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AVIAN INFLUENZA A(H5N1) – CURRENT SITUATION

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The A(H5N1) influenza virus has re-emerged in 2003 in Asia, Africa, the Pacific Region as well as Europe and since then has become endemic in some countries. The virus is usually highly pathogenic and is associated with high morbidity and overall mortality rates that reach 61%. The cumulative number of confirmed human cases from 2003 to 2009 is 423 cases, with 258 deaths [1]. During the current year, sporadic human infections have occurred only in Egypt, China and Vietnam. In Egypt, no deaths have been reported from a total of 17 confirmed human cases in 2009, which could be an indication of altered pathogenicity of the circulating strains [2]. The article of JP Dudley published in this issue of Eurosurveillance [3] examines the age- and sex-specific rates of infection and mortality for human cases of avian influenza A(H5N1) virus in Egypt, concluding that they differ markedly from those recorded in other countries. Accelerated evolution of H5N1 was previously reported in the area, and was possibly linked to the vaccine program, as evolved circulating strains can escape from recent vaccines [4].

Ongoing research is focused on the development of appropriate vaccines against A(H5N1) circulating strains for use in humans. Clade 2.2 A(H5N1) influenza viruses that have been associated with human infections in Egypt since September 2008 are the ones with the most geographically disperse distribution and have caused outbreaks in poultry in over 60 countries in Asia, Africa and Europe. Human infections in China and Vietnam have been associated with clade 2.3 viruses. A number of reassortants have completed and others are awaiting regulatory approval to be used in vaccine production in affected areas. As antigenic heterogeneity occurs, vaccine candidates are being re-evaluated [4].

While at the moment attention is focused on the recent emergence of a new influenza A(H1N1) virus, other influenza viruses, including the avian influenza A(H5N1) strains, are still a cause for concern. With studies such as the one presenting data from Egypt the importance of constant monitoring of the geographic spread and epidemiology of circulating strains, and the determination of their genetic and antigenic characteristics is highlighted.

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Rapid communications

FIRST SEQUENCE-CONFIRMED CASE OF INFECTION WITH THE NEW INFLUENZA A(H1N1) STRAIN IN GERMANY

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Here, we report on the first sequence-confirmed case of infection with the new influenza A(H1N1) virus in Germany. Two direct contacts of the patient were laboratory-confirmed as cases and demonstrate a chain of direct human-to-human transmission.

A patient in his 30s was admitted to the department of internal medicine of a district hospital in southern Germany, on 24 April 2009 with influenza symptoms. Two days earlier, he had returned from a vacation in Mexico. He presented with fever up to 40° C, cough and dyspnoea. Headache and myalgia were not present. In addition, this patient had an unrelated, previously undiagnosed chronic disease. He was isolated on the morning of 27 April, and fever and dyspnoea resolved during that day. Since the evening of that day, he has been treated with oseltamivir. Because of his underlying medical condition he was transferred to the University Medical Centre on 28 April, where he has been in stable condition until present, with no further clinical signs of influenza.

Laboratory analysis

On 27 April 2009, the Laboratory of Medical Microbiology and Hygiene at the University of Regensburg Medical Center received a nose and throat swab of the patient for influenza PCR, because an infection with the new influenza A(H1N1) strain was suspected [1,2].

TaqMan-PCR for an 86 bp fragment of the M1 matrix protein gene was performed on the same day and was negative for influenza B, but weakly positive for influenza A (10²-10³ copies from 1 ml of swab extraction buffer). The two involved hospitals and health authorities were informed immediately. The primers used (set A, see Table) were part of an in house TaqMan-PCR system designed for conventional influenza A strains.

Sequencing of this PCR product on 28 April showed that 45 bp excluding the primers were identical to the California 04/2009 H1N1 isolate from the current outbreak (GenBank entry FJ966085.1). The 45 bp sequence differed in three nucleotide

TABLE

Oligonucleotide primers used for amplification and sequencing

A	Influenza A-specific TaqMan PCR system	forward primer (InfLA-MA2-1b) 5'-GYT CTC ATG GAR TGG CTA AAG ACA-3'	backward primer (InfLA-MA2-2) 5'-GGC ACG GTG AGC GTG AA-3'	TaqMan probe (InfLA-MA-So-2b) FAM-5'-ACC AAT CCT GTC ACC TCT GAC TAA GGG GA-3'-TAMRA	
B	Primers targeting M1 gene sequence	outer forward primer (MA-c ₁) 5'-ACC GAG GTC GAA ACG TA-3'	outer backward primer (MA-c ₂) 5'-CGA TCA AGA ATC CAC AAT ATC-3'	inner forward primer (MA-c ₃) 5'-CAG AGA CTT GAA GAT GTC TTT G-3'	inner backward primer (MA-c ₄) 5'-TTC TGR TAG GYC TGC AAA TT-3'
C	Primers targeting HA gene sequencing	outer forward primer (H1N1_HA_F1) 5'-CCG CAA ATG CAG ACA CAT TA-3'	outer backward primer (H1N1_HA_R1) 5'-CCC ATT AGA GCA CAT CCA GAA-3'	inner forward primer (H1N1_HA_F2) 5'-TGC GAA CAA TTC AAC AGA CA-3'	inner backward primer (H1N1_HA_R2) 5'-CCC AGG GAG ACT ACC AGT ACC-3'
D	Novel Influenza A(H1N1)-specific TaqMan PCR system [3]	forward primer (H1SWS) 5'-CAT TTG AAA GGT TTG AGA TAT TCC C-3'	backward primer (H1SWAs1) 5'-GGA CAT GCT GCC GTT ACA CC-3'	TaqMan probe (H1SWP) FAM-5'-ACA AGT TCA TGG CCC AAT CAT GAC TCG-3'-BBQ	

TaqMan PCR system A had been designed for conventional influenza A strains. Due to the two distinct nucleotides in the probe region, this assay may slightly underestimate the viral load of the novel influenza A(H1N1) strain. Primer system B had been designed for conventional influenza A strains. It does not exactly fit the novel influenza A(H1N1) strain in several positions, but worked well for sequencing the first German isolate.

positions from conventional human influenza A strains, two of them within the TaqMan probe region. This was considered a strong indication for infection with the new virus.

A larger 600 bp PCR fragment of the matrix protein gene was sequenced on the same evening, using primer set B (see Table). In a BLAST search it was 100% identical over a stretch of 597 nucleotides with the above mentioned California isolate, but differed in at least 5% from annotated human influenza A(H1N1) strains. Conventional porcine influenza H3N2, but also H1N1 strains, were generally more closely related to our sequence than human strains.

Therefore, we considered this isolate as the first proven case of the new influenza A(H1N1) in Germany. Health authorities and physicians were immediately informed. The 597 nucleotide sequence was submitted to GenBank on the same day (FJ970928*).

In parallel, a 1,446 bp fragment of the haemagglutinin gene was amplified and sequenced using primer set C (see Table), and submitted to GenBank (FJ974021) on 30 April. This sequence was identical to two California strains (GenBank FJ969511 and FJ966952) isolated in the current worldwide outbreak, with the exception of only one nucleotide mismatch. In addition a 1,109 bp sequence of the neuraminidase gene of our first isolate has meanwhile been deposited in GenBank (FJ984953) and in the database of the Global Initiative on Sharing Avian Influenza Data (GISAID). It had 100% similarity with the Texas/04 and Texas/05 isolates (FJ981614 and FJ966969).

Contact testing

In the presumed incubation time, the index patient had several contacts of varying closeness and duration before his admission to hospital. Contact tracing and testing through the public health authorities was started immediately. Detailed data on the contacts of the index patient before entering the hospital will be reported by the public health authorities.

Before the patient was isolated on the morning of 27 April under suspicion of new influenza, he had an estimated 19 close contacts among staff at the district hospital and one patient who stayed in the same twin room as the index case in the district hospital.

One of the nurses who had close contact with him has so far tested positive for the new influenza A (H1N1), and had influenza symptoms for a period of two days on 26-27 April. This case received oseltamivir treatment and stayed isolated at home until 5 May when she had tested negative for the new influenza A(H1N1) strain.

All other contacts among the district hospital staff and additional hospital staff who had not had contact with the index patient (a total of 32 people) were tested one or two times and have remained PCR-negative and healthy as of 7 May.

All 32 were tested and offered oseltamivir prophylaxis, but only a minority accepted the treatment. Contacts among the staff at the University Medical Centre remained healthy and were not tested, because the isolation care of the patient was continued without interruption from the beginning.

A sputum sample of the patient sharing the room with the index case was found positive on 29 April in an influenza A-specific TaqMan-PCR assay (set A, see Table). A second TaqMan-PCR assay, specific for the new influenza A(H1N1) strain (primer set D, see Table), was found positive on the same day. The patient

was isolated and treated with oseltamivir in the afternoon of 29 April, and health authorities were informed. He suffered only minor influenza-like symptoms.

Both this and the index patient have since tested negative for the new influenza A(H1N1) strain three times and have been released from isolation. Due to additional chronic diseases unrelated to influenza, however, they have not been released from the hospital yet.

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*Authors' correction:

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Rapid communications

INITIAL EPIDEMIOLOGICAL FINDINGS IN THE EUROPEAN UNION FOLLOWING THE DECLARATION OF PANDEMIC ALERT LEVEL 5 DUE TO INFLUENZA A (H1N1)

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The recent detection of a novel influenza A(H1N1) virus has led to the first WHO declaration of a Public Health Event of International Concern under the International Health Regulations (IHR 2005). Here we review the early epidemiological findings of confirmed cases in Mexico, the United States, Canada and EU/EFTA countries. Strengthened surveillance and continued, transparent communication across public health agencies globally will be necessary in coming months.

Background

Infections with swine influenza virus have been detected occasionally in humans since the 1950s and the resulting human disease is usually similar to human influenza viral infections [1-6]. Complications, including pneumonia and death, have been reported in the literature in adults without underlying disease [7]. Chains of human-to-human transmission had not previously been observed apart from an outbreak among young adult military recruits in New Jersey in 1976, causing 230 infections, 13 of whom were severe with one death [8].

