



Eurosurveillance

Europe's leading journal on infectious disease epidemiology, prevention and control

Vol. 15 | Weekly issue 8 | 25 February 2010

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Legionella, springtime and potting soils

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Citation style for this article:

Citation style for this article: de Jong B, Zucs P. Legionella, springtime and potting soils. Euro Surveill. 2010;15(8):pii=19497. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19497>

This article has been published on 25 February 2010

Legionnaires' disease has been named after the outbreak in Philadelphia 1976 when a mysterious pneumonia affected a large number of members of the American Legion, a United States military veterans association, which held a gathering at a hotel [1]. *Legionella*, the bacterium causing the disease was identified several months after this outbreak for the first time. Today we know that there are about 50 different species of *Legionella* and that not all of them seem to be pathogenic to humans. The vast majority of reported cases are infected with *L. pneumophila* by inhalation of aerosols (water droplets) containing the bacteria, which is the route of infection for most *Legionella* cases. This is also described in an article by Joseph and Ricketts in this issue [2].

However, in some instances cases are infected by other *Legionella* species. A second paper in this issue describes a possible association between handling potting soil and infection with *L. longbeachae* [3]. As pointed out by the Scottish authors, this has long been well known and documented in Australia and New Zealand. In a soil survey performed in 1989 to 1990 in Australia, 33 (73%) of 45 potting soil samples tested positive for *Legionella*; 26 (79%) of the 33 contained *L. longbeachae* [4].

On their homepage, the Auckland Regional Public Health Service as well as the other public health services in Australia and New Zealand offers the following advice on how to minimise the risk of contracting legionellosis [5]:

- Take care when dealing with compost, potting mix and any form of soil or dirt. Read the warning labels on commercially available bags of compost and potting mix.
- To minimise risk, avoid stirring up dust, avoid inhaling dust, dampen the soil/compost before use, wear a dust mask that fits tightly over nose and mouth.

As the Scottish paper indicates, these recommendations may nowadays also be valid in Europe. Cases of *L. longbeachae* infections often appear as single cases and it could prove difficult to find a link with a commercial potting soil.

According to Steele *et al.*, potting soils are made from different products [4]. In Australia, they tend to consist of composted waste products such as sawdust and hammer milled bark while in Europe peat moss is a major component. It is indicated that the use of different products emanating from wood could facilitate the occurrence of different *Legionella* bacteria in potting soil. In some parts of Europe, potting soils have bark soil as a component. However, studies from Switzerland have shown that *Legionella* spp. could also be present in potting soil containing peat moss [6].

Spring will soon come, and with the milder temperatures and increasing amounts of sunlight, gardeners all over Europe will start planting seeds and growing flowers and vegetables. These activities may involve contact with different potting soils and their dust, possibly giving rise to Legionnaires' disease. In this light of spring, cases should not only be questioned about their travel history and contact with aerosols but also if they have had any contact with potting soils or done any gardening.

Clinicians seeing patients with atypical pneumonia should be aware that the *Legionella* urinary antigen test is only valid for detection of *Legionella pneumophila* serogroup 1 and therefore other samples should be collected from the patient and submitted to the laboratory in order to be able to identify the causative agent.

In order to be able to estimate how many cases of Legionnaires' disease in Europe are attributable to potting soil, more clinical samples and samples from incriminated potting soils should be cultured. Besides gaining new insight into the epidemiology of this serious disease, the source of each infection could be traced, thus reducing the risk of subsequent cases occurring.

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A cluster of Legionnaires' disease caused by *Legionella longbeachae* linked to potting compost in Scotland, 2008-2009

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Citation style for this article:

Citation style for this article: Pravinkumar SJ, Edwards G, Lindsay D, Redmond S, Stirling J, House R, Kerr J, Anderson E, Breen D, Blatchford O, McDonald E, Brown A. A cluster of Legionnaires' disease caused by *Legionella longbeachae* linked to potting compost in Scotland, 2008-2009. Euro Surveill. 2010;15(8):pii=19496. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19496>

This article has been published on 25 February 2010

Three cases of Legionnaires' disease caused by *Legionella longbeachae* Sg 1 associated with potting compost have been reported in Scotland between 2008 and 2009. The exact method of transmission is still not fully understood as Legionnaires' disease is thought to be acquired by droplet inhalation. The linked cases associated with compost exposure call for an introduction of compost labelling, as is already in place in other countries where *L. longbeachae* outbreaks have been reported.

Legionella longbeachae has been rarely detected as the cause of respiratory illness in Scotland. Five cases have been reported in Scotland between 1995 and 2009 (Health Protection Scotland: personal communication) However, it is a well recognised type in Australia and New Zealand, where cases have been epidemiologically associated with the use of potting compost. [1, 2]

Case Reports

Case 1 was notified in 2008, admitted to hospital and was severely unwell for a number of months before recovering slowly. Case 2 became unwell in 2009 and was admitted to hospital with respiratory and gastrointestinal symptoms, but died as a result of multiple organ failure. There was no history of travel or occupational exposure. No significant environmental exposure to cooling towers or aerosol producers was identified. The patients' domestic water systems were sampled, but no *Legionella* were detected. Case 1 had recently begun growing tomatoes in a conservatory attached to the house, using potting compost for this purpose. Case 2 was a keen gardener and had spent long periods of time in the greenhouse and had used potting compost to pot plants.

Case 3 was identified in 2009 and required hospitalisation as well. Again, there was no history of foreign

travel and no significant exposure to cooling towers or aerosol producers in the vicinity. The case had been using compost to plant bulbs in pots in their garden.

The three cases had a median age of 65 years (range: 58-65 years) and were treated for community-acquired pneumonia. Cases 1 and 2 had risk factors such as smoking and underlying medical conditions for developing Legionnaires' disease.

Laboratory results

L. longbeachae Sg 1 was isolated from the first two patients. The third patient had a very high antibody titre of 1:8,192 against *L. longbeachae* Sg 1 by immunofluorescent antibody (IFA) testing [3]. Four isolates of *L. longbeachae* Sg 1 were obtained from the implicated potting composts ranging in counts from 4,000 cfu/g to 80,000 cfu/g. The identity of the *Legionella* species was confirmed by IFA and *mip* speciation (http://www.hpa-bioinformatics.org.uk/cgi-bin/legionella/mip/mip_id.cgi). Patient and environmental isolates were genotyped by amplified fragment length polymorphism (AFLP) as recommended by the European Working Group for Legionella Infections (EWGLI), although restriction fragment length polymorphism (RFLP) and pulsed-field gel electrophoresis (PFGE) [4] have been used in the past. We identified two AFLP types that we called A and B as there is currently no nomenclature from *L. longbeachae* AFLP types. Case 1 had AFLP A and the implicated compost contained both AFLP A and B. Case 2 had AFLP type B and the implicated compost contained AFLP type B. One of the compost types used by Cases 1 and 2 were of the same brand. There was no patient isolate from Case 3 but isolate from the implicated compost contained AFLP type A similar to the strain that had infected Case 1. Case 3 had used a brand of compost different from the one used by Cases 1 and 2.

The potting composts implicated in the first two cases was composed of shredded green waste that is heat-treated at above 65 °C for five to 10 days and of 30-50% peat, which is not heat-treated. A second type of compost used by Case 2 was composed of composted bark, green material and not heat-treated 75-80% peat. The compost involved in the third case was a bulb booster compost made from expanded wood fibre, coir, and bark. All the types of compost used conformed to the 'PAS 100 Standard' (the British Standards Institution's Publicly Available Specification for composted material, which outlines the minimum requirements for the process of composting, the selection of materials from which compost is made and how it is labelled [5]).

Public health measures

Following the detection of Case 1, a report highlighting the association with compost was prepared by the local National Health Service board consultant in public health medicine and was submitted through the department of consumer and trading standards of the local authority to the United Kingdom's (UK) Department of Business Innovations and Skills (BIS), which leads the regulatory reform agenda across the UK government. The report was sent to BIS with a view to consider statutory changes in terms of compost labelling and recommended that, although the incidence of *L. longbeachae* is rare in Scotland, a review of compost labelling with regards to *L. longbeachae* could be considered in the UK.

The family of Case 2 were advised against use of the greenhouse and to avoid any contact with the plants which have been re-potted using the compost under investigation. The greenhouse had to be cleared and given a chemical wash out prior to re-use. The decontamination of the greenhouse was carried out as a precautionary measure and follow-up ground soil samples were negative for *Legionella*.

For Case 3, given that the infection was likely acquired from contact with the compost in an open garden and that no other person in the house was involved in gardening, no public health control measures were deemed to be required.

Discussion

This is the first incident of two linked cases of *L. longbeachae* Sg 1 reported in Scotland. A common source was implicated and the cases were linked epidemiologically in terms of time, place and mechanism of exposure. The third case, although not directly linked, showed that the infection was not necessarily specific to a particular brand of compost. Nevertheless, the occurrence of the linked cases associated with compost exposure calls for the introduction of compost labelling as is already in place in other countries where *L. longbeachae* outbreaks have been reported. [6,7].

