified that among those aged 5-64 years with self-reported influenza, 67% took time off work or school. Furthermore, the high proportion of individuals staying in bed for at least one day due to symptoms highlights the impact on daily life from self-defined influenza morbidity. These results are in line with the findings of a household survey undertaken in France in 2000 that identified a substantial burden of illness due to influenza [16].

This survey has provided useful insights into the burden of Influenza and ILI in Sweden during a week of the 2004/05 influenza season. It proved to be logistically feasible to be undertaken in a short time and economically viable. With repetition inter and intra seasons, this survey is a tentative step towards developing a comparative scale between sentinel surveillance measures and the true burden of influenza in the population. Such a development would provide a useful tool towards monitoring and interpreting influenza activity in Sweden and throughout Europe, supporting pandemic preparedness.

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## ORIGINAL ARTICLES

## Surveillance report

# COMPLETENESS OF MALARIA NOTIFICATION IN THE NETHERLANDS 1995-2003 ASSESSED BY CAPTURE-RECAPTURE METHOD

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In 1999 in the Netherlands, the duty to notify malaria was transferred from physicians to laboratories by the new Infectious Diseases Law. To evaluate the effect of this change, we aimed to estimate completeness of malaria notification in the Netherlands from 1995-2003. We calculated it relative to sentinel laboratory and hospital admission data. Using the two-source capture-recapture method (CRM), we estimated the total number of cases to assess the completeness relative to this number.

The completeness of notification relative to sentinel data was 18.2 % (95% CI of 15.7-20.7) from 1995-1998 and 56.4 % (95% CI of 47.0-65.8) for 2000-2003. The completeness relative to the number of malaria cases admitted to the hospital was 35.1 % for the period 1995-2003. The estimated numbers of cases of malaria between 1995 and 1998 were 3123 (95% CI of 2796-3449) and 5043 (95% CI of 4343-5742) between 2000 and 2003. The completeness relative to these numbers changed from 35.5 % (95% CI of 32.1-39.7) in 1995-1998 to 36.1 % (95% CI of 31.7-41.9) for the years 2000-2003. Laboratory-based notification has significantly increased the absolute number of malaria notifications, but there was no change in completeness relative to hospital admissions. The increase in estimated malaria cases may be artificial, due to the extent of violation of CRM requirements over the study period.

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**Key words** : Capture-recapture, malaria, notification system**Introduction**

Since the new infectious diseases law was implemented in the Netherlands on 1 April 1999, laboratories are legally obliged to report malaria cases to the Municipal Health Service (GGD). Before this time, notification was only the responsibility of physicians. To evaluate this structural change in the Dutch notification system, this study, carried out in September 2004, aimed to estimate the completeness of malaria notifications in the Netherlands from 1995-2003. In this context, completeness refers to the proportion of cases detected by

the notification system. It is generally assumed that malaria, like many other infectious diseases, is underreported [1,2]. Van Hest *et al*. investigated a total number of 774 malaria cases (95% CI of 740-821) and a completeness of notification on 40.2 % in the Netherlands in 1996 using three-source CRM [3].

**Methods****Data Sources, Case Definition and Matching Algorithms**

The sentinel register (12 voluntarily reporting laboratories at the moment) included the variables month and year of birth, gender, postal code, place of residence and day of onset/date of diagnosis. The variables which were reported to the notification register included the date of notification, year of birth, date of diagnosis, date of onset, postal code, gender, reporting GGD, method of diagnosis, and the species of plasmodium. The Dutch morbidity registration organisation provided hospital admission data on principal diagnosis malaria (ICD-9 code 084\* - \* meaning all species of malaria) with the variables pathogen, date of admission, date of discharge, year of registration, year of birth, gender, postal code and place of residence after discharge. A case of malaria in this study was defined as a person with a positive blood smear for a plasmodium species.

We matched data first by using the following identifiers: year of birth, gender, year of diagnosis/request/admission (if missing: year of onset/sample) and 4-digit postal code, using an algorithm in MS-Excel®. To correct for late notification, we used safety margin of 30 days around the date of diagnosis in the GGD data and these matching pairs we reviewed manually.

We searched for additional matches in the remaining non-matched cases, using a second algorithm. This algorithm used the same identifiers, but without postal code, for the GGD records without a valid postal code (e.g. unknown, missing, abroad, homeless). To be confident we reviewed these matching pairs manually, comparing the date of diagnosis with the date of admission (+/- 3 days, hospital data) and the species (hospital data and laboratory data).

**Completeness of notification**

The completeness of notification was assessed by searching for cases which were also on the notification register as in the sentinel laboratory register or hospital admission register, respectively. To calculate the completeness (C) of notification relative to sentinel laboratory data we used the formula:  $C = a/b \times 100\%$  where a is the

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number of cases in both data sources (notification and laboratory data base) and b is the number of cases in the laboratory data base. The 95%CI of C is:  $C \pm 1.96 \sqrt{a^*(b-a)/b}$ . To calculate the completeness of notification relative to hospital admission data we used the same formulas.

### Two-source-capture-recapture Method (CRM)

CRM is adapted from biology and is applied on overlapping incomplete data sources. The two-source method is a relatively simple, feasible and reproducible method used to estimate the number of total cases, including the ones which were not observed, and subsequently to assess the completeness of the sources. We used the hospital admission data and the notification data to estimate the number of malaria cases.

On the basis of previous literature, Hook and Regal [4] conclude that the maximum likelihood estimator (MLE) (if the numbers are high enough) for the real number of cases (N) is:  $N = (a + b)^*(a + c)/a$  where a is the number of cases in both registers and b and c are the numbers in only one of the registers. The 95% CI of N is:  $N \pm 1.96 \sqrt{(a+b)^*(a+c)*b*c/a^3}$ .

To calculate the completeness of the notification register relative to the estimated number of cases (C) we used the formula:  $C = (a+b)/N*100\%$  where b is the number in only the notification register.

### Results

Completeness of notification relative to sentinel laboratory detected cases and to hospital-determined cases.

The completeness of the notification relative to the laboratory diagnosed cases was 18.2 % (95% CI of 15.7-20.7) for the period from 1995-1998 and increased significantly to 56.4 % (95% CI of 47.0-65.8) for the years 2000-2003 [TABLE 1].

The completeness of notification relative to the cases admitted to the hospital was 35.7 % (95% CI of 17.7-53.7) for the period 1995-1998 and 37.7 % (95% CI of 21.3-54.0) for the period 2000-2003 [TABLE 2]. This change is not significant.

### Completeness relative to estimated total number of cases

The first algorithm contributed 861 matching pairs, which was 84.9 % of the final matching pairs. The second algorithm contributed 153 (15.1 %) of all matched cases. Between 1995 and 2003, 2886 patients with malaria were admitted to hospital and 3382 cases were notified to the GGDs. 1014 of these cases could be found in both sources. These numbers gave a CRM estimate of 9626 (95% CI of 9226-10 025) malaria cases in these nine years, while 3123 (95% CI of 2796-3449) cases were estimated before 1999 compared to 5043 (95% CI of 4343-5742) cases after 1999. Based on the estimated numbers of total cases, as demonstrated in table 3, the completeness of notification increased minimally from 35.5 % (95% CI of 32.1-39.7) for the years 1995-1998 to 36.1 % (95% CI of 31.7-41.9) for the years 2000-2003.

### Discussion

- The increase in estimated malaria cases is assumed to be artificial, due to that the introduction of the new law enhanced the violation of the basic assumptions underlying CRM [2,4,5]:
  - Same case definition in each source: Hospital admission uses high severity of malaria case by implication. As the notification register also includes outpatients with a lower severity, the case definitions are different.
  - Same probability to be ascertained for each case: Outpatients have no probability of being on the hospital admission register.
  - Source independency: Since 1999 the dependency between cases notified from hospitals and those notified from laboratories was reduced.

TABLE 1

Number of sentinel laboratory detected malaria cases and completeness of notification relative to this number, the Netherlands, 1995-2003

Year of diagnosis	Laboratory-confirmed	Laboratory-confirmed and notified	Laboratory total	Completeness	Aggregated completeness (95% CI)
1995	3	1	4	25	18.2 (15.7-20.7)
1996	1	1	2	50	
1997	3	0	3	0	
1998	2	0	2	0	
1999	9	6	15	40	56.4 (47.0-65.8)
2000	8	18	26	69.2	
2001	11	16	27	59.3	
2002	15	10	25	40	
2003	7	9	16	56.3	
<b>Total</b>	<b>59</b>	<b>61</b>	<b>120</b>	<b>50.8</b>	

TABLE 2

Hospital admissions with malaria and completeness of notification relative to this number, the Netherlands, 1995-2003

Year of diagnosis	Hospitalised	Hospitalised and notified	Hospitalised total	Completeness	Aggregated completeness (95% CI)
1995	243	124	367	33.8	35.7 (17.7-53.7)
1996	196	144	340	42.4	
1997	254	105	359	29.2	
1998	215	131	346	37.9	
1999	252	80	332	24.1	37.7 (21.3-54.0)
2000	236	126	362	34.8	
2001	185	125	310	40.3	
2002	179	66	245	26.9	
2003	112	113	225	50.2	
<b>Total</b>	<b>1872</b>	<b>1014</b>	<b>2886</b>	<b>35.1</b>	

- Accurate classification as a case: Positive predictive value is assumed to be high for malaria, due to inclusion of laboratory diagnostics in the case definition.
- Suitability of matching: Because of incomplete notification the identifiers have not always been available; also the reliability of the given identifiers is supposed not to be optimum and to diminish, leading to under-assessment of the number of matching pairs. It is not likely to confuse cases with other cases in a rare disease like malaria in the Netherlands.
- Closed study population: Stable 'catchability' of cases exists because it is not likely that one would travel in or out of the Netherlands while suffering from acute malaria. Fatality is also low. 'Catchability' between years may have changed because of risen number of immigrants from endemic countries.
  - Laboratory-based notification has significantly increased the absolute number of malaria notification in the Netherlands [TABLE 3]. The increase in the numbers of travellers to and immigrants from endemic countries cannot explain this increase.
  - No change in completeness of notification relative to hospital admission data was observed [TABLE 2]. We therefore conclude that the increase of notified cases was mainly due to non-hospitalised cases.
  - The overestimation of the unobserved number of cases after 1999 creates the impression of a low completeness of notification by the laboratories.

**Over-all Conclusion**

The number of malaria cases and incidence is still much higher than notified, but it is likely that this study is overestimating the number of cases. Even if we consult only the number of cases which are recorded by at least one source, the surveillance system of malaria notification does not provide a realistic description of the incidence in the Netherlands.

Regarding CRM, the violation of the basic assumptions underlying the method leads to the overestimation of malaria cases and even a three-source investigation could not estimate the number of total cases because of a high dependency between notification register and laboratory reports after 1999.

**Recommendations**

- In order to facilitate the CRM as a tool in evaluating surveillance systems in general, we would recommend the reintroduction of common personal identifiers in the malaria reporting system. This might also be a benefit in other surveillance systems.
- A more complete evaluation of malaria surveillance based upon the CDC Guidelines would facilitate future CRM studies, by providing answers to some important questions on data quality, sensitivity and specificity that arose in our study.

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TABLE 3

**Distribution of observed malaria cases, estimated number of unobserved cases, total number of estimated cases and completeness, The Netherlands, 1995-2003**

Year of diagnosis	Hospital admissions	Only H *	Both, H/N ‡	Only N	Notifications	No. of unobserved cases	CRM ± MLE # (95% CI)	Completeness (95% CI)	Aggregated CRM MLE and aggregated completeness (95% CI)
1995	367	243	124	194	318	380	941 (836-1046)	33.8 (30.4-38.0)	3123 (2796-3449) 35.5 (32.1-39.7)
1996	340	196	144	157	301	214	711 (647-774)	42.4 (38.9-46.5)	
1997	359	254	105	122	227	295	776 (685-868)	29.2 (26.2-33.2)	
1998	346	215	131	132	263	217	695 (628-761)	37.9 (34.6-41.9)	
1999	332	252	80	375	455	1181	1888 (1561-2216)	24.1 (20.5-29.1)	
2000	362	236	126	411	537	770	1543 (1353-1733)	34.8 (31.0-39.7)	5043 (4343-5742) 36.1 (31.7-41.9)
2001	310	185	125	419	544	620	1349 (1189-1509)	40.3 (36.0-45.8)	
2002	245	179	66	331	397	898	1474 (1196-1751)	26.9 (22.7-33.2)	
2003	225	112	113	227	340	225	677 (605-749)	50.2 (45.4-56.2)	
<b>Total</b>	<b>2886</b>	<b>1872</b>	<b>1014</b>	<b>2368</b>	<b>3382</b>	<b>4372</b>	<b>9626</b> <b>(9226-10025)</b>	<b>35.1</b> <b>(33.7-36.7)</b>	

\* Hospitalised ± Capture-recapture method  
 ‡ Notified # Maximum likelihood estimator



# ASCERTAINMENT OF MENINGOCOCCAL DISEASE IN EUROPE

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Meningococcal disease surveillance in most countries is based upon a combination of statutory notification systems and laboratory reporting, both of which are recognised to underestimate the true burden of disease. The incidence of meningococcal disease varies throughout Europe, and although there are many reasons for this, it is important to quantify the degree of under-ascertainment in order to validate international comparisons. Here, we review the literature on the ascertainment of meningococcal disease in Europe and the available methods for estimating the degree of under-reporting. We found that the sensitivity of surveillance varies between countries and over time, with estimates ranging from 40% to 96%. We identified five methods suitable for conducting ascertainment studies, from simple comparative studies to more complicated capture-recapture and regression analyses. Studies of ascertainment may be used to identify weaknesses and biases in surveillance data, and facilitate the improvement of these systems. These findings are relevant to the surveillance of other infectious diseases, particularly those with lower mortality and a lower public profile than meningococcal disease, for which ascertainment may be worse.

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**Key words** : ascertainment, meningococcal disease

## Introduction

The incidence of meningococcal disease varies across Europe from less than 1 case per 100 000 population, up to 6 per 100 000 [1]. The overall case fatality ratio in Europe is around 8%, but there is considerable variation between individual countries, from 4% to 20% [1]. The extent to which differential ascertainment contributes to the variation in morbidity and mortality is not clear.

The priority for public health disease surveillance is not to identify every case of an infectious disease, but to monitor trends and changes in disease epidemiology in a timely manner. A surveillance system will be adequate so long as reporting is unbiased and the level of under-ascertainment is known and judged to be acceptable. For the surveillance of meningococcal disease, most European countries rely upon laboratory reporting systems, clinician notification systems, or a combination of the two. These systems are likely to underestimate the true number of cases of disease [2,3]. Laboratory confirmation of meningococcal disease is very useful for management of cases and contacts and offers a highly specific diagnosis, but it is not always possible to obtain an isolate, especially if antibiotics are administered early. The use of polymerase chain reaction (PCR) assays, which require only a clinical sample and not a live isolate, appears to improve laboratory ascertainment [4]. Clinician notifications are likely to be less specific (but may be more sensitive) than laboratory reporting, but under-reporting also seems to be a problem [5], even when such notifications are mandatory.

Assessing the degree of under-ascertainment is important for four major reasons: first, to ensure that surveillance is unbiased and representative, second, to allow the true burden of disease to be estimated (which may be useful for priority setting and economic evaluations of interventions), third, to facilitate improvements in the surveillance systems and fourth, to enable international comparisons. Here, we explore different methods for assessing the quality of surveillance and degree of under-reporting and review work that has been performed in Europe (published and unpublished) specific to meningococcal disease.

The aim of this article is to synthesise current knowledge on ascertainment of meningococcal disease in Europe and to review methods for quantifying the degree of under-ascertainment in surveillance systems.

## Literature review - Methods

A literature search was performed in PubMed to identify papers on the ascertainment of meningococcal disease published between 1970 and 2005. The following search terms were used: 'meningococcal and ascertainment'; 'meningococcal and under-reporting'; 'meningococcal and reporting'; 'meningococcal and capture-recapture'. The abstracts of retrieved papers were read and used to assess their relevance.

A subgroup of the European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS, [www.euibis.org](http://www.euibis.org)) was convened at the 7<sup>th</sup> European Monitoring Group for Meningococci (EMGM) meeting in Lanzarote in September 2003 to discuss the problem of under-ascertainment. Members of the subgroup were later contacted and asked if they were aware of any unpublished reports on the ascertainment of meningococcal disease in their country.

Questionnaires on surveillance systems completed by EU-IBIS participants in 1999 were reviewed to identify the main sources of surveillance data in Europe. These included:

- Notifications by clinicians (usually mandatory)
- Laboratory reports (from reference laboratories and/ or local laboratories, usually voluntary)
- Official death registrations

In addition, several countries have used hospital discharge data for further analysis of meningococcal disease epidemiology, but this data source is unlikely to be timely and so is not used for routine surveillance.

## Literature review - Results

Nine studies were found in the review of published literature, which were judged to be relevant and reported on more than 50 cases. Five of these were conducted in the United Kingdom (UK) [2,3,5,8], and one each in Belgium [9], France [10], Spain [11] and Sweden [12]. Additional studies were retrieved for England and Wales that used information from the enhanced surveillance system [13,14], but it was judged that the main findings relevant to this study have been reported by Davison et al [6].

A total of four unpublished reports were received from; England (C Trotter, Health Protection Agency), the Netherlands (S de Greeff et al, National Institute for Public Health and the Environment (RIVM)), France (2 reports, A Perrocheau et al, Institut de Veille Sanitaire) and Austria (S Heuberger et al, National Reference Centre for Meningococci). In addition, a capture-recapture study in Denmark had also been reported in a PhD thesis [15]. A further paper from Germany was identified as being prepared for publication

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(Schrauder A, personal communication), but results were not available for inclusion in this review.

The results from published and unpublished studies on the ascertainment of meningococcal disease are summarised in table 1. The percentage of cases ascertained in the various surveillance systems varies from 96% in Denmark (1994, notifications) at best to 40% in England (1982-95, notifications) at worst. The most recent estimates from England suggest that under-reporting for both laboratory reports (C Trotter, unpublished data) and notifications [5] is high. Registration of deaths was more complete, with a capture-recapture analysis estimating that 85% of deaths are reported. In the Netherlands, a capture-recapture analysis estimated that 59% of cases were notified and 70% of cases were referred to a laboratory. In France, ascertainment appeared to improve between 1996 and 2000, particularly for notifications (62% to 75%). In Denmark and Austria, two of the smaller countries, ascertainment is very good. In both these countries there is a low annual total of cases (fewer than 300 cases per year).

**Review of methods for measuring under-ascertainment**

**1. Comparison of data sources**

Where more than one data source on meningococcal disease exists, a good starting point is a simple comparison of the data sources.

For example laboratory reports were compared to hospital episode statistics in England and Wales by Davison et al [14].

Suitable questions to consider may include:

- What is the difference in the total number of cases?
- What is the difference in the total number of deaths / case fatality ratio?
- Are the age/ sex distributions similar?
- Are the regional distributions similar?
- Are the temporal patterns similar?

This may help to identify biases with one or other of the systems and suggest areas to investigate further, although it will not by itself allow ascertainment to be quantified.

**2. Capture – recapture methods**

Capture-recapture methods were originally designed by ecologists to estimate the number of animals in a closed population. These methods have been applied to epidemiological data to estimate the ‘true’ number of cases of a disease from two or more sources. The simple capture-recapture problem, where two data sources are used to identify the number of cases missed by both data sources is illustrated in Table 2.