On 21 April, the European Centre for Disease Prevention and Control (ECDC) was alerted of the existence of cases of respiratory illness in the United States (US) caused by a novel influenza virus [9]. On 23 April 2009, cases from Mexico were confirmed to be caused by influenza A(H1N1) virus. Initial cases in the US demonstrated no exposure to pigs, and some were clustered. In Mexico, the outbreak caused cases of severe respiratory illness and suspected deaths [9,10].

Preliminary investigations showed that six genomic segments of the virus were related to swine viruses from North America and the remaining two were from swine viruses isolated in Europe and Asia [11]. The virus was resistant to adamantanes, but susceptible to neuraminidase inhibitors [9,12].

On 25 April, the World Health Organization (WHO) declared this event a 'Public Health Event of International Concern' under the framework of the International Health Regulations (IHR 2005). On 26 April, New Zealand, Spain and the United Kingdom (UK) started investigating persons returning from Mexico with influenza-like symptoms. On 27 April, the first confirmed cases of the new influenza A(H1N1) were reported from Spain (n=1) and the UK

(n=3) in travellers returning from Mexico, and 10 additional European Union (EU) countries reported investigating cases.

On 27 and 29 April, WHO raised the pandemic alert phases to 4 and 5, respectively. Governments were requested to strengthen surveillance, to detect and treat cases early and implement infection control in all health facilities.

In the EU, the European Commission recommended that countries extend their routine seasonal influenza surveillance beyond week 20. Additionally, on 30 April 2009, an EU case definition for the novel influenza A(H1N1) virus was agreed upon by EU Member States [13].

A timeline of the events is shown in the Figure.

This article aims to review the preliminary epidemiological findings in the EU following the identification of influenza A (H1N1) in Mexico and the US.

Current global epidemiological situation

As of 7 May, 2,217 confirmed cases of influenza A(H1N1) have been confirmed worldwide, from 24 countries located in three WHO regions [14].

Countries not in the EU and European Free Trade Association (EFTA) (Non-EU/EFTA countries)

In Mexico, the epidemiological profile of 866 out of a total of 1,112 confirmed cases shows that the majority of cases occurred in the area around Mexico City (n=496, 53.8%) [15]. Forty-two deaths have been confirmed [14]. Fifty percent of cases are female and 49% of confirmed cases are under the age of 19 years [15].

In the US, 41 out of 50 states have reported 745 confirmed cases of the new influenza A(H1N1) [14]. Two deaths and 35 hospitalisations were reported. The median age of confirmed cases is 16 years, and 62% are under the age of 18 years [16].

Canada reported 201 confirmed cases of the new influenza A(H1N1) with one hospitalisation of a young girl [17]. Eight of 10 provinces and none of the territories have reported confirmed cases, with the majority reported from British Columbia (n=54), Nova Scotia (n=53) and Ontario (n=49) [18].

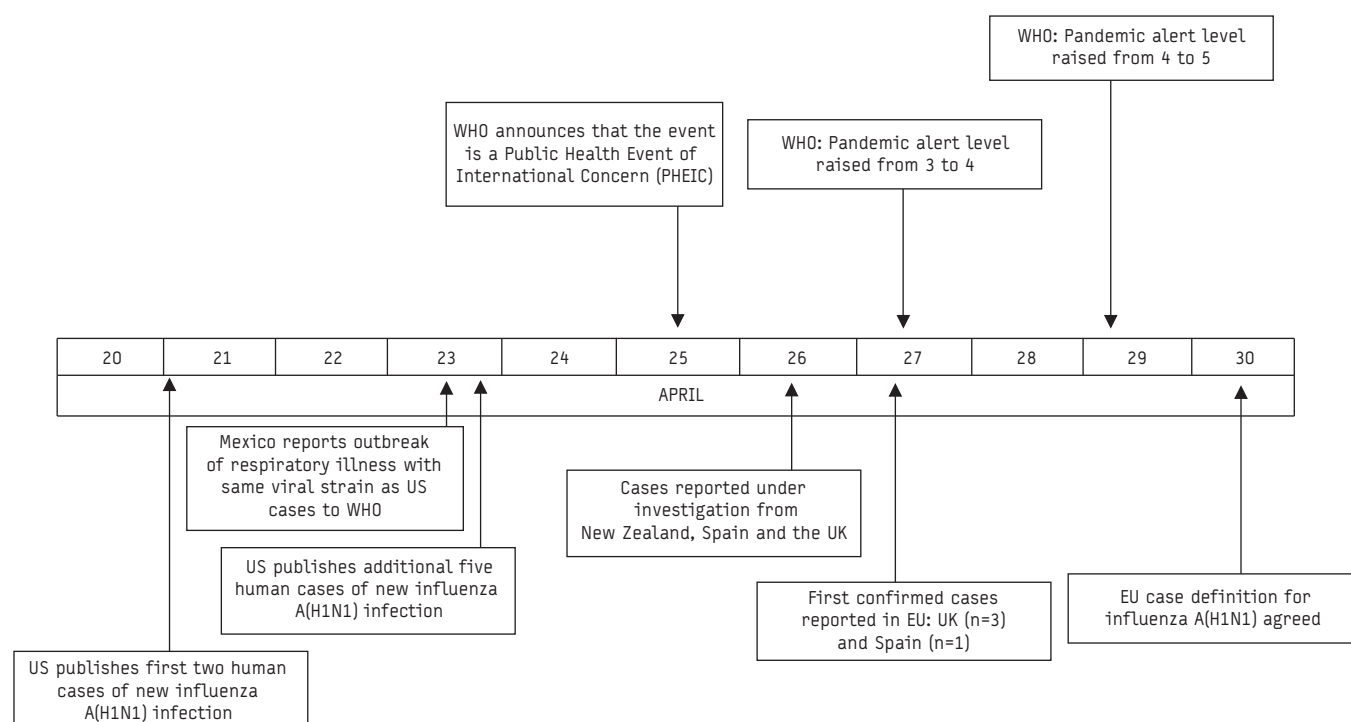
Sporadic cases have been reported from New Zealand, the Republic of Korea, Hong Kong, Israel, Costa Rica, Guatemala, Colombia and El Salvador.

EU and EFTA countries

Thirteen EU/EFTA countries have confirmed 142 cases since 27 April (Table 1). The majority of confirmed cases are from Spain

FIGURE

Timeline of major events: new influenza A(H1N1) outbreak, April 2009



EU: European Union; UK: United Kingdom; US: United States; WHO: World Health Organization.

TABLE 1

Reported current number of probable cases, cumulative number of confirmed cases and cumulative number of in-country transmission, influenza A(H1N1) outbreak 2009*

Country	Current number of probable cases	Cumulative number of confirmed cases	Cumulative number of in-country transmission
Austria	-	1	-
Denmark	0	1	-
France	3	7	-
Germany	0	9	2
Ireland	0	1	-
Italy	-	5	-
Netherlands	-	1	-
Poland	-	1	-
Portugal	0	1	-
Spain	-	81	5
Sweden	0	1	-
Switzerland	-	1	-
United Kingdom	1	32	10
Total	4	142	17

Data as of 7 May 2009, 8:00 hours (CEST) in European Union (EU) and European Free Trade Association (EFTA) countries [14].

Note: cases reported in the EU and EFTA countries correspond to the EWRS notifications by Member States or Ministry of Health websites.

(n=81) and the UK (n=32). Age and gender data are available for 35 confirmed cases (Table 2). The male-female sex ratio is 1.5, the median age is 23 years (range 3-50 years), and 49% of cases are between 20 and 29 years of age.

Seventeen confirmed cases (16%) acquired the infection through transmission within the EU. In Germany, a nosocomial cluster occurred in a nurse and patient who were exposed to a hospitalised confirmed case. Spain reported five autochthonous transmissions and the UK reported 10, including a cluster of five school children exposed to a confirmed schoolmate with travel history to the US. There is no indication of transmission occurring in the EU outside of close contacts of known cases.

Countries within the European Union have coordinated their public health measures on the basis of EU communicable disease legislation. The measures taken include: information to the public and travellers, raising awareness amongst healthcare workers and enhancing surveillance for influenza-like illness. On the basis of a risk assessment provided by the European Centre for Disease Prevention and Control (ECDC), the European Commission collaborates closely with the Member States, international organisations and third countries to ensure a coordinated response to this event on the EU level.

Discussion

Three out of six WHO regions have confirmed cases. However, community transmission, defined as transmission chains spreading beyond close contacts into the community, has to date only occurred in Mexico and in the US. EU/EFTA countries are still experiencing limited chains of transmission to close contacts of returning travellers from Mexico and the US.

Based on the experience from Mexico and the US, it appears that seeding events established by travellers from affected areas are occurring in closed community settings such as schools. The spread of the virus within these settings causes an amplification of the viral reservoir in the communities ultimately leading to community spread. In the EU, some confirmed cases have already been reported in children of school age and in close school contacts and monitoring of these events should continue to be done carefully.

TABLE 2

Gender and age distribution of confirmed cases in EU and EFTA countries, influenza A(H1N1) outbreak 2009 (n=35)

Age group (years)	Female	Male	Total
0-9	1	0	1
10-19	2	1	3
20-29	7	10	17
30-39	1	3	4
40-49	1	2	3
50-59	0	1	1
>59	0	0	0
Unknown	2	4	6
Total	14 (40%)	21 (60%)	35

EFTA: European Free Trade Association (EFTA); EU: European Union.

Half of the confirmed cases observed in the EU are between 20 and 29 years of age. This finding is influenced by the age structure of returning travellers among which most of the testing is carried out in EU/EFTA countries. It therefore does not indicate that this age group is at higher risk of disease. Most cases in the EU/EFTA countries are mild. However, more severe clinical presentation may be expected when the infection will spread in the general population.

Most of the efforts in the EU/EFTA countries are currently directed at detecting returning travellers from areas with community outbreaks, namely Mexico and the US. However, considering how the outbreak is progressing, the focus of surveillance is now shifting to the timely detection of community transmission. EU Member States are currently continuing their surveillance of seasonal influenza. As the national influenza centres are now all equipped with reagents to identify the novel influenza A(H1N1) strain, it is likely that cases that may occur in the community in the EU will be detected by virological surveillance.