It has been reported that various *Legionella* strains have been isolated from different types of potting

soils including peat [8]. In Australia, where cases and outbreaks of *L. longbeachae* have been reported, the standards for composts, soil conditioners and mulches provide clear guidance to commercial producers of compost on how to process organic materials into compost in a safe and effective way [7]. These standards also include requirements for labelling bags and promoting safe and healthy gardening practices. Public health advice includes the risk of Legionnaires' disease following exposure to compost or potting soil.

A recent article by Casati *et al.* [8] has also highlighted that potting soils are an alternative and important, but probably underestimated, source of *Legionella* infection, not only by *L. longbeachae* but also by other *Legionella* species known to cause Legionnaires' disease. The article recommends collecting environmental samples, in particular potting soils, in addition to water samples as part of environmental investigations following a case of Legionnaires' disease.

A case control study by Connor *et al.* [9] demonstrated a significant risk of acquiring *L. longbeachae* infection (odds ratio 4.74, 95% confidence interval: 1.65–13.55, $P=0.004$) associated with recent use of potting mix. The study also showed that awareness of a possible health risk with potting mix protected against illness.

Casati *et al.* highlighted that although contamination of soil by *Legionella* was until recently considered to be limited to Australia, an association between cases of Legionnaires' disease and gardening or use of potting mixes has been identified in Japan, the United States, the Netherlands and Switzerland [8]. In the UK, only nine cases of *L. longbeachae* have been reported since 1984 (Health Protection Agency, personal communication). Five of them, including the three cases in this report, occurred in Scotland. Although uncommon, our experience, and reports in other parts of the world as highlighted above indicate that Legionnaires' disease can be acquired after contact with contaminated potting soil and is not limited to aerosolisation of contaminated water.

The current guidance on the management of *Legionella* incidents, outbreaks and clusters in the community, which has been published by the Health Protection Network [10] includes a hypotheses-generating questionnaire that explores the possibility of exposure to compost, gardening and pressure hoses. It is essential that the initial risk assessment at the time of clinical management of cases includes the risk of exposure to these factors to guide investigations.

On a cautionary note, current urinary antigen tests will not detect *L. longbeachae* infection and therefore cannot be relied upon by laboratories to make a diagnosis. Therefore, in the event of a community-acquired pneumonia with no discernible cause, serum and respiratory secretions should be sent to a national *Legionella*

reference laboratory for PCR and culture, particularly if the case has a connection to gardening.

The cases reported here emphasise the need for a voluntary use in the UK of an industry-agreed warning label for potting soil, as the risk of Legionnaires' disease associated with compost is now clearly identified.

Acknowledgements

We would like to acknowledge the help of Eddie Docherty and Catherine Keachie, NHS Lanarkshire and Francis Shields, South Lanarkshire Council.

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Chikungunya infection in a French traveller returning from the Maldives, October, 2009

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Citation style for this article:

Citation style for this article: Receveur M, Ezzedine K, Pistone T, Malvy D. Chikungunya infection in a French traveller returning from the Maldives, October, 2009. *Euro Surveill.* 2010;15(8):pii=19494. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19494>

This article has been published on 25 February 2010

In the last years, cases of chikungunya fever have been reported in international travellers returning from the Indian Ocean region. The cases have been linked to the re-emergence of chikungunya fever on Indian Ocean islands in 2006. We describe the first case of chikungunya fever in a French traveller returning from Malé, an island of the Maldives islands, confirming the permanence of virus circulation by the end of 2009.

Introduction

Chikungunya virus is a mosquito-borne alphavirus found in the tropical regions of Africa and Asia where it causes endemic and epidemic chikungunya fever, an acute self-limiting febrile algo-eruptive illness [1]. Chikungunya fever has been increasingly reported in international travellers following its re-emergence on Indian Ocean islands and its spread to southern Asia thereafter [2-4]. Moreover, some African and south-east Asian countries show an endemic circulation of the virus [5] which may contribute to occurrence of the disease among travellers. The illness was suspected to have emerged in the Maldives archipelago in 2007 [6], following the sweeping succession of outbreaks that occurred in the Indian Ocean region where it first affected Kenya in 2004, Réunion Island in 2005 and southern India in 2006 [1,7]. Here we report a confirmed case of chikungunya fever in a French traveller returning from Malé island, the Maldives, where an outbreak of chikungunya fever was reported starting in January 2009.

Case report

A French male in his thirties presented at the post-travel clinic of the Department of Internal Medicine and Tropical Diseases of the University Hospital Centre, Bordeaux, France in October 2009 with symptoms of recurrent high-grade fever (up to 40°C), headache, generalised muscle aches and severe joint pain mainly affecting fingers, wrists, knees and ankles, and an itching skin rash, since three days. Two days before, he had returned directly from a holiday trip to the Maldives where he had stayed for 14 days exclusively in the northern part of Malé island.

In our centre, the patient presented with a slight macular skin rash on the trunk and limbs, a slightly swollen right knee and small joints of hands and feet. Laboratory tests at the time of presentation showed a leucocyte cell count of 4,600 white blood cells (WBC)/ μ L, a thrombocyte count of 178,000 platelets/ μ L and an elevated C-reactive protein level (27 mg/L; normal \leq 5 mg/L). Alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase were within normal limits. Blood smears for malaria and blood cultures were negative.

Chikungunya virus serology testing was conducted for specific immunoglobulin (Ig) G and M using IgM-capture and IgG-sandwich enzyme-linked immunosorbent assay (ELISA) with inactivated cell-culture-ground chikungunya virus and mouse anti-chikungunya hyperimmune ascitic fluid at the National Reference Centre for Arboviruses, Institut Pasteur, Paris, France. Serology for chikungunya virus revealed positive results for both specific IgM (optic density (OD)=1.633; serum control OD=0.073) and IgG (OD=0.475; serum control OD=0.096).

Paired serology for specific IgG and M by ELISA against dengue virus and Japanese B encephalitis were negative, as well as tests for leptospirosis, rickettsiosis, Q fever, West Nile virus and cytomegalovirus. A real-time PCR test was negative for dengue viruses and chikungunya virus RNA [8]. Fever decreased the day following the consultation, but severe joint pain persisted over six weeks until the end of December despite symptomatic treatment.

Discussion

Over the last couple of years and following successive waves of outbreaks in the Indian Ocean area since 2006, chikungunya has increasingly been reported in travellers returning from vacation in the region and in expatriates or immigrants back from visits to their home countries [2-4,9].

The new case described provides definite evidence of ongoing chikungunya virus transmission in the

Maldives. To the best of our knowledge, this case is reportedly the third confirmed chikungunya fever case imported from the Maldives since the first documented outbreak of chikungunya in Malé and other islands of the Maldives that lasted from December 2006 to April 2007 [6], followed by a suspected cluster on the Laamu Atoll from December 2008 to January 2009 [10] and the report of two confirmed cases in German travellers, a father and son returning from a 10-day visit to the Maldives mid-September 2009 [11].

The region is probably one of the most popular travel destinations in the Indian Ocean area. This may result in an increase of symptomatic travellers returning from this area and seeking medical advice at travel or primary care clinics. Hence, chikungunya together with dengue fever should be considered as an important differential diagnosis in those patients, assuming that both diseases are endemic in certain regions of India and the Indian Ocean area and may present with similar symptoms.

For more than 10 years, dengue fever was the only vector-borne viral disease reported in the Maldives. *Aedes aegypti* and *A. albopictus*, the dengue virus vectors which can also transmit the chikungunya virus, have been identified in the Maldives, with *A. aegypti* identified as the predominant vector in Malé [6]. The first chikungunya fever outbreak occurred from December 2006 to April 2007 with abrupt onset and high attack rates due to the lack of herd immunity. Epidemics may occur following an interval of 20-30 years of the virus not circulating as has been the case in western Africa and Malaysia [5, 6]. Confirmed imported cases among travellers support the assumption of endemic circulation of the virus which is consistent with the prevailing chikungunya epidemic in the Indian Ocean region.

This report highlights the need for surveillance in countries where emerging infections may be introduced by returning travellers as in the case with the Italian chikungunya fever epidemic which occurred in the province of Ravenna in 2007 [12]. It illustrates how travellers can serve as sentinel population providing information regarding the emergence or re-emergence of an infectious pathogen in a source region. Travellers can thus act as carriers who inadvertently ferry pathogens that can be used to map the location, dynamics and movement of pathogenic strains [9]. Thus, with the increase in intercontinental travel, travellers can provide insights into the level of the risk of transmission of infections in other geographical regions.

Conclusion

We report a case of dengue-like illness diagnosed as chikungunya in a tourist returning from the Maldives, a popular tourist spot. Despite the clinical similarity with dengue fever, chikungunya should be recognised early in returning travellers because of its specific protracted morbidity and its potential for causing local outbreaks in European countries, where local transmission is

possible through the presence of the receptive vector in southern European countries.

