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# *Plasmodium vivax* malaria in a Romanian traveller returning from Greece, August 2011

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**In August 2011, a *Plasmodium vivax* malaria infection was diagnosed in a Romanian traveller returning from Greece. This case together with several reports over the past decade of autochthonous cases in Greece highlight that malaria should be considered as differential diagnosis in symptomatic travellers returning from this country. Travellers may serve as sentinels of emerging vector-borne diseases.**

Malaria is considered to be eradicated in several European countries since 1975, although *Anopheles* spp. mosquito vectors remain prevalent in parts of southern and central Europe [1]. A few cases of autochthonous transmission of malaria to local residents have been reported over the last 10 years in areas where the disease has been declared eradicated (Bulgaria, France, Germany, Greece, Italy, and Spain), including the so-called airport malaria, but there has not been sustained local transmission in any specific location [2].

In this report, we describe a case of malaria in a Romanian traveller returning from Greece.

## Case report

On 1 August 2011, a 25-year-old Romanian man developed an acute febrile illness with chills, myalgia, fever, and left abdominal flank pain. He had returned from Greece on 30 July. His past medical history included a splenectomy 14 years earlier. As the symptoms persisted, on 3 August, the patient visited the family doctor who suspected a respiratory infection and prescribed a symptomatic and antibiotic treatment (amoxicillin-clavulanate). On 9 August, as there was no improvement in his symptoms, as the fever persisted and he felt an increased pain in the left flank, and after an episode of near syncope, he was admitted to the local hospital in his area of residence. Abdominal ultrasound showed a hematoma in the splenic bed (5.5 by 6.6 cm). The hematoma was surgically drained. On 11 August laboratory results revealed thrombocytopenia (57,000/mm$^3$; norm: 150,000-400,000), anaemia (Hb: 8.7 g/dl; norm 11.5-15), and leukocytosis (16,600/mm$^3$; norm: 4,000-10,000) with normal white blood cell differential count. Blood cultures taken upon each hospital admission remained negative. Thin blood smear revealed *Plasmodium* spp. trophozoites and schizonts. On the same day, the patient was transferred to 'Victor Babes' Hospital for Infectious and Tropical Diseases in Bucharest. On arrival, physical examination revealed a reduced general condition, a temperature of 37.8°C, abdomen with diffuse sensitivity to palpation, and moderate hepatomegaly. Thin and thick films revealed *Plasmodium vivax* parasitaemia of 0.05% with mature trophozoites, young schizonts, and gametocytes of *P. Vivax*. Whole blood DNA quantification using a LightScanner 32 (Idaho Technology, USA) demonstrated *P. Vivax* (1,500 copies/µl) and was negative for the other *Plasmodium* species. The patient responded quickly to the seven-day treatment of oral quinine combined with doxycycline. The clinical response was good (fever ceased after 48 hours of treatment) and the parasite clearance appropriate (negative thin and thick smear after 72 hours of antiparasitic treatment). After this treatment, the patient was given primaquine for 14 days to prevent relapses.

Patient history revealed that he had worked intermittently in agriculture in Greece, for about six years (in 2005 in Argos region and then every October to February from 2006 to 2010 in Lakonia region, in Skala and Elos localities of the Evrotas river basin). More recently, from November 2010 to 30 July 2011 he worked in the same regions (Skala and Elos) in agriculture. He had no history of travel to any malaria-endemic areas and his only other travel abroad was a two–month trip to Italy (Sicily) from September to October 2010. He had never travelled by plane, he does not live in the proximity of any international airport and there have been no reports of imported malaria cases within his residence

area in Romania. Malaria tests in the patient's relatives with whom he had travelled and worked in Greece were negative.

## Epidemiological situation in Greece

Several Anopheline vector species are known to breed in Greece, including some of the historically most important vectors in Europe including *A. atroparvus*, *A. sacharovi* and *A. superpictus* that are competent for *P. Vivax* [3]. As early as 1994 and 1995 four autochthonous malaria cases (*P. falciparum*, *P. malariae* and two *P. Vivax*) were diagnosed in Evros, northern Greece, in native residents from rural areas who stated that they had never left Greece or visited an international airport [4]. In the summer of 1998 two additional malaria cases (*P. Vivax*) were diagnosed in the same region in two patients who had been living for four years in Feres (in the Evros peripheral area, East Macedonia and Thrace, Greece) after they had immigrated from southern Albania [5]. Later, an autochthonous cluster of *P. Vivax* malaria occurred in the Evrotas river basin, Lakonia, southern Greece, from August to October 2009, with eight patients hospitalised in Sparta General Hospital, including two immigrants from Pakistan and Afghanistan and six patients, natives of Lakonia and living in different areas from the first two [6]. More recently, between June and 18 August 2011, six cases of locally-acquired *P. Vivax* malaria have been notified to the Hellenic Centre for Disease Control and Prevention through the mandatory notification system in Greece: four cases from the same agricultural wetland area of the Evrotas river basin, Lakonia, in the Peloponnese, southern Greece and two cases who reside near the city of Chalkida, Evoia, in the eastern part of Greece [7]. All cases were local residents with no history of travel to a malaria endemic area.

## Epidemiological situation in Romania

The *P. Vivax* malaria case in Romania was reported to the National Institute of Public Health within the National Malaria Surveillance Programme. In Romania, there is a national programme for surveillance and rapid communication of malaria cases. In 1948, a total of 333,198 cases of malaria were reported, but starting with 1968 Romania was declared a malaria-free country. No local transmission of malaria has been reported in Romania since then. Nevertheless, malaria remains a possible re-emerging disease especially in the southern and south-eastern part of the country, where vector-competent *Anopheles* species are prevalent [8]. In the past 10 years, 107 cases of malaria were diagnosed in the 'Victor Babes' Hospital of Infectious and Tropical Diseases in Bucharest and all of them were in travellers who had returned from malaria endemic areas, mostly from Africa [9,10].

## Discussion and conclusions

The occurrence of presumably vector-competent *Anopheles* species, together with increasingly favourable climatic conditions and the frequent availability of reservoirs of infection such as imported cases, produce an ongoing probability of autochthonous malaria appearing time and again.

This case report presented epidemiological evidence and patient history point to an infection in the Skala and Elos areas Greece. Prior to 2011, the patient had not been exposed in Greece during summer, or during periods when autochthonous cases were reported in Greece. However, it is unclear whether the reservoir of infection for this case was from migrant workers in Greece coming from South Asia or from the local population.

To the best of our knowledge, this is the second case of malaria reported recently in an international traveller who acquired the infection in an European Union (EU) country. In 2000, a German couple was diagnosed almost simultaneously with *P. Vivax* malaria after a one-week holiday in Kassandra, Chalkidiki, a Greek tourist resort [11]. No local cases had been reported at that time but it seems that sporadic local transmission must have been occurring.

Since Greece is a frequent destination for people visiting or working, any re-emergence of malaria will be of concern. Furthermore, the occurrence of malaria cases in areas considered to be malaria-free may lead to delay in diagnosis raising the possibility of exposure to vectors and even the risk of incidence of local malaria cases.

To date, there has been no recommendation for travellers to the affected areas in Greece to take any antimalarial chemoprophylactic drug. However, advice has been issued on avoidance measures regarding insect bites particularly during the evening and at night [12,13].

In the authors' opinion, the Greek interventions with the current cases should be followed closely so that Romania and other formerly malaria endemic countries in the EU remain malaria-free. Both local health authorities and practicing clinicians need to be aware that they should also include malaria in the differential diagnosis in travellers and temporary residents returning from Greece and maybe also other southern European countries. However, according to a risk assessment related to the six autochthonous cases of *P. Vivax* malaria in Greece, published by the European Centre for Disease Prevention and Control, the risk for further extension of malaria transmission into the EU is considered low at present [7].


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# Ongoing large mumps outbreak in the Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, December 2010 to July 2011

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**From December 2010 until the end of July 2011, 5,261 mumps cases were recorded in the Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, leading to an incidence of 225.8 per 100,000. Fifteen to 19 year-olds (43%) were most affected and 62% of cases were male. Mumps-specific IgM antibodies were found in about 70% of sera investigated, complications were reported in 41% of 81 hospitalised patients. The outbreak affected mainly those unvaccinated or unaware of their vaccination status and is probably due to vaccination failures during the war and post-war period (1992–1998).**

In December 2010 the cantons of Zenica-Doboj (n=40) and Central Bosnia (n=34) reported an increased number of mumps cases to the Ministry of Health of Bosnia and Herzegovina. Subsequently, the number of mumps patients continued to rise and more cantons reported cases. By the end of July 2011, a total of 5,261 cases were reported to the Ministry of Health.