Conclusion

It is still too early to predict how the outbreaks of influenza A (H1N1) will evolve in the EU/EFTA countries. Data from Mexico and the US suggest that this novel virus spreads rapidly in the communities once introduced from an affected area.

Continued strengthened surveillance efforts, coordination and information sharing amongst countries on a global level will support the EU and other affected countries in their preparedness and response for the potential spread of this novel influenza virus in the weeks and months to come.

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Rapid communications

AGE-SPECIFIC INFECTION AND DEATH RATES FOR HUMAN A(H5N1) AVIAN INFLUENZA IN EGYPT

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The age-specific infection and death profiles among confirmed human cases of influenza A(H5N1) infection in Egypt differ markedly from those recorded in other countries. The case fatality rate among human H5N1 cases in Egypt is 34%, versus an average of 66% in other countries. In Egypt, children younger than 10 years comprise 48% of reported cases, nearly twice the global average of approximately 25%, and no H5N1 fatalities have been confirmed among individuals in this age group as of 23 April 2009. Females outnumber males among confirmed H5N1 cases by a factor of nearly 2:1, and 90% of reported fatalities in Egypt have been females. The evident age and sex biases in morbidity and mortality among H5N1 cases in Egypt are phenomena that warrant further investigation and analysis.

Introduction

The first cases of human infection with avian influenza type A(H5N1) were reported from Egypt in March 2006, and a cumulative total of 67 confirmed cases including 23 fatalities have been reported as of 23 April 2009 [1]. There are evident anomalies in the age distribution and sex ratio of human mortality from influenza A(H5N1) in Egypt relative to those reported from other countries that warrant detailed investigation and analysis.

Methods

Published information on human H5N1 cases in Egypt was analysed to develop a first order comparative analysis of age-specific and sex-specific infection and mortality patterns between human H5N1 cases in Egypt and those in other areas of the world. The age and case history data of patients with confirmed influenza A(H5N1) infection in Egypt used in this analysis were derived from reports published by the United States Naval Medical Research Unit No. 3 in Cairo, Egypt [2] and the World Health Organization (WHO), available as of 23 April 2009 [1].

Results

Human H5N1 cases in Egypt are most frequently reported among children younger than 10 years, and approximately 80% of all reported cases have occurred among individuals under the age of 30 years. In Egypt, children under the age of 10 years comprise 48% of all reported cases, nearly double the current global average of approximately 25% [3]. A median age of eight years has been reported for human H5N1 cases in Egypt between March 2006 and March 2009 [2], versus a median age of 18 years for WHO-confirmed human cases globally between November 2003 and November 2006 [4].

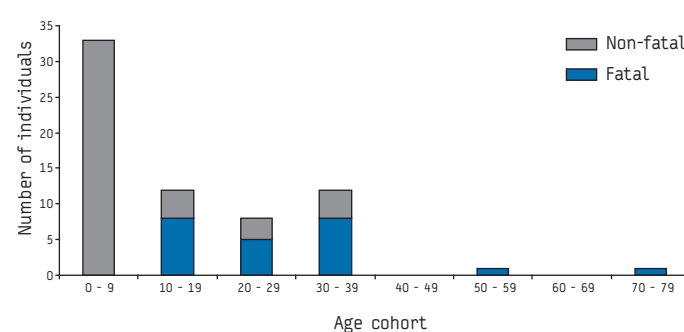
The age-specific infection and death profiles among confirmed human A(H5N1) cases in Egypt (Figure 1), differ markedly from those recorded in Asia and Indonesia when compared to cumulative data for countries worldwide other than Egypt, Nigeria, and Turkey (Figure 2). The case fatality rate from human H5N1 cases in Egypt confirmed as of 23 April 2009 is only 34% (23 of 67), versus an average of 66% among WHO-confirmed cases from all countries other than Egypt (234 of 354 cases as of 23 April 2009) [5].

Human mortality from H5N1 in Egypt is highly biased towards females (90%: 21 females, two males), with confirmed mortality only reported among individuals older than nine years. Although the sex ratio of cases in most countries is approximately 1:1, females outnumber males among confirmed cases in Egypt by a factor of nearly 2:1 (43 females:24 males). Although the average case fatality rate from H5N1 among children aged 0-9 years from all countries other than Egypt and Turkey is 59%, no confirmed fatalities among 33 children in this age cohort have been reported from Egypt as of 23 April 2009. A similar pattern is evident for H5N1 cases in Turkey during January 2006; although 11 of 21 confirmed H5N1 cases in Turkey were children in the age group 0-9 years, no confirmed fatalities were reported in this age cohort [6].

Discussion

There is increasing concern that undetected H5N1 cases may be occurring in Egypt, given the evident anomalies in observed age-specific and sex-specific case incidence and fatality rates. Although there appears to be no compelling evidence for human-to-human

FIGURE 1
Human influenza A(H5N1) cases by age and outcome, Egypt, March 2006 - April 2009 (n=67)



transmission of H5N1 in Egypt, family clusters have been observed in Egypt, and H5N1 clusters involving highly probable human-to-human transmission have been documented in China, Thailand, Vietnam, Indonesia, and Pakistan [7].

The most characteristic presentation of humans with fatal H5N1 virus infections is severe lower respiratory disease accompanied by hypercytokinaemia of the alveolar tissues. The pathology of most fatal H5N1 cases resembles those of fatal human severe acute respiratory syndrome (SARS) infections, and a suspected SARS case in China during November 2003 was subsequently confirmed as a fatal H5N1 case [8].

The existing anomalies with regard to age and sex may be attributable in part to the existence of undetected fatal or non-fatal atypical or asymptomatic human H5N1 infections. Although human infections with the H5N1 virus are typically associated with respiratory symptoms, the clinical spectrum of H5N1 infections in humans is extremely broad, and H5N1 virus has been recovered from lung, brain, large intestine, small intestine, cerebrospinal fluid, kidney, spleen, liver, pharynx, blood, and placental tissues [9]. Fatal atypical human H5N1 infections involving only gastrointestinal and neurological symptoms have been documented from patients in Vietnam and Thailand [10]. Asymptomatic human infections with H5N1 have been reported from China, Vietnam, Japan, Thailand, and Korea [11].

Clinically mild illness from highly pathogenic avian influenza (HPAI) H5N1 virus infection has been reported from children in most countries, but the early detection and treatment of possible cases may be a factor in the overall lower case fatality rate reported for H5N1 cases in Egypt. Although a median time of four days from symptom onset to hospitalisation has been reported for H5N1 cases worldwide [4], nearly 50% of confirmed cases in Egypt are admitted to hospitals within 24 hours after the first onset of symptoms, and approximately 70% are hospitalised within 72 hours after symptom onset [2].

Conclusions

The evident age and sex biases in the incidence of infection and mortality among H5N1 cases from Egypt are phenomena

that have not been fully explained, and merit further in-depth investigation and analysis. Further research is needed to understand the immediate and long-term health risks of avian influenzas for human populations, and to identify those members of exposed populations who are at greatest risk of infection and serious disease from avian influenza viruses. Although most cases in Egypt can be linked to contact with diseased poultry, increasing numbers of confirmed human H5N1 cases with no evident history of direct exposure to diseased poultry or birds are being reported from China and Indonesia. Efforts need to be made to evaluate potential background rates of asymptomatic and mild cases of human avian influenza in communities where human H5N1 clusters have been documented, and to evaluate potential instances of human-to-human transmission of H5N1 in Egypt.

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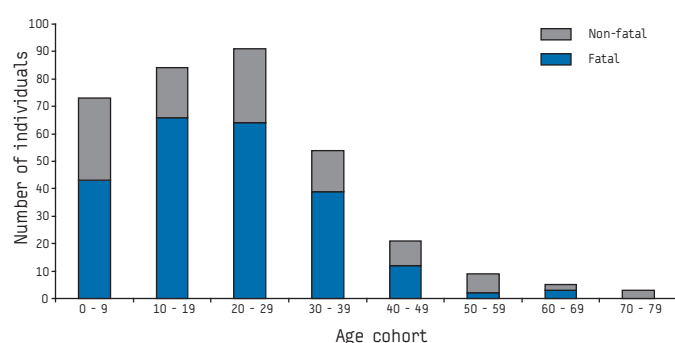
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FIGURE 2

Human influenza A(H5N1) cases by age and outcome world total, November 2003 - March 2009 (n=340)*



*WHO data as of 23 March 2009, world total excluding cases in Egypt, Nigeria, and Turkey [3].

Rapid communications

EARLY ESTIMATES OF THE EXCESS MORTALITY ASSOCIATED WITH THE 2008-9 INFLUENZA SEASON IN PORTUGAL

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The aim of this study was to estimate the excess mortality associated with the influenza activity registered in Portugal between week 49 of 2008 and week 5 of 2009. For this purpose available mortality data from the Portuguese Daily Mortality Monitoring (VDM) System were used. Several estimates of excess deaths associated with the recent recorded influenza activity were determined through statistical modelling (cyclic regression) for the total population and disaggregated by gender and age group. The results show that the impact of the 2008-9 influenza season was 1,961 excess deaths, with approximately 82% of these occurring in the age group of 75 years and older.

Background

At the end of 2008, Portugal was one of the first countries in Europe to experience an intense influenza activity that lasted a few weeks into 2009 [1]. High influenza incidence rate estimates were observed although the epidemic peak was below the previously observed maximum values. It was expected that this influenza activity should have an impact on mortality, as shown by other studies [2-3]. Available data from the Portuguese Daily Mortality Monitoring (VDM) System were used to quantify the impact. Since mid-2007, this system has been receiving information on daily mortality registered in all Portuguese Civil Register Offices from centralised databases hosted by the Institute of Information Technology in Justice at the Ministry of Justice. This study sought to give evidence of the impact of influenza activity on mortality by calculating estimates of excess deaths associated with influenza, and to test the VDM System.