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Legionnaires' disease in Europe 2007–2008

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Citation style for this article:

Citation style for this article: Joseph CA, Ricketts KD, on behalf of the European Working Group for Legionella Infections. Legionnaires' disease in Europe 2007–2008. *Euro Surveill.* 2010;15(8):pii=19493. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19493>

This article has been published on 25 February 2010

Each spring, countries that participate in the European Surveillance Scheme for Travel Associated Legionnaires' Disease (EWGLINET) are requested to submit their annual dataset of all cases of Legionnaires' disease in residents of their country with onset of illness in the preceding year. These data have been collected annually since 1994 and are used to analyse epidemiological and microbiological trends within and between countries over time. This paper presents an overview of the data collected for 2007 and 2008. A total of 5,907 cases were reported by 33 countries in 2007 and 5,960 cases by 34 countries in 2008, a similar two-year total to that recorded in 2005 and 2006 [1]. The only countries with a major difference in case numbers between 2007 and 2008 were Russia, due to a large outbreak in 2007, and Italy where cases increased by 256 in 2008 mainly due to an increase in community-acquired infections. The 779 reported deaths give a two-year case fatality rate of 6.6%. Some 243 outbreaks or clusters were detected, 150 of which were linked to travel-associated infections. As in previous years, the overall main method of diagnosis was by urinary antigen detection and the proportion of cases diagnosed by culture remained low at 8.8%, although isolation rates by country ranged from under 1% to over 40%.

Introduction

Legionnaires' disease is a bacterial infection characterised by atypical pneumonia. It is caused by *Legionella* bacteria which live in water and other moist environments, and are ubiquitous in the natural environment. When aerosolised and inhaled they can cause infection. Aerosol-generating outlets that are commonly associated with cases of Legionnaires' disease include wet cooling systems, water systems and spa pools [2].

In 1986, collaborations across Europe were established to share knowledge about *Legionella* spp. and to monitor trends in this infection. This became known as the European Working Group for Legionella Infections (EWGLI), and it currently has 36 member countries. Every year EWGLI requests a dataset from each participating country, to record the number and characteristics of the cases of Legionnaires' disease that were diagnosed in that country's residents

during the preceding year. This allows for comparison of the disease between countries, the monitoring of trends within countries and for analysis of data at the European level.

Data from the years 1996 to 2006 have been published previously [1,3-8]. This paper presents the dataset for the years 2007 and 2008.

Methods

The datasets requested from the countries contain epidemiological and microbiological information: the number of confirmed and presumptive cases, the number of deaths, the population base covered (in some countries, the institution collaborating with EWGLI only receives data for a region of the country), the method of diagnosis and the species and serogroup of any isolates obtained, age group and sex of

TABLE 1

Reported cases of Legionnaires' disease and incidence rate per million population, 1993–2008 (n=53,494)

Year	Number of cases	Number of countries contributing data ¹	Population (millions)	Rate per million
1993	1,242	19	300	4.1
1994	1,161	20	346	3.4
1995	1,255	24	339	3.7
1996	1,563	24	350	4.5
1997	1,360	24	351	3.9
1998	1,442	28	333	4.3
1999	2,136	28	398	5.4
2000	2,156	28	400	5.4
2001	3,470	29	455	7.6
2002	4,696	32	466	10.1
2003	4,578	34	468	9.8
2004	4,588	35	550	8.3
2005	5,700	35	554	10.3
2006	6,280	35	566	11.1
2007	5,907	33	523	11.3
2008	5,960	34	506	11.8

¹ With England and Wales, Northern Ireland and Scotland counted as three distinct countries.

Source: European Working Group for Legionella Infections (EWGLI) data.

the cases, category of exposure (nosocomial, travel- or community-associated), countries of travel (where appropriate), and outbreaks by type, size and suspected source.

Cases are classified as confirmed or presumptive according to the EWGLI case definitions (a classification of 'diagnosis not known' is accepted according to national reporting criteria) [9]. In addition, each case is categorised by the activities they were engaged in during their incubation period and are recorded as 'travel', 'nosocomial' or 'community' infections. Each country defines nosocomial and community categories according to their national case definitions, whereas

a European-wide case definition is used for travel-associated cases. If there is insufficient evidence to allocate a case to one of the categories (e.g. if a case spent part of their incubation period travelling and part in hospital), the case is classified as 'other'. If no exposure information is available, the case is classified as category 'not known'.

Incidence rates per million population are based on national population size, with the exception of three countries where regional incidence rates were reported in both years (Bulgaria, Lithuania and Russia), and in Romania where regional incidence rates were reported for 2008. It should be noted that these data may not

TABLE 2

Number of cases of Legionnaires' disease and incidence rate per million population, 2007-2008

Country	2007			2008		
	Population (millions)	All reported cases	Rate per million	Population (millions)	All reported cases	Rate per million
Andorra	0.1	6	73.0	0.1	1	11.9
Austria	8.3	105	12.7	8.3	100	12.0
Belgium ¹	10.6	145	13.7	10.7	138	12.9
Bulgaria	1.2	1	0.8	1.2	1	0.8
Croatia	4.4	40	9.0	4.4	30	6.8
Cyprus	N/A	N/A	N/A	0.8	9	11.4
Czech Republic	10.3	21	2.0	10.4	20	1.9
Denmark ¹	5.4	133	24.4	5.5	128	23.3
Estonia	1.3	3	2.2	1.3	7	5.2
Finland	5.3	16	3.0	5.3	15	2.8
France ¹	62.6	1,428	22.8	62.6	1,244	19.9
Germany ¹	82.3	529	6.4	82.2	522	6.3
Greece	11.0	23	2.1	11.0	27	2.5
Hungary	10.1	18	1.8	10.0	25	2.5
Ireland	4.2	16	3.8	4.2	11	2.6
Italy ¹	59.1	851	14.4	59.6	1,107	18.6
Latvia	2.3	2	0.9	2.3	5	2.2
Lithuania	3.4	2	0.6	3.4	2	0.6
Luxembourg	0.5	4	8.4	0.5	5	10.1
Malta	0.4	14	34.3	0.4	3	7.6
Netherlands ¹	16.4	321	19.6	16.4	337	20.5
Norway	4.7	35	7.5	4.8	38	7.9
Poland	38.1	13	0.3	38.1	20	0.5
Portugal	10.6	86	8.1	10.6	102	9.6
Romania	21.6	1	0.0	1.9	4	2.1
Russia	20.0	140	7.0	20.0	18	0.9
Slovakia	5.4	2	0.4	5.3	9	1.7
Slovenia	2.0	24	11.9	2.0	48	23.7
Spain ¹	44.2	1,098	24.8	44.7	1,219	27.3
Sweden	9.2	130	14.2	9.3	155	16.7
Switzerland ¹	7.6	205	26.9	7.7	220	28.6
UK - England & Wales ¹	53.7	441	8.2	54.1	358	6.6
UK - Northern Ireland	1.7	11	6.3	1.8	6	3.4
UK - Scotland	5.1	43	8.4	5.1	26	5.1

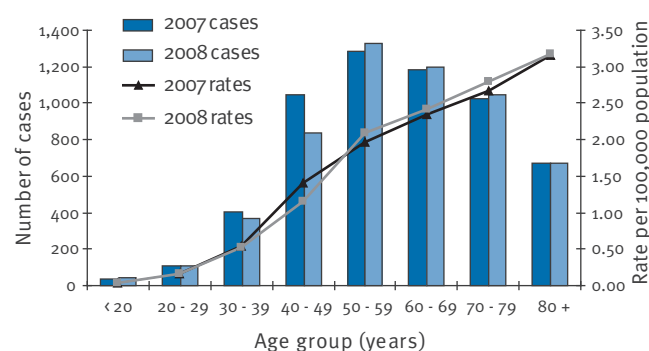
N/A: not applicable. UK: United Kingdom.

¹ Countries where data has been presented in previous years' papers.

Source: European Working Group for Legionella Infections (EWGLI) data.

be representative of the entire country if, for example, reporting is stronger in the region of the country which reports to this international scheme. Age-standardised rates are calculated from the number of cases in each age stratum and the underlying population denominator for the strata in each participant country.

FIGURE 1
Cases of Legionnaires' disease and age standardised rates per 100,000 population by age group, 2007-2008



Source: European Working Group for Legionella Infections (EWGLI) data.

The term 'outbreak' is mainly used to describe outbreaks in hospitals or community settings, and the term 'cluster' is mainly used for travel-associated cases to describe the association of more than one case with a hotel or other tourist accommodation site. Travel-associated clusters are defined as 'two or more cases associated with the same accommodation site within two years', based upon the definitions established by EWGLI's travel-associated surveillance scheme, EWGLINET [9]. All other clusters and outbreaks are defined independently by the country where the infection was acquired.

Results

In 2007, 5,907 cases were reported by 33 countries, and in 2008, 5,960 cases were reported by 34 countries (including Cyprus, who contributed data for the first time). In the 16 years for which this dataset has been collected, a total of 53,494 cases have been reported (Table 1).