## Background

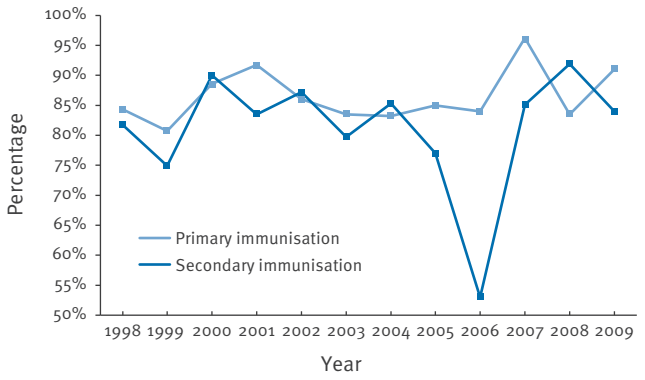
Immunisation against mumps was introduced in Bosnia and Herzegovina in 1980 in form of a combined vaccine against measles, mumps and rubella (MMR) [1]. Until 1992, it was recommended to vaccinate children between one and 14 years of age without documented history of mumps, with one dose of MMR vaccine. Between 1992 and 1995, the war caused disruptions to the routine immunisation programme, in the country, and these disruptions continued also during the post-war period (1996–1998). In 2001, a two-dose schedule with MMR vaccine was implemented throughout the country, with the first dose given at the age of 12 months and the second dose at the age of seven years and no later than 14 years. The MMR vaccine produced by the Institute of Immunology Zagreb was used until 2009 and contained the L-Zagreb strain as component, and since 2010, the Glaxo SmithKline MMR vaccine containing the Jeryl Lynn strain is employed [1,2]. The average coverage with MMR vaccine for the Federation of Bosnia and Herzegovina between 1998 and 2009 ranged from 84% to 92% for the first dose, and from 53% to 92% for the second dose (Figure 1).

Mumps is a notifiable disease in Bosnia and Herzegovina and is reported on the basis of clinical symptoms and epidemiological data. Reporting of mumps is normally done by the doctors to the Institute for Public Health, which looks for epidemic evidence and provides information to the Ministry of Health.

The first reports on mumps in Bosnia and Herzegovina date back to 1956 [3]. In the period before 1980, when vaccination against mumps was introduced, morbidity was high with an incidence ranging from 189 to 253 cases per 100,000 inhabitants per year (Figure 2). After introduction of the vaccine, incidence decreased from 123 in 1981 to 3.5 in 1992. During the war from 1992 to 1995, the reported incidence of mumps was between 7.8 and 5.1, but reporting was irregular and underreporting is likely. Between 1999 and 2002, 25 smaller

**Figure 1**

Coverage of measles, mumps and rubella vaccine in the Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, 1998–2009



outbreaks were reported with a total of 2,743 cases. The last outbreak of mumps in Bosnia and Herzegovina occurred in 2002 with a total of 410 reported cases and until December 2010 only few cases were notified [4].

At the beginning of December 2010 a mumps outbreak started in the Federation of Bosnia and Herzegovina and is still currently ongoing. This report describes the mumps outbreak in the country and includes data from December 2010 until the end of July 2011.

## Description of the outbreak

Since the start of the outbreak in December 2010, 5,261 cases have occurred in nine of the 10 cantons of the country, however, cantons are affected to a different extent. In December 2010, 85 cases were reported and the peak of the outbreak was in April 2011 with 1,240 cases reported (Figure 3).

The most severely affected cantons are Central Bosnia Canton (n=2,156 cases), Zenica-Doboj Canton (n=1,695), Sarajevo Canton (n=1,035) and Herzegovina-Neretva Canton (n=326). Together they account for about 99% of all cases. Only few cases have been reported in Una-Sana, Tuzla, Bosnian Podrinje, West Herzegovina and West Bosnia cantons, and no cases from Posavina Canton (Figure 4).

For 5,219 patients, data on age and sex are available. The majority (3,255/5,219; 62%) are male and the most affected age groups include the 15 to 19 year-olds (2,232/5,219; 43%), followed by 20 to 29 year-olds (1,254/5,219; 24%) (Figure 5).

Patients with serious clinical symptoms such as fever, temperature above 38.5, swelling of the parotid and/or salivary glands, and fatigue were hospitalised. A total of 81 patients were admitted to the Clinical Centre University of Sarajevo, but we have no data for other hospitals. The vast majority were male (67/81, 83%) and 30 of them had orchitis (30/67, 45%). One female and two male patients had meningitis (3/81, 4%).

### Vaccination status of cases

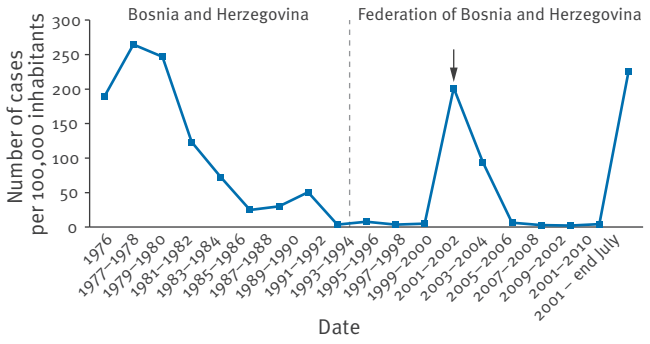
For 34% of the cases (1,774/5,219) vaccination status was unknown. About 33% of cases (1,722/5,219) were unvaccinated, 18% (939/5,219) were vaccinated with one dose of a mumps-containing vaccine, and only 15% (784/5,219) had received two doses (Figure 6).

## Laboratory findings

Samples were collected for laboratory analysis from 104 cases: throat swabs from 32, throat swabs and serum from 48 and only serum from 24 of them. The cases' age ranged from seven to 48 years (median:

**Figure 2**

Incidence of mumps cases, Bosnia and Herzegovina, January 1976–July 2011




The dotted vertical line indicates a time point from which data is only shown for the Federation of Bosnia and Herzegovina.

The arrow indicates when a two-dose schedule of measles, mumps and rubella vaccine was implemented in Bosnia and Herzegovina.

**Figure 3**

Number of mumps cases per month, Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, beginning December 2010–end July 2011 (n=5,261)

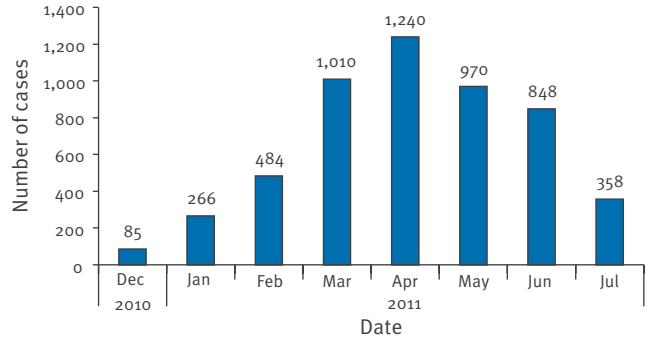
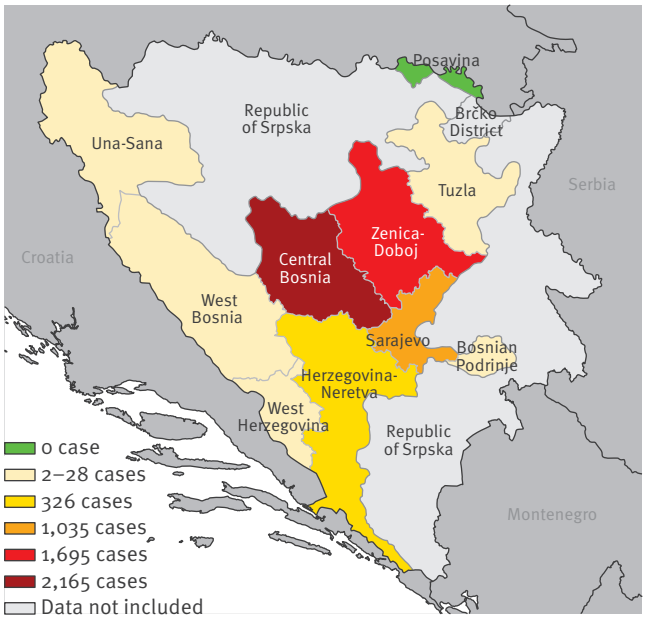



**Figure 4**

Cumulative number and geographical distribution of notified mumps cases, mumps outbreak, Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, beginning December 2009–end July 2011 (n=5,261)



22.15 ± 7.47) and 83% were male. All 72 serum samples were tested with the Siemens Enzygnost anti-parotitis virus kit for mumps-specific IgG and IgM antibodies. Sixty-eight samples were IgG positive (94%), three were borderline and one was negative. A total of 50 samples were positive for IgM (69%), eight were borderline and 14 were negative. The results of PCR and sequence analysis from throat swabs are pending.

## Control measures

In March 2011, the Federal Minister of Health declared a mumps epidemic. It was recommended to increase the vaccination coverage with two doses of MMR vaccine in children between one and 14 years of age and some schools with increased case numbers were temporarily closed.

Other epidemic control measures by public health authorities, supported by doctors and/or teachers in the schools included: (i) health education, (ii) disseminating information about general and personal sanitary and hygienic measures to take, (iii) isolating infected persons and limiting contact with them, (iv) disinfection of articles of general use and (v) frequent hand washing in order to limit further spread of the disease. The control measures were in accordance with protocols for prevention and infection control.

## Discussion and conclusions

In recent years, mumps outbreaks were reported from many countries all over the world [5-8]. In Bosnia and Herzegovina, disruption in the immunisation program during the war (1992–1995) and in the post-war period (1996–1998) left considerable numbers of children susceptible to measles, rubella and mumps [9]. The children, who were supposed to get their first vaccination between 1992 and 1998 are now between 14 and 20 years old and constitute a large proportion of the people affected by the current outbreak. Our data also show that most cases in the current outbreak (85%) either did not know their vaccination status or reported being not or incompletely vaccinated.