**TABLE 1**  
**Summary of results on ascertainment of meningococcal disease in Europe**

Country	Data source	Method	Degree of ascertainment	Reference
England, 5 regions, 1998	Enhanced surveillance	Comparison	<ul style="list-style-type: none"> <li>• 66% of cases notified</li> <li>• 76% deaths registered</li> </ul>	Davison et al [6]
England (Manchester), 1985	Case finding (review), laboratory reports, notifications	Retrospective review	<ul style="list-style-type: none"> <li>• 63% of cases notified</li> <li>• 57% cases referred for laboratory testing</li> </ul>	Davies [3]
England, 1999	Laboratory reports, hospital episode statistics	Capture-recapture	<ul style="list-style-type: none"> <li>• 53% of cases laboratory reported</li> <li>• 83% of deaths identified in death registrations</li> </ul>	Trotter et al, unpublished
England (Gloucestershire), 1982-95	Active case finding, laboratory reports, notifications	Retrospective case ascertainment	<ul style="list-style-type: none"> <li>• 40% of cases notified</li> <li>• 76% of cases laboratory confirmed</li> </ul>	Wylie et al [2]
England (Nottingham), 1980-89	Notifications, hospital case notes	Retrospective case ascertainment	<ul style="list-style-type: none"> <li>• 68% of cases notified</li> </ul>	Fortnum and Mason [5]
England, 1969-1973 (meningococcal meningitis only)	Notifications, hospital case notes	Retrospective case ascertainment	<ul style="list-style-type: none"> <li>• 50% of cases notified</li> </ul>	Goldacre et al [7]
England & Wales, 1999-2003	Enhanced surveillance; laboratory confirmed and clinically diagnosed ('probable') cases	Regression methods	<ul style="list-style-type: none"> <li>• 31% to 68% (variable by age group) of estimated serogroup C cases were laboratory confirmed</li> <li>• 20% of probable cases estimated to be due to serogroup C</li> </ul>	Granerod et al [8]
France, 1989-90	Notifications, laboratory reports	Capture-recapture	<ul style="list-style-type: none"> <li>• 51% of cases notified</li> <li>• 53% laboratory reported</li> </ul>	Hubert et al [10]
France, 1996	Notifications, laboratory reports, hospital microbiology surveillance (EPIBAC)	Capture-recapture	<ul style="list-style-type: none"> <li>• 62% of cases notified</li> <li>• 72% laboratory reported</li> <li>• 50% reported in EPIBAC</li> </ul>	Perrocheau et al, unpublished
France, 2000	Notifications, laboratory reports, hospital microbiology surveillance (EPIBAC)	Capture-recapture	<ul style="list-style-type: none"> <li>• 75% of cases notified</li> <li>• 76% laboratory reported</li> <li>• 58% reported in EPIBAC</li> </ul>	Perrocheau et al, unpublished
Belgium, 1984	Notifications, laboratory reports	Retrospective review	<ul style="list-style-type: none"> <li>• 62% of confirmed cases notified</li> <li>• 70% of confirmed cases laboratory reported</li> </ul>	De Wals et al [9]
Denmark, 1994	Notifications, hospital discharge diagnoses	Capture-recapture	<ul style="list-style-type: none"> <li>• 96% of cases notified</li> <li>• 89% of cases identified from discharge diagnoses</li> </ul>	Samuelsson, PhD thesis [15]
Spain (Barcelona), 1993-94	Notifications ('obligatory reporting'), confirmed cases	Capture-recapture	<ul style="list-style-type: none"> <li>• 79% of cases notified</li> </ul>	Panella-Noguera et al [11]
Netherlands, 1993-98	Notifications, laboratory reports, hospital admissions	Capture-recapture	<ul style="list-style-type: none"> <li>• 59% of cases notified</li> <li>• 70% submitted to national reference lab</li> <li>• 80% recorded in hospital admissions</li> </ul>	De Greeff et al, unpublished
Austria, 2002	Reference centre data (official notifications), hospital admissions	Capture-recapture	<ul style="list-style-type: none"> <li>• 87% of hospital cases notified</li> </ul>	Berghold et al, unpublished
Sweden, 1998-2002	Notifications, laboratory reports	Capture-recapture	<ul style="list-style-type: none"> <li>• 91% of cases notified</li> <li>• 85% of cases laboratory reported</li> </ul>	Jansson et al [12]

TABLE 2

## The capture-recapture method (from Tilling [16])

		'Source 1'		
		+	-	
'Source 2'	+	<i>a</i>	<i>b</i>	<i>a + b</i>
	-	<i>c</i>	<i>x</i>	<i>c + x</i>
		<i>a + c</i>	<i>b + x</i>	<i>N = a + b + c + x</i>

where *x* is the number of cases not identified in either data source

$$\frac{a}{N} = \left( \frac{a+c}{N} \right) x \left( \frac{a+b}{N} \right)$$

$$a(a+b+c+x) = (a+c)(a+b) \quad [\text{because: } N = a+b+c+x]$$

$$\text{Giving: } \hat{x} = \frac{bc}{a}$$

This method has been employed to estimate the 'true' number of cases (or deaths) due to meningococcal disease in France [10], Spain [11], England (C Trotter, unpublished), Denmark [15], Sweden [12] and the Netherlands (S de Greeff, unpublished).

To conduct an analysis like this, cases must be matched between data sources. The datasets must therefore contain adequate personal identifiers (ideally unique identifiers such as a health registration number/ national ID number). If recording errors or incomplete reports are common, then significant bias may be introduced to the study [17]. It is also important that all the cases must be 'true' cases, i.e., that the surveillance systems and case definitions are highly specific, otherwise the use of capture-recapture will overestimate the burden of disease.

In addition, there are two critical assumptions that underpin this method: (1) the data sources are independent and (2) all individuals have an equal probability of 'capture'. These assumptions are unlikely to be valid when considering epidemiological data. For example, the probability of capture may vary by age or disease severity. This problem may be overcome by stratifying by e.g. age or severity, but this may limit the power of the study. It is very unlikely that the data sources used for surveillance are entirely independent. If positive dependency exists, the global estimate will be underestimated and the exhaustivity of each source overestimated. Log linear methods may be used to model dependence between more than two sources, which may help to overcome these problems of heterogeneity of capture and of dependency between sources. Three (or more) data sources may not always be available as part of the routine surveillance system, but it is possible to conduct punctual surveys in randomly selected hospitals or laboratories. These modelling methods can detect heterogeneity between or within sources, and although the interpretation of these effects may sometimes be difficult (and results may have to be stratified), it does improve the reliability of the estimates.

For a full review of these methods, their uses and limitations see Hook and Regal, 1995 [18] and Tilling, 2001 [16]. Capture-recapture may be useful for meningococcal disease, but the results should be interpreted according to the conditions and assumptions of the method to draw valid estimates.

### 3. Retrospective review

The degree of ascertainment has also been estimated through retrospective reviews. Individuals identified from clinical case notes as having meningococcal disease were matched with the available data sources (e.g. laboratory reports, notifications) to see whether they were recorded in the official statistics. The completeness of the official records can then be estimated. This type of study was conducted in Manchester (England) in 1985 [3] and Nottingham (England) in 1980-1989 [5], both of which identified substantial under-notification of cases (only 50-67% of cases were notified). This type of analysis may not be possible in all situations. The case notes must contain sufficient information for a reasonably sensitive and specific diagnosis to be made. In addition, reviewing case notes can be very time consuming and requires a skilled individual.

### 4. Prospective follow-up

The rationale of this method is similar to the method above, except that cases are recruited to the study prospectively rather than retrospectively. For example Wylie et al [2] established an enhanced surveillance system to ascertain all suspected and confirmed cases of meningococcal disease identified by local clinicians. The cases were followed up retrospectively to identify whether they were officially notified and/ or laboratory confirmed. The advantage of a prospective approach is that standardised clinical and laboratory investigations can be carried out, rather than having to rely on possibly incomplete historical case notes. The disadvantage of this approach is that clinicians may alter their reporting practices if they are aware that a study is being conducted, so that ascertainment may be overestimated. However, this may encourage good reporting practises that are maintained beyond the duration of the study.

### 5. Regression methods

It is clear that even where very good surveillance systems are in place, it is not possible to obtain laboratory confirmation in all 'true' cases of disease. Diagnoses based on clinical evidence alone are useful but are likely to be less specific than those based on laboratory reporting, and 'false positives', i.e., cases attributable to other organisms, may be reported. The underlying aetiology of clinically defined syndromes can be examined using regression methods, which have previously been used to investigate the burden of disease attributable to rotavirus [19] and respiratory syncytial virus (RSV) [20], among others.

The temporal variability in infectious diseases is exploited by comparing the trends in laboratory reports (which are highly specific) with the trends in a clinically defined syndrome. Laboratory reports of meningococcal disease have a distinct temporal pattern and if a clinical diagnosis of meningococcal disease is specific, then there should be a high correlation between the seasonal patterns in clinical diagnoses and the seasonal patterns in laboratory reports, even if the total number of reports differ. This is also a useful way to investigate alternative aetiologies of the clinical syndrome; for example, clinical 'cases' of meningococcal disease may be due to viral infection.

The formula for calculating the expected number of 'syndrome' cases  $Y_j$  in 4-week period  $j$  is:  $Y_j = C + \sum \alpha_i L_{ij}$

Where  $L_{ij}$  is the number of laboratory reports of type  $i$  in a 4 week period  $j$  and  $\alpha_i$  is the regression co-efficient for type  $i$  used to estimate the number of 'syndrome' cases associated with each report of type  $i$  (e.g. confirmed meningococcal disease and possible alternative diagnoses such as enterovirus, *Streptococcus pneumoniae*, *Haemophilus influenzae* [6]).  $C$  is a constant representing the background number of 'syndrome' cases in each 4 week period associated with other infectious or non-infectious causes of clinically suspected meningococcal disease where the temporal trend is not strong enough to be individually significant. The values of  $\alpha_i$  and  $C$  can be estimated by least squares regression. Data may be taken from a variety of sources, or from the same source, provided that the data is representative and unbiased. Appropriate data may include, laboratory reports, hospital statistics, notifications and death registrations. Clearly, to estimate  $L_{ij}$ , the reports must be specific to a particular pathogen, although the sensitivity and specificity of different types of reports may vary (for example, laboratory reports are highly specific, but notifications based on clinical diagnoses may be less specific).

This method was recently used to investigate the aetiology of probable (i.e., clinically diagnosed cases of meningococcal disease without laboratory confirmation) cases of meningococcal disease in the England & Wales Enhanced Surveillance of Meningococcal disease (ESMD) system between 1999 and 2003, by Granerod et al (in press) [8]. The contribution of other organisms (including enterovirus, influenza and *S. pneumoniae*) to probable cases was investigated in a regression model similar to that described above.

## Discussion

We have reviewed published and unpublished reports to explore the ascertainment of meningococcal disease in Europe. In all cases the surveillance systems underestimated the burden of meningococcal disease, although there was quite a range in the estimated proportion of cases represented in the surveillance statistics, from around 40% to 96%. It is not clear what, if any, action was taken to improve surveillance following study results demonstrating poor ascertainment, but clearly, studies such as these could be used to facilitate improvements, such as reconciliation of clinical and laboratory confirmed cases.

There is no 'gold standard' of disease incidence, so a range of methods have been developed to quantify the level of ascertainment through standard surveillance sources. We reviewed these methods, ranging from simple comparison of two data sources to more complex statistical analysis such as capture-recapture or regression methods. We have not attempted to evaluate the different methods, as the appropriateness of each will depend on the research questions being addressed and the data available. The potential biases of these methods have been highlighted, and should always be considered. A precise description of the surveillance system is important because this allows qualitative assessment of potential problems that may affect the level of ascertainment.

In addition to measuring ascertainment, it is also important to consider the results of such studies in context, particularly for temporal analyses. Important factors may include epidemiological trends [21], changes in clinical practice, changes in reporting requirements [22] and the introduction of new laboratory methods (such as PCR [4]). For example, laboratory confirmation by culture may decrease as a result of the introduction of a policy to administer pre-admission antibiotics, or because of a reduction in the number of lumbar punctures performed. Surveillance is likely to have been enhanced in countries that have introduced serogroup C conjugate vaccines (including the UK, Spain, and the Netherlands) so that they may identify vaccine failures and estimate vaccine effectiveness. In addition, other countries who have not yet introduced the serogroup C conjugate vaccine may have improved their surveillance in order to be able to respond promptly to any increase in the incidence of C serogroup disease.

EU-IBIS continues to collect a large amount of data across Europe and analyses based on these data may be very powerful. However, a potential criticism of such analyses is that they may be biased by differential quality of reporting across countries. Some countries rely more on clinician notifications, others on laboratory reports, some countries report locally and collate at a national level, whereas others collect national statistics only. Because reporting systems vary between the participant countries of EU-IBIS, it will be important to consider some degree of 'quality control' of the combined data to ensure international data analyses are valid. On the laboratory side this has been achieved through the external quality assurance scheme, whereby all participating laboratories test a standard panel of isolates. Such harmonisation is more difficult to envisage for reporting and notification systems. Given the wide range of incidence experienced in Europe, it is likely that factors other than ascertainment will also be important in explaining these differences, particularly geographical variation in the prevalent meningococcal strains, some of which are more virulent than others [23]. International comparisons that are likely to be valid despite differences in the reporting systems include the proportion of cases due to different serogroups, or the impact of vaccination (taking into account the different vaccine schedules/strategies used in each country).

This study may also be relevant for other European surveillance networks. Indeed, given the characteristics of meningococcal disease - it is severe, has high mortality, all patients are admitted to hospital and cases generate much public concern - it is surprising that there is still considerable under-ascertainment in most European countries. The situation for other, less severe, infectious diseases may be much worse, and attempts should be made to quantify this.

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## SURVEILLANCE OF LISTERIA INFECTIONS IN EUROPE

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on behalf of the *Listeria* surveillance feasibility study participants

In addition to the economic consequences and threats associated with outbreaks, listeriosis remains of great public health concern, as it has one of the highest case fatality rates of all the foodborne infections (20%-30%), and has common source epidemic potential. Changes in the way food is produced, distributed and stored have created the potential for diffuse and widespread outbreaks involving many countries.

In 2002, a survey was carried out to assess the need for and the feasibility of a European network on listeria infections in humans. Data on surveillance systems and laboratory methods were collected through two postal surveys sent to the national Centres for communicable disease surveillance and to the listeria reference laboratories. Surveillance systems for listeria infections were in operation in 16 out of the 17 countries surveyed, and 16 countries had a national reference laboratory (NRL). All countries based their case definition of listeriosis on the isolation of *Listeria monocytogenes*. Fourteen NRLs performed at least one typing method on human strains. At least 13 countries already carried out or expressed willingness to carry out characterisation of isolates by pulsed field gel electrophoresis (PFGE) of *L. monocytogenes* strains isolated from human cases following a standard protocol. The participants concluded that there was a clear added value to having a European surveillance network for listeria infections, particularly for outbreak detection and investigation, and that a surveillance network based on the existing national surveillance systems was feasible.

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### Introduction

*Listeria monocytogenes* causes invasive illness, mainly in certain well-defined high-risk groups, including immunocompromised people, pregnant women and neonates. Listeriosis can, however, occur in otherwise healthy individuals, particularly in an outbreak setting. *L. monocytogenes* primarily causes abortion, septicaemia or infections of the central nervous system, with a case fatality ratio of 20%-30% [1]. It has only recently been recognised that foodborne transmission of *L. monocytogenes* can also cause a self-limiting acute gastroenteritis in immunocompetent persons [2]. The public health importance of listeriosis is not always recognised, particularly since listeriosis is a relatively rare disease compared with other common foodborne illnesses such as salmonellosis. Most countries within the European Union have an annual incidence between 2-10 reported cases per million population per year. However, because of its high case fatality rate, listeriosis ranks among the most frequent causes of death due to foodborne illness: it ranks second, after salmonellosis, in the United States (US) and France; and fourth in England and Wales [3-5].

Epidemiological investigations during the past 20 years have shown that listeriosis is a foodborne disease [6]. Discovery of *L. monocytogenes*, mainly in raw and ready-to-eat meat, poultry, seafood, and dairy products, has prompted numerous product recalls which have led to large financial losses for the food industry and numerous health scares. Effective prevention and control measures

exist, as documented in France and the US, where a threefold and a twofold reduction respectively in incidence over the past decade was attributed to increased regulatory activity, implementation of Hazard Analysis and Critical Control Points (HACCP) programmes throughout the food industry, and specific recommendations to high-risk groups [7,8]. However, several countries still have relatively high incidence, and many countries do not have a surveillance system that allows them to estimate incidence or evaluate incidence trends. Moreover, its common source epidemic potential presents a real threat and persists even in countries with a decreasing or low incidence. Changes in the way food is produced and distributed have further increased the potential for diffuse and widespread outbreaks involving many countries. Because these outbreaks can be dispersed with a limited number of cases in each country, they are likely to go undetected if information from these countries is not pooled. Improved surveillance, coordinated at a European level, combining rapid subtyping methods, cluster identification, and collaborative epidemiological investigation, can identify and halt these potentially large, outbreaks.

Because of the potential benefits of collaborative European surveillance described above, this project was initiated with the aim of defining the feasibility and scope of a European network on listeria infections, and to develop common methodologies for surveillance of listeriosis in Europe.

### Methods

The project was coordinated by the Institut de Veille Sanitaire (InVS) and the French National Reference Centre for Listeria at the Institut Pasteur, assisted by an expert panel of microbiologists and epidemiologists from nine countries. Data for the inventory were collected through two postal surveys and, when necessary, completed through telephone interviews. One questionnaire, sent to epidemiologists in charge of surveillance of communicable diseases at the national level, collected information on surveillance systems, other data sources, information flow, case definitions, data collected, frequency of reporting and analysis, outbreak detection mechanisms, reported cases and outbreaks. A second questionnaire, sent to the national reference centre (NRL), collected information about their tasks as reference laboratory, the origin of isolates, identification and typing methods and practices, antibiotic resistance surveillance, and quality assurance and control. A third questionnaire was sent out to assess the acceptability, capacity and possibility that the NRL could routinely perform typing of *L. monocytogenes*, or at regular intervals, and with a specific common protocol. During a meeting with epidemiologists and microbiologists from each participating country, the results of the inventory were presented, different scenarios for European surveillance were discussed, and recommendations for a European listeriosis surveillance network were formulated.

### Results

In total, 17 countries participated. This included 14 EU countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom (England & Wales and Scotland only); and Norway, Iceland and Switzerland. We present the results of Scotland separately from England & Wales, but count England & Wales and Scotland as a single country within the United Kingdom (UK).

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### Surveillance systems

All countries except Portugal had at least one surveillance system for listeriosis, and 12 countries had more than one system. In several countries, notification of foodborne illness (e.g., Austria and Ireland) or foodborne illness outbreaks (e.g., Belgium, the Netherlands and France) was statutory, and in theory, listeria infections could be notified through these systems. In practice, however, listeriosis cases were not notified through these systems. In this inventory, therefore, we do not consider notification of foodborne illness and outbreaks to be the same thing as a surveillance system for listeriosis. Listeriosis was statutorily notifiable in 10 countries, four countries had universal voluntary reporting, 11 countries had listeria surveillance based on their NRL, two countries had sentinel surveillance, and five countries had syndrome based surveillance of infections of the central nervous system and blood stream infections that covered listeria infections among other infections.

In 15 countries, diagnostic laboratories were involved in reporting to at least one of the surveillance systems. In addition, physicians were involved in the reporting in 13 countries. In Italy, physicians were the only notifying partners.