Incidence rates

The overall incidence per million population was 11.3 in 2007 (based on a population of 523.3 million) and 11.8 in 2008 (based on a population of 506.2 million). The fall in total population in 2008 is accounted for by

TABLE 3
Cases of Legionnaires' disease by main method of diagnosis, 2007-2008 (n=11,867)

Main method of diagnosis	<i>Legionella pneumophila</i> sg1		<i>L. pneumophila</i> other serogroup, or serogroup not determined		Other <i>Legionella</i> species or species not known		All <i>Legionella</i> cases	
	Cases	%	Cases	%	Cases	%	Cases	%
Isolation/culture	896	9.5	113	6.3	33	5.1	1,042	8.8
Urinary antigen detection	8,252	87.5	1,108	62.1	247	38.2	9,607	81.0
Serology: four-fold rise	66	0.7	92	5.2	42	6.5	200	1.7
Serology: single high titre	167	1.8	280	15.7	137	21.2	584	4.9
Respiratory antigen detection	1	0.0	1	0.1	4	0.6	6	0.1
PCR	37	0.4	149	8.3	55	8.5	241	2.0
Unknown	17	0.2	42	2.4	128	19.8	187	1.6
Total	9,436	100	1,785	100	646	100	11,867	100

Source: European Working Group for Legionella Infections (EWGLI) data.

TABLE 4
Number of cases of Legionnaires' disease and proportion by category of infection, 2007-2008 (n=11,867)

Category	2007		2008		Total cases	%
	Cases	%	Cases	%		
Nosocomial	329	5.6	419	7.0	748	6.3
Community	3,671	62.1	3,657	61.4	7,328	61.8
Travel abroad	791	13.4	689	11.6	1,480	12.5
Travel home	492	8.3	538	9.0	1,030	8.7
Other	54	0.9	32	0.5	86	0.7
Not known	570	9.6	625	10.5	1,195	10.1
Total	5,907	100.0	5,960	100.0	11,867	100.0

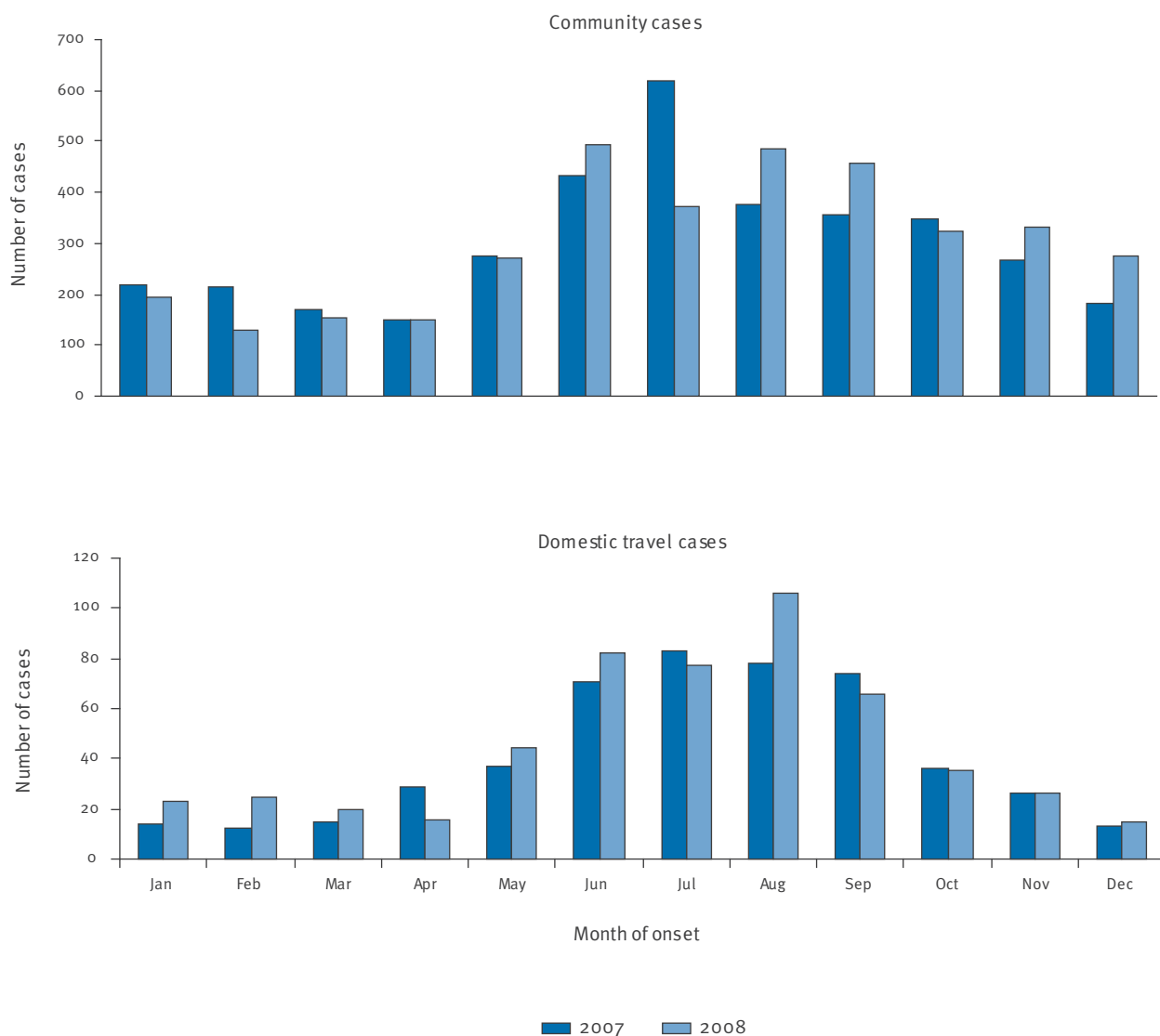
Source: European Working Group for Legionella Infections (EWGLI) data.

Romania reporting only data from one region in that year. In all other countries, the area of each country covered by their datasets remained consistent across both years. The number of reported cases for both years was highest in France, Italy and Spain, although

rates per million population were higher in some countries that had reported fewer cases (in 2007: Andorra, Denmark, Malta, the Netherlands and Switzerland; in 2008: Denmark, the Netherlands, Slovenia and Switzerland).

FIGURE 2

Cases of Legionnaires' disease acquired within country of residence by month of onset, 2007-2008



Source: European Working Group for Legionella Infections (EWGLI) data.

TABLE 5

Outbreaks of Legionnaires' disease and associated cases by category of infection, 2007-2008

Category	2007		2008		Total	
	Outbreaks	Cases	Outbreaks	Cases	Outbreaks	Cases
Nosocomial	13	48	15	50	28	98
Travel (abroad)	44	111	49	113	93	224
Travel (home)	27	77	30	69	57	146
Community	26	260	37	157	63	417
Other	1	3	1	2	2	5
Total	111	499	132	391	243	890

Source: European Working Group for Legionella Infections (EWGLI) data.

In 2007, rates were highest in Andorra (six cases, rate 73.0), followed by Malta (14 cases, rate 34.3) and Switzerland (cases 205, rate 26.9), whilst in 2008, Switzerland had the highest rate (220 cases, rate 28.6), followed by Spain (1,219 cases, rate 27.3) and Slovenia (48 cases, rate 23.7). Six countries reported incidence rates of less than one case per million population in 2007 (Bulgaria, Latvia, Lithuania, Poland, Romania and Slovakia), compared with four countries in 2008 (Bulgaria, Lithuania, Poland and Russia). Table 2 shows the rates of Legionnaires' disease per million population for all countries, with 10 of them selected for their consistent rates and in order to allow comparison with previous papers.

Case characteristics

Of the 11,867 cases reported in 2007-2008, 8,376 cases were male (70.6%), 3,176 were female (26.8%) and for 315 sex was unknown (2.7%). In both years the highest number of cases fell within the age group of 50-59-year-olds (1,288 cases in 2007, 21.8%; 1,328 cases in 2008, 22.3%). However, when age-standardised rates were calculated, the rate of infection per 100,000 population increased with increasing age with people aged 80 years or more having the highest rate at 3.16 and 3.17 per 100,000 in 2007 and 2008, respectively. This pattern was observed in both years (Figure 1).

The case fatality ratio (CFR) remained stable across the two years: 391 deaths were reported in 2007 (CFR 6.6%) and 388 were reported in 2008 (CFR 6.5%).

Microbiology

EWGLI collaborators allocate a main method of diagnosis to each reported case, taking culture as the 'gold-standard' test. Over the two years, a total of 1,042 cases were diagnosed by isolation/culture (8.8%). The primary method of diagnosis used was urinary antigen detection (81.0%), and the method of diagnosis was unknown for 187 cases (1.6%) (Table 3). This method of classifying the cases cannot take into account the fact that some will have had more than one method of diagnosis carried out, e.g. culture and urinary antigen detection or PCR and serology. In such cases the primary method is defined in the following order of preference for this analysis: culture, urinary antigen, serology, other.