Methods

Influenza activity

The information on influenza activity consisted of weekly estimates of influenza-like illness (ILI) incidence rates obtained by the Portuguese general practitioners (GP) sentinel network (Rede Médicos-Sentinela) [4] from week 41 of 2006 to week 7 of 2009 (up to 15 February 2009, inclusive). This period comprises the seasons 2006-7, 2007-8 and part of 2008-9.

Mortality

Weekly aggregated mortality data from week 1 of 2007 to week 7 of 2009 (up to 15 February 2009, inclusive) generated by the Daily Mortality Monitoring (VDM) System were used. Data were disaggregated by gender and age group (65-74 and ≥ 75 years).

Methods for calculating the estimated number of excess deaths

Statistical modelling was used to calculate the estimated number of excess deaths associated with the 2008-9 influenza epidemics.

First, all types of events potentially associated with excess mortality in the period from week 1 of 2007 to week 7 of 2009 (up to 15 February 2009, inclusive), were identified (Table 1). The periods of influenza epidemic were defined as the set of consecutive weeks with influenza virus detected and ILI incidence rate above the upper 95% confidence limit of the ILI incidence rate baseline. The heatwave period was defined as the weeks in which high temperatures were registered (two or more consecutive days with temperatures above 32°C). In both kinds of events an additional week was added to account for eventual delay of impact.

A cyclical regression model was fitted to the mortality time series after excluding the event periods (Table 1). This type of model is a multiple linear regression model whose independent variables are functions of the time sequence to adjust for the existence of long term trends and the seasonal annual pattern of mortality.

The weekly mortality predicted by the model was considered as the baseline mortality in the absence of the events potentially associated with excess mortality.

The period of excess mortality attributed to the 2008-9 influenza epidemic was defined as the set of consecutive weeks that began with two values of the observed number of deaths above the upper 95% confidence limit of the baseline and ended with two consecutive mortality values below the same limit.

TABLE 1

Events potentially associated with excess mortality observed in the period from week 1 of 2007 to week 7 of 2009 in Portugal

Event	Period (week/year)	Number of weeks
2006-7 influenza epidemic	3/2007 to 9/2007	7
July 2007 heatwave	30/2007 to 32/2007	3
2007-8 influenza epidemic	3/2008 to 7/2008	5
2008-9 influenza epidemic	49/2008 to 6/2009	10

The Figure represents a series of data, identifying the influenza epidemics and heatwave events and the baseline obtained by cyclical regression. The estimated excess deaths attributed to the 2008-9 influenza epidemic was obtained by summing the differences between the observed and the baseline mortality during the period of excess deaths, represented by dark blue bars in the Figure.

The excess deaths associated with the 2008-9 influenza season were computed by gender and age groups. Confidence intervals of the excess death estimates at 95% level were calculated by approximation to the normal distribution, using as standard error the product of the square root of the number of weeks with excess mortality by the standard deviation of the model residual. Excess mortality rates per 100,000 inhabitants were produced using the estimates of the Portuguese population at the end of 2007 [5].

FIGURE

Observed and expected weekly total mortality, weekly influenza incidence rates and potentially associated events; Portugal, January 2007 to February 2009

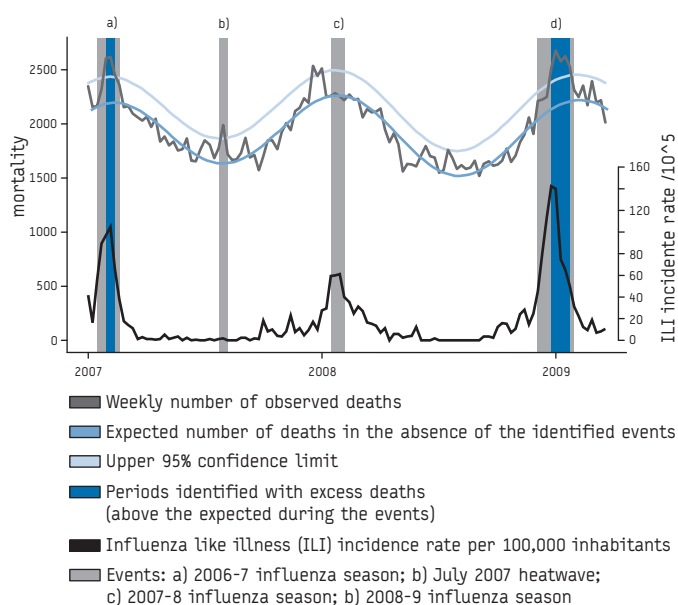


TABLE 2

Estimates of crude number of excess deaths and excess death rates, associated with 2008-9 influenza season in Portugal, in total, by sex and by age groups

	Excess deaths (95% CI)	Excess death rate/100,000 inhabitants
Total	1,961 (1,567-2,355)	18
Sex		
Men	703 (526-880)	14
Women	1161 (936-1,386)	21
Age group		
65-74	119 (75-163)	12
>=75	1,615 (1,317-1,913)	191

Statistical analysis was performed using R (www.r-project.org) package Flubase [6].

Results

The last influenza season (2008-9) was marked by more intense activity and earlier onset than the two previous seasons, with a medium to high activity between weeks 49 of 2008 and 5 of 2009, reaching a maximum value at the turn of the calendar year (Figure).

The main results indicate that although the epidemic lasted for nine weeks (from week 49 of 2008 to week 6 of 2009) excess mortality was observed only during five weeks (from week 52 of 2008 to week 4 of 2009). The overall impact was estimated to have resulted in 1,961 excess deaths, corresponding to an excess death rate of 18 per 100,000 inhabitants. The results also indicate that the impact was higher in women than in men and that 82% of the total estimated number of excess deaths occurred in individuals aged 75 years and older (Table 2).

Discussion and conclusions

The overall estimated number of excess deaths for the 2008-9 influenza season is within expected values. Past experience has shown that influenza activity and intensity can vary widely as does the respective attributable mortality. For Portugal, previous studies estimated an average of 1,773 and 2,475 deaths per epidemic period [2, 7-8].

Our results demonstrate that the currently existing tool for rapid mortality surveillance (VDM) can be used to promptly identify and estimate the impact of such public health events. A more accurate estimate could only be obtained if official routine mortality data were available.

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Surveillance and outbreak reports

TRAVEL-ASSOCIATED LEGIONNAIRES' DISEASE IN EUROPE IN 2007

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Nine hundred and forty six cases of travel-associated Legionnaires' disease were reported to the European Surveillance Scheme for Travel Associated Legionnaires' Disease (EWGLINET) with onset during 2007; 890 were confirmed and 56 were presumptive. Twenty eight cases died, giving a case fatality rate of 3.0%. 8.2% of cases were diagnosed by culture, an important increase from 5.2% in 2006.

One hundred and twelve new clusters were identified; the largest involved nine cases. Sixteen of these clusters (14.3%) occurred in countries outside EWGLINET, and three involved cruise ships. Twenty nine of the new clusters (25.9%) would not have been detected without the EWGLINET scheme. A total of 151 investigations were conducted in Europe, 42 of which were conducted at re-offending sites (where additional cases had onset after a report was received to say that investigations and control measures had been satisfactorily conducted). The names of 13 accommodation sites were published on the European Working Group for Legionella Infections (EWGLI) website; 11 of these were situated in Turkey.

Introduction

Cases of Legionnaires' disease are often associated with overnight stays in public accommodation sites which may be visited by individuals from all over the world. As such, a cluster of cases of Legionnaires' disease at a public accommodation site may involve nationals from more than one country and if the countries concerned do not share information on their cases, these clusters can go undetected. In 1987, the European Working Group for Legionella Infections (EWGLI) established a surveillance system known as 'The European Surveillance Scheme for Travel Associated Legionnaires' Disease' (EWGLINET) with the aim of identifying clusters of travel-associated cases in Europe that may not be detected by national surveillance systems alone, and initiating investigation and control measures at such sites.

In 2002, EWGLI members introduced the European Guidelines for Control and Prevention of Travel Associated Legionnaires' Disease [1], to standardise investigation and control measures conducted at cluster sites. These were endorsed by the European Commission in 2003. The history and current activities of EWGLI are described further on its website (www.ewgli.org).

This paper provides results and commentary on cases of travel-associated Legionnaires' disease reported to EWGLINET with onset in 2007.

Methods

Each of the countries that participate in the EWGLINET scheme run their own national surveillance schemes for Legionnaires' disease, which collect information on cases occurring in their residents. In order to ensure that every country reports their data to EWGLINET in a consistent manner, standardised case definitions have been developed [2]. When a travel-associated case is identified that meets these definitions, it is reported to EWGLINET's coordinating centre at the Health Protection Agency Centre for Infections in London. The coordinating centre maintains a database of all cases that have been reported to the scheme since its inception, and this is searched each time a new case is added to determine whether it is a single case or part of a cluster. These are defined in the following way [2]:

- A single case: A person who stayed, in the two to ten days before onset of illness, at a public accommodation site that has not been associated with another case of Legionnaires' disease within two years.
- A cluster: Two or more cases who stayed at or visited the same accommodation site in the two to ten days before onset of illness and whose onset is within the same two-year period.

In 2002, EWGLI determined that the investigations conducted in response to EWGLINET single and cluster case notifications should be standardised. To this end, the group introduced the European Guidelines for Control and Prevention of Travel Associated Legionnaires' Disease [1]. In response to the notification of a single case of Legionnaires' disease associated with an accommodation site, the collaborator in the country of infection is informed and is required to send the site a checklist for minimising risk of legionella infections so that the site can ensure it is following best practice. At this stage no further actions at the international level are required because the epidemiological evidence suggesting that the site is the source of infection is relatively low, although further investigations may be conducted locally.

However, if a collaborator receives a EWGLINET notification of a cluster associated with an accommodation site in their country, they are required to initiate a full investigation of the site. First, a risk assessment and initial control measures must be implemented within two weeks, and a 'Form A' report returned to the coordinating centre to record that preliminary measures have been completed. Second, environmental sampling must be carried out and control measures completed within a further four weeks, and a 'Form B'

report returned to the coordinating centre to record the completion and results of the investigation.

