Impact factor 6.15

Eurosurveillance

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

Vol. 18 | Weekly issue 23 | 06 June 2013

Surveillance and outbreak reports

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Travel-associated Legionnaires' disease in Europe, 2010

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Citation style for this article:
de Jong B, Payne Hallström L, Robesyn E, Ursut D, Zucs P, on behalf of ELDSNet (European Legionnaires' Disease Surveillance Network). Travel-associated Legionnaires' disease in Europe, 2010. Euro Surveill. 2013;18(23):pii=20498. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20498

Article submitted on 12 November 2012 / published on 06 June 2013

In 2010, the European surveillance network for travel-associated Legionnaires' disease (ELDSNet, previously EWGLINET) received reports of 864 cases of travel-associated Legionnaires' disease, of whom 24 were reported to have had a fatal outcome. As in previous years, a very low proportion of clinical isolates were obtained (45 cases, 5.6%). In the 2010 dataset, male cases outnumbered female cases by 2.6:1 and had a median age of 61 years (range: 21–96), while the median age for women was 63 years (range: 12–95). The network identified 100 new clusters in 2010, of which 44 involved only one case from each reporting country and would probably not have been detected by national surveillance schemes alone. The largest cluster (having 14 cases) was associated with a cruise ship. *Legionella* species were detected at 61 of the 100 accommodation site clusters investigated. The names of five accommodation sites were published on the ECDC website.

Introduction

Legionnaires' disease is an uncommon form of pneumonia caused by *Legionella* bacteria. It has no particular clinical features that clearly distinguish it from other types of pneumonia, and laboratory investigations must be carried out to confirm the diagnosis. It normally takes between 2 and 10 days to develop symptoms (typically five to six days) but very rarely, some cases may take two to three weeks to develop symptoms. Patients usually start with a dry cough, fever, headache and sometimes diarrhoea and many go on to get pneumonia. People over the age of 50 years are more at risk than younger people, and males are more at risk than females. Effective antibiotic treatment is available if the diagnosis is made early in the illness. Death due to the disease occurs in about 5% to 15% of travellers who develop the disease, depending on their age and health status. Smokers are more at risk than non-smokers [1].

In April 2010, ELDSNet (European Legionnaires' Disease Surveillance Network) was established, when the European surveillance scheme for travel-associated Legionnaires' disease (EWGLINET) was transferred to the European Centre for Disease Prevention

Box

European Union case definition of Legionnaires' disease

Individual cases of travel-associated Legionnaire

Clinical criteria:

Any person with pneumonia.

Laboratory criteria for case confirmation:

At least one of the following three:

- Isolation of *Legionella* spp. from respiratory secretions or any normally sterile site;
- Detection of *Legionella pneumophila* antigen in urine;
- *Legionella pneumophila* serogroup 1 specific antibody response.

Laboratory criteria for a probable case:

At least one of the following four:

- Detection of *Legionella pneumophila* antigen in respiratory secretions or lung tissue, e.g. by DFA staining using monoclonal-antibody derived reagents;
- Detection of *Legionella* spp. nucleic acid in a clinical specimen;
- *Legionella pneumophila* non-serogroup 1 or other *Legionella* spp. specific antibody response;
- *L. pneumophila* serogroup 1, other serogroups or other *Legionella* species: single high titre in specific serum antibody.

Epidemiological criteria:

At least one of the following two epidemiological links:

- Environmental exposure;
- Exposure to the same common source.

Case classification

Possible case
NA

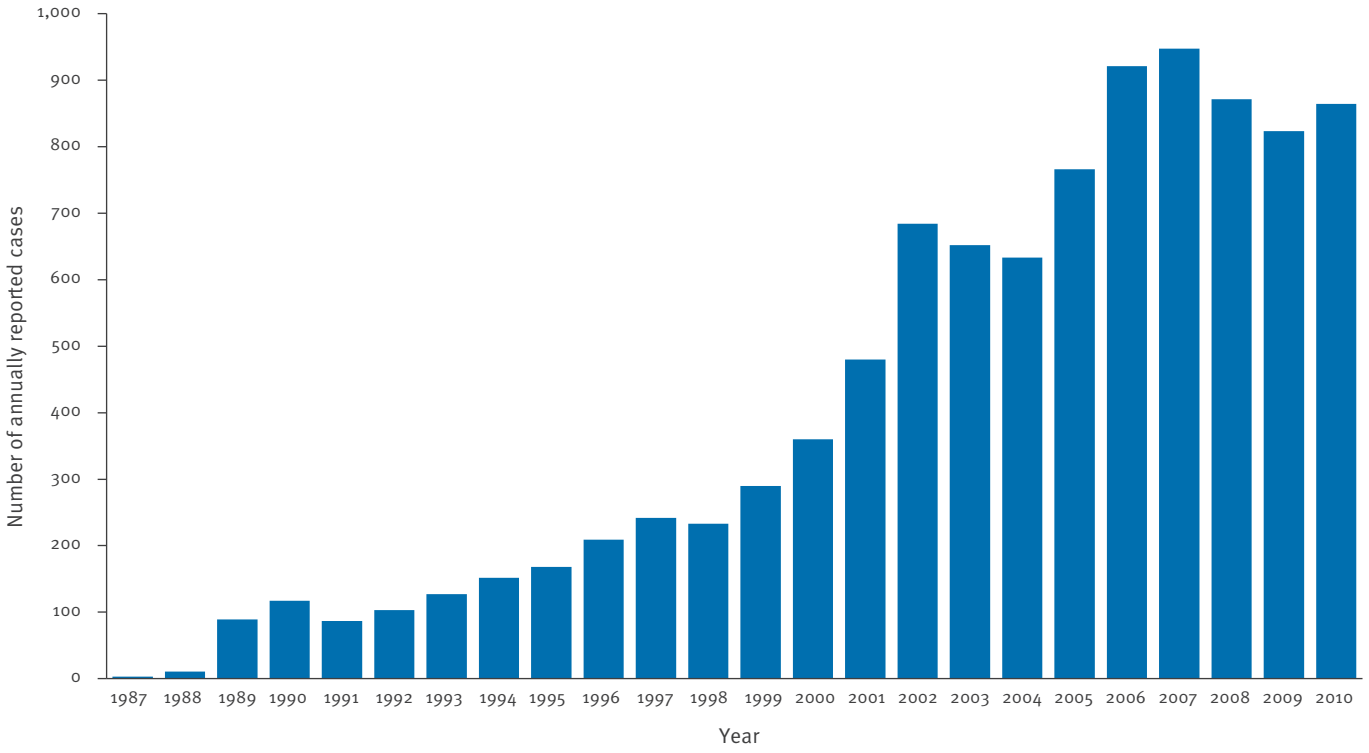
Probable case
Any person meeting the clinical criteria AND at least one positive laboratory test for a probable case OR an epidemiological link.

Confirmed case
Any person meeting the clinical and the laboratory criteria for case confirmation.

DFA: direct fluorescent antibody; NA: not applicable.
Source:[2].

Figure 1

Annual number of reported cases of travel-associated Legionnaires' disease, EU/EEA countries, 1987–2010



EEA: European Economic Area; EU: European Union.
Source: [5].

and Control (ECDC) from the former coordinating centre in London. EWGLINET was established in 1987 by the European Working Group for *Legionella* Infections, making ELDSNet/EWGLINET the oldest European infectious disease surveillance network. The added value of European surveillance has been clearly demonstrated since the late 80s [2-5]. The objectives of this article are to communicate the results of the surveillance of travel-associated Legionnaires' disease in European Union (EU)/European Economic Area (EEA) Member States for cases with onset of disease in 2010.

Methods

Legionnaires' disease is a statutorily notifiable disease in all EU/EEA Member States. The EU case definition [2] is shown (Box).

Individual cases of travel-associated Legionnaires' disease are in most circumstances diagnosed and reported by the case's country of residence to the European Surveillance System (TESSy) at ECDC. Case reports include age, sex, date of onset of disease, method of diagnosis and travel information for the different places where the case had stayed within two to ten days before onset of disease. After receiving the report, the TESSy database is searched to determine whether a new case should be classified as a single case or as part of a cluster, according to the following definitions used by the network.

A single case: a person who stayed at a public accommodation site in the two to ten days before onset of illness and the site has not been associated with any other case of Legionnaires' disease in the previous two years.

- A cluster: two or more cases who stayed at the same public accommodation site in the two to ten days before onset of illness and whose onsets were within the same two-year period.
- If there are three or cases or more with onset of disease within the same three-month period, this is called a rapidly evolving cluster and a notification is sent to all tour operators.

If there is a single case, a notification is sent to the country where the accommodation site is situated, with a copy to the reporting country. If the case is a part of a cluster, a notification is sent to all network members. When the accommodation site is outside EU and when a specific contact person for ELDSNet is known, the country concerned is included as a recipient of the notification. All notifications, except those relating to

domestic travellers, are also sent to the World Health Organization.

When a cluster is detected, a full investigation is required at the accommodation site and preliminary results from the risk assessment and start of control measures should be reported back to ECDC within two weeks of the alert, using the standard operating procedures Form A [5]. The investigation is carried out by regional or local public health authority, depending on the national rules in each country. The investigation and risk assessment carried out are described in the *EWGLI technical guidelines for the investigation, control and prevention of travel associated Legionnaires' disease* [4].

A second form, Form B, is then used to report the results of environmental sampling and the control measures applied at the site back to the coordinating centre in ECDC within a further four weeks, thus allowing six weeks in total for all investigations to be completed. If the forms are not returned within the time frames, or they report that actions and control measures are unsatisfactory, ELDSNet publishes the details of the site associated with the cluster on its website and tour operators are informed about the accommodation site being published. Information is removed from the website when the investigations and control measures are reported to have been satisfactorily completed. If a cluster is associated with more than one accommodation site, it is noted as a 'complex cluster' and all sites stayed at by the cluster cases are subject to the same investigation procedures as described above.

The data presented here is also included in the annual surveillance report for Legionnaires' disease 2010 [5]. In 2010, there were no data from Germany, but they are now part of the travel-associated Legionnaires' disease reporting scheme.

We use in this article a similar reporting format as used in previous publications on travel-associated Legionnaires' disease data, to facilitate comparison [6-9].

Table

Cases of travel-associated cases of Legionnaires' disease by reporting country, 2009–10

Reporting country	Number of reported cases	
	2009	2010
France	163	191
United Kingdom	173	154
Netherlands	109	148
Italy	169	142
Spain	65	67
Denmark	34	32
Norway	21	25
Sweden	22	20
Austria	17	19
Belgium	12	16
United States	11	11
Finland	6	8
Ireland	2	7
Czech Republic	5	5
Malta	0	5
Luxembourg	2	3
Portugal	4	3
Hungary	2	2
Croatia	1	2
Latvia	0	1
Slovenia	2	1
Bulgaria	1	0
Others	0	2
Total	**821**	**864**

Source of 2009 data: The European Surveillance System (TESSy) data downloaded 5 August 2011.

Results

A total of 864 cases of travel-associated Legionnaires' disease with onset of disease in 2010 were reported to EWGLINET/ELDSNet. This is an increase (+5.6%) compared with the 818 cases reported in 2009 [10], but does not reach the peak of 947 cases observed in 2007 (Figure 1).

Cases were reported from 19 EU/EEA countries (United Kingdom (UK) counted as one country) and two countries outside the EU (United States, 11 cases, and Croatia, 2 cases), as the cases were associated with accommodation sites in the EU. The countries that reported the most cases were France (n= 191), the UK (n=154), the Netherlands (n=148) and Italy (n=142) (Table).