The geographical regions with the highest case numbers in the current mumps outbreak largely concur with the areas that were most severely affected during previously reported rubella and measles epidemics [10,11]. Also, during the war from 1992 to 1995, immunisation was not fully implemented across the entire territory of Bosnia and Herzegovina. The program of immunisation was not the same across the Cantons. Two doses of vaccine were used in the Posavina, Herzegovina-Neretva and West Herzegovina cantons while in other cantons only one dose was implemented. Some small outbreaks occurred in Una-Sana Canton and Tuzla Canton and they had additional vaccination with monovalent parotitis vaccine and that is the probably reason for the smaller number of cases in these cantons in the current outbreak.

Similarly to the rubella outbreak in 2010 [10], more males contracted the disease (62%) and the most severely affected age group were young adolescents (15 to 19 years of age, 43%). High numbers of mumps cases in male adolescents were reported recently from several countries, such as Israel, the United Kingdom, the Netherlands and the United States [5,12-14].

The majority of cases reported during the current outbreak were diagnosed based on clinical symptoms, sometimes supported by epidemiological data. Only a few samples were collected from non-hospitalised patients for laboratory confirmation, as the clinical picture was considered typical. In about 70% of the serum samples, mumps-specific IgM antibodies were detected, confirming the clinical diagnosis.

Information about complications and hospitalisations related to the outbreak is incomplete. The available data point to complications in about 7% of the female (meningitis) and 48% of the male (meningitis and orchitis) hospitalised patients, however, total numbers of cases are low. Symptomatic meningitis has been reported to occur in up to 15% of patients and orchi-

**Figure 5**

Number of cases in relation to age and sex, mumps outbreak, Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, beginning December 2009–end July 2011 (n=5,219)

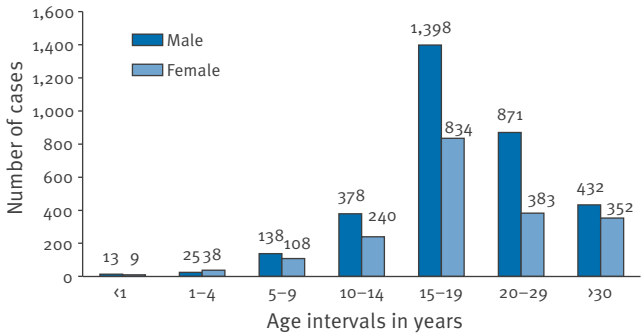
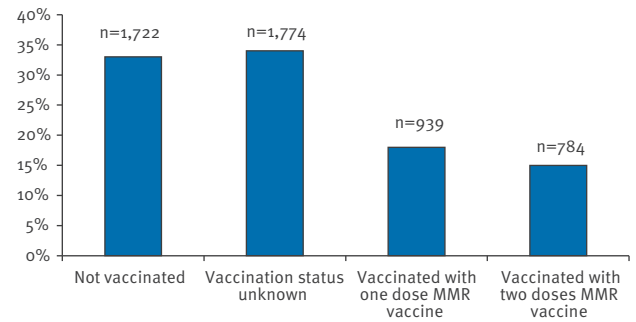



**Figure 6**

Vaccination status of patients, mumps outbreak, Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, beginning December 2009–end July 2011 (n=5,219)




MMR: Measles, mumps, rubella

tis in as many as 50% of post-pubertal males in other studies [12].

In conclusion, Bosnia and Herzegovina is currently facing a large outbreak of mumps with an incidence of 225.8 in the Federation of Bosnia and Herzegovna, in the first half of 2011. The outbreak is probably related to failures to vaccinate during the war and post-war period between 1992 and 1998. Monitoring of the immunisation status and vaccine effectiveness, high vaccination coverage rates with two doses, and catch-up campaigns are necessary to avoid measles, mumps or rubella outbreaks in the future.

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# Surveillance of hospitalised patients with influenza-like illness during pandemic influenza A(H1N1) season in Sicily, April 2009 – December 2010

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This paper describes the epidemiology of hospitalised cases with influenza-like illness (ILI) and laboratory-confirmed influenza A cases in Sicily (Italy) during the 2009 influenza pandemic. The first ILI case diagnosed as infected with pandemic influenza A(H1N1)2009 in Sicily was reported in June 2009 and it rapidly became the dominant circulating strain. In the period from 30 April 2009 through 31 December 2010, a total of 2,636 people in Sicily were hospitalised for ILI and 1,193 were laboratory-confirmed for influenza A. Basic demographic and clinical information for all hospitalised patients was collected and population mortality rates (PMRs) and case fatality ratios (CFRs) were calculated. The median age of hospitalised patients infected with pandemic influenza A(H1N1)2009 was significantly lower than that of hospitalised ILI cases in general (18.0 vs. 32.1 years; p<0.0001). Among adults, women were more susceptible than men. The majority of clinical presentations were mild, but 6.6% of hospitalised patients required admission to an intensive care unit, of whom 26.3% had confirmed influenza A. Twenty-four fatal cases were documented. The age group of 45–54 year-olds showed the highest PMRs once hospitalised, while CFRs were higher in elderly patients of 65 years and older. All fatal cases were confirmed as influenza A(H1N1)2009 and most of them had established risk factors for influenza complications.

## Introduction

Before the emergence of the influenza A(H1N1)2009 virus in April 2009 [1], descriptions of clinical illness due to human infection with swine-origin influenza had been limited to sporadic cases and an outbreak on a military base in 1976 [2]. During the pandemic period, more than 214 countries and territories worldwide reported laboratory-confirmed cases of influenza A(H1N1)2009, and approximately 2,900 deaths were reported in Europe [3].

In Italy, the virus was first detected on 2 May 2009 in an adult man returning from Mexico [4]. Since then, more than 27,000 confirmed cases have been reported, including 260 deaths [3,5]. In Sicily, the largest island of Italy with a population of about 5 million inhabitants, the first laboratory-confirmed case of influenza A(H1N1)2009 was detected on 7 June 2009 in a young man returning from the United States, and the first fatal case was reported on 19 September 2009 in a women in her 40s who did not have any underlying diseases or known risk factors.

According to the guidelines of the Italian Government Department of Health, a Regional Pandemic Influenza Preparedness and Response Plan was published in August 2009 in order to enhance the epidemiological/virological surveillance for influenza. A team of general practitioners and paediatricians (members of the national network INFLUNET) were involved as sentinel practitioners, while several hospital wards throughout Sicily exceptionally participated in the surveillance of hospitalised patients with influenza-like illness (ILI) for severe acute respiratory infection (SARI) potentially related to pandemic influenza A(H1N1)2009.

The aim of the present study was to report the influenza surveillance data describing the epidemiological characteristics of patients with ILI symptoms, laboratory-confirmed infections with pandemic influenza A(H1N1)2009, and fatal cases that occurred among hospitalised patients in Sicily from April 2009 through December 2010.

## Methods

### Surveillance and data collection

We obtained ILI surveillance data and results of laboratory-tested samples for all individuals who sought hospital medical care for ILI symptoms in the period

from 30 April 2009 through 31 December 2010 in Sicily. These data were part of the nationwide active sentinel surveillance network (INFLUNET) that is responsible for seasonal influenza surveillance in Italy and combines clinical and virological information [5].

The molecular epidemiology laboratory located in the hygiene section of the Department of Health Promotion Sciences at the University Hospital (Azienda Ospedaliera Universitaria Policlinico 'P. Giaccone') in Palermo, member of the INFLUNET network, was appointed as the Sicilian reference laboratory for the virological surveillance of 2009 pandemic influenza by decree of the Regional Government Department of Health .

According to the Regional Pandemic Influenza Preparedness and Response Plan [6], about 110 different hospital wards throughout the region (mainly from infectious diseases, paediatrics and neonatology, and internal medicine departments) sent nasopharynx swabs and/or bronchoalveolar lavages (BAL) to the diagnostic reference laboratory together with standardised questionnaires including demographic and epidemiological/clinical information (e.g. comorbid conditions).

All patient data were entered in a database and reported weekly to the National Institute of Health (Istituto Superiore di Sanità; ISS) in Rome. Data collected through INFLUNET were also part of the European Influenza Surveillance Network (EISN) database coordinated by the European Centre for Disease Prevention and Control (ECDC) [5].

## Case definitions and laboratory diagnosis

A case of ILI was defined as an individual admitted to hospital with acute respiratory illness and at least one of the following symptoms: acute onset of fever (≥38 °C), sore throat, headache, cough, muscle pain, nasal obstruction, general discomfort or asthenia.

Nasopharyngeal swabs and/or BAL from patients with ILI were homogenously collected and transported to the regional reference laboratory by using Virocult swabs (MWE, Medical Wire, UK), and tested by real-time RT-PCR according to a recommended protocol from the United States Centers for Disease Control and Prevention (CDC) [7] on an ABI Prism 7000 real-time PCR instrument (Applied Biosystems, US).