Because these measures are deemed to be important for the protection of public health across Europe, EWGLINET will publish details of any cluster site which is not properly investigated, or where the investigation is not completed on time, on its public website (www.ewgli.org). The information is then in the public domain and individual travellers or tour operators can choose for themselves whether or not to contract with these sites. The notice is removed once the relevant forms have been received.

If a site has been associated with a cluster and investigated under the guidelines, but is subsequently linked with a further case within a two year period, it is termed a 're-offending' site and a complete re-investigation is required. If two cases have more than one accommodation site in common during their incubation periods, it is not possible to know which site may have caused the infections. This situation is termed a 'complex cluster', and each site involved is investigated separately.

FIGURE 1
Number of travel-associated Legionnaires' disease cases reported to EWGLINET since the scheme began in 1987 (n=7,295)

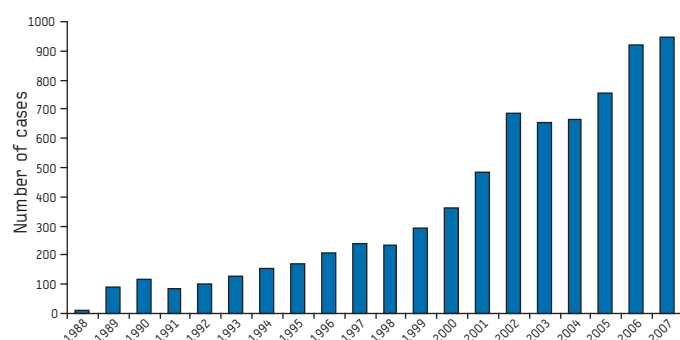


TABLE 1
Countries reporting more than 10 cases of travel-associated Legionnaires' disease to EWGLINET in 2007

Country of report	Number of cases	
	2006	2007
United Kingdom	250	236
France	174	181
Italy	130	153
The Netherlands	158	137
Spain	73	68
Sweden	28	41
Denmark	26	31
Austria	14	21
Norway	12	17
Belgium	16	15
Finland	6	14
Ireland	9	11

Note: In addition, ten other countries (including the United States), reported fewer than 10 cases and are not listed here

Results

Cases and outcomes

In 2007 the EWGLINET surveillance scheme had 35 collaborating countries of which 21 reported a total of 942 cases of travel-associated Legionnaires' disease with onset during 2007 (England and Wales, Scotland and Northern Ireland have been counted as one country). This compares with 18 countries that reported 921 cases in 2006. The United States, a country not part of the official network, reported a further four cases in American citizens who had travelled to Europe. This brought the total number of cases reported to the EWGLINET scheme with onset in 2007 to 946, a small increase of 2.7% on the number reported in 2006 and a 25.3% increase on the number of cases in 2005 (Figure 1). The mean interval between onset and report to EWGLINET was 28 days in 2007 compared with 36 days in 2006 (due to the late report of some cases from Spain) and 29 days in 2005.

The majority of the cases reported in 2007 were from the following countries: United Kingdom (236 cases), France (181), Italy (153) and the Netherlands (137) (Table 1). This represents 74.7% (707 cases) of the total number of cases for the year.

The high occurrence of infection in males continues, with cases in males outnumbering those in females at a ratio of 2.6:1 (686 males and 260 females, compared with a ratio of 2.8:1 in 2006). As in previous years, cases in 2007 mainly occurred in the older age groups with peaks in the 50-59 year age group for men (median 59 years) and the 60-69 year group in women (median 61 years).

In 2007 the peak month for onset of cases was September (157 cases), compared with August in 2006 (162 cases), continuing the established pattern of high incidence during the summer period often seen with this travel-associated disease specific network.

Outcomes were provided for 470 (49.7%) cases, and 28 deaths were notified (3.0% of the total cases). This case fatality rate is slightly less than that in 2006 (33 deaths, 3.6%). The 28 deaths were reported for cases aged 42 to 86 years (median 69 years); 23 were male and five were female. The majority of deaths in 2007 were associated with single cases (17 cases, 60.7%), although less than in 2006 when 87.9% of the reported deaths were linked to single cases. The remaining deaths in each year were associated with clusters.

Microbiology

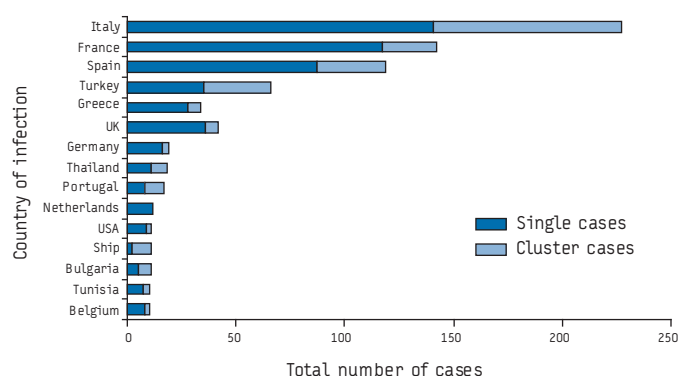
The 2007 dataset comprised cases diagnosed by urinary antigen detection, culture, serology and PCR. Under the EWGLINET case definition, 890 cases were classified as confirmed and 56 were classified as presumptive [2]. The confirmed cases consisted of 805 cases diagnosed primarily by urinary antigen detection (85.1%, a decrease from 89.2% in 2006), 78 cases diagnosed by culture (8.2%, compared with 5.2% in 2006), and seven cases diagnosed by serology fourfold rise as *L. pneumophila* serogroup 1 (0.7% compared with 0.5% in 2006). The presumptive cases consisted of a further eight cases diagnosed by serology fourfold rise as the main method of diagnosis (six diagnosed as *L. pneumophila* serogroup unknown and two as non-serogroup 1) (0.8% compared with 0.7% in 2006), 38 diagnosed primarily by single high titre (4.0%, compared with 3.6% in 2006) and 10 diagnosed primarily by PCR (1.1%, up from 0.8% in 2006).

Travel

Cases visited a total of 73 different countries during their incubation periods in 2007 (Figure 2). One hundred and eighteen cases (12.5%) visited countries outside the EWGLINET scheme and 11 cases were associated with cruise ships. Sixty six cases visited more than one European country, and three visited more than one country outside Europe. The four countries most frequently associated with infection were Italy, France, Spain and Turkey and together they accounted for 58.6% of the total 2007 data set

FIGURE 2

Countries visited by 10 or more cases of travel-associated Legionnaires' disease in 2007, by type of case, EWGLINET data



Note: A further 58 countries were visited by less than 10 cases, and do not feature on this graph.

TABLE 2

Countries where two or more clusters of travel-associated Legionnaires' disease occurred in 2007, EWGLINET data

	Country of infection	Number of clusters
Europe		
	Italy	39
	France	17
	Turkey	12
	Spain	7
	Greece	4
	Portugal	3
	Bulgaria	2
	Germany	2
	Malta	2
	United Kingdom	2
Non-Europe		
	India	3
	Thailand	3
	United Arab Emirates	2
Other		
	Cruise ships	3

Note: In addition eleven other countries were associated with only one cluster and are not listed here

(554 cases). Italy accounted for 227 (24.0%) cases, France 142 (15.0%), Spain 119 (12.6%) and Turkey 66 (7.0%).

Of the 227 cases associated with travel in Italy, 48.9% of the infections occurred among Italian nationals travelling in their own country (111 cases). For France this proportion was higher, 69.7% of cases visiting sites in France were French nationals (99 cases). For Spain 33 cases were travelling internally in their own country (27.7%). There were no Turkish nationals among the cases reported with travel to Turkey; 23 cases came from the Netherlands (34.8%) and 22 from the United Kingdom (33.3%). The proportion of cases associated with clusters in Italy was 37.9% (86 cases). In France the proportion was 17.6% (25 cases), and in Spain 26.9% (32 cases). The proportion of cases associated with clusters in Turkey increased to levels seen in previous years, at 47.0% (31 cases).

Clusters

The number of new clusters identified in 2007 was 112 compared with 124 in 2006, 94 in 2005 and 85 in 2004 (this does not include clusters which were identified in previous years and were associated with a subsequent case in 2007 ('cluster updates'); these clusters are included in the previous years' figures). This represents a decrease of 9.7% in the number of new clusters notified from 2006. A total of 278 cases (29.4%) were part of clusters in 2007. Twenty nine of the new clusters (25.9%) consisted of a single case that was reported by each of two or more countries; these would not ordinarily have been detected by national surveillance systems alone.

The largest cluster detected during 2007 involved nine cases (the same as in 2006), one of whom died, following a Baltic cruise in July and August. The ship was carrying approximately 723 passengers and 329 crew members. Seven of the cases were females and two were males; the cases were aged between 59-86 years. Investigations showed the ship's water system to be the likely source of infection.

The 2007 clusters were detected across 24 countries and on three cruise ships. Italy was associated with the highest number (39), followed by France (17), Turkey (12), Spain (7), Greece (4) and Portugal (3) (Table 2). Of the remaining clusters, 16 (14.3%) occurred in countries outside EWGLINET, a slight increase on the 12.1% outside EWGLINET in 2006.

The seasonal pattern of clusters remains in line with the high incidence of cases during the summer period, with 93 of the clusters in 2007 (83.0%) occurring between May and October. Clusters were also detected in all the other months of 2007 outside this period (by date of onset of the second case in the cluster).

Investigations and publication

One hundred and thirty one accommodation sites were associated with the 112 new clusters in 2007 (some of the clusters were complex clusters involving more than one accommodation site). Twenty two of the total number of sites (16.8%) were located in countries that had not signed up to follow the European guidelines, leaving 109 new cluster sites that required EWGLINET investigations. In addition, 42 sites were associated with cluster updates issued in 2007 where additional cases were detected after investigations had been completed and control measures were reported as satisfactory ('re-offending sites'). The guidelines require that these sites are re-investigated; accordingly, EWGLINET

requested a total of 151 investigations to be conducted in 2007, a similar number to the 146 investigations required in 2006.