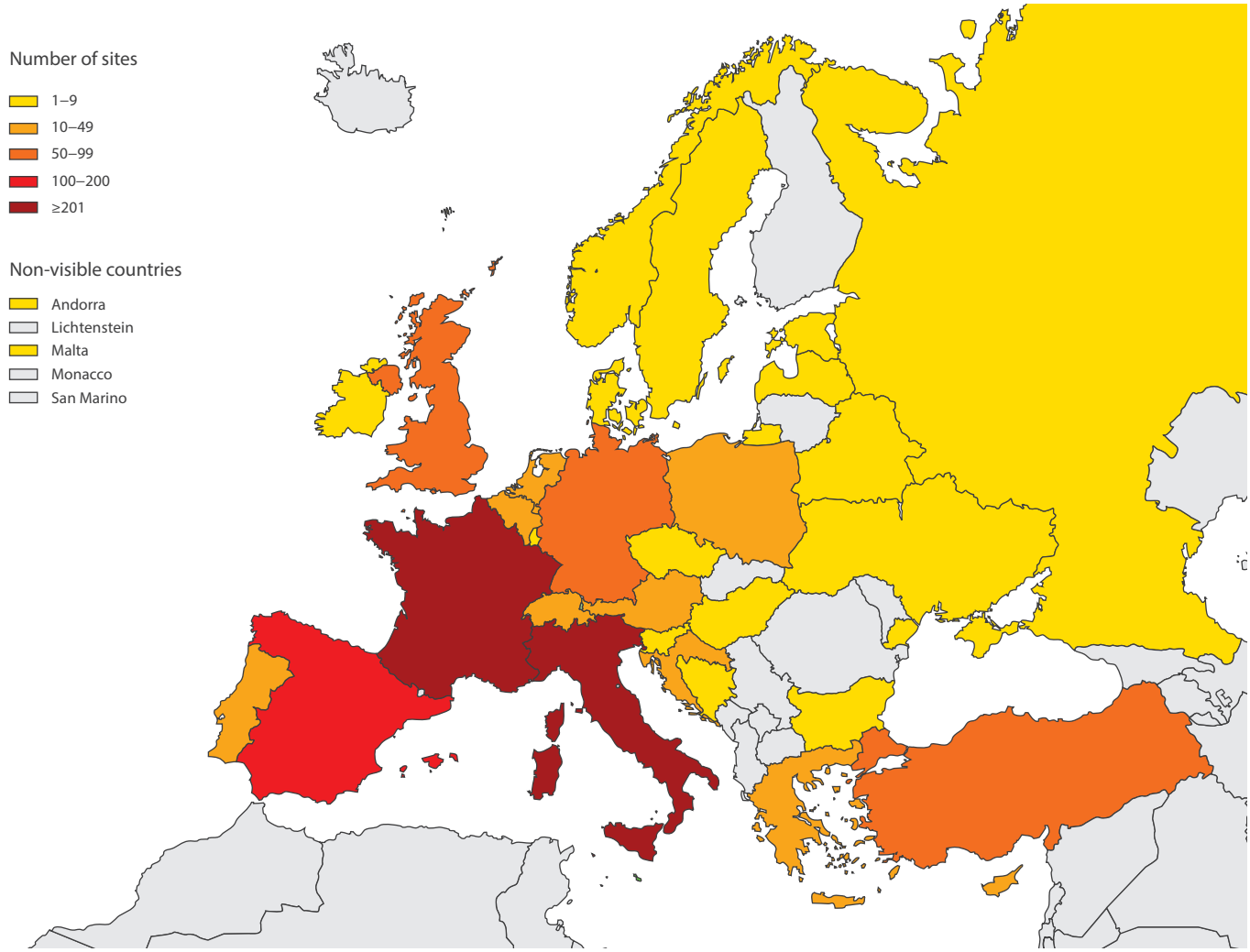
Among the reported cases, 624 (72.2%) were male and 240 (27.7%) were female, resulting in a male to female ratio of 2.6:1, which was almost identical to the ratio for 2009 (2.7:1) [10].

Cases were reported in all age groups except the youngest one, the median age being 61 years (range: 21–96) in male cases and 63 years (range: 12–95) in female cases. The highest proportion of cases was in the 60–69-year age group (male cases: n=183; female cases: n=82).

Outcome of illness was reported for 514 (59.5%) cases (voluntary reporting and different definitions are used in the reporting countries). Of these cases, 24 (4.7%)

Figure 2

Accommodation sites per destination country associated with cases of travel-associated Legionnaires' disease, EU Member States and neighbouring countries, 2010



EU: European Union.
Source: [5].

were reported to have had a fatal outcome, almost the same proportion reported in 2009. Of the four female cases who had a fatal outcome, one was aged 58 years and the other three were aged 82 years. The fatal cases among the 20 male cases were aged from 38 years up to 90 years-old; the majority of male cases with a fatal outcome were in the age group 60–69 years.

There is seasonal variation in the onset of travel-associated Legionnaires' disease: with more cases appearing during late summer [6-9]. In 2010, the number of cases peaked in August, with 156 cases, followed by September, with 136 cases. January, February, March, April and December were the months when the lowest number of cases, approximately 30 per month, had onset of disease.

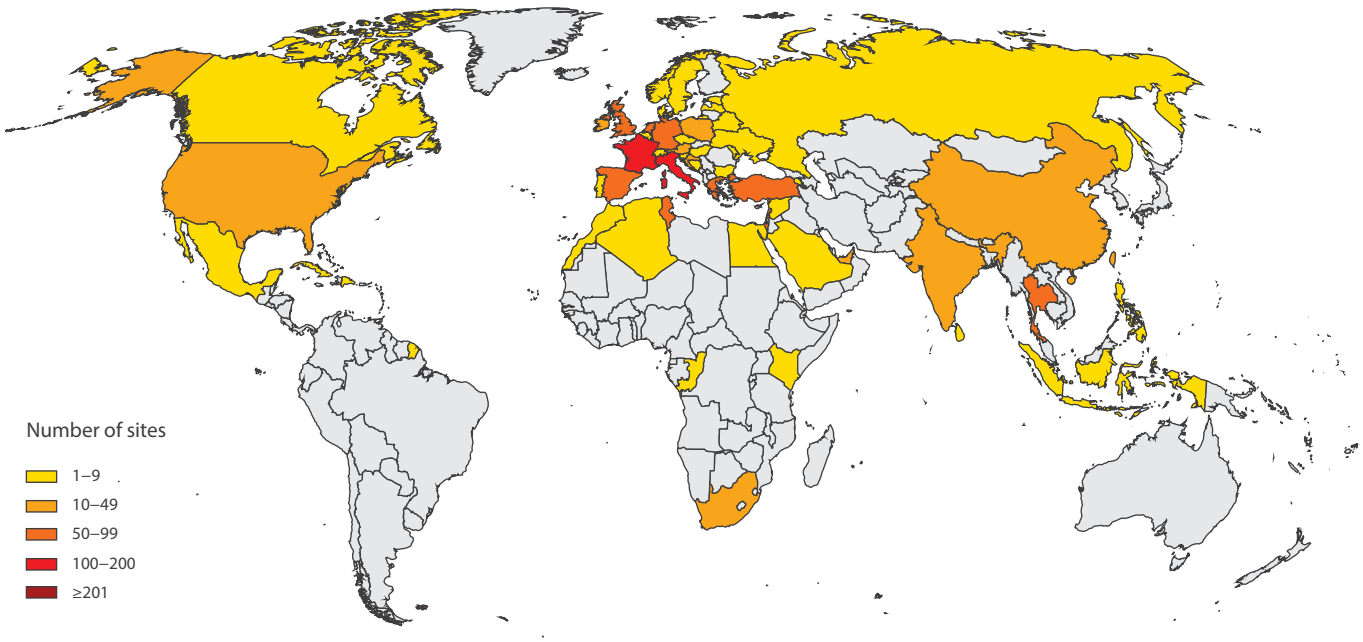
Microbiological analysis

A total of 809 (94%) cases in 2010 were reported as confirmed, according to the EU case definition. Of these, 45 (6%) were diagnosed by culture of the causative organism, a decrease from 10% in 2009. Of the culture-confirmed cases, 27 were also diagnosed by urinary antigen detection. The vast majority of confirmed cases (n=762, 94%) were diagnosed by detection of urinary antigen alone. A total of 10 cases (1%) were confirmed as being due to *Legionella pneumophila* serogroup 1 by specific antibody response.

The remaining 55 (6%) cases were classified as probable following presumptive diagnosis by single high titre (n=28, 3%), detection of *Legionella* spp. nucleic acid (n=19, 2%) and antibody response specific for *L. pneumophila* non-serogroup 1 or other *Legionella*

Figure 3

Accommodation sites per destination country associated with cases of travel-associated Legionnaires' disease worldwide, 2010



Source: [5].

spp. (n=8, 1.0%). Altogether, 672 (78%) cases were reported as being infected with *L. pneumophila* serogroup 1, three with *L. pneumophila* serogroup 3, two with *L. pneumophila* serogroup 6, one with *L. pneumophila* serogroup 12 and three with *L. pneumophila* mixed serogroups. Furthermore, 158 cases were reported as *L. pneumophila* serogroup unknown, 1 as *Legionella bozemannii* and 10 as *Legionella* species unknown. For 14 cases, the *Legionella* species was not reported. Sequence-based types were reported for 13 cases (eight from Denmark, four from the UK and one from Austria).

Travel

The 864 reported cases had made 1,279 visits to accommodation sites around the world.

They visited a total of 66 countries in the 2–10 days before onset of disease. A total of 654 (76%) cases travelled within the EU: 621 cases visited only one Member State and 33 more than one. Some 20% (n=175) of cases travelled outside the EU: 166 to a single destination and 9 to more than one non-EU country. A total of 30 cases (3%) went to both EU and non-EU destinations and 32 cases were associated with cruise ships.

Italy was the country where most cases (n=209) were infected, followed by Spain (177 cases), France (172 cases) and Turkey (48 cases). A total of 169 cases were French residents: 105 (62%) of them visited accommodation sites in France. Likewise, of the 119 Italian residents reported with Legionnaires' disease, 105 (88%) had visited accommodation sites in Italy.

The number of accommodation sites per destination country with cases of travel-associated Legionnaires' disease is shown in Figures 2 and 3.

Clusters

A total of 100 new clusters (74 in EU Member States and 26 outside the EU) were detected in 2010, involving 213 associated cases. The largest cluster was associated with a cruise ship and involved 14 associated cases. Italy had the highest number of clusters (n=24) followed by Spain (n=14), France (n=12) and Turkey (n=10). Altogether, clusters in the EU occurred in 13 Member States and on two cruise ships. Outside the EU, 26 clusters occurred in 16 countries and on one cruise ship.

Of the 100 clusters, 44 comprised single cases reported from two or more countries and would probably not have been detected without the European surveillance network. More than 50% of the clusters (n=51) were detected between July and September.

Complex clusters were more associated with accommodation sites in countries where organised tours to

Figure 4

Clusters of cases of travel-associated Legionnaires' disease per destination country in EU Member States and neighbouring countries, 2010

EU: European Union.
Source: [5].

several tourist sites took place, such as China, India, South Africa and Thailand.

Six rapidly evolving clusters were detected: Greece (n=2), Italy (n=2), Spain (n=1) and on a cruise ship (n=1).

The number of clusters per destination country is shown in Figures 4 and 5.

Investigations and publication

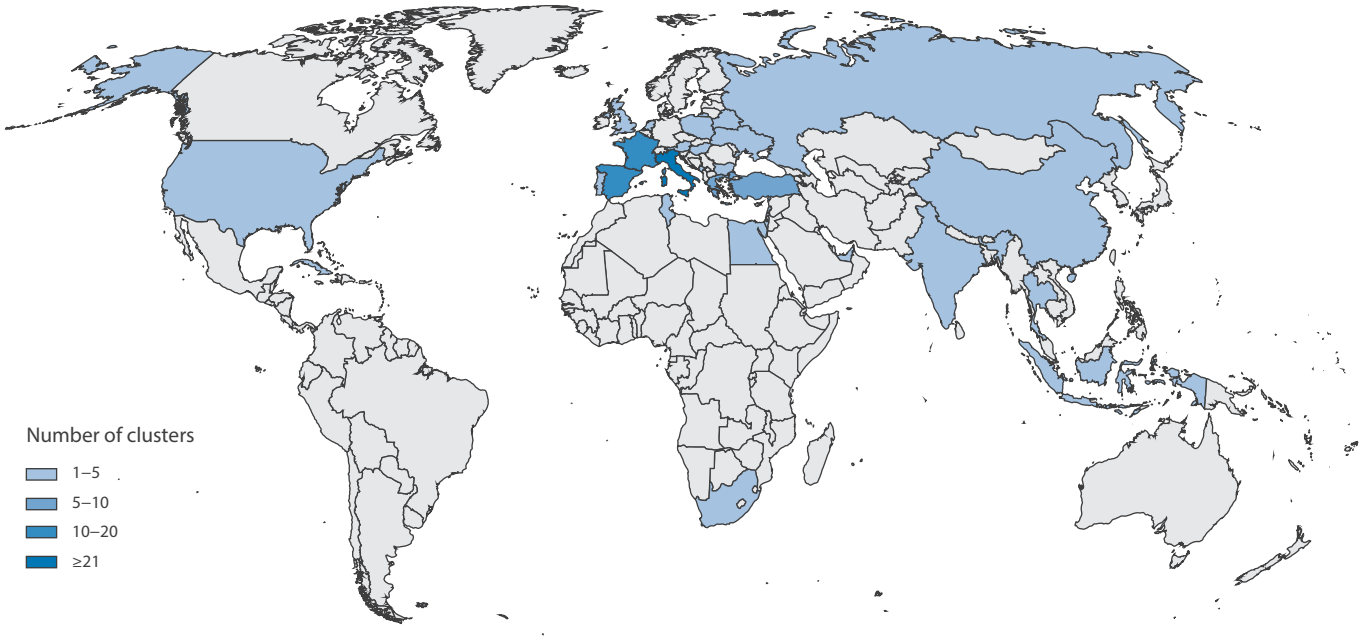
All accommodation sites associated with a cluster of travel-associated Legionnaires' disease ,situated within an EU Member State, should be investigated as described above. In 2010, 100 form Bs were returned to EWGLINET/ELDSNet, reporting detection of *Legionella* in 61 accommodation sites. The forms were returned not only by Member States but also by several non-EU countries, on a voluntary basis. However, for five sites, form B was not received or the form stated uncertainty regarding the control measures taken, so the names and locations of these sites were published on the ECDC website.