Each suspected case of ILI was laboratory-confirmed as negative for influenza A or positive for pandemic influenza A(H1N1)2009, influenza A(H3N2) or unsubtypable influenza A, as appropriate. Samples negative for pandemic influenza A(H1N1)2009 but positive for influenza A were directly sequenced by cycle sequencing, using BigDye terminator chemistry v3.1 on an ABI Prism 3130xl automatic sequencer (Applied Biosystems, US) following in-house protocols for diagnosis confirmation (protocols available upon request). Diagnosis of influenza was invariably provided within 8–24 hours after the receipt of the sample.

A fatal case was defined as a resident of Sicily with laboratory-confirmed pandemic influenza A(H1N1)2009, who died after 27 April 2009.

## Statistical analysis

Demographic and clinical information was analysed using descriptive analysis. Data were aggregated into 10-year intervals (except for the first group of 0–4 year-olds) according to age at admission. Medians and interquartile ranges (IQRs) were used to describe continuous variables, while frequency analyses for categorical variables were described with percentages.

Comparisons of continuous variables were conducted using Student's t-test or the Mann–Whitney U-test, according to data distribution, and a $p$ value $<0.05$ was considered to indicate statistical significance. Univariate logistic regression was used to examine the relation between variables of interest (age and sex) and severity of disease. For this purpose, patients were categorised into two groups according to their hospital admission in a medical intensive care unit (ICUs) or not, and stratified by age according to three arbitrarily chosen age groups (≤4 years, 15–54 years and ≥55 years). The age-group 5–14 years was used as a reference group. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Overall and age-specific population mortality rates (PMRs) for pandemic influenza A(H1N1)2009 were cumulatively calculated over the study period using the 2009 population for Sicily reported by the National Institute of Statistics [8], whereas for the comparison of mortality between different countries in Europe, standardised PMRs were estimated based on the EUROSTAT European population data and data provided by the ECDC [3,9]. Moreover, the case fatality ratios (CRFs) were calculated overall and by age group. The numerator was the reported number of fatal cases and the denominator was the cumulative number of hospitalised patients with ILI admission included in the study, both with a laboratory confirmation of influenza A(H1N1)2009 infection.

Statistical analyses were carried out with the use of STATA software for Apple (version 11.1 MP, StataCorp, US).

# Results

## Surveillance data for influenza-like illness and confirmed cases of influenza A(H1N1)2009

A total of 2,636 cases of ILI (n=1,204 females (45.7%) and n=1,432 males (54.3%)) were hospitalised during the study period (Table 1). Overall, 1,193 of 2,636 (45.3%) were confirmed as influenza A, and of those, 1,146 (96.1%) were pandemic influenza A(H1N1)2009, 42 (3.5%) were unsubtypable influenza A strains,

and only five (0.4%) were seasonal influenza A(H3N2) strains.

Among the influenza A-positive samples, females and males accounted for 47.9% and 52.1%, respectively. The median age of hospitalised patients was 25.4 years (IQR: 40.3 years), and a difference was found between influenza A-negative ILI cases and confirmed influenza A(H1N1)2009 cases (32.1 years and 18.0 years, respectively) ($p<0.0001$). When aggregated by age, ILI patients were similarly represented within each age group, while influenza A-positive individuals were younger (5–14 years) and their proportion progressively decreased in older groups ($p<0.0001$).

A total of 175 patients (6.6% of those included in the study), 129 (8.9%) with influenza A-negative ILI and 46 (3.8%) with influenza A infection were admitted to ICUs. On average, ICU patients with laboratory-confirmed influenza A(H1N1)2009 infection were younger than ICU patients with influenza A-negative ILI (median age: 40.8 years and 53.7 years, respectively). Moreover, 16 ICU patients (five influenza A-negative ILI and 11 influenza A(H1N1)2009-positive) developed severe clinical complications and required extra-corporeal membrane oxygenation (ECMO) treatment. A total of 24 ICU patients, all diagnosed as positive for pandemic influenza A(H1N1)2009 infection, died.

Figure 1 depicts the trend of total ILI and laboratory-confirmed influenza A(H1N1)2009 cases reported during the study period, by week of sampling. During the early phase of the 2009 surveillance, the majority of cases were imported from the United States/Canada, the United Kingdom/Ireland, Spain, and Malta, or related to contact with imported confirmed cases. Few cases of ILI and confirmed pandemic influenza A(H1N1)2009 were hospitalised, and only five ILI cases were identified as cases of seasonal influenza A(H3N2) (weeks 24 to 29).

All cases hospitalised from 20 July 2009 (week 30) onwards were cases of pandemic influenza A(H1N1)2009, and starting from 10 August 2009 only autochthonous cases were detected. A slight increase in the number of ILI cases was observed at the end of

**Table 1**

Characteristics of the study population of influenza-like illness cases, Sicily 30 April 2009–31 December 2010 (n=2,636)

| | Total ILI cases | Influenza A-negative cases | Influenza A-positive cases |
|---|---|---|---|
| Hospitalised patients [n (% by row)] | 2,636 | 1,443 (54.7) | 1,193 (45.3) |
| InfluenzaA(H1N1)2009 | | | 1,146 (96.1) |
| InfluenzaA unsubtypable | | | 42 (3.5) |
| InfluenzaA(H3N2) | | | 5 (0.4) |
| Sex [n (%)] | | | |
| Female | 1,204 (45.7) | 633 (43.9) | 571 (47.9) |
| Male | 1,432 (54.3) | 810 (56.1) | 622 (52.1) |
| Age [median IQR] | | | |
| All | 25.4 (40.3) | 32.1 (46.4) | 18.0 (30.8)* |
| Admitted to ICU | 50.5 (49.4) | 53.7 (53.6) | 40.8 (41.0)* |
| Managed with ECMO | 37.1 (13.0) | 40.0 (7.0) | 35.6 (12.0)* |
| Deaths | 48.5 (18.5) | NA | 48.5 (18.5) |
| Age groups [n (%)] | | | |
| 0–4 (years) | 371 (14.1) | 199 (13.8) | 172 (14.4)[a] |
| 5–14 (yers) | 434 (16.5) | 168 (11.6) | 266 (22.3)[a] |
| 15–24 (years) | 348 (13.2) | 155 (10.7) | 193 (16.2)[a] |
| 25–34 (years) | 274 (10.4) | 134 (9.3) | 140 (11.7)[a] |
| 35–44 (years) | 256 (9.7) | 133 (9.2) | 123 (10.3)[a] |
| 45–54 (years) | 231 (8.8) | 131 (9.1) | 100 (8.4)[a] |
| 55–64 (years) | 193 (7.3) | 121 (8.4) | 72 (6.0)[a] |
| 65–74 (years) | 129 (4.9) | 106 (7.3) | 23 (1.9)[a] |
| ≥75 (years) | 137 (5.2) | 127 (8.8) | 10 (0.8)[a] |
| Unknown | 263 (9.9) | 169 (11.7) | 94 (7.9) |
| ICU admission [n (% by row)] | 175 (6.6) | 129 (8.9) | 46 (3.8) |
| ECMO | 16 (9.1) | 5 (31.2) | 11 (68.8)[b] |
| Deaths | 24 (13.7) | NA | 24 (100,0)[b] |

ECMO: extra-corporeal membrane oxygenation; ICU: intensive care unit; ILI: influenza-like illness; IQR: interquartile range; NA: not applicable.

* statistically significant at $p<0.0001$.

[a] Trend analysis for proportions: $p<0.0001$.

[b] Laboratory-confirmed cases of influenza A(H1N1)2009.

September (week 39), and the peak was reached in mid-November (week 47), followed by a rapid decrease; only sporadic cases were confirmed from the turn of the year 2009/2010.

The percentage of samples positive for influenza A(H1N1)2009 was calculated for each age group, as well as the females/males ratio for these percentages (Figure 2). The highest values, both of absolute numbers and percentage of influenza A(H1N1)2009-positive samples, were reported in the age group of 5–14 year-olds, with more than 60% of positive samples. While the ratio ranged from 0.8 to 1.1 among younger individuals, it was higher among adults and elderly individuals (range: 1.4–2.1).

In order to evaluate the presence of possible correlates of the severity of disease, influenza A-negative ILI and laboratory-confirmed influenza A(H1N1)2009 cases were divided into two categories: admitted to ICU or not. Table 2 shows the odds ratios of disease severity that were calculated for confirmed cases of influenza A(H1N1)2009, comparing hospitalised non-severe cases with cases admitted to ICU for each of three arbitrarily chosen age groups ≤4 years, 15–54 years and ≥55 years vs. The reference group of 5–14 year-old patients. Overall, the odds ratio of disease severity was 3.07 (95% CI: 1.06–8.95) among patients 15–54 years of age, 3.95 (95% CI: 1.03–15.08) among elderly patients (≥55 years), and 1.61 (95% CI: 0.43–6.09) in the youngest group. In our dataset, sex was not correlated to the severity of disease.