A total of 10,715 of the cases reported to the dataset were classified as confirmed cases, and 965 were classified as presumptive. For 187 cases, the status was unknown.

The proportion of cases diagnosed by culture was similar in both years: 515 cases (8.7%) in 2007 and 527 cases (8.8%) in 2008. A similar trend was observed for the cases diagnosed by urinary antigen detection; they rose from 4,759 (80.6%) in 2007 to 4,848 (81.3%) in 2008. The proportion of cases diagnosed serologically

(including both four-fold rises and single high titres) fell from 417 (7.1%) in 2007 to 367 (6.2%) in 2008.

The overall very low proportion of cases diagnosed by culture (approximately 9%) masks the fact that the range stretched from under 1% to over 40% in individual countries. Denmark consistently has the highest proportion of cases diagnosed by culture at 40% for 2007-2008, followed by Austria, France, the Netherlands, England and Wales and Sweden at around 15-20%. In Spain, where 2,317 cases were reported for 2007-2008, diagnosis by culture was reported for only 10 of these cases (0.45%) and in Italy for only 33 of 1,958 cases (1.7%).

9,436 (79.5%) of the cases across the two-year period were caused by *Legionella pneumophila* serogroup 1. 'L. pneumophila other serogroup or serogroup not determined' accounted for 1,785 cases (15.0%), and the remaining 646 cases (5.4%) were reported as 'other *Legionella* species' or 'species not known'.

Of the 1,042 isolates obtained, 896 (86.0%) were *L. pneumophila* serogroup 1, 78 (7.5%) were *L. pneumophila* serogroups 2-16 (predominantly serogroup 3 (33 isolates; 3.2%) and serogroup 6 (13 isolates; 1.2%) and 35 (3.6%) were *L. pneumophila* serogroup unknown. Nineteen of the isolates were identified as non-pneumophila species of *Legionella*: *L. anisa* (n=2), *L. bozemanii* (n=4), *L. dumoffii* (n=1), *L. gormanii* (n=1), *L. longbeachae* (n=9), *L. maceachernii* (n=1), *L. wadsworthii* (n=1). For 14 isolates, the species of *Legionella* was not known.

Category of case

Over the two year period, 748 cases were categorised as nosocomial, 7,328 as community-acquired cases, 1,480 as being associated with travel abroad, 1,030 as associated with travel within the country of residence, 86 as 'other' and 1,195 as 'not known' (Table 4). In 2008, nosocomial cases were reported in two categories: cases associated with hospitals (n=307) and cases associated with other healthcare premises (n=112). Within countries, the proportion of cases reported to be community-acquired or travel-associated varied to the extent that a north-south divide is apparent, with northern countries having higher rates of travel-associated infections and southern countries higher rates of community-acquired infections. In Denmark, England and Wales and the Netherlands around 40% of cases are acquired as a result of travel abroad, compared with less than 10% for the southern countries France, Italy and Spain where the proportion of travel-associated cases is lower and the majority of these are related to travel within their own country of residence. In contrast, home-acquired community infection is more common in the southern countries where between 65% and 80% of cases fall into this category compared with around 50% for the northern countries specified above.

Travel within Europe accounted for 2,146 (85.5%) of the travel-associated cases over the two years. Italy was associated with the most cases (513 cases), followed by France (433 cases) and Spain (400 cases). Travel on cruise ships was associated with 11 cases in 2007 and four in 2008. Outside Europe, cases were associated with travel to the Far and Middle East (74 cases), Africa (64 cases), North and South America (57 cases), Asia (54 cases), the Caribbean (19 cases) and Oceania (two cases). The remaining cases that travelled outside Europe visited more than one country or had an unknown travel history.

A more detailed analysis of travel-associated cases of Legionnaires' disease is published each year from EWGLI's surveillance scheme EWGLINET [10]. EWGLINET operates a strict case definition for travel-associated infections (for example excluding patients for whom travel information was incomplete or those for whom travel was outside the 2-10-day incubation period), and so not all cases reported as associated with travel in this dataset can be reported to EWGLINET. Between 2007 and 2008, 2,510 travel cases were reported in the annual dataset, but only 1,795 (71.5%) were reported to EWGLINET (excluding an additional 17 cases that were reported to EWGLINET by countries outside EWGLI).

The month of onset was analysed for those cases that were acquired within the country of residence and reported as community-acquired or associated with travel in their own country. The domestic travel cases followed a similar monthly pattern of onset in both years, although the 2008 cases peaked later (the 2007 peak occurred in July (83 cases), whilst the 2008 peak occurred in August (106 cases)). In contrast, a different pattern was observed across the two years for the community-acquired cases: in 2007 there was a single peak in July (619 cases) mainly accounted for by a large outbreak in Russia (see below), whilst in 2008 there was a double peak, in June (492 cases) and August (486 cases).

Outbreaks/clusters

In 2007, EWGLI countries detected 111 outbreaks or clusters involving 499 cases (8.4% of cases in 2007); in 2008, 132 outbreaks or clusters were detected, involving 391 cases (6.6% of cases in 2008) (Table 5). The outbreaks ranged in size from two to 130 cases. The largest outbreak in 2007 occurred in Verhnaya Pyshma, Russia (130 cases, five deaths) and was attributed to an interruption of the town's hot water supply [11-12]. In 2008, the largest outbreak occurred in eastern Spain (21 cases, one death); the source was identified as a cooling tower.

Over the two year period, 28 outbreaks (11.5%) involving 98 cases were linked to hospitals or healthcare facilities in Austria, Belgium, Cyprus, Denmark, England and Wales, France, Germany, Ireland, Italy, the Netherlands, Poland and Spain. Twenty-two of these were attributed to hot or cold water systems, one to a

wet cooling system and the remaining five could not be attributed to a source. These sources are as reported by our collaborators, and the standard of investigation may vary between countries.

Sixty-three community outbreaks/clusters (25.9%) were identified across the two-year period, involving 417 cases. They occurred in Denmark, England and Wales, France, Ireland, Italy, the Netherlands, Norway, Russia, Spain and Sweden. Sources were identified for 30 (47.6%) of the community outbreaks: wet cooling systems in ten outbreaks, hot or cold water systems in 13, spas in four, a biological treatment plant in one, a footbath in one, and a condensation pipe in one. The source for the remaining 33 could not be identified.

Some 150 clusters (61.7%) were associated with travel, involving 370 cases: 93 with travel outside the country of residence, and 57 with travel within the country of residence. Hot or cold water systems were responsible for 52 of these clusters, a wet cooling system was responsible for one cluster, spa pools for two, and for the remaining 95 the source was unknown. The dataset described here contains only clusters that were detected by individual countries, it does not include clusters that were detected by pooling data across countries (i.e. clusters that comprised single cases from different countries); such clusters are detected by EWGLINET and are reported elsewhere [10].

In addition, there were two outbreaks associated with private buildings: one in 2007 which was found to be associated with a spa (three cases), and one in 2008 (two cases) for which no source could be identified.

Discussion

The overall number of cases of Legionnaires' disease for 2007-2008 (n=11,867) has remained similar to that of 2005-2006 (n=11,980). In some countries the number of reported cases remains consistently low, in others it fluctuates due to the unpredictability of large community outbreaks or the seasonal impact of meteorological factors, as has been shown previously in some northern European countries [13-14]. These fluctuations will also impact on national differences regarding peak months of onset for cases acquired in the community or during domestic travel. Data on month of onset has only been collected in this dataset for two years and, as such, trends cannot yet be determined.

However, the differences in overall trends between countries are usefully highlighted through analyses of these annual datasets and can help to emphasise where improvements in case ascertainment or control and preventive measures can be targeted. The reasons why countries such as Bulgaria, Estonia, Latvia, Lithuania and Romania report fewer than ten cases per year should be urgently reviewed by health officials to assess whether they might benefit from additional laboratory support for diagnosing legionella infections

alongside schemes to raise awareness of the disease among their hospital physicians.

It is not possible to draw firm conclusions about the number of deaths caused by Legionnaires' disease from this dataset. In some countries it is not compulsory to report deaths, and of those that are reported we do not know which were attributable to their legionellosis and which may have been associated with underlying conditions or other causes.

This two-year dataset has also shown that some countries are much more successful than others in obtaining respiratory samples for culture. A lack of isolates in many countries is problematic for public health officials when investigating outbreaks or clusters because without them, no source of infection can be microbiologically confirmed. A high proportion of isolates not only facilitate the identification of sources of infection when environmental isolates are also available for strain matching, but also make possible the identification of *L. pneumophila* non-serogroup 1 infections or other *Legionella* species. These are not normally detected by the most commonly used diagnostic method of urinary antigen detection which almost exclusively detects *L. pneumophila* serogroup 1 infections. Thus if more countries were able to obtain a greater proportion of samples for culture, it is likely that an increase in the less common strains of *L. pneumophila* would be detected such as *L. pneumophila* serogroup 3 and serogroup 6. In addition, an increasing use of PCR as a method of diagnosis in some countries should also enable more cases to be characterised at the molecular level. The dominance of *L. longbeachae* in the 'other' species of isolates is a new finding in Europe and has been linked to exposure to potting soil compost in one or two of the cases, in line with similar findings in Australia [15].