Discussion

During 2006 to 2008, the number of cases of travel-associated Legionnaires' disease reported per year had varied from 866 to 947 [7-9]. Legionnaires' disease is still underascertained in most European countries since specific testing for *Legionella* in patients with pneumonia is not a routine procedure [10]. Furthermore, use of urinary antigen detection as the only laboratory method will lead to underdetection of cases with *Legionella* non-*pneumophila* and non-serogroup 1, since the method is designed to detect only *L. pneumophila* serogroup 1. It is estimated that only

Figure 5

Clusters of cases of travel-associated Legionnaires' disease per destination country worldwide, 2010



Source: [5].

10% of all cases of Legionnaires' disease are notified to public health authorities [10].

For several years, the four countries reporting the vast majority of travel-associated cases have been France, the UK, Italy and the Netherlands. This indicates high awareness of Legionnaires' disease among clinicians in these countries. France and Italy also reported the highest numbers of cases in domestic travellers.

The proportion of cases diagnosed by culture decreased from 10% in 2009 to 5.6% in 2010. However, the decrease was not so drastic when compared with the number of culture-confirmed cases from 2005 to 2008, when the proportion varied from 4.9% to 8.2% [6-9)]. Nevertheless, clinicians should be encouraged to collect more specimens for culturing. It is important to be able to compare clinical isolates with environmental isolates from different sampling sites, to identify the source of infection and prevent any subsequent cases.

The case fatality rate for 2010 (4.7%) was lower than the 5.8–9.8% between 2006 and 2009. However, in more than 40% of the cases, the clinical outcome of the patient was unknown at the time of reporting. In the interest of timely reporting and implementation of control measures as soon as possible at the associated accommodation sites, this incompleteness of outcome data seems acceptable.

The added value of ELDSNet is easier to quantify than for other similar European surveillance networks, in that 44% of the clusters reported would most probably not have been detected without ELDSNet. Some countries do take action when a single case is reported to be associated with an accommodation site in that country, but in most countries, action is only taken after a cluster notification. Therefore, ELDSNet cluster notifications help to identify accommodation sites that might pose a risk to human health while the control measures implemented prevent further cases of Legionnaires' disease. This is demonstrated by the fact that in 61 of the 100 accommodation sites reported to have been sampled, *Legionella* bacteria were identified in the water systems.

Despite the challenges and changes in reporting systems with transition of the network to a new coordination centre in April 2010, network members have continued to report cases in a timely manner and undertake cluster management in response to notifications. This highlights the dedication and considerable added value of this network for public health in Europe.

Acknowledgements

We would like to thank all network members for reporting and all persons involved in public health programmes for the control and prevention of travel -associated Legionnaires' disease. A list of current collaborating centres can be found on the ECDC website [11]. We would also like to thank Virginia Estevez, ECDC, for her support in creating maps.

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Legionnaires' disease in Italy: results of the epidemiological surveillance from 2000 to 2011

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Citation style for this article:
Rota MC, Caporali MG, Bella A, Ricci ML, Napoli C. Legionnaires' disease in Italy: results of the epidemiological surveillance from 2000 to 2011. Euro Surveill. 2013;18(23):pii=20497. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20497

Article submitted on 03 July 2012 / published on 06 June 2013

According to the Italian Surveillance System for Legionnaires' disease (LD), physicians must fill in a form for every case and send it through the Local Health Units to the National Institute of Health (Istituto Superiore di Sanità, ISS). Forms reported in the period from 2000 to 2011 were analysed and discussed. A total of 9,803 cases of LD were reported to ISS during the study period. The median age of cases was 63 years, with a ratio male/female of 2.6 and a case fatality rate of 11.8%. The number of cases has been steadily increasing from 192 cases in 2000 to 1,235 in 2010 and 1,008 cases in 2011. The reported cases showed a geographical gradient, with the highest number notified in the north and the lowest in the south. The majority of cases (73.0%) were community-acquired, followed by travel-associated (13.5%) and healthcare-associated cases (9.3%), cases acquired in long-term care facilities (2.1%), and other types of exposure (2.1%). Even though the increasing trend of LD in Italy indicates an improvement in the ability to detect and report cases, the geographical gradient highlights the existence of low reporting areas where the epidemiological surveillance of LD should be further strengthened.

Introduction

Legionella spp. is a ubiquitous intracellular microorganism colonising natural and artificial aquatic environments, which grows at temperatures of 25 to 42°C [1-2]. Presently, a total of 55 species and more than 70 serogroups has been classified [3]; *Legionella pneumophila* serogroup 1 (Lp1) is the most frequently reported aetiological agent in community-acquired legionellosis, although also other serogroups, especially Lp4 and Lp6, are frequently involved in hospital-acquired cases and outbreaks, as well as other species commonly indicated as *Legionella* species (*L. anisa, L. bozemanii, L. dumoffii, L. longbeachae, L. micdadei*) [4-9].

Legionnaires' disease (LD) is a form of interstitial pneumonia that is normally transmitted via aerosol, i.e. inhalation of mist droplets containing the bacteria. The aerosol containing *Legionella* bacteria can be produced by contaminated water sources such as cooling towers, domestic hot-water systems, swimming and spa pools, fountains, respiratory therapy equipment, and other devices that tap into a public water supply. No inter-human transmission has been documented, therefore it can be presumed that natural and artificial aquatic environment is the only source of the infection. Individual risk factors such as long-term medical conditions, heavy smoking or alcohol abuse, and environmental risk factors may influence the likelihood to develop the infection. The problem is particularly relevant in contaminated healthcare facilities because the onset of the disease and its outcome are influenced by the patient's pre-existing pathologies and level of immunocompetence [9,10]. In addition, medical equipment, if not adequately treated, can also be a potential source of infection in hospitals (endoscopes, food or nasogastric tubes, devices for artificial respiration and oxygen therapy, dental tools, etc.) [10].

Recently, the need to strengthen epidemiological surveillance programmes, to improve diagnostic techniques and to set up preventive measures, e.g. the search for sources of infection, periodical controls of drinking water supply systems, and installation of effective disinfection systems, have become a priority [9-15].

The European Working Group for *Legionella* Infections (EWGLI) was established in 1986 with the objective of carrying out international surveillance of travel-associated LD. EWGLI was coordinated by the Health Protection Agency in London from 1993 to the end of March 2010, when the European Centre for Disease Prevention and Control (ECDC) took over the management. Since then, it has been named European Legionnaires' Disease Surveillance Network (ELDSNet) and it involves all 27 European Union (EU) Member States, Iceland and Norway [16].

In Italy, epidemiological surveillance for LD started in 1983, when the Legionellosis National Registry was established and managed by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS); notification of LD became mandatory in 1990. Since then, the number of sporadic and epidemic cases has been growing constantly, but the increase seems due to better reporting and/or improved diagnosis rather than to an increased incidence of the disease [9,17,18].

The objective of this paper is to present the results of the Italian surveillance programme during the period from 2000 to 2011.

Methods

Surveillance system

According to the National Surveillance of LD, for each case of LD diagnosed in Italy, physicians must fill in a surveillance form and send it to the Local Health Units (LHU). The LHU has to start investigations of the epidemic and the environment. The LHU staff interview cases and their relatives to assess risks of contracting LD, to find out about sources of exposure and other LD cases potentially connected to a common source. Potential sources of contamination are investigated and, jointly with the Local Agency for the Environment, water samples are collected for laboratory analysis. The completed notification form is then sent to the ISS, which monitors trends, studies the epidemiological characteristics of LD patients, and looks for clustered cases not identifiable at the local level.

The form reports the patients' socio-demographic data (age, sex, place of residence), clinical data (date of symptom onset, date of hospitalisation, patient outcome), risk factors, patient lifestyle before disease onset (exposure to any of the following settings during the 10 day-incubation period preceding symptom onset: hospitals, dental outpatient clinics, prisons and barracks, hotels, campsites and other recreational facilities such as spas, swimming pools, etc.), laboratory diagnostic tests, and whether an environmental investigation has been carried out.

The forms sent to ISS are classified according to the case definition as confirmed or probable LD, and as community-, hospital- or travel-associated LD, and are entered in a specific database and analysed. Moreover, all cases of travel-associated LD that occurred in foreign travellers who had visited Italy in the 10 days before onset of the disease, and that are reported to ISS by ECDC in the same period, are entered in the database and analysed [16].

The role of the National Reference Laboratory for *Legionella* in the epidemiological surveillance is to confirm LD diagnosis, when the regional reference laboratories lack sufficient capacity to perform the required assays and to carry out molecular typing and matching of clinical and environmental strains.

Case definition

According to the national Guidelines for *Legionella* spp. Control and Prevention [14], a confirmed case of LD is a patient presenting clinical and/or radiological signs of pneumonia associated with at least one of the following laboratory criteria: (i) isolation of *Legionella* spp. from a culture of bronco-pulmonary secretions, (ii) a four-fold increase in IgG antibody titres for *L. pneumophila* 1, and (iii) a positive urinary antigen test.

A probable case is a patient presenting clinical and/or radiological signs of pneumonia associated with a single high level of specific antibodies to *L. pneumophila* 1 (≥1:256), or a positive direct immunofluorescence test, or a positive PCR.

In healthcare settings (hospitals and care homes for the elderly), a definite healthcare-associated case is an LD case that occurred in a patient continuously hospitalised during the 10-day period before symptom onset. If hospitalisation has not been continuous, the case is considered as a possible healthcare-associated case. A healthcare-associated cluster is defined by two or more probable or confirmed cases who stayed in the same hospital in the period two to 10 days before the symptom onset and whose symptom onset was within the same six-month period [14].

Travel-associated single cases are defined as cases who, in the ten days before onset of the illness, stayed at or visited an accommodation site never before associated with cases of LD, or cases who stayed at an accommodation site linked to other cases of LD that occurred more than two years previously [13]. A travel-associated cluster is defined by two or more cases who stayed at or visited the same accommodation site in the period two to 10 days before symptom onset and whose symptom onset was within the same two-year period [13].

The term re-offenders, according to the EWGLI definition [19], applies to those accommodation sites (hotels, campsites, apartments, etc.) that are found to be associated with at least one further case within the same two-year period after a cluster had been detected and investigated.

An outbreak is defined as the occurrence of a minimum of 10 cases of LD who are associated in time and place and share a common exposure to a contaminated source.

Data analysis

Results are expressed as median and interquartile range (IQR) or as frequencies and percentage. Differences among percentages were assessed by the chi-square test or, when appropriate, by chi-square test for trend. Data were also analysed by sex and geographical area. Northern Italy included the regions of Piedmont, Lombardy, the Autonomous Province of Trento, the Autonomous Province of Bolzano, Veneto,

Friuli Venezia Giulia, Liguria, and Emilia-Romagna; central Italy included Tuscany, Umbria, Marches, and Lazio; southern Italy included Abruzzo, Molise, Apulia, Calabria, Sicily, and Sardinia.

The annual incidence of LD per million population was calculated using the Italian population data provided for the corresponding year by the National Institute of Statistics (ISTAT) [20]. All statistical analyses were performed using STATA software version 11.2 (STATA Corporation, College Station, Texas, United States).

Results

Case characteristics

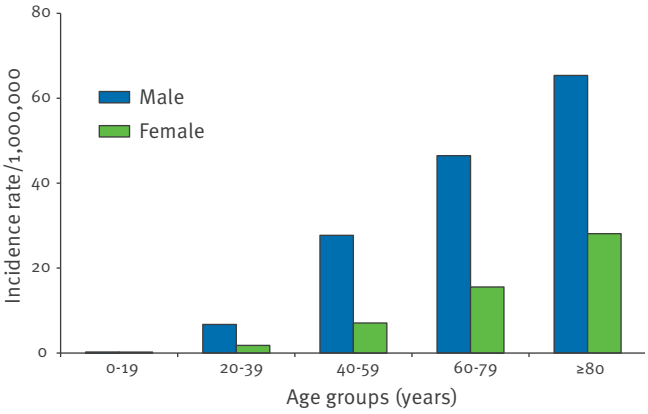
During the study period, a total of 9,803 cases of LD were reported to ISS (annual mean: 817; range: 192–1,235). The median age of cases was 63 years (IQR: 24 years), 7,068 (72.1%) were male and 2,735 (27.9%) female, a male/female ratio of 2.6. Figure 1 shows the incidence rates per 1 million population of LD cases by sex and age group. Overall, 9,295 (94.8%) cases were confirmed. The number of cases has been increasing steadily during the study years: 192 cases were notified in 2000, a three-fold increase was identified in 2002, and a further two-fold increase was registered in 2008, reaching a peak of 1,235 cases in 2010. In 2011 a small decrease was registered with 1,008 notified cases (Table).