## Mortality and case fatality ratios for influenza A(H1N1)2009 in Sicily

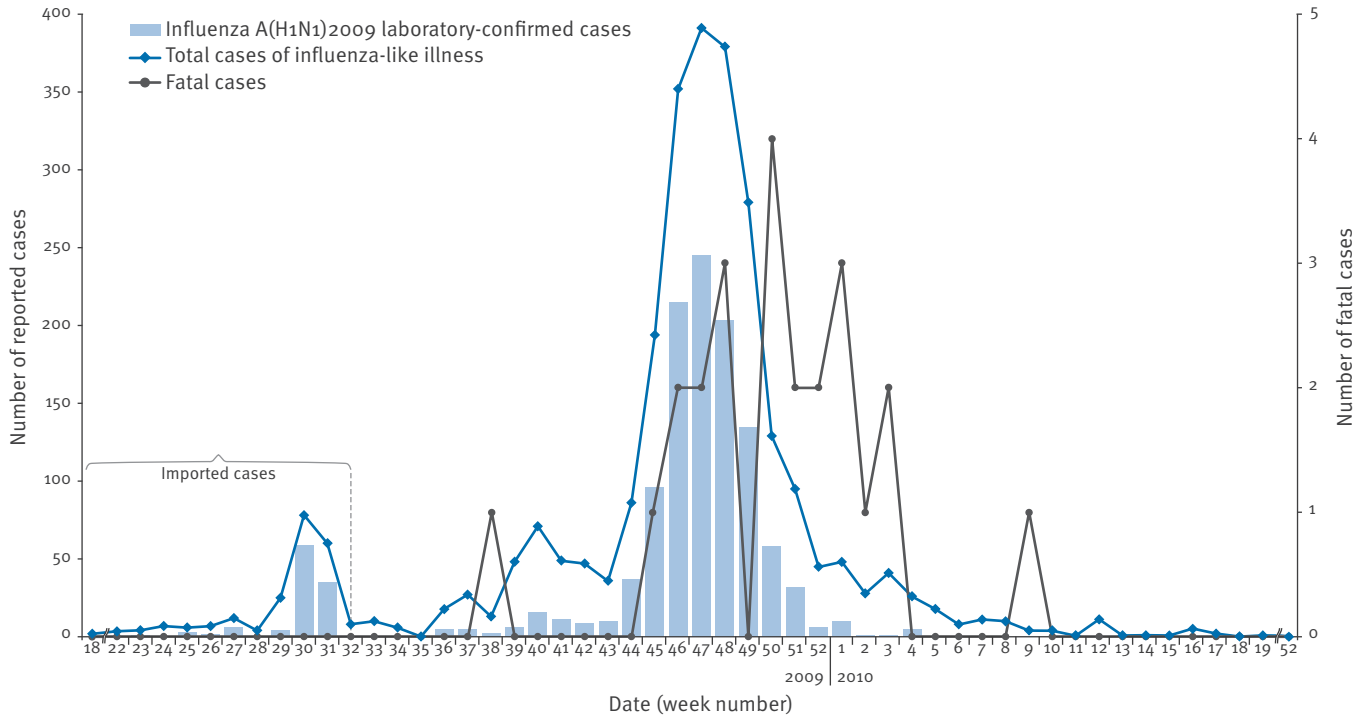
Twenty-four laboratory-confirmed fatal cases of influenza A(H1N1)2009 (median age: 48.5 years, range: 13–75 years; 11 males) were reported in Sicily from 19 September 2009 to 31 December 2010. The overall PMR for pandemic influenza was 4.81 per million inhabitants (standardised rate based on the European population: 5.01 per million inhabitants) and appeared to increase progressively with age. It was lower in adolescents (1.89 per million inhabitants) and peaked at 13.2 per million inhabitants in the age group of 45–54 year-olds. No fatal cases were reported in children under five years of age, in the 15–24 year-olds and in elderly 75 years and older (Figure 3).

The overall CFR was 2.0%, among male patients 1.8% and among female patients 2.3%. There was evidence of differences in the age-specific CFRs, with higher values in individuals between 65 and 75 years of age (CFR: 17.4%) compared to those aged 0-64 years (CFR: 1.9%) (Figure 3).

Table 3 reports the individual risk factors for 22 of 24 pandemic influenza A(H1N1) fatal cases in Sicily. Nineteen of these 22 had an underlying risk factor for severe influenza, obesity being the most common (n=8), while three individuals did not have any underlying known risk factors or comorbidities. Overall, eight of 19 fatal cases had only one risk factor, whereas 11 fatal cases suffered from more than one underlying condition.

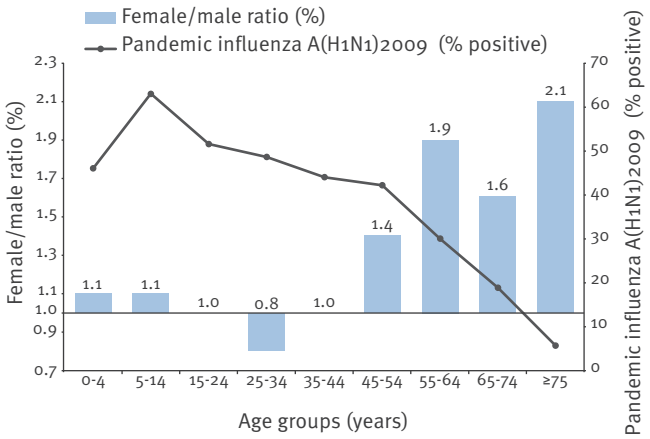
**Figure 1**

Weekly distribution of hospitalised cases of influenza-like illness (n=2,636), laboratory-confirmed (n=1,146) and fatal (n=24) influenza A(H1N1)2009 in Sicily, 30 April 2009–31 December 2010



## Figure 2

Proportion of samples positive for influenza A(H1N1)2009 and females/male ratio, by age-group, Sicily, 30 April 2009–31 December 2010




## Table 3

Reported comorbid conditions of fatal influenza A(H1N1)2009 cases, Sicily, 30 April 2009–31 December 2010 (n=22)

| Underlying risk factors | Total[a] |
|---|---|
| Patients with reported risk factors | 19 |
| One comorbid condition | 8 |
| More than one comorbid condition | 11 |
| Most common risk factors | |
| Obesity | 8 |
| Chronic heart disease | 7 |
| Chronic neurological disease | 6 |
| Chronic respiratory disease | 5 |
| Diabetes | 5 |
| Patients with no risk factors | 3 |

[a] Some patients had more than one underlying disease

## Table 2

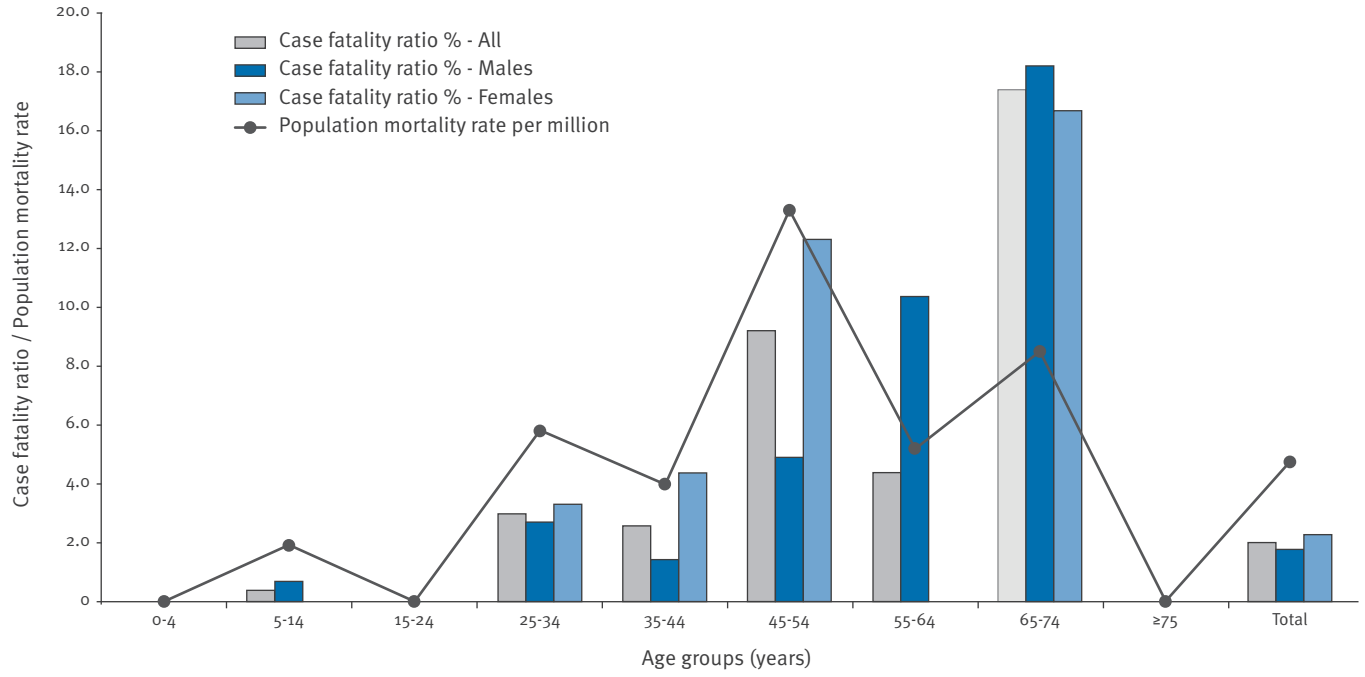
Univariable predictors of disease severity among hospitalised confirmed cases of influenza A(H1N1)2009, Sicily, 30 April 2009–31 December 2010 (n=1,146)

| Confirmed influenza A(H1N1) cases | All subjects | Disease severity | | |
|---|---|---|---|---|
| | | Non-severe outcome | Admission to ICU | OR (95% CI) |
| Sex (n=1,146) | | | | |
| Female | 550 | 527 | 24 | Reference group |
| Male | 596 | 579 | 22 | 0.69 (0.37–1.28) |
| Age groups (years) (n=1,099) | | | | |
| ≤4 | 204 | 198 | 6 | 1.61 (0.43–6.09) |
| 5–14 | 264 | 259 | 5 | Reference group |
| 15–54 | 544 | 518 | 26 | 3.07 (1.06–8.95) |
| ≥55 | 87 | 82 | 5 | 3.95 (1.03–15.08) |

CI: confidence interval; ICU: intensive care unit; OR: odds ratio.