It is encouraging that a smaller proportion of cases (7.5%) was linked to outbreaks or clusters in 2007-2008 compared with 8.6% in 2005-2006. Only one very large outbreak occurred in the 2007-2008 period. It was the first of its kind in a EWGLI participant country and involved a communal hot water supply to several blocks of residential apartments in one town in Russia [11]. Lessons have been learnt from this outbreak and new legislation introduced in Russia to prevent this in the future [12]. Very large community outbreaks such as this are normally associated with cooling towers which have the capacity to spread contaminated aerosol over many square meters and expose large populations to the source of infection. A EWGLI survey into legislation associated with cooling towers (wet cooling systems) found that in 2007 and 2008, only 12 countries or regions had legislation for the registration of cooling towers and for microbiological monitoring of *Legionella* organisms [16]. Several collaborating countries have stated that European Union-wide regulations regarding wet cooling systems are required to prevent a high proportion of cases linked to community-acquired

infection, and EWGLI has recommended that the European Centre for Disease Prevention and Control (ECDC) should take the initiative to propose such regulations. The differences in the proportion of cases acquired at home or abroad between north and south European countries behoves all countries to ensure their detection and reporting mechanisms are operated at levels that minimise the risk of legionella infection as far as is possible for all citizens.

From 1 April 2010, EWGLI's surveillance network for travel-associated Legionnaires' disease, EWGLINET, will be coordinated and managed by the ECDC, as will the collection of this annual dataset from each participant country. It is expected that EWGLI's active and enhanced surveillance activities will continue under the ECDC and will be developed further in line with the specific needs or requirements of individual countries, in order, for example, to improve ascertainment of cases in low incidence countries or to support efforts for the control and prevention of Legionnaires' disease in different countries and exposure settings.

Acknowledgements

EWGLINET (through which this annual dataset is collected) is funded by the European Centre for Disease Prevention and Control. We would like to thank all our collaborators for submitting their annual datasets for this overview of Legionnaires' disease in Europe, and Rekha Yadav and Anitra Jones for processing the data at the EWGLINET coordinating centre.

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Chronic hepatitis C in Austria, 1992–2006: genotype distribution and demographic factors

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Citation style for this article:

Citation style for this article: Maieron A, Metz-Gercek S, Hackl F, Luger C, Ziachehabi A, Strauss R, Schöfl R, Mittermayer H. Chronic hepatitis C in Austria, 1992–2006: genotype distribution and demographic factors. *Euro Surveill.* 2010;15(8):pii=19492. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19492>

This article has been published on 25 February 2010

Chronic hepatitis C is a leading cause of end-stage liver disease and, with a worldwide prevalence of up to 3%, is a pandemic infectious disease. Austria, like most western European countries can be considered as a low prevalence country. This analysis aimed to assess the distribution of hepatitis C virus (HCV) genotypes in patients with chronic HCV infection in Upper Austria. Between September 1992 and December 2006, we identified 1,318 consecutive patients who tested positive for HCV RNA. Genotyping was routinely performed in 1,239 of the 1,318 patients, and in a subgroup of 617 patients data on the source of transmission were collected. Additionally we obtained data on liver histology and body mass index in a subsample of 273 of the 617 patients. Hepatitis C genotypes 1, 2, 3, 4, 6 and co-infections were found in 80.4%, 4.5%, 12.3%, 2.7%, 0.1% and 0.2% of the patients, respectively. There was a highly significant age difference in relation to gender at the time of diagnosis of chronic hepatitis C, with women being older than men (men: 45.0 years; women: 49.3 years; $p < 0.0001$). The number of new cases of chronic hepatitis C decreased substantially over the last decade, but although risk factors for obtaining HCV are well established, we did not find a decrease in the age of first diagnosis. Besides consistent screening in defined risk groups it is important to raise awareness for risk factors for HCV acquisition and liver disease progression.

Introduction

Chronic hepatitis C is one of the leading causes of liver cirrhosis and end-stage liver disease, resulting in liver failure, hepatocellular carcinoma, liver transplantation and premature death. Thanks to antiviral treatment, 50% of patients with progressive hepatitis can be cured if the infection is diagnosed in time and treatment is available [1]. Cofactors such as alcohol intake, obesity and underlying liver-related diseases (e.g. haemochromatosis) play a major role in the progression of the liver disease [2]. Infections with hepatitis C virus (HCV) are pandemic with a worldwide prevalence

of up to 3% [3,4]. There is a large variation regarding the genotype distribution worldwide, the most prevalent in Europe and North America being genotype 1 [5]. The knowledge of genotypes in chronic hepatitis C is crucial for the choice of the therapeutic regimen and for the therapeutic outcome, because genotypes 2 and 3 are curable in more than 80%, whereas genotypes 1 and 4 are curable in only 40-50% of cases [6].

The most common ways of transmission in low resource countries are still inadequately screened blood products, insufficiently sterilised needles, syringes and other medical equipment [7] as well as needle sharing among intravenous drug users, unsafe tattooing and body piercing worldwide. Sexual and perinatal transmission can occur but are of minor importance [8]. In the past decade the knowledge about risk factors for HCV infection and their reduction or even elimination have reduced the number of new cases and this resulted in a stabilisation of the HCV prevalence in developed countries [9]. Nevertheless this development did not prevent the continued rise in cirrhosis and liver cancer that resulted from HCV infections acquired dozens of years before [10]. The age at the time of diagnosis is very important because patients that are older at the time of diagnosis are more likely to develop severe liver disease [11].

Austria is a low prevalence country as are most other western European countries [8]. In Austria there is underreporting and a lack of epidemiological background data such as suspected route and time of transmission and genotype in the national reporting data [12]. In view of the lack of national epidemiological HCV data the aim of this analysis was to present the data for one of four hepatitis clinics in Upper Austria, one of the nine Austrian states. We analysed the number of new cases, the distribution of HCV genotypes and demographic factors. In addition, we analysed the number of new infections with the difficult-to-treat HCV genotypes 1 and 4 over time in association with

TABLE 1

New cases and mean age of hepatitis C patients by year and sex, hepatitis clinic Upper Austria, September 1992 – December 2006 (n=1,318)

Year	Male mean age in years (n)	Female mean age in years (n)	Total mean age in years (n)
1992	42.3 (12)	49.6 (7)	45.1 (19)
1993	44.6 (47)	53.2 (26)	47.7 (73)
1994	46.9 (54)	49.2 (35)	47.8 (89)
1995	44.0 (61)	50.6 (31)	46.2 (92)
1996	43.2 (75)	47.9 (47)	45.0 (122)
1997	43.2 (73)	48.6 (48)	45.4 (121)
1998	43.4 (88)	46.2 (35)	44.2 (123)
1999	45.9 (81)	47.3 (43)	46.4 (124)
2000	46.0 (69)	50.0 (28)	47.1 (97)
2001	44.8 (51)	52.6 (36)	48.0 (87)
2002	48.9 (57)	51.3 (33)	49.8 (90)
2003	47.0 (51)	47.3 (36)	47.1 (87)
2004	44.8 (65)	50.1 (29)	46.4 (94)
2005	44.6 (33)	46.8 (20)	45.4 (53)
2006	45.1 (30)	52.2 (17)	47.7 (47)
Total	45.0 (847)*	49.3 (471)*	46.6 (1,318)

* Significantly different (p<0.0001).

TABLE 2

Distribution of hepatitis C virus genotypes and subtypes and patients' mean age, hepatitis clinic Upper Austria, September 1992 – December 2006 (n=1,239)

Genotype group	Genotype subtypes	Number of cases	Proportion of total (%)	Mean age (years)
Genotype 1	1b	641	51.7%	48.2*
	1a	253	20.4%	
	1a/1b	68	5.5%	
	1	31	2.5%	
	1/3a ¹	1	0.1%	
	1a/2 ¹	1	0.1%	
	1b/2 ¹	1	0.1%	
Genotype 1 Subtotal		996	80.4%	
Genotype 2	2	14	1.1%	43.4
	2a	2	0.2%	
	2a/2c	29	2.3%	
	2b	11	0.9%	
Genotype 2 Subtotal		56	4.5%	
Genotype 3	3	48	3.9%	37.7*
	3a	104	8.4%	
Genotype 3 Subtotal		152	12.3%	
Genotype 4	4	15	1.2%	39.7
	4a	4	0.3%	
	4c	2	0.2%	
	4c/4d	8	0.6%	
	4h	5	0.4%	
Genotype 4 Subtotal		34	2.7%	
Genotype 6	6	1	0.1%	47.7
Total		1,239	100.0%	46.4

* Significantly different (p<0.0001).