Listeriosis surveillance data were available at the national level in 16 countries, either at the national surveillance centre (five countries), at the NRL (one country) or at both (10 countries). These data at the national level were available as single case reports in all countries. Data transmission to the national level was immediate or weekly in all countries with the exception of Italy, where it was done quarterly.

All countries based their case definition of listeriosis on the isolation of *L. monocytogenes*, with or without specific requirements regarding site of isolation and the presence of clinical symptoms. Two countries also considered the presence of serum antibodies as laboratory confirmation of a case, but in practice, only cases with an isolate were reported.

None of the countries had a specific definition for acute listeria gastroenteritis. Theoretically, in countries with a case definition based on the isolation of *L. monocytogenes* from any site, these patients should be reported. In practice, none of the countries had acute listeria gastroenteritis cases reported, although outbreaks of acute listeria gastroenteritis had occasionally been identified and reported to the national level: in Italy in 1993 and 1997, in Denmark in 1996, and in Belgium in 2001.

In general, countries with listeriosis surveillance collected at least basic demographic data (age/date of birth and sex), contact details for the reporting institute, laboratory confirmation (date of isolation of *L. monocytogenes* or date first positive specimen received in diagnostic laboratory), and the type of investigated material. Additional information such as principal diagnosis, associated pregnancy, outcome, and travel and food history, were available in between five to 10 countries.

### National Reference Laboratories

All countries except for Ireland had an NRL. The tasks of these 16 NRLs were: microbiological surveillance (16 countries); detection of outbreaks (14 countries); provision of microbiological expertise (13 countries); research on listeria (12 countries); training (nine countries); and provision of reference material such as strains, sera, DNA profiles, protein extracts, phages, or guidelines for laboratory diagnosis (eight countries). Strains isolated from patients were sent to the NRL: in seven countries this was done systematically, and in eight countries this was done according to the will of the laboratory, or in specific situations such as outbreak or suspected outbreak settings. In Sweden and Switzerland, the sending of isolates to the NRL was statutory. In Spain, about half of the 16 autonomous communities sent their isolates to the NRL.

The NRLs also received information along with strains. This information concerned the site of isolation of the bacteria (13 countries), clinical data (11 countries), epidemiological data (10 countries), and strain characteristics (eight countries). In most countries (11 out of 17), the NRLs for human listeria also received listeria strains isolated from food, and in three countries, the NRLs received information on food strains.

### Identification

Fifteen NRLs carried out identification of listeria strains. Only four countries performed a Gram stain and a catalase test. Biochemical characterisation was performed using API-*Listeria* in eight countries, API-*coryne* in one, while four countries used home made sugars. Nine countries looked for haemolysis, six for motility. Two countries also used polymerase chain reaction (PCR) for diagnosis, and one country also used an automated system of bacterial identification.

### Characterisation of strains

Fourteen NRLs performed at least one typing method on human strains, either on an ongoing basis or at regular intervals. 13 NRLs routinely performed serotyping, either on an ongoing basis or at regular intervals. Seven countries used home made antisera, six used commercially available sera, and two used both. Thirteen countries had developed the capacity to perform DNA macrorestriction and pulsed field gel electrophoresis (PFGE) on human strains of *L. monocytogenes*, and performed it either routinely, for specific investigations or for ad hoc studies. All used the CHEF (contour-clamped homogeneous electric field) system for PFGE, and most used two enzymes, *AscI* and *ApaI*. Twelve countries said they would be willing to set up routine PFGE with image analysis, at least weekly or immediately after receiving a strain, in order to participate in a common surveillance system of human strains. Several countries, including one country not willing to carry out PFGE routinely, said they would be willing to send strains to another European laboratory to be typed by PFGE. Thirteen countries were willing to use a common standardised protocol for PFGE and to send profiles or strains to contribute to a European database. European surveillance including results of harmonised characterisation of isolates by PFGE of *L. monocytogenes* strains isolated from human cases could therefore cover at least 13 countries.

All countries who were performing or intended to perform PFGE said they would be willing to send PFGE profiles to a common European laboratory under the following conditions: access to common information (six countries), confidentiality (four), access restricted to participants only (one), and provided that strains were not distributed and profiles used only for the purpose of surveillance (one).

### Antimicrobial susceptibility testing

Ten out of 17 laboratories (including Ireland) reported performing antimicrobial susceptibility testing. Three countries used the E test method for testing, and seven countries used agar dilution breakpoints. Two countries also used the Clinical and Laboratory Standards Institute (formerly NCCLS) method and one country also used a disk diffusion method. The antimicrobial agents tested varied between countries. Laboratories most frequently tested the susceptibility of listeria for gentamicin and trimethoprim-sulfamethoxazole (seven countries); ampicillin, tetracycline and erythromycin (six countries); ciprofloxacin (five countries); or chloramphenicol, streptomycin and vancomycin (four countries).

### Quality control and quality assurance, accreditation

The NRLs in 14 countries reported having internal quality control for their identification procedures (nine countries) and/or typing procedures (nine countries).

Seven countries participated in an external quality control. Six of the seven countries used NEQAS from the Public Health Laboratory Service (PHLS) in the UK for identification procedures, and three also used another external quality control.

Seven NRLs were engaged in a quality assurance system, and five intended to be so in the near future. Six NRLs said that they were ISO/UE 17025 accredited and two more were accredited on an other standard: PHLS in the UK (Clinical Pathology Accreditation Ltd) and the NRL in the Netherlands (accredited by CCKL-test). One NRL is ISO 9001 certified.

### Outbreak detection

Real-time reporting and analysis, high sensitivity, results of typing of strains available in real time for surveillance, and the existence of outbreak detection criteria or thresholds are all surveillance system characteristics that contribute to efficient outbreak detection. Eight countries have developed outbreak detection mechanisms and thresholds. Real time reporting and analysis characterised the surveillance systems of 15 and 11 countries respectively. The estimated or assumed sensitivity was reasonably high or high in at least 10 countries. For outbreak detection, 12 countries had results of strain typing available, routinely and on a real time or weekly basis: serotyping (12 countries), biotyping (four countries), ribotyping (three countries), PFGE analysis (six countries), and phagotyping (one country).

### Reported listeria infections and outbreaks

The incidence of reported cases varied between 0.3 and 7.5 cases per million per year. The mean incidence of reported cases was 3.4 per million inhabitants (data from 16 countries, latest year available) [TABLE 1]. Five countries reported an incidence of more than four cases per million, and three of these five countries reported an

incidence of more than six per million population. These figures mostly reflect the sensitivity of the surveillance systems, as well as the incidence of the disease. However, few countries have formal evaluations or studies allowing estimation of sensitivity, geographical coverage and representativeness of their surveillance systems. In general, the surveillance systems described above covered, in principal, the entire country, except for Spain, where approximately half of the autonomous communities transmitted their data direct to the national level.

Between 1991 and 2002, a total of 19 outbreaks of invasive listeriosis were reported in nine different countries, with a total of 526 outbreak related cases ) [TABLE 2]. While the number of reported outbreaks increased gradually over time, from seven outbreaks detected in the period 1992-1996 to 11 in the period 1997-2001, the mean number of cases related to these outbreaks decreased from 57 to 11 over the same period. This suggests more efficient outbreak detection, investigation and control. In addition, four outbreaks of acute listeria gastroenteritis were reported: two outbreaks in Italy in 1993 (18 cases) and 1997 (1566 cases); an outbreak in Denmark in 1996 (3 cases); and an outbreak in Belgium in 2001 (2 cases of acute gastroenteritis and one case of invasive listeriosis).

TABLE 1

Observed number of cases and incidence of listeriosis, by country, by surveillance system (latest year available), ListerNet

Country	Year	System	Observed cases	Observed incidence* (1 000 000)
Austria	2000	Reference laboratory	14	1.7
Belgium (Flandres)	1999	Statutory notification	26	4.4
Belgium	2000	Sentinel + reference laboratory	48	4.7
Denmark	2000	Syndromic surveillance (meningitis)	6	1.1
	2001	Statutory notification	38	7.2
	2001	Reference laboratory	38	7.2
England and Wales	2001	Universal voluntary reporting and reference laboratory	144	2.7
	2000	Reference laboratory	81	1.5
Finland	2001	Statutory notification	29	5.5
France	2001	Statutory notification+ reference laboratory	187	3.2
	2000	Syndromic surveillance (CNS+blood stream infections)	148	2.5
Germany	2001	Statutory notification	220	2.7
Greece	2001	Universal voluntary reporting	3	0.3
	2001	Syndromic surveillance (meningitis)	2	0.2
Iceland	2001	Statutory notification + NRL	0	0.0
Ireland	2001	Universal voluntary reporting	6	1.6
Italy	1999	Reference laboratory	11	0.2
	1999	Statutory notification	40	0.7
	2001	Syndromic surveillance (meningitis)	31	0.5
Netherlands	2001	Sentinel surveillance	17	1.1
	2000	Syndromic surveillance (meningitis)	26	1.7
Norway	2001	Statutory notification	17	3.8
	2000	Reference laboratory	11	2.5
Portugal		No surveillance		
Scotland	2001	Universal voluntary reporting	15	2.9
Spain	2000	Universal voluntary reporting	35	0.9
	2000	Reference laboratory	60	1.5
Sweden	2001	Statutory notification	67	7.5
	2001	Reference laboratory	12	1.4
Switzerland	2000	Statutory notification	54	7.4
	2000	Reference laboratory	46	6.3

\* The observed incidence reflects both the real incidence and the sensitivity of the surveillance system. Therefore, data cannot be compared between countries without taking into account the differences in sensitivity of these surveillance systems

TABLE 2

Reported outbreaks of listeriosis and of *Listeria* gastroenteritis in Europe 1990-2002

Year	Country	Number of cases*	Transmission	Incriminated food	Potential international implication
1992	France	279	foodborne	Pork tongue in jelly (11)	Exported product
1992	Spain	24	foodborne	Unknown	
1992	Norway	6	foodborne	Sliced cold meat	
1993	France	38	foodborne	Rillettes (pork meat) (12)	Exported product
1993	Italy	18 gastroenteritis	foodborne	Rice salad (2)	
1994-95	Sweden	9	foodborne	Gravad trout (13)	
1995	France	36	foodborne	Cheese (raw cows' milk) (14)	
1995	Iceland	5	unidentified	Unidentified	
1996	Denmark	3 gastroenteritis	unidentified	Unidentified (15)	
1997	France	14	foodborne	Cheese (raw cows' milk)	Exported product
1997	Finland	5	foodborne	Cold-smoked rainbow trout (16)	
1997	Italy	1566 gastroenteritis	foodborne	Corn salad (17)	
1998-99	Finland	25	foodborne	Butter (18)	
1999	England and Wales	2	foodborne	Cheese/cheese salad/ sandwiches (19)	
1999	France	3	foodborne	Cheese (raw cow's milk)	Possible cases in Germany?
1999	France	10	foodborne	Rillettes (processed pork meat) (20)	Exported product
1999-00	Finland	10	foodborne	Vacuum-packed fish products (21)	Exported?
2000	France	32	foodborne	Pork tongue in jelly (20)	Exported ?
2000	Portugal	1	foodborne	Cheese	
2000	Spain	15	foodborne	Undetermined	
2001	Belgium	1 + 2 gastroenteritis	foodborne	Ice cream cake	Invasive illness of Belgian case diagnosed in France
2002	France	11	foodborne	Spreadable raw sausage (22)	Export to Germany, Belgium and Luxembourg

\* Cases refer to invasive listeriosis unless otherwise specified

The incriminated food at the origin of the invasive listeriosis outbreaks was processed meat products (six outbreaks), cheese (five outbreaks), processed fish products (three outbreaks), butter (one outbreak) and undetermined (three outbreaks). The incriminated products for at least six of these outbreaks were known to have been exported, creating the potential for the occurrence of outbreak related cases in other countries. Moreover, cases related to one outbreak in one country were diagnosed in a neighbouring country.

The outbreaks of gastroenteritis were linked to the consumption of contaminated rice salad and corn salad respectively, while the Belgian outbreak of gastroenteritis and invasive listeriosis was linked to a contaminated ice cream cake. The origin of one outbreak of gastroenteritis remained undetermined.

### Conclusions and recommendations

Based on the inventory, it appears that there is an appropriate basic infrastructure for a European surveillance network for listeria infections, and that the necessary harmonisation of methods is feasible considering the infrastructure already in place and the expressed willingness of countries to adapt or set up methodologies for European surveillance.

It was recommended by the representatives of the participating countries/the working group to set up a European network for the surveillance of listeria infections, with, as the main objectives, providing comparative data, monitoring trends of international importance, and rapidly detecting and investigating international outbreaks more efficiently. The network should also contribute to the strengthening of national surveillance in participating countries. In its initial phase the network should concentrate on surveillance of human

cases of listeria infection and not yet actively seek to collect data on food isolates. Once the network is well established and surveillance of human cases is operational, the possibilities of including data from food and animal surveillance should be studied.

Common case definitions should be agreed upon as well as a common minimum dataset, which could be further developed over time to include additional data (optimal dataset). Case definitions, in line with those developed by the Community Network (under decision N° 2002/253/EC, amended by Commission Decision 2003/534EC), and a minimum and optimal dataset, for which the collection is, at present, feasible for the majority of participating countries, were proposed [9].

Because of the wide disparity in listeria outbreaks, a common European database should include results of real time characterisation of strains to reinforce the ability to detect international outbreaks. The participants concluded that, at present, characterisation by both serotype and PFGE would be the most appropriate methods and the best option to meet the objectives of outbreak detection and trend analysis. The necessary harmonisation of microbiological methods and of the type of epidemiological data collected appears feasible considering the infrastructure already in place and the expressed willingness of countries to adapt or set up methodologies in the perspective of European surveillance.

The network should encourage individual countries to strengthen national surveillance of listeria infections, and should contribute to their strengthening by providing a model and specific tools for surveillance and investigations. Each country should set up a national database which combines laboratory data and data from the notification systems. Participating countries should be encouraged



to increase the sensitivity of the surveillance systems in order to reinforce the ability to detect national and international outbreaks. Countries can participate in a stepwise manner, contributing initially with the data they already have available, even if incomplete. With time, countries may wish to adapt their in-country data collection in order to cover all data fields in the database. For those countries where routine and ongoing typing of strains is difficult to carry out because of the low number of isolates, the possibility of having their strains typed in another country's NRL, should be investigated.

In addition to the harmonisation of epidemiological and microbiological methods and the creation of a common database, it was recommended that the network should develop outbreak detection algorithms and a protocol for collaborative investigation of international clusters and outbreaks. The network will need to develop principles of collaboration that should deal with access to the database by participants and by outsiders, confidentiality of country specific data, confidential and public domain reports, data protection requirements, as well as transmission to other programmes and projects. It was recommended to adapt the principles of collaboration of EnterNet to listeria [10].

Finally, the participants recommended that a project proposal be developed by the coordinators of the actual feasibility study. In May 2003, an application was submitted to the European Commission under the 2003 call for proposals in the programme of community action in the field of public health (2003-2008). Although the proposal was accepted, co-funding was not proposed by the commission until August 2004. By this time, the situation of the different partners of the project had evolved, and senior staff who committed themselves to contribute to the project had taken up other commitments. However, European investment in such a project remains a priority for the years to come. In particular, it would be important to assess how such a project could be integrated into other ongoing EU surveillance projects such as Enter-net.

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## LEGIONNAIRES' DISEASE IN EUROPE 2003-2004

KD Ricketts, CA Joseph, on behalf of the European Working Group for Legionella Infections

Once a year, countries that collaborate in the European Surveillance Scheme for Travel Associated Legionnaires' Disease (EWGLINET) are requested to submit a dataset that provides epidemiological and microbiological information on cases of legionnaires' disease (nosocomial [hospital-acquired], community and travel related) detected in their country for that year. This paper presents the data collected for 2003 and 2004. For this period, 9166 cases were reported to the dataset by 35 countries, of which 941 cases were associated with outbreaks. Fourteen countries reported a total of 218 detected outbreaks. National infection rates varied between countries from 28.7 to less than one case per million population. This information is valuable in that it allows countries to assess the effectiveness of their national surveillance schemes in detecting cases.

Over the two year period, 748 cases were reported to have died, giving a case fatality rate of 8.2%. The lack of detailed epidemiological information on deaths from legionnaires' disease is highlighted. The establishment of the European Centre for Disease Prevention and Control is seen as an opportunity to develop European collaborations more fully, and to increase further the protection of Europeans from outbreaks of legionnaires' disease.

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**Key words:** Legionnaires' disease, Europe, surveillance, travel

### Introduction

Legionnaires' disease was first identified in 1976 following an outbreak of pneumonic illness at a hotel hosting an American Legion convention. In 1986, the European Working Group for Legionella Infections (EWGLI) was established to exchange knowledge and to monitor trends of legionnaires' disease across Europe; in 1987 EWGLI established the European Surveillance Scheme for Travel Associated Legionnaires' Disease (EWGLINET).

Data on trends of legionnaires' disease in Europe between 1996 and 2002 have already been published [1-5]. This paper presents data from European countries for the years 2003-2004.

### Methods

Each year, the countries participating in EWGLINET are asked to complete an aggregated national dataset. Epidemiological and microbiological data are requested through standardised reporting forms. This has been undertaken every year since 1993 and provides a summary of the levels of legionnaires' disease in Europe, allowing EWGLI to analyse European trends and make comparisons between countries.

A confirmed case of legionnaires' disease is defined as an acute lower respiratory infection with focal signs of pneumonia on clinical examination and/or radiological evidence of pneumonia, and one or more of the following microbiological diagnoses: isolation/culture, serology (a fourfold rise in antibody titre to *Legionella pneumophila* serogroup 1), or urinary antigen test. A presumptive case requires the same clinical evidence of infection, and one or more of the following microbiological diagnoses: serology (a fourfold rise in antibody titre to non *Legionella pneumophila* serogroup 1, or a single high titre in antibody), antigen in respiratory secretion, direct fluorescent antibody (DFA), or other accepted method of diagnosis (e.g. PCR). If the method of diagnosis is not known, the cases will be classified as such ('diagnosis not known') for the purposes of the annual dataset.

A case of legionnaires' disease is further defined by exposure history. Each country allocates their cases to the categories of 'travel', 'nosocomial' (hospital acquired), and 'community' according to their national definitions. If a case falls into more than one category (for instance, if they had both travel and nosocomial history), the collaborator in the country of infection would exercise discretion in classifying the case based on their exposure history. Such instances are rare.

The data for the annual dataset is collected in seven specific tables. The first table records the number of confirmed and presumptive cases diagnosed in each country each year, and how many of those cases died. The table also asks for a population base so that a rate per million population can be calculated. The second and third tables record the methods of diagnosis used, and detailed information on the species and serogroup of any isolates collected. The fourth table requests information on age group and sex, the fifth table asks for the category of exposure (hospital [nosocomial], travel, community), and the sixth table gives the countries of travel for travel-associated cases. The seventh table gives details of outbreaks by type, size and suspected source.

Incidences per million population are used in this paper as an analysis tool, and were calculated as the number of cases reported by a country of infection, divided by the population size of that country. Regional population sizes rather than national population sizes were provided by collaborators for six countries in 2003 (Croatia, Czech Republic, Greece, Romania, Russia and Turkey) and for four countries in 2004 (Croatia, Czech Republic, Romania and Russia), because only regional data on legionnaires' disease was available to the collaborator. Regional rather than national infection rates were therefore calculated for these countries and it should be noted that these data may not be representative of the national incidences.

### Results

The number of countries reporting their annual dataset to EWGLI has increased from 19 in 1993 to 34 in 2003, and further to 35 countries in 2004 after Andorra joined the scheme. For the years 2003-2004, 9166 cases were reported. In the twelve years since data collection began, a total of 28 647 cases have been reported [TABLE 1].