## Figure 3

Population mortality rates and case fatality ratios of influenza A(H1N1)2009 cases, by age group, Sicily, 30 April 2009–31 December 2010 (n=24)



## Discussion

This paper summarises the epidemiology of influenza-like illness and pandemic influenza A(H1N1)2009 in hospitalised patients in Sicily, from April 2009 to December 2010. Influenza A(H1N1)2009 cases were significantly younger than ILI cases not confirmed as influenza A infections ($p<0.0001$), and the proportion of ILI samples positive for influenza A(H1N1)2009 reached a maximum of about 60% in younger people (5–14 years old). Similar numbers have been reported from other European countries [10,11].

In our series, higher percentages of influenza A(H1N1)2009-positive samples were reported among adult women (age groups 45–54, 55–64, 65–75 and >75 years) compared with younger female individuals. Different hypotheses could explain this. Adult women seem to be more prone to the disease than men [10], as supported in part by studies on the increased risk of severe illness in pregnant women [12]. Moreover, other authors have reported that women may be more exposed to airborne infections because of their role in child care or because they may have more contacts with older people who live in the family or with other close relatives [10].

In order to identify predictors of disease severity, the surveillance data were stratified by location of care (ICU admissions and hospital admissions other than ICU) and age group. Several studies have evaluated the risk of a severe outcome in association with specific individual risk factors such as age and sex, as well as pre-existing medical conditions. In Canada, the risk of admission to ICU was greater for females, and patients with milder disease were younger than those admitted to ICU [13]. Similar results were also found in England [14]. In our paper, higher values compared to the reference group (5–14 years of age) were observed amongst adults aged 15–54 years (OR: 3.07; 95% CI: 1.06–8.95) and older (OR: 3.95; 95% CI: 1.03–15.08), while sex was not a predictor of disease severity.

Twenty-four deaths were reported during the study period, representing a cumulative mortality of 4.81 per million inhabitants in the general population. It was similar to that reported for the whole of Italy (4.33 per million inhabitants) [5], and in the same range as in other European countries such as Germany [15], Austria [3] and the Netherlands [3] but significantly lower than that observed in United Kingdom [16] and Greece [17].

In addition, fatal influenza cases in Sicily were mainly observed in adults (45–54 years old), which is similar to Greece [17] or Canada [13], but in contrast with other countries where the proportion of deaths was significantly higher in younger people [15,16,18]. Here we reported an overall CFR of 2.0% (range: 0.3%–17.4%), that was similar to other European studies which included in the formula the total number of ILI cases with confirmed diagnosis of pandemic influenza A(H1N1)2009 to calculate ratios [17,19], but much lower than observed in previous pandemics [18].

Viral pathogenicity [20], improvement in nutritional status and housing, and the availability of healthcare might explain some of the apparent decrease in CFR from one pandemic to the next. It is widely believed that low CFRs in the 2009 pandemic resulted from aggressive early treatment with antiviral drugs such as oseltamivir and zanamivir, as well as major advances in intensive care medicine.

Although the number of patients admitted to ICU or managed with ECMO was higher during the 2009 pandemic compared with previous influenza seasons [21], the prevalence of Sicilian ILI patients admitted to an ICU was less than 7%. Of note, ICU admission was disproportionately higher among ILI cases negative for influenza A than for influenza A(H1N1)2009-positive cases (8.9% vs. 3.8%), although the disease was more severe and had a worse prognosis in influenza A(H1N1)2009-positive patients, including 11 of 16 ECMO treatments and all 24 deaths.

Viral or bacterial co- or superinfections of the respiratory tract have been suggested as a possible cause of severe disease, particularly *S. pneumoniae* [22]. However, the determinants for the progression of respiratory tract infections to fatal disease are still poorly understood and the findings on this topic are conflicting, and fail to demonstrate a clear and consistent involvement of other pathogens in severe complications of hospitalised patients with influenza A(H1N1)2009 [23-25]. In the present study, laboratory data on bacterial or viral co-infections in confirmed cases of influenza A(H1N1)2009 were not available to assess this hypothesis. Nevertheless, it is reasonable to assume that influenza infection may negatively interact and that underlying risk factors or comorbidities play a key role in the progression of the disease [14,15] or increase the risk of influenza-related complications [12,26].

Most (19 of 22) of the fatal cases of influenza A(H1N1)2009 in Sicily had at least one underlying risk factor, and 11 of them had more than one comorbid conditions. Recent reports have described high proportions of severe or fatal cases of influenza A(H1N1)2009 among obese patients [27], and in the fatal cases in Sicily obesity was the most common risk factor, alone or associated with other comorbidities. However, although obesity has been linked to higher all-cause mortality in large epidemiologic investigations [28], some studies in critical care settings reported that there was no correlation between body mass index and fatal outcome [29]. The pathophysiology of severe pandemic influenza A(H1N1)2009 in obese individuals is unknown, and further research is needed to elucidate the role of obesity in influenza mortality.

Finally, pregnancy has recently been identified as a noteworthy risk factor [12]. In our study population, only one pregnant woman was affected by influenza A(H1N1). She required rescue therapy by ECMO for severe pulmonary complications. This patient had no other underlying risk factors.

Our study is subjected to several limitations. Firstly, clinical and epidemiological data were not extracted from standardised medical records but from questionnaires provided with biological samples, that did not systematically include information about influenza-related risk factors. Secondly, it must be stressed that the estimated PMR could be liable to uncertainty because of the limited number of laboratory-confirmed fatal cases of influenza A(H1N1)2009. However, a number of deaths due to influenza A(H1N1)2009 may have remained undiagnosed.

In conclusion, the most vulnerable groups for pandemic influenza virus infection in our setting were younger people, and women were, at least in older age groups, more prone to illness. Deaths occurred in adult individuals with pre-existing risk factors, most frequently obesity. In the near future, more studies should be focused on the prevalence of co-existing or secondary bacterial or viral infections in hospitalised patients admitted with severe ILI symptoms, associated with confirmed influenza virus infections, to better define the role of influenza viruses in the severity of the disease and ultimately support prevention programmes such as vaccination, especially in particular risk groups.

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# Meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in Tampere University Hospital: a case-control study, Finland October 2002 to January 2010

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**Meticillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a frequent pathogen in blood cultures in Pirkanmaa Hospital District (HD), Finland. To study risk factors for MRSA bacteraemia and the adequacy of empirical antimicrobial treatment, we retrospectively reviewed the hospital records of 102 patients, 51 with MRSA, and 51 with meticillin-sensitive *Staphylococcus aureus* (MSSA) bacteraemias respectively, who had been admitted to Tampere University Hospital in Pirkanmaa HD, from October 2002 to January 2010. For each patient with MRSA bacteraemia, one consecutively detected unmatched patient with MSSA bacteraemia was chosen as control. Patients with MRSA bacteraemias were significantly older (median age: 73 years vs 59 years, p=0.001), were more likely to have been transferred directly from another healthcare facility or were already in the hospital at the onset of bacteraemia (39/51 vs 26/51, p=0.007) and had a higher McCabe class than patients with MSSA bacteraemia (p=0.005). Patients with MRSA bacteraemia more seldom received adequate empirical antimicrobial therapy when compared to those with MSSA bacteraemia (13/51 vs 43/51, p<0.001). Of previously known MRSA carriers 10 of 29 received adequate empirical antimicrobial therapy for their condition. The percentage of MRSA bacteraemias among all *S. aureus* bacteraemias in Pirkanmaa HD is high compared to corresponding figures for the whole of Finland.**

## Introduction

Meticillin-resistant Staphyloccus aureus (MRSA) is a significant cause of both healthcare- and community-acquired infections [1]. The spread of MRSA in hospitals and healthcare facilities is a major threat, mainly for patients with underlying conditions. Studies conducted in countries with endemic MRSA have shown that patients with MRSA bacteraemia have more comorbidities and are significantly older than those with meticillin-sensitive *S. aureus* (MSSA) bacteraemia [2-4]. The worldwide emergence of MRSA-associated infections has prompted an Expert Panel of the Infectious Diseases Society of America to publish evidence-based guidelines for the management of patients with MRSA infections [1].

MRSA has emerged as a frequent pathogen isolated in severe infections such as bacteraemia, in regions previously reported to be low-prevalence areas, for example Sweden and Finland [5,6]. From 1997 to 2003, the annual number of MRSA notifications to the National Infectious Disease Register in Finland rose over tenfold, and the proportion of MRSA among *S. aureus* blood isolates tripled, from less than 1% to 2.8% in 2004 [7].