¹ Co-infections are counted as one entry.

gender, age at time of diagnosis, route of transmis-

sion, liver histology and body mass index (BMI) in the referral population of our outpatient clinic.

FIGURE

HCV genotype distribution 1992-2006, hepatitis clinic Upper Austria, September 1992 – December 2006 (n=1,239)

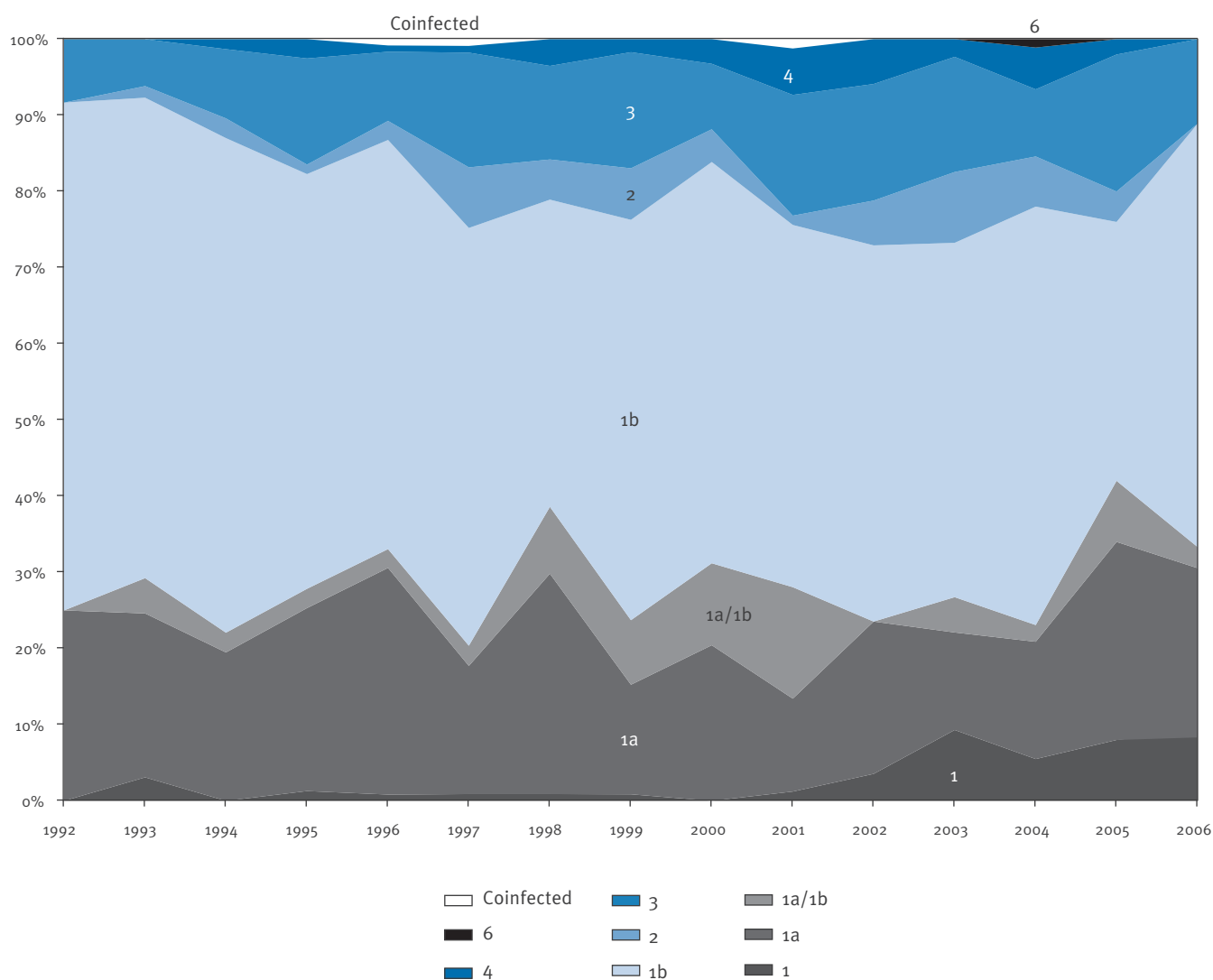


TABLE 3

Route of transmission for hepatitis C virus infection, by genotype group, hepatitis clinic Upper Austria, September 1992 – December 2006 (n=604)¹

Route of transmission ²	Genotype 1/4			Genotype 2/3		
	Number of cases	Proportion of total (%)	Mean age (years) ³	Number of cases	Proportion of total (%)	Mean age (years) ³
Unknown	205	41.4	46.8	29	26.6	43.6
Blood products	131	26.5	50.3	27	24.8	46.4
Plasma donation	78	15.8	49.5	4	3.7	45.4
Intravenous drug use	55	11.1	35.2	41	37.6	36.6
Piercing/tattoo	17	3.4	44.0	7	6.4	34.1
Needle stick injuries	8	1.6	47.5	0	0.0	-
Vaccination	1	0.2	38.5	1	0.9	56.3
Total	495	100.0	46.8	109	100.0	41.2

¹ For whom genotype was known.

² In case of more than one risk factor the one most likely to have caused the infection was assigned (e.g. in a case with unsafe tattooing and intravenous drug use, intravenous drug use was assigned)

³ Age at the time of diagnosis.

Methods

Upper Austria has 1.4 million inhabitants and four large outpatient clinics specialised in the care of hepatitis patients. Patients are referred to these clinics mainly by general practitioners, physicians responsible for the intravenous drug substitution programmes and centres for blood or plasma donation. From September 1992 to December 2006, we identified 1,319 consecutive patients (847 men (64.3%), 471 women (35.7%) and one case of unknown sex) who were referred to our outpatient clinic and tested positive for HCV by PCR. Patients were retested within one year if the first PCR test was negative and the antibody test was positive.

The baseline examination of our patients included a thorough medical check-up, the recording of the medical history and the assessment of risk factors for HCV infection which was carried out by performing standardised interviews. For the majority of the patients, our clinic was the first referral centre, only few (<5%) consulted our clinic for a second opinion.

Genotyping was performed in blood samples from 1,239 of the 1,319 patients. In a subgroup of 617 patients (410 men (66.5%) and 207 women (33.6%)) data were collected on the source of transmission, BMI, co-infection with hepatitis B virus (HBV) and co-infection with human immunodeficiency virus (HIV). Additionally, we obtained data on liver histology and BMI in a subsample of 274 of these 617 patients. All patients primarily identified as infected with chronic hepatitis C (n=1,319) were considered in the overall analysis, but in the subgroup analysis, patients with missing data on genotype or other demographic factors were excluded.

The data were stored and analysed using MS Access, MS Excel and SPSS software 13.0. The Mann-Whitney U Test and the chi-square test were used for non-parametric statistical testing.

HCV RNA from samples collected before September 1998 was detected with the Amplicor HCV test system (Roche) [13]. Samples collected between October 1998 and March 2006 were tested with the Cobas Amplicor HCV test (Roche) [14]. Since April 2006, the Cobas AmpliPrep/Cobas TaqMan HCV test (Roche) has been used for qualitative as well as quantitative detection of HCV RNA [15]. To determine the viral load in samples collected before April 2006, the Cobas Amplicor HCV monitor test, version 2.0 (Roche) [16] was used. HCV genotyping and subtyping (including detection of mixed genotypes) were carried out with the line probe assays (Innogenetics or Bayer HealthCare). The following systems were used: INNO LiPA HCV genotype assay, INNO LiPA HCV II genotype assay and Versant HCV genotype assay (LiPA) [17-19].

Results

After we began diagnosing HCV infections in September 1992, we identified 19 chronic hepatitis C patients by December 1992. Subsequently, the number of annual new cases changed over time and reached a maximum of 121-124 patients per year between 1996 and 1999 (Table 1). In each year, the majority of patients were men and there was a significant age difference with respect to gender (45.0 years in men versus 49.3 years in women; $p < 0.0001$).

Since the variation in the number of new cases was substantial over the years we decided to check whether the catchment area of our outpatient clinic had changed. There was no statistical significant variation in postal codes of patients ($p = 0.14$) and therefore we assume that our catchment area has not changed considerably over time.