Eighty two (54.3%) of the 151 Form B reports submitted to the coordinating centre reported that *Legionella* spp. was isolated from water samples taken at the accommodation site. This compares with 66.4% of reports with positive sampling results in 2006. Of the remaining 69 sites investigated, 66 (43.7% of the total) reported that legionella was not detected in samples, and three 'Form B' reports (2.0% of the total) reported 'unknown' results due to site closures.

Of the 82 sites where *Legionella* spp. was isolated from the water, *L. pneumophila* serogroup 1 was isolated from 57 sites (69.5%), at 12 sites the isolates were non-serogroup 1 (other species or serogroups) (14.6%), and the reports for 13 sites did not include enough information to categorise them in this way (15.9%).

There were 42 instances where additional cases were associated with a site after it had been investigated ('re-offending sites'). Three of these re-offences occurred at the same site; thus 40 distinct sites were associated with further cases in 2007 subsequent to a previous cluster. This compares with 33 re-offending sites in 2006, two of which re-offended twice (31 distinct sites). Nineteen of the re-offending sites in 2007 were situated in Italy, eight in Spain, six in Turkey, two in France, and one each in Austria, Czech Republic, Germany, Latvia, Portugal. Twenty three of the 42 reinvestigations (54.8%) returned positive samples (compared with 21 out of 35 reinvestigations in 2006 (60.0%). Four of the re-offending sites were part of a complex cluster (where the cases involve more than one accommodation site as a potential source).

Thirteen accommodation sites were published on the EWGLI website during 2007 for failure to return Form A or Form B reports on time, or for failure to implement appropriate control measures within the required period. These sites were located in Turkey (11), Italy (1) and France (1). This represents a significant increase from the four site names published during 2006 (nine publications in 2005, and four in 2004).

The European guidelines do not require an investigation to be carried out at sites associated with a single case report. However Italy, and occasionally other countries, do carry out such investigations and in 2007 reports were received for 107 single case sites (82 sites in 2006), of which 48 (44.9%) were reported positive for *Legionella* spp. One of these reports was received from Turkey, one from Latvia, and the rest from Italy.

Discussion

Travel-associated Legionnaires' disease continues to represent a significant public health burden in many European countries and impacts disproportionately on otherwise healthy individuals as a consequence of their travel abroad or within their own country. Improved ascertainment and better reporting to EWGLINET has increased the number of cases linked to travel from less than one hundred in 1989 to almost one thousand in 2007. Whilst this rise in cases is formidable, it probably remains an underestimate of the true incidence of travel-associated legionella infection since many studies continue to highlight the issues of underdiagnosis and underreporting of Legionnaires' disease [3,4].

As in previous years the four countries most frequently associated with cases continue to be France, Italy, Spain and Turkey. A large

proportion of cases from both Italy and France are people travelling internally within their own country. Since both countries have well established surveillance systems, these cases are likely to be due to differences in travel patterns. People from northern Europe will travel to the warmer countries of southern Europe for holidays, whilst those of southern Europe will tend to vacation closer to home.

Because the number of visitors or internal travellers in France, Italy and Spain is large, rates of infection per million visitors are much lower than in Turkey which receives fewer visitors. In 2007, rates of infection per million visitors from the UK were 2.93 for Spain compared with 13.47 for Turkey, reflecting the fact that 41 cases were reported from more than 14 million visitors from the UK to Spain compared with 22 cases from 1.6 million UK visitors to Turkey [5]. Rates of infection for other nationals such as the Dutch are known to be very high in relation to travel to Turkey [6], and more than two thirds of the 66 cases linked to Turkey in this dataset are UK and Dutch residents. The greater number of clusters detected in Turkey (12) than in Spain (7), along with the high rate of infection, suggest that control and prevention measures in tourist accommodations in Turkey are less well managed. This is also borne out by the fact that 11 of the 13 clusters published on the EWGLI website in 2007 were located in Turkey. It is hoped that Turkish health officials will take note of these findings.

The increase in the number of cases diagnosed by bacterial culture is to be welcomed since these may contribute to identifying the source of infection in accommodation sites where positive environmental samples have also been obtained. A legionella-positive environmental sample on its own is not sufficient to determine the source of infection although the likelihood that the accommodation is the source increases when clusters of two or more cases with onset of illness close together in time are linked to a site. The fall in the proportion of cluster sites with positive sampling results in 2007 (54.3% compared with 66.4% in 2006) is a return to the level observed in previous years. These levels can be compared with those reported in a French study of public accommodation sites not known to be linked to cases of Legionnaires' disease, where 18.3% were positive [7]. That the percentage of positive sites was so much higher in the EWGLINET scheme reflects the targeted nature of the cluster investigations.

At the time of report, many collaborators do not know the clinical outcome of their cases (almost 50% of cases had an unknown outcome in 2007). Hence the very low mortality rate recorded by the scheme may be the result of these unknown outcomes. Accordingly, the increased proportion of deaths linked to clusters compared with single cases in 2007 could be due to the follow-up of these clusters and better ascertainment of mortality data for this group of cases.

Travel-associated Legionnaires' disease linked to countries outside Europe is continuing to rise, as is the proportion of tourists aged 70 years or more who are visiting these countries [8]. These susceptible active elderly are at increased risk from legionella infections in countries outside the EWGLINET scheme where less well developed legionella control and prevention programmes exist. Although EWGLINET clusters that occur outside Europe are reported by EWGLI via the World Health Organization (WHO) to the ministry of health in the country concerned, minimal information on investigation and control measures is relayed back to the scheme. The Preparedness and Response Unit of the European Centre for

Disease Prevention and Control (ECDC) hosted a meeting in October 2007 between representatives of EWGLINET, the major international tour operators and the European Commission to address how this situation might be improved and several recommendations were made that are now being discussed at the international level. Since tour operators are always informed of clusters outside Europe, their role in supporting local investigations will be crucial in taking forward some of the recommendations.

In January 2010 EWGLINET will move its coordinating centre to ECDC. Transition of the scheme will take place during 2009 in order to ensure a smooth transfer of reporting and responding to cases of travel-associated Legionnaires' disease thereafter.

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* The list of EWGLINET collaborators is available at the following URL address: <http://www.ewgli.org/collaborators.htm>

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Perspectives

ESTIMATING THE GLOBAL BURDEN OF FOODBORNE DISEASES - A COLLABORATIVE EFFORT

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Illness and death from diseases caused by unsafe food are a constant threat to public health security as well as socio-economic development throughout the world. The full extent of the burden and cost of foodborne diseases associated with pathogenic bacterial, viral and parasitic microorganisms, and food contaminated by chemicals is still unknown but is thought to be substantial. The World Health Organization (WHO) Initiative to estimate the global burden of foodborne diseases aims to fill the current data gap and respond to the increasing global interest in health information. Collaborative efforts are required to achieve the ambitious task of assessing the foodborne disease burden from all causes worldwide. Recognising the need to join forces, the WHO Initiative has assembled an alliance of stakeholders which share and support the Initiative's vision, intended objectives and outcomes. One important collaborator is the European Centre for Disease Prevention and Control (ECDC) which has embarked on a burden of disease study covering at least 18 foodborne diseases in nearly 30 countries.

Burden of foodborne diseases

All countries have limited resources with which to address the health needs of their populations. Decision makers therefore need access to high-quality scientific evidence in order to prioritise resource allocation and improve public health in the most efficient and effective manner possible [1].

Surveillance data are often considered as one of the main evidence bases underpinning public health policy decisions. However traditional surveillance systems tend to capture merely a fraction of the existing disease burden. For data on foodborne diseases to be included, the affected persons need to seek medical care, provide a specimen, and test positive on laboratory tests. Moreover, the results have to be reported to the relevant health authorities [2]. The spectrum of pathogens causing infectious diseases is vast, and the diversity of these diseases makes it difficult to use surveillance data to set priorities to enable the best use of resources [3]. In addition, there are few surveillance systems which capture and attribute human illness due to infections following the ingestion of specific foods or sequelae that may be associated with foodborne infections, such as Guillain-Barré syndrome following campylobacteriosis, or epilepsy associated with neurocysticercosis following infection with the parasite *Taenia solium*.

Using the burden of disease methodology enables public health officials to circumvent some of the problems posed by the difficulty to report properly the incidence of foodborne diseases. 'Burden of disease' has been defined as the incidence and/or prevalence of morbidity, disability, and mortality associated with acute and chronic manifestations of disease [4]. The overall burden of disease is estimated using various composite measures of population health status such as the disability-adjusted life year (DALY), which is a time-based measure that combines years of life lost due to premature mortality and years of life lost due to time lived in disability or states of less than full health [5].

The burden of disease metric has been used extensively by the World Health Organization (WHO) and others to describe the global, regional and national burden from diseases [5]. Although some countries have recently quantified the national burden of foodborne diseases [6,7] the overall burden of these diseases has not been fully described to date.

Why estimate the global burden of foodborne diseases?

Through the globalisation of food marketing and distribution, both accidentally and deliberately contaminated food products can affect the health of people in numerous countries at the same time. This has been demonstrated by recent events surrounding melamine contamination in food [8]. Moreover, foodborne diseases appear to be emerging more frequently than ever before and the capacity of public health authorities to apply conventional control measures does not seem to be developing at the same speed [9]. A recent publication in *Nature* has shown that approximately 30% of all emerging infections over the past 60 years were caused by pathogens commonly transmitted through food [10]. This trend is compounded by the growing industrialisation of food and feed production as well as intensive farming which catalyses the appearance and spread of pathogens (e.g. prions associated with Bovine spongiform encephalopathy (BSE) leading to new variant Creutzfeldt-Jakob disease (vCJD) in humans during the 1990s which was caused by the use of meat and bone meal in the production of animal feeds [11]).

Diarrhoeal diseases alone - a considerable proportion of which is foodborne - kill 2.2 million people globally every year [12], but the burden arising from all foodborne diseases is clearly larger.

The heaviest share of the disease burden occurs in poor countries and jeopardises international development efforts, including the achievement of the Millennium Development Goals (MDGs). The MDGs are eight specific development goals that aim to combat extreme poverty around the world, to be met by 2015 and that were endorsed at the UN Millennium Summit in 2000 [13]. Indeed, several analyses have shown that to attain MDG 4 which focuses on reducing the under-five mortality rate by two thirds between 1990 and 2015, renewed efforts are needed to prevent and control diarrhoea, among other diseases [12].