TABLE 1

Total reported cases of legionnaires' disease and rate per million population, EWGLI, 1993-2004

Year	No. of cases	No. of countries contributing data	Population (millions)	Rate per million population
1993	242	19	300	4.14
1994	1161	20	346	3.35
1995	1255	24	339	3.7
1996	1563	24	350	4.46
1997	1360	24	351	3.87
1998	1442	28	333	4.33
1999	2136	28	398	5.38
2000	2156	28	400	5.38
2001	3470	29	455	7.6
2002	4696	32	467	10.1
2003	4578	34	468	9.8
2004	4588	35	557	8.2

The number of cases has generally increased over time, due to an increase in the number of countries reporting, although in the past two years the overall incidence has decreased, largely due to a greater total population making up the denominator [TABLE 2].

TABLE 2

Cases of legionnaires' disease and rate per million population by selected countries, EWGLI, 2003-2004

Country	Population (millions)	All reported cases 2003 (Rate)	All reported cases 2004 (Rate)
Belgium	10.4	8.9	15.6
Denmark	5.4	19.1	19.1
England and Wales	52.7	5.9	5.8
France	60.2	17.2	19.9
Germany	82.5	3.6	4.8
Italy	57.8	9.7	9.7
Netherlands	16.3	13.7	14.8
Spain	41.1	28.7	23.8
Sweden	9.0	8.8	12.1
Switzerland	7.4	24.1	20.0

**Incidence per million population**

The highest incidences were reported from Spain (28.7/1 000 000 population in 2003, 23.8/1 000 000 in 2004), Croatia (25.0/1 000 000 in 2003, 21.0/1 000 000 in 2004), and Switzerland (24.1/1 000 000 in 2003, 20.0/1 000 000 in 2004). Five countries reported rates of less than one case per million population in both years (Bulgaria, Latvia, Lithuania, Poland and the Slovak Republic), and Turkey reported a rate of 0.1/1 000 000 in 2004 (down from 4.5 in 2003 because of the increase in the denominator).

The overall incidence for Europe (as calculated from the annual dataset) was 9.8/1 000 000 in 2003 (based on a denominator population of 468 million) and 8.2/1 000 000 in 2004 (based on a denominator of 557 million).

**Category of cases**

Cases are reported to the dataset as being associated with community, nosocomial or travel-acquired infection.

For the two years 2003-2004, 656 cases were reported as nosocomial (7.6% in 2003, 6.7% in 2004), 3994 as community acquired (46.1% in 2003, 41.1% in 2004), 1150 as associated with travel abroad (12.3% in 2003, 12.8% in 2004), 764 as associated with travel in the same country as country of residence (8.1% in 2003, 8.6% in 2004), and 2560 were reported as category 'not known' (26.0% in 2003, 29.9% in 2004). An additional category of 'other' was added in 2004, and registered 42 cases (0.9% in 2004) [TABLE 3]. In 2004, cases were allocated to the 'not known' category if there was no exposure information available, and to the 'other' category if the exposure information was not sufficient to allocate them to one of the existing categories (e.g., if the collaborator was not able to separate nosocomial from community cases in their data).

TABLE 3

Cases of legionnaires' disease and proportion by category of infection, EWGLI, 2003-2004

Category of infection	2003 n (%)	2004 n (%)	Total n (%)
Nosocomial	348 (7.6%)	308 (6.7%)	656 (7.2%)
Community	2110 (46.1%)	1884 (41.1%)	3994 (43.6%)
Travel abroad	561 (12.3%)	589 (12.8%)	1150 (12.5%)
Travel home	369 (8.1%)	395 (8.6%)	764 (8.3%)
Not known	1190 (26.0%)	1370 (29.9%)	2560 (27.9%)
Other	N/A	42 (0.9%)	42 (0.5%)
<b>Total</b>	<b>4578 (100%)</b>	<b>4588 (100%)</b>	<b>9166 (100%)</b>

**Outbreaks**

In 2003 and 2004, there was a total of 218 outbreaks or clusters detected by 14 countries and involving 945 cases, 10.3% of the total cases included in the dataset [TABLE 4]. Of these 218 outbreaks, 102 (46.8%) were detected in 2003 and 116 (53.2%) were detected in 2004. The number of deaths associated with these outbreaks could not be determined from the aggregated dataset.

TABLE 4

Number of outbreaks of legionnaires' disease and associated cases by category of infection, EWGLI, 2003-2004

Category of outbreak	2003	2004	Total
Nosocomial	18 (81)	8 (28)	26 (109)
Community	20 (284)	29 (173)	49 (457)
Travel abroad	36 (99)	38 (98)	74 (197)
Travel home	27 (83)	40 (92)	67 (175)
Other (private home)	1 (5)	1 (2)	2 (7)
<b>Total</b>	<b>102 (552)</b>	<b>116 (393)</b>	<b>218 (945)</b>

Twenty six outbreaks (11.9%) involving 109 cases were linked to hospitals and occurred in Austria, Denmark, England and Wales, Germany, Italy and Spain. Twenty five of these nosocomial outbreaks were attributed to contaminated hot or cold water systems, and one to an unknown source. These sources are as reported by collaborators, and the standard of investigation may vary between countries. Some outbreaks may have had microbiological confirmation of matching between environmental and clinical strains, but this is still highly unusual. Most of the sources reported would have been identified as a 'most likely' source.

Forty nine outbreaks (22.5%) were linked to community settings, and were associated with 457 cases. They occurred in England and Wales, France, Hungary, Italy, the Netherlands, Norway, Scotland, Spain and Sweden. Cooling towers were identified as the source in 16 of the community outbreaks, four outbreaks were attributed to contaminated hot or cold water systems, three to whirlpool spas, and 26 to an unknown source.

One hundred and forty one of the outbreaks were travel associated, of which 74 (33.9%) were linked to travel outside the country of residence of the case, and 67 (30.7%) were linked to travel within the same country of residence. Where the source of infection was identified, hot or cold water systems were responsible in 38 outbreaks, whirlpool spas in seven, and the remaining 96 sources were unknown.

Two outbreaks were reported to be linked to private homes in Germany (one in each year). The source of infection was not identified for the first outbreak, reported in 2003, but the second outbreak, in 2004 was reported to be linked to a whirlpool spa.

Overall, countries reported 552 cases associated with 102 outbreaks in 2003, and 393 cases associated with 116 outbreaks in 2004. This gives an average of 4.3 cases associated with each outbreak over the two year period. The outbreaks ranged in size from two cases to 84, this latter outbreak being a 2003 community cluster in France. The largest cluster reported in 2004 was a 32 case community cluster in Spain.

**Travel-related legionella infections**

Altogether, 31 countries reported a total of 1914 travel associated cases, 764 of which were linked to travel in the patient's country of residence, and 1150 to travel abroad. (Nine countries in 2003 and eight countries in 2004 reported no travel-associated cases). Travel within Europe accounted for 82.2% of the total travel cases in 2003 (764 cases) and 88.7% in 2004 (873 cases). The remaining cases were associated with Africa, the Americas, Australia, the Caribbean, East Asia, and the Middle East.

The highest number of cases over the two year period was associated with travel to Spain (419 cases), followed by travel to France (315) and travel to Italy (308). However, 87%, 69% and 86% respectively of the travel associated cases in these countries occurred as a result of travel by Spanish, French and Italian nationals within their own country.

Of all travel-associated cases, 66 (3.4%) were in patients who had travelled in more than one European country, and 15 (0.8%) were in patients who had travelled in more than one non-European country. Five cases were associated with travelling on cruise ships (three English cases in 2003: one from Newcastle to Holland, one on a cruise around the Mediterranean, and one on a cruise between Tenerife, Madeira and Gran Canaria; and two cases in 2004: a Belgian case travelling from Greece to Italy, and a Danish case on a Mediterranean cruise).

A more comprehensive analysis of the travel-associated cases of legionnaires' disease is published separately [6]. The EWGLINET definition of a travel-associated case is any case in a person who stayed overnight at a public accommodation site during the two to ten days prior to onset of symptoms. A total of 632 cases of travel-associated legionnaires' disease from 24 countries fulfilled this definition and were reported to the EWGLINET surveillance system in 2003. Most cases that were not reported to EWGLINET were in patients who had stayed in private accommodation, or for whom travel information was incomplete, or travel did not fall within the strict 2-10 day incubation period required by EWGLINET. Eighty nine clusters were detected, 35 (39%) of which only involved one case from one country, and so would not have been detected without EWGLINET.

**Main methods of diagnosis**

Collaborators allocated a main method of diagnosis to each case, taking culture as the gold standard. Over the two years, the main method of diagnosis for 916 cases (10.0%) was culture of the organism, for 6694 cases (73.0%) it was urinary antigen detection and, in 472 cases (5.1%), the main method of diagnosis was a fourfold rise in antibody detection levels [TABLE 5]. Single high antibody titres were the main reported method for 695 cases (7.6%). The remaining cases were diagnosed by respiratory antigen detection, PCR, or the method was unknown.

In 2004, culture of the organism accounted for 491 (10.7%) of all cases, compared with 425 (9.3%) in 2003. Cases diagnosed by urinary antigen detection also increased from 3288 (71.8%) to 3406 (74.2%), while the proportion of cases diagnosed serologically, either by seroconversion or by single high titre, fell from 13.6% to 11.8%.

*L. pneumophila* sg1 infection accounted for 7007 (76.4%) of the total number of cases, 10.3% of which were diagnosed by culture, and 84.0% by urinary antigen. *L. pneumophila* other serogroup or serogroup not determined accounted for 1526 (16.6%) reports, of which 10.0% were diagnosed by culture, 41.2% were diagnosed by urinary antigen detection, and most of the remainder (38.0%) were diagnosed by serology (seroconversion or a single high titre). 633 cases (6.9%) were reported as other *Legionella* species or species unknown, the proportion increasing from 6.0% to 7.8% between 2003 and 2004.

Of the 916 isolates reported, 720 (78.6%) were due to *L. pneumophila* sg1 infection, 77 (8.4%) were *L. pneumophila* serogroup unknown, and 75 (8.2%) were serogroups 2-15. Fifteen isolates were diagnosed as other species of *Legionella*. These were reported as *L. bozemanii* (5), *L. dumoffii* (2), *L. gormanii* (1), *L. longbeachae* (6), and *L. micdadei* (1). For 29 isolates the *Legionella* species was not given.

**Deaths**

Three hundred and ninety six deaths were reported in 2004 (with a case fatality rate (CFR) of 8.6%), and 352 were reported in 2003 (with a CFR of 7.7%). Over the two year period, 748 of 9166 cases died, giving a European CFR of 8.2%. Note, however, that it is not compulsory to report deaths in some countries, and so these datasets may underestimate the true mortality attributable to legionnaires' disease.

**Discussion**

For 12 years EWGLI has been collecting its annual dataset of cases of legionnaires' disease in Europe, which is useful for analysis and in allowing comparison of trends within and between countries.

The European rates of legionnaires' disease per million population recorded by EWGLI's annual datasets since 1993 have shown an

TABLE 5

Cases of legionnaires' disease and proportion by main method of diagnosis, EWGLI, 2003-2004

Main method of diagnosis	<i>L. pneumophila</i> sg1	<i>L. pneumophila</i> (other serogroup), or serogroup not determined	Other <i>Legionella</i> species or species unknown	All cases
	n (%)	n (%)	n (%)	n (%)
Isolation	720 (10.3%)	152 (10.0%)	44 (7.0%)	916 (10.0%)
Antigen detection				
Urinary	5885 (84.0%)	629 (41.2%)	180 (28.4%)	6694 (73.0%)
Serology				
Seroconversion	140 (2.0%)	228 (14.9%)	104 (16.4%)	472 (5.1%)
Single high titre	205 (2.9%)	352 (23.1%)	138 (21.8%)	695 (7.6%)
Antigen detection				
Respiratory	9 (0.1%)	26 (1.7%)	2 (0.3%)	37 (0.4%)
PCR	9 (0.1%)	61 (4.0%)	32 (5.1%)	102 (1.1%)
Other	16 (0.2%)	10 (0.7%)	7 (1.1%)	33 (0.4%)
Unknown	23 (0.3%)	68 (4.5%)	162 (19.9%)	217 (2.4%)
<b>Total</b>	<b>7007 (100%)</b>	<b>1526 (100%)</b>	<b>633 (100%)</b>	<b>9166 (100%)</b>

(Each case counted once only)

overall increase. From 1993 to 2000, incidence varied between 3.35 and 5.38 cases per million population, but from 2001 to 2004, the incidence ranged from 7.6 to 10.1. The changes in diagnostics and strengthening of surveillance systems that have prompted this higher incidence have been discussed previously [5]. Incidence was lower in 2004 than in 2003 because the denominator (total population) increased from 468 million to 557 million. This is due partly to the addition of Andorra to the dataset in 2004, but is also due to Greece and Turkey providing population sizes only for areas of their two countries in 2003, but for the entire national populations in 2004.

The incidences recorded in the annual datasets vary widely between countries, and suggest that there may be poor ascertainment, under-reporting or a lack of diagnoses taking place in some areas of Europe. The dataset identifies those countries with unusually low rates, and shows the rates that other European countries are detecting and reporting, thereby allowing collaborators to set their own targets for improvement.

The lack of national data in a number of countries is a cause of some concern. Decision 2119/98/EC made it mandatory for European Union countries to have national surveillance systems in place for infectious diseases including legionnaires' disease [7]. Despite this, some countries still rely on laboratory reports to give an estimate of the number of cases found in their population each year, and this system does not always extend nationally.

This applies to some of the new EU countries. It is hoped that participation in EWGLINET and meeting EWGLINET's standard for good quality data will strengthen their national surveillance systems. As an example, the identification of cases by species and serogroup needs to be improved throughout Europe and reported through the system to the national level. At present, 41.2% of cases reported as '*L. pneumophila* other serogroup or serogroup not determined' were diagnosed by urinary antigen detection. Because this test detects specific antigens, it should allow countries to assign each case to a serogroup, and so EWGLI should not be receiving reports where the serogroup is unknown. This is a reporting problem in some countries; laboratories do not pass on the serogroup information, and as a result, the final dataset is less accurate than it could be. EWGLI's desire for good quality data should motivate collaborators to encourage their laboratories to report full microbiological information.

The collection of this annual dataset itself helps to strengthen national schemes. It requires all EWGLI collaborating countries to complete and clean their national datasets once a year, forwarding to EWGLI's coordinating centre as complete a set of information as is possible. An area of reporting that needs to be improved by all countries is data on deaths. The breakdown of such death data by age, sex, category of case and links to outbreaks would be extremely informative. More accurate, detailed mortality information would allow national surveillance systems (in conjunction with morbidity data) to identify particular demographic groups with high case fatality rates, thereby identifying areas to target legislation and control measures.

The annual dataset provides an opportunity to gather information on all outbreaks of legionnaires' disease that were identified in a particular year by national surveillance schemes throughout Europe. The number of nosocomial outbreaks dropped from 18 to eight between 2003 and 2004, suggesting an improvement in the control and prevention of legionnaires' disease in hospitals. In contrast, the number of outbreaks associated with travel within a case's own country increased from 17 to 40. This may be due in part to EWGLINET's recent emphasis on the importance of ensuring such cases are classified as 'travel' cases, even when no foreign travel is involved [6]. Of note also is the decrease in the number of cases associated with community outbreaks, despite the increasing number of such outbreaks. This suggests that countries are improving their response to community outbreaks when they occur, and are ensuring that the number of cases involved is kept to a minimum [TABLE 4].

With the establishment of the European Centre for Disease Prevention and Control (ECDC) [8], there is the opportunity for further growth and development of all Disease Specific Networks (DSNs), including EWGLINET. A close relationship between EWGLINET and the ECDC should make it possible to share data more widely amongst the countries of Europe, and should allow for a more effective dissemination of early warnings to ensure a greater response.

EWGLINET is a very successful DSN. More countries are submitting annual datasets to EWGLINET each year, which shows the close collaboration that has been achieved between member states and the good quality data that such collaborations can produce.

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# EUROPEAN RECOMMENDATIONS FOR THE MANAGEMENT OF HEALTHCARE WORKERS OCCUPATIONALLY EXPOSED TO HEPATITIS B VIRUS AND HEPATITIS C VIRUS

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Exposure prevention is the primary strategy to reduce the risk of occupational bloodborne pathogen infections in healthcare workers (HCW). HCWs should be made aware of the medicolegal and clinical relevance of reporting an exposure, and have ready access to expert consultants to receive appropriate counselling, treatment and follow-up.

Vaccination against hepatitis B virus (HBV), and demonstration of immunisation before employment are strongly recommended. HCWs with postvaccinal anti-HBs levels, 1-2 months after vaccine completion, >10 mIU/mL are considered as responders. Responders are protected against HBV infection: booster doses of vaccine or periodic antibody concentration testing are not recommended. Alternative strategies to overcome non-response should be adopted.

Isolated anti-HBc positive HCWs should be tested for anti-HBc IgM and HBV-DNA: if negative, anti-HBs response to vaccination can distinguish between infection (anti-HBs >50 mIU/ml 30 days after 1<sup>st</sup> vaccination: anamnestic response) and false positive results (anti-HBs >10 mIU/ml 30 days after 3<sup>rd</sup> vaccination: primary response); true positive subjects have resistance to re-infection and do not need vaccination.

The management of an occupational exposure to HBV differs according to the susceptibility of the exposed HCW and the serostatus of the source. When indicated, post-exposure prophylaxis with HBV vaccine, hepatitis B immunoglobulin or both must be started as soon as possible (within 1-7 days).

In the absence of prophylaxis against hepatitis C virus (HCV) infection, follow-up management of HCV exposures depends on whether antiviral treatment during the acute phase is chosen. Test the HCW for HCV-Ab at baseline and after 6 months; up to 12 for HIV-HCV co-infected sources. If treatment is recommended, perform ALT (amino alanine transferase) activity at baseline and monthly for 4 months after exposure, and qualitative HCV-RNA when an increase is detected.

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## Introduction

Bloodborne pathogens such as hepatitis B (HBV) and C virus (HCV) represent an important hazard for healthcare workers (HCWs) [1]. In the general population, HCV prevalence varies geographically from about 0.5% in northern countries to 2% in Mediterranean countries, with some 5 million chronic carriers estimated in Europe; while HBV prevalence ranges from 0.3% to 3%. The World Health Organization (WHO) estimates that each year in Europe 304 000 HCWs are exposed to at least one percutaneous injury with a sharp object contaminated with HBV, 149 000 are exposed to HCV and 22 000 to HIV.

The probability of acquiring a bloodborne infection following an occupational exposure has been estimated to be on average <0.3% for HIV, 0.5% for HCV and 18%-30% for HBV, depending on the type of exposure (percutaneous injuries with hollow-bore, blood-filled needles carry the highest risk of infection), the body fluid involved, and the infectivity of the patient [1].

To implement and standardise a rational management of occupational exposures to HIV, HBV and HCV among HCWs in Europe, representatives of nine European countries participated in a project funded by the European Commission, and developed a comprehensive set of recommendations.

We present here recommendations for the general management of occupational risk of bloodborne infections, HBV vaccination and management of HBV and HCV exposures. A description of the project and recommendations for HIV post-exposure management, including antiretroviral prophylaxis, has been previously published [2], and so issues related to occupational risk and prevention of HIV infection following an occupational exposure will not be discussed further.

## General policies

Exposure prevention is the primary strategy to reduce the risk of occupational bloodborne pathogen infections. All preventive efforts should be made to reduce the risk of occupational exposures.