A statistically significant upward trend was observed in the 12-year surveillance period (p<0.0001). When analysing the data by geographical area (northern, central and southern Italy), a similar upward trend was observed for each area (p<0.0001) (Figure 2). Indeed, the overall annual incidence increased from 3.4 per million inhabitants in 2000 to 16.6 per million inhabitants in 2011 (Figure 2), with a mean annual growth rate of 20.1% (range: 18.3–92.4%).

However, the reported cases showed a consistent and significant geographical gradient, with the highest number notified in the north and the lowest in the south, which did not change during the study period. In the northern regions, incidence increased from six cases per million inhabitants in 2000 to 25.1 cases per million inhabitants in 2011, in the central regions from

Figure 1

Incidence rates per 1 million inhabitants of Legionnaires' disease cases by sex and age, Italy, 2000–2011 (n=9,803)



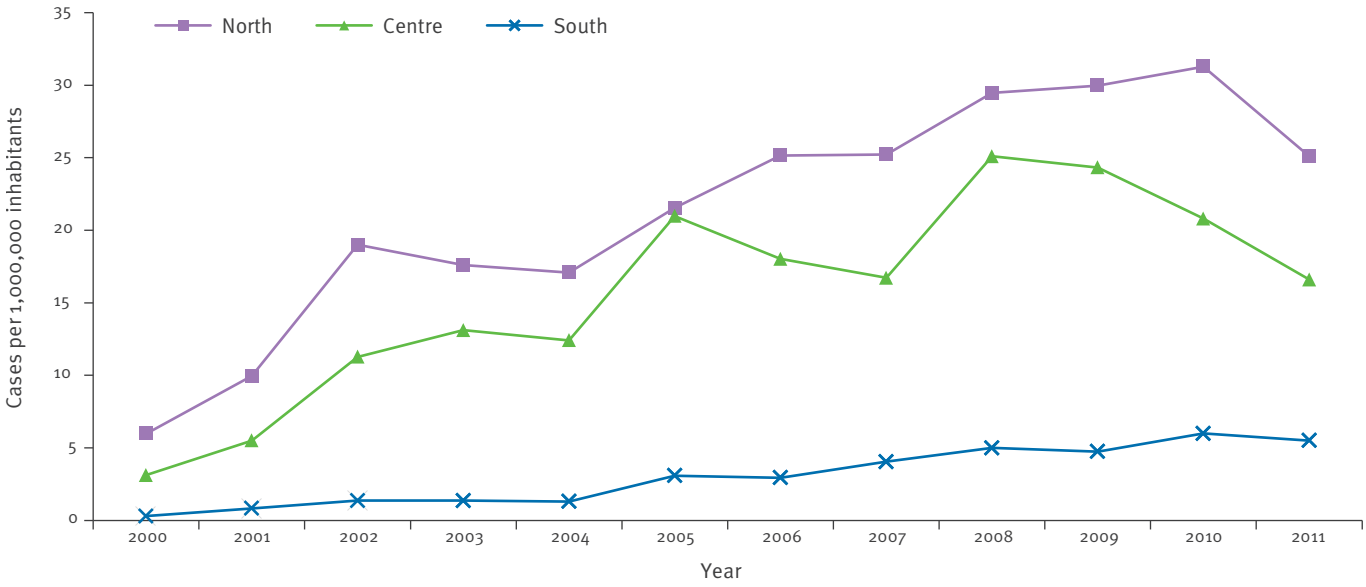
Table

Legionnaires' disease cases diagnosed by year and exposure, Italy, 2000–2011 (n=9,803)

Year	Community-acquired	Travel-associated	Healthcare-associated	Other healthcare facilities	Other exposures	Total
2000	121 (63.0%)	27 (14.1%)	40 (20.8%)	3 (1.6%)	1 (0.5%)	192
2001	211 (63.8%)	60 (18.1%)	53 (16.0%)	1 (0.3%)	6 (1.8%)	331
2002	455 (71.4%)	90 (14.1%)	76 (11.9%)	4 (0.6%)	12 (1.9%)	637
2003	449 (71.7%)	85 (13.6%)	74 (11.8%)	7 (1.1%)	11 (1.8%)	626
2004	427 (69.9%)	69 (11.3%)	98 (16.0%)	8 (1.3%)	9 (1.5%)	611
2005	664 (76,3%)	104 (12.0%)	70 (8.1%)	14 (1.6%)	18 (2.1%)	870
2006	654 (69.9%)	151 (16.1%)	87 (9.3%)	13 (1.4%)	31 (3.3%)	936
2007	663 (69.5%)	159 (16.7%)	89 (9.3%)	16 (1.7%)	27 (2.8%)	954
2008	898 (75.1%)	143 (12.0%)	94 (7.9%)	30 (2.5%)	31 (2.6%)	1,196
2009	864 (71.6%)	168 (13.9%)	102 (8.5%)	41 (3.4%)	32 (2.7%)	1,207
2010	986 (79.8%)	126 (10.2%)	65 (5.3%)	42 (3.4%)	16 (1.3%)	1,235
2011	771 (76.5%)	137 (13.6%)	65 (6.5%)	28 (2.8%)	7 (0.7%)	1,008
Total	**7,163 (73.1%)**	**1,319(13.5%)**	**913 (9.3%)**	**207 (2.1%)**	**201(2.1%)**	**9,803**

Figure 2

Legionnaires' disease incidence by year of onset and geographical area, Italy, 2000–2011 (n=9,803)



3.1 to 16.6 per million inhabitants, and in the southern regions from 0.3 to 5.5 per million inhabitants. Figure 3 shows the incidence rate by region in 2000 and 2011. When comparing the annual incidences in the three geographical areas, a statistically significant difference was observed for the entire study period, except for the year 2005 when the incidences in northern and central areas did not differ statistically (p=0.739) because two regions belonging to the central area reported a higher number of cases than usual (the reason is unknown since no outbreak were detected) (Figure 2).

Among the 9,803 notified cases, 5,326 (54.3%) reported at least one underlying disease. Chronic diseases, including respiratory or cardiac diseases and diabetes, were reported in 3,735 (70.1%) of these, cancer in 766 (14.4%), infectious diseases in 304 (5.7%), organ transplantation in 114 (2.1%), immunosuppressive condition in 74 (1.4%) cases, and other diseases in 333 cases (6.3%).

Stratifying cases by age, 3,278 out of 9,803 (33.4%) were older than 70 years. In this age group the proportion of individuals with underlying disease was 73.3%, significantly higher than among younger individuals (48.6%; p<0.0001).

The main risk factor was tobacco smoke, which was reported in 4,163 of 9,803 patients (42.5%).

Cases by setting

When analysing the cases by setting, the majority (7,163, 73.0%) were community-acquired cases, followed by 1,319 (13.5%) travel-associated cases, 913 (9.3%) healthcare-associated cases of whom 881 were confirmed and 32 were probable, and 207 (2.1%) cases acquired in long-term care facilities. Some 201 (2.1%) cases reported other types of exposure such as swimming pools, dental outpatient clinics and prison (Table).

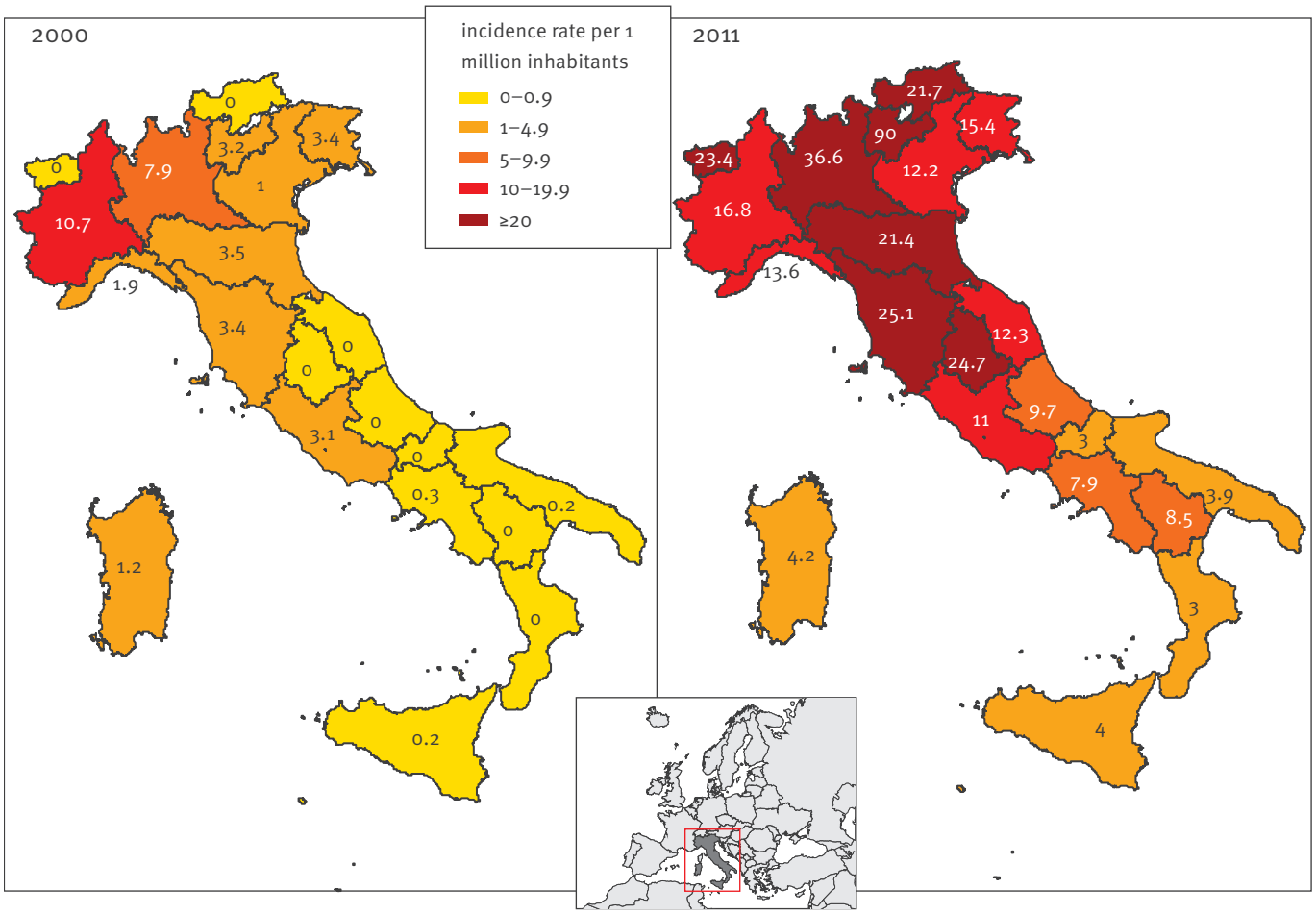
The annual number of healthcare-associated cases increased during the surveillance period from 40 cases in 2000 to a maximum of 102 cases in 2009. However, due to a more evident increase in the percentage of community-acquired cases, the proportion of healthcare-associated cases diagnosed decreased significantly. In fact, the percentage of community-acquired cases increased from 63% in the year 2000 to a maximum of 79.8% in 2010, while healthcare-associated cases decreased from 20.8% to 5.3%.

During the study period, the 913 reported healthcare-associated cases involved 228 hospitals. The mean number of cases per hospital was 4.0 (range: 1–82), whereby 116 hospitals were associated with only one case, 42 reported only sporadic cases (more than one case with no epidemiological link), and 70 reported at least one cluster. Of the latter, 29 hospitals were associated with repeated clusters up to a maximum of eight, and overall, the 70 hospitals reported 666 healthcare-associated cases.

Also the number of travel-associated LD cases that occurred in Italian tourists hospitalised in Italy rose during the study period, with some fluctuation from 27 cases in 2000 to a maximum of 168 cases in 2009

Figure 3

Legionnaires' disease incidence rate per 1 million inhabitants by region, Italy, 2000–2011 (n=9,803)



(Table and Figure 4). Moreover, EWGLI/ELDSNET reported to ISS that 904 travel-associated LD cases occurred in foreign tourists travelling to Italy; also the number of these cases increased steadily during the study period, reaching a peak in 2007 (Figure 4).

The category Other exposures showed a peak in 2006 of 3.3% of the total cases. It should be noted that among these, the most frequently reported exposures during the entire study period were dental outpatient clinics (39.3%) and swimming pools (41.8%).