In the Pirkanmaa Hospital District (HD), Finland, the number of new MRSA notifications has increased during the past 10 years and MRSA bacteraemia has emerged as a prevalent pathogen isolated in blood cultures. MRSA epidemics began in Pirkanmaa HD in 2001 [unpublished data]. Since then, Pirkanmaa HD has conducted routine surveillance for MRSA. From 2001 to 2007, Pirkanmaa HD recommended that patients admitted in Tampere University Hospital (TAUH), the central hospital of the Pirkanmaa HD, should be screened for MRSA if they had been treated in long-term care facilities of Tampere or in high-MRSA-incidence wards in Tampere city hospitals. During recent years, from 2008 to July 2011, Pirkanmaa HD recommended that all patients admitted to hospitals/healthcare institutions should be screened for MRSA if they had been treated in any hospital, healthcare institution or long-term care unit of the Pirkanmaa HD after 2001. Since August 2011, universal screening of all patients admitted to hospitals/healthcare institutions of the Pirkanmaa HD is conducted.

We here carried out a retrospective case-control study in TAUH, Finland, to compare underlying patient characteristics and the adequacy of empirical therapy in MSSA and MRSA bacteraemias.

## Methods

### Pirkanmaa Hospital District

The Pirkanmaa HD is a joint municipal authority comprising 22 municipalities and responsible for healthcare services to about 477,600 inhabitants (population in year 2009). The overall population of Finland in 2009 was 5,351,427. Thus, Pirkanmaa HD provides healthcare for 9% of the total Finnish population [8].

### Study population

The only central hospital in the Pirkanmaa HD area is TAUH. The present study comprised 51 patients with blood culture-confirmed MRSA bacteraemia and 51 unmatched control patients with MSSA confirmed bacteraemia admitted to TAUH, from October 2002 to January 2010. All MRSA bacteraemia patients ever treated in TAUH were included. Patients with polymicrobial bacteraemia were excluded (three cases) and only the first bacteraemia episode per patient, for those with multiple episodes was included. For each patient with MRSA bacteraemia a consecutively treated unmatched patient with MSSA bacteraemia was selected as control. Underlying diseases, clinical data and laboratory parameters were retrospectively reviewed from the hospital records. Patients were defined as previously known MRSA carriers, if their patient history indicated that MRSA had been detected by screening or in clinical samples prior to bacteraemia suspicion. Information regarding a previous MRSA finding was available in the patients` hospital records. Chronic diseases and sources of bacteraemia were registered. Alcohol-abuse was defined as a known social or medical problem due to alcohol use. Patients were defined as current smokers and non-smokers, i.e. those who had never smoked or had stopped smoking. McCabe classification [9] was used to determine the severity of any underlying disease.

### Diagnostics

In our hospital blood cultures are routinely taken in cases with symptoms or signs of systemic infection. To obtain blood for culture, two sequential samples of blood for anaerobic and aerobic culture (2 x (20+20ml)) were taken through venipuncture according to the manufacturer's instructions. The BACTEC 9240 (BD Diagnostic Systems, Sparks, MD, USA) blood culture system was used with standard media until November 2006, and the BactALERT (BacT/ALERT 3D (bioMérieux, Marcy l'Etoile, France) was used from December 2006.

### Case fatality

The case fatality rate was studied within 30 days after a positive blood culture.

### Antimicrobial treatment

Empirical antimicrobial treatment for MRSA was considered adequate when (i) the treatment was started or continued on the day or the day after (+1 day) the blood culture was taken, and (ii) when it was applied intravenously (with the exception of linezolid, which was considered adequate also when taken perorally) and (iii) contained at least one element with good activity against the MRSA strain in question (vancomycin, linezolid, daptomycin or teicoplanin). Intravenous clindamycin was only considered adequate when the *S. aureus* strain was susceptible to both clindamycin and erythromycin. Therapy against MSSA was considered adequate if it contained at least one intravenous regimen with good activity against MSSA. For one patient with MSSA bacteraemia receiving levofloxacin, which has a good bioavailability orally as an empiric regimen, the therapy was considered adequate.

### Statistical analysis

An SPSS package (version 10.0) was used for statistical analyses and a two-sided p-value ‹ 0.05 was taken as cut-off for statistical significance. Categorical data were analyzed by chi-square test or Fisher´s exact test when appropriate and nonparametric data by Mann-Whitney U-test. Odds ratios (ORs) were expressed with their 95% confidence intervals (CI).

## Results

The total number of MRSA bacteraemias and the proportion of MRSA bacteraemias among all bacteraemias caused by *S. aureus* in Pirkanmaa HD and in TAUH have increased during the last decade (Table 1). The first

**Table 1**

Meticillin-resistant *Staphylococcus aureus* bacteraemias relative to all *Staphylococcus aureus* bacteraemias, in Tampere University Hospital, Pirkanmaa hospital district and Finland, Finland, 2001–2010

| | Number of MRSA bacteraemias/Number of all *Staphylococcus aureus* bacteraemias, (percentage)[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Years | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 |
| Tampere University Hospital | 0/66 (0%) | 1/77 (1%) | 3/75 (4%) | 2/74 (3%) | 6/80 (8%) | 6/102 (6%) | 9/100 (9%) | 14/98 (14%) | 14/101 (14%) | 8/113 (7%) |
| Pirkanmaa Hospital District | 0/87 (0%) | 2/92 (2%) | 4/100 (4%) | 5/100 (5%) | 10/109 (9%) | 9/130 (7%) | 15/134 (11%) | 16/120 (13%) | 20/133 (15%) | 11/150 (7%) |
| Finland[b] | 4/NR (1%) | 9/NR (1%) | 7/NR (1%) | 30/NR (3%) | 27/NR (3%) | 37/NR (3%) | 32/NR (3%) | 40/NR (3%) | 30/NR (2%) | 26/NR (2%) |

MRSA: meticillin-resistant *Staphylococcus aureus*; NR: Not reported.

[a] A bacteraemia may have been reported more than once if the time between the bacteraemia episodes in a patient was ≥ 3 months.

[b] Values for Finland are according to [7].

patient with MRSA bacteraemia in TAUH was diagnosed in October 2002.

## Characteristics of patients

Baseline characteristics of patients with *S. aureus* bacteraemias included in the study are shown in Table 2. Fifty of 51 MSSA bacteraemia patients and 50 of 51 MRSA bacteraemia patients were Finnish. Of those with MRSA bacteraemia, 29 of 51 were known to be MRSA carriers prior to the bacteraemia episode. Forty four of the MRSA carriers had acquired MRSA from healthcare centres in the Pirkanmaa area while seven MRSA carrier cases were defined as community acquired. All patients with MRSA or MSSA bacteraemia were treated with an empirical antibiotic regimen, and when necessary antimicrobial treatment was changed according to culture results. Patients with MRSA bacteraemia were significantly older than those with MSSA bacteraemia, and had more severe underlying diseases (Table 2). Patients with MRSA bacteraemia were significantly more likely to have been transferred directly from another healthcare facility or were already in hospital upon bacteraemia onset (39/51 vs 26/51, p=0.007), and were more likely to have had treatment in some healthcare institution (hospital, long-term care, nursing home) during the preceding year than those with MSSA bacteraemia (47/48 vs 34/46, p=0.001, data available on 94 patients).

Disease severity did not differ between the two groups (Table 3).

In 45 of 51 of MRSA bacteraemia cases, MRSA strain type was spa type to67 (FIN-16), which is the epidemic strain type in Pirkanmaa HD [unpublished data]. Four of 51 were caused by spa type t172 (FIN-4) and two of 51 cases by to26/t4819 (FIN-10).

Nineteen of 51 MRSA bacteraemia patients and 22 of 51 of MSSA bacteraemia patients were in TAUH when bacteraemia was detected. Twenty-five of 51 MSSA bacteraemia patients and 12 of 51 MRSA bacteraemia patients were admitted to hospital from home, none of the MSSA patient and six of 51 MRSA patients from a long-term care institution, four of 51 MSSA patients and three of 51 MRSA patients from a healthcare centre ward, two of 51 MSSA patients and two of 51 MRSA patients from a regional hospital and none of the MSSA patients and nine of 51 MRSA patients from Tampere city hospitals.