Healthcare organisations should have a system readily available to their personnel that includes educational programmes, written protocols for prompt reporting, evaluation, counselling, treatment, and follow-up of occupational exposures that might place HCWs at risk of acquiring a bloodborne infection.

## Educational programmes and training

All HCWs should be informed, educated and trained about:

- The possible risks and prevention of bloodborne infections after an occupational exposure;
- The measures to prevent bloodborne pathogen exposures:
  - Implementation of standard precautions,
  - Provision of personal protective equipment and safety devices,
  - Implementation of safer procedures,
  - HBV vaccination,
  - The principles of post-exposure management and the importance of seeking urgent advice following any occupational exposure immediately after it occurs, as certain indicated interventions must be initiated promptly to maximise their effectiveness.

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### **Reporting an occupational exposure**

Local health policies should specifically identify a designated healthcare provider to whom HCWs can be urgently referred in case of exposure, and who will be responsible for post-exposure management, provision of prophylaxis and clinical and serological follow-up. Access to clinicians who can provide post-exposure care should be available during all working hours, including nights and weekends.

HCWs should be made aware in advance of the medicolegal and clinical relevance of reporting an occupational exposure, how to report it and to whom it should be reported, and have ready access to expert consultants to receive appropriate counselling, treatment and follow-up.

### **HBV vaccination**

- HCWs should be vaccinated against HBV, with a standard vaccination schedule [3].

- Before entering nursing and medical schools and before employment in healthcare settings, vaccination or demonstration of immunisation against HBV is strongly recommended [4].

- Pre-vaccination screening is not routinely indicated [5].

- Antibody titre against HBsAg (anti-HBs) should be assessed 1-2 months after completion of a 3-dose vaccination series [6].

- New vaccines or alternative schedules that could determine a higher response rate or a stronger response should be used if available [7-8].

- Combined hepatitis A and hepatitis B vaccine is recommended in case of susceptible HCWs with HCV infection or other liver diseases [9], and could be considered for all HCWs regardless of their clinical status [10].

### **Definitions**

Primary 3-dose vaccination: three standard doses (according to manufacturers) of recombinant HBV vaccine administered intramuscularly in the deltoid region, preferably with a 25 mm needle [11], at 0, 1, and 6 months.

Responders: subjects with post-vaccinal anti-HBs levels, determined at 1-2 months from the last dose of vaccine, equal to or greater than 10 mIU/mL.

Non-responders: subjects with post-vaccinal anti-HBs levels, determined at 1-2 months from the last dose of vaccine, lower than 10 mIU/mL, who tested negative for HBsAg, and anti-HBc [see section 2c].

### **Post-vaccination management**

#### **HBV vaccination responders**

- Responders are protected against HBV infection [12].

- Routine booster doses of HBV vaccine are not recommended for known responders, even if anti-HBs levels become low or undetectable [13].

- Periodic antibody concentration testing after completion of the vaccine series and assessment of the response is not recommended [14].

#### **HBV vaccination non-responders**

- 5%-10% of the adult population will not respond to standard HBV vaccination.

- Risk factors for vaccine non-response include: male sex, older age, cigarette smoking, obesity, immunodeficiency, renal failure, intragluteal vaccine administration, chronic diseases, certain HLA haplotypes and coeliac disease [15-16].

- If non-responders test HBsAg/anti-HBc negative:

- Administer a fourth dose and then retest the HCWs for response 1-2 months later [17];

- If no response has been elicited, complete a full course of conventional vaccine at the standard doses (i.e. administer a fifth and sixth dose), and retest the HCW for response 1-2 months after the last dose of vaccine [17-18].

- Possible alternative strategies, that need further evaluation, to overcome nonresponse to standard HBV vaccination are: Vaccines

containing S subunit, pre-S1 and pre-S2 particles [19-20]; Three intradermal 5 µg doses of standard vaccine, given every two weeks [21]; Combined hepatitis A and hepatitis B vaccines [22]; High-dose standard vaccine series [18, 23-24].

### **Management of isolated anti-HBc**

- Test isolated anti-HBc positive HCWs for IgM anti-HBc and HBV-DNA [25], possibly with sensitive PCR assays, to determine whether these subjects are low-level HBsAg carriers, or in the window phase, or have occult HBV infection [26-27].

- If negative for anti-HBc IgM and HBV-DNA, initiate vaccination, and test the HCW 30 days after the first dose of vaccine: an anti-HBs titre exceeding or equal to 50 mIU/mL indicates an anamnestic response (isolated anti-HBc indicated infection with HBV) [28-29]. True positive subjects with isolated anti-HBc (those with anamnestic response) have resistance to HBV re-infection and do not need to complete vaccination or to receive HBV post-exposure prophylaxis [30].

- If anti-HBs response is <50 mIU/mL 30 days after the first dose of vaccine, complete the vaccination schedule and test the HCW: an anti-HBs titre exceeding or equal to 10 mIU/mL 30 days after the third dose of vaccine indicates a primary response (isolated anti-HBc was a false positive result).

- In case of an exposure to an HBsAg positive source, manage subjects with 'unresolved' isolated anti-HBc as susceptible.

### **Management of HBsAg-positive and HCV-Ab-positive HCWs**

- HCWs who prove to be HBsAg-positive and/or HCV-Ab positive should be counselled regarding the need for medical evaluation and regarding prevention of HBV and/or HCV transmission to others.

- Evaluation of the risk they pose to patients by an expert review panel according to national and international recommendations to prevent worker-to-patient transmission is strongly recommended [31].

### **Management of occupational exposures**

#### **Immediate treatment of the exposure site**

- Percutaneous exposure: encourage bleeding and wash with soap and water.

- Cutaneous contaminations: wash with soap and water.

- Mucous membranes contamination: flush with water.

- Eyes should be irrigated with clean water, saline, or sterile irrigants.

- Although no evidence exists that using antiseptics/disinfectants reduces the risk of bloodborne pathogen transmission, their use is not contraindicated, as both viruses are enveloped and are supposed to be relatively sensitive to many chemical agents.

- The application of caustic agents (i.e. bleach) or the injection of antiseptics or disinfectants onto the wounds is not recommended [1].

#### **Risk assessment**

- In case of an occupational exposure to an at risk bloodborne infection, baseline HBV, HCV, HIV immune status of the exposed HCW should be available.

- For medicolegal reasons, store a plasma and serum sample of the exposed HCW at baseline.

- Evaluate the exposure's potential to transmit HBV, HCV, and HIV, based on the type of exposure and body material involved [2].

- Evaluate the source patient's serostatus for antibodies against HIV (HIV-Ab), HCV (HCV-Ab) and for HBsAg. If unknown, inform the source patient of the incident and obtain an informed consent. Results should be readily available. Source testing for HBsAg can be avoided when the HCW is known to be protected by vaccine or natural immunity. Direct virus assays (e.g. HBV-DNA or HCV-RNA/HCV Ag) are not recommended.

- Store a plasma and a serum sample from the source for further investigations.

- Consider as infected sources who refuse testing or cannot be tested.

**Management of exposures to HBV**

The management of a possible occupational exposure to HBV differs according to the susceptibility and serostatus of the exposed HCW [TABLES 1,2]. When necessary, post-exposure prophylaxis with HBV vaccine, hepatitis B immunoglobulin (HBIG) or both must be started as soon as possible, preferably within 24 hours from the exposure and no later than one week [32-33]. This management is no different in pregnant HCWs [34].

HBsAg-positive HCWs should receive clinical evaluation and their serostatus, as well as risk for hepatitis D, should be assessed.

If, notwithstanding optimal post-exposure management, acute B hepatitis develops, the person should be referred for medical management to a specialist knowledgeable in this area.

**Follow up**

• Serological follow-up is not recommended when post-exposure management is in accord with the above mentioned recommendations.

**Management of exposures to HCV**

Currently, there is no available prophylaxis for HCV.

Data from the literature suggest that therapy (interferon or PegIFN +/-Ribavirin) may prevent chronicisation when administered to patients with acute HCV infection [35]. However, while it is documented that viral clearance can spontaneously occur after acute infection [36], it is unclear whether treatment of the acute or early

(first six months) phase is more effective than early treatment of chronic C hepatitis [37-38]. Further studies to clarify these issues are ongoing. As medical advice and personal choices could change in the near future, an optimal follow up management of occupational HCV exposure should allow prompt identification of infection, and be cost effective, bearing in mind that estimated incidence of HCV infection following an occupational exposure is on average 0.5%.

**1. HCV-Ab positive, untested or unidentifiable source**

- Test the HCW for HCV-Ab (EIA) at baseline and 6 months from exposure; extend to 12 months for exposures to HIV-HCV co-infected sources Confirm positive results with a recombinant immunoblot assay or qualitative HCV-RNA.
- Perform ALT activity at baseline, and then monthly for 4 months after exposure.
- Perform qualitative HCV-RNA when an increased transaminase level is detected.
- Some experts would also test for HCV-Ab at 3 months, as most seroconverters are already positive at this time, and in order to reduce loss to follow-up and the anxiety of the exposed HCW.

**2. HCV-Ab negative source**

- In case of HIV infection, immunosuppression or other conditions (i.e. dialysis) associated with possible false negative results in the source, follow recommendations for exposure to an HCV positive source.

TABLE 1

Post-exposure management in case of an HBsAg+, untested or unidentifiable source

Vaccinal status against HBV in the exposed HCW	Anti-HBs	HBIG (0.06 mL/kg)	HBV vaccine	Comment
Not vaccinated	Obtain rapid results If anti-HBs >10 mUI/mL: no treatment	If anti-HBs <10 mUI/mL: administer HBIG 1 dose ASAP and repeat after 1 month	1 <sup>st</sup> dose ASAP and then accelerated schedule 1-2-12 months	Administer HBV vaccine in the deltoid muscle; HBIG can be administered i.m. simultaneously at a separate site. Assess response 1-2 months after last dose
Incompletely vaccinated or does not recall a complete vaccination schedule	As above	1 dose ASAP	Complete according to documentation or restart 0-1-2-12 months	As above
Vaccinated with an unknown antibody response	As above	As above	1 booster ASAP	As above
Non-responder to primary vaccination		1 dose ASAP and repeat after 1 month	1 <sup>st</sup> dose ASAP and then accelerated schedule 1-2-12 months	As above
Previously vaccinated with 4 doses or two complete vaccine series but non-responder		As above	Possible alternative vaccine?	
Previously vaccinated and known responder	No	No	No	

Abbreviations

HBsAg: hepatitis B surface antigen; HBV: Hepatitis B Virus; HCW: Health Care Worker; anti-HBs: antibodies against hepatitis B surface antigen; HBIG: hepatitis B immune globulins; ASAP: as soon as possible; i.m.: intramuscular

TABLE 2

Post-exposure management in case of an HBsAg-source

Vaccinal status against HBV in the exposed HCW	Anti-HBs Testing	HBV vaccine	Comment
Not vaccinated		Initiate standard schedule	Assess response 1-2 months after last dose
Incompletely vaccinated or does not recall a complete vaccination schedule		Complete according to documentation or restart standard schedule	As above
Vaccinated with an unknown antibody response	Test for anti-HBs	If anti-HBs <10 mIU/mL administer 1 booster and retest after 1-2 months If still < 10 mIU/mL complete as a 2 <sup>nd</sup> standard vaccination schedule	As above
Non-responder to primary vaccination		Repeat standard schedule	As above
Previously vaccinated with 4 doses or two complete vaccine series but non-responder		Possible alternative vaccine?	
Previously vaccinated and known responder	No	No	

Abbreviations

HBsAg: hepatitis B surface antigen; HBV: Hepatitis B Virus; HCW: Health Care Worker; anti-HBs: antibodies against hepatitis B surface antigen; HBIG: hepatitis B immune globulins; ASAP: as soon as possible; i.m.: intramuscular



## Conclusions

Accidental blood and body fluid exposures entail the risk of occupational infection by bloodborne pathogens in HCWs, mainly HBV, HCV, and HIV [39-41].

Notwithstanding effective pre- and post-exposure prophylaxis for HBV and the availability of post-exposure prophylaxis against HIV, the best approach to avert cases of occupational bloodborne infection remains to prevent these exposures.

However, the adoption of a rational pre- and post-exposure management could help to minimise consequences and costs. In this regard, the recommendations here presented are complementary to the European recommendations for post-exposure prophylaxis of HIV infection in healthcare workers [2], both being developed within a project funded by the European Commission with the aim to standardise the management of occupational exposures to HIV/bloodborne infections in Europe. These recommendations must be considered dynamic documents. Indeed, scientific evidence appearing in the literature after the consensus meetings was also included in these documents, and recommendations may change in the future with further research and scientific information, as some issues remained unresolved or controversial.

Among issues related to HBV vaccination, there was no unanimous consensus regarding the post-vaccinal anti-HBs level to be considered as protective. A minority of the expert panel suggested a more conservative approach, in which those HCWs who have post-vaccinal anti-HBs levels between 10 and 100 mIU/mL are considered as low-responders. These subjects may, due to waning antibodies, develop asymptomatic hepatitis B infection and seroconversion after exposure, although only very rare cases of chronic infection/disease have been reported [42]. For these subjects, the same recommendations used for non-responders could be applied, including HBsAg determination. Indeed, among these subjects, concurrence of hepatitis B surface antibodies and surface antigen is also possible [43].

No data directly assess the efficacy of HBIG in post-exposure prophylaxis in HCWs. The use of hepatitis B vaccine alone after exposure to HBsAg-positive blood seems to achieve comparable results to HB vaccine combined with HBIG [44]; however, the vast majority of the expert panel agrees on HBIG administration. Nonetheless, in the discussion, several reservations were expressed regarding the administration of HBIG. For exposures to a source of unknown serostatus, while the majority of the expert panel would treat as if HBsAg positive, some experts would consider the option of HBIG administration according to the probability of infection of source patient (e.g. drug user, coming from high endemicity country, etc.). In unvaccinated HCWs testing anti-HBs negative, it was suggested that testing for anti-HBc would avoid HBIG administration if the subject had natural immunity. Moreover, as a protective response should be elicited in these subjects after the first three doses of vaccine during the accelerated vaccination schedule, the administration of the second dose of HBIG could be avoided; this same reservation was expressed for vaccinated HCWs with an unknown antibody response, in view of the high probability that the subject would respond to a booster dose, and for non-responders to primary vaccination, in view of the high probability that the subject would respond to a second, accelerated vaccination schedule.

Cost-effectiveness issues could also be considered; for example, in young subjects, low-dose intramuscular or intradermal vaccination provides long-term effective protection and can be used as a cost-saving vaccination strategy [45-46].

Finally, for the management of non-responders, nucleic acid vaccines or DNA vaccines are candidate vaccines to prevent and treat viral hepatitis, and hepatitis B DNA vaccine seems to induce protective antibody responses in human non-responders to conventional vaccination [47]. The preliminary results of an ongoing trial are promising in this regard.

Regarding the management of HCV exposures, until new anti-HCV drugs such as HCV serine protease inhibitors, which may eventually be used for post-exposure prophylaxis, neutralising antibodies to

hepatitis C virus [48], or an anti-HCV vaccine are available [49], the discussion focuses on the opportunity of treating acute infection, an issue thoroughly discussed during the consensus meeting. The resulting dichotomy is mirrored in the follow-up schedule. Further well-conducted, randomised clinical trials are needed to conclusively support the treatment option. Whether treatment during the acute phase could avoid the establishment of HCV reservoirs and therefore ultimately contribute to decrease the risk of cirrhosis and hepatocellular carcinoma, however, remains to be determined. New data will be necessary to give definitive indications on these and other issues.

In the meantime, it is important to maintain surveillance of occupationally exposed HCWs, and to promote a widespread implementation of preventive strategies such as standard precautions, education on exposure risk, better sharps disposal systems, personal protective equipment, and safety-engineered sharp devices to ensure a safer working environment in the healthcare setting.

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## ORIGINAL ARTICLES

## Outbreak report

## HUMAN-TO-HUMAN TRANSMISSION OF AVIAN INFLUENZA A/H7N7, THE NETHERLANDS, 2003

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An outbreak of highly pathogenic avian influenza A virus subtype H7N7 began in poultry farms in the Netherlands in 2003. Virus infection was detected by RT-PCR in 86 poultry workers and three household contacts of PCR-positive poultry workers, mainly associated with conjunctivitis. To determine the magnitude of and risk factors for human-to-human transmission of influenza A/H7N7 in the Netherlands, a retrospective cohort study among household members of infected poultry workers was undertaken. In total, 33 (58.9%) of 56 (among 62) participants who provided blood samples had positive H7 serology, using single convalescent serum samples obtained at least 3 weeks after onset of symptoms of the

index case. Eight household members (12.9%) reported symptoms (conjunctivitis and/or ILI), of which four of five (80.0%) tested seropositive. On univariate analysis, significant risk factors for seropositivity included having at least two toilets, a pet bird, and using cloth handkerchiefs. It was not possible to obtain a stable model for binomial regression for the outcome of A/H7N7 infection. Further seroprevalence studies among contacts of asymptomatic H7 cases should be conducted.

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### Background

On 28 February 2003, the highly pathogenic avian influenza A virus subtype H7N7 (HPAI A/H7N7) was isolated for the first time in the Netherlands from poultry on a farm, identifying the start of

a large epizootic that also affected Germany and Belgium. In the Netherlands, infected poultry on 255 farms were culled, as well as poultry on 1094 surrounding farms, resulting in the killing of more than 30 million chickens [1]. Hygienic measures, and application of personal protective equipment and antiviral prophylaxis were advised. The following weeks, A/H7N7 was diagnosed by RT-PCR in 89 humans, of whom 78 had conjunctivitis. A Dutch veterinarian reported having conjunctivitis, which developed one day after he had visited an affected farm, and he died a week later from respiratory distress [2]. Three of the 89 cases were household contacts of A/H7N7 confirmed cases and had no known exposure to A/H7N7 infected poultry. This strongly suggested human-to-human transmission, either direct or indirect. All three patients had conjunctivitis, and one also had influenza-like illness (ILI).

Influenza in humans and HPAI is caused by influenza A virus, belonging to the family *Orthomyxoviridae*. All currently known influenza A virus subtypes have been found to circulate in waterfowl [3,4]. Avian influenza viruses have been known to infect humans, but transmission between humans has so far only occurred sporadically [5,6,7]. Influenza A/H7N7 in humans was first reported in 1959 [8]. In January 2004, human cases of influenza A/H5N1 related to an outbreak of avian influenza A/H5N1 were identified in Vietnam and Thailand [9] and in September 2004, probable human-to-human transmission was reported in a family cluster in Thailand [10].

Simultaneous infection of a susceptible host with a human and an animal influenza A virus could lead to re-assortment of genetic material and consequently cause the generation of a virus subtype capable of replicating and spreading between humans and with surface proteins that are novel for the human population (antigenic shift). Such strains could cause a major influenza pandemic

In order to measure secondary transmission of avian influenza A/H7N7 in household members, to identify risk factors for transmission, and to describe the clinical course of illness, we conducted a retrospective cohort study among household members of infected poultry workers.

## Methods

Patients who were A/H7N7 confirmed index cases were contacted by telephone for recruitment of their household members in the study. People living on poultry farms or those who kept poultry in their gardens (backyards) were excluded from the study.

## Definitions

**An A/H7N7 confirmed index case** was a person who had conjunctivitis and/or ILI, who had been exposed to influenza A/H7N7 infected poultry since 28 February 2003 in the Netherlands, and who had positive influenza A/H7N7 laboratory results by PCR and/or virus isolation.