In order to generate data on the full extent and cost of foodborne diseases, the WHO Department of Food Safety, Zoonoses and Foodborne Diseases (FOS) launched the Initiative during an international consultation in 2006 [4]. The Initiative aims to provide the first ever quantitative description of foodborne disease burden by 2011, when estimates of the burden of foodborne diseases worldwide will be generated according to age, sex and WHO regions for a defined list of causative agents of microbial, parasitic, and chemical origin. This information will enable policy-makers and others to:

- appropriately allocate resources to foodborne disease, prevention and control efforts;
- monitor and evaluate food safety measures;
- develop new food safety standards;
- assess the cost-effectiveness of interventions;
- quantify the burden in monetary costs, and
- attribute human illness to specific food sources to support risk management strategies [2].

Foodborne Disease Burden Epidemiology Reference Group (FERG) - an external expert group advising WHO

One of the main recommendations of the 2006 consultation was to establish a Foodborne Disease Burden Epidemiology Reference

Group (FERG) which would advise the WHO on the generation of comprehensive foodborne disease burden estimates. The principles behind the FERG are based on a detailed analysis of lessons learnt from other external WHO expert groups, such as the Monitoring and Evaluation Reference Group (MERG) for malaria or the Child Health Epidemiology Reference Group (CHERG) [14].

The FERG is a group which unites disciplines that do not traditionally tend to collaborate, such as: risk assessment and epidemiology, microbiology, virology, parasitology, toxicology and disease and exposure modelling. This multidisciplinary approach enables the group to generate comprehensive data from all major foodborne diseases. The FERG is mandated to:

- assemble, appraise and report on existing burden of foodborne disease estimates;
- conduct epidemiological reviews of mortality, morbidity and disability for each of the major foodborne diseases as determined by the FERG (for more details see the meeting report, [9]);
- provide models for the estimation of foodborne disease burden where data are lacking;
- develop cause and source attribution models to estimate the proportion of diseases that are foodborne, and
- develop user-friendly tools for foodborne disease burden studies at country level.

The FERG operates through a Core Group, five Task Forces, and ad hoc Resource Advisers.

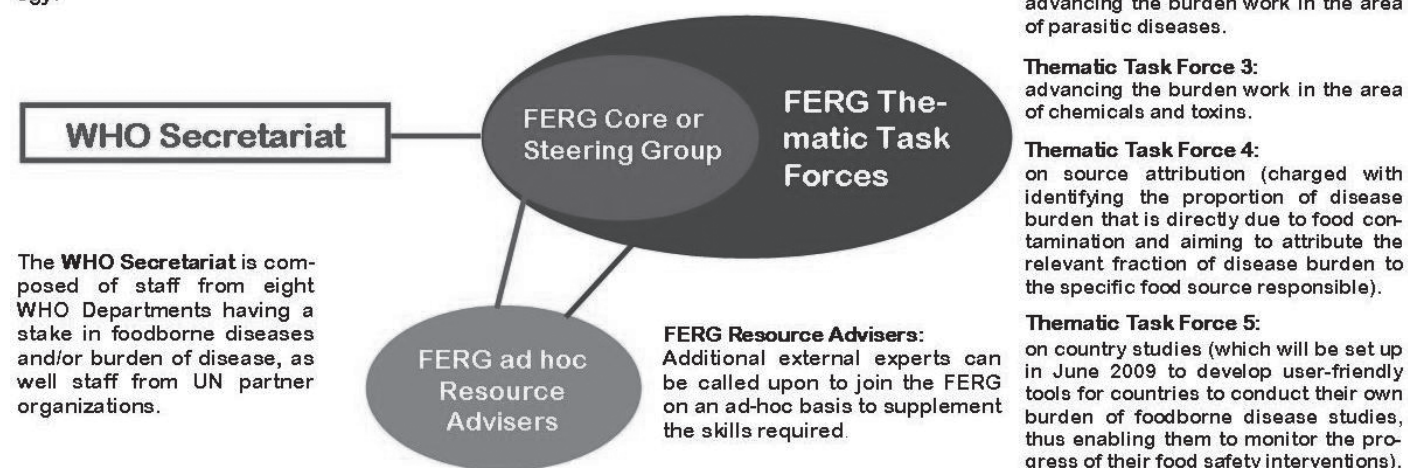
The WHO Secretariat carries out logistic, administrative, and technical support functions (Figure).

Since its establishment, the FERG has met twice to (a) decide on priority causative agents for which burden data should be generated (for more details see the meeting report, [9]), (b)

FIGURE

Composition and structure of the WHO Initiative to Estimate the Global Burden of Foodborne Diseases [9]

The **FERG Core or Steering Group** functions as steering committee and consists of scientists from each of the areas outlined in the Task Forces below. It is charged with monitoring and appraising the technical and epidemiological work of all the Task Forces and is chaired by a scientist with extensive international experience in both foodborne diseases and burden of disease methodology.



develop extensive workplans guiding the WHO Secretariat on the work to be commissioned, and (c) appraise the progress made with commissioned work. Major pieces of review, research and modelling work have been undertaken by externally commissioned scientists for the following causative agents:

- chemicals/toxins: cyanide from cassava, aflatoxin, dioxins, peanut allergens;
- parasites: intestinal protozoa, *Fasciola hepatica*, *Taenia solium*, *Echinococcus multilocularis*;
- enteric pathogens: global burden of diarrhoeal diseases in persons older than five years of age.

First interim results are expected in 2009. A peer-review system involving external reviewers increases the quality and scientific rigour of the work of the FERG.

The Task Force on Source Attribution (task force 4), aiming to attribute the relevant fraction of disease burden to the specific food source responsible, commenced its work in April 2008. The fifth FERG Task Force on country studies will commence its work in June 2009. This task force will increase the capacity of countries to conduct their own foodborne disease burden assessments. Eighteen country studies are envisaged (three in each of the six WHO regions), and will provide first-hand field data, fill data gaps identified by the FERG, and help validate the burden results generated by modelling approaches.

Partnerships - joining efforts for results

The multifactorial nature of foodborne diseases necessitates close collaboration between the WHO Initiative and a large number of partners and stakeholders, to bring together necessary expertise and resources, and minimise duplication of efforts. The Initiative is capitalising on existing WHO in-house experience with staff from several WHO departments dealing with diseases of potentially foodborne origin (including child health, parasitic and neglected tropical diseases, water and sanitation, and others), working with the Initiative.

Collaboration with external stakeholders

The Initiative relies on an alliance of external collaborators and partners who provide technical expertise, information sharing platforms, networking possibilities and/or financial support. Through the FERG members, more than 30 internationally renowned scientific institutions from all over the world have been linked with the Initiative. WHO has established close technical collaboration with several organisations involved in major global and regional burden of disease initiatives, including (among others):

- The European Centre for Disease Prevention and Control (ECDC) which has embarked on a burden of disease study covering nearly 30 countries and up to 49 infectious diseases, of which at least 18 can also be transmitted by food (see also the section below on collaboration with the ECDC).
- The Institute for Health Metrics and Evaluation (IHME) in Seattle which is updating the Global Burden of Disease data for the year 2005, the year of reference. The risk factor 'unsafe food' will not be examined by IHME, but will instead be assessed by the WHO Initiative due to its specific knowledge in this area.
- The International Collaboration on Enteric Disease Burden of Illness Studies which facilitates communication between experts who have conducted burden of enteric or foodborne infectious disease studies.

- Med-Vet-Net, a European research network for zoonoses, which will produce estimates of the disease burden and cost of illness of (selected) foodborne and zoonotic pathogens in eight European countries.

The WHO has assembled and continues to expand an alliance of funding agencies and in kind supporters for the FERG, to ensure that no individual agency, foundation, or government can exert undue influence on the Initiative. The WHO and other institutions (such as the Ministry of Health, Welfare and Sport, the Netherlands; the Centers for Disease Control and Prevention and the United States Department of Agriculture, United States; the Ministry of Health, Labour and Welfare, Japan; the Department of Health, United Kingdom) continue to make considerable financial investments in the Initiative. The WHO is currently discussing additional funding options with a number of governmental and non-governmental donors.

Stakeholder events

The Initiative has implemented a detailed communication strategy covering internal and external information sharing, mechanisms for accountability, as well as all aspects of advocacy. Key food safety stakeholders were invited to the first formal meeting of the FERG in November 2007 to give their input to the Initiative. This involvement proved to be very fruitful, and the input received from the stakeholders was endorsed in the technical deliberations of the FERG [9].

The second FERG meeting (17 to 21 November 2008) also incorporated a stakeholder gathering. Representatives from more than 30 institutions (including the WHO Member States, bi- and multilateral organisations, agricultural and food industry, consumer groups, academia as well as scientific and public media) attended the event in November 2008. Stakeholders welcomed the WHO's effort to estimate the foodborne disease burden.

Working group sessions at the meeting provided an opportunity for all participants to interact directly with the Initiative and the FERG members and to give relevant suggestions in the areas of communications, advocacy and policy [15].

Collaboration with the ECDC

The WHO has a global mandate to assemble health information, assist countries to shape the health research agenda, set norms and standards, monitor and assess health trends and provide technical support to countries. The ECDC is responsible for identifying, assessing and communicating current and emerging threats to human health from infectious diseases within the European Union (EU) [16]. The WHO and the ECDC work closely together in order to avoid duplicating efforts and to make the best use of limited resources.

In 2006 the ECDC recognised that a composite measure of disease burden, such as DALY, could be used to guide public health policy and action in the area of communicable diseases [17]. Therefore a three-month pilot study to explore the potential of the disease burden concept for seven communicable diseases was conducted [18].

A study called "Present and Future Burden of Communicable Diseases in Europe" (BCoDE) will build on the pilot results, and will make use of existing methodologies such as those developed by the

WHO for its Global Burden of Disease Study [19]. The ECDC project is planned to start in 2009 with the initial phase (methodology development, field testing and full burden study) estimated to last four years. The burden of disease estimates will subsequently be updated on a regular basis.