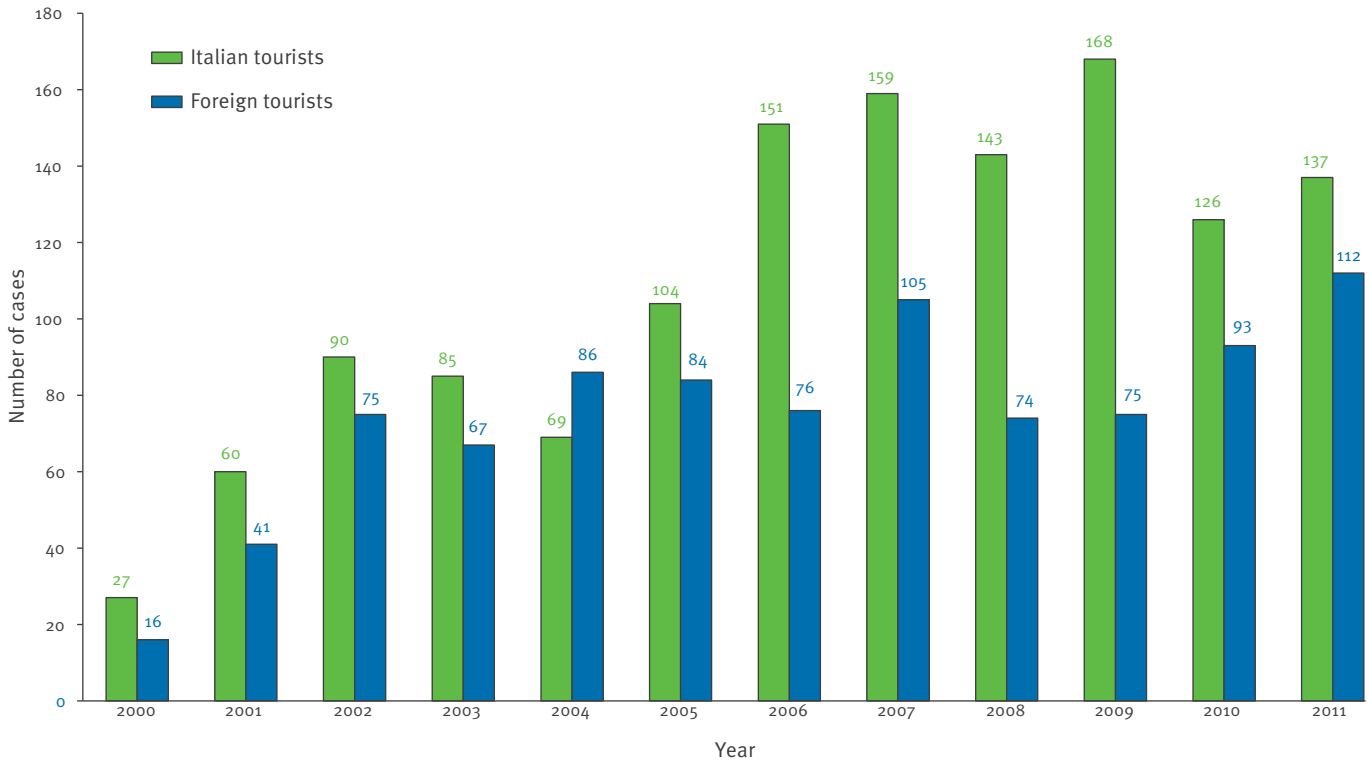
From 2002, when the *European Guidelines for Control and Prevention of Travel Associated Legionnaires' disease* were enforced in Europe and consequently also in Italy, to 2011, 320 Italian accommodation sites were associated with clusters of LD, 79 of which were re-offenders. The number of clusters increased gradually from 2002, and peaked in 2007, when 71 clusters were notified (of which 20 occurred in re-offending sites). From 2008, the number of clusters started to decrease, and in 2011, 46 accommodation sites were reported (of which 14 were re-offenders). The largest cluster of TALD occurred in 2011 in a touristic area in northern Italy, involving 17 tourists from five European countries who had stayed in five accommodation sites [21]. According to EWGLI Guidelines [13], all these accommodation sites underwent a risk assessment and environmental controls, and 191 of the 320 sites tested positive for *Legionella* spp. Investigation results were reported within six weeks to EWGLI/ELDSNET.

Diagnostic methods and disease outcome

Overall, 92.5% of cases were diagnosed by urinary antigen test, which was the most used diagnostic method. Culture was performed in 2.3% of cases, while a four-fold increase in antibody, a single antibody titre, PCR and direct immunofluorescence were used in, respectively, 3.0, 7.4, 0.4 and 0.1% of cases (some cases may have been diagnosed with more than one method). Some 94.3% of cases were diagnosed by only one laboratory method, two methods were used in 5.4%, and three in 0.2% of cases. The use of diagnostic techniques evolved over time with an increasing proportion of urinary antigen testing (50.5% in 2000 versus 94.0% in 2011; $p<0.0001$) used as the only one

Figure 4

Travel-associated Legionnaires' disease, Italy, 2000–2011 (n=1,319)



diagnostic method. By contrast, the use of culture as a unique method has decreased from 3.6% in 2000 to 1.9% in 2011 (p=0.001).

The outcome of the disease in the study period was reported for 50.7% of the cases, with a case fatality rate of 11.8% (annual range: 8–17%) and with no differences by sex (p>0.05).

Community outbreaks

During the study period, three major community outbreaks occurred and were thoroughly investigated. In the two months from 15 August to 18 October 2003, 15 cases of LD were reported in the city of Rome. In order to identify sources of exposure to *Legionella*, environmental investigations were made along with a matched case–control study. This brought to light that people who were regular customers at a certain department store in the area had an almost 10-fold greater risk of contracting the disease (odds ratio: 9.8; 95% confidence interval: 2.1–46.0). An Lp1 was found in the store's cooling tower. The cause of the epidemic was a single strain of Lp1, and this finding was supported by phenotypic and genotypic analysis conducted on human and environmental isolates; the cooling tower was shown to be the origin of the infection [22].

From 20 July to 31 August 2006, an outbreak of 15 confirmed LD cases was detected in Venice. Extensive epidemiological and environmental investigations were conducted to identify the possible source of the outbreak; however, the lack of clinical specimens to match with environmental isolates prevented identification of the source of infection. Nevertheless, disinfection of the cooling towers identified as positive for *Legionella* spp. in the city centre was performed and no more cases were observed.

From 21 December 2005, the number of LD cases notified by the city of Cesano Maderno (a town with 30,000 inhabitants in the north of Italy) started to increase, and by 2 March 2008, 40 confirmed LD cases had been notified, with an annual local incidence ranging from 400 to 700 cases per 1 million population. Epidemiological and environmental investigations started in early 2006 and, in spite of the huge number of air and water samples collected from the patients' homes, industrial and public building cooling tower, as well as the municipal water system, clear evidence of the source of infection was never obtained, even though 49% of the patients' homes tested positive for Lp1 and the only two clinical strains available had the same genomic profile (ST23) as those cultured from 11 houses, suggesting that the household water systems were a possible source of infection. In spite of extensive prevention measures adopted nowadays, cases are still being reported, and the incidence rate in Cesano Maderno continues to be much higher than anywhere else in Italy.

Discussion

The 12-year epidemiological surveillance data show that in Italy there has been a substantial increase of reported LD cases. This increase reflects the increased incidence registered all over Europe [23]. Moreover, while in 2000 and 2001, the incidence rate in Italy was lower than the European average (3.4 and 5.8 per million inhabitants versus 5.4 and 7.6 per million inhabitants, respectively, for 2000 and 2001), since 2002 it has been higher than the European rate, with a peak in 2010 (20.5 per million inhabitants versus 12.4 per million inhabitants) [17]. In 2010, only the Netherlands, Spain, France, Slovenia, and Denmark showed higher incidence rates than Italy; nevertheless, the differences between countries must be discussed with caution, because there are many factors that influence notification rates, such as the practitioners' awareness, the compliance of clinicians with the surveillance system, and the effect of local regulations or guidelines on prevention measures [24]. In spite of the increasing reporting trend, the reported incidence rate in Europe is still lower than the true rate, which is estimated to be 100 cases per million inhabitants [25], and several countries, in particular in south–eastern Europe, are still reporting less than one case per million.

Our study highlights that in Italy, the proportion of cases associated with different exposures has changed over time. The percentage of community-acquired cases increased from 63.0% in 2000 to 76.5% in 2011, while healthcare-associated and travel-associated cases decreased from 20.8% to 6.4% and from 14.0% to 13.5%, respectively, in the same years. The reduction in travel-associated LD cases may be the result of an improvement in control and prevention measures implemented in hotels and other accommodation sites in accordance with the enhanced surveillance implemented in the European Member States that participate in EWGLINET in the past and to ELDSnet since 2010.

In the past few years, greater attention has also been paid to the prevention and control of legionellosis in healthcare facilities in Italy, although the problem of healthcare-associated legionellosis remains relevant, highlighting the difficulty in eradicating the microorganism from the water systems, despite regular maintenance and monitoring [9].

The observed increase in the number of cases of community-acquired LD in Italy is the positive outcome of enhanced surveillance and improved diagnostic capacity developed in the past decade. However, despite the impressive increase in case detection, the incidence is still being underestimated especially in the southern regions of the country as highlighted by the findings of a capture/recapture study conducted in 2002 [26] and a study on LD diagnostic capacity conducted in 2006 [27], which underlined that the level of clinical awareness regarding legionellosis is still low and the reporting, although compulsory, is still missed too often. Although the importance of screening for legionellosis of all pneumonia cases reporting risk factors for the disease is underlined every year in the annual report on legionellosis in Italy, and several training courses for health professionals have been organised both at central and local level, many physicians, especially in southern Italy, still may feel that it is not necessary to confirm the aetiological diagnosis of pneumonia as LD in order to treat it. However, from a public health perspective it is important to confirm the diagnosis and report individual cases, so that they can be fully investigated and possible clusters or outbreaks, whether community-, healthcare- or travel-associated, can be identified. The study on LD diagnostic capacity, conducted in a random sample of a third of the Italian hospitals, showed that only 68% of hospitals in the country (and 37.5% in southern Italy) were able to perform at least one diagnostic test for LD [27]. In addition, more than 50% of the hospitals were able to diagnose LD by urinary antigen and/or serology test, while only 29% of the hospitals were able to perform *Legionella* spp. isolation.

These findings were consistent with surveillance data which showed that more than 80% of cases were diagnosed in only five regions located in the north and centre of Italy and that some southern regions had not notified a single case. At the same time, it should be noted that geographical variation in LD incidence rate could partly be related to the climate and meteorological conditions, as recently suggested for other acute respiratory infections [28].

The great majority of the European outbreaks described are related to cooling towers [29-31], and also in Italy, the few community outbreaks that occurred were due to this exposure. For this reason, many European countries are implementing new regulations for cooling towers, including their compulsory registration at local and regional level. These control measures are showing encouraging results [23]. In Italy, no registration is required for cooling towers; consequently an easy and rapid investigation is not always possible.

With regard to diagnostic methods, more than 90% of cases were diagnosed by urinary antigen detection only. It is important to underline that the use of urinary antigen test alone for LD diagnosis can lead to an underestimation of the burden of the disease, because pneumonias caused by *Legionella* species or serogroups different from Lp1 are not always detected by this method. Therefore, while recognising the usefulness of the urinary antigen test, it is necessary that isolation is also attempted in all patients. In 2010, according to data provided by ECDC, 652 cases in Europe (10.3% of the total) were culture-confirmed; however, this proportion varied from 0 (in several countries) to 39.8% (Denmark), and Italy is in the lower part of this range [24]. Culture should, therefore, be attempted and promoted, since it is a precondition for matching clinical and environmental isolates during cluster or outbreak investigations carried out to find the source of infection.

Furthermore, bacterial culture of clinical specimens should be promoted since the lack of clinical samples makes the identification of the source of infection impossible in those accommodation sites where positive environmental samples have been obtained. An environmental sample positive for *Legionella* spp. is not sufficient to determine the source of infection, although the likelihood of a certain accommodation site being the source increases when clusters of two or more cases associated with the same accommodation are reported.

To reduce underestimation of the disease and to better control *Legionella* spp. environmental diffusion, epidemiological surveillance must be further strengthened in Italy, diagnostic tests should be made available in all hospitals, especially in low reporting areas, and culture should be performed whenever possible.

Acknowledgements

We would like to thank all health professionals from regions, local health departments and hospitals for submitting surveillance forms.

Conflict of interest

None declared.

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Critical care surveillance: insights into the impact of the 2010/11 influenza season relative to the 2009/10 pandemic season in England

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Citation style for this article:
Green HK, Ellis J, Galiano M, Watson JM, Pebody RG. Critical care surveillance: insights into the impact of the 2010/11 influenza season relative to the 2009/10 pandemic season in England . Euro Surveill. 2013;18(23):pii=20499. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20499

Article submitted on 23 May 2012 / published on 06 June 2013

In 2010/11, the influenza season in England was marked by a relative increase in impact on the population compared to that seen during the 2009/10 pandemic, with the same influenza subtype, A(H1N1) pdm09, circulating. The peaks in critical care bed occupancy in both seasons coincided with peaks in influenza A(H1N1)pdm09 activity, but onset of influenza in 2010/11 additionally coincided with notably cold weather, a comparatively smaller peak in influenza B activity and increased reports of bacterial co-infection. A bigger impact on critical care services was seen across all regions in England in 2010/11, with, compared to 2009/10, a notable age shift in critical care admissions from children to young adults. The peak of respiratory syncytial virus (RSV) activity did not coincide with critical care admissions, and regression analysis suggested only a small proportion of critical care bed days might be attributed to the virus in either season. Differences in antiviral policy and improved overall vaccine uptake in 2010/11 with an influenza A(H1N1)pdm09 strain containing vaccine between seasons are unlikely to explain the change in impact observed between the two seasons. The reasons behind the relative high level of severe disease in the 2010/11 winter are likely to have resulted from a combination of factors, including an age shift in infection, accumulation of susceptible individuals through waning immunity, new susceptible individuals from new births and cold weather. The importance of further development of severe influenza disease surveillance schemes for future seasons is reinforced.