**Conjunctivitis** - a possible case of A/H7N7 conjunctivitis was a household member with no known exposure to poultry and with two or more of the following symptoms since 28 February 2003: red eyes, tearful eyes, itching eyes, painful eyes, burning eyes, purulent fluid in eyes, or sensitivity to light. A confirmed case of A/H7N7 conjunctivitis was a possible case of A/H7N7 conjunctivitis with positive influenza A/H7N7 laboratory results by PCR and/or virus-isolation.

**Influenza-like illness** - a possible case of A/H7N7 influenza was a household member with no known exposure to poultry and with fever (if measured, then  $\geq 38.5^{\circ}\text{C}$ ), and at least one of the following symptoms since 28 February 2003: cough, rinorrhoea, sore throat, myalgia, or headache. A confirmed case of A/H7N7 influenza was a possible case with positive influenza A/H7N7 laboratory results by PCR and/or virus-isolation.

**Seropositive** - a serology confirmed case of A/H7N7 infection (symptomatic or asymptomatic) was a household member who had an antibody titre of 1:10 or higher for influenza A/H7N7 by haemagglutination assay [11].

## Questionnaire

Information on demographics, occupation, smoking, medical history, pets, contact with A/H7N7 confirmed index cases (including

hygienic measures by index cases and contacts), exposure to A/H7N7-infected poultry, influenza vaccination status, and symptoms since 1 March 2003 were collected using a standardised, self-administered, postal questionnaire.

## Serology

All participants were asked to provide single serum samples, at least 3 weeks after diagnosis of the primary A/H7N7 case in their household, to ascertain (sub)clinical infection with influenza A/H7N7. Sera were tested in a modified haemagglutination inhibition as described in detail by Meijer et al [11].

Ethical clearance for the study was obtained from the Dutch Medical Ethics Committee.

## Statistical analysis

Data were analysed with STATA 8.0. For multivariate analysis of significant or biologically plausible variables in univariate analysis we preferred binomial to logistic regression because of high prevalence of positive A/H7N7 serology in household members in this cohort study, which calls for adjusted risk ratio's rather than odd ratios. Fisher's exact test was used to calculate significance.

## Results

### Description of study participants

Of 86 households of A/H7N7 infected poultry workers, 63 (73.3%) households agreed to participate and 14 declined. Nine poultry workers could not be reached, of which four were immigrant workers that had returned to their home country Poland. Of the 200 household members in the 63 participating households, 104 (52%) completed and returned the questionnaire.

Of these 104, 42 were excluded, as they had either been exposed to H7N7-infected poultry, or were family members who were not living at the same address as the index case. A total of 62 household members of 25 A/H7N7 confirmed index cases were included in the study, with one single A/H7N7 confirmed index case in each of these households.

The male:female ratio was 2:3. Mean age was 27.3 years, ranging from 0 to 61 years. The mean household size was 3.5 people (range 2 – 8).

### Clinical symptoms

Eight people (12.9%) reported health complaints. Two met the case definition of conjunctivitis only, four met the case definition of ILI only and two met both case definitions. In table 1, the risk factors for conjunctivitis among household members are summarised. Attack rates were higher in those who had allergies in their medical history than in those who did not (RR = 10.3, 95% confidence interval 1.2 – 91.0).

TABLE 1

Risk factors for conjunctivitis among household members of influenza A/H7N7-infected persons, N = 62 (univariate analysis), The Netherlands, 2003

	Total no. of persons	No. of cases	RR	95% CI	P value*
Allergy in medical history	14	3	10.3	1.2-91.0	<0.05
Sharing a washcloth	8	2	5.9	0.96-35.9	0.097
Sharing a towel	12	2	4.2	0.07-26.7	0.17
Use of cloth handkerchief	22	3	5.5	0.6-49.4	0.12
Smoking	5	1	3.8	0.05-30.1	0.29
Index: good hygiene	43	4	U†	-	0.57
Pet bird inside home	9	1	2.0	0.2-16.9	0.48
Other pets living inside home	37	3	2.0	0.2-18.4	0.64

\* P value using Fisher's exact test

† U= undetermined

**Results serology**

In total, 56 of the 62 people in the cohort agreed to provide blood samples, of which 33 (58.9%) had detectable antibodies against H7. Five of eight household members with health complaints were serologically tested; four (80.0%) had detectable antibodies against H7, of which two had conjunctivitis only with onset two to six days after onset of symptoms in the index case, and two had conjunctivitis as well as symptoms of ILI with onset unknown or 5 days after onset of symptoms in the index case. Out of 24 households serologically tested, 15 (62.5%) had one or more household contacts with detectable H7 antibodies [TABLE 2].

A/H7 seroprevalence in household members was higher among those who had pet birds (e.g., canary) kept indoors at home and among those having any other indoor pets in their homes (e.g., cat, dog, hamster) than among those who did not [TABLE 3]. Furthermore, seroprevalence was higher among those who frequently used cloth handkerchiefs than among those who did not. Conversely, those who used paper handkerchief had a lower seroprevalence of H7 antibodies than those who did not. Seroprevalence was higher among those who had at least two toilets in their homes, than among those who had only one toilet. At household level, seroprevalence was higher among the 17 households that had two or more toilets in the home than

among the 7 households with only one toilet at home (RR = 2.7, 95% confidence interval 0.8-8.9, p = .061).

Family members of index patients who had their first poultry exposure on or after 5 March 2003 had lower seroprevalence, showing borderline significance, than household members of index cases with first poultry contact before 5 March.

Two (3.2%) of 62 persons received the 2002-2003 influenza vaccination.

It was not possible to develop a stable model of significant and biologically plausible risk factors in univariate analysis for binomial regression.

The HI assay had a sensitivity of 85% and a specificity of 100% at a cut-off HI titre of  $\geq 10$ . HI antibodies against influenza A/H7, A/H1, and A/H3 were not cross-reactive with the heterologous virus. None of the human sera tested showed neutralisation of the A/H7N7 virus in the microneutralisation assay.

**Discussion**

We describe the occurrence of infection with avian influenza A virus subtype H7N7 in household contacts of human A/H7N7 confirmed index cases, in the absence of contact with infected poultry. Thirty three of 56 household members (58.9%) had an A/H7N7

TABLE 2

**Seroprevalence of H7-antibodies among household contacts by number of susceptibles (n=56) within the household, The Netherlands, 2003**

Number of susceptibles per household	Number of households	Total number of susceptibles	Number of contacts with H7-antibodies	Prevalence (%)
1	12	12	4	33%
2	1	2	2	100%
3	7	21	13	62%
4	2	8	4	50%
5	0	0	0	
6	1	6	6	100%
7	1	7	4	57%
<b>Total</b>	<b>24</b>	<b>56</b>	<b>33</b>	<b>33%</b>

TABLE 3

**Risk factors for positive H7 serology of household members of influenza A/H7N7-infected persons, N = 56 (univariate analysis), The Netherlands, 2003**

	Total no. of persons	No. of cases	RR	95 % CI	P value*
Female sex	34	17	0.7	0.5-1.04	0.091
Aged 19 years or over	36	21	0.97	0.6-1.5	0.90
Two or more toilets at home	45	31	3.8	1.1-13.5	0.0045
Pet bird inside home	7	7	1.9	1.4-2.5	0.034
Other pets living inside home	34	21	1.1	0.7-1.8	0.59
Use of cloth handkerchief	17	14	1.7	1.1-2.5	0.022
Use of paper handkerchief	27	12	0.61	0.4-0.99	0.034
Use of soap for handwashing	20	9	0.65	0.4-1.1	0.075
Good hygiene by index case	39	26	2.2	0.8-5.9	0.068
Poultry exposure by index case: 5 March + later	32	15	0.63	0.4-0.99	0.075
Sharing bedroom with others	40	22	0.8	0.5-1.3	0.43
Burning sensation in eyes	5	5	1.8	1.4-2.3	0.071
Smoking	5	5	1.8	1.4-2.3	0.071
Healthy, no medical history	36	18	0.67	0.4-1.0	0.068
Allergy in medical history	13	10	1.4	0.96-2.2	0.20
Use of oseltamivir	2	2	1.6	1.3-2.0	0.53
Conjunctivitis **	4	4	1.8	1.4-2.3	0.14
Influenza-like illness **	3	2	1.1	0.5-2.6	1.0

\* P value using Fisher's exact test

\*\* Association with, rather than risk factor for, positive H7 serology

infection confirmed by RT-PCR or serology, four of 62 household members (6.5%) met the possible case definition of conjunctivitis and all four cases (100%) had positive H7 serology.

The authors assume that the presence of H7-antibodies is indicative of a past AI A/H7N7 infection. This is supported by the results of another study in which the prophylactic use of oseltamivir was found to significantly reduce the seroprevalence of H7 antibodies in professionals exposed to infected poultry using the same serological test [12]. In that study, a significant association was found between the presence of H7 antibodies and the occurrence of eye symptoms, after correcting for prophylactic use of oseltamivir.

When using the adjusted HI assay, but not when using the microneutralisation assay, we detected a measurable antibody response in a high proportion of sera from persons exposed to laboratory-confirmed A/H7N7 infected persons. Evidence that these antibodies are real comes from three observations. First, any cross reaction of the A/H7 specific HI-assay with antibodies against A/H1 or A/H3 viruses would have been detected in the sera from persons recently vaccinated with the seasonal human influenza vaccine, but no reaction (0%) in the A/H7 HI assay was found. Second, as the sera of the recently vaccinated persons were collected in autumn 2002, just before the H7 epizootic started, the anti-H7 antibodies in the household contacts can not be explained as being the result of previous circulation of A/H7 virus. Third, none of the samples collected in autumn 2002 from 100 recently vaccinated persons had reactivity with the adjusted H7 assay [11]. This suggests that our results cannot be explained by aspecific reactivity of the adjusted HI-assay.

Our results suggest that during the outbreak of avian influenza A virus, subtype H7N7, household members of poultry workers were at increased risk of avian influenza either by direct (person to person) or by indirect (fomite) transmission. Previous observations of influenza transmission within households had shown secondary attack rates among household members of influenza cases in the same high range as observed in our study [13]. These high secondary attack rates are in contrast with findings for subtype A/H9N2 and A/H5N1, where no to limited secondary transmission was observed among healthcare workers and household contacts of cases [5,6,7,14,15]. However, we used a method for the detection of antibodies against the H7 virus which has a high analytical sensitivity. Detailed studies to analyse person to person transmission of H5 and H9 with the same methodology are sparse. Interestingly, for H9, a recent publication showed that in 44.6% of suspected cases of H9N2 infection and in 33.5% of the general population in Shantou city in China, antibody titres against H9 could be detected [16]. This observation suggests that secondary transmission of H9 viruses may be more common than has previously been assumed. In addition, the primary site of infection, the conjunctiva for H7 virus and the airway epithelium for H5 and H9 virus, and the possible difference in virus receptor expression on the conjunctiva and the airway epithelium together with the difference in affinity of the respective viruses for these receptors, may also account for the observed differences.

Although sharing bath towels and washcloths, and using cloth handkerchiefs seemed to increase the risk of clinical conjunctivitis, none of these observations was statistically significant, presumably due to lack of study power. However, it seems plausible to assume that patients with a viral conjunctivitis are more likely to expose household members to virus when sharing towels and washcloths or using cloth handkerchiefs. This is supported by our observation of higher seroprevalence among people using cloth handkerchiefs and of lower seroprevalence among those using paper (disposable) handkerchiefs, all of which were statistically significant. Studies on transmission of other viral conjunctivitis within households identified crowding and high numbers of persons per bathroom as risk factors [17, 18, 19, 20,21].

Seroprevalence was significantly higher among those who had at least two toilets in their homes than among those who had only one toilet. We have no explanation for this result. Hygienic measures, such as using soap for handwashing and good hygiene by the index case, associated with seropositivity were of borderline significance.

Although we observed higher seroprevalence in those household members who had pet birds kept indoors at home, this cannot account for all seropositive secondary cases, as only 7 of all 33 cases had indoor birds at home. However, this finding raises the question of whether indoor pet birds could play a role in the household transmission of avian influenza virus, especially since six of seven cases with pet birds in the home were part of the same household. It is conceivable that these animals could serve as an amplifier for multiplication and shedding of the virus in the home environment. This deserves further attention in future outbreaks, for example, by monitoring and screening pet birds in the homes of poultry workers.

It was not possible to perform binomial regression for the outcome of A/H7N7 infection, presumably due to low numbers in the cohort.

If the detection of H7 antibodies is indicative for human (subclinical) influenza A/H7N7 infection, then the secondary spread of A/H7N7 to household contacts is on an unexpectedly large scale. Although the pathogenicity of the A/H7N7 virus seemed to be low, the high transmissibility is directly related to an increased risk for double infection and reassortment. Current outbreak control measures did not take transmission to household contacts into account. This also raises the question of whether or not subclinical A/H7N7 cases can transmit the virus efficiently to other close contacts, which would imply that outbreak control strategy for A/H7N7 should be thoroughly revised. Consideration may be given to early isolation of cases and quarantine of contacts. Prophylactic treatment with oseltamivir should be considered for all household contacts of poultry workers during outbreaks of avian influenza, although its role must be further assessed in order to determine the risk of developing antiviral resistance. Moreover, in order to assess the role of fomites in secondary transmission of the A/H7N7 virus, further studies of contacts outside the household should be performed, as well as investigations to obtain background information on the spread of A/H7N7 in the general population of the Netherlands.

The study had the following limitations. Non-response was high and may be associated with rates of illness (selection bias), but we see no reason why it would have differed between exposed and non-exposed members of the cohort, therefore not biasing the estimate of the risk ratios. However, selection bias is not likely to play a major role with respect to seroprevalence, since most household members with detectable antibodies were asymptomatic.

In conclusion, our study suggests that human-to-human transmission of HPAI A/H7N7 can occur within household contacts in the absence of contact with infected poultry. Monitoring of clinical symptoms alone in household contacts of confirmed A/H7N7 cases underestimates the extent of human-to-human spread. In addition, our results suggest that cloth handkerchiefs, having indoor pet birds at home or having at least two toilets at home could be risk factors for household transmission A/H7N7 .

Taking all the results together, we recommend that during an outbreak of avian influenza: 1) Household members should be encouraged to use paper handkerchiefs instead of cloth handkerchiefs; 2) Household members of poultry workers exposed to A/H7N7 should be advised on enhanced general hygiene measures; 3) In the case that oseltamivir prophylaxis is offered to exposed poultry workers in future A/H7N7 epizootics, this should also be considered for household members of A/H7N7 cases; 4) Indoor pet birds of poultry workers should be screened and monitored during future outbreaks of avian influenza, in order to determine the role of indoor birds in household transmission of the virus; and 5) Further seroprevalence studies among contacts of asymptomatic persons with positive H7 serology should be conducted in order to assess the risk of person to person transmission, and consequently the potential for a new pandemic strain, in the absence of symptoms.

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ORIGINAL ARTICLES

Outbreak report

LATE DETECTION OF A SHIGELLOSIS OUTBREAK IN A SCHOOL IN MADRID

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Even though shigellosis in Spain is rare, an indigenous outbreak is occasionally detected. We describe an outbreak in a school in Madrid caused by person-to-person transmission of *Shigella sonnei*. After the detection of *Shigella sonnei* in a stool sample from a 3 year old girl, an investigation at her school was initiated. Questionnaires were distributed to the parents of 520 pupils attending the school. A case was defined as a school case if it was the first case in a child's household, and as a household case if other members of the household had fallen ill first.

We identified 88 cases (60 pupils and 28 of their family members). The attack rate (AR) was 12% in the school and 32% in the families. There was a significant association between higher AR and lower age. The outbreak lasted for two months. The length and the shape of the epidemic curve of the 60 cases in pupils suggests person-to-person transmission. *Shigella sonnei* isolated from 5 different cases were typed by pulsed field gel electrophoresis (PFGE) and was found to be an identical strain. The prolonged duration of the outbreak was probably due to delayed detection, and stopped as soon as control measures were introduced.

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Key words : *Shigella sonnei*, outbreak, person-to-person transmission

## Introduction

On 31 May 2004, *Shigella sonnei* was isolated from a stool sample of a 3 year-old girl with gastroenteritis attending a school in Madrid. Our initial contact with the school identified 20 additional pupils with similar complaints during the month of May, most of them in children aged 3-5 years.

The school includes all levels from pre-school to secondary school, and also has a kindergarten. There are two classes in each year with 25 to 30 pupils in every class. The distribution was 148 pupils in preschool, 312 in primary school and 60 in the first year of secondary school.

Shigellosis in Spain has decreased markedly from about 1%-5% of all stool sample isolates in the 1980s [1,2] to less than 1% in the late 1990s [3,4]. Most of the cases reported are in travellers returning from developing countries [5]. Most sporadic non-imported waterborne [6,8] or foodborne [9] outbreaks, and some outbreaks transmitted by person-to-person-spread [10] are detected.

Shigellosis is an invasive infection of the colon that is spread by the faecal-oral route. The low infective dose (10-100 bacteria) favours a high transmissibility. The incidence is high in developing countries and affects children more than adults [11]. In contrast to most other enteropathogens, the only reservoir of *Shigella sp.* is humans [12].

We conducted an investigation to confirm the existence of an outbreak and to identify the source and mode of transmission, in order to prevent the occurrence of more cases.

## Methods

### 1. Case finding

To identify cases among pupils and their families, we distributed a questionnaire to the parents of all pupils in preschool (3-5 years), primary school (5-11 years) and first year of secondary school (11-12 years). The questionnaire collected information about the occurrence of gastroenteritis in their children since 15 April 2005.

Additionally, parents of pupils with gastroenteritis according to the questionnaires were interviewed by telephone to identify other cases among household members and collect their date of onset.

At our first visit at the school we contacted the parents and the physicians of pupils who were absent on that day due to gastroenteritis to make sure that stool samples were collected and antibiotic treatment considered.

### 2. Case definition

We defined a probable case as:

Any pupil at the school or anyone in their households who had acute onset of diarrhoea (>3 loose stools/day) after 15 April 2004 lasting for at least 3 days and at least two of the following symptoms:

- Blood and/or mucus in stool
- Fever (>38°C)
- Abdominal pain

A confirmed case was a probable case with *Shigella sonnei* isolated from a stool sample. A case in a pupil was defined as a school case if it was the first case in the child's household. A household case was a case with date of onset after a school case had occurred in that household within the week before onset of symptoms.

## 3. Epidemiological study

We performed a descriptive analysis and calculated attack rates per educational level and in households.

## 4. Laboratory investigations

Stool cultures from some probable cases were performed according to standard methods [13]. Resistance to antibiotics was assessed using the minimal inhibitory concentration (MIC) of ampicillin, amoxicillin/clavulanic acid, cefotaxime, ceftazidime, nalidixic acid, ciprofloxacin, chloramphenicol, trimethoprim-sulfamethoxazole and tetracycline, determined by E-test (AB Biodisk, Izasa, Spain). For genotyping by pulsed field gel electrophoresis (PFGE) to identify the infective strain, the restriction enzyme *XbaI* (Roche, Spain) was used, following the agreed protocol from the Salm-gene project [14]. PFGE profiles were assigned to pulse types on the basis of one or more band differences between strains.

## 5. Environmental investigations

We visited the school to look at distribution and condition of toilets and canteens. No environmental samples were taken.

## Results

The outbreak lasted two months [FIGURE]. Several clusters in time suggest waves compatible with person-to-person transmission.

When the first notification was received, 40 cases had already occurred in the school.