Genotype distribution

HCV genotypes (gt) 1, 2, 3, 4, 6 were found in 80.4%, 4.5%, 12.3%, 2.7%, and 0.1% of the patients, respectively, and co-infections in 0.2%. The major subtypes were 1b (51.7%), 1a (20.4%) and 3a (8.4%), (Table 2). Three patients had a co-infection with two genotypes

TABLE 4

Relation between body mass index, liver fibrosis score and hepatitis C virus genotype group, hepatitis clinic Upper Austria, September 1992 – December 2006 (n=273)

Fibrosis	Fibrosis score	Genotype 1/4/6			Genotype 2/3		
		Number of cases	Proportion of total (%)	Mean BMI	Number of cases	Proportion of total (%)	Mean BMI
Fibrosis 0-2	0	51	22.2%	25.4	10	23.3%	24.0
	1	51	22.2%	25.6	8	18.6%	25.3
	2	56	24.3%	26.1	18	41.9%	23.6
Fibrosis 0-2 Subtotal		158	68.7%	25.7	36	83.7%	24.1
Fibrosis 3-4	3	20	8.7%	26.6	2	4.7%	21.9
	4	52	22.6%	26.9	5	11.6%	25.7
Fibrosis 3-4 Subtotal		72	31.3%	26.8	7	16.3%	24.6
Total		230	100.0%	26.1	43	100.0%	24.2

BMI: Body mass index.

(1a/2, 1/3a, 1b/2). Two patients, a couple with a history of intravenous drug use, underwent successful antiviral treatment and eliminated virus genotype 3a. Both were re-infected after needle-sharing with a mutual friend with genotype 2a. Genotypes 4 and 6, which are rarely detected in central Europe, were found in patients originating from other continents, mostly immigrants from Egypt (genotype 4 in 32 patients) and Vietnam (genotype 6 in one patient). Patients with genotypes 4 and 6 were mostly men (three women with genotype 4).

Between 1992 and 1996, we observed a high prevalence of genotype 1, ranging between 83.1% and 92.2%. After that period, the prevalence of genotype 1 decreased, varying from 73.7% to 78.4%, whereas the prevalence of the other genotypes increased or remained relatively stable (gt 2: 0-2.7%; gt 3: 9.1-16.2%; gt 4: 0-2.7%; gt 6: one patient) (Figure).

There was a continuous increase in the proportion of HCV patients who were not native Austrians, from 0% in 1992 to 15.8% in 2006. This did not influence the number of genotype 1 cases because migration was from countries with similar genotype distributions as Austria such as the Balkans, Turkey and the territories of the former Soviet Union, now known as the Commonwealth of Independent States. In 2006, 10-12% of the inhabitants of Upper Austria had been born abroad [20].

Characteristics and risk factors

Patients infected with genotype 1 were significantly older at the time of diagnosis than patients with genotype 3 (mean age: 48.2 years versus 37.7 years, $p < 0.0001$; see Table 2) and they showed a different distribution of risk factors for HCV acquisition in the subgroup analysis. Blood products and plasma donation were the most frequent risk factors for HCV acquisition in genotype 1 and 4 patients, but in the majority of patients the mode of transmission was unknown. In patients with genotype 2 or 3, the most common risk factor was intravenous drug use. The risk factor distributions and the mean age relating to genotype group are given in Table 3.

72 patients (11.6%) had overcome an infection with HBV. Three patients still suffer from chronic hepatitis B infection and only one patient was co-infected with HIV. We did not observe any connection between the HCV genotype group and the proportion of HBV-co-infected patients (gt 1/4: 10.7%; gt 2/3: 11.0%).

For a subgroup of 273 patients we also obtained histological information. It was notable that more than 30% of patients with genotype 1 or 4 showed bridging fibrosis or cirrhosis. In patients with genotype 2/3 advanced fibrosis was noted in 16.3% only. The results also revealed that a higher BMI coincided with an advanced liver fibrosis. Patients infected with HCV genotype 1, 4 or 6 showed a mean BMI of 26.1 kg/m²

and patients with genotype 2 or 3 a mean BMI of 24.2 kg/m² (Table 4).

Discussion

Austria is one of the countries in Europe with the lowest HCV prevalence; less than 0.5% of the total population are infected. According to this estimation our data represent around 20% of all HCV-infected patients in Upper Austria [21]. Overall our results show a change in the number of cases diagnosed over time reaching a maximum between 1996 and 1999 (121-124 patients per year) and a drop between 2000 and 2006 (10). This decline in new HCV cases is in line with Austrian reporting data published by the Federal Ministry of Health, Family and Youth [22], although it has to be mentioned that the reporting data are biased by underreporting as shown by Strauss *et al.* [12].

The sensitivity of the PCR test improved over the study period. This should not have caused a bias in our results, but a very few patients may have been missed due to the detection limit of PCR testing. The number of newly diagnosed HCV cases might be influenced by migration. The proportion of individuals not born in Austria has increased over the years among the patients in our analysis as well as in the general population. A considerable number of our patients were from Egypt and from the Commonwealth of Independent States.

Regarding the distribution of HCV genotypes, our results are very similar to those from other European countries. In our data, genotype 1 was the most prevalent (80.4%), followed by genotype 3 (12.4%). Genotype 1b was the most frequent subtype and accounted for more than 50% of all HCV-infected patients in our clinic. Observations by Haushofer *et al.* for Vienna and surrounding areas in the year 2001 [23] and by Ross *et al.* (2000) and Goeser *et al.* (1995) for Germany [24,25] yielded very similar results. The rate of genotype 3 in Germany ranged from 33.6% in 2003 to 35.7% in 2005 [26]. In a report from Slovenia from 1997, genotype 3 accounted for approximately 20% of cases [27] and in Italy in 2003, genotype 3 was found in about 12% of chronic hepatitis C patients [28]. All genotype 4 patients in our population came from Egypt (2.8%), where the prevalence of genotype 4 is nearly 90% [29] due to insufficient sterilisation of the needles used for intravenous treatment of schistosomiasis in the 1960s and 1970s [30]. The prevalence of genotype 4 outside of Egypt varies from 1% in Germany [18] to 10% in Spain [31].

In our sample, the proportion of HCV genotype 1 decreased over time, whereas the proportion of genotype 3 increased slightly. The shift of the genotype distribution may be associated with the change of risk factors for HCV acquisition, since HCV is nowadays mostly transmitted via intravenous drug use [32]. Blood products and plasma donation now play a minor role in causing new infections because of strict screening procedures, whereas the risk of acquiring HCV

through intravenous drug use has remained the same [33,34]. The overall incidence of new HCV infections has been decreasing in all developed countries including Austria. Nevertheless, the change in incidence will not prevent the increase of liver cirrhosis and liver cancer still resulting from HCV infections transmitted decades ago [10].

Surprisingly, the median age at time of diagnosis has not changed over time although the risk factors for HCV infection are well known. This might be important for therapeutic considerations because it is known that therapy is less efficient in older patients due to the progression of liver disease and longer time of being infected [11]. Unfortunately, the medical history with the time of infection given by the patient was not reliable or not available in most of the cases, and therefore the lag between the age at time of infection and age at time of diagnosis can not be given.

Another startling finding was that women were significantly older at the time of diagnosis than men. This might be because women have fewer risk cofactors such as non-alcoholic fatty liver disease (NASH) and alcohol intake, usually leading to elevated liver enzyme levels and further investigation [35]. According to Guerrini *et al.* [35], heavy drinking is overrepresented in the male population. Papatheodoridis *et al.* [36] reported that up to 15% of Greek blood donors show elevated liver enzyme levels that are most likely due to NASH. They also found a strong association of NASH with the male sex, which suggests that earlier diagnosis of HCV infection in men might be due to a higher frequency of elevated liver enzyme levels in the male population. Similar data are available for the United States, with a strong association between elevated alanine transaminase (ALT) values and risk factors for NASH [10,37]. Recent publications suggest that disease progression is strongly associated with alcohol intake, obesity, the metabolic syndrome and hepatic steatosis, all of which emphasise that the patient's age at the time of diagnosis seems to be related to the presence of these host factors [1,11,38]. We have shown here that disease progression is associated with higher BMI, higher age at time of diagnosis, and probably with risk factors that are more prevalent in men.

In general, HCV infection is detected under the following two circumstances: most commonly, a patient with chronic hepatitis C is found to have elevated liver enzyme levels, which leads to further investigation and subsequent diagnosis. Another possibility is that patients are detected by screening for HCV antibodies in well-defined risk groups. Although there have been clear recommendations (9) for HCV screening in risk groups since the late 1990s, the mean age at the time of the first diagnosis did not change in our population between 1992 and 2006. It was very surprising that the age of patients with an unknown source of transmission was significantly lower than that of patients infected via blood products or plasma donation. This leads to

the question why persons with known risk factors are not diagnosed earlier. Lack of knowledge about HCV risk factors (use of blood products before 1991, haemophilia, haemodialysis, HCV-positive mother, intravenous drug use, plasma donation in the 1970s (39), piercing and acupuncture, unsafe tattooing, nosocomial infections (40)) might be the main reason for the late diagnosis of HCV infection.

Conclusions

The number of new cases of chronic hepatitis C has decreased substantially over the past decade. There has been a major change in the risk factors for HCV acquisition, with blood products and plasma donation now playing only a minor role. While the risk factors have changed over time, the genotype distribution remained relatively stable. Although risk factors for obtaining HCV are well established we did not find a decrease in the age of first diagnosis. Besides consistent screening in defined risk groups it is important to raise awareness of the risk factors for HCV acquisition and the progression of liver disease [41].

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