Introduction

Following the emergence of the novel pandemic influenza A(H1N1)pdm09 virus in April 2009, the United Kingdom (UK) experienced two waves of pandemic virus activity in summer and autumn 2009 resulting in widespread infection in the population, particularly in younger age groups with 65% of 5 to14 year-olds estimated to be infected post-second wave [1,2]. Although overall case-severity was low [3], a substantial number of severe cases (hospitalisations, intensive care admissions and fatalities) were reported, particularly in children under five years-old and individuals with underlying clinical risk factors for severe influenza [4,5]. In 2010/11, despite apparent widespread influenza A(H1N1)pdm09 infection in 2009/10 [2], the first post-pandemic influenza season was marked by reports of an early rapid increase in influenza A(H1N1) pdm09 cases admitted to intensive care, together with an increase in community indicators such as calls to health service help lines over the Christmas period [4,6-8]. The impact and pressure reported on these services at this time over the Christmas period was greater than that seen during the 2009 pandemic in England [6,7,9], with a notable age shift in hospitalised cases apparent from children <15 years of age to young adults aged 15 to 64 years [1,7,9]. The observation of increased influenza A(H1N1)pdm09 impact in the immediate post-pandemic period has been reported in only a few other European countries (Ireland, Denmark and Greece) [4,10,11].

The intensity and severity of any influenza season is influenced by a variety of factors related to the virus, the host and the environment [12-14]. Continual genetic evolution of the influenza virus can modify its ability to invade host tissues and subsequent interaction with the host's immune system. If the virus differs significantly antigenically from previously circulating viruses, there may be an insufficient immune response raised following infection, potentially resulting in a more severe outcome [12]. Various host factors will also dictate the severity of influenza infection – such as age and presence of underlying chronic disease [13]. These can be modified by interventions such as prior vaccination or the use of antivirals. Environmental factors such as cold temperature and low levels of humidity can enhance transmission, both in terms of the stability of the virus and vulnerability of the host to infection [14]. Finally, other viruses or bacteria, often with their own seasonality, may circulate and interact with influenza,

potentially interfering with infection [15] or affecting symptoms through co-infection [16].

In an article in Eurosurveillance, Mytton and colleagues highlighted the increased impact of the 2010/11 influenza season in England compared to the 2009 pandemic and suggested this may be related to differences in intervention strategy between the two periods [6]. One of the data sources examined was critical care bed occupancy with suspected and confirmed influenza cases, with the peak occupancy observed in 2010/11 four times that seen in the pandemic year. This paper analyses this data source in more detail, presenting it alongside data on respiratory virus and bacterial circulation and ambient temperature, together with information on public health interventions over that period to interpret the observed increase in impact.

Methods

The majority of hospitals in England are public and part of the National Health Service (NHS), with many containing critical care beds (including intensive care units and high dependency units). Daily critical care bed occupancy data were available from the Department of Health co-ordinated Winterwatch scheme [17] for both the 2009/10 and 2010/11 influenza seasons for the majority of 163 NHS acute trusts in England (157 in 2009/10 and 163 in 2010/11). Data were collected daily from Monday to Friday from week 51 2010 (week commencing 20 December) to 7 2011 (week commencing 14 February), and from week 29 2009 (week commencing 13 July) to 8 2010 (week commencing 15 February) on the total number of patients who were occupying critical care beds with confirmed or suspected influenza by age group (‹5 years, 5–15 years, 16–64 years and ≥65 years) and by Strategic Health Authority (East of England, East Midlands, London, North East, North West, South East, South West, West Midlands and Yorkshire and Humber). For both seasons, data were not collected for four days over the Christmas period. Where results are presented as rates per 100,000 of the population, the population denominator for the 2009/10 season corresponds to the Office for National Statistics (ONS) mid-2009 England estimates and the 2010/11 season to the mid-2010 estimates, both of which are available by age group and region [18,19]. As daily information was only available on the total number of patients in critical care and not on new admissions, the daily prevalence of critical care bed occupancy – critical care bed days – with patients with suspected influenza, was compared. The overall burden of influenza in each season on critical care was then determined by calculating the cumulative number of critical care influenza bed days in 2010/11 and 2009/10.

The data collected from Winterwatch are suspected influenza cases. It cannot be assumed such critical care bed occupancy results solely from influenza infection, as it could also be due to other respiratory infections. Weekly positivity of typical winter circulating respiratory viruses (defined as the proportion of all samples tested weekly that tested positive for a given respiratory virus) by week of sample in England from the English Respiratory Datamart system (RDS) [1,7] were examined for the 2009/10 pandemic period and the 2010/11 influenza season (from week 20 2009 to week 8 2011). Samples received through this system are collected and tested by participating hospitals from secondary care (and to a lesser extent from primary care). This included influenza A(H1N1)pdm09, other influenza A subtypes, influenza B, adenovirus, parainfluenza, respiratory syncytial virus (RSV), rhinovirus and human metapneumovirus (hMPV). Influenza activity was assessed by positivity rates to reduce the effect of possible changes in laboratory testing in the year following the pandemic. Influenza-like illness (ILI) consultation rates were not considered in this study; changes in healthcare seeking behaviour during the pandemic and in the subsequent influenza season mean that the ILI rates seen are unlikely to be a true reflection of ILI in the community. As there were reports of an increased number of bacterial co-infections in 2010/11 [20] and these data were not available through RDS, weekly counts of invasive *Streptococcus pyogenes* and *S. pneumoniae* by week of sample in England were retrieved from Labbase, the national laboratory reporting database [21].

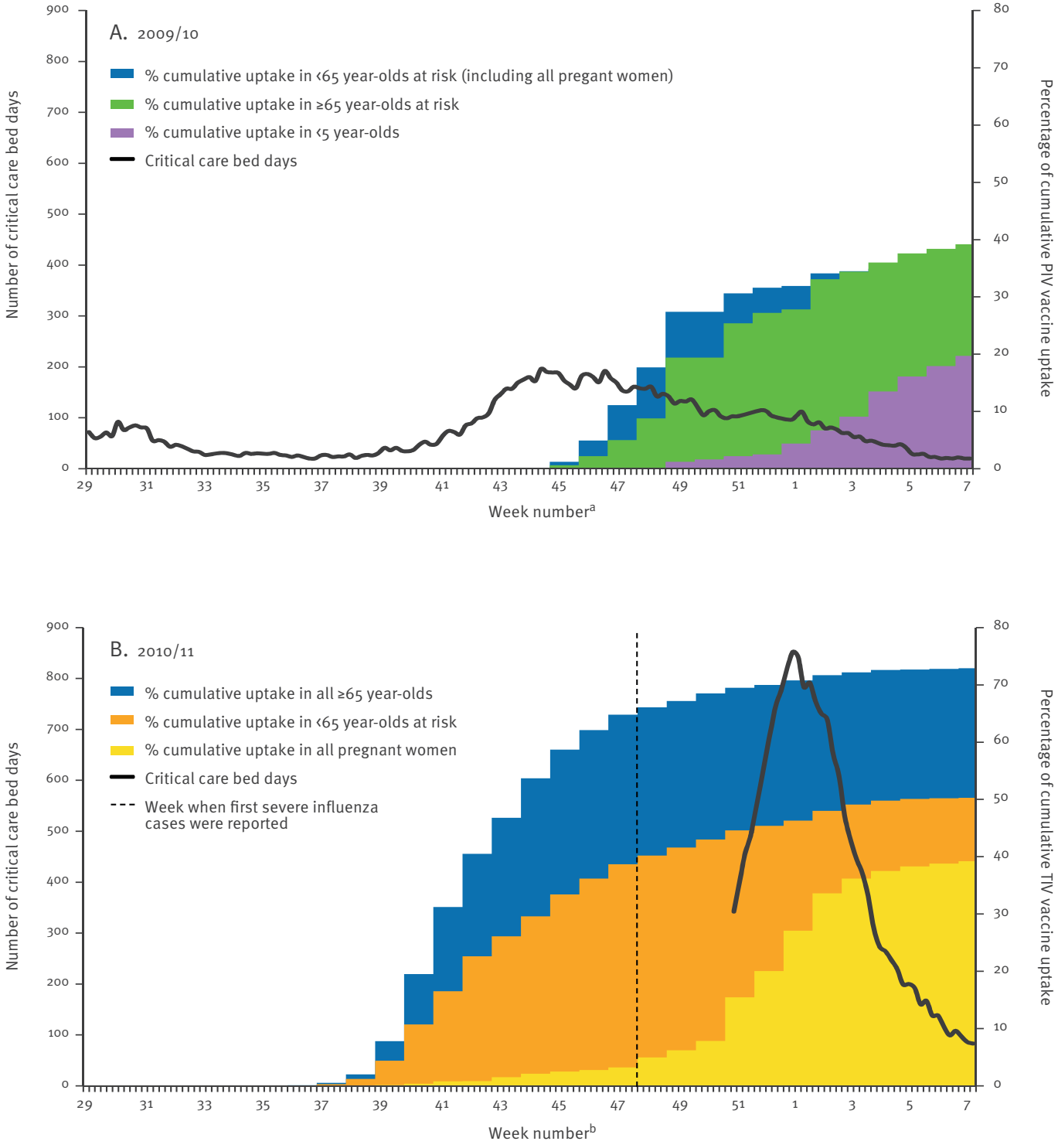
The Joint Committee for Vaccination and Immunisation (JCVI) recommended that the groups offered the monovalent pandemic influenza vaccine (PIV) in October 2009 should include both (i) individuals aged 65 years and older in a clinical risk group for severe influenza and (ii) individuals aged six months to under 65 years in clinical risk groups for severe influenza. All pregnant women were also offered vaccination. Furthermore, all healthy children aged six months up to five years were offered PIV from December 2009 [1]. A trivalent seasonal influenza vaccine (TIV) containing the influenza A(H1N1)pdm09 strain was recommended for use in 2010/11 and offered to all those aged 65 years-old and above and to those aged six months to 65 years-old falling in a clinical risk group. All pregnant women were also offered vaccination with TIV for the first time in 2010/11 [7]. Weekly percentage uptake of vaccinations in the eligible groups across England was reported through Immform, the Department of Health web portal [22].

Daily mean and minimum Central England Temperature (CET), a measurement which is broadly representative of temperatures across England, was obtained over the study period from the Met Office [23]. Weeks of notably cold weather were reported when minimum daily temperatures were below 2°C for more than two consecutive days [24].

Once retrieved, the timing of critical care bed occupancy was compared to respiratory virus activity, influenza vaccine uptake and changes in antiviral usage policy in the two seasons. In an attempt to further validate the contribution of respiratory viruses, a negative

Figure 1

Daily number of critical care beds occupied with suspected influenza cases in England and weekly cumulative percentage vaccination uptake by risk groups in England in 2009/10 and 2010/11 influenza seasons



PIV: monovalent pandemic influenza vaccine; TIV: trivalent seasonal influenza vaccine.