We distributed 520 individual questionnaires to parents of pupils at the school. Among the pupils 60 cases (54 probable and 6 confirmed) were identified (Attack Rate (AR) = 12%), in 34 boys and 26 girls.

Of these 60 cases, 47 were defined as school cases and 13 as household cases [TABLE 1]. Of the 47 school cases, 25 caused between one and three more cases in a total of 130 household members exposed. Forty one of the 130 exposed household members met the household case definition (including the 13 household cases among pupils), with an AR in households of 32%). The mean incubation period was 5 days and the median 3 days (range = 0-7).

TABLE 1

Distribution of school cases and household cases among pupils and their household contacts, outbreak in a school in Madrid, April-June 2004

	School cases	Household cases	Total
Pupils	47	13	60
Household contacts	0	28	28
<b>Total</b>	<b>47</b>	<b>41</b>	<b>88</b>

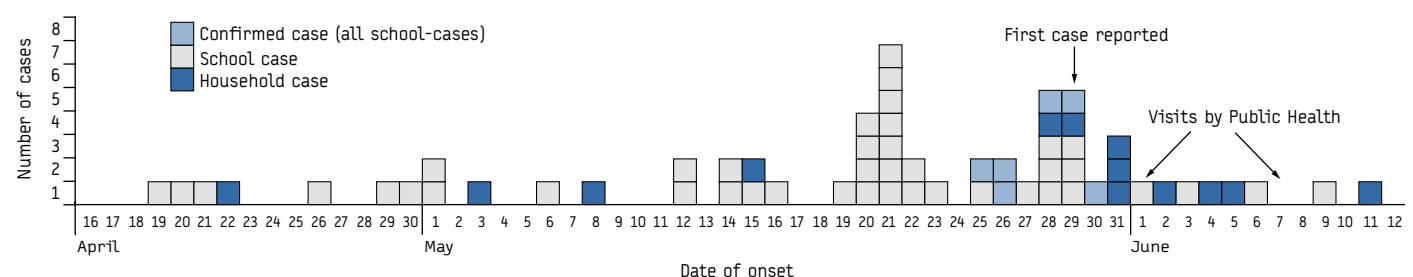
Of the 25 cases that caused secondary cases in their households, 24 were preschool pupils.

No cases were identified in teachers and there was no indication of spread to the community beyond the pupils' households.

The most frequent symptoms were diarrhoea (100%), fever >38°C (98%), abdominal pain (92%), nausea or vomiting (62%) and blood

FIGURE

Epidemic curve of shigellosis, outbreak in a school in Madrid, April-June 2004



or mucus in stool (51%). The duration of symptoms ranged from 3 to 14 days with a mean of 7 days. One pupil was admitted to hospital.

The AR was higher in lower educational level [TABLE 2]. Only one case occurred in a secondary school pupil. Using this as a reference, the risk ratio (RR) in primary school level was 2.8 (95% CI: 0.4-21.4) and in preschool 17.5 (95% CI: 2.5-126.6).

TABLE 2

**Incidence and risk ratio (RR) of shigellosis according to educational level, outbreak in a school in Madrid, April-June 2004**

Educational level	No. of pupils	No. of cases	Incidence (%)	RR	95% CI
Secondary school	60	1	1.7	Ref.	
Primary school	312	15	4.8	2.8	0.4-21.4
Preschool	148	44	29.7	17.5	2.5-126.6
<b>Total</b>	<b>520</b>	<b>60</b>	<b>11.5</b>		

Eight faecal samples were taken for culture from the 60 cases in pupils, and *Shigella sonnei* was isolated from six of these. Five of the isolates were phenotyped and genotyped. They all corresponded to phase I of *Shigella sonnei* serotype D and had identical profiles of susceptibility. The typing by PFGE of these five strains confirmed that they were identical and different from other strains analysed at the same time.

When visiting the school we found that preschool pupils (3-5 years) had separate toilets from the older pupils, and were not always accompanied to the toilet by members of staff. The toilets had textile towels for shared use.

We recommended ensuring that the youngest pupils were always accompanied to the toilets by members of staff, replacing the textile towels with disposable paper towels, and emphasising to the children the importance of proper hand washing after using the toilets. We also recommended making sure that any pupil with diarrhoea remained at home until the symptoms had resolved completely. There was a follow-up visit one week later to ensure that the recommended measures had been implemented.

After the second visit to the school, only two further cases occurred in pupils. The last case was defined as a household case. The school closed for the summer holidays on 22 June, and no further cases were registered during the last 11 days of term.

### Discussion

This outbreak of shigellosis had been occurring for more than a month before it was detected but ceased as soon as control measures were installed.

The suspicion of a common source was discarded since the epidemiological curve suggests person-to-person transmission. It is possible that cases with mild symptoms, excluded by the case definition, still contributed to spread.

Shigellosis usually shows a higher attack rate in children than in adults [8] and children under 4 years of age are most susceptible [10]. Outbreaks in school settings, mainly in preschool age groups, are relatively frequent [10, 15] with an attack rate of secondary cases in their household contacts that may reach 40% [16, 17].

The household attack rate is in concordance with other studies [15, 16] and confirms a person-to-person transmission even outside the school setting.

The distribution of the school cases according to educational level suggests different exposures at different levels. We did not consider an observational study of children's behaviour in the toilets necessary to deduce that it was likely to be related to the less well-developed hygiene habits of younger pupils who had their own toilets not shared with the older pupils. Of the 25 cases causing secondary cases in the pupils' households, all but one were in preschool pupils, which supports our theory of age and hygiene.

The isolates of *Shigella sonnei* from five different patients had similar patterns of antibiotic susceptibility. The molecular typing results confirmed that they were identical. Cases' symptoms were relatively severe compared with previous outbreaks of shigellosis in Spain [6], with 50% of the cases having dysentery and a high percentage having fever, abdominal pain and vomiting.

Initially, the existence of an outbreak was not evident since the person-to-person transmission did not cause an accumulation of cases. Stool samples were not taken, hence the absence of specific treatment and delayed installation of control measures that contributed to the dissemination of the infection [18]. In contrast with gastroenteritis caused by other bacteria, antibiotics are usually indicated in shigellosis, to reduce contagiousness.

In Spain, shigella infection is notifiable by laboratories. If paediatric physicians can be encouraged to take more samples, outbreaks could be detected more rapidly.

Controlling outbreaks of shigellosis requires timely reporting so that close contacts of a case can be informed of the need for strengthened hygiene, and when outbreaks occur in a school setting, it is important that ill children stay at home until their diarrhoea has ceased completely [15].

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**OUTBREAK OF VEROTOXIN PRODUCING *E. COLI* O157 INFECTIONS INVOLVING OVER FORTY SCHOOLS IN SOUTH WALES, SEPTEMBER 2005**

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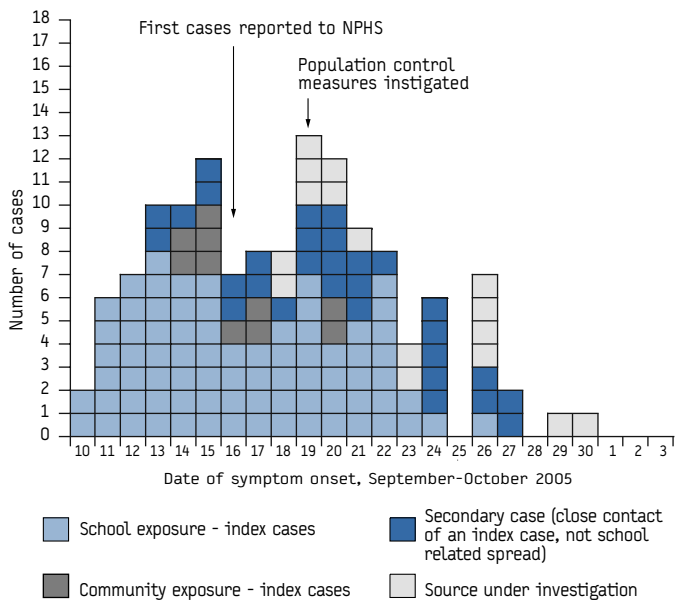
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(<http://www.eurosurveillance.org/ew/2005/051006.asp#1>)

By 3 October 2005, 157 cases of infection had been reported in an outbreak of verotoxin producing *Escherichia coli* (VTEC) O157 in south Wales in the United Kingdom [1,2]. A case was defined as any person living in south Wales who presented with bloody diarrhoea or had a faecal isolate of presumptive VTEC O157 in September. Ninety seven of the cases have been microbiologically confirmed as VTEC O157, and all are phage type (PT) 21/28 and produce verotoxin (VT) 2, with the exception of one case that is PT32 VT2. Four other microbiologically confirmed cases of *E. coli* O157 infection have phage types not associated with the outbreak (three VT-negative strains of PT1, and one isolate of PT8, VT1+2), and have been excluded from the outbreak case list because the patients have plausible alternative histories to explain their infection.

Sixty seven males and 90 females are affected, and 65% of cases (102/157) are in children of school age. Dates of symptom onset range from 10 to 30 September (Figure), and over forty schools have recorded cases. There has been one death, in a 5 year old boy.

**FIGURE**

**Cases of VTEC O157 infection with known date of onset, outbreak in south Wales, September 2005 (n=133). Source: National Public Health Service for Wales, 4 October 2005**



Evidence suggests a link between the outbreak and a supplier of cooked meats to the school meals services. The distribution of cases is small numbers of cases in a large number of schools, and suggests a centrally distributed product with low levels of contamination rather than a problem in individual schools. This was followed by secondary person-to-person spread.

Ten of the first 18 primary cases in infected schoolchildren with early symptom onset dates before 17 September were contacted between 16 and 20 September. All reported having eaten lunch in the school canteen, compared with 8 out of 13 controls who were selected at random from the school register (p<0.05). Overall, approximately 60% of children in the affected areas eat lunch in their school canteens each day.

A single main supplier distributes cooked meats to the affected

schools. Local authorities took action on 19 September, after identifying practices that could result in contamination of cooked meat at the supplier's premises, and the Food Standards Agency Wales issued a food alert on 21 September [3].

*E. coli* O157 has been isolated from three samples of sliced cooked meat obtained by environmental health staff. Isolates have been confirmed as PT21/28, VT2 and examined by pulsed field gel electrophoresis (PFGE). Results on cultures from two samples have so far shown that PFGE profiles of strains from the food samples are indistinguishable from those found in people with the infection. PFGE typing is continuing on the third strain. Contaminated cooked meats have been associated with previous outbreaks of VTEC O157 infection in the United Kingdom [4,5].

Control measures to remove ready-to-eat foods (that is, foods not cooked on the premises) from schools, and to cancel educational activities that facilitate person-to-person spread, have been in place since the week beginning 19 September and are under constant review by the outbreak control team.

*This article has been adapted from reference 2.*

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**CHOLERA IN BELGIAN TOURISTS AFTER TRAVEL TO TURKEY**

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Two confirmed and four probable cases of cholera have been reported in Belgian tourists returning from travel to Turkey. On 22 September 2005, the Gezondheidsinspectie (Health Inspectorate) in Antwerp was notified of the isolation of *Vibrio cholerae* in stool sample from a 62 year old woman. She was admitted to hospital in Antwerp on 17 September immediately after returning from a trip to Turkey, with watery diarrhoea, dehydration and renal failure. The clinical picture was initially unclear because she had undergone stomach surgery to treat cancer not long before the tour. The patient was admitted to hospital for four days and was treated with quinolones. Further testing confirmed infection with *V. cholerae* O1 biotype El Tor, serotype Inaba.

After notification of this case, an investigation was begun to collect epidemiological information, ascertain any other potential cases, identify the source and coordinate control measures. All tour group members were interviewed about potential exposures during the trip.

A second female patient had contracted severe gastrointestinal symptoms on 18 September. She was treated as an outpatient. A stool culture was also positive for *V. cholerae* O1. She was treated with quinolones and recovered. Four other patients, two men and one woman, contracted severe gastroenteritis shortly after their return. They were seen by their general practitioners and were treated with symptomatic therapy. Stool cultures were performed after these patients

had recovered and did not grow *V. cholerae*. All patients recovered after four days. No secondary cases were detected. The attack rate for the tour group was 6/8 (75%).

The tour group had travelled around west Turkey on a 14 day package tour. Group members, three men and three women, were aged between 58 and 68 years. They used a private bus, and at the end of their trip, they took an internal flight from Ankara to Istanbul.

During the journey they stayed at different hotels and visited Istanbul, Bursa, Efeze, Afrodiasias, Pamukkale, Kusadasi, Antalya, Cappadocia, Ilhara and Ankara. They ate in several small restaurants and also ate food bought at markets and shops. During the internal flight, a salad was served.

### Control measures

All tour group members were informed of the risks, and advised to contact their general practitioner and provide a stool sample. General practitioners were advised about treatment and follow-up. Patients were advised to limit their contacts and to apply hygienic measures to prevent further transmission. Patients were not automatically admitted to hospital nor systematically treated with antibiotics. The World Health Organization (WHO), the Turkish health authorities and the European Early Warning and Response System (EWRS) were informed immediately after detection of the cases.

### Discussion

Cholera is an acute bacterial enteric disease caused by an infection with *V. cholerae*, serogroup O1 or O139. *V. cholerae* includes two biotypes - the classical type and El Tor type. Each biotype has 3 serotypes (Inaba, Ogawa, and rarely Hikojima). Cholera may be present in an asymptomatic state, as a mild disease or as the typical syndrome characterised by a sudden onset and profuse, painless, watery diarrhoea. The incubation period varies from a few hours to five days and patients are infectious while they have diarrhoea and up to 7 days after [1,2].

Databases of cholera cases reported to the WHO last recorded cholera cases in Turkey in 1977, and no data was supplied from 1978-1992. To date, there have been no other recent cases of cholera reported from Turkey [3].

Only the two patients confirmed to have cholera were treated with antibiotics. The other patients received symptomatic treatment and recovered quickly. The patients had only a few contacts, and were not working on or participating in activities which could have facilitated secondary transmission.

The attack rate was rather high (75%). A seventh patient developed minimal diarrhoea five days after return from Turkey but was not considered as a probable case. The high attack rate probably represents a high infective dose and there could potentially be other cases in Turkish residents or in visiting tourists. There are unofficial reports of cholera outbreaks in countries in the region surrounding Turkey, such as Iran, Tajikistan and Afghanistan. [4,5,6]

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## SALMONELLA TYPHIMURIUM DT104 OUTBREAK LINKED TO IMPORTED MINCED BEEF, NORWAY, OCTOBER – NOVEMBER 2005

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3. Norwegian Food Safety Authority, Oslo, Norway

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(<http://www.eurosurveillance.org/ew/2005/051110.asp#1>)

### Outbreak alert

On 3 November 2005, four cases of multidrug-resistant *Salmonella* Typhimurium DT 104 infections were notified to the Infectious Disease Epidemiology Department by the Reference Laboratory of the Norwegian Institute of Public Health. The four isolates had identical multi-locus VNTR analysis (MLVA)-profiles (2-7-11-7-3) and antimicrobial resistance pattern (Amp-Chlor-Tet-Sulph-Strep-Nal). The same MLVA profile and resistance pattern was also detected in a routine sample of mixed meat that consisted of both Norwegian meat and meat imported from Poland. Further testing of unmixed samples showed salmonella growth only in the imported meat. This isolate was subsequently confirmed to have the same MLVA profile as found in the cases. Since sporadic infections by multidrug-resistant *S. Typhimurium* are very rare in Norway [1], detection of these cases prompted an immediate investigation.

### Outbreak investigation

Three of the four patients were interviewed on 4 November to determine the time of symptom onset, illness duration and exposure history during the week before illness onset. These patients became ill between 2 September and 2 October and did not report any recent travel outside Norway before onset of symptoms. All three patients reported eating minced beef before becoming ill, and all of them tasted raw meat during food preparation. The beef product was bought frozen at national supermarket chain A during September. This information was immediately communicated to the Norwegian Food Safety Authority, which started tracing of the suspected beef. On 8 November, another patient was confirmed to have a salmonella infection with an MLVA pattern identical to one found in the index patients. This patient became ill on 7 October and also consumed the suspected meat.

An urgent enquiry was sent through the Enter-net network on 4 November and an alert was posted on the European Early Warning and Response System on 5 November. In response, Denmark reported two cases of *S. Typhimurium* DT104 with identical MLVA-profile and resistance pattern, one in a patient who had travelled to Poland. Some other countries have also reported cases of *S. Typhimurium* DT104 with the same resistance pattern. However, this is a relatively common type and further investigation and typing are needed in order to assess a possible link to the outbreak in Norway.

### Product tracing and recall

The investigation indicated that the implicated beef was imported from Poland in June 2005. The consignment was accompanied by documentation that the batch had been controlled for salmonella and tested negative. The consignment was divided in three parts by the importer. The first part was sent to supplier 1, who took a routine sample of the meat. This sample tested positive for salmonella and had an MLVA profile indistinguishable to that of the cases. This meat was not released to the market. The second part of the original consignment was delivered to supplier 2 that produced minced beef and subsequently distributed it in frozen 400 gram packages in September and October via supermarket chain A. The remaining part of the initial shipment was stored by the importer; testing of this meat recovered *S. Typhimurium* DT104 with the same MLVA profile. Another sample was obtained from leftover frozen minced beef that was stored in a freezer of one of the cases: testing of this sample is pending. Based on epidemiological and microbiological data, the imported meat used for preparation of minced beef was suspected to be the source of this outbreak and the product was recalled from the market on 5 November. In addition, an announcement through mass media was made on the same day to warn the public not to consume this meat.

## Discussion

The outbreak investigation implicated imported raw beef as the source of the outbreak. The beef was processed into minced meat in Norway, and subsequently distributed for sale via a national supermarket chain. The outbreak probably occurred over several weeks and since only a limited number of people were affected, it is possible that cooking the meat may have inactivated the bacteria, thereby preventing more cases. The product was recalled from the market according to zero tolerance policy for salmonella based on the National Food Law. Each year, approximately 1500–2000 cases of salmonellosis are reported in Norway, of which approximately 75–80% acquired infection abroad [3]. The National Salmonella Control Programme documented that cattle, swine, and poultry in Norway as well as domestically produced food products of animal origin are virtually free from salmonella [2]. Therefore, similarly to Finland and Sweden, Norway has negotiated the agreement requiring documentation of salmonella testing of meat and egg imports from EU countries [3]. The meat implicated in this outbreak was also accompanied by such documentation.

The application of MLVA typing method has been critical in both detecting this outbreak and determining the source. The MLVA method has been used as a routine typing tool for *S. Typhimurium* isolates received by Reference Laboratory of the Norwegian Institute of Public Health since 2004 [4]. This laboratory routinely receives all salmonella isolates from human, animal, food and feed samples for further typing. In comparison with PFGE gels, the MLVA fingerprinting method is fast and easy-to-use providing high-resolution discrimination between *S. Typhimurium* DT104 isolates, which are often genetically similar. Since *S. Typhimurium* DT104 is commonly isolated, it may be difficult to detect differences in strains with the use of another typing technique. Therefore, the MLVA method may be a valuable tool in determining the source of the outbreak. Moreover, the easy strain identification makes it possible to rapidly share results between countries in case of outbreaks. The detection of this outbreak through application of molecular methods highlights the importance of genetic characterisation of human and food isolates in order to identify possible clusters. The presence of an established system for tracing of food products facilitated a rapid recall of the implicated meat.

## Acknowledgements

We would like to thank all patients and health personnel that contributed to this investigation. We are also grateful to the Statens Serum Institute in Denmark for collaboration.