**Table 2**

Characteristics and underlying conditions of patients with *Staphylococcus aureus* bacteraemia, Tampere University Hospital, Finland, October 2002–January 2010 (n=102)

| Character | Patients with MSSA N=51 | Patients with MRSA N=51 | OR (95% CI) | p-value |
|---|---|---|---|---|
| Age, median (quartiles) | 59 (48–72) | 73 (60-78) | | 0.001 |
| Male | 38 | 32 | 1.7 (0.7–4.1) | 0.200 |
| Cancer | 11 | 13 | 1.2 (0.5–3.1) | 0.641 |
| Diabetes (type 1 or 2) | 12 | 19 | 1.9 (0.8–4.6) | 0.132 |
| McCabe class ≥2[a] | 14 | 28 | 3.2 (1.4–7.4) | 0.005 |
| Rheumatoid arthritis | 2 | 2 | 1 (0.1–7.4) | 1.000 |
| Cardiac disease[b] | 25 | 30 | 1.5 (0.7–3.2) | 0.321 |
| Current smoking[c] | 7 | 12 | 2.3 (0.8–7.1) | 0.126 |
| Alcohol abuse | 11 | 12 | 1.1 (0.4–2.8) | 0.813 |
| Haemodialysis treatment before bacteraemia episode | 6 | 9 | 1.6 (0.5–4.9) | 0.402 |
| Chronic obstructive pulmonary disease | 2 | 6 | 3.3 (0.6–17.0) | 0.141 |
| Liver cirrhosis | 2 | 3 | 1.5 (0.2–9.6) | 0.647 |
| Glucocorticoid therapy[d] | 12 | 16 | 1.5 (0.6–3.6) | 0.375 |
| Asthma | 3 | 6 | 2.1 (0.5–9.0) | 0.295 |
| Chronic ulcer | 12 | 11 | 0.9 (0.4–2.3) | 0.813 |
| Admitted to hospital directly from home | 25 | 12 | 0.3 (0.1–0.7) | 0.007 |
| Patient stayed in a healthcare facility one year prior to bacteraemia[e] | 34 | 47 | 16.6 (2.1–133.8) | 0.001 |
| Patient stayed in a healthcare facility 90 days prior to bacteraemia[f] | 4 | 5 | 0.9 (0.2–3.5) | 0.836 |
| Known-MRSA carrier prior to bacteraemia episode | 3 (6%) | 29 (57%) | 21 (5.8–76.7) | <0.001 |

MSSA: meticillin-sensivite *Staphylococcus aureus*; MRSA: meticillin-resistant *Staphylococcus aureus*.

[a] McCabe class≥2: rapidly or ultimately fatal underlying disease.

[b] Coronary artery disease, valvular heart disease, cardiac myopathy or congestive heart failure.

[c] Data available for 64 patients.

[d] ≥5mg/day of systemic prednisolone (or equivalent dose of another corticosteroid) during the preceding 30 days.

[e] Data available for 94 patients, 48 with MRSA and 46 with MSSA.

[f] Data available for 80 patients, 47 with MRSA and 33 with MSSA.

## Antimicrobial treatment

MRSA bacteraemia patients more seldom received adequate empirical antimicrobial therapy than those with MSSA bacteraemia (13/51 vs 43/51, p<0.001). Altogether 10 of 29 of those previously known to be MRSA carriers received inadequate empirical antimicrobial therapy. Ninety-eight of 100 patients in the study eventually received adequate antimicrobial treatment after susceptibility testing became available (data for changes in antibiotic treatment were missing for two MRSA cases, these patients having been transferred to regional hospitals). The delay until adequate antimicrobial treatment had a median 0 days (range: 0–10) in MSSA bacteraemia patients and a median two days (range: 0–5) in MRSA bacteraemia patients. Demographics or underlying diseases were not statistically significantly associated with the adequacy or inadequacy of antimicrobial treatment in MRSA bacteraemia (data not shown). The adequacy of treatment was not associated with the mode of admission (whether admission was direct from another hospital/healthcare facility or direct from home to hospital) (data not shown). Empirical antimicrobial therapy administered to patients is given in Table 4.

## Discussion

The present study shows that in Pirkanmaa HD, a notable percentage (7–15% during recent years) of all *S. aureus* blood culture isolates are currently meticillin-resistant strains. The percentage of MRSA bacteraemias among all *S. aureus* bacteraemias in Pirkanmaa HD is high compared to corresponding figures for the whole of Finland. This may reflect the high rate of new MRSA notifications per year in our HD [7], or alternatively suggest that some regions in Finland, such as ours, are more affected by MRSA. Although Scandinavian countries including Finland have been considered low prevalence countries, substantial regional variations are common [7,10].

By retrospectively reviewing the hospital records of 102 patients with *S. aureus* bacteraemias, who had been admitted to TAUH from October 2002 to January 2010, we found that patients with MRSA bacteraemia were significantly older than those with MSSA and/or had higher McCabe class and/or had previous MRSA carrier status. In accordance with previous reports [2] comorbidities and healthcare facility stay were significant factors associated with the risk of MRSA bacteraemia. Interestingly, the risk factors for MRSA bacteraemia in our study did not differ from the risk factors reported in counties where MRSA is endemic [3,4]. Most of MRSA bacteraemia cases in the present study were caused by the spa type t067 (FIN-16), which has caused a wide ongoing epidemic in Pirkanmaa HD since 2001.

MRSA bacteraemia was associated with an increased risk of inadequate empirical antimicrobial therapy. Inadequate empirical therapy was common also for patients previously known to be MRSA carriers. Despite a low statistical power due to a low number of patients, the present study is in line with the findings of a recent multicentre study in nine western European countries indicating that empirical antimicrobial treatment frequently fails in patients with MRSA bacteraemia [10]. Cefuroxime, which is not effective in MRSA bacteraemia, has been a widely used empirical regimen among patients with community-acquired bacteraemia in Finland [11]. It has been used to treat patients with common infections such as skin and soft tissue infections. Intravenous cefuroxime was by far the most common agent chosen as an empirical antibiotic therapy in *S. aureus* bacteraemia in this study. The present study indicates that local guidelines for empirical antimicrobial therapy should be updated for MRSA endemicity, guidelines should be made available on the internet and doctors should be widely informed on the new guidelines to be published. This may be done for example in the form of an electronic bulletin. MRSA is a potential cause of severe infections in MRSA carriers. Vancomycin is now recommended empirically for all previously known MRSA carriers with suspected or documented sepsis or other severe infection or infection potentially caused by *S. aureus* (i.e. osteomyelitis,

**Table 3**

Case fatality, sources of bacteraemia and adequacy of treatment in patients with *Staphylococcus aureus* bacteraemia, Tampere University Hospital, Finland, October 2002–January 2010 (n=102)

| Character | MSSA N=51 | MRSA patients N=51 | OR (95% CI) | p-value |
|---|---|---|---|---|
| Case fatality[a] | 11 | 12 | 1.1 (0.4-2.8) | 0.813 |
| Empirical treatment adequate | 43 | 13 | 0.1 (0.0-0.2) | <0.001 |
| Focus known | 38 | 42 | 1.6 (0.6-4.2) | 0.336 |
| Skin | 20 | 17 | 0.8 (0.3–1.7) | 0.537 |
| Osteomyelitis | 10 | 4 | 0.3 (0.1–1.2) | 0.084 |
| Arthritis | 3 | 3 | 1.0 (0.2–5.2) | 1.000 |
| Endocarditis | 3 | 0 | 0.5 (0.4–0.6) | 0.243 |
| Catheter-related | 11 | 14 | 1.4 (0.6–3.4) | 0.490 |
| Device infection | 4 | 12 | 3.6 (1.1–12.1) | 0.029 |

[a] The case fatality rate was studied within 30 days after a positive blood culture.

**Table 4**

Empirical antimicrobial treatment in patients with *Staphylococcus aureus* bacteraemia, Tampere University Hospital, Finland, October 2002–January 2010 (n=102)

| Empirical treatment | MRSA bacteraemia (n=51) | MSSA bacteraemia (n=51) |
|---|---|---|
| Cephalosporins | 29 | 38 |
| Vancomycin | 8 | 2 |
| Piperazillin-tazobactam | 8 | 1 |
| Clindamycin | 2 | 4 |
| Linezolid | 4 | 0 |
| Daptomycin | 1 | 0 |

MRSA: meticillin-resistant *Staphylococcus aureus*; MSSA: meticillin-sensitive *Staphylococcus aureus*.

endocarditis, post-surgery infections) in Pirkanmaa HD. Moreover, although the importance of administering an antimicrobial agent with good activity against MRSA to MRSA carriers has been highlighted in hospital hygiene education of staff in our institution, this may not be sufficient. Information regarding a previous MRSA finding has appeared in patients' electronic hospital records for many years. This information has been made more conspicuous during the last years, as an electronic alert system for MRSA has been constructed for hospital records.

Novel molecular methods may offer some advance in reducing the time frame for detecting *mecA* gene, the major determinant for meticillin resistance in *S. aureus*, in patients with *S. aureus* bacteraemia. These methods may be used to guide empiric antimicrobial therapy before definite culture-based susceptibility testing is available [12]. Also, in the case of bacteraemia in a MRSA carrier, molecular methods for the detection of *mecA* gene are now adapted for clinical use to speed up microbiological diagnosis.

Some limitations must be conceded here. There were altogether 92 patients with MRSA bacteraemias in Pirkanmaa HD during the period 2001 to January 2010 (Table 1), most of these patients having been treated in TAUH. However, we did not study the hospital records of patients treated in other hospitals than TAUH. Only one bacteraemia episode (the first) per patient was included in the study and patients with polymicrobial bacteraemias were excluded. As the study was retrospective by design, the data regarding socioeconomic status and travel history were not acquirable. The data regarding the number of days of hospital prior to bacteraemia and data regarding a contact with a known MRSA carrier could not be obtained. Although not done in the present study, the use of total MSSA bacteraemia patients (2001–2010) as a control group would have increased the statistical power of this study.

The present study is a case-control study with regard to the assessment of risk factors for meticillin resistance. The study was not designed to assess comparative outcomes, effects of appropriate vs. inappropriate empirical treatment or risk factors for death. The risk factors for meticillin resistance were studied because the case-control patients here were not matched for age, sex or other characteristics. Some work indicates that advanced age would be a significant factor associated with the adequacy of empirical therapy in MRSA bacteraemia [13], but this was not confirmed in the present study.

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