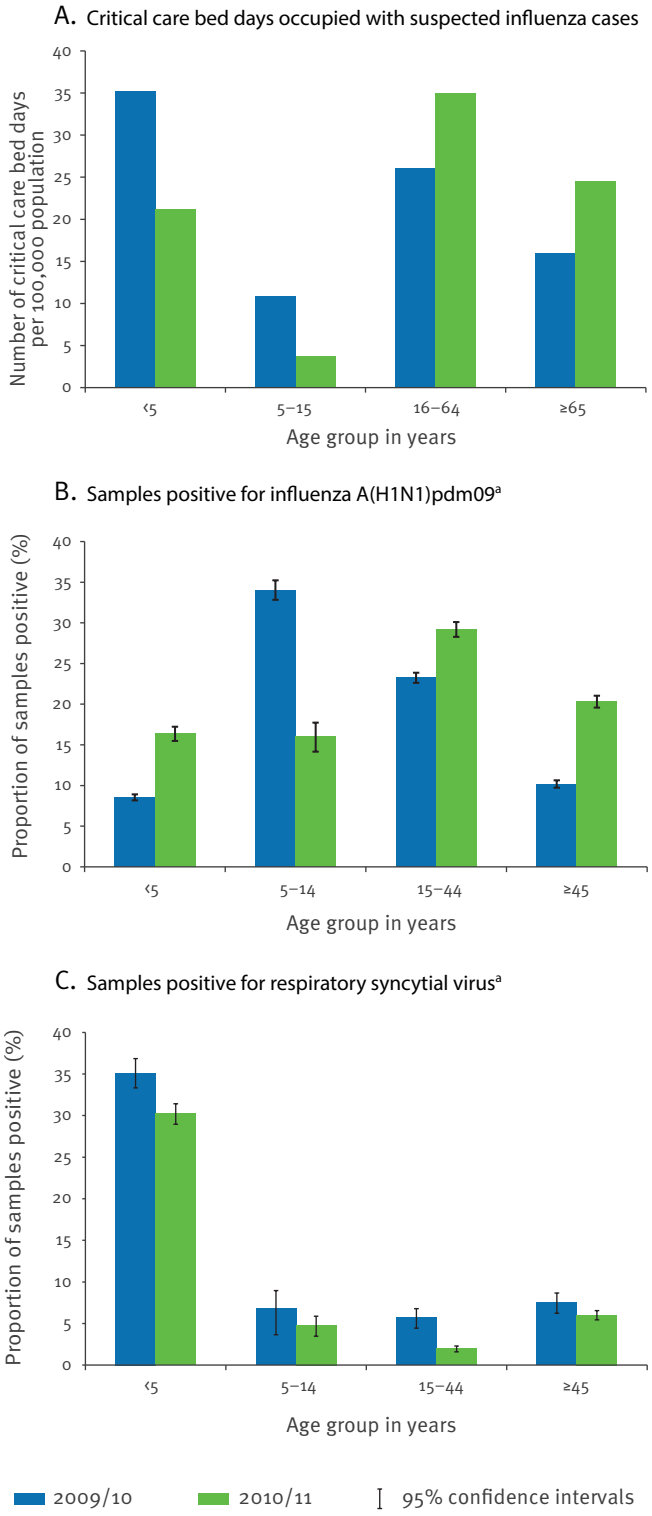
Uptake of vaccine is only monitored for the groups in which vaccination is recommended. While PIV in 2009/10 was recommended for all <5 year-olds, TIV was not recommended for all <5 year-olds in 2010/11 and so the uptake in this group is not shown in panel B. In 2009/10, uptake in <65year-olds at risk for severe influenza included all pregnant women regardless of whether they had an underlying risk factor. In 2010/11, uptake in <65year-olds at risk included pregnant women only if they had an underlying risk factor.

[a] Begining 13 July 2009.

[b] Begining 19 July 2010.

Figure 2

Overview by age groups of cumulative number of critical care bed days occupied with suspected influenza cases per 100,000 population, and cumulative proportions of samples positive for influenza A(H1N1)pdm09 and respiratory syncytial virus, England, influenza seasons 2009/10 and 2010/11



[a] Data obtained through the Respiratory Datamart system.

binomial regression model with an identity link (assuming an additive effect of the respiratory viruses) was used to model the weekly number of critical care bed days, including weekly positivity of respiratory viruses through RDS (as outlined above) as potential explanatory variables. As information on RSV positivity was only collected from week 47 2009 in RDS when it was already circulating, values for positivity for preceding weeks were extrapolated back to zero based on information from other surveillance systems. Linear interpolation of critical care bed days was carried out for the four days when Winterwatch data was not collected each season. To allow for a delay in hospitalisations from infection onset, viral positivity was lagged by up to two weeks and, as seasonal influenza A strains can vary in severity, an interaction term between influenza A positivity and season was included if significant. Stepwise regression was carried out through comparison of Akaike information criterion (AIC) values to remove variables that did not contribute to the model. Remaining variables were kept if their corresponding model coefficients were significant ($p<0.05$) and biologically credible (greater than zero). Information on *S. pyogenes* and *S. pneumoniae* positivity was not available and so their corresponding activity was not included in the regression analysis.

The number of critical care bed days each week attributed to a given respiratory virus was obtained by multiplying the number of bed days by the virus-specific coefficient [25] and summing across each season.

Results

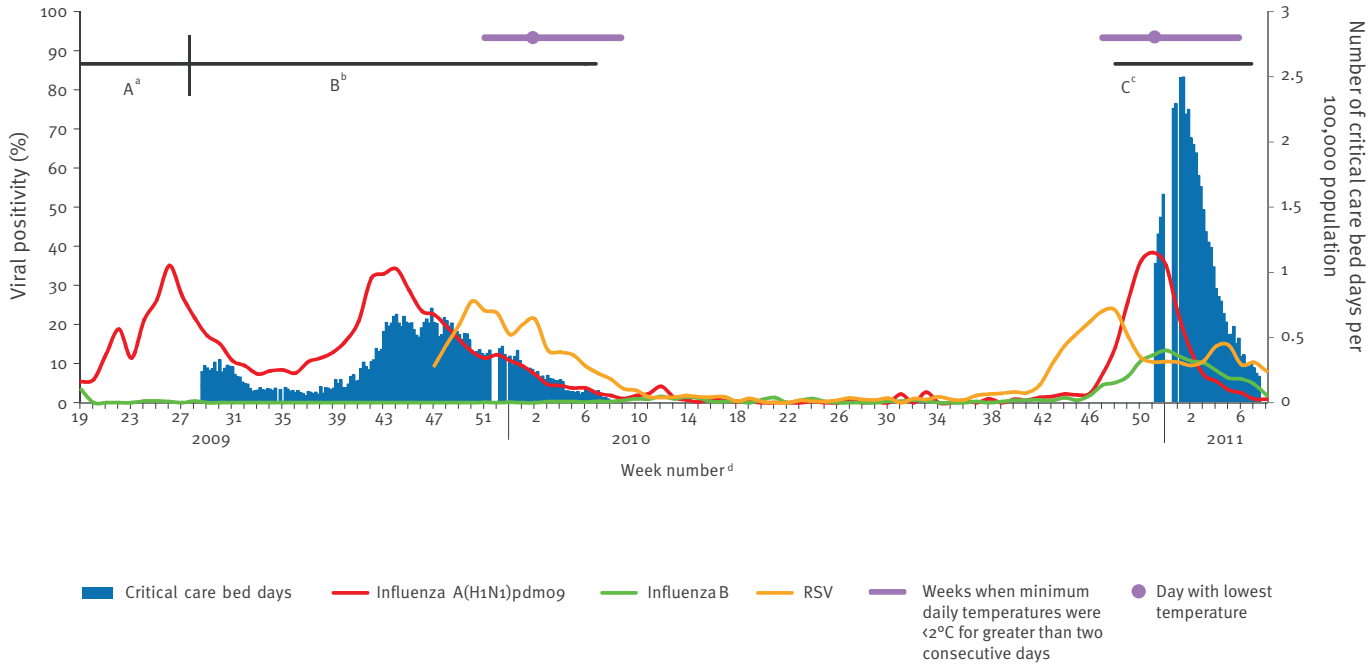
Overall critical care burden by age group and region in 2009/10 and 2010/11

As previously reported [6], a larger burden of suspected influenza cases occupying critical care beds was seen in winter 2010/11 compared to 2009/10, despite a shorter period of time over which influenza activity was detected. In addition, data on critical care bed occupancy was available for only nine weeks in 2010/11 compared to 32 weeks in 2009/10 (Figure 1). The total cumulative number of critical care bed days occupied by patients with suspected influenza in England was almost 30% higher in 2010/11 compared to 2009/10 (15,304 bed days compared to 11,831).

A notable upward shift was observed in the age distribution of critical care bed occupants with suspected influenza in 2010/11 compared to 2009/10 (Figure 2A). On the peak day in both seasons, the majority of critical care bed occupants with suspected influenza were in the 16 to 64 year-old group (82.1% of patients in 2009/10 compared to 78.6 % in 2010/11). However when the population rate was calculated by age group and compared by season, the cumulative number of critical care bed days per 100,000 population was comparatively higher in 2010/11 for adults aged over 15 years (highest rate in 2010/11 of 35.0/100,000 in 16 to 64 year-olds), while children aged 15 years or younger

Figure 3

Daily number of critical care beds occupied per 100,000 population with suspected influenza cases and weekly positivity of influenza A(H1N1)pdm09, influenza B and respiratory syncytial virus recorded in England, influenza seasons 2009/10 and 2010/11



RSV: respiratory syncytial virus.
Positivity is defined as the proportion of all samples tested weekly that tested positive for a given respiratory virus.

[a] Antivirals distributed as treatment of cases and prophylaxis of close contacts through Flu Response Centres.
[b] Antivirals distributed as treatment for all via the National Pandemic Flu Service and the National Health Service.
[c] Antivirals distributed as treatment to those in intensive care with underlying clinical risk factors via the National Health Service.
[d] Starting 10 May 2009.

were comparatively more affected during 2009/10 (highest rate in 2009/10 of 35.3/100,000 in under five year-olds). The largest number of critical care beds occupied with suspected influenza cases in 2009/10 by region on the peak day was in London (39 cases, 19.9%), whereas on the peak day in 2010/11 the largest was in the North West (169 cases, 19.9%).

Respiratory virus activity in 2009/10 and 2010/11

Influenza A(H1N1)pdm09 was the dominant circulating respiratory virus in both seasons, reaching a peak weekly positivity in 2009/10 of 35.1% in week 26 2009 and 34.2% in week 44 2009, and in 2010/11 of 38.4% in week 51 2010 as detected through RDS (Figure 3). There was additional notable co-circulation of influenza B in 2010/11, reaching a peak of 13.4% positivity in week 52 2010 compared to a peak of 1.6% the previous season (week 12 2010) (Figure 3). A low number of other influenza A viruses (where subtyped, all subtypes were A(H3)) were detected in both 2009/10 and 2010/11 (with a peak positivity of 3.2% in week 52 2009 and 2.5% in week 52 2010). Overall, an age shift was evident in influenza A(H1N1)pdm09 positive samples in RDS between the first two waves of the pandemic (highest positivity in 5–14 year-olds in 2009/10) and the 2010/11 season (highest positivity in 15–44 year-olds) (Figure 2B) which corresponds to the age shift seen in critical care bed days (Figure 2A).

Overall RSV positivity reached a similar peak level in both seasons, 26.0% in week 50 2009 and 23.6% in week 48 2010, although a bimodal distribution either side of peak influenza A(H1N1)pdm09 positivity was observed in 2010/11, with a second peak positivity of 14.7% in week 5 2011 (Figure 3). Overall positivity was highest in under five year-olds in both seasons (Figure 2C), with a comparatively increased positivity in those aged 45 year-olds and older in 2010/11 during December and January relative to the same age group in December and January 2009/10.

Adenovirus, parainfluenza and hMPV activity remained low during the 2009/10 and 2010/11 winter seasons not

exceeding 10% during this period apart from a peak in adenovirus of 17.3% in week 51 2009 (data not shown). Rhinovirus had the highest positivity of 35.8% in week 40 2010 which decreased down to 1.8% by week 52 2010 when reported critical care bed occupancy started to increase.

Allowing for a one to two week lag in influenza detection to hospitalisation, suspected influenza-associated critical care bed days in the 2010/11 season coincides with influenza A(H1N1)pdm09 and influenza B activity reported through RDS, with the shape more closely mirroring that of the pandemic strain (Figure 3). The first peak of RSV positivity in 2010/11 occurred three weeks prior to that of influenza A(H1N1)pdm09 and the second occurred after the number of suspected influenza-associated critical care bed days had already started to decline. In 2009/10, influenza A(H1N1)pdm09 positivity followed a similar pattern to critical care bed occupancy with very low influenza B positivity seen (Figure 3). RSV activity peaked six weeks after influenza A(H1N1)pdm09 and after the peak of critical care bed occupancy in 2009/10.

The final regression model contained significant terms for influenza A(H1N1)pdm09 positivity lagged by two weeks and RSV positivity – no critical care bed days were significantly attributed to influenza B, other influenza A subtypes or other respiratory viruses (Table). Visual inspection of the model showed a good fit to the data, although an overestimation of the number of critical care bed days was seen at the beginning of the critical care bed dataset in 2009/10 and a slight underestimation was seen at the peak of occupancy in 2010/11. The majority of critical care bed days were attributed to influenza A(H1N1)pdm09, 13,142 (95% confidence interval (CI): 11,278–15,005) in 2009/10 and 17,785 (95% CI: 15,217–20,354) in 2010/11. The number attributed to RSV was 1,825 (95% CI: 0–3,689) in 2009/10 and 795 (95% CI: 0–3,364) in 2010/11. This compares to a total number of critical care bed days of 12,629 in 2009/10 and 17,939 in 2010/11 after linear interpolation for days of missing data.

Weekly reports of Labbase *S. pyogenes* specimens remained low during 2009/10 and 2010/11, peaking at 62 in week 14 2010 and 77 in week 52 2010. *S. pneumoniae* invasive specimens increased in number during the winter compared to the summer months in both 2009/10 and 2010/11, reaching a notable peak of 270 in week 53 2009 and 389 in week 52 2010. This compares to weeks of peak critical care bed occupancy in week 44 2009 and week 1 2011.