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## MALARIA CASES AND DEATHS IN UK TRAVELLERS RETURNING FROM THE GAMBIA

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Six cases of falciparum malaria have occurred in United Kingdom (UK) travellers who have recently returned from The Gambia [1]. Two patients are known to have died, and a further two are seriously ill. The patients, aged between 31 and 61 years, all returned to the UK and became ill in the second half of November 2005. Five had been on holidays lasting between one and two weeks, all in resorts within 20km of the Atlantic coast, with some patients having been on fishing or bird-watching excursions. The sixth patient had visited The Gambia several times on business and had travelled a little further inland than the other patients. All of the patients had taken either no or inadequate chemoprophylaxis.

The Gambia is a popular 'winter sun' destination for UK travellers, who account for nearly half of all tourist visits to the country [2] (around 30 000 UK tourists visited The Gambia in 2004 [3]). Malaria is highly endemic in The Gambia, with year-round transmission and over 100 000 cases reported annually in local residents [4].

*Plasmodium falciparum* is the most common type of malaria in The Gambia, and accounts for over 90% of cases in travellers returning to the UK from The Gambia. Falciparum malaria is the most severe form of the disease, and can rapidly progress to serious illness and death. Nearly 4% of falciparum malaria cases in travellers returning from The Gambia (2000–2004) were fatal.

Over the past six years, the annual number of cases in travellers returning to the UK from The Gambia has decreased, but the case fatality rate has increased (Table). Most cases of *P. falciparum* malaria were in travellers who did not take chemoprophylaxis.

## FIGURE

Total numbers of *Plasmodium falciparum* malaria cases in travellers returning to the UK from The Gambia, reported to the UK Malaria Reference Laboratory, compared with reported cases acquired in all countries worldwide, 2000–2005 [5]

Year	Cases returning from The Gambia				
	Cases from all countries	Number of cases (% of all cases)	Number of Deaths	Case fatality rate	Percentage known to have taken prophylaxis*
2000	1576	121 (7.7)	4	3.3%	38.0%
2001	1576	74 (4.7)	1	1.4%	25.7%
2002	1469	46 (3.1)	2	4.3%	32.6%
2003	1339	48 (3.6)	3	6.3%	6.3%
2004	1221	31 (2.5)	2	6.5%	19.4%
2005**	855	8 (0.9)	1	12.5 %	30.0%

\* The denominator is all falciparum case reports from The Gambia, including those where prophylaxis status was unknown

\*\* To end of August 2005. Please note that the main holiday season to The Gambia from the UK is during the UK winter months

Travellers to the Gambia and other malarious countries should seek medical advice on appropriate measures before travelling. The risk of malaria can be reduced by taking appropriate chemoprophylaxis, and by bite avoidance through suitable clothing, insect repellents and bed nets [6].

There is significant chloroquine resistance in The Gambia, so chloroquine (which can be obtained without prescription in the UK) is not recommended as chemoprophylaxis [7]. According to UK guidelines, travellers should instead use atovaquone/proguanil (Malarone), or doxycycline or mefloquine (Lariam). These regimes are only available on prescription, and doxycycline or mefloquine should be started at least one week before travelling. Full details are available in the 2003 UK guidelines [8], and the UK National Travel Health Network and Centre (<http://www.nathnac.org>) can provide up-to-date advice to clinicians on travellers with complex medical needs or travel itineraries.

Organising preventive measures, medical advice and prescriptions may be difficult when holidays are booked at short notice, and a cluster of cases were reported in the UK in December 2003 associated with trips to The Gambia that had been booked shortly before departure [9]. 'Late booking' holidays are increasingly available through internet-based travel companies.

The Federation of Tour Operators and Association of British Travel Agents have been informed about these cases. They are taking steps to alert their members about this issue, and the need to remind travellers to malarious areas to seek medical advice prior to departure.

This series of cases in people returning from The Gambia is associated predominantly with tourism. However, most malaria cases in the UK occur in former residents of malaria-endemic countries, mainly West Africa, who return home to visit friends or family [10]. Most have not taken appropriate chemoprophylaxis. All travellers to such areas, irrespective of where they were born, should take medical advice and appropriate preventive measures to reduce their risk of malaria.

Travellers who fall ill following a visit to a malarious area should seek prompt medical attention, and be aware that malaria can present up to a year or more after return [10]. Healthcare professionals should always take a travel history from anyone with a fever or flu-like illness, and be aware that absence of fever does not exclude the diagnosis of malaria. If the travel history includes travel to a malarious area in the previous year, blood films should be examined without delay.

*This article is adapted by the authors from reference 1.*

## SHORT REPORTS

### FIRST ISOLATION OF *CLOSTRIDIUM DIFFICILE* PCR RIBOTYPE 027, TOXINOTYPE III IN BELGIUM

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Outbreaks of diarrhoea due to *Clostridium difficile* ribotype 027, toxinotype III have been reported in North America, United Kingdom, and the Netherlands [1-4], and this toxinotype has also been isolated from patients in Belgium. Recently, it has been suggested that the severity of the disease is associated with hyperproduction of toxins A and B by this new variant strain [5].

By 19 September 2005, four patients in the Jan Yperman hospital in Leper, southwest Belgium, had been infected. There was one death due to complications of *C. difficile*-associated diarrhoea and an underlying condition. All patients were female, aged over 70 and had spent longer than 2 weeks in hospital. Two patients were treated with quinolones, a third patient with a betalactam antibiotic and the fourth patient, who had a milder form, received no antibiotics at all. In the Jan Yperman hospital, the incidence of *C. difficile*-associated diarrhoea increased from 10 per 10 000 admissions in January – August 2005 to 33 per 10 000 patient admissions in September 2005.

The strain was characterised as PCR ribotype 027 and toxinotype III at the reference laboratory at Leiden University Medical Center. It also contained the binary toxin and had an 18bp deletion in a toxin regulator gene (*tcdC*). As determined by E-tests, the isolates were resistant to ciprofloxacin (MIC>32 mg/l) and susceptible to clindamycin (MIC=2 mg/l) and metronidazole (MIC=0.19 mg/ml). These characteristics are similar as the strain that has been isolated from outbreaks in the United States, Canada, the UK and the Netherlands.

Contact tracing did not reveal the origin of this strain. The hospital has taken additional infection control measures and used the guidelines recently published by Centre for Infectious Disease Control at the National Institute for Public Health and the Environment (RIVM) in Bilthoven (<http://www.rivm.nl>). Subsequently, the Health

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Inspectorate and the Clostridium Reference Centre in Brussels, Belgium, were informed.

## Acknowledgements

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### RUBELLA OUTBREAK IN AN UNVACCINATED RELIGIOUS COMMUNITY IN THE NETHERLANDS LEADS TO CASES OF CONGENITAL RUBELLA SYNDROME

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The first children with congenital rubella syndrome (CRS) associated with the recent rubella outbreak in the Netherlands [1] have been born. During the outbreak, which started in September 2004, 387 serologically confirmed cases of rubella were notified. The most recent postnatally acquired case had an onset date around mid-September, suggesting that circulation of the virus has now ended. The geographical location of the outbreak closely matched areas of low vaccine coverage (see [http://www.rivm.nl/vtv/object\\_map/o1503n21466.html](http://www.rivm.nl/vtv/object_map/o1503n21466.html)). The rubella outbreak predominantly affected an

unvaccinated religious community [1]. In the beginning of 2005, the outbreak spread to a Canadian community with historical, religious and social links with the affected Dutch community [2].

Postnatally acquired rubella is generally mild. However, rubella acquired during early pregnancy can lead to severe birth defects known as congenital rubella syndrome (CRS). CRS may occur in 90% of infants born to mothers who were infected in the first ten weeks of pregnancy [3].

During the rubella outbreak in the Netherlands, 29 women were reported to have been infected with rubella virus during their pregnancy. None of these women were vaccinated and all belonged to the orthodox religious community affected by the outbreak. To date, 16 children are known to have been born out of these pregnancies; one pregnancy ended in intrauterine death. Serology results at birth are available for all of these children. Of the 16 children, eight were IgM negative and eight were IgM positive. In addition, one IgM positive child was reported whose mother had not been notified as a rubella patient. Results of virus propagation and PCR are not yet complete. Of the nine IgM positive children, three had multiple serious defects at birth including microcephaly, cerebral calcification, hepatosplenomegaly, cardiovascular and auditory defects; one child was reported to have only auditory defects. After completing the collection of clinical data on these children, World Health Organization case definitions for CRS [4] will be applied. The remaining five children who tested IgM positive, and all eight IgM negative children, were reported to be healthy at birth.

Further cases of CRS associated with this outbreak are expected, emphasising the important public health impact of this rubella outbreak and the need to find ways to protect women of childbearing age. Enhanced surveillance for CRS is carried out by the National Institute for Public Health and the Environment (RIVM) in collaboration with municipal health authorities and the Netherlands Paediatric Surveillance Unit (NSCK).

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## TRANSMISSION OF HIV/AIDS IN EUROPE CONTINUING

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The transmission of HIV/AIDS continues in Europe, according to the 2004 annual surveillance data released by the European Centre for the Epidemiological Monitoring of HIV/AIDS (EuroHIV; <http://www.eurohiv.org>) [1]. HIV/AIDS remains a major public health issue in Europe, with increasing numbers of people living with HIV [2]. The nature of the epidemic and its implications for public health policies varies in different countries [3,4]. Within the European Union, sexual transmission of HIV, both heterosexual and homosexual, continues to dominate.

### Continued HIV transmission in the WHO European Region

In 2004, 71 755 new diagnoses of HIV were reported in countries in the World Health Organization (WHO) European Region (which includes all European Union (EU) countries). This number is similar to the number reported in 2003 (72 843). The number of newly

diagnosed cases in 2004 is lower than the peak observed in 2001 (113 930 cases), but is nearly twice the number of reports in 1999 (39 602). Four countries reported rates of more than 200 new HIV diagnoses per million of the population in 2004: Estonia (568), Portugal (280), the Russian Federation (239) and Ukraine (212).

In 2004, 10 855 AIDS cases were reported in the WHO European Region, slightly lower than the number reported for 2003 (11 633). While AIDS incidence has been declining in Europe as a whole, it has increased continuously in eastern Europe and for the first time in 2004 has exceeded that of the west (27.4 versus 19.5 per million).

### Trends in the European Union

In 23 of the 25 EU countries (national data not available for Italy or Spain), 21 164 newly diagnosed cases of HIV were reported in 2004 (a rate of 59 per million). Between 2001 and 2004, there was a 23% increase in the annual number of newly diagnosed HIV cases, up from 14 028 in 2001 to 17 281 in 2004 (data available for 20 countries: to compare 2001 data with 2004, some countries had to be excluded). The largest relative increases have been reported in western EU countries (43% in 11 countries and 69% in the United Kingdom) and 17% in central European countries. In contrast, there was a marked relative decrease in reports from the Baltic states in 2004 (-49%) following the high number of new diagnoses in 2001 in Estonia and Latvia associated with injecting drug use. Numbers of new diagnoses in the Baltic states remain relatively high, despite the decrease.

### Risk groups in the European Union

In the European Union, the majority of newly diagnosed HIV cases in 2004 for which transmission route was reported (data missing for 23%) were infected through heterosexual contact (9059, 56%). Nearly a third of cases (4975, 31%) were in homo/bisexual men and 12% (1961) were in injecting drug users. Since 2001, there has been an increase in the number of cases with a reported heterosexual transmission group (48%), especially among individuals originating from countries with generalised epidemics, and amongst homosexual and bisexual men (35%). There has been a decrease among injecting drug users (31%).

The importance of appropriate and timely surveillance data to support and develop policies for the prevention and control of the HIV epidemic in Europe remains. In the European Union, the predominant mode of transmission is heterosexual, although many of the individuals infected this way may have acquired their infection outside Europe [5]. Prevention and care programmes must be adapted to reach these populations. Despite the continued promotion of safer sex amongst homosexual and bisexual men, the number of HIV reports has increased since 2001, and emphasises the need for innovative and better targeted health promotion campaigns also in this community.

*This EuroHIV report is dedicated to the memory of Andrea Infuso, project leader of EuroTB and a dear and respected colleague and friend, who died suddenly on 20 September 2005 at the age of 44.*

*The author would like to clarify that the HIV data reported in the article is by year of report, not diagnosis.*

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2018 Antwerpen  
*Quarterly, print and online versions available.*  
*In Dutch.*  
<http://www.vlaanderen.be/epibu/>

*Infectious Diseases in the Spotlights*  
Institut Scientifique de la santé Publique Louis Pasteur  
14, rue Juliette Wytsman  
B-1050 Bruxelles  
*Weekly, online only. In English.*  
[http://www.iph.fgov.be/epidemio/epien/plaben/idnews/index\\_en.htm](http://www.iph.fgov.be/epidemio/epien/plaben/idnews/index_en.htm)

**Bulgaria**

Epidemiological Surveillance  
National Centre of Infectious and Parasitic Diseases  
26 Yanko Sakazov Blvd.  
Sofia 1504  
*Print version available, online version available soon. In Bulgarian, titles translated into English.*  
<http://www.ncipd.org/bulletin.php>

**Cyprus**

Newsletter of the Network for Surveillance and Control of Communicable Diseases in Cyprus  
Medical and Public Health Services  
Ministry of Health  
Markou Drakou 10  
1449 Nicosia  
*Biannual, print and online versions available.*  
*In Greek.*

**Czech Republic**

*Zpravy CEM*  
(Monthly Bulletin of Centre Epidemiology and Microbiology)  
Centrum epidemiologie a mikrobiologie Státního zdravotního ústavu (Centre of Epidemiology and Microbiology, National Institute of Public Health)  
Srobarova 48  
100 42 Praha 10  
*Monthly, print and online versions available, in Czech with some important notifications in English.*  
<http://www.szu.cz/cema/adefaultt.htm>

EPIDAT  
Notifications of infectious diseases in the Czech Republic  
<http://www.szu.cz/cema/epidat/epidat.htm>

**Denmark**

*EPI-NEWS*  
Department of Epidemiology  
Statens Serum Institut  
Artillerivej 5  
DK-2300 København S  
*Weekly, print and online versions available.*  
*In Danish and English.*  
<http://www.ssi.dk>

**England and Wales**

*Communicable Disease Report Weekly (CDR)*  
Health Protection Agency  
61 Colindale Avenue  
London NW9 5EQ  
*Weekly, online only. In English.*  
<http://www.hpa.org.uk/cdr>

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*Kansanterveys*  
Department of Infectious Disease Epidemiology  
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Mannerheimintie 166  
00300 Helsinki  
*Monthly, print and online versions available.*  
*In Finnish.*  
<http://www.ktl.fi/porta/suomi/julkaisut/kansanterveyslehti/>

**France**

*Bulletin épidémiologique hebdomadaire*  
Institut de veille sanitaire  
12, rue du Val d'Osne  
94415 Saint-Maurice Cedex  
*Weekly, print and online versions available.*  
*In French.*  
<http://www.invs.sante.fr/beh/default.htm>

**Germany**

*Epidemiologisches Bulletin*  
Robert Koch-Institut  
Presse, Öffentlichkeitsarbeit, Bibliotheken  
Nordufer 20  
D-13353 Berlin  
*Weekly, print and online versions available.*  
*In German.*  
[http://www.rki.de/DE/Content/Infekt/EpidBull/epid\\_bull\\_\\_node.html](http://www.rki.de/DE/Content/Infekt/EpidBull/epid_bull__node.html)

**Hungary**

*Epinfo (Epidemiológiai Információs Hetilap)*  
National Center For Epidemiology  
Gyalí ut 2-6  
1097 Budapest  
*Weekly, online version available. In Hungarian.*  
<http://www.antsz.hu/oekepinfo/szoveg/Heti2004/hetiindit04.htm>

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*EPI-INSIGHT*  
Health Protection Surveillance Centre (HPSC)  
25-27 Middle Gardiner Street  
Dublin 1  
*Monthly, print and online versions available.*  
*In English.*  
<http://www.ndsc.ie/EPI-Insight/>

**Italy**

*Notiziario dell'Istituto Superiore di Sanità*  
Istituto Superiore di Sanità  
Reparto di Malattie Infettive  
Viale Regina Elena 299  
I-00161 Roma  
*Monthly, online only. In Italian and English.*  
<http://www.iss.it/pub/serie.php?id=4>

*Bolletino Epidemiologico Nazionale (BEN)*  
Istituto Superiore di Sanità  
Reparto di Malattie Infettive  
Viale Regina Elena 299  
I-00161 Roma  
*Monthly, online only. In Italian and English.*  
<http://www.epicentro.iss.it/ben/>

**Latvia**

*Epidemiologijas Biļeteni*  
State Public Health Agency  
7 Klījanu Street  
1012 Rīga  
*Online. In Latvian.*  
<http://www.sva.lv/epidemiologija/bileteni/>

**Netherlands**

*Infectieziekten Bulletin*  
Rijksinstituut voor Volksgezondheid en Milieu  
PO Box 1  
NL-3720 Bilthoven  
*Monthly, print and online versions available.*  
*In Dutch, some summaries in English.*  
<http://www.rivm.nl/infectieziektenbulletin/>

**Northern Ireland**

*Communicable Disease Monthly Report*  
Communicable Disease Surveillance Centre  
(Northern Ireland)  
McBrien Building, Belfast City Hospital,  
Lisburn Road  
Belfast BT9 7AB  
*Monthly, print and online versions available.*  
*In English.*  
<http://www.cdscni.org.uk/publications/>

**Norway**

*MSIS-rapport*  
Folkehelseinstituttet  
Postboks 4404 Nydalen  
N-0403 Oslo  
*Weekly, print and online versions available.*  
*In Norwegian.*  
<http://www.folkehelsa.no/nyhetsbrev/msis/>

**Poland**

Reports on cases of infectious disease and poisonings in Poland  
Instytut Naukowo-Badawczy (National Institute of Hygiene)  
ul. Chocimska 24  
00-791 Warszawa  
*Fortnightly. In Polish and English.*

**Portugal**

*Saúde em Números*  
Direcção-Geral da Saúde  
Alameda D. Afonso Henriques 45  
1049-005 Lisboa  
*Sporadic, print only. In Portuguese.*  
Ministry website: <http://www.dgsaude.pt/>

**Romania**

*Info Epidemiologia*  
Bulletin of the National Center for Surveillance and Control of Communicable Diseases, Institute of Public Health of Bucharest  
1-3 Dr Leonte Street (Strada Dr.Leonte 1-3)  
Sector 5 Bucharest Romania  
*Sporadic, print only.*

**Scotland**

*Health Protection Scotland Weekly Report*  
Health Protection Scotland  
Clifton House, Clifton Place  
Glasgow, G3 7LN  
Scotland  
*Weekly, print and online versions available.*  
*In English.*  
<http://www.show.scot.nhs.uk/scieh/wrhome.html>

**Slovenia**

*CNB Novice*  
Institut za varovanje zdravja Republike Slovenije  
Center za nalezljive bolezni  
Trubarjeva 2  
Ljubljana  
*Monthly, online only. In Slovene.*  
<http://www.ivz.si/ivz/aktualno/>

**Spain**

*Boletín Epidemiológico Semanal*  
Centro Nacional de Epidemiología - Instituto de Salud Carlos III  
C/ Sinesio Delgado 6 - 28029 Madrid  
*Bi-weekly, print and online versions available.*  
*In Spanish.*  
<http://193.146.50.130/htdocs/bes/bes.htm>

**Sweden**

*EPI-aktuell*  
Smittskyddsinstitutet  
171 82 Solna  
*Weekly, online only. In Swedish.*  
<http://193.146.50.130/htdocs/bes/bes.htm>  
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