While there is some overlap between the two studies with regards to the diseases (about one third of the diseases covered in the EU-wide study involving foodborne pathogens are also being investigated by the FERG), the effort of the WHO Initiative focuses on the global picture of all major foodborne diseases, including those resulting from chemical and numerous parasitic hazards which are not covered by the ECDC's study. Additionally, the FERG aims to attribute causes of disease burden to particular food commodities, where possible. To ensure a synergistic approach, scientists from the ECDC and all relevant networks are represented as advisers on the FERG.

Conclusions

Assessing the global burden of foodborne diseases from all major causes using summary health metrics in the form of the DALY is needed to help decision makers allocate appropriate resources to food safety control and prevention. To tackle this large task, the Initiative to Estimate the Global Burden of Foodborne Diseases combines the WHO's public health leadership capacity with the independent expert advice of FERG, and relies on an inter-sectoral alliance of partners and stakeholders.

Multi-stakeholder partnerships work best if aligned with the strategic interests of each party. This is the case for the ECDC and the WHO Initiative. Both institutions aim to estimate the burden of foodborne diseases by capitalising on their respective strengths. The ECDC will generate burden data on communicable diseases (including those transmitted by food) for European countries whereas the WHO will focus on the global burden of foodborne diseases from all major causes. Based on complementary strengths, this process will enable both institutions to avoid duplication of efforts, share technical expertise and data, as well as ensure comparability of burden results.

The WHO Initiative is continuously seeking to broaden its cooperation with external partners. The annual stakeholder meetings have proven to be an effective platform for fostering constructive dialogue and interaction between the WHO, the FERG and the food safety stakeholder community. These meetings will increase in size and importance to further catalyse international collaboration and funding for effective foodborne diseases prevention and intervention measures.

Authors' disclaimer

The findings and conclusions in this publication are those of the authors and do not necessarily represent the decisions or policies of their respective institutions.

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Letters

NATIONAL PNEUMOCOCCAL VACCINATION PROGRAMMES FOR CHILDREN IN EUROPE, 2001-2007: UPDATE FROM IRELAND

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To the editor: With reference to the article by Carvalho Gomes et al. entitled "Use of seven-valent pneumococcal conjugate vaccine (PCV7) in Europe, 2001-2007" (<http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19159>), published on 26 March 2009, I wish to point out that in addition to the introduction of a universal PCV vaccination programme in September 2008, the Health Services Executive of Ireland also organised a PCV7 catch-up programme for children up to the age of 24 months (one or two doses depending on age).

Additionally, since October 2002, PCV7 has been recommended for at risk children up to the age of 24 months. In September 2008, this age group was expanded to include at risk children up to five years of age (one or two doses, depending on age and risk factor).

Recommended vaccines are free for children.

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Letters

NATIONAL PNEUMOCOCCAL VACCINATION PROGRAMMES FOR CHILDREN IN EUROPE, 2001-2007: UPDATE FROM TURKEY

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To the editor: With reference to the article by Carvalho Gomes et al. entitled "Use of seven-valent pneumococcal conjugate vaccine (PCV7) in Europe, 2001-2007" (<http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19159>), published on 26 March 2009, we wish to point out that Turkey has introduced a universal PCV7 vaccination programme into the national childhood vaccination programme in November 2008.

The vaccine is recommended at two, four and six months of age with a booster dose at 12 months of age. The programme is fully reimbursed. In addition, a catch-up programme has been implemented for infants born between May 2008 and November 2008.

We hereby would like to draw your attention to this information since the article described PCV7 vaccination programmes in Europe up to March 2009.

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AUTHORS' REPLY: NATIONAL PNEUMOCOCCAL VACCINATION PROGRAMMES FOR CHILDREN IN EUROPE, 2001-2007 – UPDATED TABLE

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To the editor: With reference to our article “Use of seven-valent pneumococcal conjugate vaccine (PCV7) in Europe, 2001-2007” (<http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19159>), published on 26 March 2009, we would like to present an updated table showing the characteristics of national pneumococcal vaccination programmes for children in 32 European countries (Table) with additional information from Ireland and Turkey received following the publication of the article.

This update will only reflect changes made until March 2009, when data on PCV7 vaccination programmes were collected for the purposes of the article. However, the table also includes an update on the Hungarian PCV7 vaccination programme that had already been announced in the original article, and has now come into effect in April 2009. An addition has been made to the entry for Spain to clarify that the vaccine is free to all children under the age of five who belong to at-risk groups.

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TABLE

Characteristics of national pneumococcal vaccination programmes for children in 32 European countries

Country	Extent of PCV7 vaccination programme	Date of implementation	Vaccination regimen ^a	Catch-up programme	Reimbursement	Comments
Austria	Universal	September 2004	3+1	No	No	Free of charge for children under the age of two years in risk groups.
Belgium	Universal	January 2005	2+1	Yes ^b	Total	Free of charge for children under the age of two years since January 2007.
Bulgaria	None	-	-	-	-	Inclusion of PCV7 as a recommended vaccine on an individual voluntary basis is being considered based on a decision of the expert committee on national immunisations (24 July 2008).
Croatia	Risk-based	November 2006	3+1	n/a	Total	
Cyprus	Universal	August 2008	3+1	Yes	Total	Since August 2008 free of charge for children at the ages of two, four and six months, with a booster dose at the age of 12-15 months (3+1). In addition, a catch-up programme is implemented for children up to the age of 59 months.
Czech Republic	Risk-based	January 2007	3+1	n/a	Total	Free of charge for children under the age of five years since January 2007.
Denmark	Universal	October 2007	2+1	Yes ^c	Total	
Estonia	None	-	-	-	-	
Finland	Risk-based	January 2009	2+1	n/a	Total	Since January 2009, free of charge for children under the age of five years in risk groups. In addition, one dose of pneumococcal polysaccharide vaccine is given to children over the age of two years in risk groups.
France	Universal	June 2006	2+1	Yes ^d	Cost sharing/ Total	In October 2008, the vaccination regimen changed from 3+1 to 2+1. 65% of the price of PCV7 is reimbursed by social security. The rest is reimbursed by private insurance (for the 80% of the population that have one). The vaccine is free of charge in mother and child care services.
Germany	Universal	July 2006	3+1	Yes ^e	Total	Since January 2008, reimbursement of all recommended vaccinations has been regulated on a national level.
Greece	Universal	March 2006	3+1	Yes ^b	Total	Fully reimbursed since March 2008.
Hungary	Universal	April 2009	2+1	Yes ^b	Total	Since April 2009, PCV7 has been given on a voluntary basis and free of charge to children at the ages of two and four months, with a booster dose at 15 months of age (2+1 regimen). From October 2008 to March 2009, PCV7 was given on a voluntary basis and free of charge to children under the age of two years with the 3+1 regimen.
Iceland	Risk-based	December 2006	2+1	n/a	No	
Ireland	Universal	September 2008	2+1	Yes ^b	Total	Vaccine is given at the age of two, six and 12 months; for catch-up, one or two doses are given (age-dependent). Recommended vaccines are free.
	Risk-based	October 2002	3+1	n/a	Total	In 2002, vaccine recommended for at risk children up to 24 months of age (two or three doses, plus/minus booster, depending on age). In 2008, the age group 'at risk' was expanded to include children up to five years of age (one to two doses, depending on age and risk factor). Recommended vaccines are free.
Italy	Universal/ Risk-based	May 2005	2+1	No	Cost sharing/ Total (Regional variation)	In 15 of 20 regions, PCV7 is offered to all children either free of charge or with cost sharing. In five regions, PCV7 is recommended to children at risk only and is free of charge.
Latvia	None	-	-	-	-	Voluntary vaccination of children in risk-groups is planned for 2009.
Lithuania	None	-	-	-	-	
Luxembourg	Universal	October 2004	3+1	Yes ^d	Total	
Malta	Risk-based	January 2007	3+1	n/a	Total	
The Netherlands	Universal	June 2006	3+1	-	Total	
Norway	Universal	July 2006	2+1	Yes	Total	PCV7 was introduced in the national childhood vaccination programme on 1 July 2006, with a catch-up programme for children born after 1 January 2006.
Poland	None	-	-	-	-	

Portugal	None	-	-	-	-	The Portuguese National Vaccination Committee is in the process of discussing the implementation of PCV7 into the national vaccination programme.
Romania	None	-	-	-	-	
Slovakia	Universal	April 2008	2+1	n/a	Cost sharing	Universal: recommended to children under the age of two years as complementary (optional) vaccination for optimal individual protection, 96% of the costs are reimbursed by the national health insurance.
	Risk-based	January 2006	2+1		Total	Free of charge to children under the age of two years belonging to risk groups.
Slovenia	Risk-based	September 2005	3+1	n/a	Total	Fully reimbursed since September 2005.
	Risk-based	June 2001	3+1	n/a	Total	Since June 2001, free of charge for children under the age of five years belonging to risk groups.
Sweden	Universal	January 2009	2+1	n/a	Total	Since January 2009, PCV7 has been part of the national childhood vaccination programme and is recommended to all children born from October 2008 onwards.
Switzerland	Universal	November 2005	2+1	Yes ^d	Total	Universal: recommended as complementary (optional) vaccination for optimal individual protection; fully reimbursed since August 2006.
	Risk-based	July 2001	3+1			Risk-based: fully reimbursed since July 2001.
Turkey	Universal	November 2008	3+1	Yes ^f	Total	Since November 2008, PCV7 has been part of the national childhood vaccination programme and is recommended at the ages of two, four and six months with a booster dose at the age of 12 months.
United Kingdom	Universal	September 2006	2+1	Yes ^b	Total	Free to all children.

n/a = not applicable;

a Number of PCV7 doses given during first year + number of booster doses;

b Until 23 months of age for all children;

c Until 18 months of age for all children;

d Until 23 months of age for all children and until 59 months of age for children with particular co-morbidities;

e Until 59 months of age for children with particular co-morbidities;

f Administered to infants born from May 2008 to November 2008.

Source: EUVAC.NET