In 2009/10, the weeks during which minimum temperatures were below 2°C for greater than two consecutive days (weeks 51 2009–8 2010) occurred seven weeks after the peak in critical care bed occupancy in week 44 2009. However in 2010/11, the weeks of low temperatures (weeks 47 2010–5 2011) coincided with the first reports of increases in severe cases of influenza, with the peak in influenza activity and critical care bed occupancy occurring four weeks later in week 1 2011 (Figure 3).

Table

Estimated critical care bed day attribution in each respective 2009/10 and 2010/11 influenza season by virus, using a negative binomial regression model, England

Virus[a]	Attributed critical care bed days[a,b] (95% confidence interval)	
	2009/10	2010/11
Influenza A(H1N1)pdm09	13,142 (11,278–15,005)	17,785 (15,217–20,354)
Respiratory syncytial virus (RSV)	1,825 (0–3,689)	795 (0–3,364)

[a] Viral activity initially assessed and not included in the final model include: influenza B, other influenza A subtypes, adenovirus, parainfluenza, rhinovirus and human metapneumovirus.

[b] Attributed critical care bed days = (A(H1N1)pdm09 positivity (two week lag))*Season + RSV positivity. Whereby positivity is defined as the proportion of all samples tested weekly that tested positive for a given respiratory virus.

Interventions

The PIV vaccination programme began after the autumn 2009 pandemic influenza wave had already peaked (Figure 1). This meant that at the peak of critical care bed occupancy at the end of October (week 44), uptake in both 65 year-olds and older in a clinical risk group, and under 65 year-olds in a clinical risk group (including pregnant women) had only reached 0.1% (Figure 1A). Final cumulative uptake of PIV across England in target groups at the end of the influenza season was 35.4% for those under 65 years in a clinical risk group and 14.9% for pregnant women [26]. The PIV programme in healthy children under five years-old did not start until December 2009, which was over four weeks after the critical care bed peak in the autumn 2009 wave. The programme reached a final cumulative uptake of 23.6%.

In the 2010/11 season, when the first cases of severe influenza were reported in week 48 2010, uptake of TIV in all 65 year-olds and older was already 66.1% and 40.2% in under 65 year-olds in a clinical risk group (Figure 1B). Uptake in pregnant women was only 5.0%. At the peak of critical care bed occupancy in 2010/11, uptake had reached 70.8% in 65 year-olds and older, 46.3% in under 65 year-olds in a clinical risk group and 27.1% in pregnant women.

The changes in antiviral usage policy over 2009 to 2011 are indicated in Figure 3. During the containment phase at the beginning of the pandemic, antivirals

were distributed to the first detected cases as treatment with prophylaxis of their close contacts through Flu Response Centres set up by the Health Protection Agency (HPA) in collaboration with the NHS [27]. Following a sharp increase in the number of cases in June 2009, with evidence of community transmission, the treatment phase began on 2 July 2009 when antivirals were offered as treatment for all suspect cases, and prophylaxis was no longer offered other than in certain specific circumstances. Individuals with underlying clinical risk factors were assessed and received antivirals through the NHS and clinical cases without underlying risk factors were managed through the National Pandemic Flu Service (NPFS), a national telephone and internet-based service set up shortly after the start of the treatment phase. This was continued until February 2010.

During winter 2010/11, antivirals were administered through the NHS following standard National Institute for Health and Care Excellence (NICE) guidance for use during seasonal influenza activity to those with underlying clinical risk factors for severe disease [28].

Discussion

In the winter of 2010/11, the first post-pandemic season, influenza activity due to influenza A(H1N1)pdm09 viruses was high, with a bigger impact on critical care services from suspected influenza cases and a marked age shift in cases from children to adults, relative to 2009/10. There were differences in antiviral policy between the seasons and overall vaccine uptake with an influenza A(H1N1)pdm09 strain-containing vaccine was much higher at the peak level of critical care activity in 2010/11 compared with 2009/10. The peaks in suspect influenza critical care admissions in both seasons coincided with peaks in influenza A(H1N1)pdm09 positivity, but additionally in 2010/11 coincided with influenza B positivity, notably cold weather and increased reports of *S. pneumoniae* infection. Infections due to RSV and other respiratory viruses do not appear to make a large contribution to these critical care admissions in either season.

Following influenza A(H1N1)pdm09 activity in 2009/10, the pandemic virus continued to circulate in the UK with increased activity and impact the following season. The increase in critical care bed occupancy in 2010/11 relative to 2009/10 seems to be driven primarily by influenza A(H1N1)pdm09 and coincided with increases in influenza A(H1N1)pdm09 positivity and other indicators of influenza activity, including general practitioner (GP) consultations, hospitalisations and excess deaths [1,7,9]. In addition, regression analysis suggests that influenza A(H1N1)pdm09 contributed to the increase of critical care admissions of patients with suspected severe influenza rather than other influenza strains. Although influenza B was circulating in 2010/11 and peak positivity coincided with the peak in critical care bed occupancy, terms for this virus were not significant in the regression analysis, suggesting little contribution to intensive care unit admissions. Through other data sources, cases of influenza B confirmed hospitalised patients and fatalities were reported in 2010/11, though the proportions were low, with the proportion of severe cases due to influenza B increasing with time over the season and the highest rates of hospitalisation seen in children [7,9].

The pandemic influenza virus did appear to circulate predominantly in older age groups in 2010/11 compared to 2009/10. A higher proportion of adults aged over 15 years were admitted to critical care in the winter of 2010/11 relative to that observed during the pandemic in England, with the highest proportion seen in 16 to 64 year-olds. This age shift has been documented following previous pandemics [29] and is in agreement with observations from other surveillance systems in England and elsewhere following the 2009 pandemic, such as in Taiwan and Greece [3,9,11,30,31]. Circulation of the pandemic virus in 2009 mainly occurred in children [1]. The consequences for the following season therefore were lower numbers of susceptible children, but there still remained a pool of susceptible adults within which circulation of the virus could occur once transmission started [2]. The age-dependency in infection-severity of influenza A(H1N1)pdm09 infection is well documented [4], with increasing severity with increasing age at infection. The burden and severity of underlying chronic conditions also increases with increasing age which can be exacerbated by influenza infection. Therefore this observed age shift to older age groups is likely to have been associated with an overall increase in infection severity and thus impact. Other potential contributory factors may include reinfection, resulting from waning immunity and/or vaccine-related-immunity, and introduction of new susceptible infants [31,32].

The circulating influenza A(H1N1)pdm09 viruses were found to be well matched to the influenza A/California/07/2009 strain in the trivalent influenza vaccine used at the time in 2010/11 [7], with reported vaccine effectiveness in 2010/11 of 51% against GP attended virologically confirmed infection, compared to 72% for the adjuvanted monovalent pandemic influenza vaccine used in 2009 [33,34]. Although the PIV was more effective than the 2010/11 TIV, it was supplied generally late in the 2009 pandemic. At the peak of critical care impact in 2010/11, and indeed several weeks prior to when the first severe influenza cases were reported, uptake of the TIV was at very much higher levels than that seen at the peak of critical care impact in 2009/10 with the monovalent pandemic vaccine. Therefore the lower impact of pandemic influenza in 2009/10 cannot be attributed to comparatively higher and more timely vaccine uptake during the pandemic, than in 2010/11.

It has been suggested that a reduced level of antiviral usage in 2010/11 compared to that during the 2009 pandemic could be an explanation of the increased impact

of influenza in the following season [6]. It is unclear, however, how many hospitalisations were averted from distribution of antivirals through the NPFS and the NHS during this pandemic period. Although it is not known during the pandemic what proportion of symptomatic infections in the community received antivirals, only a relatively small proportion of cases that were hospitalised with confirmed influenza infection, 10 to 12%, had reportedly received antivirals prior to admission [5,35], with most cases receiving antivirals after admission. Considering the low level of reported effectiveness of antivirals in preventing hospitalisation of influenza cases [36], using the screening method [37] a crudely estimated 15% of suspect cases received antivirals in the community (assuming 25% effectiveness [36] and 12% of hospitalised cases received antivirals prior to admission). Therefore their use in the community during the pandemic is unlikely to fully explain the difference in impact seen through the Winterwatch scheme between 2009/10 and 2010/11.

Of the other winter circulating respiratory viruses that might explain suspected influenza critical care admissions, RSV positivity was high, though compared to critical care bed occupancy, RSV activity occurred later than the peak in 2009/10 and earlier in 2010/11 than critical care occupancy, suggesting little contribution in both seasons. This observation is supported by the regression analysis which attributed only a small proportion of critical care bed days to RSV in both seasons. No notable circulation of other respiratory viruses was observed at this time. A peak was seen in the number of *S. pneumoniae* invasive infections which, unlike 2009/10 coincided with the peak in critical care bed occupancy in 2010/11 and the circulation of influenza, however no information was available on the number of samples tested, preventing calculation of the positivity and a comparison between seasons. Bacterial co-infections amongst influenza cases were reported in 2010/11 in the UK complicating seasonal influenza, which may have contributed to increases in case severity and thus impact [20].

Compared with 2009/10, lower temperatures were seen in 2010/11 and the timing coincided with the beginning of influenza activity whereas the peak of the second pandemic wave in 2009 occurred prior to winter climate. Transmission of influenza is dependent on temperature, with cold weather thought to favour it [14,31]. From the viral point of view, if the transmission and impact of the virus changed, it could be argued that this resulted from changes in the influenza virus. Despite several genetic changes leading to an increase in genetic diversity observed amongst the 2010/11 circulating pandemic viruses in the UK relative to seen in 2009/10, no significant antigenic drift was detected and there were no immediately obvious genetic differences between viruses recovered from fatal and severe cases compared with those with mild disease [7,38]. However, genome-wide changes observed in pandemic viruses from 2010/11 have been reported and might have influenced the biological properties of the virus, improving virus fitness and consequently have an impact on virulence and/or transmission [39]. The combination of this, together with the existence of a large pool of susceptible young adults and the possibility of waning antibody protection in children infected the previous season [31,32] may explain the occurrence of further spread of influenza in the population.

There are some limitations with the data used for this analysis. Only prevalence data on critical care bed occupancy of suspected cases were available - no information of length of stay of each patient was collected, with evidence suggesting that, on average, there was a longer length of stay in critical care in the post-pandemic period [40]. There was no coverage through Winterwatch on critical care bed occupancy during the first wave of the pandemic. However, the number of laboratory-confirmed hospitalisations in England in the first wave was less than that seen during the second wave [5] and comparatively lower severity noted [1,3]. It is therefore likely to have resulted in critical care bed occupancy levels similar to, or lower than, seen in the second pandemic wave. It is also important to note this is an ecological study: no individual-level information was available on infection, co-infection or intervention uptake through the Winterwatch data source. Additionally, the outcome of each patient was not known. Observations from separate mortality surveillance schemes operating during these seasons have been reported elsewhere [7] but for future seasons, individual-level severe influenza surveillance will be invaluable to build on these observations and directly assess potential associations.

Some countries observed influenza A(H1N1)pdm09 circulation in 2010/11, others experienced a predominately influenza B season in 2010/11 (e.g. Norway) and yet others predominately an A(H3N2) season (e.g. Canada, United States) [10,41,42]. In the countries where influenza A(H1N1)pdm09 circulated, only a few reported a similar relative increased impact in 2010/11 (e.g. Greece, Taiwan, Denmark and Ireland) [4,10,11]. Such a post-pandemic phenomena has been documented previously, e.g. following the 1918 pandemic [43]. The reasons for this large range of observations between countries are likely to be multifactorial and require further exploration.

The intensity and impact of influenza A(H1N1)pdm09 virus activity in 2010/11 in England was not predicted and occurred at a time of year when extreme cold weather was being experienced and hospital resources were already stretched [8,44]. Data from previous pandemics indicate the occurrence of substantial waves of influenza activity following initial pandemic waves, and might therefore have been an indication that substantial activity would be expected in the winter of 2010/11. On the other hand, serological population based data indicated that a large proportion of the population had experienced influenza A(H1N1)pdm09

infection in 2009/10, many with a sub-clinical illness. The reasons behind the comparative increase in impact of severe influenza in 2010/11 relative to 2009/10 are thus likely to have resulted from a combination of factors, including an age shift in infection, accumulation of susceptible individuals through waning immunity, new susceptible individuals from new births, cold weather and a possible change in the virus. Although the majority of critical care bed days are likely to have resulted from influenza A(H1N1)pdm09 in both seasons, the mechanism resulting in increased impact still remains uncertain. For future seasons, it is important that severe influenza disease surveillance schemes are further developed to collect and analyse data in a timely fashion to inform prevention and control activities.

Acknowledgements

We are grateful to our colleague Hongxin Zhao and laboratories participating in the Respiratory Datamart scheme, our colleague Fateha Begum and the team at ImmForm for coordinating and reporting seasonal influenza vaccine uptake data, and André Charlett for helpful statistical advice.

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